Journal of the Mexican Chemical Society
ISSN: 1870-249X
editor.jmcs@gmail.com
Sociedad Química de México
México

Martínez-Mora, Eder I.; Caracas, Miguel A.; Escalante, Carlos H.; Madrigal, Damian A.; Quiroz-Florentino, Héctor; Delgado, Francisco; Tamariz, Joaquín
Divergent and Selective Functionalization of 2-Formylpyrrole and its Application in the Total Synthesis of the Aglycone Alkaloid Pyrrolemarumine
Journal of the Mexican Chemical Society, vol. 60, núm. 1, enero-marzo, 2016, pp. 23-33
Sociedad Química de México
Distrito Federal, México

Article

J. Mex. Chem. Soc. **2016**, *60(1)*, 23-33

ISSN 1870-249X

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 Joaquín 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

Received November 3rd, 2015; Accepted January 5th, 2016.

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.

Resumen. Se prepararon eficientemente diversos pirroles 1,2- y 1,2,5-subtituidos a través de la funcionalización regioselectiva del 2-formilpirrol (**5a**). Esta metodología se aplicó en el desarrollo de la primera síntesis total de la pirrolemarumina (**4b**), que es la aglicona del alcaloide pirrólico natural correspondiente 4"-*O*-α-L-ramnopiranósido, la cual se realizó partiendo de **5a** a través de un proceso en siete etapas y en un rendimiento global de 28%.
Palabras clave: 2-formilpirrol; formilación de Vilsmeier-Haack; alcaloides pirrólicos; pirrolemarumina.

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 antibiotic, 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 (*Zizania 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

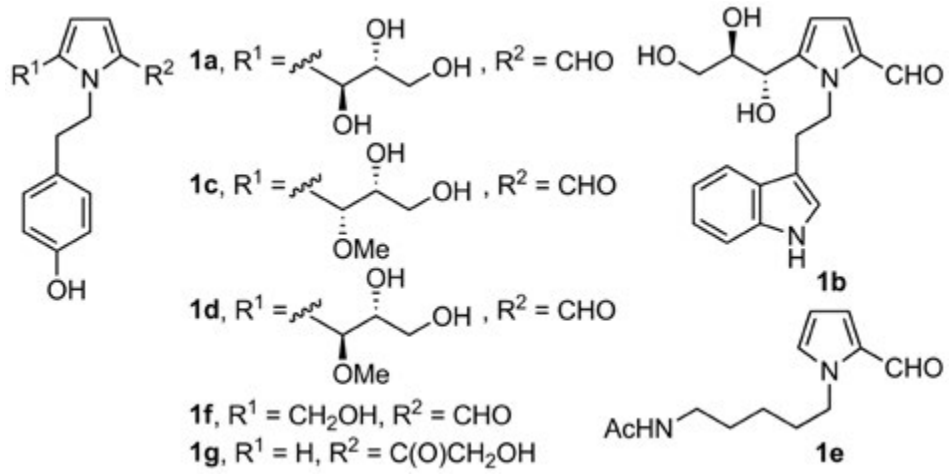


Fig. 1. Structures of jiangrines A-E (**1a-e**), pyrrolezanthine (**1f**) and fusarine (**1g**).

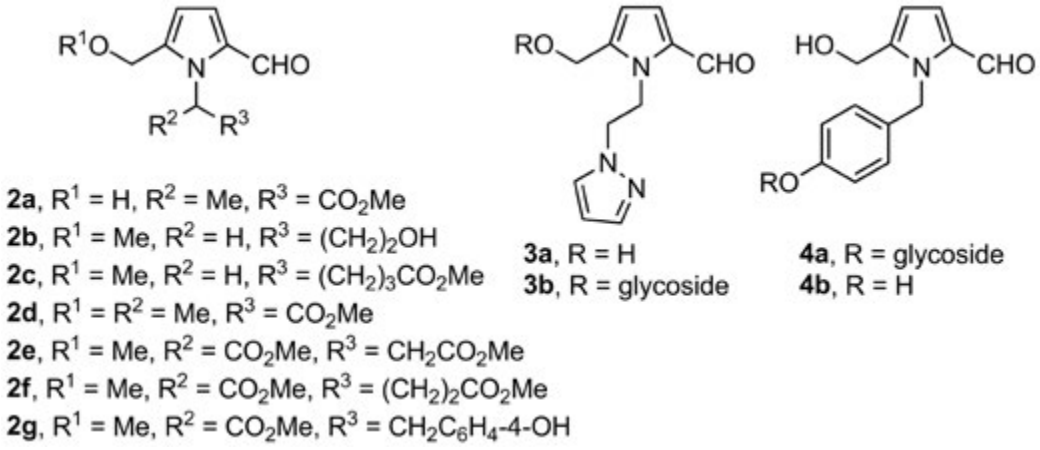


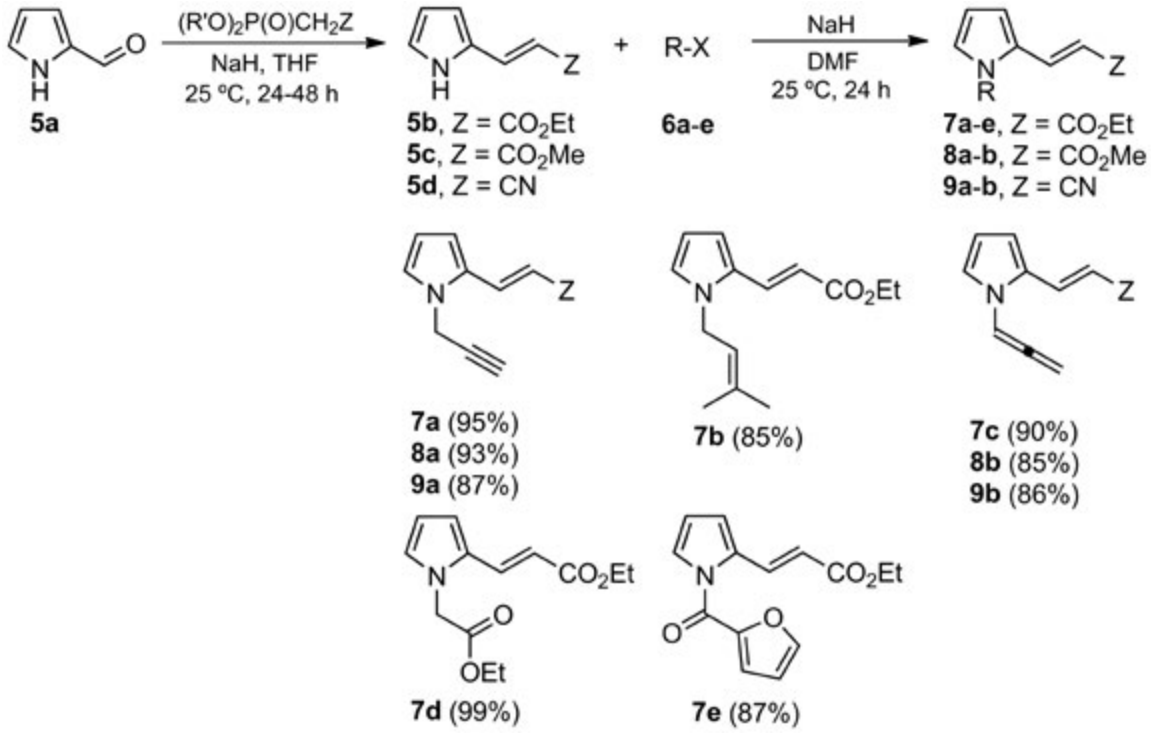
Fig. 2. Structures of makomotines **2a-c**, 2-formyl pyrroles **2d-g** and **3a-b**, pyrrolemarumine 4”-*O*-a-L-rhamnopyranoside (**4a**) and pyrrolemarumine (**4b**).

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-(pyrrol-2-yl)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].



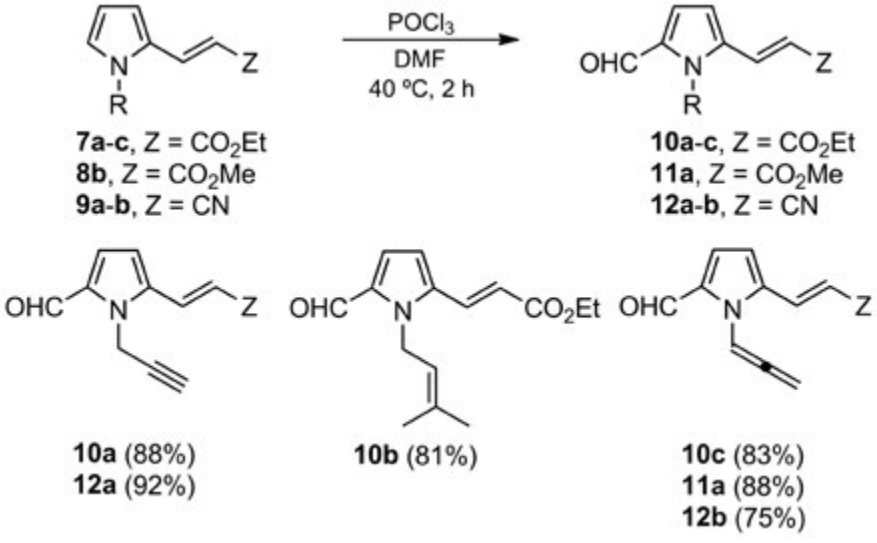
Scheme 1. Preparation of 1,2-disubtituted pyrroles **7a-e**, **8a-b**, and **9a-b**.

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.

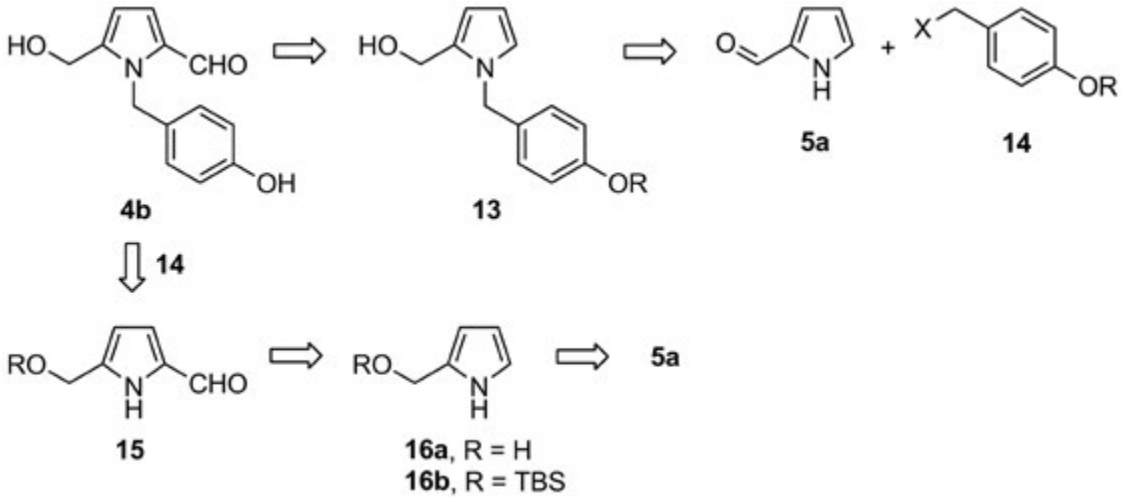
The highly regioselective preparation of these 1,2,5-trisubstituted pyrroles in good overall yields prompted us to explore the use of 2-formylpyrrole (**5a**) as an efficient starting material for the total synthesis of a naturally occurring 2-formyl pyrrole alkaloid, such as pyrrolemarumine (**4b**). 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



Scheme 2. Synthesis of formyl pyrroles **10a-c**, **11a** and **12a-b**.

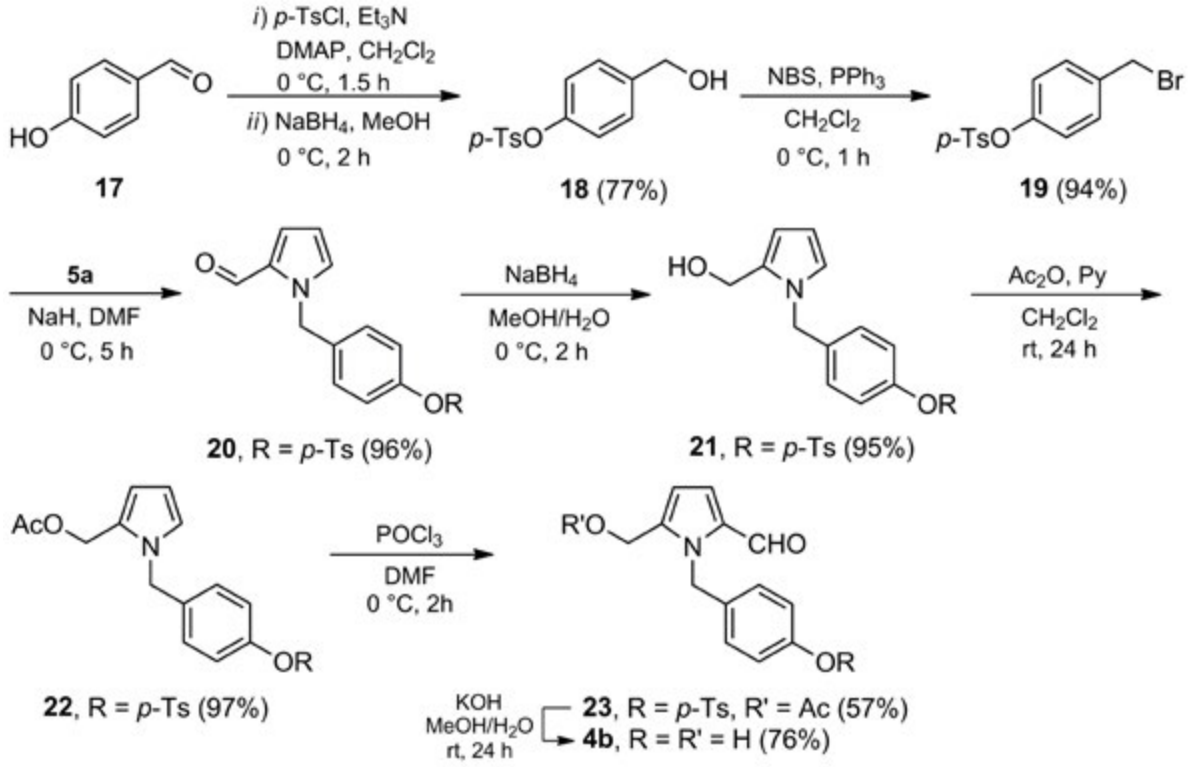


Scheme 3. Dual retrosynthesis for the preparation of the aglycone pyrrolemarumine (**4b**).

(**5a**) with the diverse reagents herein described. A dual retrosynthetic scheme was proposed (Scheme 3), which included the approach starting from the *N*-benzylation of **5a**, followed by formylation of intermediate **13** to furnish the desired product **4b**. The alternative more convergent pathway would be the *N*-benzylation 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 4. Total synthesis of the aglycone pyrrolemarumine (**4b**).

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 pyrroles 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. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (300 MHz) and Varian VNMR (500 MHz) instruments, with $CDCl_3$ as the solvent and TMS as internal standard. Signal assignments were based on 2D NMR spectra (HMQC, HMBC). Mass spectra (MS) were recorded on Polaris Q-Trace GC Ultra (Finnigan Co.) and Hewlett-Packard 5971A spectrometers. High-resolution mass spectra (HRMS), in electron impact mode, were obtained with a Jeol JSM-GCMateII apparatus. Elemental analyses were performed on a CE-440 Exeter Analytical instrument. Analytical thin-layer chromatography was carried out using E. Merck silica gel 60 F_{254} coated 0.25 plates, visualized by using a long- and short-wavelength UV lamp. Flash column chromatography was performed over Natland International Co. silica gel (230-400 and 230-400 mesh). All air moisture sensitive reactions were carried out under N_2 using oven-dried glassware. THF was freshly distilled over sodium, as was DMF and CH_2Cl_2 over CaH_2, prior to use. MeOH was distilled over sodium. Et_3N was freshly distilled from NaOH. All other reagents were used without further purification.

Ethyl (*E*)-3-(1*H*-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 ºC 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 (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to give **5b** (0.157 g, 90%) as a reddish solid. R_f = 0.55 (hexane/EtOAc, 7:3); mp 58-59 °C. IR (film): $\overline{\nu}$ = 2981, 1683, 1622, 1544, 1446, 1366, 1268, 1181, 973, 736 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 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). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 60.3 ($CO_2CH_2CH_3$), 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 (CO_2Et). 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-(1*H*-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), and trimethyl phosphonoacetate (1.140 g, 6.31 mmol) in dry THF (5 mL) and stirring at 25 ºC for 24 h, **5c** (0.782 g, 98%) was obtained as a colorless solid. R_f = 0.63 (hexane/EtOAc, 7:3); mp 78-79 °C. IR (KBr): $\overline{\nu}$ = 3261, 2947, 1683. 1628, 1552, 1328, 1414, 1303, 1231, 1193, 1132, 1030, 966, 844, 755, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, CO_2CH_3), 6.12 (d, *J* = 15.9 Hz, 1H, H-2), 6.22-6.27 (m, 1H, H-4'), 6.52-6.56 (m, 1H, H-3'), 6.88-6.92 (m, 1H, H-5'), 7.59 (d, *J* = 15.9 Hz, 1H, H-3), 9.70 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.4 (CO_2CH_3), 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 (CO_2CH_3). MS (70 eV): *m/z* 151 (100) $[M]^+$, 120 (42), 119 (90), 92 (36), 91 (33), 65 (25).

(*E*)-3-(1*H*-Pyrrol-2-yl)acrylonitrile (5d) and (*Z*)-3-(1*H*-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 ºC for 24 h, **5d** (0.563 g, 91%) and **5d'** (0.029 g, 5%) were obtained as colorless liquids.

Data for **5d**: R_f = 0.56 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3313, 2924, 2209, 1613, 1445, 1411, 1314, 1128, 1096, 1036, 956, 796, 738 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 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'), 7.20 (d, *J* = 16.5 Hz, 1H, H-3), 9.46 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): 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).

Data for **5d'**: R_f = 0.61 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3383, 2924, 2205, 1606, 1447, 1375, 1127, 1094, 1038, 741 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.96 (d, *J* = 11.7 Hz, 1H, H-2), 6.26-6.32 (m, 1H, H-4'), 6.57-6.64 (m, 1H, H-3'), 6.95 (d, *J* = 11.7 Hz, 1H, H-3), 6.98.-7.04 (m, 1H, H-5'), 9.63 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 84.4 (C-2), 110.3 (C-4'), 118.0 (C-3'), 120.0 (C-1), 123.7 (C-5'), 127.9 (C-2'), 138.0 (C-3). MS (70 eV): *m/z* 118 (32) $[M]^+$, 111 (88), 109 (56), 97 (84), 95 (93), 85 (49), 83 (59), 81 (100), 71 (58), 69 (69).

Ethyl (*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-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 N_2**,** 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 (Na_2SO_4) 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. R_f = 0.26 (hexane/EtOAc, 9:1). IR (film): $\overline{\nu}$ = 3288, 1696, 1622, 1468, 1365, 1279, 1265, 1174, 1034, 965, 723 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.5 Hz, 3H, $CO_2CH_2CH_3$), 2.46 (t, *J* = 2.5 Hz, 1H, H-3''), 4.24 (q, *J* = 7.5 Hz, 2H, $CO_2CH_2CH_3$), 4.76 (d, *J* = 2.5 Hz, 2H, H-1''), 6.18 (d, *J* = 15.5 Hz, 1H, H-2), 6.22 (ddd, *J* = 4.0, 3.0, 1.0 Hz, 1H, H-4'), 6.68 (dd, *J* = 4.0, 1.5 Hz, 1H, H-3'), 6.94 (dd, *J* = 3.0, 1.5 Hz, 1H, H-5'), 7.63 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 ($CO_2CH_2CH_3$), 36.7 (C-1''), 60.2 ($CO_2CH_2CH_3$), 74.4 (C-3''), 77.3 (C-2''), 110.0 (C-4'), 112.5 (C-3'), 113.7 (C-2), 125.5 (C-5'), 128.8 (C-2'), 131.6 (C-3), 167.6 (CO_2Et). 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 $C_{12}H_{13}NO_2$ $[M]^+$: 203.0946; found 203.0936.

Ethyl (*E*)-3-(1-(3-Methylbut-2-en-1-yl)-1*H*-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. R_f = 0.36 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2977, 1700, 1622, 1472, 1444, 1324, 1276, 1163, 1037, 968, 723 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 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 (ddd, *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). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4 ($CO_2CH_2CH_3$), 17.9 (C-4'' or C-5''), 25.6 (C-5'' or C-4''), 45.2 (C-1''), 60.1 ($CO_2CH_2CH_3$), 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 (CO_2Et). 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 $C_{14}H_{19}NO_2$ $[M]^+$: 233.1416; found 233.1413.

Ethyl (*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (7c): 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, **7c** (0.111 g, 90%) was obtained as a colorless oil. R_f = 0.23 (hexane/EtOAc, 9:1). IR (film): $\overline{\nu}$ = 2925, 1702, 1623, 1463, 1258, 1175, 1037, 852, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 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 (t, *J* = 6.5 Hz, 1H, H-1''), 7.69 (d, *J* = 15.5 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 60.3 ($CO_2CH_2CH_3$), 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 (CO_2Et), 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 $C_{12}H_{13}NO_2$ $[M]^+$: 203.0946; found 203.0945.

Ethyl (*E*)-3-(1-(2-Ethoxy-2-oxoethyl)-1*H*-pyrrol-2-yl)acrylate (7d): Following the method of preparation for **7a**, by using **5b** (0.050 g, 0.30 mmol), NaH (60%) (0.015 g, 0.38 mmol) and ethyl bromoacetate (**6c**) (0.061 g, 0.36 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **7d** (0.075 g, 99%) was obtained as a colorless oil. R_f = 0.49 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2982, 1751, 1699, 1471, 1366, 1326, 1290, 1263, 1207, 1175, 967, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (q, *J* = 7.1 Hz, 6H, 2 $CO_2CH_2CH_3$), 4.23 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.24 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.74 (s, 2H, H-1''), 6.16 (d, *J* = 15.3 Hz, 1H, H-2), 6.25 (ddd, *J* = 3.6, 2.4, 0.9 Hz, 1H, H-4'), 6.72 (dd, *J* = 3.6, 1.5 Hz, 1H, H-3'), 6.79 (dd, *J* = 1.5, 0.9 Hz, 1H, H-5'), 7.45 (d, *J* = 15.3 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.1 ($CO_2CH_2CH_3$), 14.3 ($CO_2CH_2CH_3$), 48.4 (C-1''), 60.2 ($CO_2CH_2CH_3$), 62.0 ($CO_2CH_2CH_3$), 110.3 (C-4'), 112.2 (C-3'), 113.8 (C-2), 126.7 (C-5'), 129.4 (C-2'), 131.5 (C-3), 167.6 (CO_2Et), 168.0 (CO_2Et). MS (70 eV): *m/z* 251 (74) $[M]^+$, 223 (5), 206 (44), 179 (32), 133 (31), 104 (100), 103 (94), 102 (61), 78 (26). HRMS (EI): *m/z* calcd. for $C_{13}H_{17}NO_4$ $[M]^+$: 251.1158; found 251.1158.

Ethyl (*E*)-3-(1-(Furan-2-carbonyl)-1*H*-pyrrol-2-yl)acrylate (7e): Following the method of preparation for **7a**, by using **5b** (0.050 g, 0.30 mmol), NaH (60%) (0.015 g, 0.38 mmol) and 2-furoyl chloride (**6d**) (0.040 g, 0.36 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 2.5 h, **7e** (0.069 g, 87%) was obtained as a reddish oil. R_f = 0.43 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 1698, 1623, 1567, 1465, 1391, 1339, 1271, 1178, 1031, 853, 765 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 4.23 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 6.25 (d, *J* = 16.0 Hz, 1H, H-2), 6.34 (dd, *J* = 3.5, 3.0 Hz, 1H, H-4´), 6.65 (dd, *J* = 3.5, 1.5 Hz, 1H, H-4''), 6.83 (dm, *J* = 3.5 Hz, 1H, H-3'), 7.36 (dd, *J* = 3.5, 0.5 Hz, 1H, H-3''),

7.50 (dd, *J* = 3.0, 1.5 Hz, 1H, H-5'), 7.72 (dd, *J* = 1.5, 0.5 Hz, 1H, H-5''), 8.05 (d, *J* = 16.0 Hz, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2\mathit{C}H_3$), 60.3 ($CO_2\mathit{C}H_2CH_3$), 112.4 (C-4'), 112.6 (C-4''), 115.5 (C-3'), 116.9 (C-2), 122.0 (C-3''), 125.4 (C-5'), 132.1 (C-2´), 134.0 (C-3), 146.4 (C-2''), 147.6 (C-5''), 156.9 (N*C*O), 166.9 (*C*O_2Et). MS (70 eV): *m/z* 259 (50) $[M]^+$, 231 (11), 203 (32), 186 (18), 158 (22), 119 (12), 95 (100), 63 (9). HRMS (EI): *m/z* calcd. for $C_{14}H_{13}NO_4$ $[M]^+$: 259.0845; found 259.0851.

Methyl (*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-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 ºC for 1.5 h, **8a** (0.233 g, 93%) was obtained as a colorless oil. R_f = 0.70 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3243, 2951, 1690, 1622, 1468, 1331, 1286, 1173, 972, 731 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (t, *J* = 2.4 Hz, 1H, H-3''), 3.78 (s, 3H, $CO_2C\mathit{H}_3$), 4.75 (d, *J* = 2.4 Hz, 2H, H-1''), 6.18 (d, *J* = 15.6 Hz, 1H, H-2), 6.20-6.23 (m, 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'), 7.64 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 36.7 (C-1''), 51.5 ($CO_2\mathit{C}H_3$), 74.5 (C-3''), 77.3 (C-2''), 110.0 (C-4'), 112.6 (C-3'), 113.2 (C-2), 125.6 (C-5'), 128.6 (C-2'), 131.8 (C-3), 168.0 (*C*O_2Me). MS (70 eV): *m/z* 189 (17) $[M^+]$, 174 (40), 158 (43), 130 (100), 118 (11), 103 (22), 91 (14), 77 (19). Anal. calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.80; H, 5.82; N, 7.40.

Methyl (*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-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 ºC for 1 h, **8b** (0.107 g, 85%) was obtained as a dark solid. R_f = 0.77 (hexane/EtOAc, 7:3); mp 54-55 °C. IR (KBr): $\overline{\nu}$ = 2924, 1704, 1622, 1460, 1436, 1263, 1168, 1030, 966, 723 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, $CO_2C\mathit{H}_3$), 5.51 (d, *J* = 6.3 Hz, 1H, H-3''), 6.19 (d, *J* = 15.6 Hz, 1H, H-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, H-1''), 7.69 (d, *J* = 15.6 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.4 ($CO_2\mathit{C}H_3$), 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), 167.8 (*C*O_2CH_3), 203.8 (C-2''). MS (70 eV): *m/z* 189 (11) $[M]^+$, 158.0 (7), 130 (100), 103 (20), 77 (13). Anal. calcd. for $C_{11}H_{11}NO_2$ (189.21): C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.86; N, 7.39.

(*E*)-3-(1-(Prop-2-yn-1-yl)-1*H*-pyrrol-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 ºC for 1.5 h, **9a** (0.229 g, 87%) was obtained as a colorless oil. R_f = 0.66 (hexane/EtOAc, 7:3). IR (KBr): $\overline{\nu}$ = 3237, 2208, 1608, 1470, 1412, 1295, 1085, 951, 728 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (t, *J* = 2.4 Hz, 1H, H-3''), 4.71 (d, *J* = 2.4 Hz, 2H, H-1''), 5.56 (d, *J* = 16.2 Hz, 1H, H-2), 6.22 (ddd, *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 (dd, *J* = 2.6, 1.5 Hz, 1H, H-5'), 7.32 (d, *J* = 16.2 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): 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), 126.6 (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 $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.86; H, 5.13; N, 17.93.

(*E*)-3-(1-(Propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylonitrile (9b): Following the method of preparation for **7a**, by using **5d** (0.100 g, 0.85 mmol), NaH (60%) (0.068 g, 1.70 mmol) and propargyl bromide (**6a**) (0.200 g, 1.70 mmol) in dry DMF (1.0 mL), and after stirring at 0 ºC for 1 h, **9b** (0.114 g, 86%) was obtained as a colorless oil. R_f = 0.74 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2925, 2209, 1610, 1463, 1410, 1320, 1134, 956, 892, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55 (d, *J* = 6.3, 1H, H-3''), 5.56 (d, *J* = 16.2 Hz, 1H, H-2), 6.27 (dd, *J* = 3.8, 2.7 Hz, 1H, H-4'), 6.67 (dd, *J* = 3.8, 1.5 Hz, 1H, H-3'), 6.91 (t, *J* = 6.3 Hz, 1H, H-1''), 6.95 (dd, *J* = 2.7, 1.5 Hz, 1H, H-5'), 7.34 (d, *J* = 16.2 Hz, 1H, H-3). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 87.0 (C-3''), 90.7 (C-2), 96.4 (C-1''), 111.2 (C-4'), 112.5 (C-3'), 119.0 (C-1), 124.8 (C-5'), 128.0 (C-2'), 137.0 (C-3), 203.7 (C-2''). MS (70 eV): *m/z* 156 (100) $[M]^+$, 155 (100), 130 (20), 128 (42), 101 (6).

Ethyl (*E*)-3-(5-Formyl-1-(prop-2-ynyl)-1*H*-pyrrol-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 °C and maintained for 2 h. The reaction mixture was quenched with an aqueous solution of NaOH 2N until neutral, CH_2Cl_2 (250 mL) was added, the organic layer dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (30 g/g crude, hexane/EtOAc, 98:2) to give **10a** (0.101 g, 88%) as a white solid. R_f = 0.59 (hexane/EtOAc, 7:3); mp 90-91 °C. IR (KBr): $\overline{\nu}$ = 1705, 1659, 1628, 1472, 1449, 1409, 1309, 1270, 1234, 1183, 1048, 783 cm'^{1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H_3}$), 2.38 (t, *J* = 2.7 Hz, 1H, H-3''), 4.28 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H_2}CH_3$), 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, H-3), 9.60 (s, 1H, C*H*O). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2\mathit{C}H_3$), 34.4 (C-1''), 60.8 ($CO_2\mathit{C}H_2CH_3$), 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 (*C*O_2Et), 179.9 (*C*HO). 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 $C_{13}H_{13}NO_3$: 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-(3-methylbut-2-enyl)-1*H*-pyrrol-2-yl)acrylate (10b): Following the method of preparation for

10a, by using DMF (0.038 g, 0.52 mmol), $POCl_3$ (0.080 g, 0.52 mmol) and **7b** (0.100 g, 0.43 mmol), and after stirring at 40 ºC for 2 h, **10b** (0.091 g, 81%) was obtained as a white solid. R_f = 0.34 (hexane/EtOAc, 7:3); mp 74-75 °C. IR (film): $\overline{\nu}$ = 1706, 1663, 1625, 1475, 1307, 1244, 1184, 1051, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 6.9 Hz, 3H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 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). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.3 ($CO_2CH_2CH_3$), 18.2 (C-4'' or C-5''), 25.6 (C-5'' or C-4''), 43.4 (C-1''), 60.7 ($CO_2CH_2CH_3$), 110.9 (C-3'), 120.3 (C-2), 120.4 (C-2''), 124.3 (C-4'), 130.8 (C-3), 133.3 (C-5'), 135.5 (C-3''), 137.3 (C-2'), 166.5 (CO_2Et), 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* calcd. for $C_{15}H_{19}NO_3$ $[M]^+$: 261.1365; found 261.1358.

Ethyl (*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (10c): Following the method of preparation for **10a**, by using DMF (0.086 g, 1.18 mmol), $POCl_3$ (0.181 g, 1.18 mmol) and **7c** (0.200 g, 0.99 mmol), and after stirring at 40 ºC for 2 h, **10c** (0.189 g, 83%) was obtained as a pale yellow oil. R_f = 0.34 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 1709, 1660, 1445, 1370, 1261, 1190, 1036, 784 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.26 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 5.48 (d, *J* = 6.4 Hz, 2H, H-3''), 6.37 (d, *J* = 15.8 Hz, 1H, H-2), 6.70 (dd, *J* = 4.3, 0.6 Hz, 1H, H-3'), 7.02 (dd, *J* = 4.3, 0.6 Hz, 1H, H-4'), 7.62 (t, *J* = 6.4 Hz, 1H, H-1''), 7.83 (dd, *J* = 15.8, 0.6 Hz, 1H, H-3), 9.65 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2 ($CO_2CH_2CH_3$), 60.7 ($CO_2CH_2CH_3$), 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-5'), 137.3 (C-2'), 166.4 (CO_2Et), 179.5 (CHO), 203.8 (C-2''). MS (70 eV): *m/z* 231 (46) $[M]^+$, 203 (12), 158 (100), 130 (53), 103 (27), 77 (9). HRMS (EI): *m/z* calcd. for $C_{13}H_{13}NO_3$ $[M]^+$: 231.0895; found 231.0882.

Methyl (*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylate (11a): Following the method of preparation for **10a**, by using DMF (0.047 g, 0.64 mmol), $POCl_3$ (0.098 g, 0.64 mmol) and **8b** (0.100 g, 0.53 mmol), and after stirring at 40 ºC for 2 h, **11a** (0.101 g, 88%) was obtained as a brown solid. R_f = 0.65 (hexane/EtOAc, 7:3); mp 88-89 ºC. IR (film): $\overline{\nu}$ = 2950, 1706, 1656, 1627, 1449, 1310, 1275, 1201, 1046, 971, 790 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.81 (s, 3H, CO_2CH_3), 5.48 (d, *J* = 6.6 Hz, 2H, H-3''), 6.37 (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-4'), 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). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 51.8 (CO_2CH_3), 85.5 (C-3''), 95.9 (C-1''), 111.8 (C-3'), 119.6 (C-2), 123.9 (C-4'), 132.0 (C-3), 133.5 (C-5'), 137.1 (C-2'), 166.8 (CO_2CH_3), 179.4 (CHO), 203.6 (C-2''). MS (70 eV): *m/z* 217 (42) $[M]^+$, 158 (100), 130 (37), 103 (22), 77 (11). Anal. calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: 66.30; H, 5.12; N, 6.45.

(*E*)-3-(5-Formyl-1-(prop-2-ynyl)-1*H*-pyrrol-2-yl)acrylonitrile (12a): Following the method of preparation for **10a**, by using DMF (0.056 g, 0.77 mmol), $POCl_3$ (0.118 g, 0.77 mmol) and **9a** (0.100 g, 0.64 mmol), and after stirring at 40 ºC for 2 h, **12a** (0.109 g, 92%) was obtained as a white solid. R_f = 0.51 (hexane/EtOAc, 7:3); mp 103-104 ºC. IR (film): $\overline{\nu}$ = 2213, 1662, 1614, 1452, 1412, 1236, 1213, 1051, 968, 786 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (t, *J* = 2.7 Hz, 1H, H-3''), 5.38 (d, *J* = 2.7 Hz, 2H, H-1''), 5.91 (d, *J* = 16.2 Hz, 1H, H-2), 6.71 (dd, *J* = 4.4, 0.6 Hz, 1H, H-3'), 6.97 (dd, *J* = 4.4, 0.6 Hz, 1H, H-4'), 7.47 (br d, *J* = 16.2 Hz, 1H, H-3), 9.63 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 34.4 (C-1''), 74.2 (C-3''), 77.3 (C-2''), 98.6 (C-2), 111.7 (C-3'), 117.7 (C-1), 124.5 (C-4'), 133.1 (C-5'), 136.1 (C-3), 136.2 (C-2'), 180.3 (CHO). MS (70 eV): *m/z* 184 (36) $[M]^+$, 156 (34), 155 (100), 138 (34), 128 (29). HRMS (EI): *m/z* calcd. for $C_{11}H_8N_2O$ $[M]^+$: 184.0637; found 184.0637.

(*E*)-3-(5-Formyl-1-(propa-1,2-dien-1-yl)-1*H*-pyrrol-2-yl)acrylonitrile (12b): Following the method of preparation for **10a**, by using DMF (0.112 g, 1.54 mmol), $POCl_3$ (0.236 g, 1.54 mmol) and **9b** (0.200 g, 1.28 mmol), and after stirring at 40 ºC for 2 h, **12b** (0.175 g, 75%) was obtained as a colorless oil. R_f = 0.32 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 2922, 2207, 1607, 1458, 1412, 1303, 1079, 951, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.51 (d, *J* = 6.6 Hz, 2H, H-3''), 5.81 (d, *J* = 16.5 Hz, 1H, H-2), 6.70 (br d, *J* = 4.2 Hz, 1H, H-3'), 7.03 (dd, *J* = 4.2, 0.6 Hz, 1H, H-4'), 7.50 (dt, *J* = 16.5, 0.6 Hz, 1H, H-3), 7.59 (t, *J* = 6.6 Hz, 1H, H-1''), 9.68 (s, 1H, CHO). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 85.9 (C-3''), 95.7 (C-1''), 97.4 (C-2), 111.9 (C-3'), 117.8 (C-1), 123.7 (C-4'), 133.8 (C-5'), 135.8 (C-2'), 137.4 (C-3), 179.7 (CHO), 206.3 (C-2''). MS (70 eV): *m/z* 184 (70) $[M]^+$, 156 (100), 128 (30). HRMS (EI): *m/z* calcd. for $C_{11}H_8N_2O$ $[M]^+$: 184.0637; found 184.0635.

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 CH_2Cl_2 (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 $NaBH_4$ (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. R_f = 0.17 (hexane/EtOAc, 7:3). IR (film): $\overline{\nu}$ = 3368, 2925, 1597, 1502, 1369, 1197, 1174, 1150, 1092, 1015, 865, 814, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.20 (br, 1H, OH), 2.44 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 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), 7.68 (d, *J* = 8.0 Hz, 2H,

H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (*C*H$_3$), 64.2 (*C*H$_2$), 122.3 (C-2'), 127.9 (C-3'), 128.4 (C-2), 129.7 (C-3), 132.2 (C-1), 139.8 (C-4'), 145.4 (C-4), 148.8 (C-1'). MS (70 eV): *m/z* 278 (40) [M$^+$], 155 (54), 139 (10), 123 (31), 107 (46), 91 (100), 77 (10). HRMS (EI): *m/z* calcd. for $C_{14}H_{14}O_4S$ [M]$^+$: 278.0613; found 278.0604.

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 CH_2Cl_2 (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 1 h. The solvent was removed under vacuum and the residue purified by column chromatography over silica gel (10 g/g crude, hexane/EtOAc, 95:5) to afford **19** (0.876 g, 94%) as a white solid. R_f = 0.63 (hexane/EtOAc, 7:3); mp 78-79 °C. IR (KBr): $\bar{\nu}$ = 3401, 2918, 1806, 1596, 1500, 1369, 1197, 1177, 1147, 1091, 1018, 859, 810, 742, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3H, C*H*$_3$), 4.42 (s, 2H, C*H*$_2$), 6.95 (d, *J* = 8.5 Hz, 2H, H-2'), 7.28-7.33 (m, 4H, H-3', H-3), 7.70 (d, *J* = 8.0 Hz, 2H, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 (*C*H$_3$), 32.1 (*C*H$_2$), 122.7 (C-2'), 128.4 (C-2), 129.8 (C-3), 130.3 (C-3'), 132.3 (C-1), 136.7 (C-4'), 145.5 (C-4), 149.3 (C-1'). MS (70 eV): *m/z* 341 (2) [M$^+$], 261 (81), 155 (100), 91 (77). HRMS (EI): *m/z* calcd. for $C_{14}H_{13}BrO_3S$ [M]$^+$: 339.9769; found 339.9759.

4-((2-Formyl-1*H*-pyrrol-1-yl)methyl)phenyl 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, 5.86 mmol) in dry DMF (10 mL), and after stirring at 25 ºC for 5 h, **20** (2.001 g, 96%) was obtained as a white resin. R_f = 0.38 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 1662, 1597, 1503, 1477, 1404, 1371, 1319, 1198, 1177, 1154, 1092, 867, 757, 720 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3H, C*H*$_3$), 5.50 (s, 2H, C*H*$_2$), 6.27 (t, *J* = 3.6 Hz, 1H, H-4''), 6.86-6.92 (m, 2H, H-2'), 6.96 (d, *J* = 3.6 Hz, 2H, H-3'', H-5''), 7.01-7.07 (m, 2H, H-3'), 7.25-7.32 (m, 2H, H-3), 7.63-7.69 (m, 2H, H-2), 9.50 (d, *J* = 0.6 Hz, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (*C*H$_3$), 51.0 (*C*H$_2$), 110.3 (C-4''), 122.4 (C-2'), 125.0 (C-3''), 128.2 (C-3'), 128.3 (C-2), 129.7 (C-3), 131.1 (C-2''), 131.4 (C-5''), 132.0 (C-1), 136.6 (C-4'), 145.4 (C-4), 148.8 (C-1'), 179.4 (*C*HO). MS (70 eV): *m/z* 355 (27) [M]$^+$, 337 (8), 261 (14), 200 (94), 155 (54), 107 (32), 94 (100), 91 (38).

4-((2-(Hydroxymethyl)-1*H*-pyrrol-1-yl)methyl)phenyl 4-Methylbenzenesulfonate (21): $NaBH_4$ (0.099 g, 2.62 mmol) was added to a solution of **20** (1.860 g, 5.23 mmol) in a mixture of MeOH/CH_2Cl_2 (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. R_f = 0.25 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 3375, 2924, 1596, 1501, 1367, 1298, 1196, 1174, 1150, 1091, 1016, 862, 715 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (br s, 1H, OH), 2.44 (s, 3H, C*H*$_3$), 4.45 (br s, 2H, C*H*$_2$OH), 5.15 (s, 2H, H-1''), 6.11 (dd, *J* = 3.5, 2.7 Hz, 1H, H-4'''), 6.15 (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). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.7 (*C*H$_3$), 49.7 (C-1''), 56.6 (*C*H$_2$OH), 107.5 (C-4'''), 109.5 (C-3'''), 122.6 (C-2'), 123.1 (C-5'''), 127.7 (C-3'), 128.4 (C-2), 129.7 (C-3), 131.6 (C-2'''), 132.1 (C-1), 137.3 (C-4'), 145.4 (C-4), 148.7 (C-1'). HRMS (EI): *m/z* calcd. for $C_{19}H_{19}NO_4S$ [M]$^+$: 357.1035; found 357.1025.

(1-(4-(*p*-Tosyloxy)benzyl)-1*H*-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 CH_2Cl_2 (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 CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried (Na_2SO_4) 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. R_f = 0.48 (hexane/EtOAc, 7:3). IR (film): $\bar{\nu}$ = 2926, 1735, 1596, 1502, 1372, 1302, 1237, 1197, 1176, 1152, 1092, 1017, 864, 834, 815, 719 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.80 (s, 3H, C*H*$_3$CO$_2$), 2.45 (s, 3H, C*H*$_3$), 4.97 (s, 2H, C*H*$_2$), 5.09 (s, 2H, H-1''), 6.16 (dd, *J* = 3.5, 2.8 Hz, 1H, H-4'), 6.29 (dd, *J* = 3.5, 1.8 Hz, 1H, H-3'), 6.70 (dd, *J* = 2.8, 1.8 Hz, 1H, H-5'), 6.85-6.95 (m, 4H, H-2''', H-3'''), 7.28-7.34 (m, 2H, H-3^{IV}), 7.66-7.72 (m, 2H, H-2^{IV}). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 20.7 (*C*H$_3$CO$_2$), 21.7 (*C*H$_3$), 49.8 (C-1''), 57.4 (*C*H$_2$), 108.0 (C-4'), 112.0 (C-3'), 122.6 (C-3'''), 123.7 (C-5'), 126.6 (C-2'), 127.3 (C-2'''), 128.4 (C-2^{IV}), 129.8 (C-3^{IV}), 132.2 (C-1^{IV}), 137.2 (C-1'''), 145.4 (C-4^{IV}), 148.7 (C-4'''), 170.6 (CH$_3$*C*O$_2$). MS (70 eV): *m/z* 341 (14) [M - 59]$^+$, 261 (13), 203 (17), 184 (15), 155 (22), 124 (20), 107 (24), 91 (100), 77 (25). HRMS (EI): *m/z* calcd. for $C_{21}H_{21}NO_5S$ [M]$^+$: 399.1140; found 399.1129.

(5-Formyl-1-(4-(*p*-tosyloxy)benzyl)-1*H*-pyrrol-2-yl)methyl acetate (23): Following the method of preparation for **7a**, by using dry DMF (0.137 g, 1.87 mmol), $POCl_3$ (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 ºC 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 (Na_2SO_4) 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. R_f = 0.63 (hexane/EtOAc, 1:1). IR (film): $\bar{\nu}$ = 1741, 1663, 1503, 1371, 1225, 1198, 1176, 1153, 1092, 1019, 865 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (s, 3H, C*H*$_3$CO$_2$), 2.45 (s, 3H, C*H*$_3$), 5.00 (s, 2H, C*H*$_2$), 5.64 (s, 2H, H-1''), 6.49 (d, *J* = 4.0 Hz, 1H, H-3'), 6.83-6.88 (m, 2H, H-3'''), 6.88-6.93 (m, 2H, H-2'''), 6.97 (d, *J* = 4.0 Hz, 1H, H-4'),

7.28-7.32 (m, 2H, H-3^{IV}), 7.67-7.98 (m, 2H, H-2^{IV}), 9.55 (s, 1H, C*H*O). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5 (*C*H_3CO_2), 21.7 (*C*H_3), 48.0 (C-1''), 56.7 (*C*H_2), 112.9 (C-3'), 122.5 (C-3'''), 124.2 (C-4'), 127.2 (C-2'''), 128.4 (C-2^{IV}), 129.8 (C-3^{IV}), 132.4 (C-1^{IV}), 132.8 (C-5'), 136.6 (C-1'''), 137.0 (C-2'); 145.4 (C-4^{IV}), 148.8 (C-4'''), 170.2 (CHO), 179.8 (CH$_3$*C*O$_2$). MS (70 eV): *m/z* 427 (3) $[M]^+$, 367 (11), 272 (9), 261 (9), 212 (100), 196 (17), 184 (24), 155 (52), 123 (38), 108 (11), 91 (27). HRMS (EI): *m/z* calcd. for $C_{22}H_{21}NO_6S$ $[M]^+$: 427.1090; found 427.1089.

1-(4-Hydroxybenzyl)-5-(hydroxymethyl)-1*H*-pyrrole-2-carbaldehyde (Pyrrolemarumine) (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/H_2O (1:1) (3 mL) was stirred at room temperature for 24 h. MeOH was removed under vacuum and CH_2Cl_2 (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 CH_2Cl_2 (2 x 100 mL). The organic layers were dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g crude, hexane/EtOAc, 1:1) to afford **4b** (0.069 g, 76%) as a pale yellow resin. R_f = 0.35 (hexane/EtOAc, 1:1). IR (film): $\bar{\nu}$ = 3333, 2970, 1644, 1516, 1456, 1371, 1243, 1173, 1046, 1011, 822, 784, cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 4.48 (br s, 1H, CH_2OH), 4.57 (br s, 2H, CH_2OH), 5.65 (s, 2H, H-1'), 6.27 (d, *J* = 3.9 Hz, 1H, H-4), 6.71-6.78 (m, 2H, H-3''), 6.89-6.96 (m, 2H, H-2''), 6.98 (d, *J* = 3.9 Hz, 1H, H-3), 8.43 (br s, 1H, Ar-O*H*), 6.53 (s, 1H, C*H*O). ^{13}C NMR (75.4 MHz, acetone-d_6): δ = 48.3 (C-1'), 56.7 (*C*H_2OH), 110.7 (C-4), 116.1 (C-3''), 124.8 (C-3), 128.7 (C-2''), 130.0 (C-1''), 133.3 (C-2), 144.4 (C-5), 157.5 (C-4''), 180.0 (*C*HO). MS (70 eV): *m/z* 231 (11) $[M]^+$, 214 (11), 125 (100), 108 (82), 107 (80), 96 (48), 77 (39), 68 (18). DART-MS *m/z* calcd. for $C_{13}H_{14}NO_3$ $[M + H]^+$: 232.0967; found: 232.0974.

Acknowledgments

We thank R. Bautista and A. Jerezano for their help in spectrometric measurements, and Bruce Allan Larsen for proofreading the manuscript. J.T. acknowledges SIP/IPN (Grants 20130686, 20140858 and 20150917) and CONACYT (Grants 83446 and 178319) for financial support. E.I.M.-M., M.A.C., C.H.E., D.A.M. and H.Q.-F. thank CONACYT for awarding a scholarship, and also SIP/IPN (PIFI) and the Ludwig K. Hellweg Foundation for scholarship complements. F.D. and J.T. are fellows of the EDI-IPN and COFAA-IPN programs.

References

1. a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435-446. b) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143-1191.
2. a) Faghih, R.; Gopalakrishnan, S. M.; Gronlien, J. H.; Malysz, J.; Briggs, C. A.; Wetterstrand, C.; Ween, H.; Curtis, M. P.; Sarris, K. A.; Gfesser, G. A.; El-Kouhen, R.; Robb, H. M.; Radek, R. J.; Marsh, K. C.; Bunnelle, W. H.; Gopalakrishnan, M. *J. Med. Chem.* **2009**, *52*, 3377-3384. b) La Regina, G.; Bai, R.; Coluccia, A.; Famiglini, V.; Pelliccia, S.; Passacantilli, S.; Mazzoccoli, C.; Ruggieri, V.; Sisinni, L.; Bolognesi, A.; Rensen, W. M.; Miele, A.; Nalli, M.; Alfonsi, R.; Di Marcotullio, L.; Gulino, A.; Brancale, A.; Novellino, E.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Hamel, E.; Lavia, P.; Silvestri, R. *J. Med. Chem.* **2014**, *57*, 6531−6552. c) Crucitti, G. C.; Métifiot, M.; Pescatori, L.; Messore, A.; Madia, V. N.; Pupo, G.; Saccoliti, F.; Scipione, L.; Tortorella, S.; Esposito, F.; Corona, A.; Cadeddu, M.; Marchand, C.; Pommier, Y.; Tramontano, E.; Costi, R.; Di Santo, R. *J. Med. Chem.* **2015**, *58*, 1915-1928.
3. a) El Sayed, K. A.; Hamann, M. T.; El-Rahman, H. A. A.; Zaghloul, A. M. *J. Nat. Prod.* **1998**, *61*, 848-850. b) Zhan, Z.; Feng, Z.; Yang, Y.; Li, L.; Jiang, J.; Zhang, P. *Org. Lett.* **2013**, *15*, 1970-1973.
4. a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264-287. b) Gupton, J. T.; Banner, E. J.; Sartin, M. D.; Coppock, M. B.; Hempel, J. E.; Kharlamova, A.; Fisher, D. C.; Giglio, B. C.; Smith, K. L.; Keough, M. J.; Smith, T. M.; Kanters, R. P. F.; Dominey, R. N.; Sikorski, J. A. *Tetrahedron* **2008**, *64*, 5246-5253. c) Al-Mourabit, A.; Zancanella, M. A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep.* **2011**, *28*, 1229-1260.
5. Han, L.; Gao, C.; Jiang, Y.; Guan, P.; Liu, J.; Li, L.; Xu, L.; Huang, X. *J. Nat. Prod.* **2014**, *77*, 2605-2610.
6. Ding, L.; Dahse, H.-M.; Hertweck, C. *J. Nat. Prod.* **2015**, *75*, 617-621.
7. Choi, J.-H.; Suzuki, T.; Kawaguchi, T.; Yamashita, K.; Morita, A.; Masuda, K.; Yazawa, K.; Hirai, H.; Kawagishi, H. *Tetrahedron Lett.* **2013**, *135*, 18032-18035.
8. Youn, U. J.; Kil, Y.-S.; Nam, J.-W.; Lee, Y. J.; Kim, J.; Lee, D.; Lee, J.-H.; Seo, E.-K. *Helv. Chim. Acta* **2013**, *96*, 1482-1487.
9. Kikuchi, T.; Ikedaya, A.; Toda, A.; Ikushima, K.; Yamakawa, T.; Okada, R.; Yamada, T.; Tanaka, R. *Phytochem. Lett.* **2015**, *12*, 94-97.
10. Sahakitpichan, P.; Mahidol, C.; Disadee, W.; Ruchirawat, S.; Kanchanapoom, T. *Phytochemistry* **2011**, *72*, 791-795.
11. Lederer, M. O.; Baumann, M. *Bioorg. Med. Chem.* **2000**, *8*, 115-121.
12. a) Quiroz-Florentino, H.; Aguilar, R.; Santoyo, B. M.; Díaz, F.; Tamariz, J. *Synthesis* **2008**, 1023-1028. b) Quiroz-Florentino, H.; García, A.; Burgueño-Tapia, E.; Tamariz, J. *Nat. Prod. Res.* **2009**, *23*, 1355-1362.
13. Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
14. a) Pfefferkorn, J. A.; Choi, C.; Song, Y.; Trivedi, B. K.; Larsen, S. D.; Askew, V.; Dillon, L.; Hanselman, J. C.; Lin, Z.; Lu, G.; Robertson, A.; Sekerke, C.; Auerbach, B.; Pavlovsky, A.; Harris, M. S.; Bainbridge, G.; Caspers, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4531-4537. b) Pfefferkorn, J. A.; Bowles, D. M.; Kissel, W.; Boyles, D. C.; Choi, C.; Larsen, S. D.; Song, Y.; Sun, K.-L.; Miller, S. R.; Trivedi, B. K. *Tetrahedron* **2007**, *63*, 8124-8134.
15. Mendieta, A.; Jiménez, F.; Garduño-Siciliano, L.; Mojica-Villegas, A.; Rosales-Acosta, B.; Villa-Tanaca, L.; Chamorro-Cevallos, G.; Medina-Franco, J. L.; Meurice, N.; Gutiérrez, R. U.; Montiel, L. E.; Cruz, M. C.; Tamariz, J. *Bioorg. Med. Chem.* **2014**, *22*, 5871-5882; and references cited therein.

16. a) Tietze, L. F.; Brumby, T.; Pfeiffer, T. *Liebigs Ann. Chem.* **1988**, 9-12. b) Bashiardes, G.; Safir, I.; Barbot, F. *Synlett* **2007**, 1707-1710. c) Albano, V. G.; Gualandi, A.; Monari, M.; Savoia, D. *J. Org. Chem.* **2008**, *73*, 8376-8381.
17. Fleming, C. L.; Ashton, T. D.; Gaur, V.; McGee, S. L.; Pfeffer, F. M. *J. Med. Chem.* **2014**, *57*, 1132-1135.
18. a) Barker, P.; Gendler, P.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4849-4853. b) Tsuchimoto, T. *Chem. Eur. J.* **2011**, *17*, 4064-4075.
19. Fichigami, R.; Namba, K.; Tanino, K. *Tetrahedron Lett*. **2012**, *53*, 5725-5728.
20. Gieβler, K.; Griesser, H.; Göhringer, D.; Sabirov, T.; Richert, C. *Eur. J. Org. Chem*. **2010**, *19*, 3611-3620.
21. Mercey, J. M.; Toube, T. P. *J. Chem. Res*. **1987**, *3*, 62.