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Divergent and Selective Functionalization of 2-Formylpyrrole and its Application in the Total Synthesis of the Aglycone Alkaloid Pyrrolemarumine

Eder I. Martínez-Mora,‡ Miguel A. Caracas,‡ Carlos H. Escalante, Damian A. Madrigal, Héctor Quiroz-Florentino, Francisco Delgado, and Joaquin Tamariz*

Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prolongación de Carpio y Plan de Ayala S/N. 11340, México, D.F., Mexico
Fax: +5255-5729-6300/46211; E-mail: jtamarizm@gmail.com; jtamariz@woodward.encb.ipn.mx;† Equivalent contributions
* Corresponding author

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Abstract. Diverse 1,2- and 1,2,5-substituted pyrroles were efficiently prepared through a regioselective functionalization of 2-formylpyrrole (5a). This methodology was applied for the first total synthesis of pyrrolemarumine (4b), the aglycone of the corresponding natural pyrrole alkaloid 4”-O-α-L-rhamnopyranoside. The synthesis of 4b was achieved starting from 5a through a seven-step process in 28% overall yield.

Key words: 2-formylpyrrole; Vilsmeier-Haack formylation; pyrrole alkaloids; pyrrolemarumine.

Introduction

Pyrroles are ubiquitous five-membered heterocycles forming part of the structure of a large number of natural products [1] and pharmacologically active compounds [2]. Alkaloids isolated from diverse natural sources, such as higher order plants [3] and marine species [4] display a substituted single pyrrolic ring or pyrrole-fused polycyclic or heterocyclic scaffolds, which are distinguished by their strong antibacterial, anticancer, antifeedant and antiviral activity.

Pyrrole-2-aldehyde derivatives represent a unique variety of alkaloid natural products isolated from fungi, microorganisms, plants, and edible fruits, among other natural sources. For example, jiangrines A-E (1a-e) and pyrrolezanthine (1f), which exhibit anti-inflammatory activity, were isolated from the fermentation broth of Jiangella gansuensis (Fig. 1) [5]. Fusarine (1g) is a naturally occurring 2-acyl pyrrole isolated from the culture broth of Fusarium incarnatum (HKI0504), an endophytic fungus of the mangrove plant Aegiceras corniculatum [6]. Makomotines 2a-c were isolated from an edible gall called Makomotake (Zizia latifolia infected with Ustilago esculenta) found in Japan, China and other Asian countries [7]. Pyrrole alkaloids 2d-g have been isolated from an extract of the fruits of Lycium chinense Miller (Solanaceae), which is used as a traditional tonic medicine for treating liver and kidney failures [8]. From the seeds of watermelon (Citrullus lanatus (Thunb.)), 2-formyl pyrroles 3a-b were isolated that exhibit modest inhibitory activity on melanogenesis [9]. The naturally occurring pyrrole alkaloid pyrrolemarumine 4”-O-α-L-rhamnopyranoside (4a), recently isolated from leaves of Moringa oleifera Lam., was hydrolyzed to yield the new aglycone pyrrolemarumine (4b) [10] (Fig. 2). Despite their potential biomedical properties and relatively simple structure, the synthesis for most of these unusual 1,2- and 1,2,5-substituted pyrrole alkaloids has not yet been reported [11]. Therefore, a synthetic approach to any of these compounds needs to be designed on the basis of the selective functionalization of pyrrole or 2-formylpyrrole (5a).

The structure and promising pharmacological profile of these compounds fits well into our ongoing research program of carrying out the transformation of simple five-membered heterocycles into fine chemicals and more complex natural products [12]. Hence, we herein investigated the reactivity of 2-formylpyrrole (5a) as the key starting material for the synthesis of a series of 1,2- and 1,2,5-trisubstituted pyrroles, as well as in the first total synthesis of compound 4b.

Results and discussion

Synthesis of 1,2-Disubstituted Pyrroles

2-Formylpyrrole (5a) was used as the starting material for the divergent synthesis [13] of novel 1,2-substituted pyrrole...
derivatives of the ethyl 3-acrylates 7a-e, methyl acrylates 8a-b and acrylonitriles 9a-b (Scheme 1). These vinylogous electron-deficient pyrroles were selected because they may be applied as potential precursors for the preparation of more complex and polysubstituted pyrroles as HMG-CoA reductase inhibitors [14], whose pharmacological activity is also found in our potent hypolipidemic compounds [15].

Previous studies have reported the direct N-alkylation by NaH-promoted deprotonation of commercially available 5a with diverse primary alkyl halides to furnish the series of 1-substituted 2-formylpyrroles [16]. This method was also useful for the preparation of the series of new 1,2-substituted pyrroles 7-9 starting from 5b-d, which are the Horner-Wadsworth-Emmons derivatives of 5a. Thus, under mild reaction conditions, pyrroles 7a-e were synthesized in high yields (Scheme 1). Pyrrole 7c was prepared in a single-step procedure by using 5b, propargyl bromide (6a) and an excess of NaH. Similarly, in the case of methyl acrylate 5c, the reaction with 6a provided either N-propargyl pyrrole 8a or N-allenyl pyrrole 8b in high yields. The latter was generated by direct isomerization of 8a or through the cascade alkylation of 5c with 6a in the presence of an excess of NaH, similar to 7c. Likewise, N-alkylation of 3-(pyrrole-2-y)acrylonitrile (5d) led to N-substituted pyrroles 9a-b in good yields, under similar mild reaction conditions.

**Regioselective Synthesis of 1,2,5-Substituted Pyrroles**

Evaluation of the reactivity and regioselectivity of the formylation of pyrroles 7 was exemplified by using pyrroles 7a-c. Thus, the latter were formylated under the usual Vilsmeier-Haack conditions to give rise to the corresponding 5-formyl derivatives 10a-c in good yields (81-88%) (Scheme 2). Interestingly, in all the substrates the C-5 formyl regioisomer was exclusively obtained and no mixtures of the three possible C-3/C-4/C-5 formyl isomers were observed. This is in agreement with previous reports for an analogous substrate [17], though there is a broad tendency to provide no selective ratios of regioisomers [17,18].
A behavior similar to pyrroles 7a-c was found when methyl acrylate 8b and acrylonitriles 9a-b were formylated to afford the corresponding 1,2,5-trisubstituted pyrroles 11a and 12a-b, respectively.

The highly regioselective preparation of these 1,2,5-trisubstituted pyrroles in good overall yields prompted us to explore the use of 2-formylpyrrole (5a) as an efficient starting material for the total synthesis of a naturally occurring 2-formyl pyrrole alkaloid, such as pyrrolemarumine (4b). The latter compound was chosen because most of the natural alkaloids illustrated in figures 1-2 display the same 2,5-functionalities in the pyrrole core.

**Total Synthesis of Pyrrolemarumine (4b)**

The total synthesis of pyrrolemarumine (4b), the aglycone of the natural pyrrole alkaloid 4a, was designed based on the insights gained from observing the behavior of 2-formylpyrrole

\[ \text{5a} \xrightarrow{\text{(RO)}_2\text{P(O)}\text{CH}_2\text{Z}, \text{NaH, THF, 25 \degree C, 24-48 h}} \text{5b, Z = CO}_2\text{Et, 5c, Z = CO}_2\text{Me, 5d, Z = CN}} \]

\[ + \text{R-X, NaH, DMF, 25 \degree C, 24 h} \xrightarrow{} \text{7a-e, Z = CO}_2\text{Et, 8a-b, Z = CO}_2\text{Me, 9a-b, Z = CN}} \]

\[ \text{7a (95%), 8a (93%), 9a (87%) }\]

\[ \text{7b (85%), 8b (85%), 9b (86%) }\]

\[ \text{7d (99%), 7e (87%) }\]

\[ \text{7a-c, Z = CO}_2\text{Et, 8b, Z = CO}_2\text{Me, 9a-b, Z = CN}} \]

\[ \text{10a-c, Z = CO}_2\text{Et, 11a, Z = CO}_2\text{Me, 12a-b, Z = CN}} \]

\[ \text{10a (88%), 10b (81%), 10c (83%)}\]

\[ \text{12a (92%), 11a (88%), 12b (75%)}\]

Scheme 1. Preparation of 1,2-disubstituted pyrroles 7a-e, 8a-b, and 9a-b.

Scheme 2. Synthesis of formyl pyrroles 10a-c, 11a and 12a-b.
(5a) with the diverse reagents herein described. A dual retrosynthetic scheme was proposed (Scheme 3), which included the approach starting from the N-benzylolation of 5a, followed by formylation of intermediate 13 to furnish the desired product 4b. The alternative more convergent pathway would be the N-benzylolation of 2,5-disubstituted pyrrole 15, which would be previously functionalized from 5a.

Because of the obvious advantages of a convergent synthesis, the second approach was investigated first. Although pyrrole 5a was readily reduced with sodium hydride to yield the corresponding 2-hydroxymethyl pyrrole (16a), this had to be protected with a TBS group to afford the silane derivative 16b and in this way avoid decomposition. However, further degradation of this substrate under the formylation conditions led us to abandon this route and attempt the first approach.

In order to introduce the benzyl moiety into the pyrrole framework, the synthetic route followed the reaction conditions depicted in Scheme 1, whereby the benzyl bromide derivative

![Scheme 3. Dual retrosynthesis for the preparation of the aglycone pyrrolemarumine (4b).](image)

![Scheme 4. Total synthesis of the aglycone pyrrolemarumine (4b).](image)
19 gave 2-formylpyrrole 20 in high yield (Scheme 4). Derivative 19 was prepared from 4-hydroxybenzaldehyde (17) in good overall yield (72%) through a two-step reaction sequence, including intermediate 18.

The reduction of 20 with sodium borohydride provided the corresponding alcohol 21 in high yield, followed by acetylation to yield acetate 22. This protection was provided due to the instability shown by the hydroxyl group during the subsequent formylation step, which is similar to what occurred during the first approach. The latter reaction carried out under standard conditions brought the formyl group into the desired position of the pyrrole ring, resulting in 23 in a modest yield. Hydrolysis of the protective groups of the latter compound furnished the desired product 4b in a 43% overall yield for the two steps, and in a 28% overall yield for the seven steps starting from 17. The spectral data of the synthetic product 4b was in agreement with the data reported for the aglycone natural product [10].

Conclusions

In summary, a divergent synthetic approach for the preparation of 1,2-di- and 1,2,5-tri-substituted pyroles starting from 2-formylpyrrole (5a) has been achieved, including the first total synthesis of the aglycone alkaloid pyrrolemarumine (4b) in a high overall yield. The scope and efficiency of this approach is currently under evaluation for the synthesis of other 1,2,5-tri-substituted pyrrole alkaloids from the series of natural compounds 1-3, and the results will be reported in due course.

Experimental Section

General: Melting points were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. 1H and 13C NMR spectra were recorded on a Varian Mercury (300 MHz) and a Jeol JNM-GCMatEII apparatus. Elemental analyses were performed on a Perkin-Elmer 2000 spectrophotometer. Mass spectra (MS) were recorded on a Finnigan GC Ultra spectrometer. Light micrographs were obtained with a Jeol JSM-6300 apparatus. Spectra (HRMS), in electron impact mode, were obtained with a Hewlett-Packard 5971A spectrometers. Spectra (1H and 13C NMR) were recorded on a Jeol JNM-GCMatEII apparatus.

Experimental Section

General: Melting points were determined with an Electrothermal capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 2000 spectrophotometer. 1H and 13C NMR spectra were recorded on Varian Mercury (300 MHz) and Varian VNMR (500 MHz) instruments, with COCl2 as the solvent and TMS as internal standard. Signal assignments were based on 2D NMR spectra (HMOC, HMBC). Mass spectra (MS) were recorded on a Varian Mercury (300 MHz) instrument, in electron impact mode, with a Jeol JNM-GCMatEII apparatus. Elemental analyses were performed on a Perkin-Elmer 2000 spectrophotometer. Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F254 coated 0.25 plates, visualized by using a long- and short-wavelength UV lamp. Flash column chromatography was performed on Natland International Co. silica gel (230-400 and 230-400 mesh). All air moisture sensitive reactions were carried out under N2 using oven-dried glassware. THF was freshly distilled over sodium, as was DMF and CH2Cl2 over CaH2 prior to use. MeOH was distilled over sodium. Et3N was freshly distilled from NaOH. All other reagents were used without further purification.

Ethyl (E)-3-(1H-Pyrrol-2-yl)acrylate (5b) [19]: To a solution of 5a (0.100 g, 1.05 mmol) in anhydrous THF (2 mL) at 0 °C, NaH (60%) (0.042 g, 1.05 mmol) was added. The mixture was stirred at 0 °C under nitrogen for 30 min and triethyl phosphonoacetate (0.235 g, 1.05 mmol) was added dropwise. After stirring at room temperature for 48 h, EtOAc (30 mL) was added, the mixture washed with water (2 x 15 mL), the organic layer dried (Na2SO4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/4 crude, hexane/EtOAc, 98:2) to give 5b (0.157 g, 90%) as a reddish solid. Rf = 0.55 (hexane/EtOAc, 7:3); mp 58-59 °C. IR (film): ν = 2981, 1683, 1622, 1544, 1446, 1366, 1268, 1181, 973, 736 cm−1. 1H NMR (300 MHz, CDCl3): δ = 1.31 (t, J = 7.1 Hz, 3H, CO2CH2CH3), 4.24 (q, J = 7.1 Hz, 2H, CH2CO2CH2CH3), 6.09 (d, J = 15.9 Hz, 1H, H-2), 6.25-6.29 (m, 1H, H-4'), 6.53-6.58 (m, 1H, H-3'), 6.89-6.94 (m, 1H, H-5'), 7.59 (d, J = 15.9 Hz, 1H, H-3), 9.34 (br s, 1H, NH). 13C NMR (75.4 MHz, CDCl3): δ = 14.3 (CO2CH2CH3), 60.3 (CO2CH2CH3), 110.7 (C-4'), 111.0 (C-2), 114.2 (C-3'), 122.6 (C-5'), 128.4 (C-2'), 134.6 (C-3), 168.1 (CO2Et). MS (70 eV): m/z = 165 (12) [M]+, 164 (22) [M- 1]+, 150 (5), 138 (42), 88 (100), 86 (18), 56 (12).

Methyl (E)-3-(1H-Pyrrol-2-yl)acrylate (5c) [20]: Following the method of preparation for 5b, by using 5a (0.500 g, 5.26 mmol), NaH (60%) (0.252 g, 6.31 mmol), trimethyl phosphonoacetate (1.140 g, 6.31 mmol) in dry THF (5 mL) and stirring at 25 °C for 24 h, 5c (0.782 g, 98%) was obtained as a colorless solid. Rf = 0.63 (hexane/EtOAc, 7:3); mp 78-79 °C. IR (KBr): ν = 3261, 2947, 1638. 1628, 1552, 1328, 1414, 1303, 1231, 1193, 1312, 1030, 966, 844, 755, 738 cm−1. 1H NMR (300 MHz, CDCl3): δ = 3.75 (s, 3H, CO2Et). 6.12-6.16 (m, 1H, H-3), 6.52-6.56 (m, 1H, H-5'), 6.88-6.92 (m, 1H, H-5'), 7.59 (d, J = 15.9 Hz, 1H, H-3), 9.70 (br s, 1H, NH). 13C NMR (75.4 MHz, CDCl3): δ = 51.4 (CO2Et), 110.2 (C-2), 110.6 (C-4'), 114.5 (C-3'), 122.7 (C-5'), 128.3 (C-2'), 134.9 (C-3), 168.6 (CO2Et). MS (70 eV): m/z = 151 (100) [M]+, 120 (42), 119 (90), 92 (36), 91 (33), 65 (25).

(E)-3-(1H-Pyrrol-2-yl)acrylonitrile (5d) and (Z)-3-(1H-Pyrrol-2-yl)acrylonitrile (5d') [21]: Following the method of preparation for 5b, by using 5a (0.500 g, 5.26 mmol), NaH (60%) (0.252 g, 6.31 mmol), diethylcyanomethylphosphonate (1.117 g, 6.31 mmol) in dry THF (5 mL) and stirring at 25 °C for 24 h, 5d (0.563 g, 91%) and 5d' (0.029 g, 5%) were obtained as colorless liquids.

Data for 5d: Rf = 0.56 (hexane/EtOAc, 7:3). IR (film): ν = 3313, 2924, 2209, 1613, 1445, 1411, 1314, 1128, 1096, 1036, 956, 796, 738 cm−1. 1H NMR (300 MHz, CDCl3): δ = 5.44 (d, J = 16.5 Hz, 1H, H-2), 6.22-6.30 (m, 1H, H-4'), 6.50-6.56 (m, 1H, H-3'), 6.91-6.97 (m, 1H, H-5'). 13C NMR (75.4 MHz, CDCl3): δ = 87.0 (C-2), 110.9 (C-4'), 114.9 (C-3'), 119.9 (C-1), 123.7 (C-5'), 127.7 (C-2'), 140.0 (C-3). MS (70 eV): m/z = 118 (100) [M]+, 117 (12), 92 (11), 91 (34), 67 (13).
Ethyl (E)-3-(1-(Prop-1-yn-1-yl)-1H-pyrrol-2-yl)acrylate (7a):

To a solution of 5b (0.200 g, 1.21 mmol) in dry DMF (2.0 mL) at 0 ºC and under N₂, NaH (60%) (0.058 g, 1.46 mmol) was added. The mixture was stirred at 0 ºC for 15 min, and propargyl bromide (6a) (0.144 g, 1.21 mmol) was added dropwise. After stirring at 0 ºC for 1 h, EtOAc (20 mL) was added and the mixture was washed with water (2 x 10 mL). The organic layer was dried (Na₂SO₄) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 9:1) to give 7a (0.234 g, 95%) was obtained as a pale yellow oil. Rₜ = 0.26 (hexane/EtOAc, 9:1). IR (film): ν = 3288, 1696, 1622, 1468, 1365, 1279, 1265, 1174, 1034, 965, 723 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.32 (t, J = 7.5 Hz, 3H, CO₂CH₂CH₂), 2.46 (t, J = 2.5 Hz, 1H, H-3’), 4.24 (q, J = 7.5 Hz, 2H, CO₂CH₂CH₂), 4.76 (t, J = 2.5 Hz, 2H, H-1’), 6.18 (d, J = 15.5 Hz, 1H, H-2’), 6.22 (dd, J = 4.0, 3.0, 1.0 Hz, 1H, H-4’), 6.68 (dd, J = 4.0, 1.5 Hz, 1H, H-1), 6.94 (dd, J = 3.0, 1.5 Hz, 1H, H-5’), 7.63 (d, J = 15.5 Hz, 1H, H-3), 13C NMR (125 MHz, CDCl₃): δ = 14.4 (CO₂CH₂CH₂), 36.7 (C-1’’), 60.2 (CO₂CH₂CH₂), 74.4 (C-3’’), 73.3 (C-2’’), 110.4 (C-1’’), 112.5 (C-3’’), 112.7 (C-2’’), 125.5 (C-5’’), 128.8 (C-2’’), 131.6 (C-3’ ’), 167.6 (CO₂Et). MS (70 eV): m/z 203 (8) [M⁺], 174 (16), 158 (26), 131 (34), 130 (100), 119 (16), 103 (19), 91 (24), 77 (42), 63 (24). HRMS (EI): m/z calcd. for C₁₂H₁₇NO₂ [M⁺]: 203.0946; found 203.0936.

Ethyl (E)-3-(1-(3-Methylbut-2-en-1-yl)-1H-pyrrol-2-yl)acrylate (7b):

Following the method of preparation for 7a, by using 5b (0.100 g, 0.61 mmol), NaH (60%) (0.029 g, 0.73 mmol) and prenyl bromide (6b) (0.108 g, 0.73 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, 7b (0.121 g, 85%) was obtained as a reddish oil. Rₜ = 0.36 (hexane/EtOAc, 7:3). IR (film): ν = 2977, 1700, 1622, 1472, 1444, 1324, 1276, 1163, 1037, 968, 723 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 1.31 (t, J = 7.0 Hz, 3H, CO₂CH₂CH₂), 1.75 (d, J = 1.0 Hz, 3H, H-4’’ or H-5’’), 1.79 (br s, 3H, H-5’’ or H-4’’), 4.23 (q, J = 7.0 Hz, 2H, CO₂CH₂CH₂), 4.57 (d, J = 7.0 Hz, 2H, H-1’’), 5.28 (tm, J = 6.8 Hz, 1H, H-2’’), 6.13 (d, J = 16.0 Hz, 1H, H-2), 6.16-6.17 (dd, J = 3.5, 2.5, 0.5 Hz, 1H, H-4’’), 6.64 (dd, J = 3.5, 1.5 Hz, 1H, H-3’’), 6.79 (dd, J = 2.5, 1.5 Hz, 1H, H-5’’), 7.60 (d, J = 16.0 Hz, 1H, H-3). ¹³C NMR (125 MHz, CDCl₃): δ = 14.4 (CO₂CH₂CH₂), 17.9 (C-4’’ or C-5’’), 25.6 (C-5’’ or C-4’’), 45.2 (C-1’’), 60.1 (CO₂CH₂CH₂), 109.3 (C-4’’), 111.5 (C-3’’), 112.7 (C-2’’), 120.0 (C-2’’), 125.3 (C-5’’), 128.7 (C-2’’), 132.4 (C-3’’), 136.5 (C-3’’), 167.8 (CO₂Et). MS (70 eV): m/z 233 (12) [M⁺], 208 (25), 194 (70), 184 (57), 168 (71), 154 (100), 144 (61), 130 (82), 117 (91), 115 (65), 91 (44), 77 (26). HRMS (EI): m/z calcd. for C₁₄H₁₉NO₂ [M⁺]: 233.1416; found 233.1413.

Ethyl (E)-3-(1-(Furan-2-carbonyl)-1H-pyrrol-2-yl)acrylate (7e):

Following the method of preparation for 7a, by using 5b (0.100 g, 0.61 mmol), NaH (60%) (0.048 g, 1.21 mmol) and propargyl bromide (6a) (0.144 g, 1.21 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, 7e (0.111 g, 90%) was obtained as a colorless oil. Rₜ = 0.23 (hexane/EtOAc, 9:1). IR (film): ν = 2925, 1702, 1623, 1463, 1258, 1157, 1037, 852, 722 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.32 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₂), 4.24 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₂), 5.53 (d, J = 6.5 Hz, 2H, H-3’’), 6.19 (d, J = 15.5 Hz, 1H, H-2), 6.27 (dd, J = 3.9, 2.7 Hz, 1H, H-4’’), 6.69 (dd, J = 3.9, 1.5 Hz, 1H, H-3’’), 6.94 (dd, J = 2.7, 1.5 Hz, 1H, H-5’’), 7.04 (td, J = 6.5 Hz, 1H, H-1’’), 7.69 (d, J = 15.5 Hz, 1H, H-3’’). ¹³C NMR (75.4 MHz, CDCl₃): δ = 14.3 (CO₂CH₂CH₂), 60.3 (CO₂CH₂CH₂), 86.9 (C-3’’), 97.0 (C-1’’), 111.1 (C-4’’), 112.5 (C-3’’), 114.1 (C-2’’), 123.9 (C-5’’), 128.9 (C-2’’), 131.7 (C-3’’), 167.5 (CO₂Et), 203.8 (C-2’’). MS (70 eV): m/z 203 (43) [M⁺], 175 (100), 158 (30), 130 (71), 129 (47), 103 (21), 91 (10), 77 (18). HRMS (EI): m/z calcd. for C₁₂H₁₇NO₂ [M⁺]: 203.0946; found 203.0945.
Methyl (E)-3-(1-(Prop-2-yn-1-yl)-1H-pyrrolo-2-yl)acrylate (8a): Following the method of preparation for 7a, by using 5c (0.200 g, 1.33 mmol), NaH (60%) (0.064 g, 1.59 mmol) and propargyl bromide (6a) (0.189 g, 1.59 mmol) in dry DMF (2.0 mL), and after stirring at 0 °C for 1.5 h, 8a (0.233 g, 93%) was obtained as a colorless oil. Rf = 0.70 (hexane/EtOAc, 7:3). IR (film): v = 3237, 2208, 1608, 1470, 1412, 1368, 1145, 1085, 951, 728 cm⁻¹. δ = 32.4 (C-1’’), 51.5 (C=O). 1H NMR (300 MHz, CDCl₃): δ = 3.46 (t, J = 2.4 Hz, 2H, H-1’’), 6.19 (d, J = 15.6 Hz, 1H, H-2), 6.67 (dd, J = 3.7, 1.5 Hz, 1H, H-3’’). Anal. calcd. for C₁₁H₁₃NO₂: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.80; H, 5.82; N, 7.40.

Methyl (E)-3-(1-(Prop-2-yn-1-yl)-1H-pyrrolo-2-yl)acrylate (8b): Following the method of preparation for 7a, by using 5c (0.100 g, 0.66 mmol), NaH (60%) (0.053 g, 1.33 mmol) and propargyl bromide (6a) (0.156 g, 1.33 mmol) in dry DMF (1.0 mL), and after stirring at 0 °C for 1 h, 8b (0.107 g, 85%) was obtained as a dark solid. Rf = 0.77 (hexane/EtOAc, 7:3); mp 54-55 ºC. IR (KBr): v = 2924, 1704, 1622, 1460, 1436, 1263, 1168, 1030, 966, 723 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 3.77 (s, 3H, CO₂CH₃), 5.51 (d, J = 6.3 Hz, 1H, H-3’’), 6.19 (d, J = 15.6 Hz, 1H-2), 6.26 (dd, J = 3.9, 3.0 Hz, 1H, H-4’’), 6.69 (dd, J = 3.9, 1.5 Hz, 1H, H-3’’), 6.93 (dd, J = 3.0, 1.5 Hz, 1H, H-5’’), 7.02 (t, J = 6.3 Hz, 1H-1’’), 7.69 (d, J = 15.6 Hz, 1H, H-3). 13C NMR (75.4 MHz, CDCl₃): δ = 51.4 (CO₂CH₃), 86.8 (C-3’’), 96.8 (C-1’’), 111.1 (C-4’’), 112.5 (C-3’’), 113.5 (C-2’’), 124.0 (C-5’’), 128.8 (C-2’’), 131.9 (C-3), 167.6 (CO₂CH₃), 203.8 (C-2’’). MS (70 eV): m/z 189 (11) [M]+, 150 (7), 130 (100), 103 (20), 77 (13). Anal. calcd. for C₁₁H₁₃NO₂: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.86; N, 7.39.

Ethyl (E)-3-(1-(Prop-2-yn-1-yl)-1H-pyrrolo-2-yl)acrylonitrile (9a): Following the method of preparation for 7a, by using 5d (0.200 g, 1.70 mmol), NaH (60%) (0.081 g, 2.03 mmol) and propargyl bromide (6a) (0.242 g, 2.03 mmol) in dry DMF (2.0 mL), and after stirring at 0 °C for 1.5 h, 9a (0.229 g, 87%) was obtained as a colorless oil. Rf = 0.66 (hexane/EtOAc, 7:3). IR (KBr): v = 3237, 2208, 1608, 1470, 1412, 1295, 1085, 951, 728 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 2.50 (t, J = 2.4 Hz, 2H, H-3’’), 4.71 (d, J = 2.4 Hz, 2H, H-1’’), 5.56 (d, J = 16.2 Hz, 1H, H-2), 6.22 (2d, J = 3.7, 2.6, 0.6 Hz, 1H, H-4’’), 6.68 (dd, J = 3.7, 1.5 Hz, 1H, H-3’’), 6.93 (d, J = 2.6, 1.5 Hz, 1H, H-5’’), 7.32 (d, J = 16.2 Hz, 1H, H-3). 13C NMR (75.4 MHz, CDCl₃): δ = 36.8 (C-1’’), 74.9 (C-3’’), 76.9 (C-2’’), 90.6 (C-2’’), 110.3 (C-4’’), 112.6 (C-3’’), 119.3 (C-1), 126.8 (C-5’’), 128.0 (C-2’’), 137.0 (C-3). MS (70 eV): m/z 156 (40) [M]+, 155 (100), 130 (18), 128 (24). Anal. calcd. for C₁₅H₁₄N₂O: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.86; H, 5.13; N, 17.93.

Ethyl (E)-3-(5-Formyl-1-(prop-2-ynyl)-1H-pyrrolo-2-yl)acrylate (10a): Dry DMF (0.043 g, 0.59 mmol) was added to phosphorus oxychloride (0.091 g, 0.59 mmol) at 0 ºC, and the resulting mixture was stirred for 10 min. Then, 7a (0.100 g, 0.49 mmol) was added dropwise and the temperature was slowly raised to 40 ºC and maintained for 2 h. The reaction mixture was quenched with an aqueous solution of NaOH 2N until neutral, CH₂Cl₂ (250 mL) was added, the organic layer dried (Na₂SO₄) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g) crude, hexane/EtOAc, 98:2) to give 10a (0.101 g, 88%) as a white solid. Rf = 0.59 (hexane/EtOAc, 7:3); mp 90-91 °C. IR (KBr): v = 1705, 1659, 1628, 1472, 1449, 1409, 1309, 1270, 1234, 1183, 1048, 783 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 1.35 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 2.38 (t, J = 2.7 Hz, 1H, H-3’’), 4.28 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 5.39 (d, J = 2.7 Hz, 2H, H-1’’), 6.47 (d, J = 15.6 Hz, 1H, H-2), 6.70 (dd, J = 4.2, 0.6 Hz, 1H, H-3’’), 6.96 (dd, J = 4.2, 0.9 Hz, 1H, H-4’’), 7.72 (d, J = 15.6 Hz, 1H-1, H-3’’), 9.60 (s, 1H, CHO). 13C NMR (75.4 MHz, CDCl₃): δ = 14.3 (CO₂CH₂CH₃), 34.4 (C-1’’), 60.8 (CO₂CH₂CH₃), 73.6 (C-3’’), 77.7 (C-2’’), 111.6 (C-3’’), 121.4 (C-2’’), 124.7 (C-4’’), 130.0 (C-3), 132.8 (C-5’’), 137.5 (C-2’’), 166.3 (CO₂Et), 179.9 (CHO). MS (70 eV): m/z 231 (M⁺, 18), 203 (41), 202 (100), 174 (37), 158 (41), 130 (42), 103 (24), 77 (9). Anal. calcd. for C₁₃H₁₄NO₂: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.61; N, 6.03.
Ethyl (E)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1H-pyrrole-2-yl)acrylate (10c): Following the method of preparation for 10a, by using DMF (0.086 g, 1.18 mmol), POCl₃ (0.181 g, 1.18 mmol) and 7c (0.200 g, 0.99 mmol), and after stirring at 40 °C for 2 h, 10c (0.189 g, 83%) was obtained as a pale yellow oil. Rf = 0.34 (hexane/EtOAc, 7:3); mp 74-75 °C. IR (film): v = 1706, 1663, 1625, 1475, 1307, 1244, 1184, 1051, 772 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 1.34 (t, J = 6.9 Hz, 3H, CO₂CH₂CH₃), 1.71 (br s, 3H, H-4’ or H-5’), 1.85 (br s, 3H, H-5” or H-4”), 4.26 (q, J = 6.9 Hz, 2H, CO₂CH₂CH₃), 5.15 (br s, 3H, H-1”, H-2”), 6.39 (d, J = 15.9 Hz, 1H, H-2), 6.66 (dd, J = 4.2, 0.6 Hz, 1H, H-3”), 6.92 (dd, J = 4.2, 0.6 Hz, 1H, H-4”), 7.60 (d, J = 15.9 Hz, 1H, H-3), 9.58 (s, 1H, CHO). 13C NMR (75.4 MHz, CDCl₃): δ = 14.3 (CO₂CH₂CH₃), 18.2 (C-4’” or C-5”), 25.6 (C-5’” or C-4”), 43.4 (C-1’”), 60.7 (CO₂CH₂CH₃), 110.9 (C-3’), 120.3 (C-2’), 120.4 (C-2”), 124.3 (C-3’”), 130.8 (C-3’), 133.3 (C-3”), 135.5 (C-3’”), 137.3 (C-3”), 166.5 (CO₂Et), 179.8 (CHO). MS (70 eV): m/z 261 (M⁺, 7), 225 (15), 202 (17), 188 (56), 167 (20), 155 (20), 148 (100), 119 (24), 73 (20). HRMS (EI): m/z calcld. for C₁₃H₁₉NO₃ [M⁺]: 261.1365; found 261.1358.

Methyl (E)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1H-pyrrole-2-yl)acrylate (11a): Following the method of preparation for 10a, by using DMF (0.047 g, 0.64 mmol), POCl₃ (0.098 g, 0.64 mmol) and 8b (0.100 g, 0.53 mmol), and after stirring at 40 °C for 2 h, 11a (0.101 g, 88%) was obtained as a brown solid. Rf = 0.65 (hexane/EtOAc, 7:3); mp 88-89 °C. IR (film): v = 2950, 1706, 1656, 1627, 1449, 1310, 1275, 1201, 1046, 971, 790 cm⁻¹. 1H NMR (300 MHz, CDCl₃): δ = 3.81 (s, 3H, CO₂CH₃), 5.48 (d, J = 6.6 Hz, 2H, H-3’”), 5.47 (d, J = 15.6 Hz, 1H, H-2), 6.70 (d, J = 4.3 Hz, 1H, H-3’), 7.02 (d, J = 4.3 Hz, 1H, H-2”), 7.60 (t, J = 6.6 Hz, 1H, H-1”), 7.82 (d, J = 15.6 Hz, 1H, H-3), 9.65 (s, 1H, CHO). 13C NMR (75.4 MHz, CDCl₃): δ = 14.2 (CO₂CH₃), 60.7 (CO₂CH₂CH₃), 85.6 (C-3’”), 95.9 (C-1’”), 111.8 (C-3’), 120.2 (C-2’), 124.0 (C-4’), 131.8 (C-3’), 133.4 (C-3’”), 137.3 (C-3”), 166.4 (CO₂Et), 179.5 (CHO), 203.8 (C-2’’). MS (70 eV): m/z 231 (46) [M⁺], 231 (12), 158 (100), 130 (53), 103 (27), 77 (9). HRMS (EI): m/z calcld. for C₁₃H₁₉NO₃ [M⁺]: 231.0895; found 231.0882.

4-(Hydroxymethyl)phenyl 4-Methylbenzenesulfonate (18): Triethylamine (0.829 g, 8.19 mmol) was added to a mixture of 4-hydroxybenzaldehyde (17) (0.500 g, 4.09 mmol) and DMAP (0.050 g, 0.41 mmol) in CH₂Cl₂ (15 mL), which was stirred at room temperature for 20 min. p-Toluenesulfonyl chloride (1.171 g, 6.14 mmol) was added at 0 °C and the mixture was stirred for 1.5 h. The solvent was removed under vacuum, the residue was dissolved in MeOH (10 mL) and NaBH₄ (0.080 g, 2.05 mmol) was added at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 1:1) to give 18 (1.187 g, 77%) as a pale yellow oil. Rf = 0.17 (hexane/EtOAc, 7:3). IR (film): v = 3368, 2925, 1597, 1502, 1369, 1197, 1150, 1092, 1015, 865, 814, 691 cm⁻¹. 1H NMR (500 MHz, CDCl₃): δ = 2.20 (br, 1H, OH), 2.44 (s, 3H, CH₃), 4.63 (s, 2H, CH₂), 6.94 (d, J = 8.8 Hz, 2H, H-2”), 7.25 (d, J = 8.8 Hz, 2H, H-3”), 7.29 (d, J = 8.0 Hz, 2H, H-3).
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4-(Bromomethyl)phenyl 4-Methylbenzenesulfonate (19): Triphenylphosphine (0.860 g, 3.80 mmol) was added to a solution of 18 (0.760 g, 2.73 mmol) in CH₂Cl₂ (20 mL). After stirring at room temperature for 10 min, NBS (0.580 g, 3.28 mmol) was added at 0 °C, and the mixture was stirred at this temperature for 2 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 7:3). IR (film): ν = 3375, 2924, 1596, 1501, 1367, 1298, 1196, 1174, 1150, 1091, 1016, 862, 715 cm⁻¹. 

4-(2-Formyl-1H-pyrrol-1-yl)methylphenyl 4-Methylbenzenesulfonate (20): According to the method for the preparation of 7a, by using 2-formylpyrrol (5a) (0.558 g, 5.86 mmol), NaH (60%) (0.281 g, 7.03 mmol) and compound 19 (2.00 g, 8.56 mmol) in dry DMF (10 mL), and after stirring at 25 °C for 5 h, 20 (2.001 g, 96%) was obtained as a white resin. Rf = 0.38 (hexane/EtOAc, 7:3). IR (film): ν = 1662, 1597, 1503, 1477, 1404, 1371, 1319, 1198, 1177, 1154, 1092, 876, 757, 720 cm⁻¹. 

4-(2-(Hydroxymethyl)-1H-pyrrol-1-yl)methylphenyl 4-Methylbenzenesulfonate (21): NaN₃ (0.099 g, 2.62 mmol) was added to a solution of 20 (1.860 g, 5.23 mmol) in a mixture of MeOH/CH₂Cl₂ (1:1) (20 mL) at 0 °C, and the mixture was stirred at this temperature for 2 h. The solvent was removed under vacuum and the crude product purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 7:3) to afford 21 (1.777 g, 95%) as a colorless oil. Rf = 0.25 (hexane/EtOAc, 7:3). IR (film): ν = 3375, 2924, 1596, 1501, 1367, 1298, 1196, 1174, 1150, 1091, 1016, 862, 715 cm⁻¹. 

(1-(4-(p-Tosyloxy)benzyl)-1H-pyrrol-2-yl)methyl acetate (22): Pyridine (0.806 g, 10.19 mmol) was added to a solution of 21 (1.821 g, 5.09 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C. After stirring for 30 min, acetic anhydride (1.048 g, 10.19 mmol) was added and the mixture was stirred at room temperature for 24 h, followed by washing with water (100 mL) and an aqueous solution of HCl 5% until neutral. The aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers were dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to give 22 (1.974 g, 97%) as a yellow oil. Rf = 0.48 (hexane/EtOAc, 7:3). IR (film): ν = 2926, 1735, 1596, 1502, 1327, 1302, 1237, 1197, 1176, 1152, 1097, 864, 834, 815, 719 cm⁻¹. 

(5-Formyl-1-(4-(p-tosyloxy)benzyl)-1H-pyrrol-2-yl)methyl acetate (23): Following the method of preparation for 7a, by using dry DMF (0.137 g, 1.87 mmol), POCl₃ (0.287 g, 1.87 mmol) and 22 (0.680 g, 1.70 mmol) in dry DMF (6.0 mL), and after stirring at 0 °C for 30 min, the reaction mixture was quenched with an aqueous solution of KOH 1M (30 mL) and extracted with EtOAc (2 x 100 mL). The organic layer was dried (Na₂SO₄) and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 8:2) to give 23 (0.209 g, 57%) as a pale yellow resin. Rf = 0.63 (hexane/EtOAc, 1:1). IR (film): ν = 1741, 1663, 1503, 1371, 1225, 1198, 1176, 1153, 1092, 1019, 865 cm⁻¹. 

H NMR (300 MHz, CDCl₃): δ = 5.12 (1H, OH), 4.75 (1H, CH₂OH), 5.15 (2H, H-1''), 6.11 (dd, J = 3.5, 2.7 Hz, 1H, H-4''), 6.05 (dd, J = 3.5, 1.8 Hz, 1H, H-3''), 6.65 (dd, J = 2.7, 1.8 Hz, 1H, H-5''), 6.86-6.97 (m, 4H, H-2', H-3'), 7.26-7.33 (m, 2H, H-3), 7.65-7.71 (m, 2H, H-2). 

MS (EI): m/z = 278 (40) [M⁺], 155 (54), 139 (10), 123 (31), 107 (46), 91 (100), 77 (10). HRMS (EI): m/z calcd. for C₁₉H₁₉O₂S [M⁺]: 278.0613; found 278.0604.
1-(4-Hydroxybenzyl)-5-(hydroxymethyl)-1H-pyrrrole-2-carbaldehyde (Pyrrrolemarum (+)) (4b) [10]: A mixture of compound 23 (0.167 g, 0.39 mmol) and KOH (0.088 g, 1.56 mmol) in a mixture of MeOH/H₂O (1:1 (3 mL) was stirred at room temperature for 24 h. MeOH was removed under vacuum and CH₂Cl₂ (50 mL) was added. The mixture was washed with water (50 mL) and an aqueous solution of HCl 5% until neutral. The aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The organic layers were dried (Na₂SO₄) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 1:1). IR (film): ν = 3333, 2970, 1644, 1516, 1456, 1371, 1243, 1173, 1046, 1011, 822, 784, cm⁻¹. HRMS (EI): m/z calculated for C₁₂H₁₄NO₃ [M⁺] : 232.0974; found: 232.0974.

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References

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