Synthesis of (*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-ene Derivatives Using Organophosphorous Reagents

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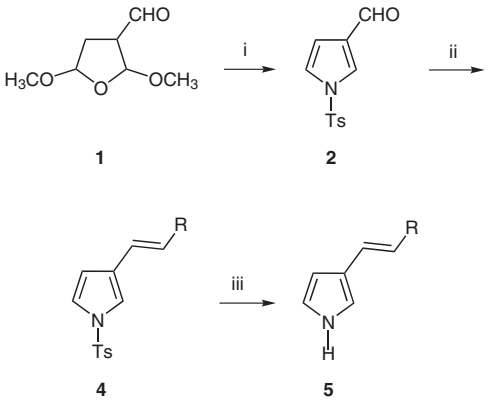
Abstract: The synthesis of (*E*)-3-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-ene derivatives from 1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde by the Horner–Wadsworth–Emmons (HWE) reaction, is described. However, the HWE reaction with diethyl methoxymethylphosphonate and diethyl (2-methoxyethoxy)methylphosphonate gave a different product, namely, diethyl {1-methoxy(or methoxyethoxy)-2-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]vinyl}phosphonates, respectively. (*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enes were easily hydrolysed to (*E*)-3-(1*H*-pyrrol-3-yl)prop-2-enes, two of which are natural products.

Key words: pyrroles, phosphonates, Horner–Wadsworth–Emmons reaction

3-(1*H*-Pyrrol-3-yl)prop-2-enes are considered an important class of chemical compounds because of their application in the synthesis of a variety of molecules of biological interest. For example they have been used for the synthesis of several members of the pyrrolobenzodiazepine family of anticancer antibiotics, of certain analogues of porphobilinogen that constitute the major structural component of all naturally occurring porphyrins, and of analogues of various amino acids.[1] Despite these reports, 3-(1*H*-pyrrol-3-yl)prop-2-enes have not yet been studied thoroughly.

Keller-Schierlein and co-workers[2] described the isolation of propenoic acid **5a** and of propenamide **5b** from *Streptomyces parvulus* (Scheme 1). Larsen and Hjeds[3] synthesised **5a** by performing initially a Doebner condensation between methyl 3-formyl-1*H*-pyrrole-1-carboxylate and malonic acid, followed by basic hydrolysis. The amide **5b** was synthesised by Keller-Schierlein and co-workers[2] by the action of ammonia on the acid chloride of compound **5a**. The first application of organophosphorus chemistry towards the synthesis of this type of compounds was described by Magnus[4] who synthesised methyl 4-[(*E*)-3-(benzyloxy)-3-oxoprop-1-enyl]-1-(toluene-4-sulfonyl)-1*H*-pyrrole-2-carboxylate by reacting the anion of phosphonate ester $(EtO)_2P(O)CH_2CO_2Bn$ with methyl 4-formyl-1-(toluene-4-sulfonyl)-1*H*-pyrrole-2-carboxylate. Nishikawa[5] followed a similar methodology to synthesise



a, R = CO_2H; **b**, R = $CONH_2$; **c**, R = $CONMe_2$; **d**, R = CO_2Et; **e**, R = COMe; **f**, R = CN

Scheme 1 *Reagents and conditions*: (i) $TsNH_2$, TsOH, toluene, reflux, 3 h; (ii) (a) 95% NaH, *t*-BuOK or LDA (Table 1), THF, –40 °C (or –78 °C when LDA used); (b) phosphonate **3a**–**e** or **f**, THF, –40 to 0 °C, then –40 °C; (c) aldehyde **2**, THF, 0 – 5 °C; (d) aq sat. NH_4Cl; (iii) K_2CO_3, MeOH, r.t. 18 h.

5d using phosphonate ester **3d** (Table 1) and 1*H*-pyrrole-3-carbaldehyde. The ester **5d** was hydrolyzed to the acid **5a** and then used to synthesise *N*-[4-(4-benzhydrylpiperazin-1-yl)butyl]-3-(1*H*-pyrrol-3-yl)acrylamide.

Considering the advantages of the Horner–Wadsworth–Emmons (HWE) reaction over the Wittig reaction[6], we chose phosphonates **3a**–**f** (Table 1) as substrates and studied the reaction of their anions with carbaldehyde **2** (Scheme 1). A search in the literature revealed that 1*H*-pyrrole-3-carbaldehydes have been synthesised by eight routes, which are the acid-catalysed isomerisation of 1*H*-pyrrole-2-carbaldehydes,[7] Vilsmeier–Haack formylation or Friedel–Crafts acylation at position 4 of 2-substituted 1*H*-pyrroles followed by removal of the deactivating substituent,[8] Vilsmeier–Haack formylation of 1-(triisopropylsilyl)-1*H*-pyrrole and then removal of the bulky trialkylsilyl moiety,[9] Friedel–Crafts acetylation of 1-(arylsufonyl)-1*H*-pyrrole followed by transformation of acetyl to formyl,[10] and reaction of commercially available 2,5-dimethoxytetrahydrofuran-3-carbaldehyde with primary amines.[11a] In the latter reaction Hamdan and Wasley[11b] used benzenesulfonamide in boiling acetic acid and obtained 1-benzenesulfonyl-1*H*-pyrrole-3-carbaldehyde in 53% yield. Heating the latter in methanol contain-

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Table 1 Conversion of 1-Tosyl-1*H*-pyrrole-3-carbaldehyde **2** into Olefins **4a–f** or **10a**,**b**

Entry	Phosphonate	Base (equiv)	Time (h)	Product	Yield (%)[a]
1	$(EtO)_2P(O)CH_2CO_2H$ (**3a**)	LDA (2)	12	**4a**	67
2	$(EtO)_2P(O)CH_2CONH_2$ (**3b**)	*t*-BuOK (2)	12	**4b**	58
3	$(EtO)_2P(O)CH_2CONMe_2$ (**3c**)	NaH (1.2)	0.5	**4c**	82
4	$(EtO)_2P(O)CH_2CO_2Et$ (**3d**)	NaH (1.2)	0.5	**4d**	74
5	$(EtO)_2P(O)CH_2COMe$ (**3e**)	NaH (1.1)	12	**4e**	88
6	$(EtO)_2P(O)CH_2CN$ (**3f**)	NaH (1.1)	12	**4f**	76
7	$(EtO)_2P(O)CH_2OMe$ (**3g**)	LDA (1.2)	4	**10a**	44
8	$(EtO)_2P(O)CH_2O(CH_2)_2OMe$ (**3h**)	LDA (1.2)	4	**10b**	39

[a] Yields of isolated products.

ing potassium carbonate afforded 1*H*-pyrrole-3-carbaldehyde in excellent yield. We found it more convenient to heat 2,5-dimethoxytetrahydrofuran-3-carbaldehyde in toluene with 4-toluenesulfonamide and a catalytic amount of 4-toluenesulfonic acid since the product, **2** (Scheme 1) was isolated in 72% yield.

Pyrrole **2** was preferred over 1*H*-pyrrole-3-carbaldehyde for the HWE reaction because only a single step is required for its preparation. Moreover, the tosyl group of pyrrole **2** confers stability to the pyrrole ring, neutralises its acidic nature, and, activates the formyl group into undergoing addition reactions under milder conditions.

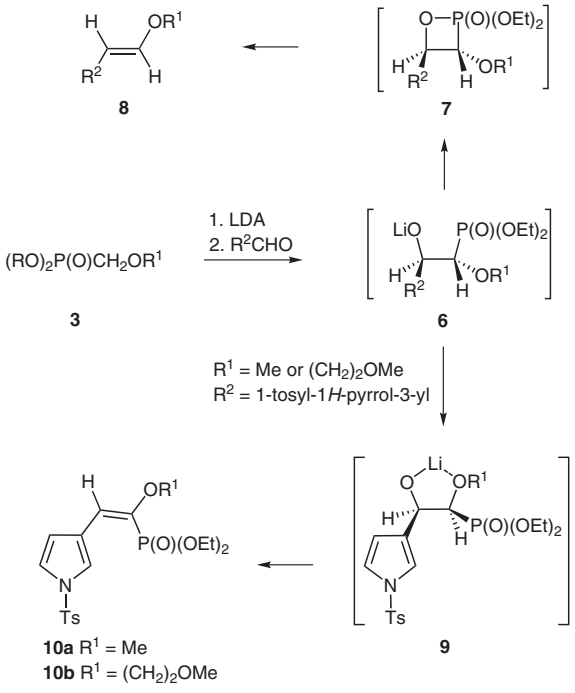
Phosphonates **3c**[12] and **e**[13] were easily prepared by the Michaelis–Arbuzov reaction between triethylphosphite and the corresponding alkyl halides in good yields, whereas phosphonates **3a**,**b**,**d** and **f** were commercially available (Table 1).

Treatment of phosphonates **3c**,**d**,**e** and **f** with a slight excess of NaH (1.1–1.2 equiv) lead to the corresponding monocarbanions whereas treatment of **3a** with LDA (2 equiv) or **3b** with *t*-BuOK (2 equiv) lead to the corresponding dicarbanions. Addition of a solution of aldehyde **2** to these anions and reaction at room temperature for 0.5 to 12 hours led to propenoates **4a–f** in moderate to good yields (Scheme 1, Table 1). Compound **4c** which is formed in excellent yield, is a potential key intermediate for the synthesis of unsaturated analogues of porothramycin.[14] The reactions are stereoselective and only the *E*-isomers of compounds **4a–f** were obtained since in ^1H NMR spectra of these compounds the two vinylic protons appear as doublets with *J* values of 15–16 Hz.

It has been reported by Kluge and Clousdale[15] that when phosphonates **3** (R^1 = alkyl or silyl) (Scheme 2) were treated with LDA and then the resulting non-stabilised carbanions reacted with aldehydes or ketones, the formed intermediate, i.e. deprotonated β-hydroxyphosphonates **6**, could be converted into enol ethers **8**, in either one step by heating to reflux or in two steps by adding water to give β-hydroxyphosphonates, that were then treated with *t*-BuOK.

Unexpected results were obtained when phosphonate **3g** or **3h** was treated with LDA (1.2 equiv) in THF at –78 °C, pyrrole-3-carbaldehyde **2** added, and then the reaction mixture allowed to reach room temperature before being heated to reflux for four hours. The work-up involved the addition of an aqueous solution of $NaHCO_3$ that gave instead of the corresponding enol ethers **8**, the vinylphosphonates **10a**,**b** (Scheme 2).

Only one similar reaction has been reported in the literature, namely the treatment of diethyl α-benzyloxymethylphosphonate with two equivalents of LDA and diethyl chlorophosphate to give an intermediate methylenebis-



Scheme 2

phosphonate lithium salt, which reacted with formaldehyde to afford diethyl α-benzyloxyvinylphosphonate.[16] The mechanistic explanation we propose for the unusual outcome of the reaction between alkoxymethylphosphonates **3g**,**h** and aldehyde **2** is as follows. In the first step the deprotonated phosphonate **3** adds to the carbonyl group to give intermediate lithium alkoxide **6**. In the normal HWE-reaction the enol ether **8** is formed via a four-membered transition state **7** and elimination of diethyl phosphate. In the case of α-alkoxy-substituted phosphonates **3g**,**h** the primary adduct **6** can be expected to exist as conformation **9**, where chelation of the Li-cation by the α-alkoxy group is possible. This prevents the formation of a four-membered intermediate **7** leading to enol ethers **8**. Thus β-elimination of LiOH from **9** occurs similarly to an aldol condensation resulting in α-alkoxy substituted vinylphosphonates **10a**,**b**. The difference in the outcome of the reaction of the alkoxymethylphosphonates **3** with 1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde **2** (formation of **10**) on one hand and with aliphatic and aromatic aldehydes or ketones in the other (formation of **8**), is obviously attributed to the effect of the toluene-4-sulfonyl substituent of **2**.

In conclusion, we have presented a short, efficient synthesis of 1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde and an efficient method for the preparation of (*E*)-3-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-ene derivatives, by reacting 1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde with appropriate phophonates. The reaction of 1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde with diethyl methoxymethylphosphonate or diethyl methoxyethoxymethylphophonate did not give the expected enol ethers but the corresponding vinylphosphonic acid diethyl esters by a type of aldol condensation, for which a mechanistic interpretation is proposed.

Melting points were taken on a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer, as Nujol mulls and liquids between NaCl discs. NMR spectra were measured at 300 MHz on Bruker AC 300 spectrometer, at 250 MHz on a Bruker AM 250 spectrometer or at 400 MHz on a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained using a JEOL JMS-AX 505W or a Bruker Apex III high resolution instruments Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out for all separations using Merck 9385 silica gel. Solvents and reagents were used as received from commercial suppliers, except for CH_2Cl_2, MeOH, THF, EtOAc and hexane, which were purified and dried according to standard procedures.

1-(Toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde (2)

2,5-Dimethoxytetrahydrofuran-3-carbaldehyde (9.61 g, 60 mmol) was added dropwise to a stirred solution of 4-toluenesulfonamide (10.27 g, 60 mmol) and 4-toluenesulfonic acid (1.14 g, 6 mmol) in anhyd toluene (100 mL). The resulting mixture was refluxed for 3 h. After cooling, the mixture was diluted with EtOAc (125 mL) and washed with aq 10% $NaHCO_3$ (3 × 25 mL), brine (25 mL) and then dried (Na_2SO_4). Evaporation of the solvent in vacuo followed by recrystallisation of the residual solid from Et_2O–hexane (1:3) gave the product (10.8 g, 72%); mp 62–62.5 °C (Lit.[17] mp 61–62 °C).

(*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]-2-propene Derivatives 4a–f and Diethyl {1-Alkoxy-2-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]vinyl}phosphonates 10a,b; General Procedure

The appropriate base [95% NaH, *t*-BuOK or LDA (prepared from diisopropylamine and 1.5 M *n*-BuLi in hexane), 14.4 to 30 mmol, Table 1] was suspended in anhyd THF (10 mL) under argon, and cooled to –40 °C (or –78 °C when LDA used). A solution of phosphonate **3** (12 mmol) in anhyd THF (15 mL) kept at the same temperature, was added dropwise. The stirred mixture was allowed to warm to 0 °C and then cooled again to –40 °C before adding dropwise a solution of **2** (10.9 mmol) in anhyd THF (15 mL). The mixture was stirred for the allocated time (Table 1) while the temperature was maintained at 0–5 °C and then poured into aq sat. NH_4Cl solution (50 mL) [or the mixture was allowed to reach r.t. before being refluxed for 4 h, and then poured into a sat. aq solution of $NaHCO_3$ (50 mL) for **3g**,**h**]. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL) [or extracted with EtOAc (3 × 15 mL) for **3g**,**h**]. The combined organic extracts were washed with brine (25 mL) and dried (Na_2SO_4). The organic solvents were evaporated under vacuo and the crude product purified either by recrystallisation or by column chromatography. Reaction conditions are given in Table 1.

(*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enoic Acid (4a)

Obtained as yellow microcrystals (EtOAc–hexane, 1:4); yield: 2.14 g (67%); mp 184–185 °C.

IR (Nujol): 1690, 1340, 1150 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 6.23 (d, *J* = 15.9 Hz, 1 H, H-α), 6.77 (t, *J* = 2.8 Hz, 1 H, H-4), 7.37 (dd, *J* = 3.3, 1.5 Hz, 1 H, H-5), 7.42 (d, *J* = 15.9 Hz, 1 H, H-β), 7.45 (d, *J* = 8.3 Hz, 2 H, H-3′, H-5′), 7.78 (br s, 1 H, H-2) 7.86 (d, *J* = 8.3 Hz, 2 H, H-2′, H-6′), 12.21 (s, 1 H, OH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.1, 111.8, 118.4, 122.7, 123.2, 124.9, 126.9 (d), 130.4 (d), 134.8, 136.2, 145.8, 167.7.

MS (EI, 70 eV): *m*/*z* (%) = 292 (19), 291 (100, [M^+]), 155 (5), 139 (6), 136 (8), 119 (17).

HRMS-EI: *m*/*z* calcd for $C_{14}H_{13}NO_4S$ [M^+]: 291.0565; found: 291.0561.

(*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enamide (4b)

Obtained as colourless solid after column chromatography (EtOAc–hexane, 1:2 to 1:0) and recrystallisation (EtOAc–hexane, 1:2); yield: 1.83 g (58%); mp 195–196 °C.

IR (Nujol): 3320, 3120, 1670, 1340, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3 H, CH_3), 5.71 (br s, 2 H, NH_2), 6.16 (d, *J* = 15.5 Hz, 1 H, H-α), 6.45 (dd, *J* = 3.3, 1.5 Hz, 1 H, H-4), 7.13 (t, *J* = 2.8 Hz 1 H, H-5), 7.29–7.31 (m, 3 H, H-3, H-3′, H-5′), 7.45 (d, *J* = 15.5 Hz, 1 H, H-β), 7.75 (d, *J* = 8.3 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 111.7, 117.9, 123.1, 123.9, 125.4, 126.8 (d), 130.2 (d), 134.4, 136.7, 146.1, 168.1.

MS (EI, 70 eV): *m*/*z* (%) = 290 (48, [M^+]), 234 (12), 155 (14), 135 (100), 108 (15), 91 (75), 65 (18).

HRMS-EI: *m*/*z* calcd for $C_{14}H_{14}N_2O_3S$ [M^+]: 290.0725; found: 290.0725.

(*E*)-*N*,*N*-Dimethyl-3-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enamide (4c)

Obtained as colourless solid after column chromatography (EtOAc–hexane, 1:4 to 9:1) and recrystallisation (EtOAc–hexane, 3:7); yield: 2.43 g (82%); mp 139–140 °C.

IR (Nujol): 1670, 1340, 1150 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, tosyl CH_3), 2.95 (s, 3 H, amide CH_3), 3.03 (s, 3 H, amide CH_3), 6.40 (dd, *J* = 3.3, 1.5 Hz, 1 H, H-4), 6.51 (d, *J* = 15.3 Hz, 1 H, H-α), 7.05 (dd, *J* = 3.3, 2.6 Hz, 1 H, H-5), 7.19–7.24 (m, 3 H, H-2, H-3′, H-5′), 7.38 (d, *J* = 15.3 Hz, 1 H, H-β), 7.68 (d, *J* = 8.4 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 35.8, 37.3, 111.2, 116.8, 121.5, 122.1, 125.7, 126.9 (d), 130.1 (d), 134.0, 135.6, 145.4, 166.6.

MS (EI, 70 eV): *m*/*z* (%) = 318 (48, [M^+]), 274 (72), 229 (11), 180 (21), 163 (100), 91 (32).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{18}N_2O_3S$ [M^+]: 318.1038; found: 318.1042.

Ethyl (*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enoate (4d)

Obtained as colourless solid after column chromatography (EtOAc–hexane, 1:4 to 9:1) and recrystallisation (EtOAc–hexane, 1:4); yield: 2.57 g (74%); mp 108–109 °C.

IR (Nujol): 1720, 1340, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3 H, ester CH_3), 2.41 (s, 3 H, tosyl CH_3), 4.24 (q, *J* = 7.1 Hz, 2 H, ester CH_2), 6.13 (d, *J* = 15.8 Hz, 1 H, H-α), 6.48 (dd, *J* = 3.3, 1.5 Hz, 1 H, H-4), 7.15 (dd, *J* = 3.3, 2.6 Hz, 1 H, H-5), 7.31–7.33 (m, 3 H, H-2, H-3′, H-5′), 7.48 (d, *J* = 15.8 Hz, 1 H, H-β), 7.77 (d, *J* = 8.2 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.1, 59.9, 111.8, 118.4, 122.7, 123.2, 124.9, 126.9 (d), 130.4 (d), 134.8, 136.2, 145.8, 168.6.

MS (EI, 70 eV): *m*/*z* (%) = 319 (100, [M^+]), 274 (49), 247 (21), 155 (63), 135 (26), 119 (23), 118 (20), 91 (87).

HRMS-EI: *m*/*z* calcd for $C_{16}H_{17}NO_4S$ [M^+]: 319.0876; found: 319.0868.

(*E*)-4-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]but-3-en-2-one (4e)

Obtained as colourless microcrystals (EtOAc–hexane, 3:7); yield: 3.05 g (88%); mp 93–94 °C.

IR (Nujol): 1680, 1660, 1340, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, CH_3), 2.41 (s, 3 H, CH_3), 6.41 (d, *J* = 16.1 Hz, 1 H, H-α), 6.48 (d, *J* = 2.6 Hz, 1 H, H-4), 7.15 (s, 1 H, H-5), 7.31 (d, *J* = 8.1 Hz, 2 H, H-3′, H-5′), 7.33 (d, *J* = 16.1 Hz, 1 H, H-β), 7.36 (s, 1 H, H-2), 7.76 (d, *J* = 8.2 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.1, 111.8, 118.4, 122.7, 123.2, 124.9, 126.9 (d), 130.4 (d), 134.8, 136.2, 145.8, 168.6.

MS (EI, 70 eV): *m*/*z* (%) = 289 (65, [M^+]), 274 (41), 155 (42), 134 (51), 114 (28), 100 (28), 95 (24), 91 (100), 57 (26), 51 (35).

HRMS-EI: *m*/*z* calcd for $C_{15}H_{15}NO_3S$ [M^+]: 289.0773; found: 289.0772.

(*E*)-3-[1-(Toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]prop-2-enenitrile (4f)

Obtained as colourless solid after column chromatography (EtOAc–hexane, 1:4 to 9:1) and recrystallisation (EtOAc–hexane, 1:2); yield: 2.40 g (76%); mp 120–122 °C.

IR (Nujol): 2250, 1340, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 5.54 (d, *J* = 16.4 Hz, 1 H, H-α), 6.41 (s, 1 H, H-4), 7.15 (s, 1 H, H-2), 7.18 (d, *J* = 16.4 Hz, 1 H, H-β), 7.33 (m, 3 H, H-5, H-3′, H-5′), 7.77 (d, *J* = 8.1 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.6, 95.1, 110.0, 122.0 122.1, 122.6, 124.2, 127.1 (d), 130.3 (d), 135.2, 142.2, 145.8.

MS (EI, 70 eV): *m*/*z* (%) = 272 (45, [M^+]), 221 (30), 155 (67), 125 (13), 111 (22), 91 (100), 71 (28), 55 (26).

HRMS-EI: *m*/*z* calcd for $C_{14}H_{12}N_2O_2S$ [M^+]: 272.0619; found: 272.0612.

Diethyl {1-Methoxy-2-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]vinyl}phosphonate (10a)

Obtained as yellow microcrystals after column chromatography (EtOAc–hexane, 1:1 to 1.0) and recrystallisation (EtOAc–hexane, 1:1); yield: 1.98 g (44%); mp 100–102 °C.

IR (Nujol): 1640, 1340, 1150 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.15–1.91 (m, 6 H, 2 × OCH_2CH_3), 2.37 (s, 3 H, tosyl CH_3), 3.81 (s, 3 H, OCH_3), 4.05–4.20 (m, 4 H, 2 × OCH_2Me), 6.53 (s, 1 H, H-4), 6.58 (d, *J* = 10.3 Hz, 1 H, H-α), 7.10 (s, 1 H, H-5), 7.29 (d, *J* = 8.1 Hz, 2 H, H-3′, H-5′), 7.46 (s, 1 H, H-2), 7.75 (d, *J* = 8.1 Hz, 2 H, H-2′, H-6′).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.2 (d), 20.8, 58.9, 62.3 (d), 109.9, 114.6, 120.1, 120.8, 121.4, 126.9 (d), 130.0 (d), 135.2, 142.9, 145.2.

MS (EI, 70 eV): *m*/*z* (%) = 413 (100, [M^+]), 306 (10), 278 (19), 258 (21), 248 (34), 202 (57), 155 (31), 138 (19), 106 (21), 91 (61), 65 (32).

HRMS-EI: *m*/*z* calcd for $C_{18}H_{24}NO_6PS$ [M^+]: 413.0990; found: 413.0983.

Diethyl {1-Methoxyethoxy-2-[1-(toluene-4-sulfonyl)-1*H*-pyrrol-3-yl]vinyl}phosphonate (10b)

Obtained as an oil after column chromatography (EtOAc–hexane, 1:4 to 1.2); yield: 1.94 g (39%).

IR (Nujol): 1635, 1340, 1150 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 1.2 Hz, 6 H, 2 × CH_2CH_3), 2.39 (s, 1 H, tosyl CH_3), 3.45 (s, 1 H, OCH_3), 3.66 (t, *J* = 4.2 Hz, 2 H, CH_2OMe), 4.09–4.17 (m, 6 H, 3 × OCH_2), 6.56 (s, 1 H, H-4), 6.60 (s, 1 H, CH=), 7.09 (dd, *J* = 3.2, 2.4 Hz, 1 H, H-5), 7.28 (d, *J* = 8.5 Hz, 2 H, H-3′, H-5′), 7.77 (d, *J* = 8.5 Hz, 2 H, H-2′, H-6′), 7.80 (s, 1 H, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.8 (d), 22.1, 59.4, 62.8 (d), 70.8, 72.1, 115.3, 121.1, 121.7, 122.0, 122.3, 122.9, 127.5 (d), 130.5 (d), 136.3, 145.6.

MS (EI, 70 eV): *m*/*z* (%) = 457 (61, [M^+]), 412 (3), 370 (4), 261 (100), 244 (5), 214 (3), 164 (3), 106 (6).

HRMS-EI: *m*/*z* calcd for $C_{20}H_{28}NO_7PS$ [M^+]: 457.1324; found: 457.1318.

Detosylation of (*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-ene Derivatives 5a–d,f; General Procedure

A solution of **5** (10 mmol) and K_2CO_3 (50 mmol) in anhyd MeOH (30 mL) was stirred under argon at r.t. for 18 h. The mixture was poured into ice-water (150 mL) and the pH adjusted to 6–7 with 1 N HCl. The mixture was extracted with EtOAc (3 × 25 mL), washed with brine (50 mL) and dried (Na_2SO_4). The solvent was removed under vacuo and the crude product was purified by recrystallisation.

(*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-enoic Acid (5a)

Yield: 1.22 g (89%); mp 179–180 °C (Lit.[2] mp 180–182 °C).

(*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-enamide (5b)

Yield: 1.27 g (93%); mp 143–144 °C (Lit.[2] mp 141–142 °C).

(*E*)-*N*,*N*-Dimethyl-3-(1*H*-pyrrol-3-yl)prop-2-enamide (5c)

Obtained as pale-yellow microcrystals (EtOAc–hexane, 1:1); yield: 1.44 g (88%); mp 171–173 °C.

IR (Nujol): 3400, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97 (s, 3 H, CH_3), 3.06 (s, 3 H, CH_3), 6.36 (s, 1 H, H-4), 6.47 (d, *J* = 15.1 Hz, 1 H, H-α), 6.69 (s, 1 H, H-5), 6.89 (s, 1 H, H-2), 7.55 (d, *J* = 15.1 Hz,1 H, H-β), 9.19 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.91, 37.38, 105.80, 112.10, 119.91, 121.08, 121.41, 136.96, 168.02.

MS (EI, 70 eV): *m*/*z* (%) = 164 (28, [M^+]), 121 (28), 120 (100), 92 (50), 65 (25), 39 (13).

HRMS-EI: *m*/*z* calcd for $C_9H_{12}N_2O$ [M^+]: 164.0950; found: 164.0946.

Ethyl (*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-enacetate (5d)
Obtained as colourless oil after column chromatography (EtOAc–hexane, 1:4 to 1:1); yield: 1.58 g (95%).

IR (Neat): 3150, 1720, 1340 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.1 Hz, 3 H, ester CH_3), 4.22 (q, *J* = 7.1 Hz, 2 H, ester CH_2), 6.12 (d, *J* = 15.8 Hz, 1 H, H-α), 6.46 (dd, *J* = 3.8, 2.5 Hz, 1 H, H-4), 6.78 (d, *J* = 2.5 Hz, H-2) 7.02 (dd, *J* = 3.8, 2.5 Hz, 1 H, H-5), 7.66 (d, *J* = 15.8 Hz, 1 H, H-β), 8.75 (br s, 1 H, NH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.4, 60.1, 106.5, 113.3, 120.1, 120.7, 121.6, 139.1, 168.3.

MS (EI, 70 eV): *m*/*z* (%) = 165 (87, [M^+]), 120 (100), 92 (27), 65 (12), 43 (9).

HRMS-ESI: *m*/*z* calcd for $C_9H_{11}NO_2$ + Na [M +Na]$^+$: 188.0687; found: 188.0686.

(*E*)-3-(1*H*-Pyrrol-3-yl)prop-2-enenitrile (5f)
Obtained as a light-brown solid; yield: 1.11 g (94%); mp 106–108 °C.

IR (Nujol): 3380, 2250 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.49 (d, *J* = 16.3 Hz, 1 H, H-α), 6.41 (dd, *J* = 4.0, 2.6 Hz, 1 H, H-4), 6.82 (d, *J* = 2.5 Hz, 1 H, H-5), 7.02 (dd, *J* = 4.0, 2.6 Hz, 1 H, H-2), 7.34 (d, *J* = 16.3 Hz, 1 H, H-β), 8.77 (br s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 90.0, 105.6, 119.6, 120.3, 120.4, 121.4, 144.7.

MS (EI, 70 eV): *m*/*z* (%) = 118 (100, [M^+]), 91 (19), 67 (19), 50 (4).

HRMS-EI: *m*/*z* calcd for $C_7H_6N_2$ [M^+]: 118.0531; found: 118.0529.

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