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The application of vinylogous iminium salt derivatives to efficient formal syntheses of the marine alkaloids lamellarin G trimethyl ether and ningalin B

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ABSTRACT

Studies directed at the synthesis of lamellarin G trimethyl ether and ningalin B via vinylogous iminium salt derivatives are described. The successful strategy relies on the formation of a 2,4-disubstituted pyrrole or a 1,2,3,4-tetrasubstituted pyrrole from a vinylogous iminium salt or vinylogous iminium salt derivative. Subsequent transformations of these highly substituted pyrroles lead to efficient and regiocontrolled formal syntheses of the respective pyrrole containing natural products.

1. Introduction

The first lamellarin alkaloids were initially isolated from marine prosobranch mollusks and reported[1] by Faulkner and Clardy in 1985 and, since that time, great interest has emerged[2] as a consequence of their very interesting biological activity.[3] The lamellarins can be viewed as having three types of structural motifs as represented in Figure 1, in which a carbonyl group at C-2 and oxygenated aryl groups at C-3 and C-4 are always present. The more structurally complex lamellarins **2** and **3** possess isoquinoline and lactone functionality in addition to the basic pyrrole core. There are over 30 compounds to date that are considered to be members of this family of marine alkaloids and Steglich[4] has suggested that this class of natural products arises from secondary metabolites of 3,4-dihydroxyphenylalanine. Bailly[5] has shown that a number of lamellarins have a clear specificity for acting on DNA manipulating enzymes such as topoisomerase I. Lamellarins that contain the isoquinoline architecture show the most promising bioactivity as inhibitors of HIV-1 integrase,[6] as cytotoxic[7] and multi-drug resistance reversal agents[8] for various cancer cell lines. A number of important reviews[9] have appeared, which discuss the specific mode of actions of these alkaloids along with structure–activity relationships.

The first synthesis of the lamellarins was accomplished by Steglich[4] and co-workers whereby lamellarin G trimethyl ether was prepared based on a biomimetic approach as presented in Scheme 1.

A key intermediate in Steglich's route is a pentasubstituted pyrrole **7**, which is prepared from a symmetrical bis-ketoacid **5** via condensation with arylethylamine **6** thereby generating the highly functionalized pyrrole **7**. This pentasubstituted pyrrole is then lactonized with lead tetraacetate and this is followed by an intramolecular cross-coupling reaction, which incorporates a decarboxylation step and results in the desired lamellarin G trimethyl ether (**8**). A variety of different synthetic approaches to lamellarin G trimethyl ether (**8**) have been reported by Opatz,[10] Handy,[11] Iwao,[12] and Ruchirawat[13] and a number of recent reviews[14] describe alternative approaches to various lamellarins by other workers in the field. We have previously reported formal syntheses of related pyrrole containing natural products (Fig. 2) such as polycitone A[15] (**14**), ningalin B[16] (**16**), lukianol A[17] (**17**), and permethyl storniamide[18] (**18**). We have also completed a total synthesis of the pyrrolopyrimidine alkaloids rigidin[19] (**9**) and rigidin E (**13**). In this paper we now describe the evolution of our strategy as it relates to the modular and the convergent syntheses of lamellarin G trimethyl ether (**8**).

2. Results and discussions

One of the synthetic strategies that we have employed[15–19] in the past utilizes a 2,4-disubstituted pyrrole, which can be prepared

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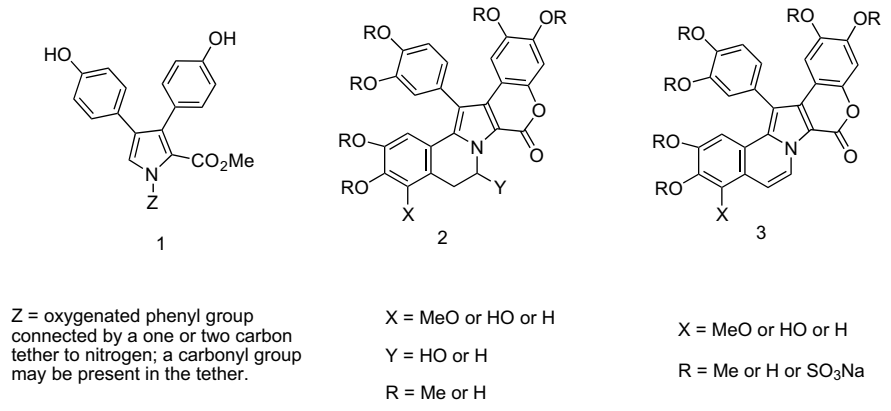
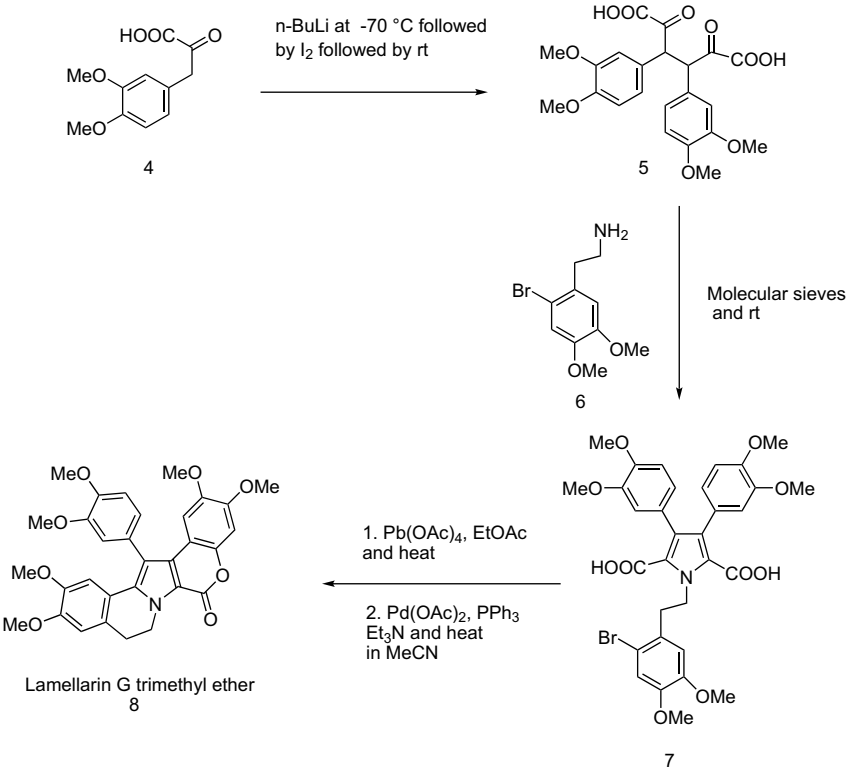


Figure 1. Lamellarin marine natural products.

from an appropriate vinamidinium salt, as a basic building block for the construction of many of the natural products depicted in Figure 2. Such pyrroles have been formylated at C-5 by a microwave accelerated version[18] of the Vilsmeier–Haack–Arnold procedure and further elaborated to yield storniamide type alkaloids. We have already mentioned that pentasubstituted pyrrole **7** (Scheme 1) was a key intermediate in Steglich's synthesis of lamellarin G trimethyl ether and we have opted to use our general strategy to prepare this highly functionalized pyrrole **7**. A formylated pyrrole **19**, which has already been described in our storniamide paper,[18] was iodinated with subsequent Suzuki cross-coupling to yield a tetrasubstituted pyrrole **21** in 50% yield for two steps after purification. N-alkylation of such tetrasubstituted pyrroles has been accomplished in the past by our group and also Boger's group[20] by employing base mediated reaction with arylethyl mesylates or arylethyl halides. The mesylate required for the alkylation step was prepared by bromination of 2-(3,4-dimethoxyphenyl)ethanol (**22**) with NBS to give 2-(2-bromo-4,5-dimethoxyphenyl)ethanol[11] (**23**), which was then reacted with methanesulfonyl chloride in the presence of triethylamine yielding 2-(2-bromo-4,5-dimethoxyphenethyl) methanesulfonate (**24**). One of the problems with such alkylations is the formation of styrenes via an elimination pathway and careful temperature control for these reactions becomes crucial. By running this alkylation with microwave heating at 70 °C we overcame this side reaction and provided the desired pentasubstituted pyrrole **25** very cleanly in 67% yield. Subsequent oxidation of the formyl group was accomplished with sodium chlorite to yield the corresponding acid **26** in 84% yield and the final hydrolysis step to prepare the Steglich synthon **7** (96% yield) was carried out in aqueous DMSO at 80 °C. The hydrolysis step was surprisingly sluggish perhaps due to the sterically hindered nature of the ester group. The overall yield of the Steglich synthon was 27% from the formylpyrrole **19** and, although our strategy has significantly more steps than Steglich's scheme, our route provides a very modular approach for the



Scheme 1. Steglich synthesis of lamellarin G trimethyl ether.

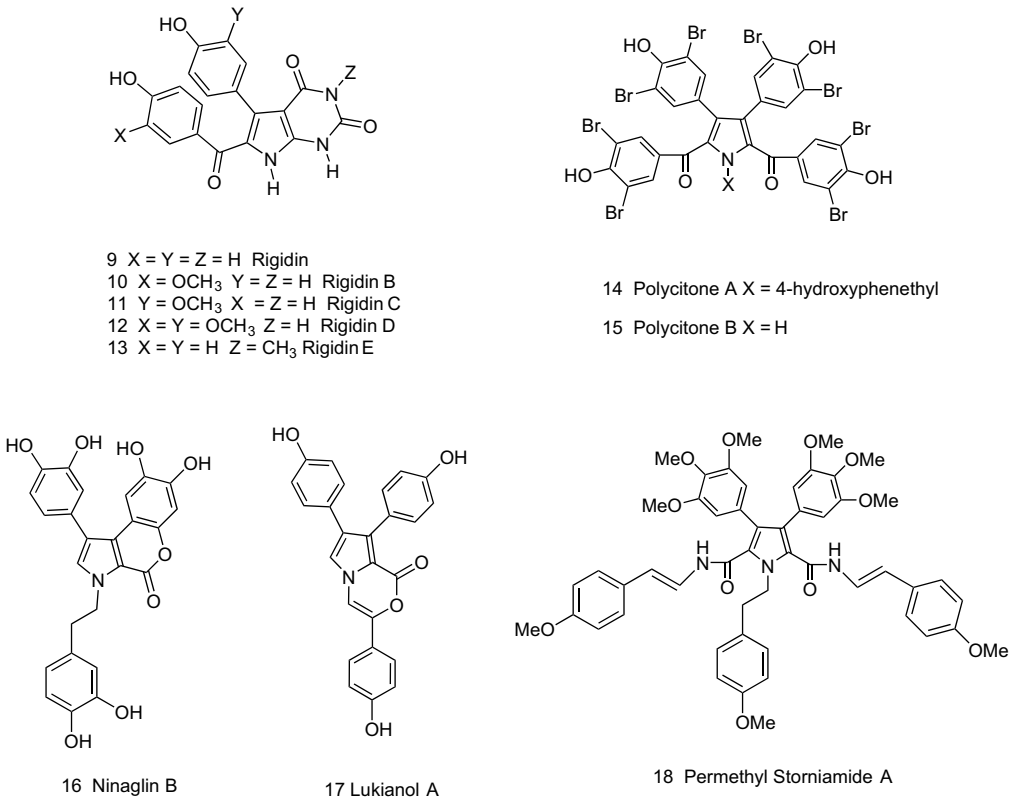


Figure 2. Pyrrole containing marine natural products.

preparation of SAR guided analogs and subsequent biological evaluation of these substances.

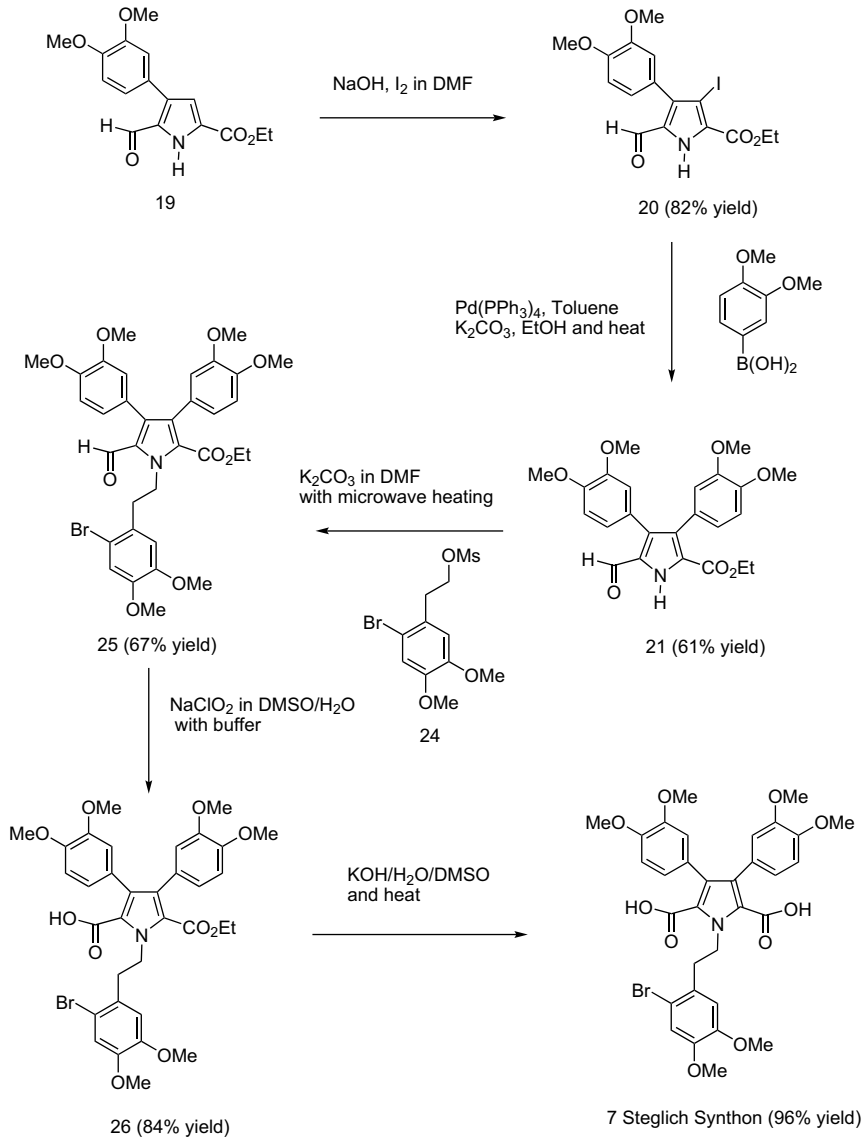
During the course of our work on our initial route (Scheme 2) to the Steglich synthon **7**, we decided to look at a more convergent manner for introducing N-substitution on possible pyrrole intermediates. We were intrigued by the report of Pfefferkorn[21] and co-workers at Pfizer in which case they were able to cleanly prepare ethyl *N*-isopropyl glycinate by reaction of isopropyl amine with ethyl α-bromoacetate without detecting any over alkylation products. As a result, we reacted (Scheme 3) 2 equiv of 3,4-dimethoxyphenyethylamine (**27**) with ethyl α-bromoacetate in THF at room temperature. The second equivalent of the amine is used to neutralize the hydrogen bromide that is generated and precipitates as the salt, which is removed by filtration. The filtrate is concentrated to give nearly analytical pure *N*-2-(3,4-dimethoxyphenylethyl)glycine ethyl ester (**28**) in 96% yield. This material was used without further purification and was brominated with NBS to give *N*-2-(2-bromo-4,5-dimethoxyphenylethyl)glycine ethyl ester (**29**) in 78% yield. With appropriately *N*-substituted glycine esters **28** and **29** in hand, we wanted to test the ability of such compounds to undergo successful condensation with vinylogous iminium salts or their derivatives in generating *N*-substituted pyrroles in good yield.

We have previously reported[17,22] that *N*-methylglycinate esters react (Scheme 4) cleanly with β-chloroenals such as **30**, which are derived from chloropropenimium salts, and produce 1,2,3,4-tetrasubstituted pyrroles in yields in the 90% range. When we reacted *N*-2-(3,4-dimethoxyphenylethyl)glycine ethyl ester (**28**) with such a β-chloroenal (as a mixture of *E* and *Z* isomers) with microwave heating in DMF for 3 h, the desired pyrrole **32** was obtained in 54% yield. No attempt was made to optimize this reaction and, given that a proof of concept was established, we proceeded to apply such conditions to our alternative synthesis of the Steglich synthon **7**.

We have reported[16] (Scheme 5) the preparation of 3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (**33**) and we have used this material as a mixture of *E* and *Z* isomers and also as the pure *E*-isomer in our synthesis of ningalin B hexamethyl ether (**36**). The *E*-isomer, which is predominant when the chloroenal is formed, normally precipitates during workup and can be easily isolated in pure form. Alternatively, one can workup the product so as to isolate a 4:1 mixture of *E*:*Z* isomers.

With this material in hand, we reacted (Scheme 6) the pure *E*-isomer with *N*-2-(2-bromo-4,5-dimethoxyphenylethyl)glycine ethyl ester (**29**) with microwave heating in DMF at 150 °C for a three-hour period in which case we isolated an 83% yield of the desired tetrasubstituted pyrrole **37**. When the reaction was repeated with the mixture of *E* and *Z* isomers of chloroenal **33**, an 88% yield of tetrasubstituted pyrrole **37** was obtained. This reaction proved to be very clean and efficient thereby generating a very highly functionalized pyrrole. Formylation of pyrrole **37**, using our microwave accelerated version of the Vilsmeier–Haack–Arnold reaction, produced a 92% yield of pentasubstituted pyrrole **25**, which was chromatographically and spectroscopically identical to the material (Scheme 2) that we had generated by our initial route thereby constituting an alternative formal synthesis of the Steglich synthon (Scheme 1).

As a consequence of our earlier studies[16] (Scheme 5) on ningalin B hexamethyl ether, we realized that we should now be able to extrapolate (Scheme 7) our new more convergent approach to this alkaloid as well. Reaction of *N*-2-(3,4-dimethoxyphenylethyl)glycine ethyl ester (**28**) with 3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (**33**, as a mixture of *E* and *Z* isomers) with microwave heating in DMF for 3 h produced (Scheme 7) the desired tetrasubstituted pyrrole **38** in 98% yield. Base mediated hydrolysis of this material resulted in a 68% yield of carboxylic acid **39**, which was spectroscopically and chromatographically identical to the

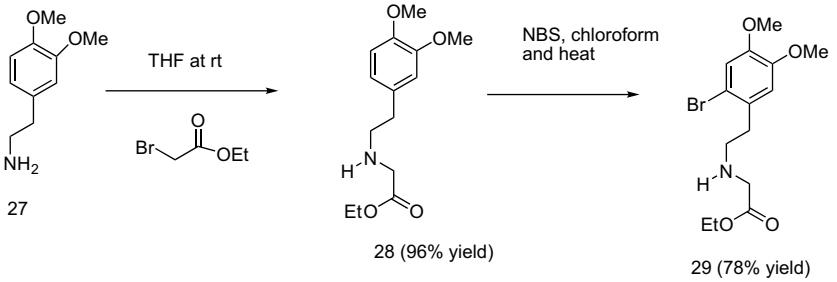


Scheme 2. Gupton group route 1 to Steglich synthon.

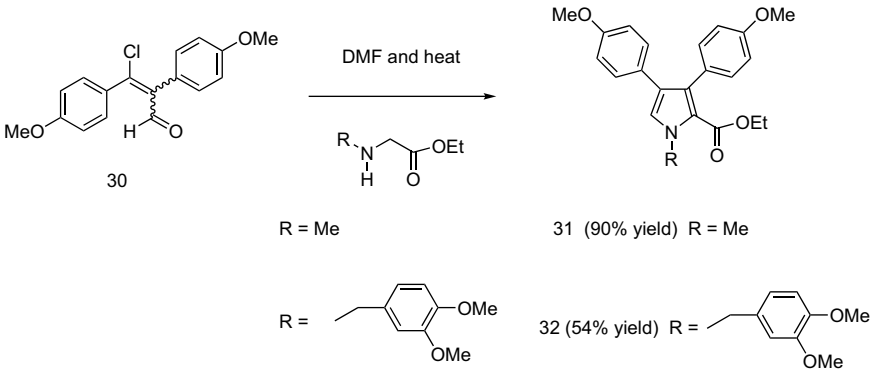
material previously reported by the Steglich group[4] and our research group[16] as a precursor to ningalin B hexamethyl ether.

3. Conclusions

In this paper we have reported two new methods for the formal synthesis of lamellarin G trimethyl ether (**8**) thereby establishing both a modular (Scheme 2) and a convergent (Scheme 6) synthesis for this biologically important class of marine alkaloids. Such methodology relies on the use of readily available vinylogous iminium salt derivatives along with microwave accelerated reaction conditions. In addition, the convergent approach (Scheme 6) was also successfully applied to an improved formal synthesis (Scheme 7) of the marine alkaloid ningalin B. This methodology should facilitate further studies directed at probing the structure–activity relationships for the lamellarins, the ningalins and other related



Scheme 3. Preparation of *N*-substituted glycines.



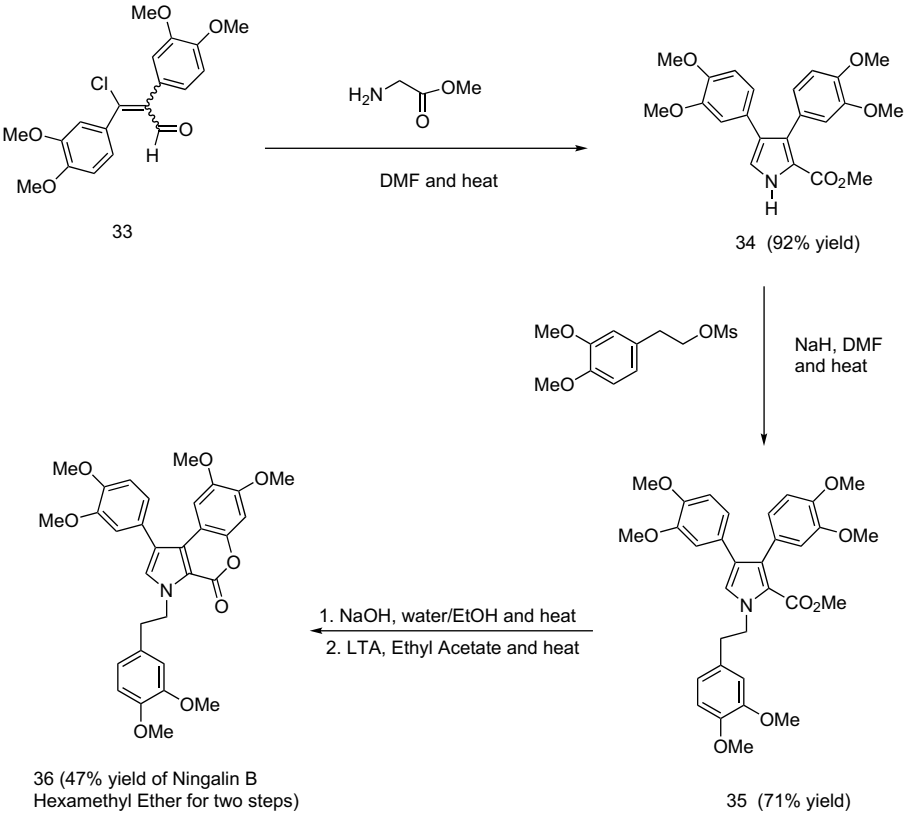
Scheme 4. Convergent synthesis of *N*-substituted pyrroles.

classes of important marine natural products and their derivatives.[23]

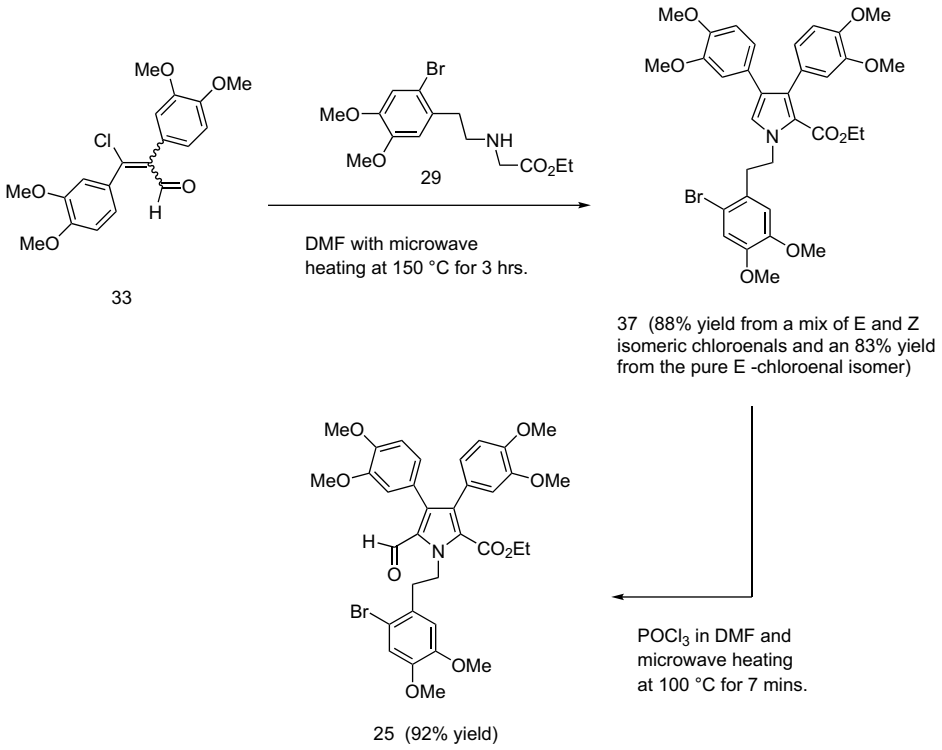
4. Experimental

4.1. General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific) and all reactions were carried out under a nitrogen or argon atmosphere. All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a Bruker 300 MHz spectrometer or a Bruker 500 MHz spectrometer in either $CDCl_3$, DMSO-d_6 or acetone-d_6 solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High resolution mass spectra were provided on a Biotof Q electrospray mass spectrometer at the University of Richmond. Low resolution GC–MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Flash chromatographic separations were carried out on a Biotage SP-1 instrument, which had been equipped with a silica cartridge, and ethyl acetate/hexane was used as the eluant. The desired, pyrrole containing products were eluted within the range of 6–8 column volumes of eluant with a mix of 60–80% ethyl acetate/20–40% hexane. Microwave accelerated reactions were carried out in a Biotage Liberator system. Microwave reactions were controlled at a constant temperature whereby the microwave power was allowed to fluctuate so as to maintain a constant temperature and safe pressure limits. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. Vinamidinium salts utilized for pyrrole formation were prepared according to standard procedures.[24] All purified reaction products gave TLC results, GC–MS spectra, flash



Scheme 5. Gupton group initial route to ningalin B hexamethyl ether.

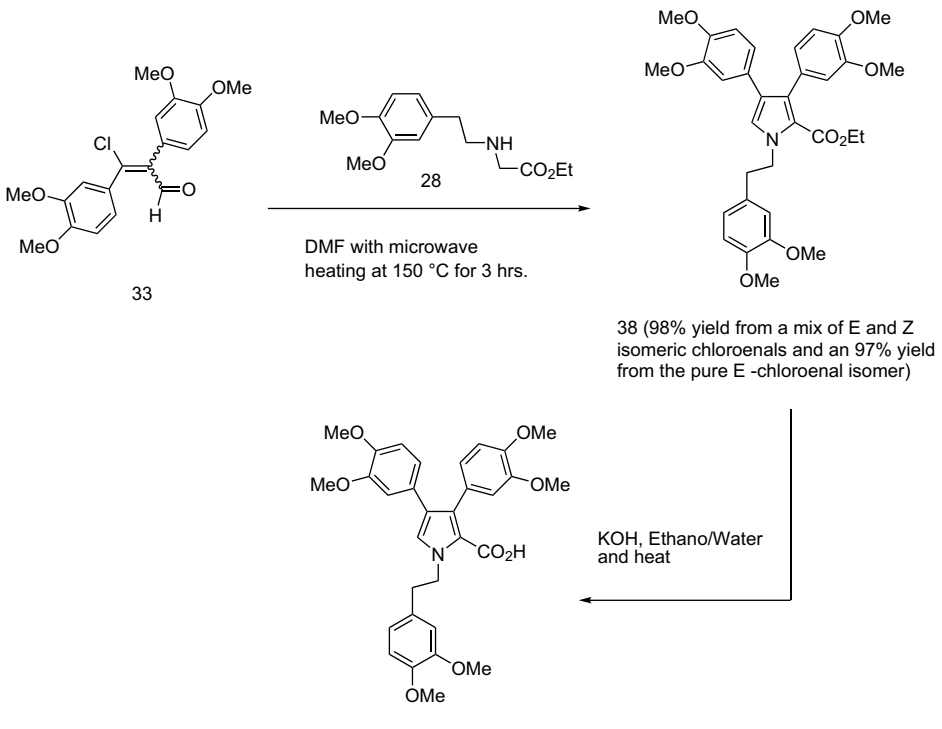


Scheme 6. Gupton group route 2 to Steglich synthon.

chromatograms and ^{13}C NMR spectra consistent with a sample purity of >95%. When the preparation of an analytical sample is reported, the crude reaction product was of sufficient purity to be used in subsequent steps without further purification.

*4.1.1. Ethyl 2-formyl-3-(3,4-dimethoxyphenyl)-4-iodopyrrole-5-carboxylate (**20**)*

Into a three-necked, round bottom flask, equipped with a stir bar was charged 0.500 g (16.5 mmol) of ethyl 2-formyl-3-(3,4-



Scheme 7. Gupton group route 2 to ningalin B synthon.

dimethoxyphenyl)pyrrole-5-carboxylate[18] (**19**), 15 mL of DMF, and 0.369 g (65.9 mmol) of powdered KOH. The resulting mixture was stirred for 30 min and 0.836 g (32.9 mmol) of iodine was added in one portion. The reaction vessel was capped and wrapped with aluminum foil and the resulting mixture was stirred for 48 h at room temperature. The reaction mixture was subsequently diluted with 45 mL of 20% aqueous sodium thiosulfate and extracted with 3×30 mL of ethyl acetate. The combined organic phases were washed with 30 mL of brine and dried over anhydrous magnesium sulfate. The drying agent was then removed by filtration and the filtrate was concentrated in vacuo to give 0.580 g (82% yield) of a light brown solid. This material was of sufficient purity for use in subsequent reactions. However, an analytical sample was prepared by flash chromatography using an ethyl acetate/hexane gradient. The purified product exhibited the following physical properties: mp 175–177 °C; ^{1}H NMR (DMSO-d_6) δ 13.19 (br s, 1H), 9.49 (s, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.00 (d, J=2.0 Hz, 1H), 6.93 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 4.33 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), and 1.36 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.8, 159.3, 149.6, 148.8, 139.7, 130.9, 127.4, 124.1, 123.5, 113.9, 111.0, 61.9, 56.1, 55.0, and 14.3; IR (neat) 3383, 1713, and 1658 cm^{-1}; HRMS (ES) m/z calcd for $C_{16}H_{16}NO_5INa$ 451.9965, found 451.9972.

4.1.2. Ethyl 5-formyl-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (*21*)

Into a dry, 7 mL microwave reaction vessel were placed 0.200 g (0.466 mmol) of ethyl 2-formyl-3-(3,4-dimethoxyphenyl)-4-iodopyrrole-5-carboxylate (**20**), 6 mL of a 3:1 mixture of toluene/ethanol, 0.254 g (1.39 mmol) of 3,4-dimethoxyphenylboronic acid, potassium carbonate (0.219 g, 1.58 mmol), 0.107 g (0.093 mmol) of palladium tetrakistriphenylphosphine, and 2 drops of water. The reaction vessel was sealed (Crymper seal) and heated by microwaves at 110 °C for 1 h in a Liberator Microwave Reactor. This process was repeated for two additional runs and the three crude reaction mixtures were combined and passed through a short plug of silica. The silica plug was washed with 50 mL of ethyl acetate and the combined filtrate was washed with 2×50 mL of 10% NaOH solution and 50 mL of brine. After drying the organic phase over anhydrous magnesium sulfate and filtering off the drying agent, the reaction mixture was concentrated in vacuo and the resulting crude product was purified by flash chromatography with a hexane/ethyl acetate gradient, which resulted in 0.376 g (61% yield) of a solid that exhibited the following properties: mp 161–163 °C; ^{1}H NMR (DMSO-d_6) δ 9.61 (br s, 1H), 6.88 (d, J=8.4 Hz, 1H), 6.83 (d, J=8.4 Hz, 1H), 6.76 (d of d, J=2.1 Hz, J=8.4 Hz, 1H), 6.74 (d, J=2.1 Hz, 1H), 6.70 (d, J=2.1 Hz, 1H), 6.64 (d of d, J=2.1 Hz, J=8.4 Hz, 1H), 4.15 (q, J=7.2 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.58 (s, 3H), 3.52 (s, 3H), and 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.3, 160.3, 148.8, 148.6, 148.4, 148.1, 134.9, 130.3, 129.8, 124.0, 123.9, 123.8, 123.4, 123.3, 114.3, 113.8, 111.0, 110.5, 61.2, 55.9, 55.8, 55.7, 55.6, and 14.2; IR (neat) 1685 and 1658 cm^{-1}; HRMS (ES) m/z calcd for $C_{24}H_{25}NO_7INa$ 462.1523, found 462.1525.

4.1.3. 2-Bromo-4,5-dimethoxyphenethyl alcohol (*23*)

3,4-Dimethoxyphenethyl alcohol (**22**, 3.00 g, 0.0164 mol) was dissolved in 100 mL of chloroform and placed in a round bottom flask, which had been equipped with a stir bar and reflux condenser. To the reaction mixture was added 3.22 g (0.0181 mol) of *N*-bromosuccinimide and the resulting mixture was heated at reflux for 6 h. After cooling to room temperature, the reaction mixture was washed with 20% aqueous sodium thiosulfate, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield 4.26 g (100% yield) of an oil. The resulting material could be used without further purification and exhibited[11] the following properties: bp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 1H), 6.81 (s, 1H), 3.87–3.90 (m, 8H), and 2.98 (t, J=6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 148.5, 148.4, 129.8, 115.8, 114.4, 113.9, 62.4, 56.2, 56.1, and 39.0; IR (neat) broad absorption 3413 cm^{-1}; HRMS (ES) m/z calcd for $C_{10}H_{13}BrO_3Na$ 282.9940, found 282.9941.

4.1.4. 2-Bromo-4,5-dimethoxyphenethyl methanesulfonate (*24*)

A 2.69 g (0.0103 mol) sample of 2-bromo-4,5-dimethoxyphenethyl alcohol (**23**) was dissolved in 60 mL of methylene chloride and placed into a 100 mL round bottom flask, which had been equipped with a stir bar. To this mixture was added 2.16 mL (0.0154 mol) of triethylamine and the resulting mixture was stirred for 5 min, cooled in an ice-water bath, and methanesulfonyl chloride (1.00 mL, 0.0123 mol) was added dropwise. After the resulting solution had stirred for 1 h, the reaction mixture was extracted with 2×20 mL of 10% hydrochloric acid and 20 mL of brine solution. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield 3.33 g (95% yield) of an red solid, which could be used without further purification and exhibited the following physical properties: mp 97–100 °C; ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 1H), 6.80 (s, 1H), 4.43 (t, J=7.0 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.15 (t, J=7.0 Hz, 2H), and 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 148.9, 148.6, 127.4, 115.7, 114.3, 114.0, 68.7, 56.2, 56.1, 37.4, and 35.7; IR (neat) 1336 and 1161 cm^{-1}; HRMS (ES) m/z calcd for $C_{11}H_{15}BrO_5Na$ 360.9716, found 360.9708.

4.1.5. Ethyl N-2-(2-Bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)-5-formylpyrrole-2-carboxylate (*25*)

4.1.5.1. Method A. A 0.300 g (0.682 mmol) sample of ethyl 5-formyl-3,4-bis(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**21**) was placed into a 20 mL microwave reactor vessel along with potassium carbonate (0.283 g, 2.04 mmol), 12 mL of dry DMF, and a stir bar. The mixture was placed under a nitrogen blanket and stirred for 1 h after which 1.158 g (3.41 mmol) of 2-bromo-4,5-dimethoxyphenethyl methanesulfonate (**24**) was added in one portion. The reaction vessel was sealed and heated by microwaves at 70 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with 20 mL of ethyl acetate and 30 mL of water. After separating the phases, the aqueous phase was extracted with 3×20 mL of ethyl acetate and the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material was purified by flash chromatography with a Biotage 25S silica column using an ethyl acetate/hexane gradient. The purified product (0.314 g, 67% yield) exhibited the following physical properties: mp 50–53 °C; ^{1}H NMR (acetone-d_6) δ 9.64 (s, 1H), 7.08 (s, 1H), 6.91 (d, J=7.0 Hz, 1H), 6.81–6.84 (m, 2H), 6.75 (d, J=2.0 Hz, 1H), 6.63 (d, J=2.0 Hz, 1H), 6.62 (s, 1H), 6.59 (d of d, J=2.0 Hz, J=8.5 Hz, 1H), 5.11 (t, J=6.5 Hz, 2H), 3.92 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 3.62 (s, 3H), 3.12 (t, J=6.5 Hz, 2H), and 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 182.3, 161.3, 148.5, 148.3, 148.2, 148.1, 148.0, 147.9, 137.5, 129.4, 129.1, 129.0, 128.1, 126.1, 124.2, 123.7, 122.8, 115.1, 114.7, 113.9, 113.8, 113.4, 110.6, 110.3, 61.1, 56.1, 55.9, 55.8, 55.7, 55.6, 46.3, 37.5, and 13.7; IR (neat) 1709 and 1654 cm^{-1}; HRMS (ES) m/z calcd for $C_{34}H_{37}NO_9Br$ 682.1652, found 682.1666.

4.1.6. Ethyl N-2-(2-bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)-2-carbethoxypyrrole-5-carboxylic acid (*26*)

Ethyl *N*-[2-(2-bromo-4,5-dimethoxyphenethyl)]-3,4-bis-(3,4-dimethoxyphenyl)-5-formylpyrrole-2-carboxylate (**25**, 0.220 g, 0.322 mmol) was dissolved in 40 mL of DMSO and placed in a 100 mL round bottom flask, which had been equipped with a stir bar. Sodium hydrogen phosphate monohydrate (0.044 g, 0.322 mmol) was dissolved in 10 mL of water and added to the reaction mixture. The resulting solution was cooled in an ice/water bath and a solution of 0.087 g (0.967 mmol) sodium chlorite in 10 mL of water was added to the reaction mixture, dropwise

with stirring. The resulting mixture was stirred for 20 h at room temperature, made acidic with 6 M hydrochloric acid, and extracted with 3×30 mL of ethyl acetate. The combined organic phases were washed with 1×50 mL of brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a dark brown solid (0.260 g, 84% yield). An analytical sample was prepared by radial chromatography on a 2 mm thick plate of silica with a hexane/ethyl acetate gradient and the resulting purified material exhibited the following physical properties: mp 135–137 °C; ^{1}H NMR (acetone-d_6) δ 7.07 (s, 1H), 6.75–6.77 (m, 2H), 6.66–6.70 (m, 2H), 6.63 (s, 1H), 6.59 (d, J=2.0 Hz, 1H), 6.55 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 5.09 (t, J=6.5 Hz, 2H), 3.94 (q, J=7.0 Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.64 (s, 3H), 3.62 (s, 3H), 3.15 (t, J=6.5 Hz, 2H), and 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 162.2, 161.2, 149.1, 148.9, 148.4, 148.3, 148.2, 148.1, 130.9, 130.0, 129.4, 127.4, 125.5, 123.1, 122.9, 115.9, 115.7, 115.2, 115.1, 114.1, 114.0, 110.9, 110.8, 110.7, 60.1, 55.6, 55.3, 55.2, 55.1, 55.0, 45.7, 37.5, and 13.1; IR (neat) 1705 and 1666 cm^{-1}; HRMS (ES) m/z calcd for $C_{34}H_{36}NO_{10}BrNa$ 720.1415, found 720.1405.

4.1.7. *N-2-(2-Bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2,5-dicarboxylic acid (**7**)*

A 250 mL three-necked, round bottom flask was equipped with a condenser, thermometer, and stir bar. Into the flask was placed 30 mL of a 50:50 DMSO/water mixture along with powdered potassium hydroxide (0.225 g, 4.01 mmol) and ethyl *N*-2-(2-bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)-2-carbethoxypyrrole-5-carboxylic acid (**26**, 0.200 g, 0.286 mmol). The reaction mixture was heated at 80 °C for 72 h, cooled to room temperature, adjusted to pH 2 with 6 M hydrochloric acid, and diluted with 40 mL of water. The resulting mixture was extracted with 3×30 mL of ethyl acetate and the combined organic phases were washed with 30 mL of brine. After drying over anhydrous magnesium sulfate and filtering off the drying agent the organic phase was concentrated in vacuo to leave an orange solid (0.192 g, 96% yield). An analytical sample was prepared by trituration of the crude solid with a small amount of ethyl acetate and the resulting material exhibited the following physical properties: mp 182–185 °C (lit. 201 °C); ^{1}H NMR (DMSO-d_6) δ 7.08 (s, 1H), 6.75 (d, J=8.0 Hz, 2H), 6.63 (s, 1H), 6.53–6.55 (m, 4H), 4.90 (t, J=7.0 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.69 (s, 6H), 3.52 (s, 6H), and 3.02 (t, J=7.0 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 163.0, 148.9, 148.7, 147.8, 147.7, 129.8, 129.6, 127.5, 125.1, 123.1, 116.1, 115.2, 114.2, 114.1, 111.2, 56.4, 55.9, 55.8, 55.7, 46.2, and 37.8; IR (neat) 1712 cm^{-1}; HRMS (ES) m/z calcd for $C_{32}H_{32}NO_{10}BrNa$ 692.1102, found 692.1091.

4.1.8. *N-2-(3,4-Dimethoxyphenylethyl)glycine ethyl ester (**28**)*

Into a 100 mL round bottom flask, which had been equipped with a stir bar, was placed ethyl bromoacetate (1.800 g, 0.0108 mol) along with 10 mL of dry THF. To this reaction vessel was added 3,4-dimethoxyphenethylamine (**27**, 3.907 g, 0.0216 mol) and the resulting reaction mixture was stirred for 24 h. The solid by-product (3,4-dimethoxyphenethylammonium bromide) was removed by filtration and the filtrate was concentrated in vacuo to produce 2.755 g (96% yield) of an oil, which was sufficient for use in subsequent reactions. An analytical sample was obtained by Kugelrohr bulb to bulb distillation and the resulting distillate exhibited the following properties: bp 160–161 °C at 1.6 Torr; ^{1}H NMR ($CDCl_3$) δ 6.56–6.62 (m, 3H), 3.97 (q, J=7.5 Hz, 2H), 3.67 (s, 3H), 3.64 (s, 3H), 3.21 (br s, 2H), 2.68 (t, J=7.0 Hz, 2H), 2.57 (t, J=7.0 Hz, 2H), and 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 148.9, 147.4, 132.2, 120.5, 112.0, 111.4, 60.4, 55.7, 55.6, 50.6, 50.5, 35.7, and 14.0; IR (neat) 1735 cm^{-1}; HRMS (ES) m/z calcd for $C_{14}H_{22}NO_4$ 268.1543, found 268.1572.

4.1.9. *N-2-(2-Bromo-4,5-dimethoxyphenylethyl)glycine ethyl ester (**29**)*

N-2-(3,4-Dimethoxyphenylethyl)glycine ethyl ester (**28**, 2.000 g, 0.00748 mol) was placed in a 100 mL round bottom flask, which had been equipped with a stir bar. To the flask were added 50 mL of chloroform and *N*-bromosuccinimide (1.465 g, 0.00823 mol) and the resulting mixture was refluxed for 6 h. After cooling the reaction mixture to room temperature, the chloroform solution was extracted with 3×30 mL of 20% sodium thiosulfate solution, 3×30 mL of saturated sodium bicarbonate solution, and 1×30 mL of brine. The organic phase then was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a dark oil (2.022 g, 78% yield). An analytical sample was prepared by Kugelrohr bulb to bulb distillation and the resulting distillate exhibited the following properties: bp 154–155 °C at 1.6 Torr; ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H), 6.76 (s, 1H), 4.16 (q, J=7.5 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.42 (br s, 2H), 2.85 (br s, 4H), and 1.25 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 148.4, 148.2, 131.0, 115.7, 114.2, 113.4, 60.7, 56.1, 56.0, 50.9, 49.3, 36.3, and 14.2; IR (neat) 1728 cm^{-1}; HRMS (ES) m/z calcd for $C_{14}H_{21}NO_4Br$ 346.0649, found 346.0658.

4.1.10. *Ethyl N-2-(3,4-dimethoxyphenethyl)-3,4-bis-(4-methoxyphenyl)pyrrole-2-carboxylate (**32**)*

N-2-(3,4-Dimethoxyphenylethyl)glycine ethyl ester (**28**, 0.172 g, 0.644 mmol) was placed into a 10 mL microwave reactor vessel along with 3-chloro-2,3-bis(4-methoxyphenyl)propenal (**30**, 0.150 g, 0.495 mmol, a mixture of *E* and *Z* isomers) and 5 mL of DMF. The reaction vessel was sealed and heated by microwaves at 150 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was taken up in ethyl acetate (50 mL) and washed with 3×15 mL of 5% hydrochloric acid and 1×50 mL of brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a dark brown solid (0.172 g, 54% yield). An analytical sample was prepared by flash chromatography with a Biotage 25S silica column using an ethyl acetate/hexane gradient and the resulting material exhibited the following properties: mp 34–37 °C; ^{1}H NMR (acetone-d_6) δ 7.10 (d, J=8.5 Hz, 2H), 7.00 (s, 1H), 6.96 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.5 Hz, 2H), 6.77 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 6.73 (d, J=2.0 Hz, 1H), 6.72 (d, J=8.0 Hz, 1H), 4.60 (t, J=7.0 Hz, 2H), 4.02 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.05 (t, J=7.0 Hz, 2H), and 0.98 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.8, 158.4, 157.8, 148.9, 147.8, 131.8, 131.2, 131.0, 129.1, 128.5, 127.2, 126.1, 123.7, 120.9, 119.6, 113.6, 112.9, 112.3, 111.4, 59.6, 56.0, 55.8, 55.2, 55.1, 51.7, 37.9, and 13.8; IR (neat) 1685 cm^{-1}; HRMS (ES) m/z calcd for $C_{31}H_{33}NO_6Na$ 538.2200, found 538.2190.

4.1.11. *Ethyl N-2-(2-bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**37**)*

4.1.11.1. Method A. *E*-3-Chloro-2,3-bis(3,4-dimethoxyphenyl)-chloroenal (**33**, 1.241 g, 3.60 mmol) was placed into a 20 mL microwave reactor vessel, which had been equipped with a stir bar, along with 15 mL of dry DMF and *N*-2-(2-bromo-4,5-dimethoxyphenylethyl)glycine ethyl ester (**29**, 1.000 g, 2.80 mmol). The reaction vessel was sealed and heated by microwaves at 150 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was taken up in ethyl acetate (50 mL) and washed with 6×20 mL of 5% hydrochloric acid and 1×50 mL of brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a dark brown solid (1.199 g, 83% yield). An analytical sample was prepared by flash chromatography on a Biotage 25S column using a hexane/ethyl acetate gradient and the resulting material exhibited the following physical properties: mp 47–48 °C; ^{1}H NMR (acetone-d_6) δ 7.12 (s, 1H), 6.94 (s, 1H), 6.89 (d, J=8.0 Hz, 1H), 6.81 (d,

J=2.0 Hz, 1H), 6.75 (d, J=8.5 Hz, 1H), 6.69 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 6.64 (d of d, J=2.0 Hz, J=8.5 Hz, 1H), 6.61 (s, 1H), 6.54 (d, J=2.0 Hz, 1H), 4.66 (t, J=7.0 Hz, 2H), 4.01 (q, J=7.0 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 3.50 (s, 3H), 3.19 (t, J=7.0 Hz, 2H), and 0.98 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7, 148.4, 148.2, 148.0, 147.7, 147.1, 130.9, 129.6, 128.8, 127.2, 126.0, 123.8, 123.0, 119.9, 119.6, 115.3, 114.3, 114.2, 113.6, 111.4, 110.9, 110.4, 59.7, 56.1, 55.9, 55.8, 55.7, 55.3, 49.5, 38.0, and 13.9; IR (neat) 1685 cm^{-1}; HRMS (ES) m/z calcd for $C_{33}H_{37}NO_8Br$ 654.1697, found 654.1673.

4.1.11.2. Method B. A mixture of *E* and *Z* isomers of 3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (**33**, 0.070 g, 0.190 mmol) was placed into a 10 mL microwave reactor vessel, which had been equipped with a stir bar, along with 5 mL of dry DMF and *N*-2-(2-bromo-4,5-dimethoxyphenylethyl)glycine ethyl ester (**29**, 0.087 g, 0.25 mmol). The reaction vessel was sealed and heated by microwaves at 150 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo and the residue was taken up in ethyl acetate (50 mL) and washed with 6×15 mL of 5% hydrochloric acid and 1×50 mL of brine. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to leave a dark brown solid (0.111 g, 88% yield). This material had identical physical properties (^{1}H NMR and TLC behavior) to the material prepared by Method A.

*4.1.12. Ethyl N-2-(2-bromo-4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)-5-formylpyrrole-2-carboxylate (**25**)*

4.1.12.1. Method B. Phosphorous oxychloride (0.392 mL, 4.29 mmol) was added to DMF (15 mL) with cooling in a 20 mL microwave reactor vessel, which had been equipped with a stir bar. After stirring for 45 min, ethyl *N*-[2-(2-bromo-4,5-dimethoxyphenethyl)]-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**37**, 0.935 g, 1.43 mmol) was added to the reaction vessel and the vessel was sealed and heated by microwaves at 100 °C for 7 min. After cooling to room temperature, the reaction mixture was diluted with 60 mL of water and extracted with 3×50 mL of ethyl acetate and the combined organic phases were washed with 50 mL of brine and dried over anhydrous magnesium sulfate. The organic phase was filtered and concentrated in vacuo to leave a dark brown solid (0.910 g, 92% yield). An analytical sample was prepared by flash chromatography on a Biotage 25M column using a hexane/ethyl acetate gradient and the resulting material exhibited spectral and physical properties identical to the material prepared by Method A.

*4.1.13. Ethyl N-2-(4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**38**)*

4.1.13.1. Method A. A 10 mL microwave reaction vessel was equipped with a stir bar and placed under a nitrogen atmosphere. Into the reaction vessel were placed *E*-3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (**33**, 0.150 g, 0.413 mmol), *N*-2-(4,5-dimethoxyphenylethyl)glycine ethyl ester (**28**, 0.144 g, 0.537 mmol), and 6 mL of dry DMF. The reaction vessel was sealed and heated by microwaves at 150 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with 50 mL of ethyl acetate and extracted with 3×20 mL of 5% hydrochloric acid and once with 20 mL of brine. After drying over anhydrous magnesium sulfate and filtering off the drying agent the organic phase was concentrated in vacuo to leave a yellow solid (0.230 g, 97% yield). The crude product was purified by flash chromatography on a Biotage 25S column using an ethyl acetate/hexane gradient in which case 0.204 g (86% yield) of a yellow solid was obtained and this compound exhibited the following physical properties: mp 128–131 °C; ^{1}H NMR (acetone-d_6) δ 7.05 (s, 1H), 6.91 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 6.82 (d J=2.0 Hz, 1H), 6.78 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 6.70–6.72 (m, 3H), 6.67 (d of d, J=2.0 Hz, J=8.0 Hz, 1H), 6.57 (d, J=2.0 Hz, 1H), 4.61 (t, J=7.0 Hz, 2H), 4.04 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.51(s, 3H), 3.06 (t, J=7.0 Hz, 2H), and 0.98 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 161.7, 148.9, 148.4, 148.2, 147.9, 147.8, 147.2, 131.1, 130.9, 129.0, 127.4, 125.8, 123.7, 123.1, 120.9, 119.8, 119.7, 114.4, 112.3, 111.6, 111.4, 111.1, 110.6, 59.7, 56.0, 55.9, 55.7, 55.5, 55.4, 55.3, 51.6, 37.9, and 13.9; IR (neat) 1676 cm^{-1}; HRMS (ES) m/z calcd for $C_{33}H_{37}NO_8Na$ 598 2411, found 598.2410.

4.1.13.2. Method B. A 10 mL microwave reaction vessel was equipped with a stir bar and placed under a nitrogen atmosphere. Into the reaction vessel was placed a mixture of *E* and *Z* isomers of 3-chloro-2,3-bis(3,4-dimethoxyphenyl)chloroenal (**33**, 0.200 g, 0.551 mmol), *N*-2-(4,5-dimethoxyphenylethyl)-glycine ethyl ester (**28**, 0.192 g, 0.717 mmol), and 6 mL of dry DMF. The reaction vessel was sealed and heated by microwaves at 150 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with 50 mL of ethyl acetate and extracted with 3×20 mL of 5% hydrochloric acid and once with 20 mL of brine. After drying over anhydrous magnesium sulfate and filtering off the drying agent the organic phase was concentrated in vacuo to leave a yellow solid (0.311 g, 98% yield). The crude product was purified by flash chromatography on a Biotage 25S column using an ethyl acetate/hexane gradient in which case 0.189 g (60% yield) of a yellow solid was obtained. This material had identical physical properties (^{1}H NMR and TLC behavior) to the material prepared by Method A.

*4.1.14. N-2-(4,5-Dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylic acid (**39**)*

A 250 mL three-necked, round bottom flask was equipped with a condenser, thermometer, and stir bar. Into the flask was placed 20 mL of a 50:50 ethanol/water mixture along with powdered potassium hydroxide (0.110 g, 1.96 mmol) and ethyl *N*-2-(4,5-dimethoxyphenethyl)-3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**38**, 0.189 g, 0.328 mmol). The reaction mixture was heated at reflux for 24 h, cooled to room temperature, adjusted to pH 2 with 6 M hydrochloric acid, and diluted with 30 mL of water. The resulting mixture was extracted with 3×30 mL of ethyl acetate and the combined organic phases were washed with 30 mL of brine. After drying over anhydrous magnesium sulfate and filtering off the drying agent the organic phase was concentrated in vacuo to leave a yellow solid (0.180 g, 68% yield). An analytical sample was prepared by passing the yellow solid through a short plug of silica gel with a hexane:ethyl acetate gradient whereby the resulting yellow solid exhibited proton and carbon NMR spectra identical to those previously reported[16] by our research group.

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