Synthesis of *N*-Protected 2-Hydroxymethylpyrroles and Transformation into Acyclic Oligomers

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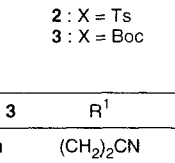
The synthesis of *N*-tosylated and *N*-Boc-protected 2-hydroxymethyl-pyrroles **2a–c** and **3a–d** and their transformation into di- and tripyrroles **18, 20a** and **20b** as well as the preparation of the vinyl- and ethynylpyrroles **13a**, **13b** and **15** is described. The pyrrole-2-carboxylic acid ethyl esters **7a** and **b** and the pyrrole-2-carbaldehydes **4a–d** were transformed into their *N*-protected derivatives **5a**, **5b**, **6a–d**, **8a** and **8b** in 69–97% yield and reduced to give the corresponding hydroxymethylpyrroles **2a–c** and **3a–d** in 79–96% yield; treatment of **2b** with **17**, **19a** and **19b** in 0.5% hydrochloric acid gives the dipyrrole **18** and the tripyrroles **20a** and **20b** in 20–28% yield.

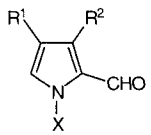
Pyrroles are important building blocks in nature. Thus, the pigments of life such as porphyrins and corrines are formed via cyclotetramerization of the pyrrole derivative porphobilinogen **(1)**. This reaction can be mimicked by the acid-catalyzed reaction of hydroxymethylpyrroles.[1,2] However, a major problem in the synthesis and transformation of pyrroles is their high sensitivity towards acids, light and oxygen. It is therefore of interest to use the *N*-protected derivatives, which should be significantly more stable, under these conditions.

1 (PBG)

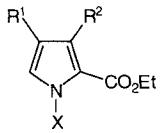


2 : X = Ts
3 : X = Boc

2 / 3	R^1	R^2
a	$(CH_2)_2CN$	CH_3
b	CH_3	CH_3
c	H	CH_3
d	H	H



4 : X = H
5 : X = Ts
6 : X = Boc



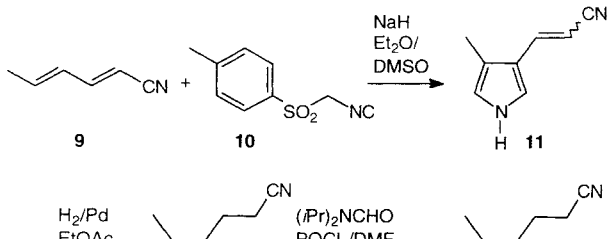
7 : X = H
8 : X = Ts

4 - 6	R^1	R^2
a	$(CH_2)_2CN$	CH_3
b	CH_3	CH_3
c	H	CH_3
d	H	H

7 / 8	R^1	R^2
a	H	CH_3
b	CH_3	CH_3

Scheme 1

In this paper we describe the synthesis of the *N*-protected 2-hydroxymethylpyrroles **2a–c** and **3a–d** and their transformation into the oligomers **18**, **20a** and **20b**. As substrates, the pyrrole-2-carbaldehydes **4a–d** and the pyrrole-2-carboxylates **7a** and **7b** were used. For the synthesis of **4a**, the van Leusen–Schöllkopf cyclization[3] of hexa-2,4-dienenitrile[4] **(9)** with tosylmethyl isocyanide (TosMIC) **(10)** followed by catalytic hydrogenation and Vilsmeier–Haack formylation[5] was used.



Scheme 2

In the formylation a regioselectivity[6] towards the 2-formyl compound **4a** was observed; with *N,N*-dimethylformamide a 4:1 ratio and with *N,N*-diisopropylformamide a 6:1 ratio was obtained. Fractional crystallization allowed the separation of **4a**. The pyrroles **4b**, **4c**, **7a** and **7b** were prepared using known procedures.[5,7,8] For the formation of the *N*-protected compounds the pyrroles **4a–d** and **7a**, **b** were deprotonated with sodium hydride in tetrahydrofuran and then reacted with either *p*-toluenesulfonyl chloride or di-*tert*-butyl dicarbonate to give **5a**, **b**, **6a–d** and **8a**, **b** in 69–97% yield.

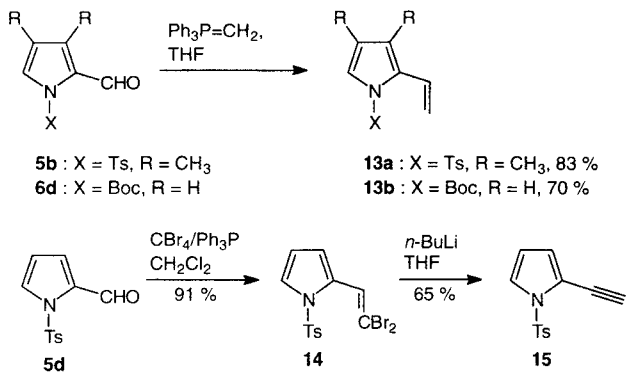
Wittig reactions of **5b** and **6d** with methyltriphenylphosphonium bromide and BuLi yielded the corresponding

Table 1. Synthesis of the *N*-Protected Pyrrole-2-carbaldehydes **5a**, **5b**, **6a–d** and Pyrrole-2-carboxylates **8a** and **8b**

Product	Educt	R^1	R^2	X	Yield (%)
5a	**4a**	$(CH_2)_2CN$	CH_3	Ts	83
5b	**4b**	CH_3	CH_3	Ts	70
6a	**4a**	$(CH_2)_2CN$	CH_3	Boc	79
6b	**4b**	CH_3	CH_3	Boc	97
6c	**4c**	H	CH_3	Boc	82
6d[a]	**4d**	H	H	Boc	94
8a	**7a**	H	CH_3	Ts	69
8b	**7b**	CH_3	CH_3	Ts	73

[a] Compound is known; ref. 9.

vinyl compounds **13a** and **13b** in 83% and 70% yield, respectively. The ethynyl compound **15** was obtained by a Corey–Fuchs reaction[10,11] from **5d**. Thus, reaction of **5d**[12] with tetrabromomethane in the presence of triphenylphosphane gave the corresponding dibromoethenyl derivative in 91% yield, which on treatment with BuLi in hexane at −78°C afforded **15** in 65% yield.



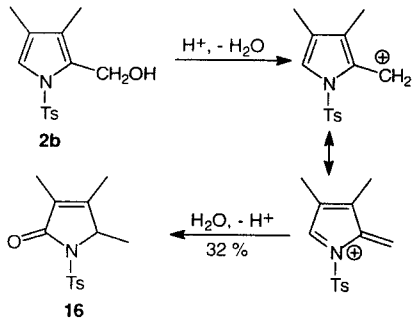
Scheme 3

The *N*-tosyl protected pyrrolecarboxylates **8a** and **8b** could easily be reduced to the corresponding hydroxymethyl derivatives without loss of the protecting group using excess lithium aluminium hydride at −10°C in diethyl ether in over 80% yield. Tetrahydrofuran is less suitable as a solvent since in this case several byproducts were obtained. The use of stoichiometric amounts[12] of lithium aluminium hydride resulted in an incomplete conversion.

For the reduction of the carbaldehydes **5a**, **b** and **6a–d** to give the hydroxymethyl compounds **2a–c** and **3a–d**, respectively, lithium borohydride was the reagent of choice to yield the desired alcohols in 79–96% yield.

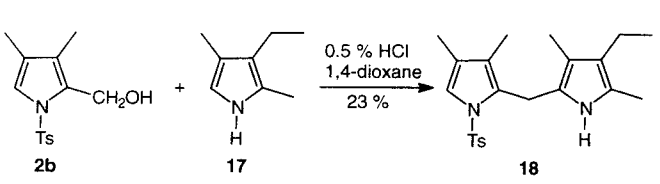
As expected, the *N*-protected hydroxymethylpyrrole derivatives **2b**, **2d**,[12] **3b** and **3d** are quite stable towards weak acids such as acetic acid. However, using stronger acids such as trifluoroacetic acid or camphor-10-sulfonic acid in dichloromethane led to decomposition. The initially deep purple colour gives evidence that an azafulvenium ion is formed.

Unexpectedly, treatment of **2b** with 5% hydrochloric acid in dioxane led to a rearrangement to give the pyrrolinone **16** in 32% yield. It can be assumed that an azafulvenium ion is generated first which reacts with water to give **16**. In addition, several side products (50%) were found which may have been formed by a ring-opening process; however, a final structural determination of these compounds was not possible.



Scheme 4

Clearly, these side products are not cyclotetra- or cyclopentamers or other oligomeric species. The obviously electrophilic properties of the assumed azafulvenium ion prompted us to react **2b** with unprotected pyrroles in the presence of acid in order to synthesize di- or tripyrrolic compounds. The best results were obtained in aqueous 1,4-dioxane containing 0.5% hydrochloric acid.



Scheme 5

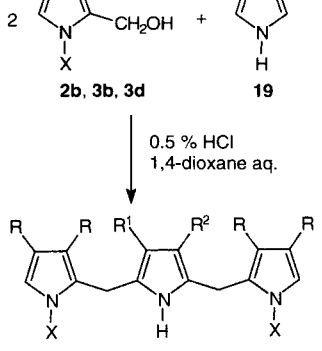


Table 2. Synthesis of the *N*-Protected 2-Hydroxymethylpyrroles **2a–c** and **3a–d**

Product	Educt	R^1	R^2	Yield (%)
2a	**5a**	$(CH_2)_2CN$	CH_3	91
2b	**5b**	CH_3	CH_3	95
2b	**8b**	CH_3	CH_3	83
2c	**8a**	H	CH_3	86
3a	**6a**	$(CH_2)_2CN$	CH_3	89
3b	**6b**	CH_3	CH_3	87
3c	**6c**	H	CH_3	79
3d	**6d**	H	H	96

Product	Substrates	R	R^1	R^2	X
20a	**2b + 19a**	CH_3	CH_3	CH_3	Ts
20b	**2b + 19b**	CH_3	CH_3	C_2H_5	Ts
20c	**3b + 19a**	CH_3	CH_3	CH_3	Boc
20d	**3d + 19a**	H	CH_3	CH_3	Boc

Scheme 6

In the reaction of **2b** with one equivalent of **17** the dimeric compound **18** was obtained in 23% yield; reaction of **19a** with excess **2b** afforded the trimeric pyrrole **20a** in 28% yield. In a similar way the reaction of **2b** and 4-ethyl-3-methylpyrrole **(19b)** gave the trimeric compound **20b** in 20% yield. In all cases the yields refer to the oligomeric pyrroles after purification by chromatography on silica gel and recrystallization. The oligomers **18**, **20a** and **20b** were the only characterizable products despite polymeric material.

Thus, the described procedure seems to be a simple and straightforward tool for the synthesis of stable dimeric and trimeric pyrroles whose isolation is easy since they crystallize readily. A main advantage of this procedure is the possibility of synthesizing unsymmetric compounds, such as **20b**.

The preparation of the oligomeric compounds **20c** and **20d** starting from the *N-tert*-butoxycarbonyl protected 2-hydroxymethylpyrroles **3b** and **3d** is less suitable since the obtained products could not be purified by crystallization. However, the formation of the trimeric compound **20c** using **3b** and **19a** is much faster than the reaction of the *N*-tosyl protected pyrrole **2b**, and even the simple pyrrole **3d** led to a trimeric pyrrole **20d**. Thus the transformation of **3b** with **19a** was nearly complete within 5 minutes whereas the reaction of **3d** with **19a** needed 20 hours. The yields of the obtained di- and tripyrrolic *tert*-butyl compounds **20c** and **20d** were 20% according to the NMR spectra obtained after column chromatography.

In contrast to the reaction of **3d** and **19a**, the 3,4-unsubstituted *N*-tosylhydroxymethylpyrrole **2d**[12] failed to undergo di- and trimerization upon treatment with acid, even using 0.5 M trifluoroacetic acid in methanol. This may be explained by the less favourable formation of the azafulvenium ion due to a lower electron density at the nitrogen compared with **3d**. However, in the presence of trifluoromethanesulfonic acid in methanol, the azafulvenium ion is formed since the corresponding methyl ether is generated in good yield.

The obtained di- and tripyrroles are sensitive to acid and oxygen; thus, decomposition takes place on standing at room temperature. This occurs more readily in the *N-tert*-butoxycarbonyl protected pyrroles.

The structure of the new compounds were mainly determined by ^1H and ^{13}C NMR spectroscopy. For **2a–c** and **3a–d** the characteristic signals are found at $\delta = 2.66–4.67$ as triplets (**2c** shows a singlet) with $J = 5.5–7.5$ Hz representing the hydroxylic proton, and the methylene protons resonate at $\delta = 4.52–4.65$ as doublets (**2c** shows a singlet) with $J = 5.5–7.5$ Hz. The terminal vinylic protons in **13a–b** give two characteristic doublets of doublets at $\delta = 5.11–5.33$ with $J = 11.0–11.5$ Hz and 1.5–2.0 Hz, and at $\delta = 5.19–5.52$ with $J = 17.5–18.0$ Hz and 1.5–2.0 Hz. For the alkyne proton of **15**, a singlet is found at $\delta = 3.42$. For the di- and tripyrrolic compounds **18** and **20a–b** the singlets at $\delta = 3.74–3.88$ are characteristic signals representing the newly formed dipyrromethylene groups.

The experiments have clearly shown that the reaction of *N*-tosyl protected hydroxymethylpyrroles such as **2b** with **17**, **19a** and **19b** is a convenient method to prepare trimeric and dimeric oligopyrroles such as **18**, **20a** and **20b** which are difficult to prepare by other methods.

All reactions were carried out in an inert atmosphere. ^1H NMR and ^{13}C NMR spectra: Varian XL-200, VXR-200, Bruker AMX-300, Varian VXR-500 S. IR: Bruker IFS-25. MS: MAT 311 A (EI/70 eV). HRMS: MAT 731. Elemental analyses: analytical laboratory of the University of Göttingen. Column chromatography: Macherey, Nagel & Co. Kieselgel 60 (0.063–0.200 mm). Analytical TLC: Macherey, Nagel & Co. (SIL G/UV_{254}). Solvents (distilled from): Et_2O (KOH or Na/benzophenone), petroleum ether bp 40–80 °C (KOH), pentane (KOH), EtOAc (CaH_2), CH_2Cl_2 (CaH_2), THF ($LiAlH_4$). Pyrrole-2-carbaldehyde was purchased from Merck, CBr_4 from Fluka. Satisfactory elemental analyses (C, H ± 0.4%) were obtained for all new compounds except for **3b**, **3c** and **20b**; for those compounds, correct HRMS was determined.

3-(4-Methyl-1*H*-pyrrol-3-yl)propionitrile (12):
NaH (600 mg of a 60% suspension in oil, 15.0 mmol) was suspended in anhyd Et_2O (15 mL) and washed twice with pentane. After cooling to 0 °C, a mixture of nitrile **9**[4] (931 mg, 10.0 mmol), TosMIC (**10**, 2.07 g, 10.5 mmol), anhyd DMSO (10 mL) and anhyd Et_2O (20 mL) was added over a period of 2 h. The resulting mixture was stirred for 2 h at 0 °C before the reaction was stopped by the addition of sat. aq NH_4Cl (10 mL) with subsequent dilution (H_2O, 150 mL). After extraction with Et_2O (3 × 50 mL), the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated. The oily residue was filtered (20 g silica gel) to give a crude mixture of the double bond isomers *E*-**11** and *Z*-**11**, which was dissolved in EtOAc (20 mL) under addition of Pd/C catalyst (1.28 g of a 5% catalyst repres. 0.60 mmol Pd). This mixture was stirred for 20 h under H_2. After separation from the catalyst and evaporation, column chromatography (50 g silica gel, EtOAc/petroleum ether 1:3) yielded 616 mg (4.60 mmol, 46%) of the desired compound as a colourless oil which crystallized upon cooling to −30 °C; mp 32–33 °C.

^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.06$ (s, 3H), 2.55 (t, $J = 7.0$ Hz, 2H), 2.81 (t, $J = 7.0$ Hz, 2H), 6.51–6.58 (m, 1H), 6.61–6.67 (m, 1H), 7.94 (br s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 9.92$, 17.89, 21.64, 115.9, 116.2, 117.0, 119.2, 120.0.

IR (film): $\nu = 3400$, 2246 cm^{-1}.

MS: $m/z = 134$ (M^+), 94 (100%).

3-(5-Formyl-4-methyl-1*H*-pyrrol-3-yl)propionitrile (4a):
To a solution of **12** (670 mg, 5.00 mmol) and diisopropylformamide (1.60 mL, 1.42 g, 11.0 mmol) in anhyd CH_2Cl_2 (15 mL) was added $POCl_3$ (550 µL, 924 mg, 6.00 mmol) very slowly at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and then for 24 h at r.t. In order to hydrolyze the intermediate iminium salt, 2.5 M NaOH (15 mL) was added with stirring and cooling with ice. The mixture was poured into H_2O (300 mL) and extracted with Et_2O (4 × 100 mL), the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated. The oily residue was purified by column chromatography (100 g silica gel deactivated with 1.5 wt.-% $NaHCO_3$, EtOAc/petroleum ether 1:3 → 2:3) to give a mixture of the two regioisomeric aldehydes. Crystallization from EtOAc/petroleum ether gave **4a** (462 mg, 2.85 mmol, 57%); mp 130 °C.

^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.26$ (s, 3H), 2.64–2.75 (m, 4H), 7.06 (s, 1H), 9.58 (s, 1H), 11.61 (br s, 1H).

^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 8.34$, 17.60, 20.15, 120.4, 121.7, 124.8, 128.7, 130.0, 177.8.

IR (KBr): $\nu = 3254$, 2240, 1656 cm^{-1}.

MS: $m/z = 162$ (M^+), 122 (100%).

N-Tosylation of Pyrrole-2-carbaldehydes and Pyrrole-2-carboxylic Acid Ethyl Esters; Typical Procedure 1:

3-Methyl-1-tosyl-1H-pyrrole-2-carboxylic Acid Ethyl Ester **(8a)**:

To a stirred suspension of NaH (258 mg of a 60% suspension in oil, 6.45 mmol) in anhyd THF (50 mL) was added 3-methyl-1*H*-pyrrole-2-carboxylic acid ethyl ester[7] (**7a**; 823 mg, 5.37 mmol) in smal portions at r.t. When the evolution of H_2 had ceased, the mixture was stirred for 1 h at r.t. before treating it with *p*-toluenesulfonyl chloride (1.13 g, 5.93 mmol). After 16 h, conversion was complete and aq NH_4Cl was added to stop the reaction. After dilution with H_2O (200 mL), the mixture was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by filtration over silica gel (20 g) and crystallized from EtOAc/petroleum ether to give **8a** (1.15 g, 3.73 mmol, 69%) as colourless crystals; mp 42 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.5 Hz, 3 H), 2.25 (s, 3 H), 2.42 (s, 3 H), 4.22 (q, J = 7.5 Hz, 2 H), 6.15 (d, J = 3.5 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 3.5 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.65, 14.19, 21.64, 60.59, 113.9, 122.1, 127.2, 127.6, 129.3, 133.9, 136.6, 144.5, 160.1.

IR (KBr): ν = 1712 cm^{-1}.

MS: m/z = 307 (M^+), 91 (100%).

3-(5-Formyl-4-methyl-1-tosyl-1H-pyrrole-3-yl)propionitrile **(5a)**:

Reaction of **4a** according to Typical Procedure 1; yield: 83%; mp 130 °C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.42 (s, 3 H), 2.58 (t, J = 7.0 Hz, 2 H), 2.78 (t, J = 7.0 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.46 (s, 1 H), 7.75 (d, J = 8.5 Hz, 2 H), 10.19 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.80, 17.86, 20.73, 21.69, 118.6, 124.3, 126.0, 127.1, 129.6, 130.3, 135.2, 135.7, 145.9, 180.8.

IR (KBr): ν = 2250, 1658 cm^{-1}.

MS: m/z = 316 (M^+), 161 (100%).

3,4-Dimethyl-1-tosyl-1H-pyrrole-2-carbaldehyde **(5b)**:

Reaction of **4b**[5] according to Typical Procedure 1; yield: 70%, mp 153 °C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 2.25 (s, 3 H), 2.41 (s, 3 H), 7.23–7.37 (m, 3 H), 7.72 (d, J = 8.0 Hz, 2 H), 10.17 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.64, 10.89, 21.66, 124.0, 126.0, 127.0, 129.4, 130.1, 135.7, 137.5, 145.6, 180.8.

IR (KBr): ν = 1666 cm^{-1}.

MS: m/z = 277 (M^+), 91 (100%).

3,4-Dimethyl-1-tosyl-1H-pyrrole-2-carboxylic Acid Ethyl Ester **(8b)**:

Reaction of **7b**[8] according to Typical Procedure 1; yield: 73%, mp 76 °C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3 H), 1.99 (s, 3 H), 2.15 (s, 3 H), 2.41 (s, 3 H), 4.22 (q, J = 7.0 Hz, 2 H), 7.29 (d, J = 8.5 Hz, 2 H), 7.34 (s, 1 H), 7.78 (d, J = 8.5 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.03, 10.99, 14.18, 21.61, 60.59, 122.0, 122.2, 124.8, 127.4, 129.3, 133.4, 136.9, 144.2, 160.3.

IR (KBr): ν = 1712 cm^{-1}.

MS: m/z = 321 (M^+).

N-*tert*-Butoxycarbonylation of Pyrrole-2-carbaldehydes; Typical Procedure 2:

2-Formyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(6d)**:

To NaH (240 mg of a 60% suspension in oil, 6.00 mmol) in anhyd THF (50 mL) was added pyrrole-2-carbaldehyde (**4d**; 475 mg, 5.00 mmol) in small portions at r.t.. When the evolution of H_2 had ceased, the mixture was stirred for 1 h at r.t. before treating it with di-*tert*-butyl carbonate (1.20 g, 1.26 mL, 5.50 mmol). After completion (~ 2 h), the reaction was quenched with aq NH_4Cl. After dilution with H_2O (200 mL), the mixture was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (45 g silica gel, EtOAc/petroleum ether 1:10 → 1:8) to yield **6d** (917 mg, 4.70 mmol, 94%) as a pale yellow oil which crystallized upon standing. An analytical sample was obtained by recrystallization from petroleum ether at − 30 °C; mp 50 °C. (Lit.[9]: oil.)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 6.28 (t, J = 3.5 Hz, 1 H), 7.19 (dd, J = 3.5, 2.0 Hz, 1 H), 7.45 (dd, J = 3.5, 2.0 Hz, 1 H), 10.32 (s, 1 H).

4-(2-Cyanoethyl)-2-formyl-3-methyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(6a)**:

Reaction of **4a** according to Typical Procedure 2; yield: 79%, mp 66 °C (petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.62 (s, 9 H), 2.34 (s, 3 H), 2.57 (t, J = 7.0 Hz, 2 H), 2.78 (t, J = 7.0 Hz, 2 H), 7.28 (s, 1 H), 10.40 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.99, 17.99, 20.85, 27.94, 85.59, 118.8, 123.2, 123.8, 130.6, 133.5, 148.2, 183.9.

IR (KBr): ν = 2248, 1742, 1662 cm^{-1}.

MS: m/z = 262 (M^+), 57 (100%).

2-Formyl-3,4-dimethyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(6b)**:

Reaction of **4b**[5] according to Typical Procedure 2; yield: 97%, mp 43 °C (petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.62 (s, 9 H), 1.98 (s, 3 H), 2.32 (s, 3 H), 7.14 (s, 1 H), 10.39 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.55, 11.09, 28.00, 84.77, 122.6, 124.0, 130.3, 135.3, 148.5, 183.9.

IR (KBr): ν = 1740, 1662 cm^{-1}.

MS: m/z = 223 (M^+), 57 (100%).

2-Formyl-3-methyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(6c)**:

Reaction of **4c**[5] according to Typical Procedure 2: yield: 82%, mp 52 °C (petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.63 (s, 9 H), 2.40 (s, 3 H), 6.12 (d, J = 3.5 Hz, 1 H), 7.32 (d, J = 3.5 Hz, 1 H), 10.41 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.86, 27.98, 85.28, 114.6, 125.9, 130.2, 136.0, 148.4, 183.8.

IR (KBr): ν = 1744, 1652 cm^{-1}.

MS: m/z = 209 (M^+), 108 (100%).

Synthesis of Ethenylpyrroles; Typical Procedure 3:

2-Ethenyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(13b)**:

Methyltriphenylphosphonium bromide (1.29 g, 3.60 mmol) was suspended in anhyd THF (35 mL), cooled to 0 °C and treated with a 1.54 M solution of BuLi in hexane (2.14 mL, 3.30 mmol). After stirring for 2 h at 0 °C, the mixture was cooled to − 78 °C, and the aldehyde **6d** (585 mg, 3.00 mmol), dissolved in anhyd THF (5 mL), was added. After additional stirring for 15 min at − 78 °C, the mixture was allowed to warm up to r.t. and was stirred for 3 h. The reaction was quenched by addition of H_2O (150 mL). Subsequent extraction with Et_2O (3 × 50 mL), washing of the combined organic layers with H_2O (50 mL) and brine (50 mL), drying (Na_2SO_4) and evaporation of the solvent gave the crude alkene **13b** which was purified by column chromatography (45 g silica gel, EtOAc/petroleum ether 1:15 → 1:10) to give **13b** (408 mg, 2.11 mmol, 70%) as a yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60 (s, 9 H), 5.11 (dd, J = 11.0, 2.0 Hz, 1 H), 5.52 (dd, J = 17.5, 2.0 Hz, 1 H), 6.13 (t, J = 3.5 Hz, 1 H), 6.42 (m, 1 H), 7.14–7.32 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.01, 83.98, 110.7, 110.8, 113.3, 121.8, 128.0, 134.5, 149.5.

IR (film): ν = 1742 cm^{-1}.

MS: m/z = 193 (M^+), 57 (100%).

2-Ethenyl-3,4-dimethyl-1-tosyl-1H-pyrrole **(13a)**:

Reaction of **5b** according to Typical Procedure 3; yield: 83%, mp 84°C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.94 (s, 3H), 1.97 (s, 3H), 2.38 (s, 3H), 5.19 (dd, J = 18.0, 1.5 Hz, 1H), 5.33 (dd, J = 11.5, 1.5 Hz, 1H), 6.99 (dd, J = 18.0, 11.5 Hz, 1H), 7.01 (s, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.39, 10.96, 21.57, 117.1, 119.0, 123.9, 124.3, 126.4, 126.9, 129.4, 129.6, 136.2, 144.4.

IR (KBr): ν = 1596 cm^{-1}.

MS: m/z = 275 (M^+), 91 (100%).

2-(2,2-Dibromoethenyl)-1-tosyl-1*H*-pyrrole (14):

A solution of CBr_4 (1.33 g, 4.00 mmol) in anhyd CH_2Cl_2 (5 mL) was cooled to 0°C and treated with Ph_3P (2.10 g, 8.00 mmol) in anhyd CH_2Cl_2 (5 mL). The resulting mixture was stirred for 30 min at 0°C, then cooled to −78°C, and the aldehyde **5d**[12] (498 mg, 2.00 mmol) in anhyd CH_2Cl_2 (5 mL) was added. After stirring for 10 min at −78°C, the mixture was allowed to warm up over a period of 15 min and was then stirred for 1 h at 0°C. The reaction was stopped by dilution with Et_2O (50 mL) and filtration over a plug of Na_2SO_4; the residue was thoroughly rinsed with Et_2O. The resulting ethereal solution was washed with H_2O, aq $NaHCO_3$, aq NH_4Cl and brine (100 mL each), dried (Na_2SO_4) and evaporated. Column chromatography (45 g silica gel, EtOAc/petroleum ether 1:6) yielded **14** (741 mg, 1.83 mmol, 91%), mp 88°C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 6.28 (t, J = 3.5 Hz, 1H), 6.83–6.89 (m, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.35 (dd, J = 3.5, 2.0 Hz, 1H), 7.64 (d, J = 8.5 Hz, 2H), 7.84 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.67, 90.33, 112.2, 116.9, 123.7, 126.3, 126.9, 129.2, 130.0, 135.5, 145.4.

IR (KBr): ν = 1594 cm^{-1}.

MS: m/z = 405 (M^+), 155 (100%).

2-Ethynyl-1-tosyl-1*H*-pyrrole (15):

A solution of the dibromovinylpyrrole **14** (405 mg, 1.00 mmol) in anhyd THF (5 mL) was cooled to −78°C and treated with 1.54 M solution of BuLi in hexane (1.40 mL, 2.16 mmol). The resulting solution was stirred for 30 min at −78°C, diluted with Et_2O (20 mL) and then allowed to warm up to r.t. After washing with aq NH_4Cl, H_2O and brine (10 mL each), the organic layer was dried (Na_2SO_4) and evaporated. Column chromatography (20 g silica gel, EtOAc/petroleum ether 1:6) yielded the pyrrolylethyne **15** (159 mg, 649 μmol, 65%) as a light grey solid, mp 86°C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.42 (s, 1H), 6.21 (t, J = 3.5 Hz, 1H), 6.58 (dd, J = 3.5, 2.0 Hz, 1H), 7.25–7.40 (m, 3H), 7.87 (d, J = 8.5 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.66, 73.88, 83.28, 111.5, 114.2, 122.5, 123.6, 127.7, 129.8, 135.2, 145.3.

IR (KBr): ν = 2108 cm^{-1}.

MS: m/z = 245 (M^+), 91 (100%).

Reduction of *N*-Tosylpyrrole-2-carboxylates; Typical Procedure 4:

[3-Methyl-1-tosyl-1H-pyrrol-2-yl]methanol **(2c)**:

$LiAlH_4$ (341 mg, 9.00 mmol) was suspended in anhyd Et_2O (20 mL) and cooled to −10°C. After addition of **8a** (614 mg, 2.00 mmol), the resulting mixture was stirred for 20 min at −10°C. The reaction was quenched by slow addition of H_2O (100 mL) and the mixture extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and evaporated. Column chromatography (45 g silica gel, EtOAc/petroleum ether 1:4 → 1:2) yielded **2c** (456 mg, 1.72 mmol, 86%), mp 61°C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.41 (s, 3H), 2.70 (br, s, 1H), 4.54 (br s, 2H), 6.13 (d, J = 3.5 Hz, 1H), 7.20 (d, J = 3.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.15, 21.61, 53.77, 114.5, 122.3, 124.5, 126.5, 129.9, 130.0, 136.2, 145.0.

IR (KBr): ν = 3354 cm^{-1}.

MS: m/z = 265 (M^+), 91 (100%).

(3,4-Dimethyl-1-tosyl-1H-pyrrol-2-yl)methanol **(2b)**:

Reaction of **8b** according to Typical Procedure 4; yield: 83%; mp 98°C (EtOAc/petroleum ether).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.86 (s, 3H), 1.88 (s, 3H), 2.35 (s, 3H), 4.52 (d, J = 5.5 Hz, 2H), 4.67 (t, J = 5.5 Hz, 1H), 7.04 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 8.77, 9.77, 20.87, 51.99, 119.0, 122.3, 124.0, 126.8, 129.6, 130.6, 136.1, 144.4.

IR (KBr): ν = 3532 cm^{-1}.

MS: m/z = 279 (M^+, 100%).

2b was also obtained from **5b** in 95% yield according to Typical Procedure 5 (reaction temperature: 20°C).

Reduction of *N*-Protected Pyrrole-2-carbaldehydes; Typical Procedure 5:

2-Hydroxymethyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(3d)**:

A cooled (−10°C) solution of **6d** (1.76 g, 9.00 mmol) in anhyd THF (50 mL) was treated with $LiBH_4$ (784 mg, 36.0 mmol) and stirred for 2 h at −10°C. Then, the mixture was poured into H_2O (400 mL) with subsequent ethereal extraction (4 × 100 mL). The combined organic layers were washed with brine (150 mL) and dried (Na_2SO_4). The crude product remaining after evaporation was purified by filtration (40 g silica gel, EtOAc/petroleum ether 1:8 + 0.5% Et_3N) to give **3d** (1.70 g, 8.63 mmol, 96%) as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (s, 9H), 3.60 (t, J = 7.5 Hz, 1H), 4.65 (d, J = 7.5 Hz, 2H), 6.10 (t, J = 3.5 Hz, 1H), 6.15–6.21 (m, 1H), 7.16 (dd, J = 3.5 Hz, 2.0 Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.98, 57.68, 84.49, 110.4, 113.5, 121.9, 134.8, 149.9.

IR (film): ν = 3434, 1738, 1724 cm^{-1}.

MS: m/z = 197 (M^+), 57 (100%).

3-(5-Hydroxymethyl-4-methyl-1-tosyl-1H-pyrrol-3-yl)propionitrile **(2a)**:

Reaction of **5a** according to Typical Procedure 5 (reaction time: 90 min); yield: 91%, mp 110°C (EtOAc/petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3H), 2.40 (s, 3H), 2.56 (t, J = 7.0 Hz, 2H), 2.66–2.77 (m, 3H), 4.53 (d, J = 7.0 Hz, 2H), 7.18 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.15, 17.73, 21.50, 21.61, 53.89, 119.0, 120.0, 123.3, 123.8, 126.6, 130.1, 130.6, 135.9, 145.2.

IR (KBr): ν = 3474, 2256 cm^{-1}.

MS: m/z = 318 (M^+), 91 (100%).

4-(2-Cyanoethyl)-2-hydroxymethyl-3-methyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(3a)**:

Reaction of **6a** according to Typical Procedure 5; yield: 89%, mp 62°C (EtOAc/petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.59 (s, 9H), 2.00 (s, 3H), 2.53 (t, J = 7.0 Hz, 2H), 2.71 (t, J = 7.0 Hz, 2H), 3.64 (t, J = 7.5 Hz, 1H), 4.60 (d, J = 7.5 Hz, 2H), 6.99 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.97, 17.90, 21.60, 28.00, 54.69, 84.41, 118.2, 119.2, 121.0, 122.4, 130.9, 149.9.

IR (KBr): ν = 3500, 2244, 1724 cm^{-1}.

MS: m/z = 264 (M^+), 43 (100%).

2-Hydroxymethyl-3,4-dimethyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester **(3b)**:

Reaction of **6b** according to Typical Procedure 5; oil, yield: 87%.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.60 (s, 9H), 1.94 (s, 3H), 1.98 (s, 3H), 3.73 (t, J = 7.5 Hz, 1H), 4.61 (d, J = 7.5 Hz, 2H), 6.90 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.01, 10.19, 28.05, 54.92, 83.64, 117.8, 121.6, 122.5, 130.1, 150.2.

IR (film): $\nu = 3536, 1720\,cm^{-1}$.

MS: $m/z = 225\ (M^+)$, 57 (100%).

2-Hydroxymethyl-3-methyl-1H-pyrrole-1-carboxylic Acid tert-Butyl Ester (**3c**):

Reaction of **6c** according to Typical Procedure 5; oil, yield: 79%.

^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.60$ (s, 9H), 2.07 (s, 3H), 3.66 (t, $J = 7.5$ Hz, 1H), 4.63 (d, $J = 7.5$ Hz, 2H), 5.99 (d, $J = 3.5$ Hz, 1H), 7.08 (d, $J = 7.5$ Hz, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 11.03, 28.01, 54.59, 84.09, 113.0, 120.6, 122.2, 130.1, 150.1$.

IR (film): $\nu = 3544, 1722\,cm^{-1}$.

MS: $m/z = 211\ (M^+)$, 57 (100%).

1,5-Dihydro-3,4,5-trimethyl-1-tosylpyrrol-2-one (16):

To a solution of 1,4-dioxane (20 mL) and 10% aq HCl (20 mL) was added **2b** (165 mg, 591 μmol). After stirring for 30 min at r.t., the mixture was neutralized with aq NaOH, diluted with H_2O (150 mL) and extracted with Et_2O (3 × 80 mL). The organic layers were washed with brine and dried (Na_2SO_4); evaporation and column chromatography (18 g, silica gel, EtOAc/petroleum ether 1:6 → 1:2) yielded **16** as an oil (52.0 mg, 186 μmol, 32%) which crystallized upon standing. An analytical sample was obtained by recrystallization from EtOAc/petroleum ether, mp 88 °C.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (d, $J = 6.5$ Hz, 3H), 1.78 (s, 3H), 1.94 (s, 3H), 5.13 (br q, $J = 6.5$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.91 (d, $J = 8.0$ Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 8.56, 11.71, 17.79, 21.52, 87.46, 126.00, 127.5, 129.0, 139.0, 143.0, 160.0, 172.3$.

IR (film): $\nu = 1604\,cm^{-1}$.

MS: $m/z = 279\ (M^+)$, 124 (100%).

Synthesis of Di- and Tripyrrolic Compounds; Typical Procedure 6:

2-(4-Ethyl-3,5-dimethyl-1H-pyrrolyl-2-yl)methyl-3,4-dimethyl-1-tosyl-1H-pyrrole (**18**):

To a solution of **2b** (558 mg, 2.00 mmol) and 3-ethyl-2,4-dimethylpyrrole (kryptopyrrole; **17**) (246 mg, 2.00 mmol) in 1,4-dioxane (38 mL) was added 10% aq HCl (2.00 mL). The mixture was stirred for 4 h at r.t., **2b** (55.8 mg, 0.20 mmol) was added and after an additional 1.5 h of stirring, the reaction was stopped by neutralization with aq $NaHCO_3$ (20 mL) with subsequent dilution (H_2O, 150 mL) and ethereal extraction (3 × 50 mL). The combined organic layers were washed with H_2O (5 × 100 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated. Column chromatography (45 g silica gel, EtOAc/petroleum ether 1:8 + 1% Et_3N) and subsequent crystallization from petroleum ether yielded the dipyrromethane **18** (176 mg, 458 μmol, 23%) as pink plates, mp 129 °C (petroleum ether).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.5$ Hz, 3H), 1.87 (s, 3H), 1.93 (d, $J = 1.0$ Hz, 3H), 2.00 (s, 3H), 2.03 (s, 3H), 2.34 (q, $J = 7.5$ Hz, 2H), 2.38 (s, 3H), 3.88 (s, 2H), 6.99 (d, $J = 1.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.75 (br s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 9.17, 9.43, 10.43, 10.95, 15.81, 17.68, 21.42, 21.53, 112.6, 118.7, 120.1, 121.1, 121.8, 123.0, 123.2, 126.4, 128.5, 129.6, 136.4, 144.1$.

IR (KBr): $\nu = 3440\,cm^{-1}$.

MS: $m/z = 384\ (M^+)$, 229 (100%).

2,5-Bis(3,4-dimethyl-1-tosyl-1H-pyrrol-2-ylmethyl)-3,4-dimethyl-1H-pyrrole (**20a**):

Reaction of 2.50 equiv of **2b** with **19a** according to Typical Procedure 6 (reaction time: 4 h); yield: 28%, mp 200 °C (EtOAc/petroleum ether; decomposition).

^1H NMR (300 MHz, CD_2Cl_2): $\delta = 1.74$ (s, 6H), 1.87 (s, 6H), 1.93 (d, $J = 1.0$ Hz, 6H), 2.35 (s, 6H), 3.74 (s, 4H), 6.94 (d, $J = 1.0$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 4H), 7.34 (d, $J = 8.5$ Hz, 4H), 7.53 (br s, 1H).

^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 9.10, 9.29, 10.39, 21.58, 21.71, 113.4, 119.1, 122.2, 123.5, 123.7, 126.6, 128.7, 129.7, 136.6, 144.4$.

IR (KBr): $\nu = 3444\,cm^{-1}$

MS: $m/z = 617\ (M^+)$, 135 (100%).

2,5-Bis(3,4-dimethyl-1-tosyl-1H-pyrrol-2-ylmethyl)-3-ethyl-4-methyl-1H-pyrrole (**20b**):

Reaction of 2.00 equiv of **2b** with **19b** according to Typical Procedure 6 (reaction time: 4 h); yield: 20%.

^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.5$ Hz, 3H), 1.72 (s, 3H), 1.73 (s, 3H), 1.91 (d, $J = 1.0$ Hz, 3H), 1.92 (d, $J = 1.0$ Hz, 3H), 1.94 (s, 3H), 2.34 (s, 3H), 2.34 (s, 3H), 2.35 (q, $J = 7.5$ Hz, 2H), 3.74 (s, 2H), 3.79 (s, 2H), 6.93 (d, $J = 1.0$ Hz, 1H), 6.95 (d, $J = 1.0$ Hz), 7.06 (d, $J = 8.0$ Hz, 2H), 7.09 (d, $J = 8.0$ Hz, 2H), 7.29–7.34 (m, 4H), 7.56 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 9.06, 9.20, 9.22, 10.41, 15.76, 17.66, 21.38, 21.43, 21.54, 112.6, 118.8, 118.9, 119.8, 121.5, 122.2, 123.1, 123.2, 123.27, 123.3, 126.45, 126.5, 128.2, 128.4, 129.3, 129.4, 136.4, 136.5, 143.6, 143.7$.

MS: $m/z = 631\ (M^+)$, 91 (100%).

2,5-Bis[3,4-dimethyl-1-(tert-butoxycarbonyl)-1H-pyrrol-2-ylmethyl]-3,4-dimethyl-1H-pyrrole (**20c**):

Reaction of 2 equiv of **3b** and 1 equiv of **19a** according to Typical Procedure 6 (reaction time: 5 min); oil, yield: 20%.

MS: $m/z = 509\ (M^+)$, 57 (100%).

2,5-Bis[1-(tert-butoxycarbonyl)-1H-pyrrol-2-yl-methyl]-3,4-dimethyl-1H-pyrrole (**20d**):

Reaction of 2 equiv of **3d** and 1 equiv of **19a** according to Typical Procedure 6 (reaction time: 20 h); oil, yield: 20%.

^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.61$ (s, 18H), 1.97 (s, 6H), 4.09 (s, 4H), 5.80–5.88 (m, 2H), 6.05 (t, $J = 3.5$ Hz, 2H), 7.10–7.18 (m, 2H), 8.22 (br s, 1H).

MS: $m/z = 453\ (M^+)$, 341 (100%).

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