Modular Preparation of Diverse Dipyrrolemethanes

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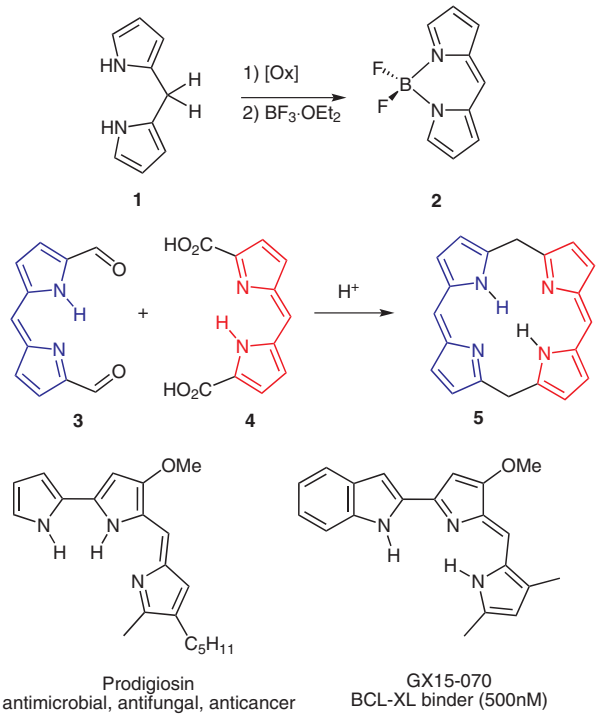
Abstract: A modular synthesis of polyfunctional dipyrrolemethanes is presented. Diverse side chains are introduced to 2-carboxypyrrole building blocks in two to four steps, resulting in a collection of substituted pyrroles that, when condensed in one step, give rise to diverse structural features.

Key words: modular libraries, BODIPY, dipyrrolemethane, Prodigionsin, porphyrin

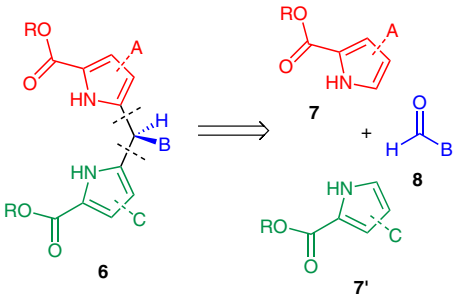
The dipyrrolemethane core 1 is of central importance in several areas of research in the chemical and biological sciences (Scheme 1). Most notably a change in oxidation and chelation with BF_2 affords the incredibly versatile BODIPY core **2** that when functionalized appropriately has been studied extensively as a fluorophore.[1] First reported in 1968[2] advances continue including recent reports to make near-infrared emitters[3] as well as selective chemical sensors that are compatible with cells.[4] Most applicable to the work we present include BODIPYS with carboxy groups flanking the dipyrrolemethane/ene core,[5–7] the step-wise preparation of unsymmetric and highly functionalized porphyrins **5**[8] that come from **3** + **4** and related supramolecular species[9,10] as well as the notable antimicrobial, antifungal and anticancer natural product Prodigiosin[11–15] found in *Serratia marcescens,* and a potent synthetic analogue GX15-070 that binds to Bcl-X_L presumably through Bak peptide mimicry.[16]

The synthesis of a structurally diverse library of dipyrrolemethanes from modular components in a few synthetic steps would provide new advanced precursors for the applications seen in Scheme 1 and also afford opportunities for high-throughput screening in these areas. Our ultimate interest stems from the application of the dipyrrolemethane scaffold as a platform for spatially mimicking side-chain features of peptide α-helices in an effort to develop small molecule peptidomimetics,[17–20] via combinatorial methods.[21,22]

We began by examining the feasibility of construction of dipyrrolemethane scaffold **6** from a variety of modular building blocks. Pyrroles **7**, **7′** and aldehyde **8** were identified as obvious building blocks (Scheme 2). Aldehydes can be readily acquired or prepared from a variety of precursors; 3- and 4-substituted pyrrole-2-carboxylates, however, required some selection of best methods. We report that the latter can be prepared readily on gram scale from commercial materials in only a few steps. As illustrated, component **7** is installed twice to give both A and C side-chains that can be identical or different. If prepared symmetrically a collection of ten aldehydes **8** and ten pyrroles **7** (20 total compounds) would give rise to a 100 member library. The development of a nonsymmetrical route, where pyrroles **7** were attached to solid support and condensed with **8** and **7′** could increase the collection to 1000 compounds (10 **7**s × 10 **8**s × 10 **7′**s) in one step.



Scheme 1 Diverse chemically functional and biologically active dipyrrolemethenes



Scheme 2 Deconstruction of dipyrrolemethane scaffold into readily accessible building blocks.

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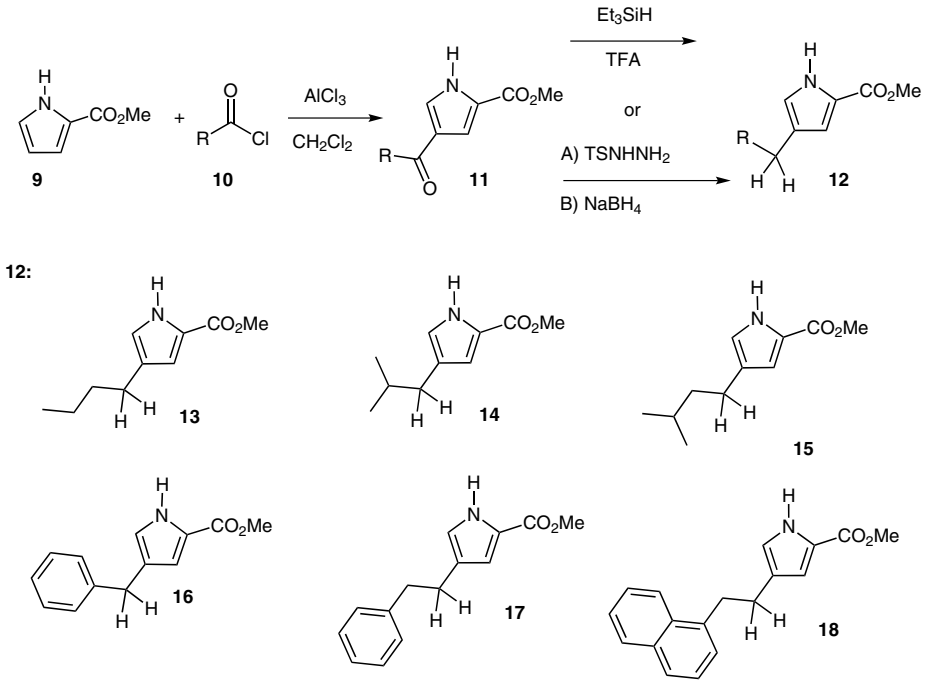


Scheme 3 Strategy # 1 towards diverse 4-pyrroles **12** (≡ **13**–**18**, Table 1)

An updated review illustrates some of the more useful preparations of 3- and 4- substituted pyrrole-2-carboxylates.[23] Our selection of methods was predicated on a rapid introduction of functionality in as few steps as possible from common building blocks. We aimed to incorporate two key features in our final scaffolds: 1) aliphatic and aromatic side chains at A, B, and C positions (Scheme 2) and 2) 2-carboxylic acid/ester functional group. The latter serves as a means to tune water solubility and as a point of chemical derivatization or attachment. Ultimately the 2-carboxy group has regiochemical consequences that favor the construction of **6** (*vide infra*).

Methyl pyrrole-2-carboxylate (**9**) is a commercially available pyrrole that undergoes regioselective Friedel–Crafts acylation with **10** under the action of aluminum trichloride (Scheme 3) to give 4-acylpyrroles **11** in excellent yields (Table 1).[24,25]

While nitromethane–dichloromethane combinations are often employed in this reaction it was found that 100% dichloromethane is the most general solvent in the presented examples. Acyl chlorides **10** are a readily available source of aliphatic and aromatic groups and thus afford a variety of 4-substituted pyrroles. We envisioned that removal of the carbonyl group would avoid any complications in our final condensation step (Scheme 2). Ionic hydrogenation with triethylsilane (TES)[26] worked very well on small scale, but failed above 1.0 gram. This route also required chromatographic separation prior to reduction. The ketone products **11** were ultimately converted into the saturated analogues **12** via tosylhydrazone formation and

Table 1 4-Substituted Methyl Pyrrole-2-carboxylates **13**–**18** Prepared[a]

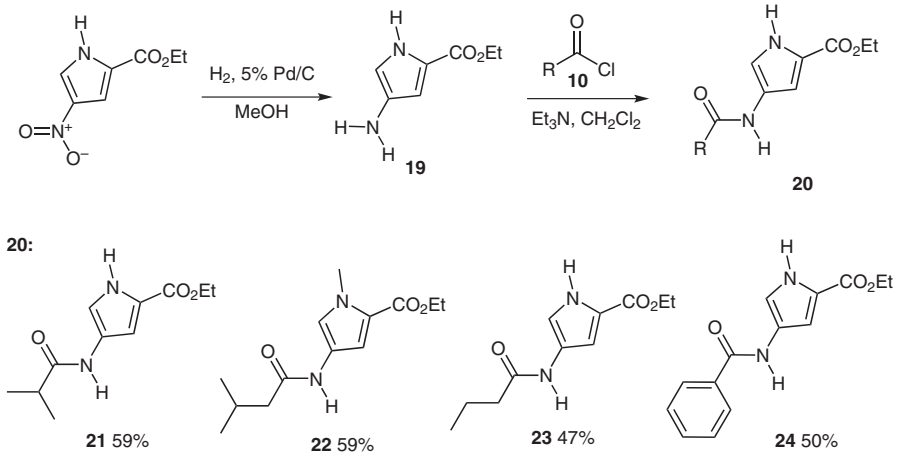
RCOCl **10** R	Yield (%)[b] of **11**	Yield (%) by TES–TFA	Yield (%)[c] by hydride reduction of hydrazone
n-Pr	93	31[d], 3[e] (**13**)	81 (**13**)
i-Pr	93		91 (**14**)
CH_2CHMe_2	87	58[d] (**15**)	66 (**15**)
Ph	97		68 (**16**)
CH_2Ph	71	64[d], 24[e] (**17**)	56 (**17**)
CH_2-1-naphthyl	94		55 (**18**)

[a] See Scheme 3 for product structures **13**–**18**.
[b] Isolated crude yield, >95% pure by ^{1}H NMR analysis.
[c] Isolated, purified yield after two steps from **11** on >5 g scale.
[d] Isolated yield after column chromatography on <1 g scale.
[e] Isolated yield after column chromatography on >1 g scale.

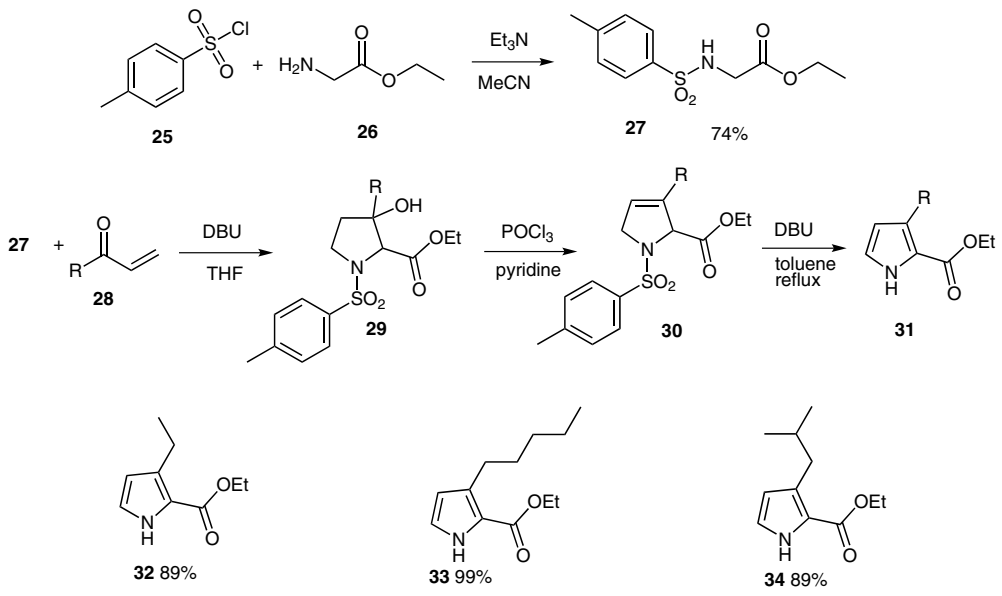
subsequent reduction using sodium borohydride. Sodium borohydride was found to be equivalent to the reported use of cyanoborohydride for this application.[27] This second route to **12** provided us with a distinct advantage for purification; crude acylated pyrroles **11** could be used for hydrazone formation, these products were highly crystalline and could be recrystallized affording analytically pure hydrazones on large scale. The subsequent reduction was very clean, but in this latter route only one column was required for the three steps, oftentimes recrystallization was possible. Despite the addition of an extra manipulation this latter route was the most general and efficacious. Pyrroles **12** are specifically identified as **13**–**18**.

The acylation of **9** with *n*-butyryl chloride proceeded on scales greater than 10 grams to give **11** (R = *n*-Pr) in 93% yield, in high purity without chromatographic purification (Table 1, see SI for full details). Other commercially available acyl chlorides proceeded smoothly. 1-Naphthylacetyl chloride (prepared from the corresponding acid with oxalyl chloride) gave the desired acylation product in 94% yield. Ionic hydrogenation was moderately successful on smaller than 1 gram scale to yield the desired pyrroles **12**, but upon scaling up results were inconsistent and often disappointing in our hands (see entry for **17**). Efforts to fully explain this result were forgone, instead opting for a strategy that would be higher-yielding and allow for easier purification – the use of tosylhydrazine and sodium borohydride produced acceptable results on large scale.

In parallel with our Friedel–Crafts strategy the acylation of aminopyrrole **19** was also explored, prepared in one step from available 4-nitropyrrole-2-carboxylic acid ethyl ester and promptly used without purification (Scheme 4).[28] Commercial acyl chlorides **10** were used for introducing amides at 4-pyrrole position. In this instance we would not anticipate interference from the amide carbonyl (nor the nitrogen) in the final condensation step with an aldehyde (Scheme 2). Four amide pyrroles **21**–**24** were prepared in acceptable yield on multi-gram scale.



Scheme 4 Strategy # 2 towards diverse 4-pyrroles



Scheme 5 Strategy # 1 towards diverse 3-pyrroles (isolated yield for final step reported)

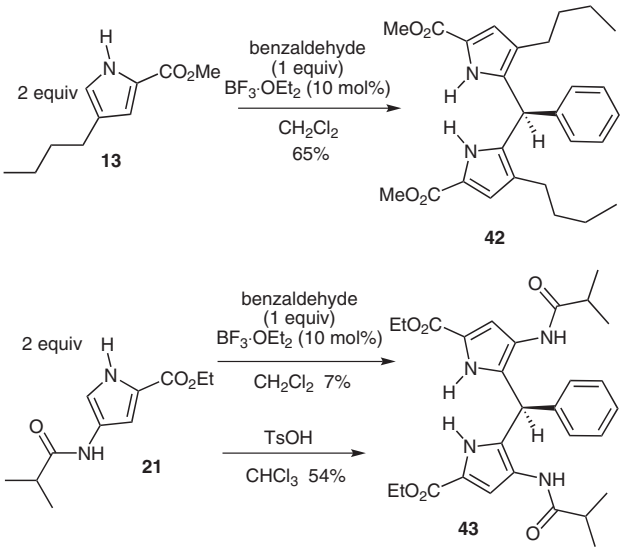
There are several other methods for the preparation of 4-pyrroles that we are aware of, but of all the strategies the previous two were found to be both the most simplistic and effective methods for easily generating a collection of differing compounds in few steps. The construction of diverse 3-substituted pyrroles, however, was less straightforward. Two useful routes for these compounds are described next.

Our first strategy to prepare diverse 3-pyrroles follows from literature reports that combine ethyl *N*-*p*-toluenesulfonylgycinate (**27**) with various α,β-unsaturated ketones.[29,30] The strength of this strategy lies in the availability and ease of access to diverse aliphatic and aromatic α,β-unsaturated ketones. Conjugate and direct addition of ethyl *N*-*p*-toluenesulfonylglycinate (**27**) to **28** results in construction of the pyrrolidine scaffold **29** under the action of base (Scheme 5). $POCl_3$-mediated dehydration yields pyrroline **30**, which under treatment with base undergoes an elimination of *p*-toluenesulfinate group with tautomerization giving the pyrrole scaffold **31**. Ethyl 3-ethylpyrrole-2-carboxylate (**32**) was prepared directly from ethyl vinyl ketone (**28**, R = Et), while ethyl 3-pentylpyrrole-2-carboxylate (**33**) was prepared from oct-1-en-3-one. The isobutyl-3-pyrrole **34** required preparation of the α,β-unsaturated ketone; isovaleraldehyde was alkylated with vinylmagnesium bromide in 92% yield, subsequent Swern oxidation[31] gave the requisite ketone in 63% yield. These 3-pyrroles were isolated in acceptable yield on gram scale.

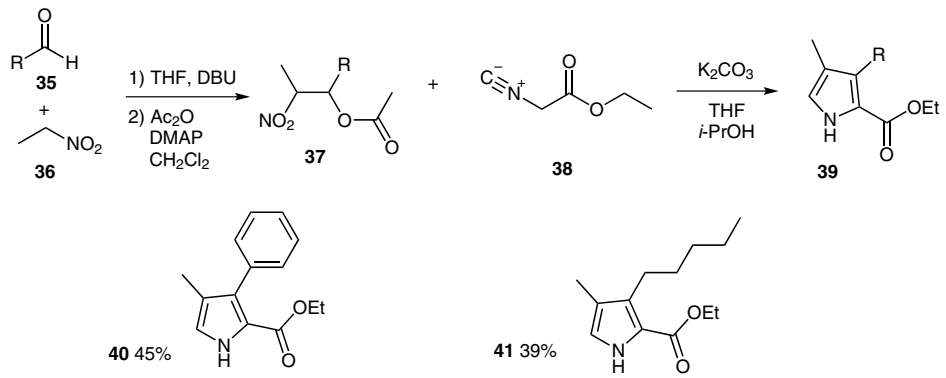
While less efficient than our two strategies for the preparation of 4-substituted pyrroles, we were still able to complete the synthesis of these starting materials in three steps from readily available materials affording different aliphatic substituents.

The final strategy explored for the preparation of diverse 3-substitued pyrroles begins with the condensation of aldehyde **35** with nitroethane (**36**), followed by acylation with acetic anhydride to give **37** (Scheme 6). Subsequent reaction with ethyl isocyanoacetate (**38**) under the action of potassium carbonate gives the pyrrole scaffold. The resulting ethyl 3-substituted 4-methyl-1*H*-pyrrole-2-carboxylate **39** has diverse substituents at the 3-position and retains a methyl group at the 4-position.[32] Attempts to start the sequence with nitromethane to eliminate this extra methyl group were unsuccessful. Ten grams of **40** was prepared from benzaldehyde in 45% overall yield and 10 grams of **41** from hexanal in 39% overall yield. We anticipate that this reaction has equal potential for a variety of substituents at the 3-position, though at this time the sequence was not explored broadly.

Having executed four unique routes towards 3- and 4-substituted pyrroles on multi-gram scale their assembly was tested with aldehydes to give a variety of dipyrrolemethanes. Numerous combinations of bulky and small pyrrole substituents, aromatic and aliphatic pyrrole substituents as well as aromatic and aliphatic aldehydes were tested. The majority of permutations demonstrated were successful. The preparation began with pyrrole **13** bearing an *n*-butyl side chain at the 4-position. The condensation with benzaldehyde was attempted using Lewis acid catalysis based on a known report and dipyrrolemethane **42** was thus prepared (Scheme 7).[5] In the initial stages of this work it was found that the amidepyrrole **21** did not have the same success, and thus Brønsted acids such as *p*-toluenesulfonic acid was found to work better to prepare **43**. This latter set of conditions proved to be more general, for example, including **42**.



Scheme 7 Scaffold assembly of dipyrrolemethanes



Scheme 6 Strategy # 2 towards diverse 3-pyrroles (isolated yield for overall sequence reported)

Several examples are presented, meant to sample the chemical combinations we might encounter in a final library. For aldehydes benzaldehyde and *n*-aliphatic aldehydes were used. Pyrrole **13** was found to afford dipyrrolemethanes with benzaldehyde and propanal in equal efficiency to give **42** and **44** (Figure 1). Pyrrole **15** gave dipyrrolemethane **45** upon condensation with propanal in acceptable yield. The more hindered benzyl-substituted pyrrole **16** gave less satisfactory results for the formation of **46**. The homologous benzylpyrrole **17** also gave a low yield of dipyrrolemethane **47**. Benzylic aldehydes such as phenylacetaldehyde work well (data not shown), and 1-naphthylacetaldehyde gives dipyrrole **48** in good yield. Both aromatic aldehydes and aliphatic aldehydes reacted with amide-substituted (aliphatic **21** and aromatic **24**) pyrroles to give dipyrrolemethanes **43** and **49**, respectively. The 3-substituted pyrroles proved to be more problematic. Dipyrroles **51** and **52** (from **32** and **33**, respectively) were isolated in very low yield under standard reaction conditions. These reactions might benefit from further optimization in polar aprotic solvents. The inconsistency between reactions of 4-pyrroles and 3-pyrroles

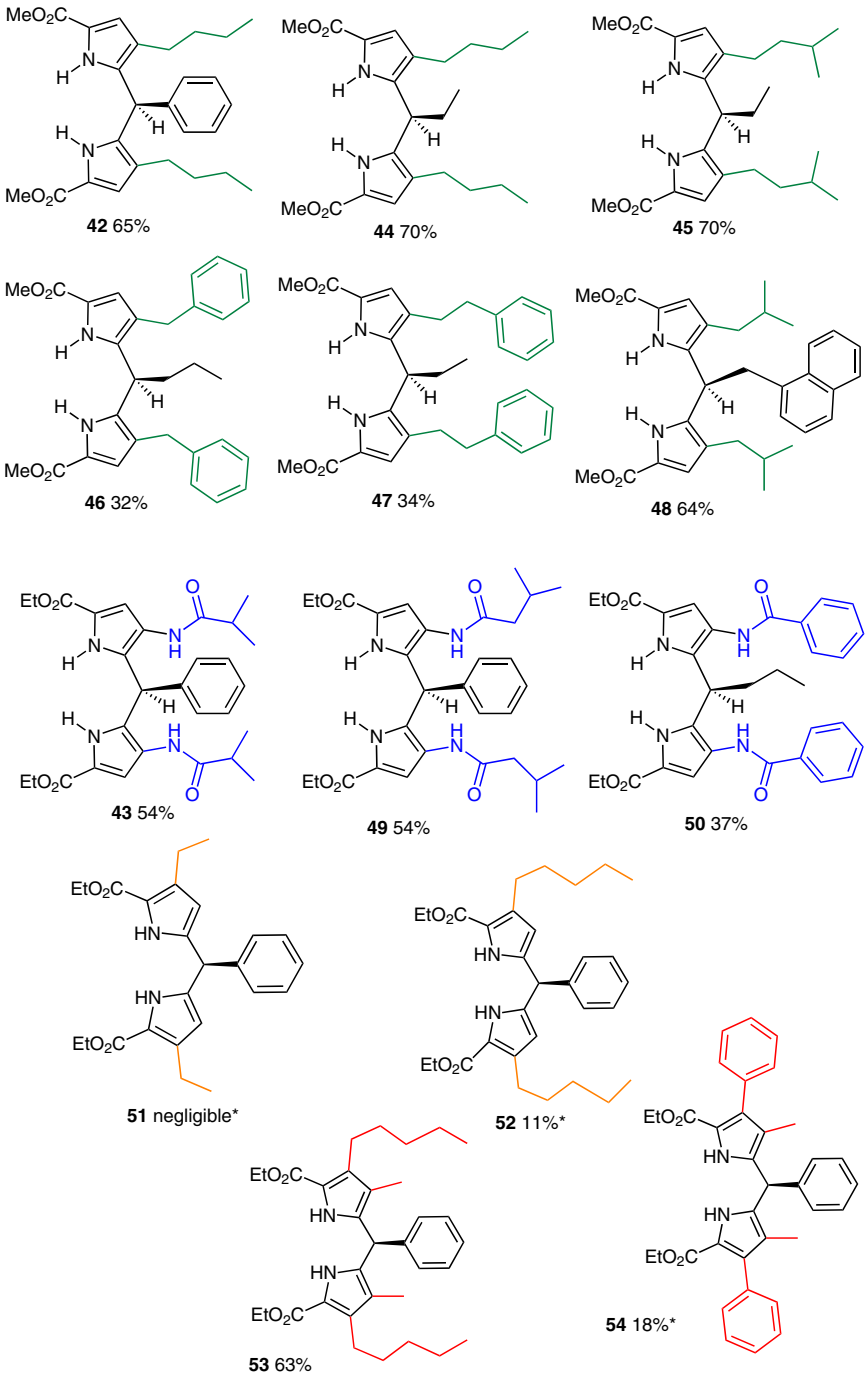
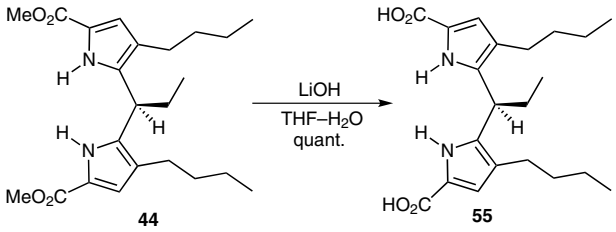


Figure 1 Assembled diverse dipyrrolemethanes with isolated yields given. Green side chains come from 4-pyrrole strategy # 1, blue come from 4-pyrroles strategy # 2, orange from 3-pyrrole strategy # 1, red from 3-pyrrole strategy # 2. All reactions done in chloroform with *p*-toluenesulfonic acid as catalyst (* = unoptimized yield).

poses a challenge in terms of final library construction, however, 4-methyl-3-pentylpyrrole **41** gave dipyrrolemethane **53** in good yield from condensation with benzaldehyde; the 3-phenyl analogue, however, gave **54** in low yield.

Finally the saponification of two of our final products was tested as a means to enhance water solubility and functionalization. Treatment of **44** with LiOH in THF–water[33] resulted in clean conversion to diacid **55** (Scheme 8), similarly the diamide **43** survived these conditions to give corresponding diacids in excellent yield.



Scheme 8 Saponification of dipyrrolemethane esters

We have thus demonstrated the synthesis of a variety of symmetric dipyrrolemethanes from readily prepared pyrroles. This small collection of molecules displays diverse hydrophobic side chains. From this collection of molecules we are interested in studying their suitability as α-helix peptidomimetics[17–22] and their construction on solid support to give unsymmetric counterparts; in the immediate term their application as new BODIPY fluorophores is under study and will be reported in a sequel.

^{1}H NMR was acquired on a Bruker Apollo 400 MHz, a Bruker Avance-II 400 MHz (NSF MRI CHE-0521665), or a Bruker Fourier 300 spectrometer at 298 K, ^{13}C was acquired at 100 or 75 MHz at 298 K. Data was processed (iNMR 3.5.1) using a Fourier transform with exponential weighting. NMR solvents were purchased from Cambridge Isotope Laboratories and residual solvent peak was used to as an internal standard. All chemicals were used as received, unless otherwise noted. SiliaFlash® P60 Academic Silica Gel, 40–63 μm, 60A was purchased from Silicycle. Mass analyses were conducted at the University of California Riverside High Resolution Mass Spectrometry Facility, Riverside, CA, USA.

Regioselective Acylation of Methyl 2-Pyrrolecarboxylate (9);[24,25] General Procedure

Methyl 2-pyrrolecarboxylate (**9**; 5.0 g, 40 mmol) and acyl chloride **10** (52 mmol) were dissolved in anhyd CH_2Cl_2 (50 mL) under argon and cooled to 0 °C in an ice/water bath. $AlCl_3$ (16.0 g, 120 mmol) was added slowly to the flask and left overnight to stir while it warmed to r.t. The reaction was determined to be complete by TLC (typically in 3:1 hexane–EtOAc), carefully poured into ice water (50 mL), separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to dryness on a rotary evaporator. The resulting products **11** could be purified by column chromatography, but were typically suitable for subsequent reaction without purification as determined by ^{1}H NMR analysis.

Small-Scale Ionic Reduction of Methyl 4-Acyl-2-pyrrolecarboxylates 11;[26] General Procedure

Pyrrole **11** (2 mmol) was dissolved in TFA (2.28 g, 20 mmol) to which was added triethylsilane (512 mg, 4.4 mmol). The reaction mixture was stirred and monitored for the disappearance of **11** by TLC analysis (typically in 1:1 hexane–EtOAc). After stirring for 24 h, sat. aq $NaHCO_3$ (15 mL) was added dropwise and the mixture was extracted with Et_2O (3 × 20 mL, with careful venting). The combined extracts were dried (Na_2SO_4), filtered, and concentrated to dryness on a rotary evaporator. The resulting crude material required column chromatography (4:1 hexane–EtOAc, typically) to afford analytically pure **12** (≡ **13**–**18**) in moderate yields.

Two-Step Reduction of Methyl 4-Acyl-2-pyrrolecarboxylates 11 with Tosylhydrazine Followed by Borohydride;[27] General Procedure (Scheme 3)

Pyrrole **11** (73 mmol) was mixed with *p*-toluenesulfonylhydrazine (16.4 g, 88 mmol) in absolute EtOH (73 mL). The reaction mixture was refluxed for 2 h and left to stir overnight at r.t. The resulting precipitate was collected by vacuum filtration and then dried further by rotary evaporation. Crude tosylhydrazone (20 mmol) was dissolved in glacial AcOH (80 mL) and treated with $NaBH_3CN$ or $NaBH_4$ (40 mmol) slowly and portionwise. The mixture was stirred for 2 h at 40 °C, then carefully poured into ice cold water (300 mL). The mixture was extracted with Et_2O (3 × 100 mL). The combined extracts were washed carefully with sat. aq $NaHCO_3$ (200 mL), dried (Na_2SO_4), filtered, and concentrated to dryness on a rotary evaporator. The resulting crude material required column chromatography (1:1 hexane–EtOAc, typically) or recrystallization from toluene–hexane mixtures to afford analytically pure **12** (≡ **13**–**18**) in very good yield.

Methyl 4-Butyl-2-pyrrolecarboxylate (13)

Yield: 9.67 g (81%); tan solid.

^{1}H NMR and MS data were consistent with the proposed structure and a literature report.[34]

Methyl 4-(2-Methyl)propyl-2-pyrrolecarboxylate (14)

Yield: 5.39 g (91%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 6 H), 1.71–1.81 (sept, *J* = 6.9 Hz, 1 H), 2.32 (d, *J* = 7.2 Hz, 2 H), 3.83 (s, 3 H), 6.72–6.74 (m, 2 H), 9.02 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 29.8, 36.2, 51.4, 115.8, 121.7, 122.0, 125.4, 162.0.

MS: *m*/*z* (M + H) calcd for $C_{10}H_{16}NO_2$: 182.26; found: 182.

Methyl 4-(3-Methyl)butyl-2-pyrrolecarboxylate (15)

Yield: 6.85 g (66%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.6 Hz, 6 H), 1.42–1.48 (q, *J* = 6.9 Hz, 2 H), 1.53–1.63 (sept, *J* = 6.6 Hz, 1 H), 2.42–2.48 (q, *J* = 8.1 Hz, 2 H), 3.83 (s, 3 H), 6.75–6.76 (m, 2 H), 9.33 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 24.5, 27.5, 40.2, 51.4, 115.0, 120.8, 122.1, 126.8, 161.8.

MS: *m*/*z* (M + H) calcd for $C_{11}H_{17}NO_2$: 196.26; found: 196.14.

Methyl 4-Benzyl-2-pyrrolecarboxylate (16)

Yield: 7.40 g (68%); brown solid.

^{1}H NMR for **16** was consistent with the proposed structure and a literature report.[35]

MS: *m*/*z* (M + H) calcd for $C_{13}H_{13}NO_2$: 216.25; found: 216.10.

Methyl 4-(2-Phenyl)ethyl-2-pyrrolecarboxylate (17)

Yield: 6.30 g (56%); brown solid.

^{1}H NMR for **17** was consistent with the proposed structure and a literature report.[35]

MS: *m*/*z* (M + H) calcd for $C_{14}H_{15}NO_2$: 230.02; found: 230.

Methyl 4-[2-(1-Naphthyl)]ethyl-2-pyrrolecarboxylate (18)

Yield: 4.28 g (55%); yellow wax.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (m, 2 H), 3.34 (m, 2 H), 3.86 (s, 3 H), 6.71 (s, 1 H), 6.86 (s, 1 H), 7.29 (m, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.50 (m, 2 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 7.6 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 8.87 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 34.8, 51.8, 115.3, 121.3, 122.5, 123.9, 125.7, 125.8, 126.1, 126.2, 126.3, 127.0, 129.1, 132.1, 134.2, 138.2, 162.0.

MS: *m*/*z* (M + H) calcd for $C_{17}H_{14}NO_2$: 280.34; found: 280.14.

Acylation of Ethyl 4-Nitroethyl-2-pyrrolecarboxylate;[28] General Procedure

Nitropyrrole ethyl ester (1.78 g, 9.4 mmol) was treated with 5% Pd/C (0.38 g) in MeOH (48 mL). A rubber septum was attached and the reaction flask was purged with H_2 gas. A rubber balloon filled with H_2 gas was then attached to the round-bottomed flask via a syringe and the reaction was stirred vigorously for 16 h at which time TLC (9:1 $CHCl_3$–MeOH) indicated consumption of starting material. The reaction was gravity filtered with MeOH rinsing, concentrated to dryness, and used immediately. The crude amine (1.51 g, ~9.4 mmol) was dissolved in CH_2Cl_2 (48 mL), treated with Et_3N (2.6 mL, 18.8 mmol), and cooled to 0 °C in an ice/water bath. Acyl chloride **10** (9.4 mmol) was added dropwise over 10 min and the reaction mixture was allowed to stir for 16 h while warming to r.t. TLC (4:1 $CHCl_3$–MeOH) indicated that the reaction was complete. The reaction mixture was partitioned between $CHCl_3$ (40 mL) and H_2O (40 mL) and extracted with $CHCl_3$ (2 × 20 mL). The combined extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography (eluent: 10% MeOH in $CHCl_3$) to give analytically pure materials.

Ethyl 4-(2-Methyl)propanamide-2-pyrrolecarboxylate (21)

Yield: 0.61 g (59% for two steps); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.9 Hz, 6 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 2.50 (quint, *J* = 6.9 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 6.70 (dd, *J* = 2.7, 1.5 Hz, 1 H), 7.45 (br s, 1 H), 7.49 (dd, *J* = 3.0, 1.8 Hz, 1 H), 9.18 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.8, 35.9, 60.6, 106.1, 114.4, 120.4, 124.2, 161.1, 174.6.

Ethyl 4-(3-Methyl)butanamide-2-pyrrolecarboxylate (22)

Yield: 0.638 g (59%); white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (m, 6 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 2.18–2.19 (m, 3 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 6.68 (q, *J* = 1.6 Hz, 1 H), 7.14 (br s, 1 H), 7.50 (q, *J* = 1.6 Hz, 1 H), 8.94 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 22.6, 26.4, 46.4, 60.6, 106.0, 114.2, 120.5, 124.1, 160.9, 170.0.

Ethyl 4-Butanamide-2-pyrrolecarboxylate (23)

Yield: 0.47 g (47%); brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.6 Hz, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H), 1.73 (sept, *J* = 7.6 Hz, 2 H), 2.30 (t, *J* = 7.2 Hz, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 6.69 (m, 1 H), 7.39 (br s, 1 H), 7.48 (m, 1 H), 9.13 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.4, 19.1, 38.8, 60.5, 106.0, 114.2, 120.4, 124.0, 160.9, 170.5

Ethyl 4-Benzanamide-2-pyrrolecarboxylate (24)

Yield: 1.10 g (50%); tan solid.

^{1}H NMR for **24** was consistent with the proposed structure and a literature report.[36]

Ethyl 3-Alkylpyrrole-2-carboxylates 32–34

These compounds were prepared according to literature procedures[29,30] from benzyl *N*-*p*-toluenesulfonylglycinate (**27**)[37] and α,β-unsaturated ketones **28**.

Ethyl 3-Ethylpyrrole-2-carboxylate (32)

Prepared from glycinate **27** and methyl vinyl ketone; yield: 6.90 g (89%); yellow oil.

^{1}H NMR was consistent with the proposed structure and a literature report.[38]

MS: *m*/*z* (M + H) calcd for $C_9H_{14}NO_2$: 168.21; found: 168.

Ethyl 3-Pentylpyrrole-2-carboxylate (33)

Prepared from glycinate **27** and 1-octen-3-one; yield: 0.247 g (99%); orange wax.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.8 Hz, 3 H), 1.33–1.37 (m + t, 7 H), 1.57–1.64 (m, 2 H), 2.79 (t, *J* = 7.6 Hz, 2 H), 4.31 (q, *J* = 6.8 Hz, 2 H), 6.11 (t, *J* = 2.8 Hz, 1 H), 6.82 (t, *J* = 2.4 Hz, 1 H), 9.45 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 14.6, 22.7, 27.0, 30.6, 31.9, 60.0, 111.5, 118.9, 121.6, 133.5, 161.8.

MS: *m*/*z* (M + H) calcd for $C_{12}H_{20}NO_2$: 210.29; found: 210.

Ethyl 3-(2-Methyl)propylpyrrole-2-carboxylate (34)

Prepared from glycinate **27** and 5-methylhex-1-ene-3-one; the latter was prepared by literature procedure;[39] yield: 20.04 g (89%); clear oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 6 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.81–1.91 (sept, *J* = 6.8 Hz, 1 H), 2.66 (d, *J* = 6.8 Hz, 2 H), 4.28–4.33 (q, *J* = 6.8 Hz, 2 H), 6.09 (t, *J* = 2.8 Hz, 1 H), 6.83 (t, *J* = 2.8 Hz, 1 H), 9.00 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 22.6, 29.9, 36.1, 59.9, 112.4, 119.2, 121.4, 132.2, 161.8.

MS: *m*/*z* (M + H) calcd for $C_{11}H_{18}NO_2$: 196.27; found: 196.

Ethyl 3-Substituted 4-Methylpyrrole-2-carboxylates 40, 41

These compounds were prepared following a known report, with complete details in the ESI[32] as well as a second reference.[40]

Ethyl 3-Phenyl-4-methylpyrrole-2-carboxylate (40)

Prepared from benzaldehyde; yield: 6.51 g (45%); off-white solid.

^{1}H NMR for was consistent with the proposed structure and a literature report.[41]

MS: *m*/*z* (M + H) calcd for $C_{14}H_{16}NO_2$: 230.28; found: 230.

Ethyl 3-Pentyl-4-methylpyrrole-2-carboxylate (41)

Prepared from hexanal; yield: 13.0 g (39%); cream colored solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 1.31–1.37 (m, 4 H), 1.47–1.54 (quint, *J* = 7.6 Hz, 2 H), 2.03 (s, 3 H), 2.71 (t, *J* = 7.6 Hz, 2 H), 4.27–4.33 (m, 2 H), 6.65 (d, *J* = 2.8 Hz, 1 H), 8.72 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 13.8, 14.2, 22.3, 24.6, 30.2, 31.7, 59.5, 118.5, 119.8, 119.9, 131.4, 161.3.

Dipyrrolemethanes; Typical Procedures

Dipyrrolemethane 42; Typical Procedure 1

Using $Et_2O{\cdot}BF_3$: Preparation of dipyrrolemethane **42** with $Et_2O{\cdot}BF_3$ was conducted following a literature procedure;[5] yield: 51.6 mg (65%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 6 H), 1.22–1.34 (sext, *J* = 7.2 Hz, 4 H), 1.39–1.49 (sext, *J* = 7.2 Hz, 4 H), 2.31 (t, *J* = 7.2 Hz, 4 H), 3.68 (s, 6 H), 5.63 (s, 1 H), 6.77 (d, *J* = 2.4 Hz, 2 H), 7.02–7.04 (m, 2 H), 7.26–7.28 (m 3 H + $CHCl_3$), 9.12 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 25.1, 32.4, 40.0, 51.3, 116.3, 120.7, 123.7, 127.5, 128.0, 129.0, 132.5, 139.2, 161.3.

Dipyrrolemethane 43; Typical Procedure 2

Using Strong Acid: Pyrrole **21** (0.22 mmol) and benzaldehyde (0.11 mmol) were dissolved in CH_2Cl_2 (2 mL), treated with *p*-TsOH (10

mg) and stirred for 12 h at which time TLC analysis ($CHCl_3$) indicated consumption of starting material. The reaction mixture was concentrated to dryness and purified by column chromatography ($CHCl_3$–MeOH, 30:1) to give analytically pure **43**;[42] yield: 117.6 mg (54%); cream colored solid.

^{1}H NMR (400 MHz, $CDCl_3$ + 5% CD_3OD): δ = 0.92–0.95 (2 d, *J* = 6.9 Hz, 12 H), 1.15 (t, *J* = 7.2 Hz, 6 H), 2.29 (sept, *J* = 6.9 Hz, 2 H), 4.09 (q, *J* = 7.2 Hz, 4 H), 5.45 (s, 1 H), 6.77 (s, 2 H), 6.94–6.96 (d, *J* = 2.7 Hz, 2 H), 7.14–7.17 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$ + 5% CD_3OD): δ = 14.3, 19.3, 19.6, 35.2, 60.5, 112.4, 120.4, 127.7, 128.7, 129.0, 138.2, 161.3, 177.3.

Dipyrrole 44
Yield: 57.0 mg (70%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 6 H), 1.35–1.39 (m, 4 H), 1.49–1.51 (m, 4 H), 2.17 (quint, *J* = 7.6 Hz, 2 H), 2.37–2.49 (m, 4 H), 3.78 (s, 6 H), 4.12 (t, *J* = 7.6 Hz, 1 H), 6.75 (d, *J* = 2.8 Hz, 2 H), 10.32 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 13.6, 22.3, 25.2, 27.0, 32.9, 35.0, 51.4, 116.5, 120.6, 123.3, 135.6, 162.7.

Dipyrrole 45
Yield: 77 mg (70%); tan solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 12 H), 1.39 (q, *J* = 8.0 Hz, 4 H), 1.59 (sept, *J* = 6.4 Hz, 2 H), 2.13 (quint, *J* = 7.0 Hz, 2 H), 2.33–2.47 (m, 4 H), 3.78 (s, 6 H), 4.10 (t, *J* = 8.0 Hz, 1 H), 6.74 (d, *J* = 2.4 Hz, 2 H), 10.00 (s, 2 H).

Dipyrrole 46
Yield: 21.2 mg (32%); cream colored solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.2 Hz, 3 H), 1.11 (sext, *J* = 8.0 Hz, 2 H), 2.00 (q, *J* = 7.6 Hz, 2 H), 3.69 (br s, 4 H), 3.80 (s, 6 H), 4.20 (t, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 2.4 Hz, 2 H), 7.07–7.09 (m, 4 H), 7.17–7.21 (m, 2 H), 7.24–7.28 (m, 4 H), 10.26 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 21.9, 24.8, 32.1, 39.9, 51.1, 116.6, 121.0, 124.0, 127.9, 129.4, 132.9, 161.9.

MS: *m*/*z* calcd for $C_{30}H_{33}N_2O_4$: 485.59 (M + H); found: 485 (85%); *m*/*z* (M + Na) calcd for $C_{30}H_{32}N_2O_4$ + Na: 507.57; found: 507 (100%).

Dipyrrole 47
Yield: 70 mg (34%); pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.2 Hz, 3 H), 1.81 (quint, *J* = 7.6 Hz, 2 H), 2.62–2.67 (m, 4 H), 2.74–2.79 (m, 4 H), 3.77 (t, *J* = 8.0 Hz, 1 H), 3.80 (s, 6 H), 6.76 (d, *J* = 2.4 Hz, 2 H), 7.08–7.10 (m, 4 H), 7.18–7.24 (m, 6 H), 9.50 (s, 2 H).

MS: *m*/*z* (M + H) calcd for $C_{31}H_{35}N_2O_4$: 499.61; found: 499 (45%); *m*/*z* (M + Na) calcd for $C_{31}H_{34}N_2O_4$ + Na 533.60; found: 521 (55%).

Dipyrrole 48
Yield: 151.0 mg (64%); cream colored solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62 (d, *J* = 6.6 Hz, 6 H), 0.66 (d, *J* = 6.6 Hz, 6 H), 1.29 (sept, *J* = 6.6 Hz, 2 H), 1.95 (d, *J* = 7.2 Hz, 4 H), 3.81 (s, 6 H), 3.88 (d, *J* = 7.8 Hz, 2 H), 4.71 (t, *J* = 7.8 Hz, 1 H), 6.67 (d, *J* = 2.7 Hz, 2 H), 6.99 (d, *J* = 7.2 Hz, 1 H), 7.20 (m, 1 H), 7.44–7.47 (m, 2 H), 7.66 (m, 1 H), 7.82–7.84 (m, 1 H), 7.99–8.01 (m, 1 H), 10.20 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8, 29.9, 35.2, 35.5, 38.1, 52.2, 117.7, 121.2, 122.9, 123.5, 125.8, 126.0, 126.5, 127.6, 127.8, 129.5, 132.1, 134.5, 135.2, 135.8, 163.1.

MS: *m*/*z* (M + H) calcd for $C_{32}H_{39}N_2O_4$: 515.66; found: 515 (70%); *m*/*z* (M + Na) calcd for $C_{32}H_{38}N_2O_4$ + Na: 537.64; found: 537 (90%).

Dipyrrole 49
Yield: 14.6 mg (54%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.91 (m, 12 H), 1.22 (t, *J* = 6.9 Hz, 6 H), 2.04–2.07 (m, 6 H), 4.09–4.18 (m, 4 H), 5.65 (s, 1 H), 6.90 (d, *J* = 2.7 Hz, 2 H), 7.09–7.11 (m, 2 H), 7.24–7.30 (m, 3 H), 9.86 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 22.5, 26.3, 39.8, 45.7, 60.6, 111.9, 119.7, 121.1, 127.8, 128.3, 128.6, 129.2, 137.5, 160.9, 172.4.

MS: *m*/*z* (M + H) calcd for $C_{31}H_{41}N_4O_6$: 565.68; found: 565 (95%); *m*/*z* (M + Na) calcd for $C_{31}H_{41}N_4O_6$ + Na: 587.66; found: 587 (100%).

Dipyrrole 50
Yield: 0.60 g (37%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 6 H), 2.01 (q, *J* = 7.6 Hz, 2 H), 4.22 (q, *J* = 6.4 Hz, 4 H), 4.32 (t, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 2.4 Hz, 2 H), 7.38 (t, *J* = 7.2 Hz, 4 H), 7.50 (t, *J* = 7.2 Hz, 2 H), 7.85 (d, *J* = 7.2 Hz, 4 H), 8.33 (s, 2 H), 10.71 (s, 2 H). Traces of Et_2O are present in the spectrum provided in the Supporting Information.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.5, 18.3, 20.9, 34.9, 60.5, 112.4, 118.8, 120.8, 127.5, 128.7, 131.9, 132.0, 134.1, 161.3, 167.6.

MS: *m*/*z* calcd for $C_{32}H_{35}N_4O_6$: 571.64 (M + H); found: 571 (100%); *m*/*z* (M + Na) calcd for $C_{32}H_{34}N_4O_6$ + Na: 593.63; found: 593 (40%).

Dipyrrole 52
Yield: 6.6 mg (11%); beige powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.4 Hz, 6 H), 1.25 (m), 1.33 (t, *J* = 7.2 Hz, 6 H), 2.58 (m, 4 H), 4.29 (q, *J* = 7.2 Hz, 4 H), 5.18 (s, 1 H), 6.29 (d, *J* = 2.8 Hz, 2 H), 7.15–7.18 (m, 3 H), 7.23–7.27 (m, 2 H), 8.73 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.3, 25.1, 30.5, 32.1, 39.1, 60.0, 119.8, 121.8, 126.5, 128.6, 128.8, 128.9, 131.2, 144.8, 162.2.

Dipyrrole 53
Yield: 70.0 mg (63%); white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9 (t, *J* = 6.8 Hz, 6 H), 1.28–1.36 (m, ~12 H), 1.52 (quint, *J* = 7.6 Hz, 4 H), 1.79 (s, 6 H), 2.70 (q, *J* = 7.2 Hz, 4 H), 4.25 (q, *J* = 7.2 Hz, 4 H), 5.50 (s, 1 H), 7.11 (m, 2 H), 7.30–7.35 (m, 3 H), 8.28 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.28, 13.7, 14.0, 22.2, 24.9, 30.2, 31.7, 41.0, 59.6, 117.6, 117.7, 127.8, 128.6, 129.4, 132.0, 133.3, 139.3, 162.1.

Dipyrrole 54
Yield: 21.5 mg (18%); orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 6.9 Hz, 6 H), 1.81 (s, 6 H), 4.06 (q, *J* = 7.2 Hz, 4 H), 5.64 (s, 1 H), 7.21–7.24 (m, 2 H), 7.30–7.41 (m, 13 H), 8.81 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.6, 14.1, 41.4, 60.1, 117.8, 117.9, 126.8, 127.5, 127.8, 128.5, 129.4, 130.5, 131.8, 132.4, 134.8, 138.8, 161.4.

MS: *m*/*z* calcd for $C_{35}H_{35}N_2O_4$: 547.66 (M + H); found: 547 (100%); *m*/*z* (M + Na) calcd for $C_{35}H_{34}N_2O_4$ + Na: 569.65; found: 569 (30%).

Saponification of Dipyrrole 44 to Diacid-Dipyrrole 55
Dipyrrole **44** (46.5 mg, 0.115 mmol) and LiOH (28 mg, 1.15 mmol) were heated in 1:1 THF–H_2O (2 mL) at 70 °C for 2 h.[33] EtOH (4 mL) was added and TLC analysis clearly indicated consumption of starting material. The reaction was further diluted with H_2O (20 mL), acidified to pH ~3 with aq 1 M HCl and extracted with $CHCl_3$ (3 × 15 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4), filtered, and concentrated to give the title compound; yield: 42.0 mg (~100%); red-brown crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H), 0.96 (t, *J* = 7.2 Hz, 6 H), 1.37–1.45 (m, 4 H), 1.52–1.60 (m, 4 H), 2.09 (quint, *J* = 7.6 Hz, 2 H), 2.43–2.56 (m, 4 H), 4.13 (t, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 2.4 Hz, 2 H), 11.35 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.45, 12.83, 22.51, 25.38, 27.89, 33.15, 34.88, 118.39, 119.90, 124.03, 137.70, 166.06.

MS: *m*/*z* (M + H – CO_2) calcd for $C_{20}H_{31}N_2O_2$: 331.47; found: 331 (100%); *m*/*z* (M + Na) calcd for $C_{21}H_{30}N_2O_4$ + Na: 397.46; found: 397 (25%).

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