# A Short and Efficient Synthesis of 3,4-Dialkoxypyrroles

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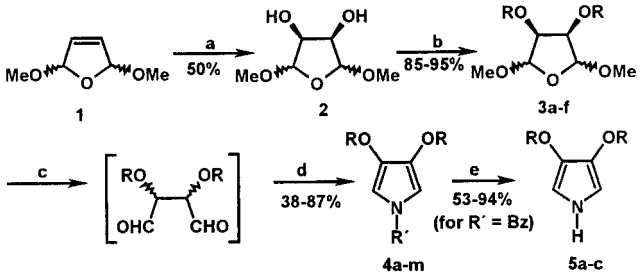
**Abstract:** 3,4-Dialkoxypyrroles are obtained in four steps from commercially available 2,5-dimethoxy-2,5-dihydrofuran **(1)**. The dihydrofuran **1** is first oxidized by $KMnO_4$ to the diol **2** which is bisalkylated to **3a–d.** Reaction of the in situ generated dialdehydes with a primary amine affords the *N*-substituted dialkoxypyrroles **4a–m**. *N*-Benzyl-3,4-dialkoxypyrroles and *N*-allyl-dialkoxypyrroles are cleaved by sodium in liquid ammonia affording *N*-unsubstituted dialkoxypyrroles **5a–c** in good overall yield.

**Key words**: dihydroxydihydrofuran, tetraalkoxyfurans, *O*,*N*-exchange, *N*-benzyl cleavage, *N*-allyl cleavage

The most simple synthesis of porphyrins is the condensation of symmetric 2,5-unsubstituted pyrroles with an aldehyde and subsequent or concommitant dehydrogenation,[1] however, the preparation of suitable precursors, e.g. 3,4-diethylpyrrole, require several steps and only few established protocols exist.[2] Another series of suitable symmetric pyrrole precursors are 3,4-dialkoxypyrroles, the synthesis of which has only recently been accomplished.[3,4] A variety of octaalkoxyporphyrins[4,5] have been obtained, including tetra-crowned porphyrins[6] and also liquid crystalline species with decyloxy side chains.[7] Furthermore, dialkoxypyrroles are electrochemically oxidized to highly conducting polypyrroles linked uniformly in 2,5 position.[8]

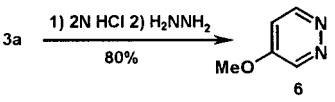
Although substantial quantities of 3,4-dimethoxypyrrole **(5a)** can be prepared in six straightforward steps with 22% total yield, this is not generally true for higher homologs.[4] In this paper we describe a significantly shorter synthesis of *N*-substituted 3,4-dialkoxypyrroles **4a–m** in three steps, and *N*-unsubstituted pyrroles **5** in one additional step (Scheme).




| 3 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| R = | Me | Et | n-$C_5H_{11}$ | allyl | benzyl | 5-hexenyl |
| (%) | 90 | 80 | 95 | 93 | 85 | 87 |

| 4 | a | b | c | d | e | f | |
|---|---|---|---|---|---|---|---|
| R = | Me | Me | Me | Me | Me | Me | |
| R´= | Me | n-Prop | t-Bu | benzyl | -$(CH_2)_2$CN | allyl | |
| (%) | 79 | 74 | 87 | 73 | 71 | 65 | |
| **4** | **g** | **h** | **i** | **j** | **k** | **l** | **m** |
| R = | Et | n-$C_5H_{11}$ | allyl | allyl | benzyl | benzyl | 5-hexenyl |
| R´= | t-Bu | benzyl | allyl | benzyl | benzyl | allyl | benzyl |
| (%) | 81 | 77 | 86 | 74 | 66 | 38 | 45 |

| 5 | a | b | c |
|---|---|---|---|
| (%) | 94 | 94 | 53 |




Reagents and conditions: (a) $KMnO_4/H_2O$; (b) RBr or $R_2SO_4$/NaOH or $ROSO_2Me$/NaH in dioxane; (c) 1. 2 N HCl or $H_2SO_4$ for 30 min or TosOH/THF/$H_2O$, 70 °C for 2 h, 2. then buffer to pH 6 with NaOAc; (d) $R'NH_3^+$ $Cl^-$, 25 °C, 10 to 15 h; (e) 1.2 equiv Na in liq $NH_3$, then $H_2O/NH_4Cl$

**Scheme**

Commercial 2,5-dimethoxy-2,5-dihydrofuran **(1)**[9] is a mixture of the achiral *cis* and racemic *trans* forms with various compositions depending on the source, e.g. 70:30,[10] or 54:46 in this work. The oxidation of **1** with $KMnO_4$ yields **2**[11] in much the same diastereomeric ratio of the achiral *ttc* and chiral *cct* isomers, although under certain conditions[10] *cis*-**1** is reported to react faster. In our hands, higher boiling fractions of **2** from simple vacuum distillation consist of almost pure *ttc*-**2**. A third isomer with all *cis* arrangement of all four substituents obviously has been never observed.[10] Depending on the nature of the alkylating agent different procedures have been developed for the alkyation step. Due to the generally high yields in these procedures to give the diastereomeric mixtures of 3,4-dialkoxy-2,5-dimethoxytetrahydrofurans **3a–f** the configuration of **2** was actually of no importance since in the final step of the synthesis all stereocenters are lost.

While the reaction of 2,5-dimethoxytetrahydrofuran with primary amines in acetic acid, known as Elming–Clausson–Kaas synthesis,[12] gives moderate to good yields of *N*-substituted pyrroles, the tetraalkoxytetrahydrofurans **3a–f** do not react under these conditions. On the other hand, the diastereomers of **2** and **3a** have been successfully used as precursors of tropinone structures in Robinson–Schöpf syntheses.[13,14] In these cases the tetrahydrofuran derivatives were first hydrolyzed in aqueous mineral acid to give the corresponding free or methylated tartaric aldehydes

which were then reacted with methylamine hydrochloride and acetonedicarboxylic acid in buffered aqueous solution. A bisphenylhydrazone of 2,3-dimethoxytartaric aldehyde was isolated proving the presence of the dialdehyde.[14] Similarly, in the course of this work, 4-methoxypyridazine **(6)** was obtained by treating the solution with hydrazine hydrate. When methylamine hydrochloride alone was added to the dialdehyde solution, 3,4-dimethoxy-*N*-methylpyrrole was isolated in 20% yield. Further optimization of this reaction finally showed that good to excellent isolated yields of *N*-substituted dialkoxypyrroles **4a–m** are obtained in a two-phase system with chloroform.

The desired direct formation of *N*-unsubstituted dialkoxypyrroles **5** with ammonia instead of primary amines has not yet been achieved. Therefore it was necessary to find *N*-substituents which would be easily cleaved from the pyrrole nitrogen. In our previous preparation of dialkoxypyrroles,[5] the nitrogen atom of diethyl 3,4-dihydroxypyrrole-2,5-dicarboxylate was protected with a benzyl group which after dialkylation was cleaved by either catalytic hydrogenolysis or solvolysis in $CF_3CO_2H/H_2SO_4$ but neither method was applicable for the debenzylation of pyrroles **4d,h,j,k,m**. However, *N*-debenzylation by reductive cleavage with sodium in liquid $NH_3$ followed by quenching with aqueous $NH_4Cl$[15] smoothly proceeded to give the NH-pyrroles **5a–c**. The same method is applicable for *N*-allyl pyrroles as demonstrated with **4f** as a substrate. Since the *O*-benzyl and *O*-allyl substituents of **4i,j,k,l** are likewise cleaved under these conditions, *N*-unsubstituted diallyloxy- and dibenzyloxy pyrroles are, at present, not accessible by this method. The allyl group is also removed with stoichiometric MeMgI under Ni catalysis,[16] but again, *O*-allyl and *O*-benzyl substituents are attacked as well. A further approach for *N*-deprotection was attempted via retro-Michael cleavage of **4e** but this compound was inert to various basic conditions.

In summary we have presented a straightforward route to symmetrical 3,4-dialkoxypyrroles.

The following analytical instruments were used: Beckman Acculab 1 or 2 (IR), Hitachi U 2000 (UV/Vis), Bruker AW 80, Bruker WM 250 or Bruker ARX 400 ($^1$H NMR and $^{13}$C NMR spectra; TMS as internal standard in $CDCl_3$ unless noted otherwise); Varian MAT 112 S (EI-MS (70 eV)); Büchi 510 apparatus (melting points, uncorrected). Elemental analyses were performed by the Analytical Laboratory of the University of Regensburg. Solvents were purified according to recommended procedures.[17] Compound **1** was obtained from Fluka, the diastereomeric mixture of **2** was prepared according to Ref. 12, 6-(methanesulfonyloxy)hexene was prepared by a general procedure[18] and used without purification.

### 3,4-Dialkoxy-2,5-dimethoxytetrahydrofurans 3a–f; General Procedures

**Procedure A** (*for* **3a,b**): A stirred mixture of **2** (0.13 mol) and powdered KOH (0.82 mol) in THF (260 mL) was heated at reflux for 1 h. Within 3 h a solution of the corresponding dialkyl sulfate (0.39 mol) in THF (150 mL) was added. Stirring and heating were continued for 16 h and $H_2O$ (100 mL) was added. After 1 h the mixture was diluted with $H_2O$ (600 mL) and extracted with $Et_2O$ (150 mL) and $CH_2Cl_2$ (4 × 150 mL). The product was purified by fractional distillation *in vacuo*.

**Procedure B** (*for* **3c–e**): A mixture of **1** (20 mmol), KOH (0.10 mol), the corresponding alkyl bromide and solvent (40 mL) was heated under stirring for 18 h. The product was isolated by fractional distillation.

**Procedure C** (*for* **3f**): To a mixture of **2** (5 mmol) in dioxane (15 mL) was added NaH (240 mg, 10 mmol) and the mixture stirred at r.t. until gas evolution had ceased. The corresponding alkyl mesylate (10 mmol) was added and the mixture stirred for 20 h. $H_2O$ (20 mL) was added and the product extracted with $Et_2O$ and distilled.

The analyses and spectroscopic data of **3a–f** were obtained from the diastereomeric *cct*/*ttc* mixtures, except for **3b**.

#### 2,3,4,5-Tetramethoxytetrahydrofuran (3a)

20.04 g (90%); colorless oil; bp 106–110 °C/13 Torr (Lit:[13] bp 95 °C/12 Torr).

IR (film): ν = 2980, 2920, 2820, 1190, 1030, 980, 940 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): *ttc*: δ = 3.44 (s, 3 H, $OCH_3$), 3.47 (s, 3 H, $OCH_3$), 3.84 (AA', 2 H, H3/H4), 5.00 (BB', 2 H, H2/H5); *cct*: δ = 3.40 (s, 3 H, $OCH_3$), 3.49 (s, 3 H, $OCH_3$), 3.50 (s, 3 H, $OCH_3$), 3.51 (s, 3 H, $OCH_3$), 3.65 (m, 1 H, H3), 3.91 (m, 1 H, H4), 5.00 (m, 1 H, H2), 5.05 (m, 1 H, H5).

$^{13}$C NMR ($CDCl_3$): δ = 55.50, 55.58, 56.41, 58.49, 58.55, 59.06, 79.47, 81.44, 83.42, 102.45, 105.93, 107.06.

EI-MS, 70 eV: *m*/*z* (%) = 161 (1, $M^+ - OCH_3$), 132 (2, $M^+ - OCH_3 - CHO$), 101 (100, $M^+ - 2\ OCH_3 - CHO$), 45 (32, $C_2H_5O^+$).

Anal. $C_8H_{16}O_5$ (192.2): calcd C 50.00, H 8.39; found C 49.22, H 8.08.

#### 3,4-Diethoxy-2,5-dimethoxytetrahydrofuran (ttc–3b)

23.03 g (80%); colorless oil; bp 110–113 °C /13 Torr.

IR (film): ν = 2900, 2810, 1140, 1030, 970 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 1.24 (t, *J* = 7.02 Hz, 6 H, $OCH_2CH_3$), 3,44 (s, 6 H, $OCH_3$), 3.62 (m, 4 H, $OCH_2$), 3.91 (AA', 2 H, H3/H4), 4.99 (BB', 2 H, H2/H5).

$^{13}$C NMR ($CDCl_3$): δ = 15.24, 55.56, 66.27, 81.88, 107.71.

EI-MS, 70 eV: *m*/*z* (%) = 189 (5, $M^+ - OCH_3$), 160 (6, $M^+ - OCH_3 - CHO$), 129 (69 $M^+ - 2\ OCH_3 - CHO$), 115 (100, $M^+ - OCH_3 - OC_2H_5 - CHO$), 87 (38).

Anal. $C_{10}H_{20}O_5$ (220.3): calcd C 54.53, H 9.15, found C 53.45, H 9.01.

#### 2,5-Dimethoxy-3,4-dipentoxytetrahydrofuran (3c)

5.78 g (95%); colorless oil; bp 95–115 °C/0.005 Torr.

IR (film): ν = 2950, 2930, 2860, 1195, 1040, 995 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): *ttc*: δ = 0.87–0.92 (m, 6 H, $CH_3$), 1.27–1.36 (m, 8 H, $CH_2CH_2$), 1.58–1.69 (m, 4 H, $CH_2$), 3.43 (s, 6 H, $OCH_3$), 3.71 (m, 4 H, $OCH_2$), 3.88 (AA', 2 H, H3/H4), 4.98 (BB', 2 H, H2/H5); *cct*: δ = 0.87–0.92 (m, 6 H, $CH_3$), 1.27–1.36 (m, 8 H, $CH_2CH_2$), 1.58–1.69 (m, 4 H, $CH_2$), 3.47 (m, 4 H, $OCH_2$), 3.48 (s, 3 H, $OCH_3$), 3,70 (m, 1 H, H4), 3,93 (m, 1 H, H3), 3.97 (s, 3 H, $OCH_3$), 5.00 (m, 1 H, H5), 5.02 (m, 1 H, H2).

$^{13}$C NMR ($CDCl_3$): *ttc*: δ = 13.95, 22.47, 28.22, 29.47, 55.54, 71.08, 82.10, 107.74; *cct*: δ = 13.94, 13.94, 22.46, 22.46, 28.16, 28.14, 29.35, 29.32, 56.07, 55.57, 71.33, 71.58, 78.20, 80.17, 102.72, 106.81.

EI-MS, 70 eV: *m*/*z* (%) = 244 (1, $M^+ - OCH_3 - CHO$), 213 (54, $M^+ - 2\ OCH_3 - CHO$), 157 (100, $M^+ - 2\ OCH_3 - CHO - C_4H_8$), 87 (79, $M^+ - 2\ OCH_3 - CHO - C_4H_9 - C_5H_{10}$).

Anal. $C_{16}H_{32}O_5$ (304.4): calcd C 63.12, H 10.59, found C 63.22, H 10.10.

#### 3,4-Diallyloxy-2,5-dimethoxytetrahydrofuran (3d)

4.54 g (93%); yellowish oil; bp 92 °C/0.06 Torr.

IR (film): ν = 3080, 2920, 1645, 1195, 1030, 995 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): *ttc*: δ = 3.43 (s, 6 H, $OCH_3$), 3.96 (AA', 2 H, H3/H4), 4.12 (m, 4 H, $OCH_2$), 5.03 (BB', 2 H, H2/H5), 5.25 (m, 4 H, $=CH_2$), 5.92 (m, 2 H, CH=); *cct*: δ = 3.42 (s, 3 H, $OCH_3$), 3.43 (s, 1 H, H4), 3.45 (s, 3 H, $OCH_3$), 3.96 (m, 1 H, H3), 4.12 (m, 4 H, $OCH_2$), 4.94 (m, 2 H, H2/H5), 5.25 (m, 4 H, $=CH_2$), 5.92 (m, 2 H, CH=).

$^{13}C$ NMR ($CDCl_3$): δ = 55.53, 55.55, 56.20, 71.65, 71.90, 72.04, 76.55, 76.96, 78.88, 81.31, 102.64, 106.66, 107.64, 117.38, 117.62, 117.71, 134.35, 134.60.

EI-MS, 70 eV: *m/z* (%) = 153 (10, $M^+ - 2\ OCH_3 - CHO$), 127 (23, $M^+ - OCH_3 - CHO - C_3H_5O$), 112 (8, $M^+ - 2\ OCH_3 - CHO - C_3H_5$), 97 (16, $M^+ - 2\ OCH_3 - CHO - C_3H_5O + H$), 85 (1, $M^+ - 2\ OCH_3 - C_3H_5O - C_3H_6$), 41 (100, $C_3H_5^+$).

Anal. $C_{12}H_{20}O_5$ (244.3): calcd C 59.00, H 8.25, found C 56.92, H 7.98.

**3,4-Dibenzyloxy-2,5-dimethoxytetrahydrofuran (3e)**
5.88 g (85%); bp 160–162 °C/0.01 Torr.

IR (film): ν = 3090 vw, 3060, 3030, 2912, 1199, 992 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): *ttc*: δ = 3.40 (s, 6 H, $OCH_3$), 3.99 (AA', 2 H, H3/H4), 4.59 (d, *J* = 12.14 Hz, 2 H, PhC$H_A$), 4.64 (d, *J* = 12.4 Hz, 2 H, PhC$H_B$), 5.04 (BB', 2 H, H2/H5), 7.24–7.42 (m, 10 H, Ph); *cct*: δ = 3.30 (s, 3 H, $OCH_3$), 3.51 (s, 3 H, $OCH_3$), 3.73 (m, 1 H, H3), 3.95 (m, 1 H, H4), 4.57 (d, *J* = 12.19 Hz, 1 H, PhC$H_A$), 4.64 (d, *J* = 12.19 Hz, 1 H, PhC$H_B$), 4.66 (d, *J* = 12.53 Hz, 1 H, PhC$H_C$), 4.71 (d, *J* = 12.53 Hz, 1 H, PhC$H_D$), 4.95 (m, 1 H, H2), 4.99 (m, 1 H, H5), 7.24–7.42 (m, 10 H, Ph).

EI-MS, 70 eV: *m/z* (%) = 106 (45, PhCHO), 105 (43, PhCO), 91 (100, $C_7H_7^+$), 77 (53, $C_6H_5^+$).

Anal. $C_{20}H_{24}O_5$ (344.4): calcd C 69.75, H 7.02, found C 70.09, H 6.94.

**3,4-Bis(hex-1-en-6-oxy)-2,5-dimethoxytetrahydrofuran (3f)**
1.42 g (87%); bp 100–110 °C/ 0.04 Torr.

IR (film): ν = 3075, 2925, 1647, 1145, 995 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): *ttc*: δ = 1.39–1.68 (m, 8 H, $CH_2CH_2$), 2.02–2.12 (m, 4 H, C$H_2$CH=$CH_2$), 3.43 (s, 6 H, $OCH_3$), 3.54 (dd, $J_1$ = 6.48 Hz, $J_2$ = 0.91 Hz, 4 H, $OCH_2$), 3.87 (AA', 2 H, H3/H4), 4.97 (BB', 2 H, H2/H5), 4.91–5.04 (m, 4 H, $=CH_2$), 5.80 (ddt, $J_1$ = 16.97 Hz, $J_2$ = 10.16 Hz, $J_3$ = 6.96 Hz, 2 H, C*H*=$CH_2$); *cct*: δ = 1.39–1.68 (m, 8 H, $CH_2CH_2$), 2.02–2.12 (m, 4 H, C$H_2$CH=), 3.42 (s, 3 H, $OCH_3$), 3.45 (s, 3 H, $OCH_3$), 3.50–3.64 (m, 4 H, $OCH_2$), 3.68–3.71 (m, 1 H, H4), 3.90–3.93 (m, 1 H, H3), 4.91–4.96 (m, 4 H, $=CH_2$), 4.98–5.00 (m, 1 H, H5), 5.02–5.06 (m, 1 H, H2), 5.71–5.88 (m, 2 H, CH=).

$^{13}C$ NMR ($CDCl_3$): δ = 25.26, 25.31, 25.37, 29.08, 29.11, 29.24, 33.37, 33.40, 33.47, 55.36, 55.57, 55.80, 70.84, 71.14, 74.25, 80.20, 82.13, 82.99, 102.68, 107.71, 108.16, 109.77, 114.48, 114.77, 138.33, 138.66, 138.73.

MS-EI, 70 eV: *m/z* (%) = 297 (2, $M^+$–$OCH_3$), 237 (18, $M^+$–2 $OCH_3$–CHO), 185 (14), 169 (64, $M^+$–2 $OCH_3$–CHO–$C_5H_8$), 155 (3, $M^+$ – 2 $OCH_3$ – CHO – $C_6H_{10}$), 87 (81, $M^+ - 2\ OCH_3 - CHO - C_6H_{10} - C_5H_8$), 54 (100).

Anal. $C_{18}H_{32}O_5$ (328.5): calcd C 65.28, H 9.82; found C 63.99, H 9.42.

***N*-substituted 3,4-Dialkoxypyrroles 4a–m; General Procedures**
**Procedure A** (*for* **4a–g**): The water soluble ether acetals **3a–b** (1 mmol) were hydrolyzed with aq 2N HCl or $H_2SO_4$ (0.34 mmol) at 70 °C for 30 min. From an aliquot of the hydrolysis solution the bisphenylhydrazone of dimethoxytartaric aldehyde, mp 124 °C was isolated.[14] The solution of the dialdehyde thus obtained was combined with a suspension of NaOAc•$3H_2O$ (1.0 g, 7.1 mmol) and the hydrochloride of the corresponding primary amine (5 mmol) in $CHCl_3$ (15 mL), and the mixture was stirred for 24 h. The $CHCl_3$ phase was washed with aq satd $NaHCO_3$ solution (10 mL), dried ($MgSO_4$) and the residue purified by chromatography with $Et_2O$ over a short silica gel column.

**Procedure B** (*for* **4h–m**): The hydrolysis of water insoluble **3c–f** (1 mmol) was performed in a mixture of $CF_3CO_2H$ (77 μL, 1 mmol), and $H_2O$ (150 μL) for 50 to 90 min. $CHCl_3$ (20 mL), solid NaOAc•3 $H_2O$ (0.96 g, 7 mmol) and the amine (5.0 mmol) were added subsequently and the mixture was stirred for 24 h at r.t. The product was isolated and purified by column chromatography on silica gel.

**3,4-Dimethoxy-1-methylpyrrole (4a)**
Pale yellow oil; 74 mg (79%) from a 127 mg **3a**, spectroscopic data as given in Ref. 3.

**3,4-Dimethoxy-1-propylpyrrole (4b)**
Pale yellow oil; 327 mg (74%) from 500 mg **3a**.

IR (Film): ν = 3160, 3120, 2990, 1590, 1570, 1560 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ = 0.89 (t, 3 H, $CH_3$, *J* = 7.38 Hz,), 1.72 (m, 2 H $NCH_2CH_2CH_3$), 3.62 (t, 2 H, $NCH_2$, *J* = 7.03 Hz), 3.73 (s, 6 H, $OCH_3$), 6.09 (s, 2H, 2,5-Pyrrole-H).

EI-MS, 70 eV: *m/z* (%) = 169 (100, $M^+$), 154 (33,$M^+ - CH_3$), 140 (32, $M^+ - C_2H_5$), 126 (31, $M^+ - C_3H_7$).

Anal. $C_9H_{15}NO_2$ (169.2): calcd C 63.88, H 8.93, N 8.28, found C 61.91, H 8.93, N 7.45.

**1-(*tert*-Butyl)-3,4-dimethoxypyrrole (4c)**
413 mg (87%) from 500 mg **3a**; mp 74 °C.

IR (KBr): ν = 3160, 3120, 2990, 1575, 1508 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ = 1.45 (s, 9 H, $CH_3$), 3.74 (s, 6 H, $OCH_3$), 6.25 (2 H, 2,5-Pyrrole-H).

$^{13}C$ NMR ($CDCl_3$): δ = 30.10, 54.40, 58.62, 99.58, 137.18.

EI-MS, 70 eV: *m/z* (%) = 183 (60, $M^+$), 168 (18, ($M^+ - CH_3$), 127 (89, $M^+ - C_4H_8$), 112 (100, $M^+ - C_4H_8, - CH_3$).

Anal. $C_{10}H_{17}NO_2$ (183.3): calcd C 65.54, H 9.35, N 7.64, found C 64.84, H 8.99, N 7.37.

**1-Benzyl-3,4-dimethoxypyrrole (4d)**
Colorless oil; 484 mg (73%) from 585 mg **3a**.

IR (film): ν = 3170, 3140, 3100, 3060, 3030, 2980, 1590, 1560 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ = 3.72 (s, 6 H, $OCH_3$), 4.85 (s, 2 H, C$H_2$Ph), 6.12 (s, 2 H, 2,5-Pyrrole-H), 7.08–77.12 (m, 2 H, Ph), 7.23–7.36 (m, 3 H, Ph).

$^{13}C$ NMR ($CDCl_3$): δ = 54.10, 58.60, 103.08, 126.96, 127.60, 128.65, 137.85, 138.34.

EI-MS, 70 eV, *m/z* (%) = 217 (26, $M^+$), 202 (10, $M^+ - CH_3$), 91 (100, $C_7H_7^+$).

Anal. $C_{13}H_{15}NO_2$ (217.3): calcd C 71.87, H 6.96, N 6.45, found C 71.64, H 7.06, N 6.42.

**1-(2-Cyanoethyl)-3,4-dimethoxypyrrole (4e)**
Colorless oil; 296 mg (71%) from 443 mg **3a.**

IR (film): ν = 3150, 3110, 2940, 2250, 1580, 1510 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ = 2.69 (t, 2 H, $NCH_2$, *J* = 6.62 Hz), 3.73 (s, 6 H, $OCH_3$), 3.99 (t, 2 H, $CH_2CN$, *J* = 6.62 Hz), 6.13 (s, 2 H, 2,5-Pyrrole-H).

$^{13}$C NMR ($CDCl_3$): δ = 20.40, 46.12, 58.57, 102.23, 117.27, 138.58.

EI-MS, 70 eV: *m*/*z* (%) = 180 (87, $M^+$), 165 (45, $M^+ - CH_3$), 140 (100, $M^+ - CH_2CN$), 125 (24, $M^+ - CH_3 - CH_2CN$).

Anal. $C_9H_{12}N_2O_2$ (180.2) calcd C 60.00, H 6.71, N 15.55; found C 59.85; H 6.83; N 15.34.

**1-Allyl-3,4-dimethoxypyrrole (4f)**
Colorless oil; 585 mg (65%) from 1.04 g of **3a.**

IR (film): ν = 3120, 3090, 3080, 2980, 1570, 1540 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 3.73 (s, 6 H, $OCH_3$), 4.27 (ddd, 2 H, $NCH_2$, $J_1$ = 5.79 Hz, $J_2$ = 1.56 Hz, $J_3$ = 1.56 Hz), 5.14 (ddt, 1 H, $=CH_{trans}$, $J_1$ = 16.89 Hz, $J_2$ = 1.56 Hz, $J_3$ = 1.56 Hz), 5.18 (ddt, 1 H, $=CH_{cis}$, $J_2$ = 1.43 Hz, $J_3$ = 1.43 Hz, $J_1$ = 10.23 Hz), 5.93 (ddt, $J_1$ = 16.89 Hz, $J_2$ = 10.23 Hz, $J_3$ = 5.79 Hz, 1 H, $NCH_2CH{=}CH_2$), 6.09 (s, 2 H, 2,5-Pyrrole-H).

$^{13}$C NMR ($CDCl_3$): δ = 52.84, 58.61, 102.55, 117.33, 134.42, 137.63.

MS-EI, 70 eV: *m*/*z* (%) = 167 (100, $M^+$), 152 (83, $M^+ - CH_3$), 136 (17, $M^+ - OCH_3$), 126 (12, $M^+ - C_3H_7$), 41 (97, $C_3H_7^+$).

Anal. $C_9H_{13}NO_2$ (167.2) calcd C 64.65, H 7.84, N 8.38, found C 64.39, H 7.68, N 8.36.

**1-*tert*-Butyl-3,4-diethoxypyrrole (4g)**
Yellowish oil; 1.27 g (81%) from 1.63 g **3b**.

IR (film): ν = 3150, 2980, 1570, 1545 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 1.37 (t, 6 H, $OCH_2CH_3$, $J$ = 7.00 Hz), 1.43 (s, 9 H, $CH_3$), 3.93 (q, 2 H, $OCH_2$, $J$ = 7.00 Hz,), 6.24 (s, 2 H, 2,5-Pyrrole-H).

$^{13}$C NMR ($CDCl_3$): δ = 30.10, 54.29, 55.59, 66.95, 100.62, 136.22.

EI-MS, 70 eV: *m*/*z* (%) = 211 (100, $M^+$), 196 (19, $M^+ - CH_3$), 182 (14, $M^+ - C_2H_5$), 155 (33, $M^+ - C_4H_8$), 126 (95, $M^+ - C_4H_8, - C_2H_5$).

Anal. $C_{12}H_{21}NO_2$ (211.3) calcd C 68.21, H 10.02, N 6.63, found C 65.30; H 9.68; N 6.21.

**1-Benzyl-3,4-dipentoxypyrrole (4h)**
Colorless oil; 350 mg (77%) from 321 mg **3c**.

IR (film): ν = 3140, 3090, 3064, 3030, 2950, 1580, 1555 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 0.92 (t, 6 H, $CH_3$, $J$ = 7.01 Hz), 1.30–1.80 (m, 12 H, $CH_2CH_2CH_2$), 3.83 (t, 4 H, $OCH_2$, $J$ = 6.73 Hz), 4.83 (s, 2 H, $CH_2Ph$), 6.11 (s, 2 H, 2,5-Pyrrole-H), 7.08–7.12 (m, 2 H, Ph), 7.23–7.37 (m, 3 H, Ph).

$^{13}$C NMR ($CDCl_3$): δ = 14.00, 22.50, 28.22, 29.22, 53.37, 54.03, 71.79, 104.33, 126.90, 127.51, 128.60, 137.20, 138.52.

EI-MS, 70 eV: *m*/*z* (%) = 329 (5, $M^+$), 258 (19, $M^+ - C_5H_{11}$), 189 (23, $M^+ - 2 \times C_5H_{10}$), 91 (100, $C_7H_7^+$).

Anal. $C_{21}H_{31}NO_2$ (329.5) calcd C 76.55, H 9.48, N 4.25, found C 74.03, H 9.21, N 4.24.

**1-Allyl-3,4-diallyloxypyrrole (4i)**
Yellowish oil; 1.51 g (86%) from 1.96 g **3d**.

IR (film): ν = 3137, 3082, 3014, 2983, 1646, 1576, 1553 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 4.25 (ddd, $J_1$ = 5.88 Hz, $J_2$ = 1.51 Hz, $J_3$ = 1.44 Hz, 2 H, $NCH_2$), 4.41 (ddd, $J_1$ = 5.58 Hz, $J_2$ = 1.46 Hz, $J_3$ = 1.52 Hz, 2 H, $OCH_2$), 5.17 (ddt, $J_1$ = 10.31 Hz, $J_2$ = 1.44 Hz, $J_3$ = 1.19 Hz, 1 H, $NCH_2CH{=}CH_{cis}$), 5,21 (ddt, $J_1$ = 10,54 Hz, $J_2$ = 1.61 Hz, $J_3$ = 1.46 Hz, 2 H, $OCH_2CH{=}CH_{cis}$) 5.31 (ddt, $J_1$ = 16.78 Hz, $J_2$ = 1.51 Hz, $J_3$ = 1.19 Hz, 1 H, $NCH_2CH{=}CH_{trans}$), 5.35 (ddt, $J_1$ = 17.28 Hz, $J_2$ = 1.61 Hz, $J_3$ = 1.52 Hz, 2 H, $OCH_2CH{=}CH_{trans}$), 5.91 ddt, $J_1$ = 16.78 Hz, $J_2$ = 10.31 Hz, $J_3$ = 5.88 Hz, 1 H, $NCH_2CH{=}CH_2$), 6.06 (ddt, $J_1$ = 17.28 Hz, $J_2$ = 10.31 Hz, $J_3$ = 5.58 Hz, 2 H, $OCH_2CH{=}CH_2$), 6.10 (s, 2 H, 2,5-Pyrrole-H).

$^{13}$C NMR ($CDCl_3$): δ = 52.77, 72.65, 104.16, 116.99, 117.24, 134.38, 134.40, 136.52.

EI-MS, 70 eV: *m*/*z* (%) = 219 (42, $M^+$), 178 (87, $M^+ - C_3H_5$), 150 (49, $M^+ - C_3H_5, - CO$), 41 (100, $C_3H_5^+$).

Anal. $C_{13}H_{17}NO_2$ (219.3) calcd C 71.21, H 7.81, N 6.39, found C 68.98, H 7.62, N 5.96.

**1-Benzyl-3,4-diallyloxypyrrole (4j)**
Pale yellow oil; 811 mg (74%) from 1.00 g of **3d**.

IR (film): ν = 3137, 3084, 3028, 2983, 1647, 1577, 1554 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 4.42 (ddd, $J_1$ = 5.65 Hz, $J_2$ = 1.47 Hz, $J_3$ = 1.54 Hz, 4 H, $OCH_2$), 4.83 (s, 2 H, $CH_2Ph$), 5.23 (ddt, $J_1$ = 10.44 Hz, $J_2$ = 1.47 Hz, $J_3$ = 1.52 Hz, 2 H, $=CH_{cis}$), 5.36 (ddt, $J_1$ = 17.44 Hz, $J_2$ = 1.54 Hz, $J_3$ = 1.52 Hz, 2 H, $=CH_{trans}$), 6.04 (ddt, $J_1$ = 17.44 Hz, $J_2$ = 10.44 Hz, $J_3$ = 5.65 Hz, 2 H, $CH_2CH{=}CH_2$), 6.13 (s, 2 H, 2,5-Pyrrole-H), 7.06–7.11 (m, 2 H, Ph), 7.24–7.37 (m, 3 H, Ph).

$^{13}$C NMR ($CDCl_3$): δ = 54.05, 72.62, 104.72, 117.10, 126.88, 127.57, 128.62, 134.35, 136.75, 138.36.

EI-MS, 70 eV, *m*/*z* (%) = 269 (6, $M^+$), 228 (17, $M^+ - C_3H_5$), 200 (7, $M^+ - C_3H_5, - CO$), 91 (100, $C_7H_7^+$).

Anal. $C_{17}H_{19}NO_2$ (269.3) calcd C 75.81, H 7.11 N 5.20, found C 74.96 H 6.98, N 4.94.

**1-Benzyl-3,4-dibenzyloxypyrrole (4k)**
Colorless crystals; 395 mg (66%) from 559 mg **3f**; mp 82–83 °C.

IR (KBr): ν = 3135, 3087, 3062, 3030, 2922, 1575, 1553 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 4.78 (s, 2 H, $NCH_2Ph$), 4.95 (s, 4 H, $OCH_2Ph$), 6.09 (s, 2 H, 2,5- Pyrrole-H), 7.00–7.46 (m, 15 H, Ph).

$^{13}$C NMR ($CDCl_3$): δ = 54.01, 73.81, 105.29, 126.80, 127.53, 127.66, 127.73, 128.30, 128.62, 136.93, 137.93, 138.34.

EI-MS, 70 eV: *m*/*z* (%) = 369 (8, $M^+$), 278 (29, $M^+ - C_7H_7$), 91 (100, $C_7H_7^+$).

Anal. $C_{25}H_{23}NO_2$ (369.5) calcd C 81.27, H 6.27, N 3.79, found: C 80.81, H 6.04, N 3.64.

**1-Allyl-3,4-dibenzyloxypyrrole (4l)**
Yellow oil; 508 mg (38%) from 1.42 g of **3f**.

IR (film): ν = 3140, 3087, 3064, 3031, 2911, 1643, 1574, 1553 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 4.20 (ddd, $J_1$ = 5.68 Hz, $J_2$ = 1.68 Hz, $J_3$ = 1.41 Hz, 2 H, $NCH_2$), 4.96 (s, 4 H, $OCH_2Ph$), 5.05 (ddt, $J_1$ = 16.99 Hz, $J_2$ = 1.39 Hz, $J_3$ = 1.68 Hz, 1 H, $=CH_{trans}$), 5.13 (ddt, $J_1$ = 10.19 Hz, $J_2$ = 1.39 Hz, $J_3$ = 1.41 Hz, 1H, $=CH_{cis}$), 5.87 (ddt, $J_1$ = 16.99 Hz, $J_2$ = 10.19 Hz, $J_3$ = 5.68 Hz, 1 H, $NCH_2CH{=}CH_2$), 6.0 (s, 2 H, 2,5-Pyrrole-H), 7.24–7.44 (m, 10 H, Ph).

$^{13}$C NMR ($CDCl_3$): δ = 52.73, 73.88, 104.67, 117.22, 127.62, 127.64, 128.29, 134.33, 136.81, 138.02.

EI-MS, 70 eV: *m*/*z* (%) = 319 (13, $M^+$), 228 (40, $M^+ - C_7H_7$), 200 (29, $M^+ - C_7H_7 - CO$), 91 (100, $C_7H_7^+$).

Anal. $C_{21}H_{21}NO_2$ (319.4) calcd C 78.97; H 6.63; N 4.39; found C 78.23, H 6.65, N 4.17.

**1-Benzyl-3,4-bis(hex-1-en-5-oxy)pyrrole (4m)**
Colorless oil; 234 mg (45%) from 486 mg **3e**. IR (film): ν = 3135, 3074, 3030, 2935, 1640, 1579, 1553 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 1.54–2.09 (m, 12 H, $CH_2CH_2CH_2$), 3.84 (t, $J$ = 6.55 Hz, 2 H, $OCH_2$), 3.84 (s, 2 H,

C$H_2$Ph), 4.94 (ddt, $J_1$ = 10.16 Hz, $J_2$ = 2.13 Hz, $J_3$ = 1.24 Hz, 2 H, =$CH_{cis}$), 5.00 (ddt, $J_1$ = 17.12 Hz, $J_2$ = 2.13 Hz, $J_3$ = 1.59 Hz, 2 H, =$CH_{trans}$), 5.81 (ddt, $J_1$ = 17.12 Hz, $J_2$ = 10.16 Hz, $J_3$ = 6.63 Hz, 2 H, C$H$=$CH_2$), 6.11 (s, 2 H, 2,5-Pyrrole-H), 7.05–7.10, 2 H, Ph), 7.23–7.35 (m, 3 H, Ph).

$^{13}$C NMR ($CDCl_3$): δ = 25.35, 28.98, 33.47, 54.04, 104.37, 114.46, 126.91, 127.53, 128.60, 137.14, 138.44, 138.74.

EI-MS, 70 eV: *m*/*z* (%) = 353 (8, $M^+$), 270 (32, $M^+ - C_6H_{11}$), 242 (10, $M^+ - C_6H_{11}$, – CO), 189 (33, $M^+ - 2\ C_6H_9$); 91 (100, $C_7H_7^+$).

Anal. $C_{13}H_{31}NO_2$ (353.5) calcd C 78.15, H 8.84, N 3.96; found: C 77.77; H 8.72; N 4.10.

**3,4-Dialkoxypyrroles 5a–c by *N*-Debenzylation: General Procedure**

The pyrrole (5 mmol) in anhyd THF (5 mL) was added dropwise to a solution of sodium (230 mg, 10 mmol) in liquid ammonia (ca. 50 mL) at –78 °C. When the blue colour had faded (1.5 to 2.5 h) aq $NH_4Cl$ (535 mg in 30 mL $H_2O$) was carefully added. After evaporation of $NH_3$ the aquoeus phase was extracted with $CH_2Cl_2$. The pyrroles were purified by chromatography on a silica gel column using $Et_2O$ as an eluent.

**3,4-Dimethoxypyrrole (5a)**

Colorless crystals; 125 mg (94%) from 285 mg **4d;** mp 93 °C (Lit:[3] mp 93–94 °C) or 127 mg (78%) from 240 mg of **4f**.

**3,4-Dipentoxypyrrole (5b)**

Colorless crystals; 212 mg (94%) from 312 mg of **4h**; mp 36 °C (pentane).

IR (KBr): ν = 3403, 3140, 2960, 1587, 1547 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 0.88–0.94 (m, 6 H, $CH_3$), 1.29–1.48 (m, 8 H, $CH_2CH_2$), 1.64–1.88 (m, 4 H, $OCH_2CH_2$), 3.86 (t, 4 H, $OCH_2$, $J$ = 6.74 Hz), 6.21 (d, $J$ = 3.24 Hz, 2 H, 2,5-Pyrrole-H), 6.97 (br, 1 H, NH).

$^{13}$C NMR ($CDCl_3$): δ = 13.97, 22.48, 28.20, 29.19, 71.74, 100.97, 137.72.

EI-MS, 70 eV: *m*/*z* (%) = 239 (3, $M^+$), 168 (6 $M^+ - C_5H_{11}$), 125 (8, $M^+ - 2\ C_4H_9$), 99 (100, $M^+ - 2\ C_5H_9$).

Anal. $C_{14}H_{25}NO_2$ (239.4) calcd C 70.25, H 10.53, N 5.85; found C 70.32, H 10.61, N 10.38.

**3,4-Bis(hex-1-en-5-oxy)pyrrole (5c)**

Colorless oil; 100 mg (53%) from 255 mg **4j**; mp 26 °C (pentane).

IR (film): ν = 3392, 3180, 3147, 2942, 1641, 1586, 1548 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 250 MHz): δ = 1.48–1.60 (m, 4 H, $CH_2$), 1.72–1.84 (m, 4 H, $CH_2$), 2.06–2.15 (m, 4 H, $CH_2$), 3.87 (t, 4 H, $J$ = 6.59 Hz, $OCH_2$), 4.95 (ddt, $J_1$ = 10,20 Hz, $J_2$ = 2.14 Hz, $J_3$ = 1.28 Hz, 2 H, =$CH_{cis}$), 5.01 (ddt, $J_1$ = 17.16 Hz, $J_2$ = 2.14 Hz, $J_3$ = 1.56 Hz, 2 H, =$CH_{trans}$), 5,82 (ddt, $J_1$ = 17.16 Hz, $J_2$ = 10.19 Hz, $J_3$ = 6.61 Hz, 2 H, =CH), 6.21 (d, $J$ = 3.18 Hz, 2 H, 2,5-Pyrrole-H), 6.99 (br, 1 H, NH).

$^{13}$C NMR ($CDCl_3$): δ = 25.36, 28.96, 33.47, 71.51, 101.00, 114.48, 137.65, 138.74.

EI-MS, 70 eV: *m*/*z* (%) = 263 (26, $M^+$), 180 (11, $M^+ - C_6H_{11}$), 152 (8, $M^+ - C_6H_{11}$ – CO), 99 (100, $M^+ - 2 \times C_6H_9$).

Anal. $C_{16}H_{25}NO_2$ (263.4) calcd C 72.97, H 9.57, N 5.32; found C 73.55, H 9.64, N 5.07.

**3,4-Dimethoxypyrrole (5a) by Ni-Catalyzed Deallylation of 4f**

A solution of **4f** (297 mg, 1.78 mmol) in anhyd benzene (2 mL) was added to a suspension of bis(triphenylphosphine)nickel dichloride (116 mg, 0.177 mmol) and 1.77 M ethereal MeMgI (1.27 mL, 2.25 mmol) in anhyd benzene (2.5 mL) und anhyd $Et_2O$ (3.5 mL) and stirrred for 20 h at reflux temperature. EtOH (1 mL) and $H_2O$ (15 mL) were added and the product was extracted with $Et_2O$; yield: 119 mg (53%).

**Multigram Preparation of 5a**

A solution of **3a** (9.72 g, 0.05 mmol) in 1 M $H_2SO_4$ (8.14 mL) was heated at 85 °C for 30 min during which time a MeOH/ $H_2O$ mixture (ca 2 mL) was distilled at maximum 85 °C head temperature. The residue was cooled to r.t. and added to a well stirred suspension of benzylammonium hydrochloride (35.6 g, 0.25 mol) in $H_2O$ (15 mL) and $CHCl_3$ (300 mL) and stirred for 17 h. The $CHCl_3$ phase was washed with satd aq $NaHCO_3$ solution (2 × 100 mL) and dried ($MgSO_4$). After removal of the solvent the solid residue was purified by sublimation (80 °C/0.01 Torr) to give 9.3 g (84%) of **4d**. A THF solution (50 mL) of **4d** was slowly added to a solution of Na (2.0 g) in liquid $NH_3$ (300 mL). After 4h, workup as given above gave 5.0 g of **5a** (94%) after sublimation.

**4-Methoxypyridazine (6)**

To the hydrolyzed and buffered solution (procedure A) from **3a** (0.392 g, 2.04 mmol) was added hydrazine sulfate (1.33 g, 10.2 mmol) and the mixture heated at 95 °C for 36 h. Extraction with $Et_2O$ yielded 0.18 g oil (80 %) which crystallized on cooling; mp 40 °C (Lit. 42–44 °C,[19] mp 32–36 °C[20]).

IR (KBr): ν = 3090, 2980, 1580, 1380, 1310$cm^{-1}$.

$^1$H NMR: δ = 3.93 (s, 3 H, $OCH_3$), 6.88–6.92 (m, 1 H, H5), 8.92–8.99 (m, 2 H, H3/H6).

EI-MS, 70 eV: *m*/*z* (%) = 116 (100, $M^+$), 52 (42), 39 (65).

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