Efficient Syntheses of 2-Carbomethoxy-3,4-Disubstituted Pyrroles by the Condensation of Vinylogous Amides with Aminomalonate

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There has been growing interest in the syntheses of pyrrole containing marine natural products (Figure 1) such as ningalins (**1**),[1] polycitone,[2] storniamides,[3] lukianols (**2**),[4] and lamellarins (**3**)[5,6] due to their interesting biological activities. Among them, lamellarins are one of the rapidly growing classes of marine natural products, and more than thirty lamellarins have been identified since their first isolation[5] from the prosobranch mollusk *Lamellaria* sp. in 1985.

The common structural feature of these natural products is a 3,4-diaryl-substituted pyrrole bearing 2- or 2,5-carboxylates. The efficient preparation of this pyrrole is the main theme reported in the literature.[7-17] Among many synthetic approaches, Boger *et al.* recently reported the synthesis of various pyrrole containing marine natural alkaloids and their analogues based on a common heterocyclic azadiene Diels-Alder strategy.[7,8] Fürstner *et al.* employed a titanium-induced ring closure reaction to construct the pyrrole (**4**) from the appropriately substituted vinylogous amide.[9] Banwell[11] and Wong[16] also synthesized the Fürstner synthon (**4**) by using Stille type coupling reactions between the appropriately functionalized aryl compounds and pyrroles. Gupton *et al.* reported a synthetic method for preparing the same synthon (**4**) utilizing a vinylogous iminium salt derivative that was prepared from the vinylogous amide (**6**, Scheme 1).[17,18] The vinylogous iminium salt was condensed with a glycine ester in basic conditions (NaH/DMF) to give **4** in 77% yield. Their attempts of synthesizing **4** by cyclocondensation between the vinylogous amide (**6**) and glycine methyl ester were unsuccessful under either acidic or basic conditions.

Despite numerous approaches for synthesizing 3,4-diaryl-substituted pyrroles, our aim was to develop a more efficient and flexible route in order to generate a pyrrole library containing marine natural alkaloids and their analogues. We turned our attention to the vinylogous amide (**6**) and commercially available dimethyl aminomalonate hydrochloride as building blocks for pyrrole systems. The condensation of aminomalonates with the 1,3-dicarbonyl compounds has been used for preparing substituted pyrroles.[19-22] However, as far as we know, the cyclocondensation of aminomalonates with vinylogous amides has not been reported.[23] Herein we report our findings that the vinylogous amides react with dimethyl aminomalonate hydrochloride to form the 2-carbomethoxy-3,4-disubstituted pyrroles (Scheme 1).

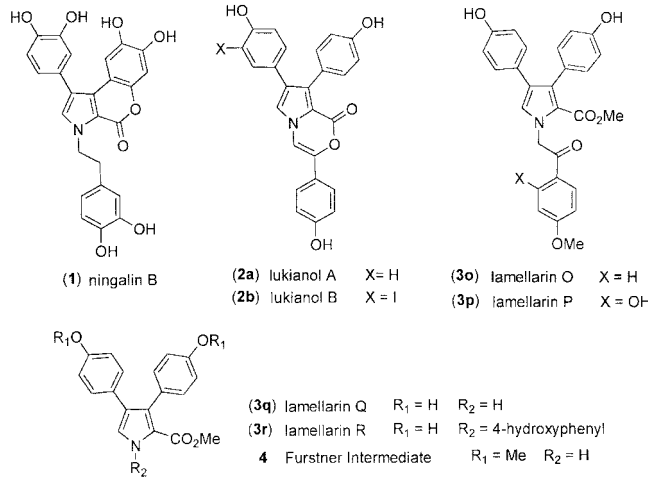
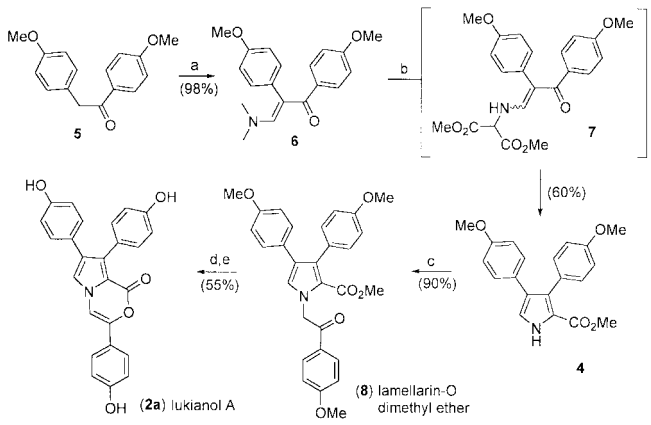


Figure 1. Structures of representative pyrrole containing marine natural products.



Scheme 1. Reagents and conditions: (a) 4 equiv. *N*,*N*-dimethylformamide dimethyl acetal, toluene, reflux, 16 h; (b) dimethyl aminomalonate hydrochloride, AcOH (0.5 M), rt, 1 h; then AcOH (0.02 M), reflux, 12 h; (c) 4-$MeOC_6H_4COCH_2Br$, K_2CO_3, acetone, 70 °C, 4 h; (d) *t*-BuOK, H_2O, Et_2O, 0 °C to rt; then Ac_2O, NaOAc, reflux, 3 h; (e) BBr_3, CH_2Cl_2, -78 °C to rt, 12 h.

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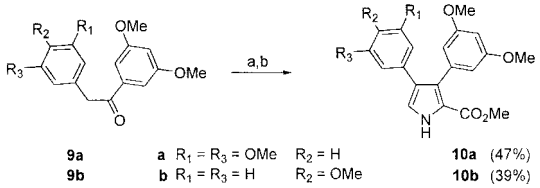
The requisite vinylogous amide (**6**) was readily prepared in 98% yield from commercially available desoxyanisoin (**5**) with *N,N*-dimethylformamide dimethyl acetal (4 equiv., toluene, reflux, 16 hr) as literature procedure.[17,24] The cyclocondensation reaction was simply carried out by stirring the high concentration (0.5 M) solution of equimolar mixtures of the vinylogous amide (**6**) and dimethyl aminomalonate hydrochloride in acetic acid at room temperature for 1 hr to yield the presumed intermediate (**7**)[25] *via* an acid-catalyzed nucleophilic substitution reaction. The mixture was then diluted with additional acetic acid to 0.02 M and heated under reflux for 12 hr to facilitate the intramolecular ring closure of **7**, and the loss of the methoxycarbonyl moiety producing the desired pyrrole (**4**) in 60% yield after silica gel column purification. The ^{1}H and ^{13}C NMR spectral data of the obtained pyrrole (**4**) were in good agreement with the reported.[9,16] Acetic acid was found to be the preferable diluting solvent for this transformation. Other solvents such as DMF, DMA, benzene, toluene, acetonitrile, and water resulted in low yields (less than 5%).

Taking into consideration the synthetic utility for a pyrrole library construction, we believe that our approach is more suitable and efficient than Guptons. Although our one-step transformation (from **6** to **4**) resulted in lower yield (60%) compare to Guptons two step sequence (70%), our procedure offers advantages over previous one: (i) experimental convenience, since it does not require the anhydrous reaction conditions (NaH/DMF), and (ii) removal of the vinylogous iminium salt formation step.

This simple sequence could also be applied to different α-aryl ketones. Treatments of **9a** and **9b**[26] in a similar manner provided the corresponding diaryl-substituted pyrroles (**10a** and **10b**) with modest overall yields as shown in Scheme 2.

The obtained pyrrole (**4**) could be converted to lamellarin *O*-dimethyl ether (**8**) and lukianol A (**2a**) by employing the precedent procedure.[9,16] *N*-Alkylation of **4** with *p*-methoxyphenacyl bromide provided lamellarin *O*-dimethyl ether (**8**) in 90% yield. Hydrolysis of the methyl ester of **8** and subsequent treatment with Ac_2O/NaOAc, followed by demethylation with BBr_3 led to the formation of lukianol A (**2a**) in a 55% overall yield.

In conclusion, the chemistry described herein provides an efficient synthetic method for 2-carbomethoxy-3,4-diaryl-substituted pyrroles. The vinylogous amides, which are readily prepared from α-aryl ketones and *N,N*-dimethylformamide dimethyl acetal, react with dimethyl aminomalonate hydrochloride to form the 2-carbomethoxy-3,4-diaryl-substituted pyrroles. Further application of this methodology to various types of 2-carbomethoxy-3,4-disubstituted pyrrole synthesis is now under investigation.



Scheme 2. Reagents and conditions: (a) 4 equiv. *N,N*-dimethylformamide dimethyl acetal, toluene, reflux, 16 h; (b) dimethyl aminomalonate hydrochloride, AcOH (0.5 M), rt, 1 h; then AcOH (0.02 M), reflux, 12-16 h.

Experimental Section

General. NMR spectra were recorded on Varian instrument (^{1}H NMR: 300 MHz and ^{13}C NMR: 75 MHz) with the solvent peak as internal references. All chemicals were reagent grade and used as purchased. All non-aqueous reactions were carried out under an argon atmosphere in dry solvents, unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) using E. Merck silica gel plates 60 F_{254}. The spots were detected under UV light (254 nm and 366 nm). Flash column chromatography was conducted on E. Merck silica gel 60-particle size 0.04-0.063 mm.

General procedure for the syntheses of vinylogous amides. To a solution of α-aryl ketone (5.35 mmol) in toluene (27 mL) was added *N,N*-dimetylformamide dimethyl acetal (2.84 mL, 21.4 mmol). The solution was heated to reflux under argon atmosphere for 16 h. The solvent was removed under a reduced pressure to yield a yellow solid. The solid was recrystallized using hexane/ethyl acetate (4 : 1) to afford pure vinylogous amide.

3-Dimethylamino-1,2-bis-(4-methoxy-phenyl)-propenone (6). Yield = 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (s, 6H), 3.79 (s, 6H), 6.76 (dt, 2H, J = 9.0, 2.4 Hz), 6.80 (dt, 2H, J = 8.7, 2.4 Hz), 7.05 (dt, 2H, J = 8.7, 2.4 Hz), 7.35 (s, 1H), 7.42 (dt, 2H, J = 9.0, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.2 (2C), 55.1, 55.2, 111.3, 112.7 (2C) 113.1 (2C), 129.9, 130.9 (2C), 132.9 (2C), 134.2, 153.1, 158.0, 164.5, 194.0; IR (KBr) 2835, 1603, 1583, 1560, 1506, 1385, 1296, 1248, 1170 cm^{-1}; MS (EI) *m/z* 311 (M^+, 54), 294 (58), 146 (34), 135 (100), 92 (46), 77 (83).

1,2-Bis-(3,5-dimethoxy-phenyl)-3-dimethylamino-propenone. Yield = 99%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.71 (s, 6H), 3.67 (s, 12H), 6.27 (br s, 3H), 6.36 (t, 1H, J = 2.4 Hz), 6.56 (d, 2H, J = 2.4 Hz), 7.27 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.3 (2C), 55.3 (2C), 55.4 (2C), 99.0, 102.1, 106.5 (2C), 106.8, 110.3 (2C), 111.6, 139.2, 143.7, 153.8 (2C), 160.1 (2C), 194.1; IR (KBr) 2935.9, 1591.4, 1456.4, 1423.6, 1386.9, 1304.0, 1203.7, 1155.5, 1062.9 cm^{-1}; MS (EI) *m/z* 371 (M^+, 100), 354 (76), 344 (65), 316 (48), 234 (16), 165 (100), 137 (50), 122 (39).

1-(3,5-Dimethoxy-phenyl)-3-dimethylamino-2-(4-methoxy-phenyl)-propenone. Yield = 97%; ^{1}H NMR (300 MHz, acetone-d_6) δ 2.74 (s, 6H), 3.72 (s, 6H), 3.77 (s, 3H), 6.42 (t, 1H, J = 2.4 Hz), 6.53 (d, 2H, J = 2.4 Hz), 6.83 (dt, 2H, J = 9.0, 2.4 Hz), 6.83 (dt, 2H, J = 9.0, 2.4 Hz), 7.30 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 43.5 (2C), 55.4, 55.6 (2C), 101.9, 107.2 (2C), 111.6, 113.6 (2C), 130.8, 134.0 (2C), 145.5, 154.0 (2C), 159.1, 161.0, 193.6; IR (KBr) 2934.0, 1631.9, 1572.1, 1512.3, 1423.6, 1385.0, 1309.8, 1242.3, 1203.7, 1153.5, 1061.0 cm^{-1}; MS (EI) *m/z* 341 (M^+, 100), 324 (90), 314 (63), 286 (60), 204 (21), 165 (100), 121 (68).

General procedure for the syntheses of 2-carbomethoxy-3,4-disubstituted pyrroles. To a solution of 0.64 mmol of vinylogous amide in 1.2 mL of glacial acetic acid (0.5 M) was added 0.64 mmol of dimethyl aminomalonate hydrochloride. The resulting mixture was stirred at room temperature under argon atmosphere for 1 h. Then the mixture was diluted with 31 mL of glacial acetic acid (0.02 M) and heated to reflux for 12 h. After it was cooled to ambient temperature, the acetic acid was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (40 mL) and washed with saturated sodium bicarbonate solution. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Final purification was accomplished by column chromatography using hexane/ethyl acetate (4 : 1 to 3 : 1) as eluent.

3,4-Bis-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic acid methyl ester (4). Yield = 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.77 (s, 3H), 3.82 (s, 3H), 6.75 (dt, 2H, *J* = 9.0, 2.4 Hz), 6.85 (dt, 2H, *J* = 9.0, 2.4 Hz), 7.02 (d, 1H, *J* = 3.0 Hz), 7.03 (dt, 2H, *J* = 8.7, 2.4 Hz), 7.25 (dt, 2H, *J* = 8.7, 2.4 Hz), 9.26 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.2, 55.09, 55.12, 77.2, 113.0 (2C), 113.6 (2C), 119.3, 120.1, 126.4, 127.0, 129.0, 129.4 (2C), 131.8 (2C), 158.0, 158.4, 161.5; IR (KBr) 3308, 1676, 1612, 1533, 1442, 1381, 1248 cm^{-1}; MS (EI) *m/z* 337 (M^+, 29), 305 (100), 290 (23), 69 (27), 57 (62), 55 (60).

3,4-Bis-(3,5-dimethoxy-phenyl)-1*H*-pyrrole-2-carboxylic acid methyl ester (10a). Yield = 47%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (s, 6H), 3.62 (s, 6H), 3.65 (s, 3H), 6.19 (t, 1H, *J* = 2.4 Hz), 6.24 (d, 2H, *J* = 2.4 Hz), 6.33 (t, 1H, *J* = 2.4 Hz), 6.39 (d, 2H, *J* = 2.4 Hz), 7.02 (d, 1H, *J* = 3.3 Hz), 9.40 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.4, 55.1 (2C), 55.3 (2C), 98.8, 99.6, 119.7, 120.3, 126.4, 129.1, 136.1, 136.3, 160.0 (2C), 160.4 (2C), 161.5; IR (KBr) 3298, 2930, 1682, 1595, 1552, 1442, 1379, 1263, 1240, 1203, 1155 cm^{-1}; MS (EI) *m/z* 397 (M^+, 100), 365 (100), 364 (25), 346 (9), 226 (19), 183 (22).

3-(3,5-Dimethoxy-phenyl)-4-(4-methoxy-phenyl)-1H-pyrrole-2-carboxylic acid methyl ester (10b). Yield = 39%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 6H), 3.66 (s, 3H), 3.68 (s, 3H), 6.33 (t, 1H, *J* = 2.4 Hz), 6.36 (d, 2H, *J* = 2.4 Hz), 6.68 (dt, 2H, *J* = 8.7, 2.4 Hz), 6.95-7.00 (m, 3H), 9.22 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.3, 55.1, 55.2 (2C), 99.5, 108.9 (2C), 113.6 (2C), 119.4, 120.0, 126.4, 126.9, 128.9, 129.3 (2C), 136.2, 149.4, 158.0, 159.9, 161.6; IR (KBr) 3265, 1718, 1612, 1439, 1377, 1292, 1224, 1153 cm^{-1}; MS (EI) *m/z* 367 (M^+, 100), 335 (100), 320 (6), 168 (12), 149 (18).

Lamellarin *O* Dimethyl Ether (8).[9,16] A suspension of pyrrole **4** (15 mg, 0.044 mmol), 4-methoxy phenacylbromide (20.5 mg, 0.088 mmol), and K_2CO_3 (52 mg, 0.37 mmol) in acetone was heated at 70 °C for 4 h under Ar. Filtration of the salts and evaporation of the solvents, followed by flash column chromatography using hexane/ethyl acetate (3 : 1) as eluent offered **8** in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 5.67 (s, 2H), 6.65 (dt, 2H, *J* = 8.7, 2.4 Hz), 6.75 (dt, 2H, *J* = 8.7, 2.4 Hz), 6.86 (s, 1H), 6.89-6.97 (m, 4H), 7.09 (dt, 2H, *J* = 8.7, 2.4 Hz), 7.96 (dt, 2H, *J* = 9.0, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.8, 55.1, 55.50, 55.54, 112.8 (2C), 113.5 (2C), 114.1 (2C), 119.8, 124.7, 127.0, 127.1, 127.90, 127.93, 129.4 (2C), 130.3 (2C), 131.1, 131.4, 131.8 (2C), 157.8, 158.2, 162.3, 164.0, 191.8; IR (KBr) 2924, 1689, 1603, 1441, 1244, 1172 cm^{-1}; MS (EI) *m/z* 485 (M^+, 86), 350 (42), 290 (10), 135 (100), 107 (12), 77 (15).

Lukianol A (2a).[9,16] To a susupension of *t*-BuOK (40 mg, 0.36 mmol) in Et_2O (2 mL) was added H_2O at 0 °C under Ar. After stirring for 5 min, to it was added the solution of **8** (17 mg, 0.035 mmol) in Et_2O (2 mL). The reaction mixture was stirred at rt for 1 hr, then quenched with water (5 mL). The organic layer was separated. After acidification of the aqueous layer with 1 N HCl, it was extracted with Et_2O and CH_2Cl_2. The combined organic layers were dried and concentrated. The residue was dissolved in Ac_2O (3 mL) and NaOAc (60 mg) was added. The reaction mixture was heated to reflux for 3 h. After it was cooled to ambient temperature, the acetic acid was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and washed with saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography to give a white solid (11 mg). To a solution of above solid (11 mg) in CH_2Cl_2 (2 mL) was added the 1.0 M solution of BBr_3 in CH_2Cl_2 (0.2 mL) at -78 °C under Ar, and the reaction was allowed to warm to rt over 12 h. Dilution with EtOAc and water, followed by standard workup and silica gel column chromatography gave **2a** (7.9 mg, 55% from **8**) as a white solid. ^{1}H NMR (d_6-DMSO) δ 6.66 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.59 (s, 1H), 8.06 (s, 1H), 9.44 (br. s, 2H), 9.83 (br. s, 1H); ^{13}C NMR (d_6-DMSO) δ 103.2, 112.2, 114.8, 115.3, 116.1, 120.4, 121.7, 123.4, 124.2, 125.8, 127.6, 129.0, 129.7, 140.0, 141.1, 153.8, 156.6, 156.7,158.8; HRMS calcd for $C_{25}H_{17}NO_5$ (M^+) 411.1107, found 411. 1112.

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25. The rather unstable presumed intermediate (**7**) could be isolated from the reaction mixture by rapid silica gel column chromatography, then transformed into the pyrrole (**4**) in boiling acetic acid with a lower overall yield (*ca.* 25-30%). The full characterization of **7** is not an easy task due to its unstability.
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