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The application of vinylogous iminium salt derivatives to the synthesis of Ningalin B hexamethyl ether

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Abstract—A vinylogous iminium salt derivative has been used to prepare a 2,3,4-trisubstituted pyrrole synthon in a regioselective, efficient and convenient manner. This pyrrole synthon was subsequently converted to the multidrug-resistant (MDR) reversal agent, Ningalin B hexamethyl ether, via alkylation, hydrolysis and oxidative lactonization steps. This methodology provides an alternative pathway to this important class of pyrrole containing marine natural products. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The isolation[1] and synthesis of pyrrole-containing marine natural products and related derivatives continues to be a very active area of research given the interesting bioactivity exhibited by such compounds (Fig. 1).

The Boger research group has recently completed[2] an efficient and versatile total synthesis of Ningalin B and related derivatives by application of the their well established heterocyclic azadiene Diels–Alder/retrograde Diels–Alder methodology which provides for the construction of a 4,5-diaryl-1,2-diazine-3,6-dicarboxylic acid ester. This diazine is then subjected to a reductive ring contraction to yield a 3,4-diarylpyrrole-2,5-dicarboxylic acid ester which becomes the key synthon for the construction of Ningalin B (Scheme 1).

This same strategy has also been used by the Boger group[3] for the efficient preparation of other members of this class of alkaloids such as Ningalin A, Lamellarin O, Lukianol A and Permethyl Storniamide. Alternative approaches to the synthesis of Lamellarin and Lukianol alkaloids have been developed by Furstner[4] (Scheme 2), Banwell[5] (Scheme 3), Steglich,[6] Ishibashi[7] and Wong.[8] Furstner has utilized a titanium mediated, intramolecular cyclization of a 1,5-dicarbonyl compound as a key step for pyrrole synthesis, whereas Wong has utilized silylated pyrroles as building blocks for subsequent cross-coupling chemistry. Steglich has applied a very elegant biomimetic approach to the synthesis of Lamellarin G trimethyl ether which creates the key pyrrole synthon by reaction of a primary amine with a symmetrical 1,4-diketone. Banwell has used several approaches which involve both intermolecular and intramolecular cross-coupling reactions as well as the cyclization of azomethine ylids. Azomethine ylid cyclization has also been employed by Ishibashi in his synthesis of Lamellarin D and H.

Much of the interest in such alkaloids arises from their observed cytotoxicity against various cancer cell lines and more importantly from their ability to act as multidrug-resistant (MDR) reversal agents[2] at non-cytotoxic concentrations thereby allowing many standard chemotherapeutic agents to be used in concert, and in potentially lower concentrations. The MDR activity is thought to be due to the action of such compounds on P-glycoprotein efflux pumps[9] which function at the cellular level. As part of a QSAR study[2] undertaken by Boger and colleagues, Ningalin B hexamethyl ether was found to have good MDR activity when used in conjunction with vinblastine or doxorubicin as compared to the use of verapamil, which is a standard MDR reversal agent.

For some years, our research group has been interested in utilizing vinylogous iminium salt derivatives[10] as key intermediates for the regioselective synthesis of heterocyclic compounds in general and highly functionalized pyrroles in particular. We have also previously reported[11] an efficient, relay synthesis of Lukianol A and related compounds by such methodology and now report extending this methodology to a convenient and efficient synthesis of Ningalin B hexamethyl ether.

Keywords: chloropropeniminium salt; β-chloroenal; trisubstituted pyrrole; Ningalin B.

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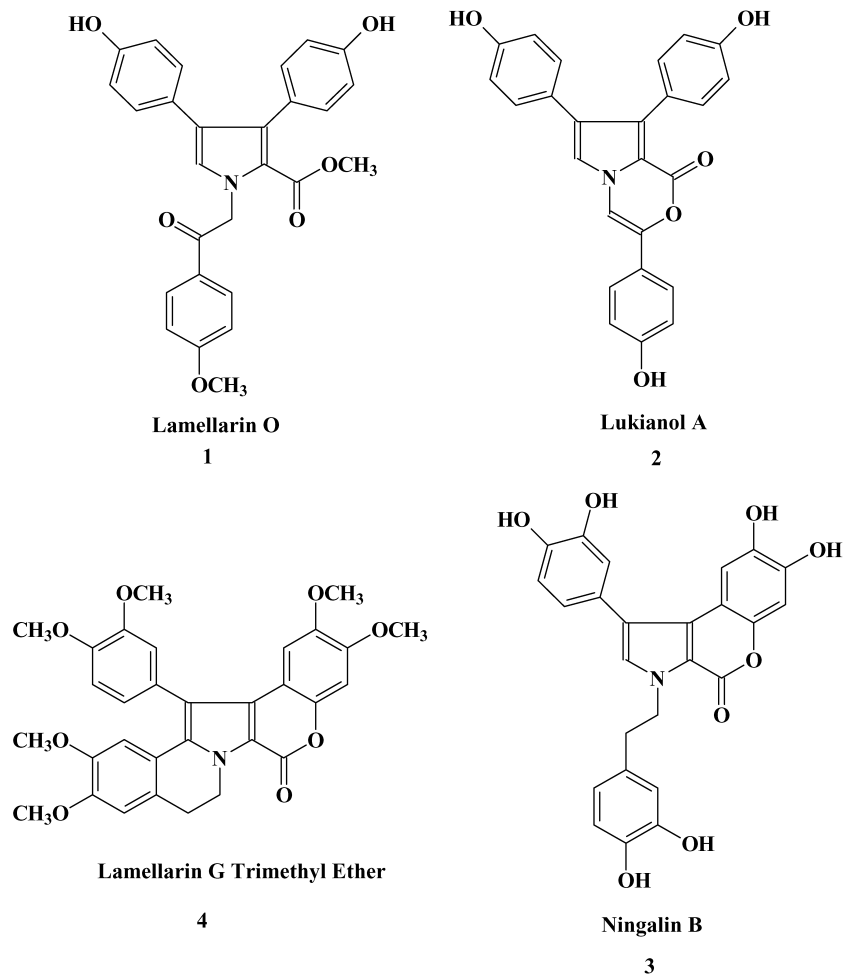
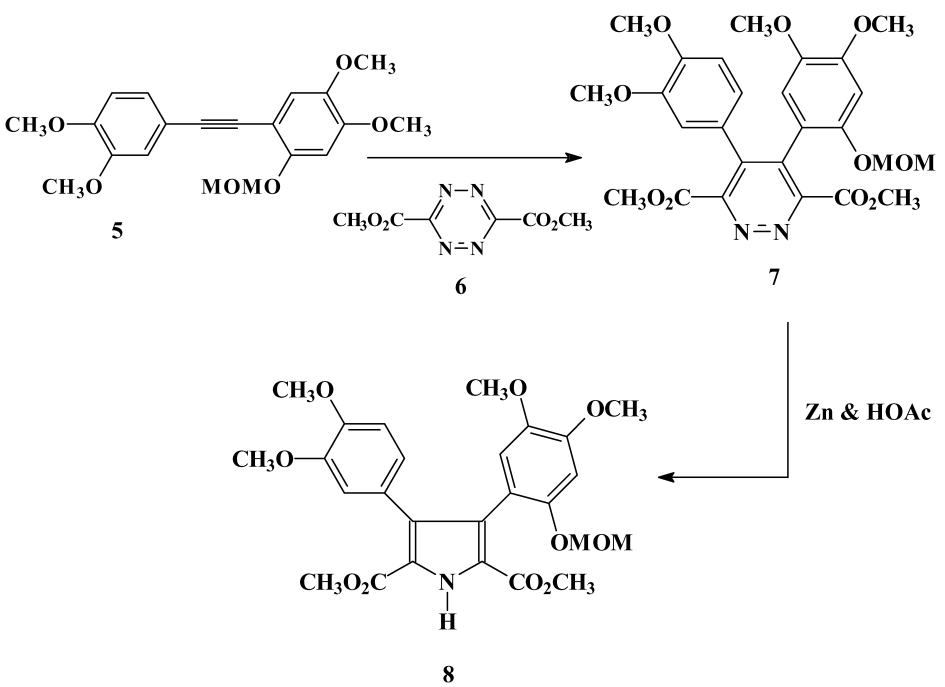
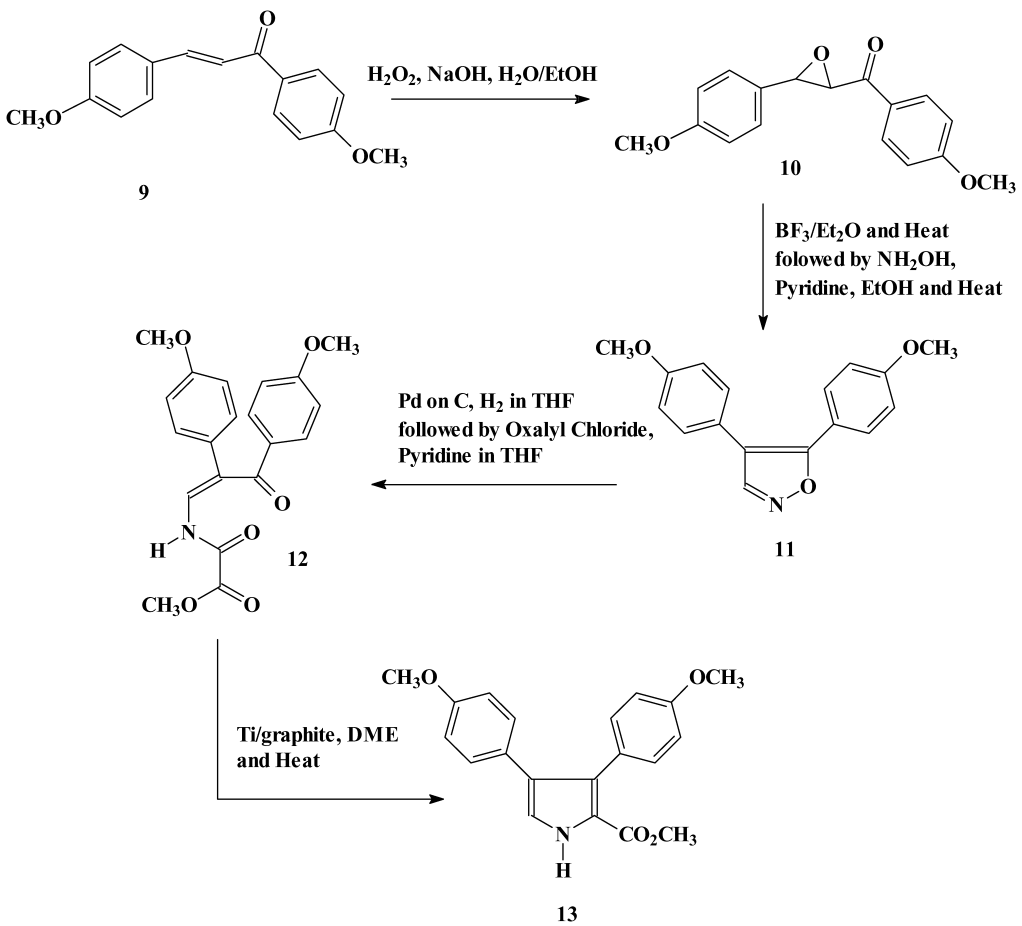


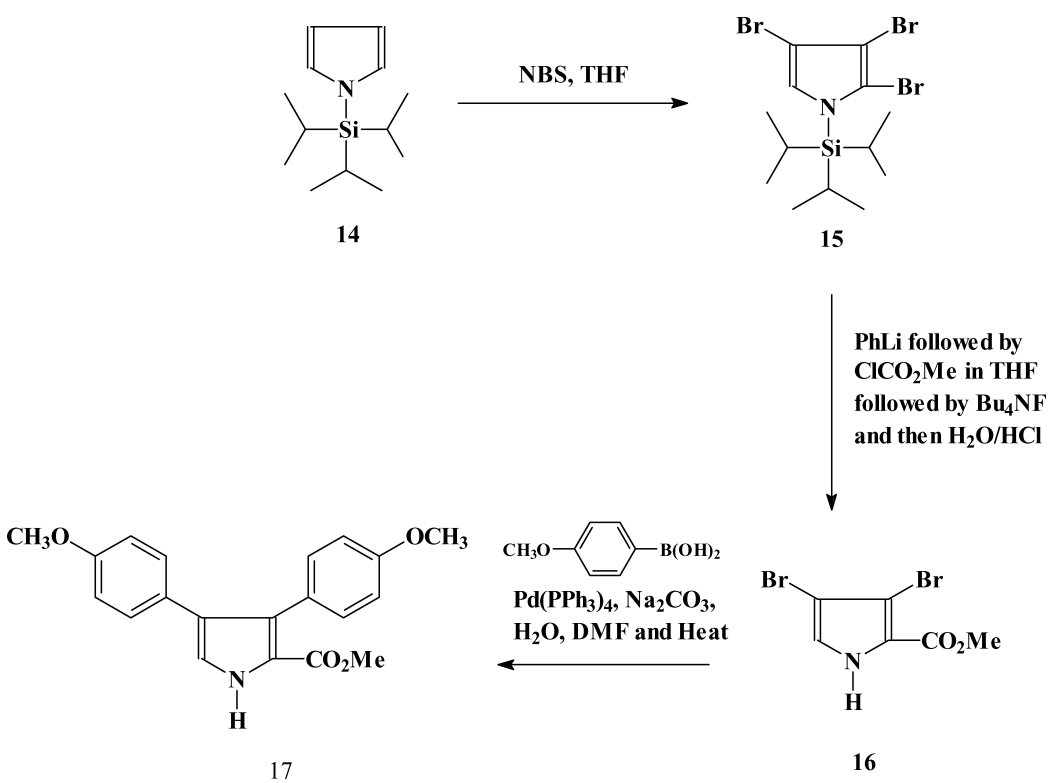
Figure 1.



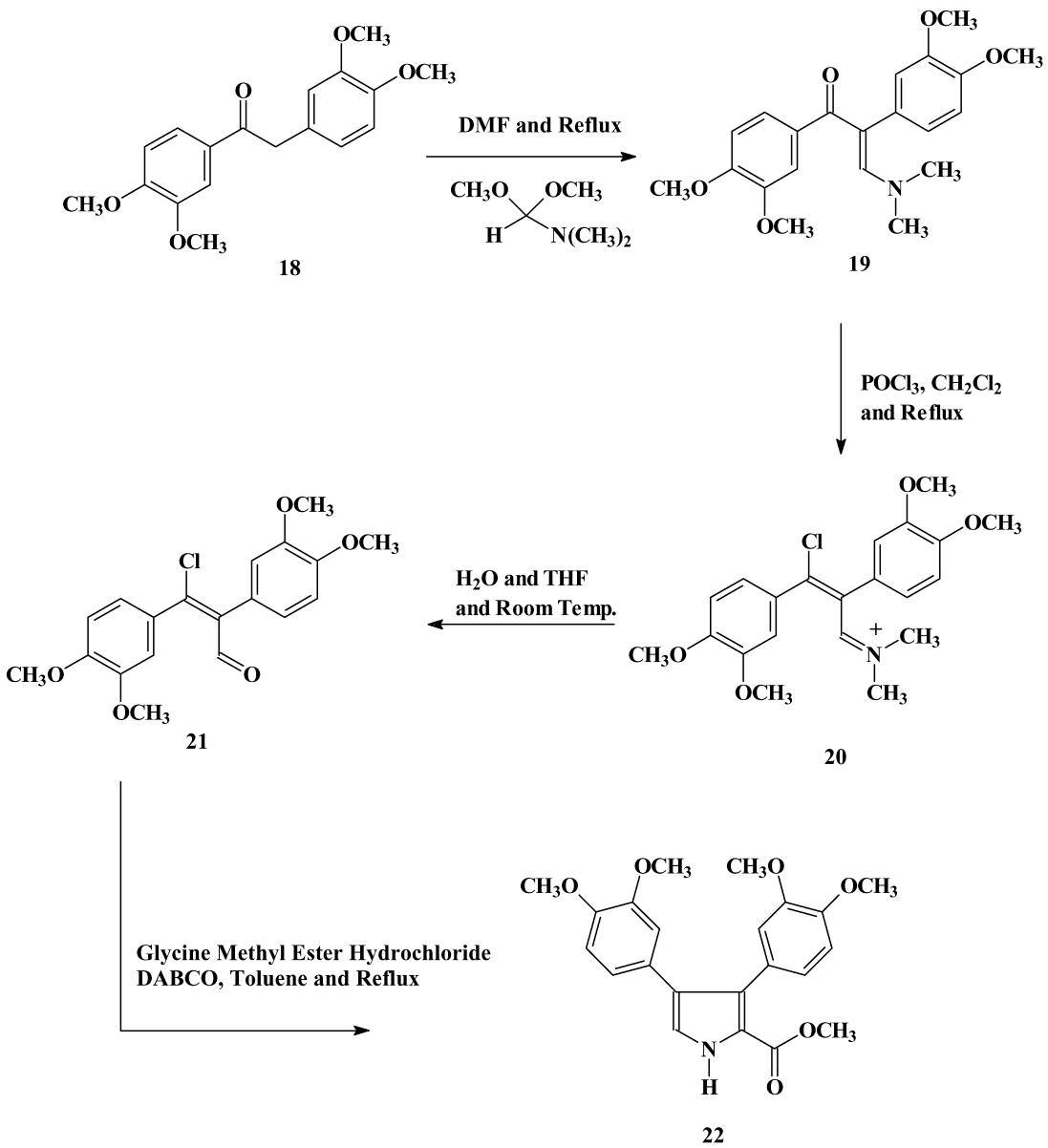
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

2. Results and discussion

Our strategy for the synthesis of Ningalin B hexamethyl ether (**32**) relies on the regioselective preparation of 2-carbomethoxy-3,4-diarylpyrroles (**22**) as outlined in Scheme 4. The starting ketone (desoxyveratroin, **18**) has been previously prepared,[12] used in a variety of applications, and is readily available by reaction of 1,2-dimethoxybenzene (veratrole) with 3,4-dimethoxyphenylacetyl chloride under Friedel–Crafts conditions.

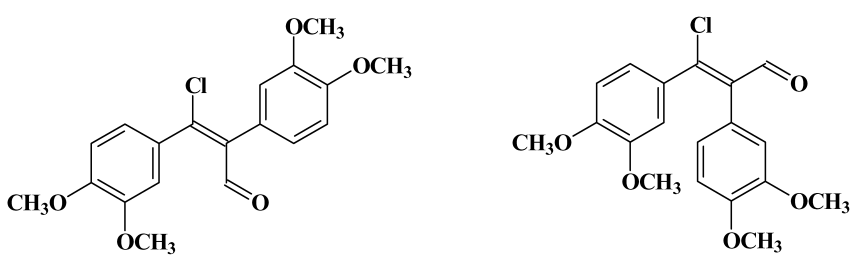
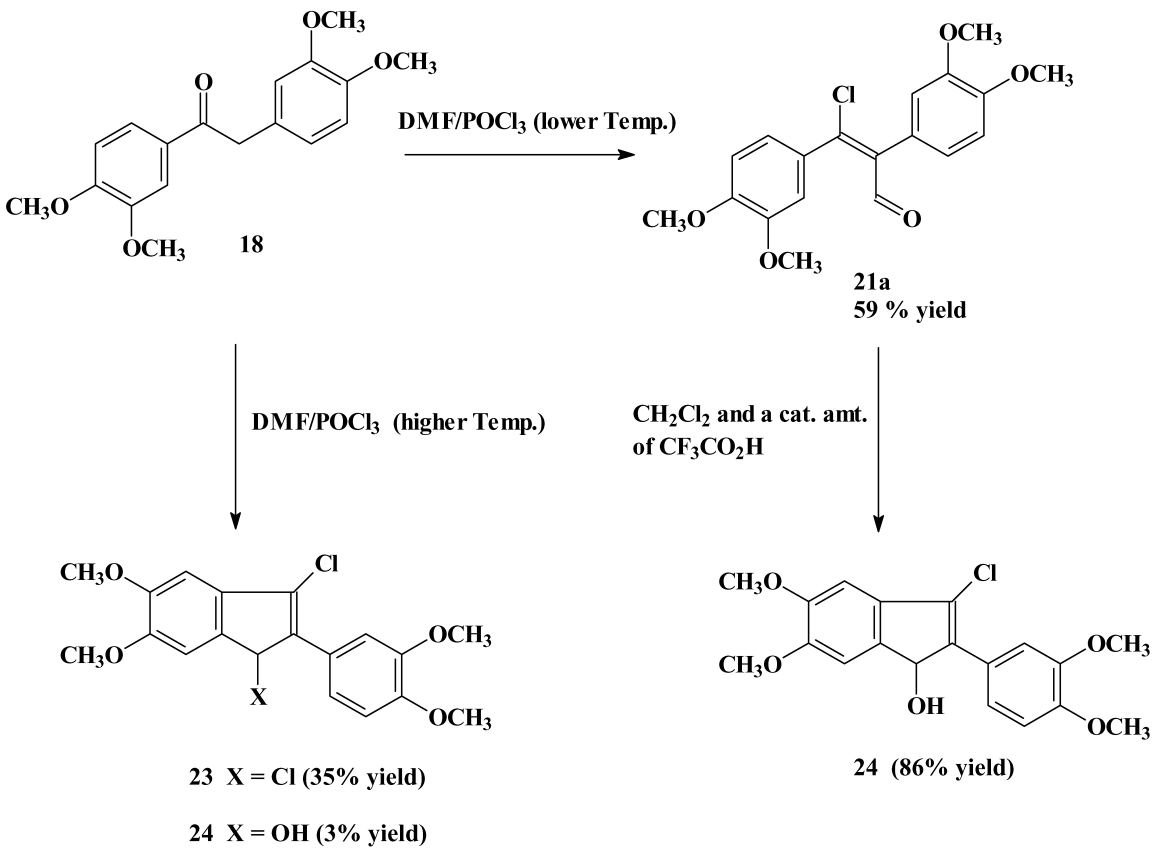
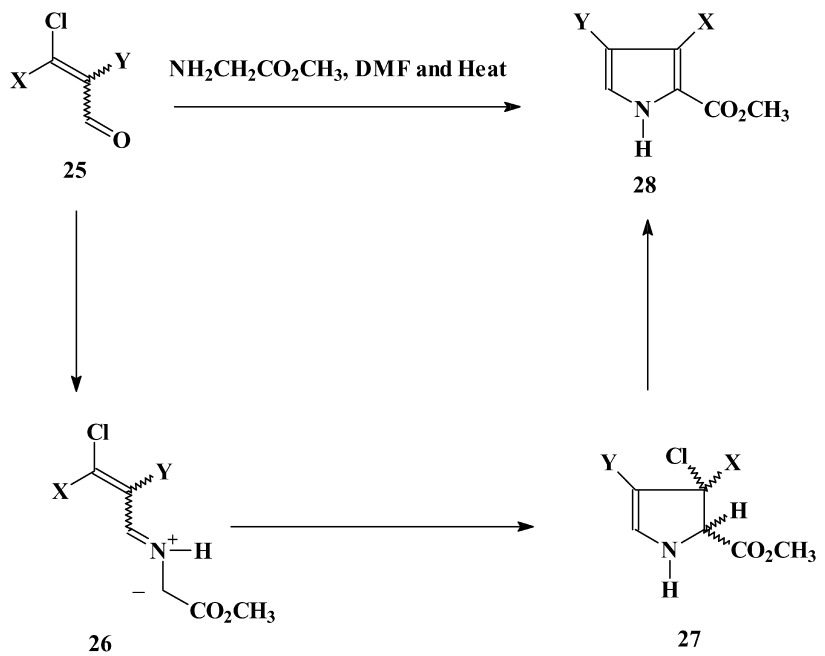


Figure 2.

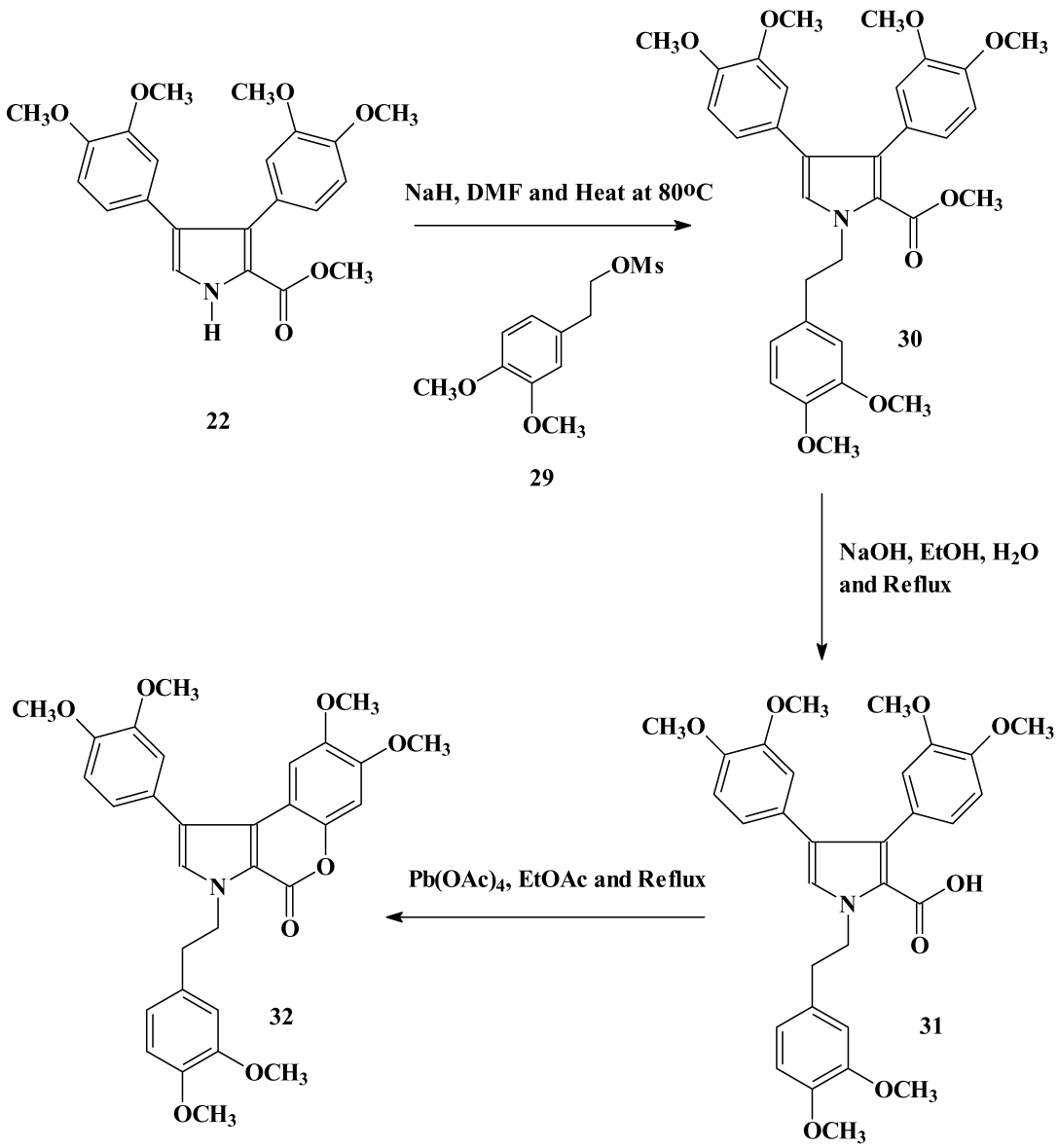


Scheme 5.

Desoxyveratroin (**18**) is then refluxed with *N*,*N*-dimethylformamide dimethyl acetal in dimethylformamide to produce the corresponding vinylogous amide (**19**) very cleanly in 78% isolated yield. This compound has been previously prepared by Dominguez and co-workers[13] in a similar fashion. The vinylogous amide was subsequently treated with phosphorous oxychloride in refluxing methylene chloride followed by water/THF in which case an initial crop of analytically pure *E*-β-chloroenal (**21a**) was obtained in 41% yield after dilution of the reaction mixture with additional water. Subsequent crystallization from the mother liquor produced a 14% yield of the *Z*-β-chloroenal (**21b**), Fig. 2.



Scheme 6.



Scheme 7.

The *E* and *Z* β-chloroenals (**21a** and **21b**, respectively) are easily differentiated from each other in the proton NMR spectrum by virtue of a larger downfield shift (~1 ppm) of the aldehyde proton when it is *cis* to the chloro group as in **21b** as opposed to being *cis* to the aromatic ring as in **21a**. Alternatively, if the crude aqueous reaction mixture is subjected to an extractive workup with ethyl acetate, a quantitative yield of *E*- and *Z*-β-chloroenals is obtained with a 4:1 ratio of *E*/*Z* isomers. Elliot and co-workers[14] have reported the preparation of the *E*-β-chloroenal (**21a**) (59% yield) directly from desoxyveratroin by reaction under Vilsmeier conditions (DMF/phosphorous oxychloride). This transformation is reported to be very temperature sensitive and can give several different products depending on the reaction conditions (Scheme 5). The *E*-β-chloroenal (**21a**) represents an interesting substrate and we have treated this compound with trifluoroacetic acid at room temperature for 3 h in methylene chloride in which case an 86% yield of analytically pure indenol (**24**) was obtained. This reaction further confirms the stereochemical assignment of the *E*-β-chloroenal (**21a**) and suggests that this substance may well be a useful synthon for a variety of indene targets as has been suggested by Elliot and co-workers.[14] In addition, the *E*-β-chloroenal (**21a**) has been the subject of a patent for use as an antiviral agent.[15]

In previous work[10] we have reacted glycinate ester hydrochlorides with analogous β-chloroenals in refluxing DMF with and without bases (sodium hydride being the base of choice). The reaction is thought to proceed in the manner depicted in Scheme 6.

Refluxing a mixture of *E*-β-chloroenal (**21a**) with glycine methyl ester hydrochloride in DMF produced the expected 2,3,4-trisubstituted pyrrole (**22**) (Scheme 4) but after evaluating a variety of solvents with and without bases, the combination of toluene and DABCO was found to give the best yields (>90%) and purity of the desired material. In the past[10] we have used mixtures of *E*- and *Z*-β-chloroenals for such pyrrole-forming reactions in which case somewhat

lower yields of the desired 2,3,4-trisubstituted pyrroles were always obtained. Reaction of the pure *Z*-β-chloroenal (**21b**) with glycine methyl ester hydrochloride under similar conditions produced a gross mixture of products suggesting that for the disubstituted β-chloroenals (**25**), the *E* isomer is uniquely preferred for pyrrole formation. In should also be noted that previous work[10] in our laboratory had established the regioselective nature of such pyrrole-forming reactions and that the 2,3,4-trisubstituted pyrrole was always produced as the major regioisomer. The overall efficiency of the reaction sequence illustrated in Scheme 4 allowed for the preparation of multigram quantities of the key pyrrole synthon (**22**). With the requisite 2,3,4-trisubstituted pyrrole (**22**) in hand, the following reaction sequence (Scheme 7) was carried out to complete the synthesis of Ningalin B hexamethyl ether.

The pyrrole synthon (**22**) was alkylated by a procedure similar to that developed by Boger and co-workers[2] with the exception that sodium hydride/DMF was used along with the mesylate ester of 2′-(3,4-dimethoxyphenyl)ethanol. A 71% yield of the *N*-phenethylpyrrole (**30**) was obtained after chromatographic purification. An excess of the mesylate ester was used in this reaction to minimize the competing elimination to the corresponding styrene. The *N*-phenethylpyrrole (**30**) was then subjected to basic hydrolysis with sodium hydroxide in aqueous ethanol producing the respective carboxylic acid (**31**) in 90% yield and in an analytically pure form. It was anticipated that the last step in the sequence could be accomplished by using lead tetraacetate (LTA) oxidation conditions, which had been developed by Steglich and co-workers[6] for a similar transformation in the preparation of Lamellarin G trimethyl ether. When the pyrrole carboxylic acid was heated with LTA in refluxing ethyl acetate, a 52% yield of Ningalin B hexamethyl ether (**32**) was obtained.[16] The Ningalin B hexamethyl ether prepared by our methodology was identical by proton and carbon NMR spectra and also IR spectra to Ningalin B hexamethyl ether prepared by Boger and co-workers.[17] The oxidative lactonization appeared to be highly regioselective but small amounts of an impurity were detected in the crude product prior to chromatography. This side product may be attributed to competing oxidation at the alternative *ortho* position of the aromatic ring at the 3-position of the pyrrole.

3. Conclusions

We have demonstrated that β-chloroenals, which are formally derived from chloropropeniminium salts, are convenient and efficient precursors to regioselectively functionalized pyrroles which are in turn precursors to marine natural product derivatives such as Ningalin B hexamethyl ether. In addition, the *E*-β-chloroenal isomer exhibited unique selectivity for the formation of the desired trisubstituted pyrrole synthon. The overall yield for the five-step, chloroenal-based synthesis (assuming the use of the Elliot procedure for the preparation of **21a**) is 18%. Since chloroenal intermediates can be easily assembled from α-substituted ketones,[10] this methodology should provide substantial flexibility for the rapid preparation of a diverse group of Ningalin B analogs. The reaction conditions employed in this methodology are very amenable to scale up so that multigram quantities of analogs could be efficiently obtained. Given that such substances exhibit the ability to act as MDR reversal agents at non-cytotoxic concentrations, our synthetic approach should complement those currently available for the synthesis of this important class of bioactive agents.

4. Experimental

4.1. General[18]

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific) and all reactions were carried out under a nitrogen atmosphere. All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were obtained on either a GE Omega 300 MHz spectrometer or a Bruker 500 MHz spectrometer in either $CDCl_3$ or d_6-DMSO solutions. IR spectra were recorded on a Nicolet Avatar 320 FTIR spectrometer with an HATR attachment. High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska at Lincoln. Melting points and boiling points are uncorrected. Radial chromatographic separations were carried out on a Harrison Chromatotron using silica gel plates of 2 mm thickness with a fluorescent backing. Flash chromatographic separations were carried out on a Biotage Horizon HFC instrument, which had been equipped with a #1542-2 silica cartridge.

4.1.1. 3′-Chloro-2′,3′-bis-(3,4-dimethoxypheny)-2-propenal (21a and 21b). Into a 250 mL flask which had been equipped with a condenser and magnetic stirring bar and had been placed under a nitrogen atmosphere was added 2.50 g (6.74 mmol) of 3′-(*N*,*N*-dimethylamino)-1′,2′-bis-(3,4-dimethoxyphenyl)-2-propen-1-one[13] (**19**) and 100 mL of dry methylene chloride. To the stirring solution was added dropwise 2.58 g (16.8 mmol) of phosphorous oxychloride and the mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo yielding a dark solid. To the solid was added 80 mL of a 1:1 solution of THF/water and this mixture was allowed to stir at room temperature for 1 h. An additional 50 mL of water was added and the solution was allowed to stir for another 30 min. The resulting solid (**21a**) (*E*-isomer, 1.00 g, 41% yield) was collected by vacuum filtration and exhibited the following properties: mp 181–182°C (lit.[14] 183–184°C); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 6.81–6.96 (m, 4H), 7.10–7.13 (m, 2H) and 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 55.9, 56.1, 110.3, 110.9, 112.5, 113.1, 122.7, 124.5, 126.6, 128.3, 139.9, 148.6, 149.0, 149.1, 151.6, 154.8 and 190.3; FTIR (neat) 1662 and 1572 cm^{-1}; HRMS calcd for $C_{19}H_{19}ClO_5$ (M+) *m/z* 362.0921 found 362.0918. The remaining filtrate was allowed to stir in an ice bath for an additional hour and the resulting solid (**21b**) (*Z*-isomer, 0.343 g, 14% yield) was collected by vacuum filtration and exhibited the following properties: mp 136–138°C; ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 3.64 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 6.49 (s, 1H), 6.56 (d, *J*=9 Hz, 1H), 6.67–6.77 (m, 3H), 7. 00 (d, *J*=9 Hz, 1H) and 10.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.6, 55.9, 56.1, 56.2, 110.3, 111.1,

112.9, 113.8, 123.3, 123.5, 126.9, 129.4, 136.0, 147.9, 148.8, 148.8, 150.1, 150.5, and 191.6; FTIR (neat) 1660 and 1592 cm^{-1}; HRMS calcd for $C_{19}H_{19}ClO_5$ (M+) *m/z* 362.0921 found 362.0909.

4.1.2. 3-Chloro-2′-(3,4-dimethoxyphenyl)-5′,6′-dimethoxy-1*H*-inden-1-ol (24). A round bottom flask was equipped with magnetic stirring and 0.22 g (0.61 mmol) of the *E*-β-chloroenal (**21a**) along with 30 mL of dry methylene chloride was placed in the flask. The mixture was cooled in an ice bath and 5 drops of trifluoroacetic acid were added and the mixture was stirred for 3 h at room temperature. The reaction mixture was extracted with saturated aqueous bicarbonate and dried over anhydrous sodium sulfate. After filtering off the drying agent and removing the solvent in vacuo, a solid (**24**) (0.19 g, 86% yield) was obtained. An analytical sample was prepared by recrystallization of a small amount of **24** from methanol and the resulting solid exhibited the following properties: mp 186–189°C (lit.[14] 189–190°C); ^{1}H NMR ($CDCl_3$) δ 1.79 (d, *J*=9 Hz, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 5.50 (d, *J*=9 Hz, 1H), 6.95–6.98 (m, 2H), 7.17 (s, 1H), 7.42 (dd, *J*=2, 9 Hz, 1H) and 7.55 (d, *J*=2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 55.9, 56.2, 56.3, 75.8, 102.8, 107.5, 111.1, 111.4, 121.4, 125.5, 133.6, 134.6, 138.9, 148.71, 148.76, 148.82 and 149.9; FTIR (neat) 3266 cm^{-1}; HRMS calcd for $C_{19}H_{19}ClO_5$ (M+) *m/z* 364.0921 found 364.0922.

4.1.3. Methyl 3′,4′-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (22). Into a 250 mL flask was placed 1.40 g (3.86 mmol) of *E*-3′-chloro-2′,3′-bis-(3,4-dimethoxyphenyl)-2-propenal (**21a**), 1.45 g (11.6 mmol) of glycine methyl ester hydrochloride and 100 mL of toluene. To the stirred suspension was added 0.66 g (5.79 mmol) of DABCO (1,4-diazbicyclo[2.2.2]octane) and the resulting mixture was heated at reflux for 24 h. The reaction mixture was allowed to cool to room temperature and was washed water (3×30 mL), with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 1.40 g (92% yield) of a yellow-brown solid (**22**) which was sufficiently pure for use in subsequent reactions. An analytical sample was prepared by subjecting a portion of the solid (**22**) to chromatography on silica gel (50:50 ethyl acetate/hexanes as the eluant). The material resulting from chromatographic purification exhibited the following properties: mp 66–68°C; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 6.57 (broad s, 1H), 6.74 (broad s, 2H), 6.83 (broad s, 3H), 7.08 (d, *J*=3 Hz, 1H) and 9.16 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.5, 55.8, 55.9, 56.0, 110.6, 111.1, 111.9, 114.4, 119.4, 120.0, 120.3, 123.3, 126.5, 126.9, 127.3, 129.0, 147.4, 148.0, 148.1, 148.4 and 161.6; FTIR (neat) 3320 and 1685 cm^{-1}; HRMS calcd for $C_{22}H_{23}NO_6$ (M+) *m/z* 397.1525 found 397.1514.

4.1.4. 3,4-Dimethoxyphenethyl methanesulfonate (29). Into a 100 mL flask was placed 0.51 g (2.74 mmol) of 3,4-dimethoxyphenethyl alcohol, 40 mL of dry methylene chloride, and 0.42 g (4.11 mmol) of dry triethylamine. The reaction mixture was cooled to 0°C and 0.38 g (3.30 mmol) of methanesulfonyl chloride was added. After stirring for 5 min. at 0°C and at room temperature for 30 min, the reaction mixture was extracted three times with 20 mL of 10% aqueous hydrochloric acid, once with 20 mL of water, once with 20 mL of brine and subsequently dried over anhydrous sodium sulfate. After filtration, and concentration in vacuo, 0.70 g (89% yield) of an oil (**29**) was obtained which was used without further purification. This compound exhibited the following physical properties: bp 168–169°C at 0.2 mm; ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3H), 3.00 (t, *J*=7 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.39 (t, *J*=7 Hz, 2H) and 6.74–6.83 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 35.0, 37.0, 55.8, 70.6, 111.5, 112.3, 121.0, 128.9, 148.0 and 149.0; FTIR (neat) 1348 and 1169 cm^{-1}; HRMS calcd for $C_{11}H_{16}SO_5$ (M+) *m/z* 260.0718 found 260.0708.

4.1.5. Methyl *N*-3,4-dimethoxyphenethyl-3′,4′-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (30). Into a 250 mL flask, which had been placed under a nitrogen atmosphere was added 0.25 g (7.55 mmol) of sodium hydride (60% dispersion in mineral oil). The sodium hydride was washed with hexane and 50 mL of dry DMF was added. A solution consisting of 1.20 g (3.02 mmol) of methyl 3,4-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylate (**22**) in 50 mL of DMF was added dropwise to the stirred suspension. The reaction mixture was allowed to stir at room temperature for 35 min and this was followed by the addition of 1.58 g (6.04 mmol) of 3,4-dimethoxyphenethyl methanesulfonate in 10 mL of DMF. The reaction mixture was heated at 70°C for 12 h, cooled to room temperature and quenched with 2 mL of methanol. The solution was poured into 100 mL of water and extracted with ethyl acetate (3×50 mL). The organic extracts were combined and washed once with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude material was subjected to chromatography on silica gel (50:50 ethyl acetate/hexanes as the eluant) to give 1.20 g (70.5% yield) of a yellow solid (**30**) which exhibited the following properties: mp 51–52°C; ^{1}H NMR ($CDCl_3$) δ 3.05 (t, *J*=7 Hz, 2H), 3.55 (s, 3H), 3.62 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.54 (t, *J*=7 Hz, 2H), 6.44 (d, *J*=2 Hz, 1H), 6.59 (d of d, *J*=2, 6 Hz, 1H), 6.69 (d, *J*=8 Hz, 1H) and 6.72–6.84 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 37.9, 50.8, 51.7, 55.4, 55.73, 55.76, 55.81, 55.85, 55.91, 110.5, 111.0, 111.4, 111.6, 112.2, 114.3, 119.1, 120.0, 120.9, 123.0, 123.8, 126.2, 127.3, 128.6, 130.0, 131.0, 147.2, 147.7, 148.1, 148.3, 148.8 and 162.1; FTIR (neat) 1685 cm^{-1}; HRMS calcd for $C_{32}H_{35}NO_8$ (M+) *m/z* 561.2363 found 561. 2347.

4.1.6. *N*-3,4-Dimethoxyphenethyl-3′,4′-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylic acid (31). Into a 250 mL flask was placed 1.03 g (1.85 mmol) of methyl *N*-3,4-dimethoxyphenethyl-3′,4′-bis(3,4-dimethoxyphenyl)-pyrrole-2-carboxylate (**30**) and 125 mL of ethanol. After stirring for several minutes, the mixture became homogeneous and 0.29 g (7.34 mmol) of sodium hydroxide in 125 mL of water was added. The resulting reaction mixture was heated at reflux for 16 h, cooled to room temperature and made acidic with 6 M hydrochloric acid. The mixture was stirred in an ice/water bath followed by the slow addition of 200 mL of water. A yellow solid crystallized, which was vacuum filtered and air dried, to yield 0.90 g (90% yield) of an orange solid (**31**) which was sufficiently pure for use in subsequent reactions. An analytical sample was prepared by subjecting a portion of the solid (**31**) to

recrystallization from methanol in which case the resulting material exhibited the following properties: mp 79–80°C; ^{1}H NMR ($CDCl_3$) δ 3.06 (t, J=8 Hz, 2H), 3.57 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.56 (t, J=8 Hz, 2H), 6.42 (d, J=2 Hz, 1H), 6.56 (d of d, J=2.5, 9 Hz, 1H), 6.60 (d, J=2 Hz, 1H), 6.69 (d, J=9 Hz, 1H), 6.75 (d of d, J=2, 9 Hz, 1H) and 6.79–6.89 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 37.8, 52.2, 55.4, 55.6, 55.7, 55.8, 55.9, 110.8, 111.0, 111.4, 111.5, 112.1, 114.3, 117.9, 120.0, 120.9, 123.1, 124.2, 126.9, 127.7, 130.9, 132.4, 147.3, 147.8, 148.3, 148.4, 148.5, 148.9 and 164.7; FTIR (neat) 3343, 1689 and 1646 cm^{-1}; HRMS calcd for $C_{31}H_{33}NO_8$ (M+) m/z 547.2206 found 547.2232.

4.1.7. Ningalin B hexamethyl ether (32). Into a 100 mL flask which had been placed under a nitrogen atmosphere was added 0.200 g (0.365 mmol) of *N*-3,4-dimethoxyphenethyl-3′,4′-bis-(3,4-dimethoxyphenyl)pyrrole-2-carboxylic acid (**31**) and 40 mL of ethyl acetate. LTA (0.94 g, 0.213 mmol) was added in one portion and the reaction mixture was heated at reflux for 5 h. The solution was allowed to cool to room temperature, filtered through a small plug of 50/50 celite/silica gel and washed twice with 20 mL of 20% aqueous citric acid solution. After extraction with brine and drying over anhydrous sodium sulfate, the ethyl acetate solution was filtered, and concentrated in vacuo to give 0.12 g (52% yield) of a yellow solid. An analytical sample was prepared by subjecting the yellow solid to flash chromatography[16] (ethyl acetate/hexane mobile phase with gradient elution) to give a pale yellow (**32**) solid which exhibited the following physical properties; mp 183–187°C (lit.[2] 186–187°C); ^{1}H NMR ($CDCl_3$) δ 3.11 (t, J=7 Hz, 2H), 3.56 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.65 (t, J=7 Hz, 2H), 6.58 (d, J=1.5 Hz, 1H), 6.70 (dd, J=8, 2 Hz, 1H), 6.74 (s, 1H), 6.79 (d, J=8 Hz, 1H), 6.88 (d, J=1.4 Hz, 1H), 6.92–6.96 (m, 3H), and 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.8, 51.0, 55.8, 55.9, 56.0, 56.1, 100.6, 104.8, 110.4, 111.1, 111.3, 112.1, 113.1, 114.9, 119.1, 120.0, 122.1, 126.7, 127.2, 130.6, 131.9, 145.6, 146.2, 147.8, 148.6, 148.8, 148.9, 149.1 and 155.5; MS (M+) m/z 545.

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18. All purified compounds gave a single spot upon tlc analysis on silica gel 7GF using an ethyl acetate/hexane mixture as eluent. All purified compounds gave ^{13}C NMR and ^{1}H NMR spectra indicative of compounds >95% pure.