Synthesis of Orthogonally Protected Pyrrole Tricarboxylic Acid Derivatives: Versatile Building Blocks for Pyrrole-Containing Compounds

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Dedicated to Prof. Albrecht Berkessel on the occasion of his 50th birthday

Abstract: The large-scale synthesis of three new orthogonally protected pyrrole tricarboxylates **1**–**3** is described. Using different cleavage conditions, each of the three carboxylates can be set free selectively without affecting the others, making these pyrrole derivatives versatile synthetic building blocks for a wide range of applications in natural product or supramolecular chemistry.

Key words: pyrroles, carboxylic acids, protecting groups, transesterifications, oxidations

Substituted pyrroles are versatile synthetic building blocks for a variety of applications ranging from natural products to pharmaceutical agents and supramolecular chemistry.[1] For our own specific purposes, the design of artificial receptors for biologically relevant substrates[2] or self-assembling zwitterions[3] we were interested in pyrrole tricarboxylic acids of the general structure shown in Figure 1. The two carboxyl groups in position 2 and 5 of the pyrrole ring are needed for further attachment of specific binding sites such as a guanidino or an amide group whereas the side-chain carboxyl group serves as a handle to attach the resulting guanidiniocarbonyl pyrrole binding motif to either a solid support or for linking two or more of these recognition motifs into a multivalent display. For this purpose, however, a sequential and selective transformation of the three carboxylic acid groups is necessary. Whereas in principle the side-chain carboxylate is more reactive than the two pyrrole carboxylates and can be reacted at least with some selectivity, a distinction between the latter two is not possible based on their intrinsic reactivity. Even the selective transformation of the side-chain carboxylate, for example its hydrolysis into the corresponding acid, requires a careful control of the reaction conditions to avoid mixtures of products.[4] The use of orthogonal protecting groups offers a solution to this problem. We were therefore interested in developing a versatile approach, which allows the large-scale synthesis of a variety of new pyrrole triesters with varying substitution patterns at the three ester groups. The corresponding target compounds **1**–**3** are summarized in Figure 1. All triesters are new compounds that have not been described in the literature so far.[5]

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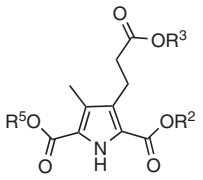
We chose the corresponding *tert*-butyl, benzyl and methyl/ethyl esters as orthogonal protecting groups.[6] Whereas the *tert*-butyl ester can be cleaved easily under acidic conditions (e.g. TFA in CH_2Cl_2), the benzyl ester can be removed by hydrogenolysis (H_2/Pd) and the methyl/ethyl ester by basic hydrolysis (LiOH in MeOH). Choosing the correct substitution pattern of the three carboxyl groups as in **1**, **2** or **3** each of the carboxylates can be set free subsequently without affecting the remaining esters in the molecule. These three derivatives therefore allow for maximum synthetic flexibility in any further desired transformation of these useful synthetic building blocks.

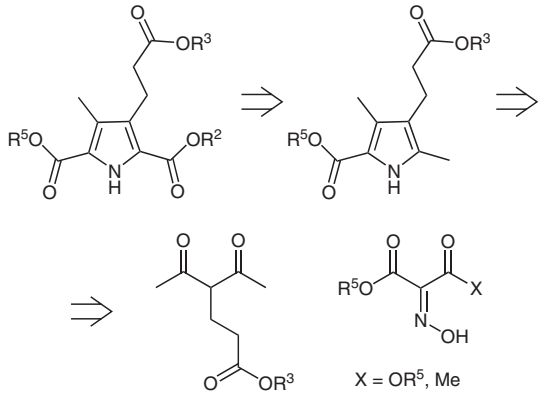


	R^2	R^3	R^5
1	*t*-Bu	Bn	Et
2	Me	*t*-Bu	Bn
3	Bn	Me	*t*-Bu

Figure 1 Triply orthogonally protected pyrrole tricarboxylates.

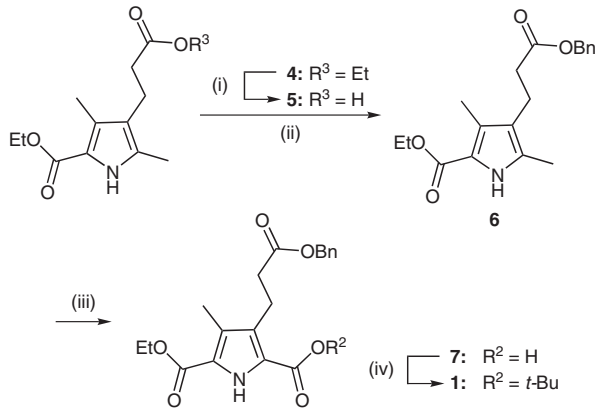
The general synthetic procedure is described in Scheme 1. The triesters can be traced back to the α-methyl pyrrole from which they can be synthesized by selective α-oxidation and subsequent esterification in position R^2. The α-methyl pyrroles can be prepared by Knorr-type cyclization of a β-diketone (e. g. the R^3-4-acetyl-5-oxohexanoate) with an α-amino-β-dicarbonyl compound, which can be obtained by reduction from the corresponding oxime.[7] Due to the frequent instability of many of these aminocarbonyl compounds the reduction of the oxime to the amine is in general performed in situ in the presence of the second carbonyl compound to start the Knorr reaction immediately after release of the amine.[8]

Our first target compound was triester **1** (Scheme 2). The preparation started from the pyrrole diester **4** synthesized according to methods described in the literature.[8b,9] The carboxylic acid **5** was obtained by treatment of **4** with NaOH in EtOH and water at 60 °C.[10] To avoid the transesterification to the methyl ester we chose EtOH as a solvent even though the solubility of **4** in EtOH is rather limited compared to MeOH. Selective hydrolysis of the side-chain ethyl ester was thus achieved and the desired product was obtained in 80% yield. In the next step the free side-chain carboxylic acid group of **5** was transformed into the benzyl ester by reaction with benzyl chlo-



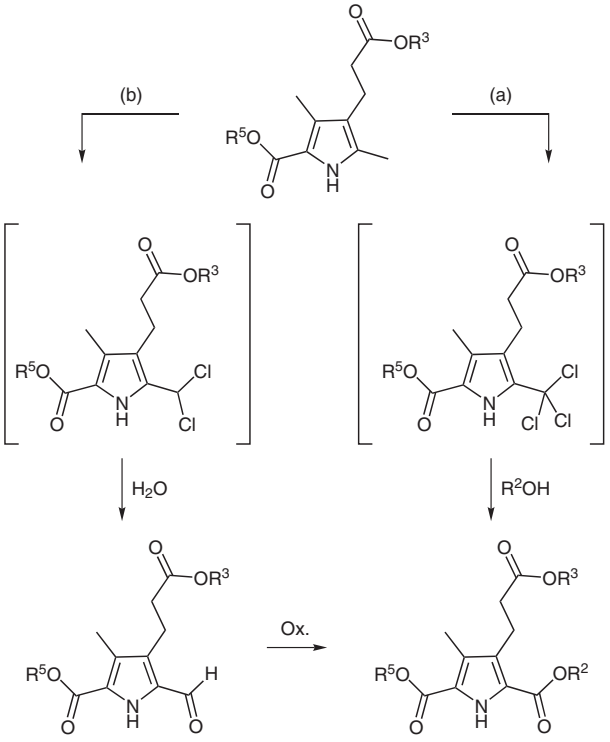
Scheme 1 Retrosynthetic analysis of the tricarboxylates.

ride in DMF–Et_3N to give the diester **6** in 90% yield.[11] Attempts to directly transform the starting diester **4** into **6** by transesterification with benzylate failed due to significant amounts of dibenzyl derivative in the product mixture. Even the transesterification of the ethyl ester derivative of **15** (Scheme 6, R^3 = Et instead of Me) with NaOBn in refluxing toluene led to transesterification at both ester positions, although position R^5 is derived from a rather unreactive electron-rich pyrrole carboxylate and *tert*-butyl esters in general are assumed to be inert towards basic transesterification.



Scheme 2 *Reagents and conditions*: (i) NaOH, H_2O, EtOH, 60 °C, 3.5 h, 80%. (ii) BnCl, DMF–Et_3N (2:1), r.t., 24 h, 90%. (iii) SO_2Cl_2, AcOH, 0 °C, 5 h; H_2O, 0–4 °C, 1.5 h, 92%. (iv) Oxalyl chloride, CH_2Cl_2, DMF (cat.), r.t., 1 h; *t*-BuOK, *t*-BuOH, 40 °C, 2 h, 50%.

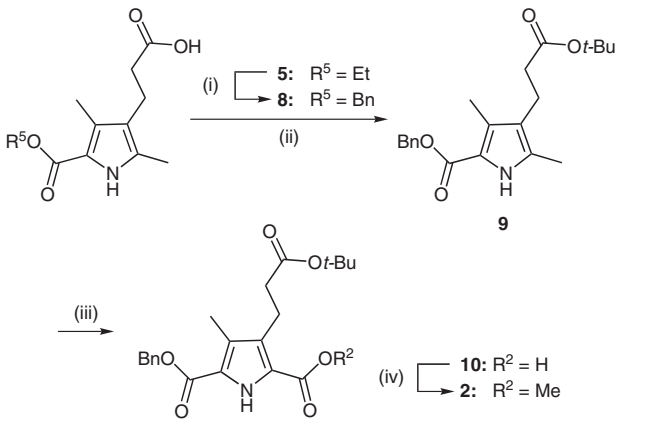
The next step required the oxidation of the α-methyl group to introduce the third carboxylic acid group. For methyl pyrroles in general a wide range of procedures and reaction conditions are described for this transformation in the literature. The most common one is the radical chlorination with subsequent hydrolysis (Scheme 3, route a).[12] This oxidation can be carried out with or without basic quenching of the liberated hydrochloric acid. The yields reported vary from < 30–99%, significantly depending also on other functionalities present in the molecule. The problem of this reaction step is mainly the instability of the resulting pyrrole carboxylic acids.[13] Upon prolonged reaction times especially under acidic conditions or even during work up, pyrrole carboxylic acids tend to decarboxylate which very often significantly reduces the yields of isolated product in this oxidation step. Good yields are often found for products, which easily crystallize and are thereby removed from the aggressive reaction mixture.



Scheme 3 Threefold α-chlorination followed by hydrolysis or alcoholysis (a, right part) or twofold α-chlorination, hydrolysis and subsequent oxidation (b, left part) to obtain pyrrole tricarboxylates.

For the hitherto unknown compound **7**, we first chose a standard procedure.[14] The α-methyl group in **6** was oxidized by treatment with sulfuryl chloride in AcOH followed by aqueous workup at 0 °C. Fast precipitation avoided decomposition of the resulting carboxylic acid **7**, otherwise quite sensitive to acidic conditions. After addition of water to the reaction mixture (which led to liberation of HCl from the hydrolysis of the trichloride and by decomposition of unreacted SO_2Cl_2) a change in the color of the reaction mixture from slightly yellow to brown indicated the beginning of decomposition during workup, but fortunately in this case the product precipitated immediately after pouring into ice-water, thereby removing it from the aggressive reaction medium and giving a yield of 92%. In contrast to this, for example, the direct oxidation of the diethyl ester **4** only gave trace amount of acid under the same conditions, because the product does not crystallize as easily as **7**. Compound **7** was then transformed into the corresponding acyl chloride using oxalyl chloride in CH_2Cl_2 with a catalytic amount of DMF. Finally, the new pyrrole triester **1** was obtained by reaction of this acyl chloride with *t*-BuOK in *tert*-BuOH in 50% yield.

The three carboxylic acid groups in this triester **1** or the free acid **7** can be released in nearly any desired sequence except for one limitation: The cleavage of the benzylic ester in the side-chain has to occur prior to the hydrolysis of the ethyl ester in position 5. Therefore, triester **1** does not allow to further react both carboxylates attached to the pyrrole ring before the side-chain carboxylate is transformed. To circumvent this problem, we were interested in triester **2**, in which the side-chain carboxylate is now protected as the *tert*-butyl ester and the α-positions of the pyrrole as benzyl and methyl esters, respectively. This triester **2** together with the corresponding free acid **10** allows any of the three carboxylates to react in any order.



Scheme 4 *Reagents and conditions*: (i) NaOBn, BnOH, 10–20 mbar, 100 °C, 6 h, 64%. (ii) Oxalyl chloride, CH_2Cl_2, DMF (cat.), r.t., 2 h, *t*-BuOK, *t*-BuOH, 40 °C, 6 h, 72%. (iii) SO_2Cl_2 (2 equiv), K_2CO_3 (4 equiv), Et_2O, 0 °C, 2 h; H_2O, r.t., 0.5 h, then $KMnO_4$ (1 equiv), acetone–H_2O (1:1), r.t., 2 h, 42%. (iv) DMF, MeI (1 equiv), K_2CO_3, 1 d, 45%.

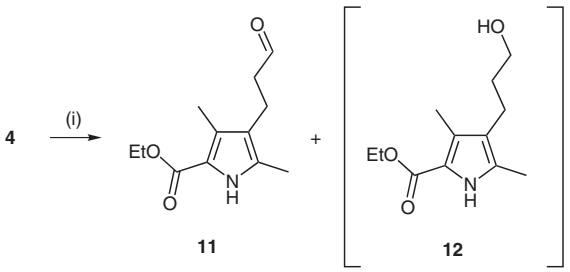
The synthesis of **2** also started from the carboxylic acid **5** (Scheme 4). The remaining ethyl ester group in position 5 was exchanged for a benyzl ester by treatment with sodium benzylate in benzyl alcohol at 100 °C over a period of 6 hours under reduced pressure (10–20 mbar) to remove the liberated EtOH to give **8** in 64% yield. These conditions proved to be mild enough to avoid decomposition. The same reaction at atmospheric pressure and a temperature of 140 °C, conditions similar to those found in the literature for related systems,[12c,15] resulted only in very low yields (< 16%) when applied to **5**. Compound **8** was then esterified via the acyl chloride (obtained from its reaction with oxalyl chloride) and subsequent treatment with *t*-BuOK in *tert*-BuOH at 40 °C to give **9** in 72% yield. In analogy to the synthesis of **7**, direct oxidation of the α-methyl group to the carboxylic acid using sulfuryl chloride was attempted in various solvents, but even under very mild and slightly basic conditions only decomposition of the product was observed. Only trace amounts of the desired carboxylic acid **10** could by isolated.

Another approach to avoid decarboxylation of the free carboxylic acid is to use an alcohol instead of water for hydrolysis of the intermediate trichloride to directly obtain the corresponding ester.[16] We tried this for the oxidation of **4** to the corresponding benzyl ester (R^2 = Bn) by quenching the reaction mixture with benzyl alcohol instead of water (see Scheme 3, route a). After flash chromatography the ^1H NMR indicated a mixture of the benzylic ester and some unwanted by-products (according to NMR the aldehyde resulting from incomplete oxidation of the methyl group even in the presence of excess sulfuryl chloride). We could not separate this mixture either by column chromatography or by crystallization.

We finally succeeded in preparing **10** in acceptable yields by performing the oxidation in two subsequent steps (Scheme 3, route b). First, chlorination of **9** with 2 equivalents of sulfuryl chloride in Et_2O at 0 °C followed by aqueous workup gave the corresponding aldehyde, which was then oxidized without further purification in situ by treatment with $KMnO_4$ in acetone–water at room temperature. This provided the hitherto unknown pyrrole derivative **10** in 42% overall yield. The oxidation of the intermediate pyrrole aldehyde (which was identified via NMR in the reaction mixture) with $KMnO_4$ represents obviously much milder conditions than the direct oxidation using excess sulfuryl chloride preventing the decomposition of the resulting free carboxylic acid. Hence, route b is an alternative for highly sensitive compounds. Compound **10** was then reacted with MeI in DMF in the presence of K_2CO_3 to obtain the triester **2** in a yield of 45%. Triester **2** or the free acid **10** now allow to further transform both carboxylic acid groups attached to the pyrrole before the side-chain ester.

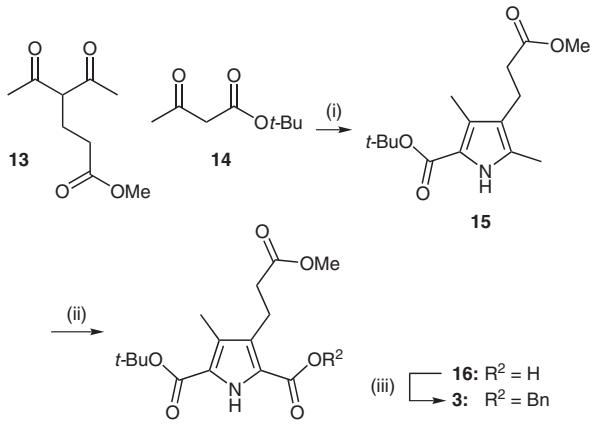
The two triesters **1** and **2**, synthesized here for the first time, now offer a broad flexibility for the introduction of other functionalities into this pyrrole skeleton via their ester groups. Furthermore, besides hydrolysis and subsequent ester or amide formation via the free acid, the ester groups could also be transformed into other even more versatile functionalities via the corresponding aldehydes or alcohols. For example, in a first experiment we were able to obtain the side-chain aldehyde **11** by reaction of **4** with DIBAL-H at –78 °C in toluene (Scheme 5).[17] Hence, the side-chain ester can be selectively reduced while keeping the pyrrole ester intact. The aldehyde functionality offers additional synthetic flexibility, for example via imine formation or reductive amination. However, in this first experiment substantial amounts (15%) of the corresponding alcohol were also formed, although TLC still indicated a trace of unreacted starting material. Further optimization would be required to find the best reaction conditions for aldehyde formation. For example, protection of the pyrrole nitrogen could be beneficial[18] or the use of $LiHAl(Ot\text{-}Bu)_3$ instead of DIBAL-H.[19] However, we have not yet investigated this approach any further.

The two new pyrrole derivatives **1** and **2** can be prepared on multi gram scales via the synthesis described above, but the total sequences are still rather time-consuming and require extensive purification by flash chromatography. Furthermore, the starting material **4** is not commercially available and has also to be synthesized (two steps with a total yield of 59%). We therefore developed an even sim-



Scheme 5 *Reagents and conditions*: (i) toluene, –78 °C, 1 M DIBAL-H in toluene (stepwise 2.5 equiv), 4 h, 46%.

pler approach to another not yet described pyrrole triester **3**, which also offers maximum flexibility with regard to further transformations of the carboxylates. Its synthesis however requires only four steps starting from the readily available and inexpensive starting material **13** and **14** (Scheme 6). Furthermore, the intermediate products, mainly the acid **16**, can be easily purified simply by crystallization. No flash chromatography is required to purify any of the intermediates.



Scheme 6 *Reagents and conditions*: (i) $NaNO_2$, AcOH–H_2O, 0 °C, 12 h, then **13**, Zn, 65 °C, 12 h, 32%. (ii) Et_2O, SO_2Cl_2 (3.2 equiv), K_2CO_3, –20 °C to reflux, 8 h, 49%. (iii) BnBr, DMF, K_2CO_3, 98%.

The acetoacetate **13** could be easily prepared in a one-pot synthesis from methyl acrylate and pentane-2,4-dione in 88% yield after distillation according to a known literature procedure.[8a,20] Commercially available **14** was reacted with sodium nitrite in AcOH to give the corresponding oxime which was reduced in situ with zinc in the presence of **13** to give the pyrrole **15** in a 32% yield after crystallization from hexane–isopropanol.[21] For the oxidation of the methyl group in **15** we found the complete chlorination using sulfuryl chloride in Et_2O in the presence of K_2CO_3 to be the best method.[12e,22] The trichlorinated product could easily be separated from the excess K_2CO_3 by filtration and was then directly hydrolyzed without further isolation with NaOAc in 50% water in dioxane to give the free acid **16** in a good yield of 49% after crystallization. The basic in situ quenching of the liberated HCl with carbonate is crucial for the yield. Not only to avoid decarboxylation of the pyrrole carboxylic acid once it is formed (see above), but also because of the acid-sensitive *tert*-butyl ester which is otherwise cleaved. The free acid **16** can then easily be converted into triester **3** with benzyl bromide and K_2CO_3 in DMF in quantitative yield. Aqueous workup followed by column chromatography gave the triester **3** in 98% yield. Hence, triester **3** was synthesized from commercially available starting materials on a multi gram scale in only four steps without any intermediate chromatographic purification needed in between in 14% overall yield in excellent purity.

In conclusion, we present here the versatile and large-scale synthesis of three new triply orthogonally protected pyrrole tricarboxylates **1**–**3**. Even though their synthesis followed the same general approach (Scheme 1), each compound required a careful optimization of the reaction conditions especially for the oxidation of the α-methyl group. This step was crucial for the total yield. With the procedures developed here multi-gram quantities of these versatile synthetic building blocks can now easily be prepared.

Reaction solvents were dried and distilled under Ar before use. All other reagents were used as obtained from either Aldrich or Fluka. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 400 or AC 250 and the chemical shifts are reported relative to the deuterated solvents. Peak assignments are based on either DEPT, 2D NMR studies and/or comparison with literature data. Melting points were measured on a Büchi SMP-20 apparatus and are not corrected. IR spectra were collected on a Perkin-Elmer FT-IR 1600 instrument. MS data were measured on a Bruker Daltonic mikro TOF or a Finnigan MAT 8200 spectrometer.

4-(2-Carboxyethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (5)

A suspension of **4** (14.0 g, 52.4 mmol) in EtOH (56 mL), 1 N ethanolic NaOH (150 mL) and water (15 mL) was stirred for 3.5 h at 60 °C. The solvent was then removed under reduced pressure, and the remaining solid was dissolved in water and precipitated with diluted sulfuric acid. The precipitate was filtered off and washed with water (3 × 50 mL). Compound **5** (9.90 g, 41.4 mmol, 79%) was obtained as colorless crystals; mp 194 °C.

IR (KBr): 3290 (s), 2911 (m), 1708 (s), 1670 (s), 1457 (m), 1281 (s), 1258 (s), 1103 (m), 940 (m), 773 (s), 623 (w) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.13 (s, 3 H, pyrrole-CH_3), 2.17 (s, 3 H, pyrrole-CH_3), 2.27 (t, J = 7.6 Hz, 2 H, pyrrole-CH_2CH_2), 2.55 (t, J = 7.6 Hz, 2 H, pyrrole-CH_2), 4.18 (q, J = 7.1, 2 H, $CO_2CH_2CH_3$), 11.0 (s, 1 H, NH), 12.0 (s, 1 H, CO_2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.4, 10.8 (pyrrole-CH_3), 14.6 ($CO_2CH_2CH_3$), 19.3 (pyrrole-CH_2), 34.9 (pyrrole-CH_2CH_2), 58.7 ($CO_2CH_2CH_3$), 115.9, 119.5, 125.8, 130.5 (pyrrole-C_q), 160.8 (CO_2Et), 174.0 (CO_2H).

MS (EI, 70 eV): *m*/*z* (%) = 239 (28) $[M]^+$, 180 (60), 134 (101).

4-(2-Benzyloxycarbonylethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (6)

A solution of **5** (9.90 g, 41.4 mmol) in anhyd DMF (250 mL), Et_3N (120 mL) and benzyl chloride (70.0 mL, 60.9 mmol) was stirred for 24 h at r.t. The solvent was then removed at 75 °C under reduced pressure. The remaining solid was dissolved in CH_2Cl_2 (200 mL), extracted with a sat. solution of $NaHCO_3$ (3 × 100 mL) and water (3 × 100 mL) and the organic phase was concentrated to dryness.

The remaining red oil was treated with hexane (15 mL), filtered off and washed with small amounts of hexane. After drying, **6** (12.2 g, 36.9 mmol, 90%) was obtained as colorless crystals; mp 75 °C.

IR (KBr): 3317 (s), 3283 (s), 2988 (s), 2955 (m), 1730 (s), 1659 (s), 1441 (s), 1267 (s), 1148 (s), 1092 (s), 1026 (m), 955 (m), 773 (s), 748 (s), 698 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.17 (s, 3 H, pyrrole-CH_3), 2.27 (s, 3 H, pyrrole-CH_3), 2.48 (t, *J* = 7.7 Hz, 2 H, pyrrole-CH_2CH_2), 2.72 (t, *J* = 7.7 Hz, 2 H, pyrrole-CH_2), 4.29 (q, *J* = 7.20 Hz, 2 H, $CO_2CH_2CH_3$), 5.10 (s, 2 H, benzyl-CH_2), 7.32 (m, 5 H, aryl-H), 8.58 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7, 11.6 (pyrrole-CH_3), 14.7 ($CO_2CH_2CH_3$), 19.8 (pyrrole-CH_2), 35.2 (pyrrole-CH_2CH_2), 59.8 ($CO_2CH_2CH_3$), 66.3 (benzyl-CH_2), 117.2, 120.1, 129.8, 136.1 (pyrrole-C_q), 128.3, 128.3, 128.7 (aryl-C_q), 161.8 (CO_2Et), 173.1 (CO_2Bn).

MS (EI, 70 eV): *m*/*z* (%) = 329 (58) $[M]^+$, 284 (12), 238 (100), 167 (15), 134 (70), 91 (67), 41 (18).

3-(2-Benzyloxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 5-Ethyl Ester (7)

A solution of sulfuryl chloride (2.13 mL, 26.5 mmol) in glacial AcOH (20 mL) was added dropwise over a period of 1 h to a solution of **6** (2.50 g, 7.59 mmol) in glacial AcOH (40 mL). The resulting solution was stirred for 4 h at r.t. Water (8 mL) was added and the solution was stirred for another 30 min. The solution was poured into ice-water (200 mL) and stored for 1 h at 4 °C. The precipitate was filtered off and **7** (2.18 g, 6.07 mmol, 80%) was obtained as a white solid; mp 75 °C.

IR (KBr): 3299 (s), 3938 (m), 1736 (s), 1702 (s), 1559 (m), 1471 (m), 1446 (m), 1269 (s), 1152 (s), 757 (m), 1015 (m), 957 (m), 699 (m), 620 (m), 496 (m) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.18 (s, 3 H, pyrrole-CH_3), 2.53 (t, *J* = 7.8 Hz, 2 H, pyrrole-CH_2CH_2), 2.95 (t, *J* = 7.8 Hz, 2 H, pyrrole-CH_2), 4.23 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 5.06 (s, 2 H, benzyl-CH_2), 7.29–7.35 (m, 5 H, aryl-H), 11.50 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.7 (pyrrole-CH_3), 14.2 ($CO_2CH_2CH_3$), 19.8 (pyrrole-CH_2), 34.4 (pyrrole-CH_2CH_2), 59.8 ($CO_2CH_2CH_3$), 65.3 (benzyl-CH_2), 121.4, 122.6, 125.7, 136.2 (pyrrole-C_q), 127.8, 127.9, 128.4, 128.5 (aryl-C_q), 160.4 (CO_2H), 161.6 (CO_2Et), 172.2 (CO_2Bn).

MS (EI, 70 eV): *m*/*z* (%) = 343 (15) $[M - O]^+$, 268 (11), 210 (82), 164 (30), 91 (81).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_6^+$: 382.1261; found: 382.1264.

3-(2-Benzyloxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 2-*tert*-Butyl Ester 5-Ethyl Ester (1)

A solution of oxalyl chloride (1.21 mL, 14.1 mmol) in anhyd CH_2Cl_2 (10 mL) was added to a solution of **7** (1.69 g, 4.71 mmol) in anhyd CH_2Cl_2 (70 mL) with catalytic amounts of anhyd DMF stirred for 1 h at r.t. The solution was concentrated to dryness under reduced pressure and the remaining brown oil was dissolved in anhyd *t*-BuOH (40 mL). The reaction mixture was heated to 40 °C and *t*-BuOK (1.05 g, 9.42 mmol) was added in small portions. After 2 h of stirring at 40 °C the solvent was removed under reduced pressure and the remaining brown oil was dissolved in CH_2Cl_2 (100 mL). This solution was washed with 1 M $NaHSO_4$ (50 mL), a sat. solution of $NaHCO_3$ (3 × 50 mL) and water (2 × 50 mL). The organic phase was concentrated to dryness under reduced pressure and the remaining brown oil was purified by flash chromatography (SiO_2, hexane–EtOAc, 5:1). Compound **1** (980 mg, 2.36 mmol, 50%) was obtained as a yellow oil; R_f 0.36.

IR (nujol mull): 3446 (w), 1712 (s), 1457 (s), 1376 (s), 1281 (m), 1159 (m), 725 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.55 [s, 9 H, $C(CH_3)_3$], 2.26 (s, 3 H, pyrrole-CH_3), 2.56 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2CH_2), 3.02 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2), 4.33 (q, *J* = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 5.11 (s, 2 H, benzyl-CH_2), 7.31–7.35 (m, 5 H, aryl-H), 9.36 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1 (pyrrole-CH_3), 14.5 ($CO_2CH_2CH_3$), 20.4 (pyrrole-CH_2), 28.8 [$C(CH_3)_3$], 35.2 (pyrrole-CH_2CH_2), 60.7 ($CO_2CH_2CH_3$), 66.3 (benzyl-CH_2), 82.2 [$C(CH_3)_3$], 121.5, 123.1, 126.9, 136.2 (pyrrole-C_q), 128.3, 128.4, 128.6, 128.7 (aryl-C_q), 160.3 (CO_2Et), 161.1 (CO_2t-Bu), 172.9 (CO_2Bn).

MS (EI, 70 eV): *m*/*z* (%) = 415 (12) $[M]^+$, 359 (26), 268 (100), 250 (98), 160 (23), 91 (81), 57 (18).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{29}NNaO_6^+$: 438.1887; found: 438.1878.

4-(2-Carboxyethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (8)

A solution of **5** (3.78 g, 15.8 mmol) in benzyl alcohol (100 mL) was added to a solution of sodium (726 mg, 31.6 mmol) in benzyl alcohol (50 mL). The reaction mixture was heated to reflux at 10–20 mbar and 100 °C for 6 h. The solvent was removed under reduced pressure, and the remaining solid was dissolved in water (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The organic phase was extracted with a sat. solution of $NaHCO_3$ (3 × 100 mL). The combined aqueous phases were acidified with concd sulfuric acid to pH = 3 and stored at 4 °C for 2 h. The precipitate was filtered off and washed with water (2 × 30 mL) and hexane (2 × 30 mL). Compound **8** (3.03 g, 10.1 mmol, 64%) was obtained as a reddish, crystalline solid; mp 127 °C.

IR (KBr): 2918 (s), 1721 (m), 1673 (s), 1455 (s), 1270 (s), 1219 (m), 1162 (s), 1091 (s), 933 (m), 696 (s) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.13 (s, 3 H, pyrrole-CH_3), 2.17 (s, 3 H, pyrrole-CH_3), 2.27 (t, *J* = 7.7 Hz, 2 H, pyrrole-CH_2CH_2), 2.54 (t, *J* = 7.6 Hz, 2 H, pyrrole-CH_2), 5.24 (s, 2 H, benzyl-CH_2), 7.31–7.41 (m, 5 H, aryl-H), 11.1 (s, 1 H, NH), 12.0 (s, 1 H, CO_2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.4, 10.8 (pyrrole-CH_3), 19.2 (pyrrole-CH_2), 34.8 (pyrrole-CH_2CH_2), 64.2 (benzyl-CH_2), 115.4, 119.7, 126.4, 131.0 (pyrrole-C_q), 127.6, 127.7, 128.4, 137.1 (aryl-C_q), 160.5 (CO_2Bn), 173.9 (CO_2H).

MS (EI, 70 eV): *m*/*z* (%) = 301 (16) $[M]^+$, 242 (18), 134 (20), 91 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{19}NO_4^+$: 301.1305; found: 301.1307.

4-(2-*tert*-Butoxycarbonylethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (9)

A solution of oxalyl chloride (853 μL, 9.90 mmol) in anhyd CH_2Cl_2 (10 mL) was added dropwise to a solution of **8** (1.00 g, 3.32 mmol) in anhyd CH_2Cl_2 (20 mL) with catalytic amounts of anhyd DMF and stirred for 2 h at r.t. The solution was concentrated to dryness under reduced pressure and the remaining solid was dissolved in *t*-BuOH (40 mL). The solution was heated to 40 °C and *t*-BuOK (747 mg, 6.65 mmol) was added in small portions. The reaction mixture was stirred at 40 °C for 2 h. The solvent was removed under reduced pressure, and the remaining brown oil was dissolved in CH_2Cl_2 (30 mL) and washed with a 1 M $NaHSO_4$ (2 × 25 mL), a sat. solution of $NaHCO_3$ (2 × 25 mL) and water (25 mL). The organic phase was concentrated to dryness under reduced pressure and the remaining solid was washed with hexane (25 mL). Compound **9** (960 mg, 2.67 mmol, 80%) was obtained as a pink, crystalline solid; mp 93 °C.

IR (KBr): 2983 (m), 2927 (m), 1729 (s), 1657 (s), 1454 (s), 1367 (m), 1268 (s), 1150 (s), 1092 (s), 769 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 2.20 (s, 3 H, pyrrole-CH_3), 2.29 (s, 3 H, pyrrole-CH_3), 2.32 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2CH_2), 2.65 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2), 5.29 (s, 2 H, benzyl-CH_2), 7.32–7.42 (m, 5 H, aryl-H), 8.56 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 11.7 (pyrrole-CH_3), 19.8 (pyrrole-CH_2), 28.2 [$C(CH_3)_3$], 36.4 (pyrrole-CH_2CH_2), 65.6 (benzyl-CH_2), 80.3 [$C(CH_3)_3$], 116.7, 120.7, 130.2, 136.8 (pyrrole-C_q), 128.2, 128.2, 128.7 (benzyl-C_q), 161.4 (CO_2Bn), 172.7 (CO_2t-Bu).

MS (EI, 70 eV): *m*/*z* (%) = 357 (23) $[M]^+$, 301 (26), 242 (44), 166 (70), 91 (100), 57 (97).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{27}NO_4^+$: 357.1933; found: 357.1934.

3-(2-*tert*-Butoxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 5-Benzyl Ester (10)

A solution of sulfuryl chloride (3.66 mL, 45.5 mmol) in anhyd Et_2O was added dropwise to a solution of **9** (5.40 g, 15.2 mmol) in anhyd Et_2O (200 mL) with K_2CO_3 (13.5 g, 114 mmol) at 0 °C and it was stirred for 2 h at 0 °C. Water (10 mL) was added to the reaction mixture and it was stirred for 30 min at r.t. The solvent was removed under reduced pressure and the remaining solid was dissolved in acetone (150 mL). A solution of $KMnO_4$ (5.57 g, 14.0 mmol) in acetone–water (1:1, 100 mL) was added dropwise over the period of 1 h and the resulting mixture was stirred for 1 h at r.t. $Na_2S_2O_4$ was added until the purple color disappeared. The precipitating MnO_2 was filtered off and the colorless solution was extracted with EtOAc (3 × 50 mL). The organic phase was washed with water (3 × 30 mL) and concentrated to dryness under reduced pressure. Compound **10** (2.45 g, 6.32 mmol, 42%) was obtained as an off-white solid; mp 134 °C.

IR (KBr): 2967 (w), 2932 (w), 1708 (m), 1670 (s), 1355 (m), 1262 (s), 1147 (s), 821 (m) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.35 [s, 9 H, $C(CH_3)_3$], 2.20 (s, 3 H, pyrrole-CH_3), 2.33 (t, *J* = 7.8 Hz, 2 H, pyrrole-CH_2CH_2), 2.88 (t, *J* = 7.8 Hz, 2 H, pyrrole-CH_2), 5.28 (s, 2 H, benzyl-CH_2), 7.33–7.47 (m, 5 H, aryl-H), 11.59 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.88 (pyrrole-CH_3), 19.8 (pyrrole-CH_2), 27.7 [$C(CH_3)_3$], 35.5 (pyrrole-CH_2CH_2), 65.3 (benzyl-CH_2), 79.5 [$C(CH_3)_3$], 121.0, 123.0, 126.2, 128.6 (pyrrole-C_q), 127.9, 128.4, 136.4 (benzyl-C_q), 160.2 (CO_2H), 161.6 (CO_2Bn), 171.7 (CO_2t-Bu).

MS (EI, 70 eV): *m*/*z* (%) = 331 (11) $[M - C_4H_8]^+$, 91 (100), 57 (33).

HRMS (EI): *m*/*z* $[M - C_4H_8]^+$ calcd for $C_{17}H_{17}NO_6^+$: 331.1048; found: 331.1050.

Dichloride Intermediate

^1H NMR (400 MHz, DMSO-d_6): δ = 1.41 [s, 9 H, $C(CH_3)_3$], 2.27 (s, 3 H, pyrrole-CH_3), 2.38 (t, *J* = 7.3 Hz, 2 H, pyrrole-CH_2CH_2), 2.72 (t, *J* = 7.3 Hz, 2 H, pyrrole-CH_2), 5.34 (s, 2 H, benzyl-CH_2), 7.05 (s, 1 H, $CHCl_2$), 7.30–7.45 (m, 5 H, aryl-H), 9.10 (s, 1 H, NH).

Aldehyde Intermediate

Mp 96 °C.

IR (KBr): 2975 (m), 2923 (m), 1724 (s), 1657 (s), 1471 (m), 1370 (m), 1250 (m), 1161 (s), 1082 (m), 731 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 [s, 9 H, $C(CH_3)_3$], 2.31 (s, 3 H, pyrrole-CH_3), 2.46 (t, *J* = 7.5 Hz, 2 H, pyrrole-CH_2CH_2), 3.00 (t, *J* = 7.5 Hz, 2 H, pyrrole-CH_2), 5.33 (s, 2 H, benzyl-CH_2), 7.38–7.47 (m, 5 H, aryl-H), 9.46 (s, 1 H, NH), 9.81 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.0 (pyrrole-CH_3), 19.0 (pyrrole-CH_2), 28.2 [$C(CH_3)_3$], 36.6 (pyrrole-CH_2CH_2), 66.8 (benzyl-CH_2), 81.0 [$C(CH_3)_3$], 124.3, 127.3, 130.2, 132.6 (pyrrole-C_q), 128.6, 128.7, 128.9, 135.6 (benzyl-C_q), 160.7 (CO_2Bn), 171.7 (CO_2t-Bu), 179.9 (CHO).

MS (EI, 70 eV): *m*/*z* (%) = 371 (1) $[M]^+$, 315 (21), 91 (100), 57 (28).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{25}NO_5^+$: 371.1723; found: 371.1725.

3-(2-*tert*-Butoxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 2-Methyl Ester 5-Benzyl Ester (2)

A solution of **10** (100 mg, 258 μmol), MeI (16.2 μL, 260 μmol) and K_2CO_3 (74.0 mg, 535 μmol) in anhyd DMF (15 mL) was stirred at 0 °C for 10 min and at r.t. for 1 d. Water (10 mL) was added and the stirring was continued for 10 min. After dilution with Et_2O (30 mL), the organic layer was washed with water (3 × 15 mL), dried over $MgSO_4$ and concentrated to dryness in vacuo. Compound **2** (47.0 mg, 117 μmol, 45%) was obtained as a pale yellow solid; mp 84 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 2.31 (s, 3 H, pyrrole-CH_3), 2.40 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2CH_2), 3.00 (t, *J* = 8.0 Hz, 2 H, pyrrole-CH_2), 3.87 (s, 3 H, CO_2CH_3), 5.33 (s, 2 H, benzyl-CH_2), 7.35–7.44 (m, 5 H, aryl-H), 9.40 (s, 1 H, NH).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 10.3 (pyrrole-CH_3), 20.3 (pyrrole-CH_2), 28.3 [$C(CH_3)_3$], 36.1 (pyrrole-CH_2CH_2), 51.9 (CO_2CH_3), 66.5 (benzyl-CH_2), 80.3 [$C(CH_3)_3$], 121.7, 127.4, 130.4, 135.9 (pyrrole-C_q), 128.5, 128.6, 128.8 (benzyl-C_q), 160.8 (CO_2CH_3), 161.1 (CO_2Bn), 171.7 (CO_2t-Bu).

MS (EI, 70 eV): *m*/*z* (%) = 401 (1) $[M]^+$, 345 (17), 299 (17), 91 (100), 57 (21).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{27}NNaO_6^+$: 424.1731; found: 424.1736.

4-(2-Methoxycarbonylethyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (15)

tert-Butyl acetoacetate **14** (64.8 g, 410 mmol) was dissolved in AcOH (115 mL) and cooled down to 5 °C. A solution of sodium nitrite (27.5 g, 399 mmol) in water (95 mL) was added slowly via an addition funnel and the resulting solution was stirred overnight at 5 °C. To assure complete conversion the disappearance of **14** was obtained by TLC monitoring (deactivated SiO_2, cyclohexane–EtOAc, 4:1; R_f 0.29). The resulting solution was added to a suspension of **13** (75.5 g, 405 mmol), NaOAc (82.5 g, 1.01 mol) and zinc (82.5 g, 1.26 mol) in AcOH (90 mL). Further zinc (82.5 g, 1.26 mol) was added slowly in small portions and the resulting mixture was stirred overnight at 65 °C. The reaction was cooled down to r.t. and poured into an ice-water dispersion (1.5 L). The precipitate was filtered off, washed with water and dried in vacuo. The solid was dissolved in EtOH and the zinc residue was removed by filtration. After evaporation of the solvent, crystallization from hexane–*i*-PrOH led to **15** (36.2 g, 129 mmol, 32%) as a white solid; mp 96 °C.

IR (KBr): 2974 (m), 2951 (w), 2924 (m), 1738 (s), 1666 (s), 1449 (m), 1435 (m), 1364 (m), 1281 (m), 1163 (s) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.49 [s, 9 H, $C(CH_3)_3$], 2.11 (s, 3 H, pyrrole-CH_3), 2.13 (s, 3 H, pyrrole-CH_3), 2.35 (t, *J* = 7.4 Hz, 2 H, pyrrole-CH_2CH_2), 2.56 (t, *J* = 7.4 Hz, 2 H, pyrrole-CH_2), 3.56 (s, 3 H, CO_2CH_3), 10.81 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 10.3, 10.7 (pyrrole-CH_3), 19.2 (pyrrole-CH_2), 28.2 [$C(CH_3)_3$], 34.5 (pyrrole-CH_2CH_2), 51.2 (CO_2CH_3), 78.8 [$C(CH_3)_3$], 117.3, 118.8, 124.8, 129.7 (pyrrole-C_q), 160.5 (CO_2t-Bu), 172.8 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 281 (16) $[M]^+$, 225 (40), 208 (19), 152 (100), 134 (45), 41 (5).

3-(2-Methoxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 5-*tert*-Butyl Ester (16)

Compound **15** (3.29 g, 11.7 mmol) and K_2CO_3 (6.43 g, 46.6 mmol) were suspended under Ar in anhyd Et_2O (100 mL) and cooled down to –20 °C. A solution of sulfuryl chloride (3.50 mL, 37.4 mmol) in anhyd Et_2O (50 mL) was added slowly via an addition funnel. The mixture was warmed slowly to r.t. and heated to reflux for 7 h. The solvent was reduced to a few mL in vacuo without heating and the oily residue was stirred for 2 h in a solution of NaOAc (10.0 g, 122 mmol) in water–dioxane (1:1, 200 mL) at 110 °C. The solution was cooled down to 0 °C and adjusted carefully to pH = 2 with hydrochloric acid and extracted with Et_2O (3 × 100 mL). The combined organic phases were extracted with sat. $NaHCO_3$–water (1:1, 3 × 250 mL) and the combined aqueous solutions were cooled down to 0 °C. This aqueous solution was then acidified slowly and under vigorous stirring with concentrated hydrochloric acid to pH = 1–2. The precipitate was filtered off, washed with cold water (150 mL) and recrystallized from MeOH–water to give **16** (1.77 g, 5.69 mmol, 49%) as white needles; mp 169 °C.

IR (KBr): 3473 (m), 3340 (s), 2977 (m), 2952 (w), 1737 (s), 1716 (s), 1695 (s), 1674 (s), 1469 (m), 1278 (s), 1154 (s) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.52 [s, 9 H, $C(CH_3)_3$], 2.17 (s, 3 H, pyrrole-CH_3), 2.44 (t, *J* = 8.1 Hz, 2 H, pyrrole-CH_2CH_2), 2.90 (t, *J* = 8.1 Hz, 2 H, pyrrole-CH_2), 3.57 (s, 3 H, CO_2CH_3), 11.26 (s, 1 H, NH), 12.81 (br s, 1 H, CO_2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 9.68 (pyrrole-CH_3), 19.7 (pyrrole-CH_2), 30.0 [$C(CH_3)_3$], 34.3 (pyrrole-CH_2CH_2), 51.2 (CO_2CH_3), 80.6 [$C(CH_3)_3$], 122.0, 122.7, 125.0 128.5 (pyrrole-C_q), 159.9 (CO_2H), 161.7 (CO_2t-Bu), 172.7 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 311 (17) $[M]^+$, 280 (4), 255 (7), 238 (12), 211 (27), 195 (100), 164 (23), 138 (15).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{21}NO_6^+$: 311.1363; found: 311.1365.

3-(2-Methoxycarbonylethyl)-4-methyl-1*H*-pyrrole-2,5-dicarboxylic Acid 2-Benzyl Ester 5-*tert*-Butyl Ester (3)

Compound **16** (262 mg, 842 μmol), benzyl bromide (89.0 μL, 749 μmol) and K_2CO_3 (164 mg, 1.19 mmol) were suspended under Ar in anhyd DMF (15 mL) and stirred overnight. The reaction mixture was diluted with EtOAc (150 mL) and washed subsequently with sat. $NaHCO_3$ (100 mL), sat. NaCl (100 mL), sat. NH_4Cl (100 mL) and again sat. NaCl (100 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed in vacuo. After flash column chromatography (deactivated SiO_2, cyclohexane–EtOAc, 2:1) **3** (295 mg, 734 μmol, 98%) was obtained as a slightly yellow oil; R_f 0.63.

IR (KBr): 3458 (bw), 2977 (w), 2952 (w), 1738 (s), 1707 (s), 1561 (w), 1369 (w), 1282 (s), 1159 (s) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $C(CH_3)_3$], 2.25 (s, 3 H, pyrrole-CH_3), 2.48 (t, *J* = 7.8 Hz, 2 H, pyrrole-CH_2CH_2), 3.03 (t, *J* = 8.2 Hz, 2 H, pyrrole-CH_2), 3.63 (s, 3 H, CO_2CH_3), 5.32 (s, 2 H, benzyl-CH_2), 7.42–7.33 (m, 5 H, aryl-H), 9.35 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1 (pyrrole-CH_3), 20.3 (pyrrole-CH_2), 28.5 [$C(CH_3)_3$], 34.8 (pyrrole-CH_2CH_2), 51.7 (CO_2CH_3), 66.6 (benzyl-CH_2), 82.0 [$C(CH_3)_3$], 120.8, 123.6, 128.1 (aryl-C_q), 128.6, 128.8 (aryl-CH), 130.3, 135.8 (aryl-C_q), 160.5 (CO_2Bn, CO_2t-Bu), 173.5 (CO_2Me).

MS (EI, 70 eV): *m*/*z* (%) = 401 (11) $[M]^+$, 328 (7), 310 (4), 254 (36), 222 (100), 194 (9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{27}NO_6^+$: 401.1833; found: 401.1832.

3,5-Dimethyl-4-(3-oxopropyl)-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (11)

Compound **4** (441 mg, 1.65 mmol) was dissolved under Ar atmosphere in anhyd toluene (10 mL) and cooled down to –78 °C. DIBAL-H (1 M) in toluene (1.75 mL, 1.75 mmol) was added and after stirring for 1 h further DIBAL-H (1 M, 2.50 mL, 2.50 mmol) was added in 0.5 mL steps under TLC monitoring until the starting material nearly disappeared. After 4 h the reaction was quenched with 0.1 M HCl (4 mL) and warmed to r.t. After dilution with EtOAc (200 mL), sat. NaCl (200 mL) and water (until the precipitate was dissolved) were added. Then the organic phase was separated, washed with sat. $NaHCO_3$ (150 mL) and sat. NaCl (200 mL), dried with Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography (SiO_2, cyclohexane–EtOAc, 4:1) yielded **11** (175 mg, 785 μmol, 46%) as a white solid; R_f 0.26; mp 98 °C.

IR (KBr): 2924 (m), 2855 (m), 2725 (w), 1720 (s), 1654 (s), 1445 (m), 1270 (m), 1101 (m) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 2.22 (s, 3 H, pyrrole-CH_3), 2.27 (s, 3 H, pyrrole-CH_3), 2.60–2.56 (m, 2 H, pyrrole-CH_2CH_2), 2.70 (t, *J* = 7.7 Hz, 2 H, pyrrole-CH_2), 4.29 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 8.55 (s, 1 H, NH), 9.79 (t, *J* = 1.5 Hz, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5, 11.5 (pyrrole-CH_3), 14.5 ($CO_2CH_2CH_3$), 16.7 (pyrrole-CH_2), 44.6 (pyrrole-CH_2CH_2), 59.7 ($CO_2CH_2CH_3$), 117.1, 119.8, 126.7, 129.4 (pyrrole-C_q), 161.5 (CO_2Et), 202.0 (CHO).

MS (EI, 70 eV): *m*/*z* (%) = 223 (24) $[M]^+$, 180 (21), 167 (50), 134 (100), 65 (17), 39 (11).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{17}NO_3^+$: 223.1203; found: 223.1206.

4-(3-Hydroxypropyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (12)

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.74–1.67 (m, 2 H, pyrrole-CH_2CH_2), 2.21 (s, 3 H, pyrrole-CH_3), 2.27 (s, 3 H, pyrrole-CH_3), 2.46 (t, *J* = 7.7 Hz, 2 H, CH_2OH), 3.64 (t, *J* = 6.4 Hz, 2 H, pyrrole-CH_2), 4.29 (q, *J* = 7.0 Hz, 2 H, $CO_2CH_2CH_3$), 8.61 (s, 1 H, NH).

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