Synthesis of Dipyrrins Bearing Chirality Adjacent to the Conjugated Skeleton: Electron-poor Pyrroles Exhibit Dramatically Reduced Nucleophilicity

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Abstract

A dipyrrin bearing a stereogenic centre directly adjacent to the conjugated skeleton has been synthesized and complexed with Zn(II). The electron-withdrawing nature of the chiral 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituent significantly reduced the nucleophilicity of corresponding pyrroles, such that 3,3'-symmetrically substituted bis(dipyrrins) bearing this motif were inaccessible.

Keywords

Dipyrrin, dipyrromethene, complexation, electron-poor pyrrole, chirality

Introduction

The asymmetric synthesis of dipyrrinato complexes is a field of current interest as dipyrrins[1] give monoanionic, planar bidentate ligands that complex to a wide variety of metal ions. For example, chiral fluorescent boron-dipyrrinato (BODIPY)[2] complexes have been synthesized through the use of chiral dipyrrins,[3-5] and chiral metal-organic frameworks incorporating dipyrrinato ligands are also known.[6] 2,2'-Bis(dipyrrin)s (Figure 1) with methylene, ethylene or propylene linkers joining the dipyrrinato units generate dinuclear (M_2L_2) double helicates with tetrahedrally-coordinated metal ions, and mononuclear (ML) helicates are formed if the alkyl linker is four atoms or more in length.[7] The incorporation of chiral auxiliaries within the ligand allows the diastereoselective synthesis of helicates. Indeed, excellent diastereoselectivity has been obtained in the synthesis of mononuclear bis(dipyrrinato) helicates bearing templating BINOL and tartrate moieties attached *via* ethanoate groups within the linker.[8] However, the most successful asymmetric synthesis of dinuclear bis(dipyrrinato) helicates to date gives a diastereomeric ratio of only 69:31.[9-11] In all reported diastereoselective syntheses of dinuclear bis(dipyrrinato) helicates, the chiral auxiliary is attached through a pendent ester or amide linkage and thus the chiral centre itself is quite remote from the helical axis.

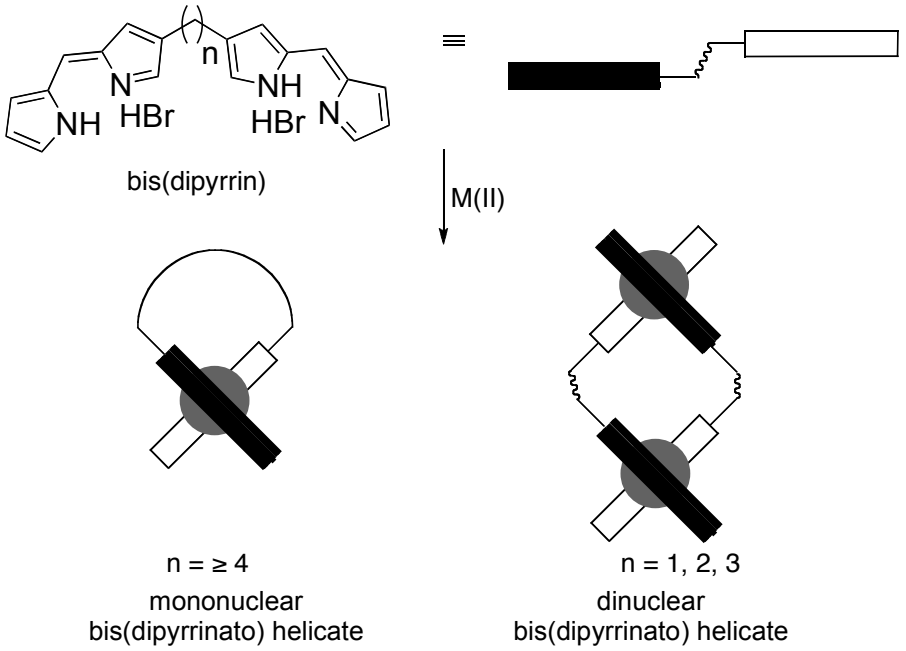


Figure 1. Complexation of bis(dipyrrin)s with varying linker length

Cognizant that the degree of stereoselectivity depends upon the effectiveness of the chiral auxiliary in inducing asymmetric complexation, and thus the distance between the site of the auxiliary and the helical axis, we explored the value of incorporating a chiral centre directly adjacent to the dipyrrin: such a motif is rare for pyrroles[12-17] and extremely rare for dipyrrins.[16,18,19] β-Keto pyrroles are readily available through Knorr-type syntheses[20,21] and asymmetric reduction would generate a chiral alcohol. Further derivitization would serve to incorporate the pyrrole into a dipyrrin and thus place a chiral centre directly adjacent to the dipyrrinato unit (Figure 2). Previous studies involving haematoporphyrin have shown that such hydroxyl groups are labile under mildly acidic conditions thus introducing the possibility of racemization through reversible elimination and addition. The lability is caused by the electron-rich nature of the pyrrole ring facilitating racemization at the pseudobenzylic position. Kumadaki provided a viable solution to potential racemization of this nature through the use of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted pyrroles[18,19] in the construction of homochiral

haematoporphyrins.[16] We herein report our work with 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrins. Our goals included the investigation of: the syntheses of dipyrrins and 2,2'-bis(dipyrrin)s incorporating 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituents; the stereochemical stability of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrins; the ability of 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituted dipyrrinato units to undergo complexation; and the potential of the 4-(2,2,2-trifluoro-1-hydroxyethyl) group to influence diastereoselective complexation, either as an alcohol or as bulkier ether/ester derivatives.

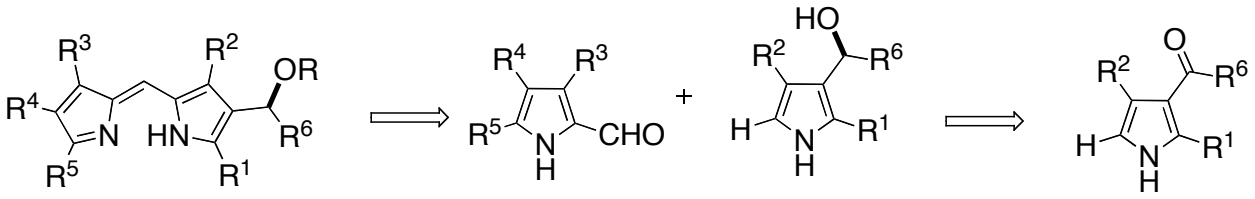
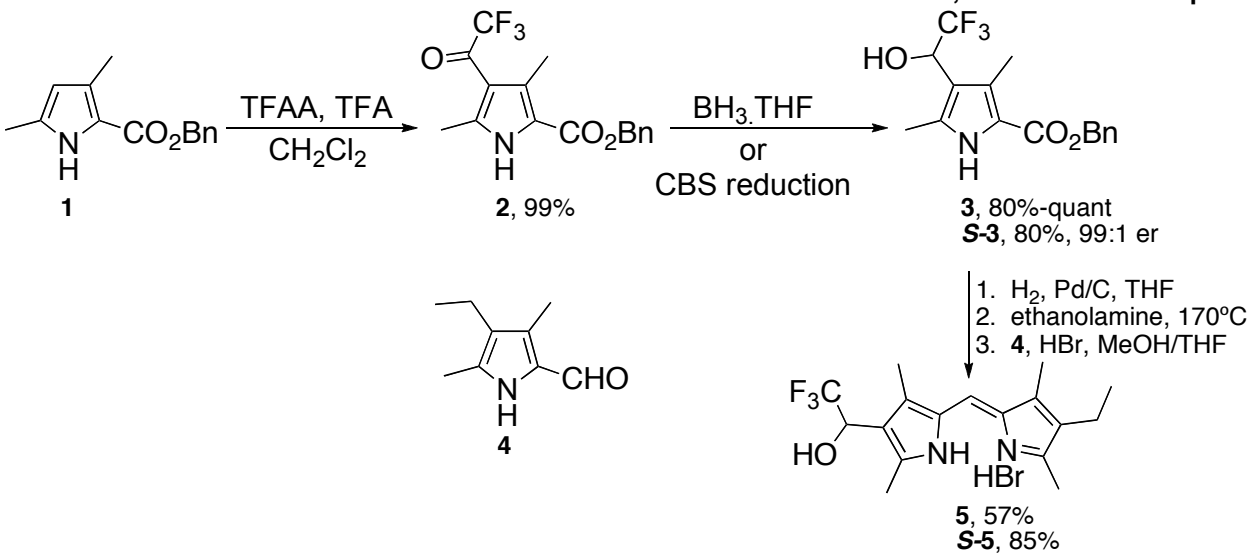


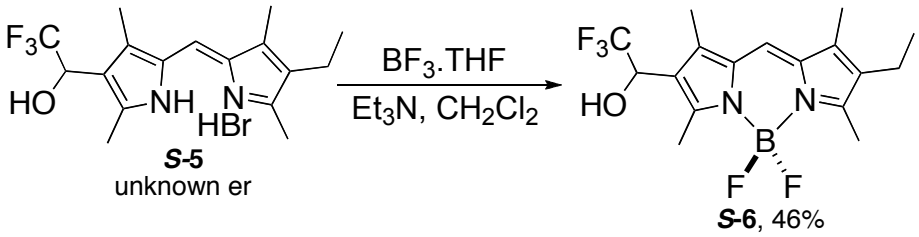
Figure 2. Retrosynthetic incorporation of chirality adjacent to dipyrrin core

Synthesis of the first dipyrrin bearing a 4-(2,2,2-trifluoro-1-hydroxyethyl)-substitutent was achieved according to Scheme 1. Benzyl 3,5-dimethyl-pyrrole-2-carboxylate (**1**)[22] was converted to the corresponding trifluoroacetoxy-substituted pyrrole **2** using TFAA under acidic conditions.[23] Reduction of **2** with borane gave racemic alcohol **3** and the use of the CBS protocol gave ***S*-3** with 99:1 enantiomeric ratio (er), akin to that reported by Kumadaki and co-workers.[16] Hydrogenolysis of the benzyl ester, followed by thermolytic decarboxylation gave the corresponding α-free pyrrole which was reacted directly with ethyl 5-formyl-2,4-dimethylpyrrole-3-carboxylate (**4**)[24] under MacDonald-type coupling conditions[1] to afford the requisite racemic dipyrrin **5**, and the single enantiomer ***S*-5**.



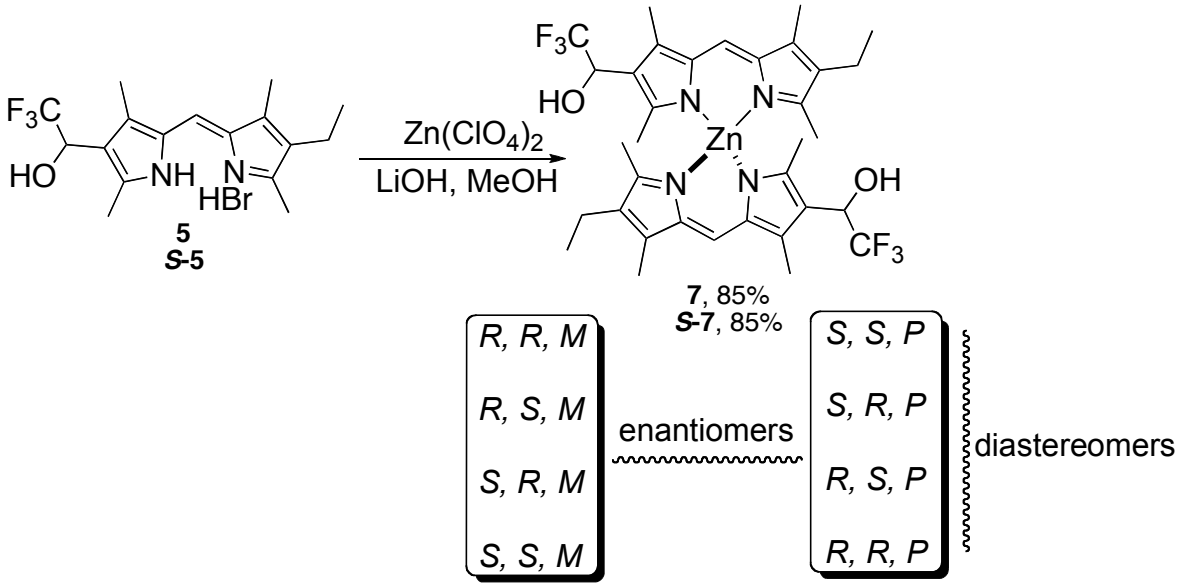
Scheme 1. Synthesis of 5

Literature precedence supports the stereochemical stability of the (2,2,2-trifluoro-1-hydroxyethyl) moiety under acidic conditions,[16,18,19] but we were concerned that the MacDonald-type[1] coupling conditions (48% HBr, MeOH/THF) might have afforded some racemization as exposure of enantiopure ***S*-3** to the same conditions resulted in loss of stereochemical integrity with the recovered material having only 76:24 er. To investigate its stereochemical purity a sample of the dipyrrin prepared from enantiopure ***S*-3** was converted into the corresponding boron-dipyrrinato (BODIPY)[2] complex **6** (Scheme 2). As boron-dipyrrinato complexes are achiral at boron and amenable to chromatography the enantiopurity of **6**, established by chiral HPLC, would reveal the enantiopurity of ***S*-5** by correlation.



Scheme 2. Synthesis of boron-dipyrrinato complex 6

HPLC-analysis (Figure S1) was used to determine that ***S*-6**, synthesized using ***S*-3**, had retained its enantiopurity during the MacDonald-type coupling step. Thus, with a source of enantiopure ***S*-5** in hand, and having secured both the synthesis and the stereochemical stability of dipyrrins bearing the 4-(2,2,2-trifluoro-1-hydroxyethyl)-group, efforts progressed to investigating the stability of the corresponding complexes and assessing the affects of the electron-withdrawing substituent, essential for stability of the chiral centre, upon complexation. Racemic **5** was treated with zinc acetate under standard conditions[10] to give the homoleptic zinc complex **7** in 64% yield. The efficiency of complexation was then improved through the use of zinc perchlorate, instead of the acetate salt, and lithium hydroxide as base: complexation using enantiopure ***S*-5** was conducted in the same manner (Scheme 3). Although the zinc complex **7** was noticeably less stable under mildly acidic conditions (silica gel, aqueous extractions, wet solvents) than dipyrrinato complexes not bearing electron-withdrawing groups, isolation of **7** in good yield was achieved by rapid precipitation from the methanolic reaction mixture upon the addition of water. Mass spectrometry confirmed the formation of a mononuclear ML_2 complex.



Scheme 3. Complexation of 5 and possible stereochemical outcomes

Efforts turned to the investigation of the stereochemical outcome of the complexation reactions to determine whether **5** had underdone complexation with simple diastereoselectivity. Previously NMR and circular dichroism (CD) spectroscopy, alongside chiral HPLC analysis, have been extremely useful for the evaluation of diastereoselective reactions involving dipyrrinato ligands. The neutral complexes are amenable to chromatography, and the helical nature of the chromophoric dipyrrinato units fixed in space through coordination to metal ions renders CD data very useful. As **5** constitutes an unsymmetrical A-B ligand architecture, the tetrahedrally-coordinated metal ion in **7** gives rise to helicity. Thus, the complexation of racemic **5** allows for the possible production of eight ($2^3 = 8$) stereoisomers; *R* and *S* for the stereocenters on the ligands, and *M* and *P* for the metal center (Scheme 3). Two species in each enantiomeric set (*R*,*S*,*P* – *S*,*R*,*P* and *R*,*S*,*M* – *S*,*R*,*M*) are identical, simplifying the possible outcomes to three (racemic) stereoisomers, with a 1:2:1 statistical ratio.

HPLC analysis of the crude product mixture obtained using racemic **5** showed one signal due to dipyrrinato complex(es) and two minor non-dipyrrinato impurities. The ChiralPak®-IA column used herein had previously proven to be superior for the resolution of dipyrrinato complexes and attempts to resolve the signals of **7** with other columns were unsuccessful. The ^{1}H NMR spectrum for the same product mixture was not useful for assigning stereoisomers but the ^{13}C nucleus allowed for improved resolution. The stereogenic carbon atom bearing the trifluoromethyl group normally appears as a quartet in the ^{13}C NMR spectrum with $J_{CF} \approx 33$ Hz. Indeed, **5** exhibits a quartet with $J_{CF} = 32$ Hz at a chemical shift of 65.8 ppm for this carbon atom. For the product mixture, the stereogenic carbon atom gave signals in the 64 ppm range that appeared as a pair of quartets of equal intensity ($J_{CF} = 33$ Hz), indicative either of a mixture of isomers or resulting from two non-equivalent dipyrrinato units within a single ML_2 complex.

Preparative HPLC served to purify the dipyrrinato complex(es) from the impurities, and ^{13}C NMR spectra of the isolated material retained the characteristic 1:1 pair of quartets. We identified that decomposition did not occur during HPLC, as NMR spectra of the initial product mixture and the material after preparative HPLC (and recombination of all fractions) were identical. Complex ***S*-7** was prepared from ***S*-5 (**Scheme 3). With enantiopure ligand, the product mixture was found to exhibit identical HPLC and NMR characteristics to **7** (prepared from racemic dipyrrin **5**), thus suggesting that the chiral HPLC column was unable to resolve isomers of **7**.

Although the coordination abilities of dipyrrin ligands have been reported previously,[26-28] a comparison of mononuclear and dinuclear analogues has not appeared. Using absorption spectroscopy, solutions of mononuclear **7**, bearing the 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituent, were compared to solutions of the per-alkyl mononuclear complex **8**[29] and the peralkyl dinuclear complex **9**[30] (Figure 3). Studies at a variety of concentrations in technical-grade CH_2Cl_2 indicated that solutions of mononuclear complexes **7** and **8** are less stable to acid-catalyzed decomplexation than the dinuclear complex **9**: spectrophotometric-grade CH_2Cl_2 did not cause any decomplexation. These studies are important as dipyrrinato complexes are typically exposed to a range of solvents (including water) during work-up, purification and analysis. As mentioned previously, the electron-deficient nature of **7** was a concern in terms of complex stability and thus discovering that dinuclear dipyrrinato complexes are more stable than their mononuclear analogues suggested that the 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituent might be more appropriate for use in bis(dipyrrinato) ligands. Furthermore, although ***S*-5** is unsymmetrical and thus gives an A-B dipyrrinato ligand that generates tetrahedrally-coordinated Zn(II) helicates, formally the helicity is a consequence only of the two differently substituted pyrrolic units, i.e. 4-ethyl *versus* 4-(2,2,2-trifluoro-1-hydroxyethyl).

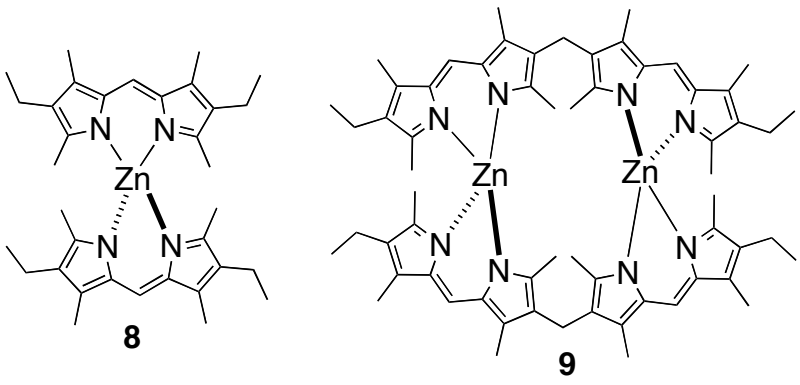


Figure 3. Mononuclear complex 8 and dinuclear complex 9

To increase the asymmetry of the ligands and improve both the stereoselectivity of complexation and the resolution by chiral HPLC, and to study the more stable dinuclear dipyrrinato complexes, efforts turned to the preparation of a bis(dipyrrin) bearing the chiral 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituent directly adjacent to the conjugated skeleton. Retrosynthetic analysis (Figure 4) of the symmetrical bis(dipyrrin) **10** reveals that the 2,2'-dipyrroles **11** and **12** are essential intermediates in the synthetic sequence, with successful condensation of **11** with **4** giving the required bis(dipyrrin). Three routes to **12** were envisaged, and each was investigated.

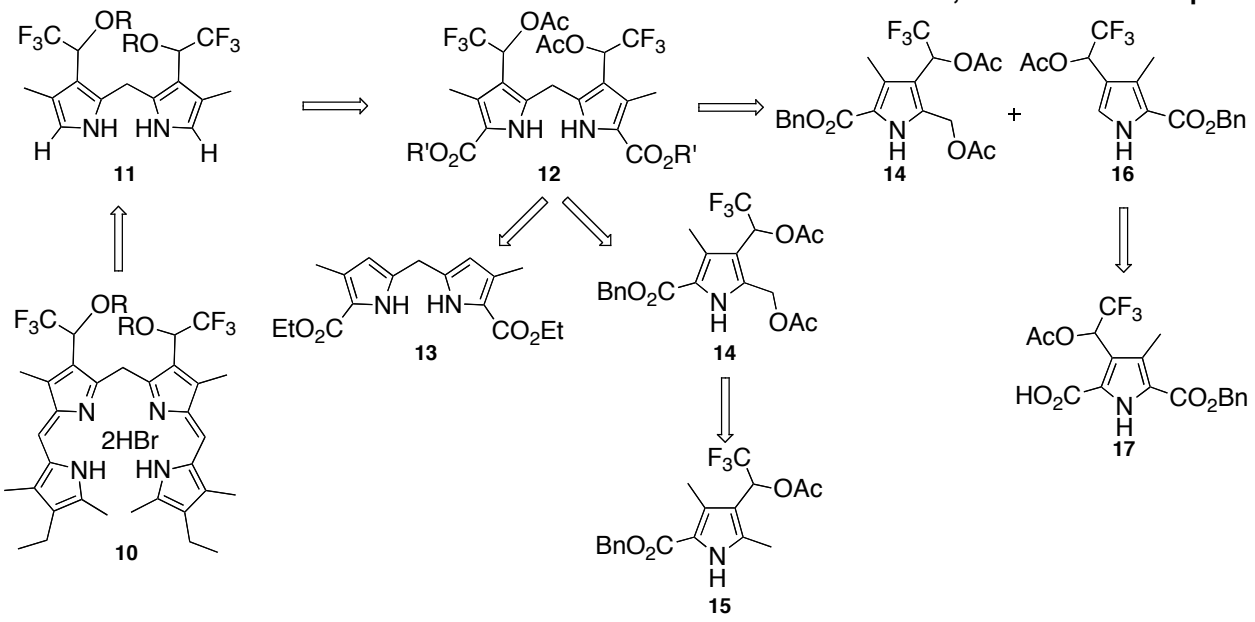
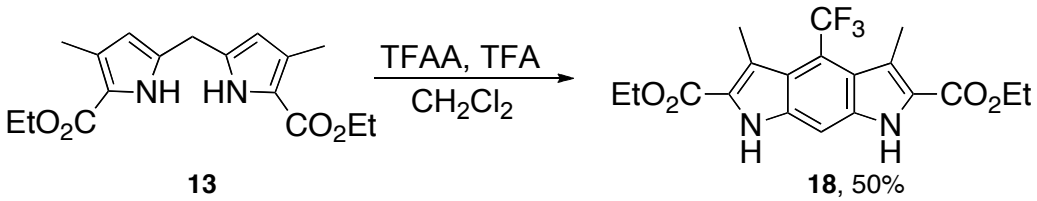


Figure 4. Retrosynthetic analysis of bis(dipyrrin) 10

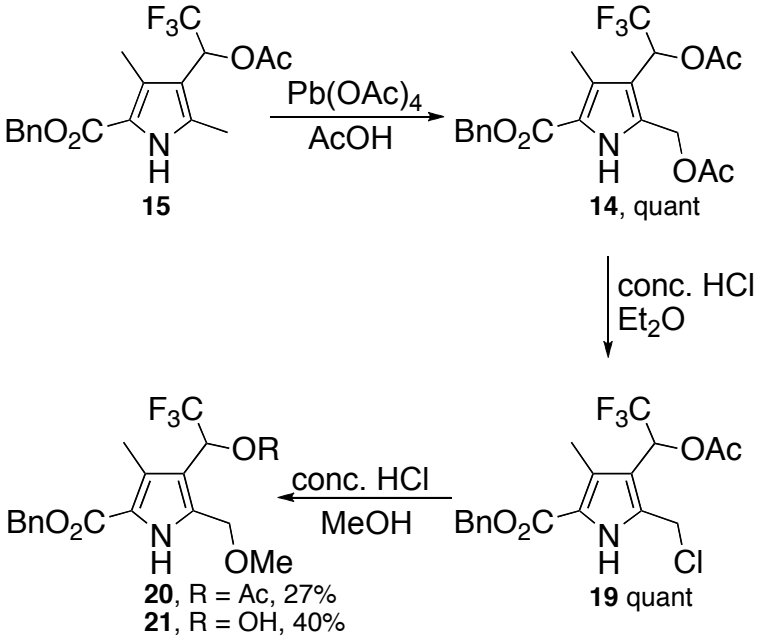
Trifluoroacylation of **13**,[31] followed by reduction of the two trifluoromethyl ketones was thought to be the most direct route to **12**. Unfortunately treatment of **13** with TFA and TFAA, under the conditions that had been successful for the synthesis of **2**, gave only the pyrrolo-[3,2-*f*]-indole **18** where presumably mono-trifluoracylation had been followed by acid-catalyzed intramolecular condensation (Scheme 4).[32-34] Since **18** exhibits indolic, rather than pyrrolic, reactivity traits, and because **18** does not feature the required prochiral signature, we sought an alternative route for the synthesis of **12**.



Scheme 4. Synthesis of 18

We thus investigated the synthesis of **12** through the homocoupling of **14**,[35] itself prepared by mono-oxidation of **15**[16] using $Pb(OAc)_4$ (Scheme 5). Homocouplings of this type,

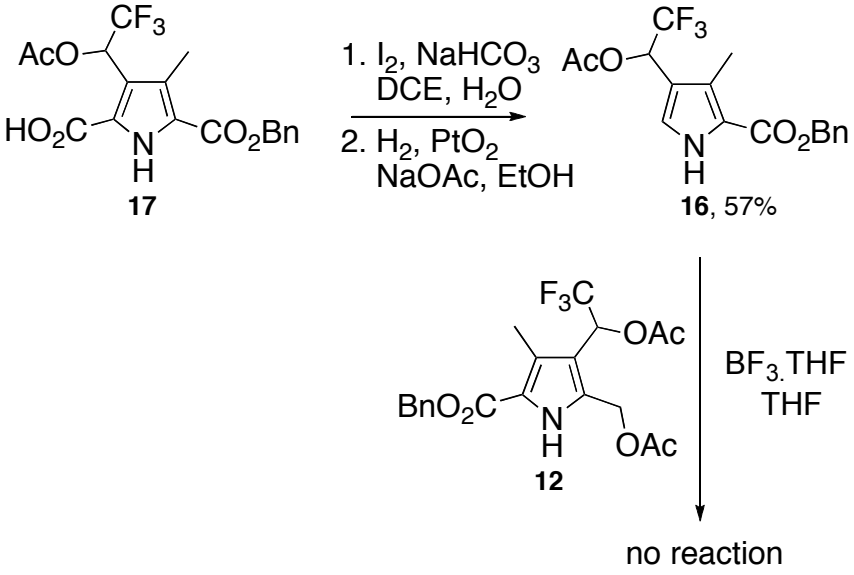
using 2-methylene pyrroles, are commonplace for the synthesis of symmetrical dipyrromethanes and involve initial ring-protonation followed by the loss of an equivalent of formaldehyde to give *in situ* 5-unsubstituted pyrroles which then produce dipyrromethanes through condensation with remaining starting material.[21,36] However, treatment of **14** with HCl served only to effect substitution to give **19** and milder conditions (Montmorillonite K-10 clay[37]) gave no reaction at all. Presumably electron-poor **14** is resilient to ring-protonation and thus substitution dominates[12] under forcing conditions, preventing the typical nucleophilic chemistry of pyrroles from occurring: the presence of the electron-withdrawing ester and 2,2,2-trifluoro-1-acetoxyethyl substituents serves to inhibit both the traditional nucleophilicity of the pyrrolic unit such that dipyrrins cannot be accessed using these intermediates.



Scheme 5. Synthesis and attempted homocoupling of 14

Our final attempts to synthesize **12** required the condensation of a 5-unsubstituted pyrrole with **14**, in effect pre-preparing the same intermediate that was not formed *in situ* within the previous strategy: this strategy is often implemented for the synthesis of unsymmetrical

dipyrromethanes.[1] Thus, **16** was prepared *via* iodinative decarboxylation of **17**[16] followed by dehalogenation of the resulting iodopyrrole (Scheme 6). Attempted reaction of **16** with **14** met with failure and only starting materials were recovered. Once again, the classic nucleophilicity of pyrroles was absent for these electron-deficient pyrroles bearing both ester and (2,2,2-trifluoro-1-acetoxyethyl) substituents. In an attempt to reduce the electron-withdrawing nature of the 4-substituent in pyrrole **20**, the *O*-acyl protecting group was omitted from the synthesis and the free alcohol was exposed to the decarboxylation conditions. Unfortunately, these conditions resulted only in decomposition and the decarboxylated product could not be isolated.



Scheme 6. Synthesis and attempted coupling of 16

Challenges associated with the low/unusual reactivity of electron-deficient pyrroles are not new. Indeed, Handy and coworkers have described problems associated with the *N*-protection of poly-halogenated pyrroles[38] and Clezy has made observations concerning problems in constructing dipyrromethanes using electron-deficient pyrroles.[31] The poor reactivity of pyrroles substituted with the 4-(2,2,2-trifluoro-1-hydroxyethyl)-substituent have prevented our synthesis of a bis(dipyrrin) bearing this chiral moiety adjacent to the conjugated skeleton. The conflicting

requirements of (i) electron-withdrawing groups to stabilize the stereocentre adjacent to the pyrrolic core and (ii) adequate nucleophilicy of the pyrrolic heterocycle render the (2,2,2-trifluoro-1-hydroxyethyl)-substituent an inappropriate group with which to introduce chirality directly adjacent to the pyrrolic core.

In summary, a dipyrrin containing a chiral 4-(2,2,2-trifluoro-1-acetoxyethyl)-substituent directly adjacent to the pyrrolic core was prepared and complexed with Zn(II). Although the corresponding mononuclear helicate was isolated in good yield, complexation occurred with poor selectivity. Attempts to prepare an analogous bis(dipyrrin), skeletons that were found to be generally more stable in solution than their monomeric homologues, were thwarted by the low reactivity of electron-deficient pyrroles. These results again demonstrate[39,40] that the balance between the reactivity and stability of pyrroles is a fine balance indeed: the search continues for moieties that facilitate the introduction of chirality directly adjacent to the pyrrolic core without concurrent inhibition of pyrrolic reactivity.

Acknowledgements

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Supplementary material

HPLC and ^{13}C NMR spectra.

Experimental

General Experimental

All reagents were purchased from Aldrich as used as received, except phosphoric acid which was purchased from Fischer Scientific and reagent grade acetonitrile which was purchased from

Caledon. Dry THF and CH_2Cl_2 were obtained from a solvent purification system and stored under nitrogen unless otherwise indicated. Dry ether was obtained *via* distillation from benzophenone sodium ketal. Unless otherwise indicated all glassware was flame-dried under vacuum prior to use, followed by a nitrogen fill. Column flash chromatography was performed using 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 an ethanolic vanillin dip. Absorption spectroscopy was performed with samples in quartz cuvettes with a standard path-length of 1 cm. HPLC separations were performed using a 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 er in compound ***S*-3** was the Chiralpak® AD-RH, also composed of amylose tris(3,5-dimethylphynylcarbamate) but with a silica support (ID 0.46 cm; length 15 cm). NMR spectroscopy utilized 500 MHz, 400 MHz, and 250 MHz spectrometers at 300 K, as indicated. All ^{1}H and ^{13}C chemical shifts (δ) are referenced to TMS at 0 ppm in the solvents indicated and are reported on the ppm scale. All coupling constants (J) are reported in Hz. ^{19}F NMR spectra were referenced to $CFCl_3$ as an external standard at 0 ppm. Mass spectra were obtained using double focusing magnetic sector (EI) and ion-trap (ESI) spectrometers. Compounds **1**,[22] **2**,[34] **3**,[16] **4**,[24] **8**,[29] **9**,[30] **13**,[31] **15**,[16] **17**[16] were prepared according to known procedures. **WARNING**: Perchlorate salts such as $Zn(ClO_4)_2$ are powerful oxidants and care should therefore be taken to avoid exothermic/explosive conditions.

2,3-Dimethyl-4-(2,2-2-trifluoroethyl-1-hydroxy-)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrole hydrobromide (5)

Pd/C catalyst (10 % on C, 0.306 g, 10 mol %) was added to a solution of pyrrole **3** (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 (87 %) which was then suspended 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 CH_2CH_2 (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 concentratation. The residue was dissolved in $CHCl_3$ and re-concentrated to yield the α-free intermediate as a yellow crystalline solid (72 %). This pyrrole (0.384 g, 1.99 mmol) and **4** (0.190 g, 2.00 mmol) were dissolved in 1:1 MeOH:THF (25 mL) and 48 % aq 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 a copious precipitate was present. Filtration and drying in air gave the title compound as a red solid (0.399 g, 57 %). mp 190-230 °C dec; δ_H (500 MHz, DMSO-d_6) 1.04 (t, J_{HH} = 8, 3H), 2.34 (s, 3H), 2.42-2.45 (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); *m/z* ESI^+ 327.1 ($M + 1 - Br^-$).

***N*,*N*'-Difluoroboryl-[2,3-dimethyl-4-(1-hydroxy-2,2-2-trifluoroethyl)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (6)**

To a suspension of **5** (1.00 g, 2.4 mmol) in CH_2Cl_2 (15 mL) under a nitrogen atmosphere was added, first, NEt_3 (6.37 mL, 45 mmol) and, second, $BF_3.OEt_2$ (6.33 mL, 51.3 mmol) giving a colour changed from brown/orange to dark orange/pink. After stirring the solution (suspension becomes a solution after the addition of $BF_3.OEt_2$) for one hour at room temperature the reaction mixture was concentrated. The residue was taken up in Et_2O and run through a plug of silica to remove baseline material and then further purified using chromatography and 1:50→1:10 ethyl acetate:hexanes as eluent to yield the title compound as a pink/red solid (0.395 g, 46%). R_f = 0.19 in 1:5 ethyl acetate:hexanes; mp 175-178 °C; λ_{max} 514 nm; δ_H (500 MHz, $CDCl_3$) 1.07 (t, J_{HH} = 7.5, 3H), 2.17 (s, 3H), 2.27 (s, 3H), 2.39 (q, J_{HH} = 7.5, 2H), 2.52 (s, 3H), 2.54 (s, 3H), 2.55 (d, J_{HH} = 3, 1H), 5.04 (qd, J_{HF} = 7, J_{HH} = 3, 1H), 7.03 (s, 1H); δ_C (125 MHz, $CDC1_3$) 9.7, 10.3, 13.2 (2C), 14.6, 17.6, 67.7 (q, J_{CF} = 33), 119.9, 120.2, 125.3 (q, J_{CF} = 280), 131.7, 134.1, 134.5, 138.0, 139.4, 152.6, 159.8; δ_F (235 MHz, $CDCl_3$) -78.77 (d, J_{FH} = 7), -146.16 to -146.85 (m); *m/z* ESI^+ 354.3 (28 %), 355.3 [$(M - F)^+$, 100 %)], 356.3 (26 %), 374.1 (20 %).

Zinc bis[2,3-dimethyl-4-(2,2-2-trifluoroethyl-1-hydroxy-)-5-(3,5-dimethyl-4-ethylpyrrol-2-ylmethylidene)pyrrolato-kN] (7)

Dipyrromethene salt **5** (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 (**CAUTION**, 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 by filtration 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, 68.1 (q, J_{CF} = 33), 68.1 (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); *m/z* ESI^+ 327.2 (ligand), 715.1 $(M + 1)^+$, 737.1 $(M + Na)^+$.

Benzyl 5-acetoxymethyl-4-(1-acetoxy-2,2,2-trifluoroethyl)-3-methylpyrrole-2-carboxylate[35]

(14)

To an acetic acid (1.0 mL) solution of pyrrole **15** (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 quenched with ethylene glycol (0.1 mL). The mixture was diluted with water (2 mL) and extracted with CH_2Cl_2 (3 x 5 mL), the combined extracts were washed with saturated sodium bicarbonate (3 x 5 mL) followed by drying over sodium sulfate and concentration. The title compound was isolated as a colourless oil (0.059 g, 99 %). 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)-3-methylpyrrole-2-carboxylate (16)

Water (2 mL) and DCE (4 mL) were added to a flask containing pyrrole **17** (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 temperature

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 layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with magnesium sulfate followed by concentration to give the iodopyrrole as an off-white solid. The crude product was 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 using 1:5 EtOAc in hexanes as an eluent to yield the title compound as a white solid (0.080 g, 57 %). 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).

Diethyl 3,5-dimethyl-4-trifluoromethylpyrrolo[3,2-*f*]indole-2-6-dicarboxylate (18)

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 **13** (0.050 g, 0.15 mmol) in CH_2Cl_2 (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 the title compound as a white solid (0.030 g, 50 %). 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); *m/z* ESI^+ 257.3 (25), 377.1 (63), 697.0 (17), 814.7 [$(2M + 23)^+$, 100], 815.8 (50), 830.6 (18).

Benzyl 4-(1-acetoxy-2,2,2-trifluoroethyl)-5-chloromethyl-3-methylpyrrole-2-carboxylate (19)

To a solution of **14** (0.054 g, 0.13 mmol) in CH_2Cl_2 (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 % aq $NaHCO_3$ (3 x 2 mL) and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification was performed using chromatography with CH_2Cl_2 as eluent to remove baseline polar impurities, producing the title compound as a white solid (0.047 g, 99 %). 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 (20)

Hydrogen chloride (35 % aq, 0.45 mL) was added to a solution of **19** (0.330 g, 0.82 mmol) in methanol (10 mL) and the mixture was to stirred overnight at reflux temperature. After concentration of the mixture, purification was accomplished using chromatography and 20 % ethyl acetate in hexanes as an eluent to give the title compound as a white solid (0.089 g, 27 %). 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 (**21**) was also isolated as a more polar, slowly

eluting compound (0.113 g, 40 %). 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).

References

(1) Wood, T. E.; Thompson, A. *Chem. Rev.* **2007**, *107*, 1831-1861.

(2) Haughland, R. P. *Handbook of Fluorescent Probes and Research Chemicals, 10th ed.*; Molecular Probes, 2006.

(3) Beer, G.; Daub, J.; Rurack, K. *Chem. Commun.* **2001**, 1138-1139.

(4) Beer, G.; Niederalt, C.; Grimme, S.; Daub, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3252-3255.

(5) Gossauer, A.; Nydegger, F.; Kiss, T.; Sleziak, R.; Stoeckli-Evans, H. *J. Am. Chem. Soc.* **2004**, *126*, 1772-1780.

(6) Murphy, D. L.; Malachowski, M. R.; Campana, C. F.; Cohen, S. M. *Chem. Commun.* **2005**, 5506-5508.

(7) Thompson, A.; Dolphin, D. *J. Org. Chem.* **2000**, *65*, 7870-7877.

(8) Al-Sheikh-Ali, A.; Cameron, K. S.; Cameron, T. S.; Robertson, K. N.; Thompson, A. *Org. Lett.* **2005**, *7*, 4773-4775.

(9) Al-Sheikh Ali, A.; Benson, R. E.; Blumentrit, S.; Cameron, T. S.; Linden, A.; Wolstenholme, D.; Thompson, A. *J. Org. Chem.* **2007**, *72*, 4947-4952.

(10) Wood, T. E.; Dalgleish, N. D.; Power, E. D.; Thompson, A.; Chen, X.; Okamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5740-5741.

(11) Wood, T. E.; Ross, A. C.; Dalgleish, N. D.; Power, E. D.; Thompson, A.; Chen, X.; Okamoto, Y. *J. Org. Chem.* **2005**, *70*, 9967-74.

(12) Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Am. Chem. Soc.* **1998**, *120*, 1741-1746.

(13) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, 1511-1516.

(14) Boiadjiev, S. E.; Lightner, D. A. *Tetrahedron: Asymm.* **2001**, *12*, 2551-2564.

(15) Hiroi, K.; Izawa, I.; Takizawa, T.; Kawai, K. *Tetradedron* **2004**, *60*, 2155-2162.

(16) Omote, M.; Ando, A.; Sato, K.; Kumadaki, I. *Tetrahedron* **2001**, *57*, 8085-8094.

(17) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370-4371.

(18) Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I. *Tetrahedron* **1996**, *52*, 13961-13970.

(19) Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I.; Shiro, M. *Heterocycles* **1998**, *47*, 65-68.

(20) Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531-11563.

(21) Paine III, J. B. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: 1978; Vol. I, Chapter 4.

(22) Regourd, J.; Comeau, I. M.; Beshara, C. S.; Thompson, A. *J. Het. Chem.* **2006**, *43*, 1709-1714.

(23) Beshara, C. S.; Thompson, A. *J. Org. Chem.* **2006**, *70*, 10607-10610.

(24) Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229-38.

(25) Werner, A.; Michels, M.; Zander, L.; Lex, J.; Vogel, E. *Angew. Chem. Int. Ed.* **1999**, *38*, 3650-3653.

(26) Amiri, A.; Comeau, I. M.; Thompson, A. *J. Het. Chem.* **2006**, *43*, 431-435.

(27) Guseva, G. B.; Antina, E. V.; Berezin, M. B. *Russ. J. Coord. Chem* **2003**, *29*, 690-693.

(28) Guseva, G. B.; Antina, E. V.; Berezin, M. B.; V'yugin, A. I. *Russ. J. Coord. Chem.* **2004**, *30*, 30-33.

(29) Wood, T. E.; Berno, B.; Beshara, C. S.; Thompson, A. *J. Org. Chem.* **2006**, *71*, 2964-2971.

(30) Zhang, Y.; Ma, J. S. *Org. Prep. Proced. Int.* **2001**, *33*, 81-86.

(31) Clezy, P. S.; Liepa, A. J. *Aust. J. Chem.* **1970**, *23*, 2443-2459.

(32) Burns, D. H.; Li, Y. H.; Shi, D. C.; Caldwell, T. M. *J. Org. Chem.* **2002**, *67*, 4536-4546.

(33) Chunchatprasert, L.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1787-1795.

(34) Song, C.; Knight, D. W.; Whatton, M. A. *Tetrahedron Lett.* **2004**, *45*, 9573-9576.

(35) Sato, H.; Kumakai, I.; Ando, A.; Omote, M. In *Jpn. Kokai Tokkyo Koho* Japan, 1999 JP 11029573.

(36) Jones, A. R.; Bean, G. P., Eds., *The Chemistry of Pyrroles*; Academic Press: London, 1977.

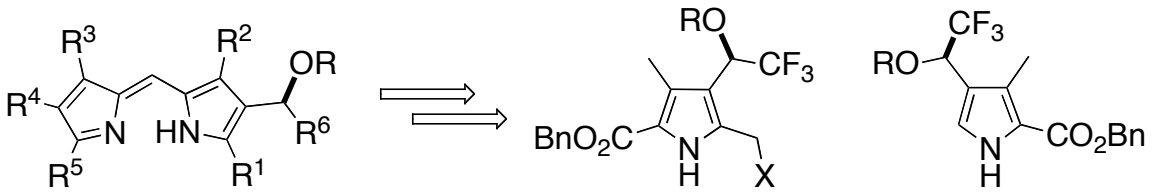
(37) Jackson, A. H.; Pandey, R. K.; Nagaraja Rao, K. R.; Roberts, E. *Tetrahedron Lett.* **1985**, *26*, 793-796.

(38) Handy, S. T.; Sabatinin, J. J.; Zhang, Y.; Vulfova, I. *Tetradedron Lett.* **2004**, *45*, 5057-5060.

(39) Garabatos-Perera, J. R.; Rotstein, B. H.; Thompson, A. *J. Org. Chem.* **2007**, ASAP, DOI 10.1021/jo070493r.

(40) Thamyongkit, P.; Bhise, A. D.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 903-910.

Table of Contents Graphic



dipyrrins with a stereogenic centre directly attached to the conjugated skeleton

extremely diminished nucleophilicity *cf* other pyrroles

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