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# Synthesis of 5-aryl-2-oxopyrrole derivatives as synthons for highly substituted pyrroles

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**Abstract**—A small library of 2-oxo-5-(hetero)arylpyrroles was prepared starting from 2,3-dioxo-5-(hetero)arylpyrrolidines. The large synthetic possibilities of these 2-oxopyrroles were investigated. The 2-oxopyrroles offer a large number of possible derivatizations including reactions with electrophiles. The chloroformylation of 2-oxo-5-(hetero)arylpyrroles provides pyrrole carbaldehydes. Some pyrrole carbaldehydes were used to synthesize polycyclic compounds like pyrrolo[3,4-*d*]pyridazinones, a thienopyrrole, a pyrrolobenz[1,4]oxazepine, a pyrrolobenzo[1,4]thiazepine, and a pyrrolobenzo[1,4]diazepine. Hereby we showed through a short exploration that the oxopyrroles and analogues are interesting and versatile synthetic building blocks.


## 1. Introduction

New versatile and easily available starting materials are of great importance in organic and medicinal chemistry to allow a combinatorial approach.

2-Oxopyrroles **1** show such versatility and they are important substructures in a variety of pharmaca, including products active against viral infections (HIV,[1,2] influenza,[3] cytomegalovirus[4]), anticancer agents,[5] and products active against microbiological diseases[6–8] (bacterial or fungal). Furthermore, 2-oxopyrroles are known as building blocks in the synthesis of alkaloids[9–12] and materials such as 2,2′-bipyrroles, terpyrroles,[13] and pigments.[14–19] Besides the well known 5-alkyl-2-oxopyrroles,[20,21] first described in 1890 by Emery,[22] relatively little attention was given toward 5-aryl-2-oxopyrrole derivatives **2** in the open literature (see Fig. 1). In our research group, we envisaged to use the 5-aryl-2-oxopyrroles as a starting material for the synthesis of highly fluorescent diketopyrrolopyrroles and potential non-nucleoside reverse transcriptase inhibitors (NNRTI). For the screening of the properties of these products a wide variability of possible substituents is necessary. Therefore we wished to develop a short, inexpensive, and simple synthesis of 2-oxopyrroles, which would allow a great variety of substituents.

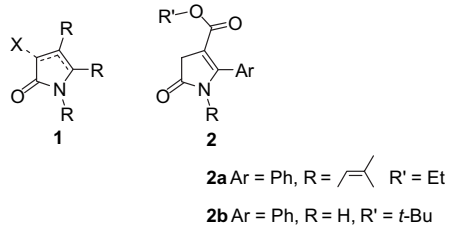


**Figure 1.** 2-Oxopyrroles **1** and 5-aryl-2-oxopyrroles **2**.

In the open literature, the synthesis of only few *N*-substituted pyrrolinones **2** was described including a five-step synthesis of an *N*-alkenylpyrrolinone **2a** via oxazolinones.[23] In the patent literature the synthesis of **2b** was described in a two-step reaction starting with a base-catalyzed condensation between di-*tert*-butyl succinate and benzonitrile.[24]

## 2. Results and discussion

Recently Morton et al. have reported a short and convenient method to synthesize **2** starting from commercially available alkyl benzoylacetates **3**.[15,25] We reinvestigated Morton's synthesis of oxopyrroles and found some limitations. The dialkyl benzoylsuccinates **4** are available via monoalkylation of alkyl benzoylacetates **3** with alkyl chloroacetates. Unfortunately, the ring closure affording the corresponding **2** was not possible starting from 4-nitrobenzoylsuccinates **4a** (X=$NO_2$). Probably the strongly electron withdrawing group did not allow condensation between the ketone function and the amine but the imine/enamine function on this

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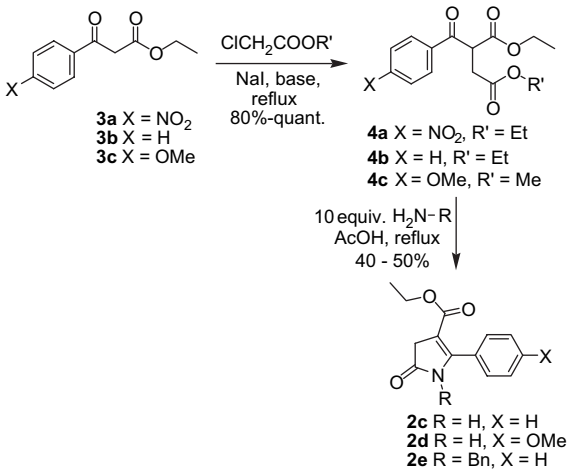
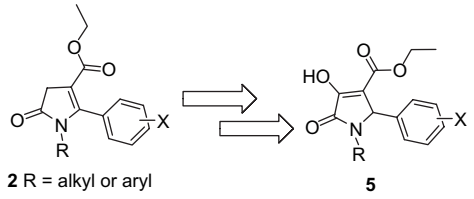
intermediate was deactivated, preventing ring closure (Scheme 1).




**Scheme 1.** Synthesis of simple 2-oxo-5-arylpyrroles **2c** and **2d** starting from benzoylacetates.

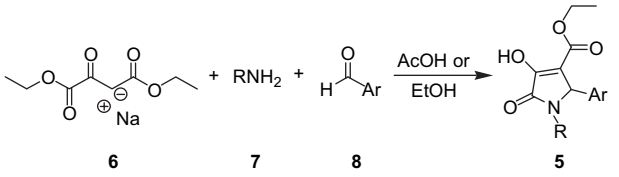
In contrast to **4a**, benzoylsuccinates **4b** and **4c** reacted with ammonium acetate and benzylamine to afford the desired oxopyrroles **2c–e** in moderate yield. The condensation in acetic acid with a large excess (10 equiv) of ammonium acetate or benzylamine gave the best results while aniline did not give any product **2** under these conditions. Clearly, the benzoylsuccinate method suffers from (i) lack of general applicability (e.g., X=$NO_2$ or aromatic R), (ii) the obligatory use of excess of amine reagent, and (iii) the modest yields in the final step. Moreover, only a few benzoylacetates **3** are commercially available at a reasonable price.

We describe here a more general synthesis of *N*-substituted (or *N*-protected) 2-oxopyrroles **2** starting from 2,3-dioxopyrrolidines **5** (Scheme 2). To obtain the latter compounds, we applied the synthesis described by Merchant and Srinivasan, and before them by Schiff.[26,27] These authors published an interesting three-component reaction starting from sodium alkyl oxalacetate with several amines and aldehydes under various reaction conditions. Most of the 2,3-dioxopyrrolidines **5** synthesized had aryl substituents at the 1- and 5-position. A significant advantage of these products **5** is the fact that most of them can be crystallized out of the reaction mixture.




**Scheme 2.** Synthesis of a great variety of 2-oxopyrroles **2** starting from **5**.

All three necessary reagents are relatively cheap and a large variety of aldehydes and amines are possible. This allowed us to create a library of **5** and subsequently of the desired oxopyrroles **2**. 2,3-Dioxopyrrolidines **5** that are new to the best of our knowledge were synthesized by us starting from sodium ethyl oxalacetate **6**, ammonia or primary amines **7**, and aromatic aldehydes **8**. Two general methods were used. The first method consists of shortly heating the reagents in acetic acid, stirring for 16–24 h at room temperature, and precipitation after addition of water. The second method consists of dissolving the reagents in ethanol and heating this mixture for about 30 min. After dilution with water and acidifying, the product could be filtered. Both methods gave the desired product **5a–l** in moderate yield but high purity (Scheme 3, Table 1).




**Scheme 3.** Synthesis of 2,3-dioxopyrrolidines via a multicomponent reaction.

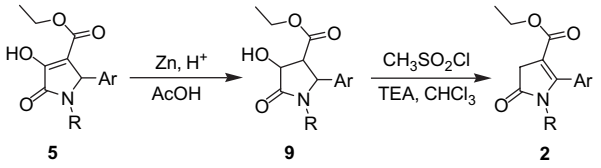
**Table 1**. Synthesis of 2,3-dioxopyrrolidines via multicomponent reaction

| Dioxopyrrolidine | 1-R | 5-Ar | Yield (%) |
|---|---|---|---|
| **5a** | 4-ClPh | 4-ClPh | 77[a] |
| **5b** | Benzyl | 4-ClPh | 32[a] |
| **5c** | Cyclohexyl | 4-ClPh | 18[a], 31[b] |
| **5d** | PMB[c] | 4-$CH_3O$Ph | 40[a] |
| **5e** | PMB[c] | 4-ClPh | 64[a] |
| **5f** | 3,4,5-$(CH_3O)_3$Ph | 3-HOPh | 38[a] |
| **5g** | H | Ph | 61[b] |
| **5h** | $CH_3$ | 4-$NO_2$Ph | 50[b] |
| **5i** | $CH_3$ | 4-$(CH_3)_2$NPh | 48[b] |
| **5j** | $CH_3$ | Ph | 59[b] |
| **5k** | $CH_3$ | 2-HOPh | 52[b] |
| **5l** | Allyl | 2-Thienyl | 62[b] |

[a] Method 1 in acetic acid.
[b] Method 2 in ethanol.
[c] *p*-Methoxybenzyl.

Dioxopyrrole **5i** was prepared in a reasonable yield but the reaction mixture had to be heated at reflux for several days instead of the usual 30 min. Acidification in this case was not necessary because **5i** precipitated out of the reaction mixture after cooling to room temperature. An excess of aqueous ammonia was used in the synthesis of **5g**.

These dioxopyrrolidines **5** could easily be transformed into the desired oxopyrrole **2**. Reduction of the enolates **5** gave the corresponding secondary alcohols **9**. Without further purification these alcohol groups could be eliminated by mesylation and treatment with base affording the pyrrolinones **2c**, **2f–j** after isomerization of the double bond (Scheme 4, Table 2).




**Scheme 4.** Transformation of dioxopyrrolidines **5** to pyrrolinones **2**.

The alcohols **9** were obtained by reduction of **5** with zinc dust in acetic acid and a few drops of sulfuric acid. As an

**Table 2**. Transformation of dioxopyrrolidines **5** to pyrrolinones **2**

| Oxopyrrole | Educt | Alcohol | *N*-R | 5-Ar | Yield (%)[a] |
|---|---|---|---|---|---|
| **2c** | **5g** | **9a** | H | Ph | 42 |
| **2f** | **5j** | **9b** | $CH_3$ | Ph | 40 |
| **2g** | **5i** | **9c** | $CH_3$ | 4-$(CH_3)_2$NPh | 40 |
| **2h** | **5b** | **9d** | Benzyl | 4-ClPh | 42[b] |
| **2i** | **5l** | **9e** | Allyl | 2-Thienyl | 51 |
| **2j** | **5a** | **9f** | 4-ClPh | 4-ClPh | 66 |

[a] Isolated overall yield starting from **5**.
[b] Triethylamine (TEA), $POCl_3$.

example the mixture of diastereoisomers of **9c**–**9c′** (87:13), obtained starting from **5i**, was separated by column chromatography. NMR spectroscopy showed that mainly the isomer with the all-trans configuration **9c** was formed. The NOESY spectrum shows that the proton in α of the ester function of the main product **9c** is located in the proximity of the aryl protons. The position of this proton with respect to the aryl ring is confirmed by the low δ-value of this proton in the $^1$H NMR spectrum due to the anisotropic effect of the ring current. The NOESY spectrum also confirmed that the 3,5-protons in β of the ester group are located at the same side of the five-membered ring. The minor product **9c′** showed in its NOESY spectrum no correlation between the proton at 4.55 and 4.68 ppm. From the $^1$H NMR and $^{13}$C NMR spectra it is clear that the signals of the ester function are shifted upfield. Hence, the ester function and the phenyl ring are on the same side as the pyrrole moiety.

Because there is no NOESY correlation between the protons at 4.55 and 4.68 ppm and the proton signal at 4.55 is shifted to higher field (in comparison with the corresponding proton of **9c**), we can assume that these protons are located on opposite sides of the ring and therefore assign the trans–cis structure **9c′** (Fig. 2).

The reduction rate is increased by heating but the reaction time should be carefully controlled in this case because of the possibility of formation of small amounts of Fischer esterification side products resulting from the alcohol **9** and acetic acid. The next step was the elimination of water from **9** in order to obtain the desired oxopyrroles **2**. Several possibilities were tested. The alcohols **9** react with acid chlorides, sulfonyl chlorides, anhydrides, $POCl_3$, and $SOCl_2$ under the influence of base. With pyridine as the base the reaction with tosyl, mesyl or phosphorus oxychloride was incomplete. With triethylamine as the base at reflux

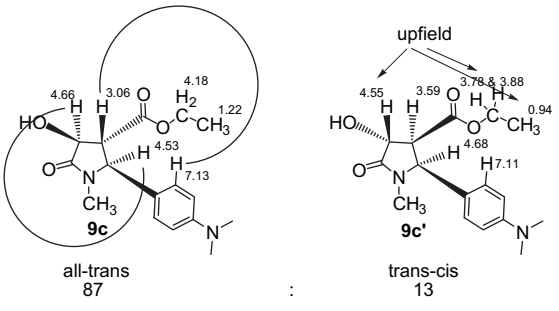



**Figure 2.** Diastereoisomers of **9c**–**9c′** obtained after reduction of **5** with zinc.

temperature in chloroform, mesylation followed by complete elimination of the corresponding sulfonic acid was accomplished at the same time to afford **2**.

The moderate yield (40–66%) of these oxopyrroles **2c**, **2f**–**j** was more than compensated by the ease of these reactions and the possibility to prepare a library of pyrrolinones **2** from readily available starting materials. Moreover, unsubstituted, *N*-aryl and *N*-alkyl-5-arylpyrrolinones **2** could also be prepared by the described method.

Pyrrolinone **2** possesses an active methylene group, which can react with electrophilic reagents. The ester function (rather a vinylogous carbamate function) and the amide function (if unsubstituted) may react with nucleophilic reagents. In comparison with the 5-alkylpyrrolinones the nitrogen atom of the 5-arylpyrrolinones is relatively shielded from electrophilic reagents. Thus, the aryl group gives the pyrrolinones extra chemical and physical stability.

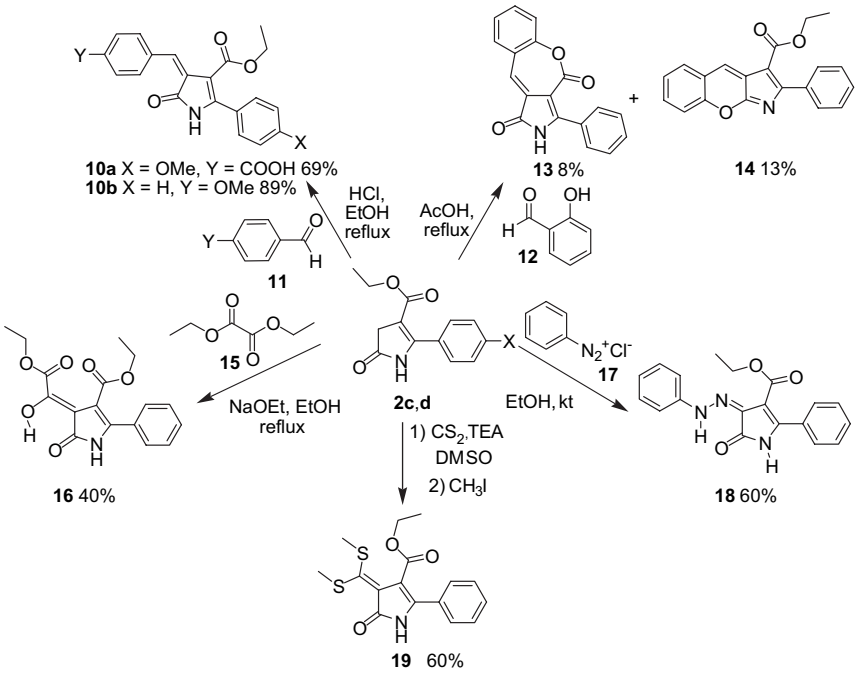
Benzylidenepyrrolinones **10** were synthesized by condensation of pyrrolinone **2** and different arylaldehydes **11**. Bright yellow compounds **10** were obtained in the *Z*-configuration. Using the *ortho*-substituted salicylaldehyde **12** and pyrrolinone **2c** in acetic acid and heating for 20 min under microwave irradiation the dioxopyrrolo[3,4-*c*]benzoxepine (DPO) **13** was obtained next to phenylchromeno[2,3-*b*]pyrrole **14**. The yellow **13** shows a strong yellow fluorescence and is only slightly soluble in common organic solvents.

As an example of a reaction between **2** and an activated ester the condensation of **2c** with diethyl oxalate **15** under basic conditions gave diester **16**, which could be isolated by filtration after acidification. Phenyldiazonium salt **17** reacted smoothly with oxopyrrole **2c** providing hydrazone **18**. Pyrrolinone **2c** was transformed into ketene dithioacetal **19** in a one pot reaction by treatment with carbon disulfide in the presence of triethylamine and subsequent methylation with 2 equiv of methyl iodide (Scheme 5).

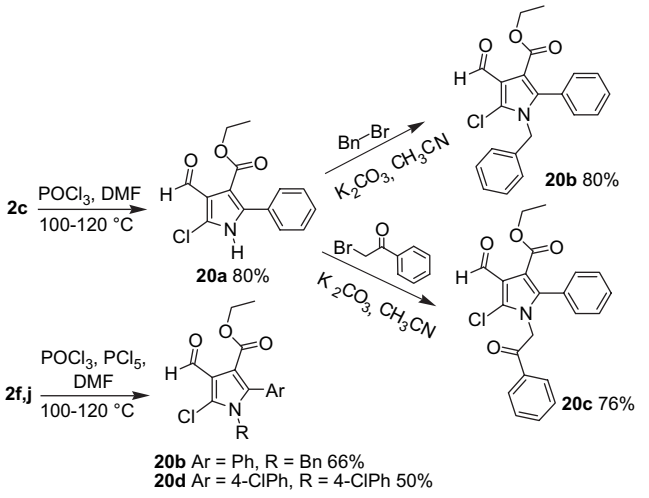
These pyrrolinones **2** seemed to be ideal building blocks for the synthesis of a large variety of multisubstituted pyrroles. In the literature, methods have been described to chloroformylate heterocyclic compounds such as pyrazolones and oxoindoles using Vilsmeier–Haack conditions affording the corresponding pyrazoles and 2-chloroindoles.[28] The synthesis of 5-aryl-2-chloro-3-formylpyrrole **20a** is based on these transformations.

At relatively high temperature (100–120 °C) and a ratio of 1:2:8 pyrrolinone (R=H)–DMF–$POCl_3$, the desired aldehyde **20a** was obtained in reasonable to good yield. The nitrogen atom on this pyrrole **20a** was easily alkylated with benzyl bromide or α-bromoacetophenone using potassium carbonate as a base to form **20b** and **20c**. The transformation of *N*-substituted pyrrolinones **2f** and **2j** into their chloroformylated derivatives **20b** and **20d** was also investigated. The addition of $PCl_5$ and the use of high temperature (120 °C) were necessary for a complete transformation (Scheme 6).

Pyrrole carbaldehydes **20a**–**d** possess at least three electrophilic reaction sites and thus provide numerous synthetic possibilities. They offer a number of interesting options for




**Scheme 5.** Reactions of **2** with various electrophiles.

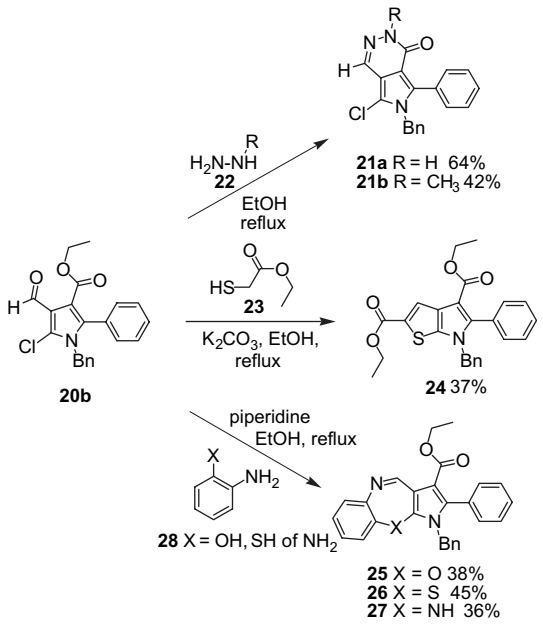



**Scheme 6.** Synthesis of pyrrole carbaldehydes **20** via chloroformylation of **2**.

ring closure besides the condensation reactions on the independent chloro, aldehyde, and ester functions.

The two adjacent carbonyl functions can react with bis-nucleophilic molecules. Thus a reagent, which contributes two atoms, can provide a six-membered ring fused to the pyrrole moiety. Hydrazines, for example, gave after reaction with **20b** pyrrolo[3,4-*d*]pyridazinones **21a** and **21b** in moderate yields (Scheme 7).

As an example of a ring fusion involving the chloro and aldehyde functions, *N*-benzylated pyrrole **20b** was used as the substrate for the cyclocondensation with ethyl mercaptoacetate **23**. 5-Phenyl-thieno[2,3-*b*]pyrrole **24** precipitated from the reaction mixture. Compounds **25**, **26**, and **27** were prepared by condensing *ortho*-substituted anilines with pyrrole carbaldehyde **21** in yields of about 40%. The synthesis




**Scheme 7.** Synthesis of poly(hetero)cycles starting from **20**.

of these compounds was based on the work of Latif.[29] All structures could readily be analyzed by $^1$H NMR spectroscopy.

## 3. Conclusion

We prepared a small library of pyrrolinones **2** starting from 2,3-dioxopyrrolidines **5**. The 2,3-dioxopyrrolidines **5** are easily prepared through the multicomponent reaction between diethyl oxalacetate and a variety of aldehydes and primary amines.

We have explored the large synthetic possibilities of the oxopyrroles. The 2-oxopyrroles offer a large number of possible derivatizations including reactions with aldehydes, diazonium salts, reactive esters, and carbon disulfide. The chloroformylation of **2** provides pyrrole carbaldehydes **20**. A number of pyrrole carbaldehydes **20** were used to synthesize polycyclic compounds. Pyrrolo[3,4-*d*]pyridazinones **21a** and **21b** were obtained after aldehyde–ester ring fusion of **2** with hydrazines **22** while chloroaldehyde ring fusions provided thienopyrrole **24**, pyrrolobenz[1,4]oxazepine **25**, pyrrolobenzo[1,4]thiazepine **26**, and pyrrolobenzo[1,4]diazepine **27**. Thus we showed by means of a short exploration that the oxopyrroles and analogues are interesting and versatile synthetic building blocks. Many possibilities offered by **2** and **20** show these compounds to be novel key intermediates in the synthesis of highly substituted pyrroles.

## 4. Experimental

### 4.1. Instrumental techniques

NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz or Bruker AMX 400 MHz) and chemical shifts ($\delta$) are reported in parts per million referenced to internal residual solvent protons (1H) or the carbon signal of deuterated solvents (13C). Mass spectrometry data were obtained with an HP MS apparatus 5989A, at 70 eV for EI spectra and with methane as reagent gas for CI spectra. UV–vis spectra were taken on a Perkin–Elmer Lambda 20 spectrometer. Melting points (not corrected) were determined using a Reichert Thermovar or Electrothermal 9200 apparatus. The microwave oven used is a Monomode Discover MW Reactor. All reactions were done in a 10 mL glass tube sealed with a Teflon stopper.

### 4.2. Materials

Chemicals and solvents were either purchased puris p.A. from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated 0.25 mm silica plates (Macherey–Nagel 60 Alugram® Sil G/UV254) were used and spots were visualized either with UV light or ethanolic phosphomolybdic acid followed by heating.

**4.2.1. 2,3-Dihydro-2-oxo 5-phenyl-1*H*-pyrrole-4-carboxylic acid ethyl ester (2c).** A suspension of ethyl benzoylacetate **3b** (20.2 g, 18.3 mL, 105 mmol), $K_2CO_3$ (15.2 g, 110 mmol), NaI (2.0 g), and ethyl chloroacetate (13.2 g, 11.6 mL, 108 mmol) in acetone/DME 120 mL:80 mL was heated under reflux for 24 h. After cooling to room temperature the salts were filtered and washed with acetone. The combined filtrates were evaporated to dryness under reduced pressure affording **4b** quantitatively with sufficient purity. This crude product **4b** was dissolved in a mixture of acetic acid (200 mL) and ammonium acetate (78.7 g, 1.02 mol) and the reaction mixture was then stirred at reflux for 3 h. After cooling to room temperature, the reaction mixture was added to ice-water (800 mL). The acquired precipitate was filtered and washed with water. The residue was recrystallized from ethanol/water 4:1. After drying under reduced pressure **2c** (11.87 g, 49% starting from benzoylacetate) was obtained as a white powder.

Compound **2c** was also obtained starting from **5g** (general procedure A+D) using 3 equiv of aqueous ammonia as amine (GP D) or starting from alcohol **9a** (general procedure A).

$^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.21 (t, 3H, $J$=7.3 Hz), 3.49 (s, 2H), 4.14 (q, 2H, $J$=7.3 Hz), 7.41–7.49 (m, 3H), 7.58–7.62 (m, 2H), 9.12 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.5, 39.1, 60.4, 105.0, 128.6, 129.1, 130.0, 130.9, 151.6, 163.6, 177.5; LRMS (CI): 232 $MH^+$; mp: 181–182 °C (lit. 173–176 °C).[30]

**4.2.2. 5-(4-Methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2d).** A suspension of ethyl (4-methoxybenzoyl)acetate (88.8 g, 0.40 mol), $K_2CO_3$ (57.9 g, 0.42 mol), NaI (8.0 g), and methyl chloroacetate (45.1 g, 36.7 mL, 0.41 mol) in acetone/DME 160 mL:240 mL was heated under reflux for 24 h. Treatment as for **2c** afforded **2d** (46.2 g, 47%) as a white powder. After extraction of the combined filtrates with dichloromethane (mL), drying over $MgSO_4$ and evaporation in vacuo, additional product **2d** (10.1 g, 10.3%) was isolated by column chromatography of the residue on silica gel ($CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.23 (t, 3H, $J$=7.3 Hz), 3.48 (s, 2H), 3.85 (s, 3H), 4.13 (q, 2H, $J$=7.3 Hz), 6.94 (d, 2H, $J$=8.8 Hz), 7.62 (d, 2H, $J$=8.8 Hz), 8.94 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.3, 39.0, 55.4, 60.1, 103.1, 113.7, 121.4, 130.6, 151.4, 161.4, 163.5, 178.0; LRMS (CI): 262 $MH^+$; mp: 101 °C.

**4.2.3. 1-Benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2e).** To crude product **4b** (1.00 mmol, 278 mg) in ethanol (15 mL) was added acetic acid (10.0 mmol, 0.60 mL) and benzylamine (10.0 mmol, 1.05 g). The reaction mixture was then heated at reflux for 4 h. After cooling to room temperature the reaction mixture was diluted with water (15 mL). The aqueous mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the viscous residue was chromatographed on silica gel (ethyl acetate/petroleum ether 9:1) to furnish the pure **2e** as a yellow oil (128 mg, 40%); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.06 (t, 3H, $J$=7.1 Hz), 3.53 (s, 2H), 4.07 (q, 2H, $J$=7.1 Hz), 4.52 (s, 2H), 6.83 (m, 2H), 7.44–7.15 (m, 8H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=14.3, 37.7, 44.3, 60.9, 105.4, 126.0, 127.4, 128.1, 128.4, 129.3, 136.0, 154.3, 163.9, 176.2; LRMS (CI): 322 $MH^+$.

### 4.3. General procedure A: synthesis of 5-aryl-2-oxopyrroles 2

The crude products or purified alcohols **9** (1 equiv) were dissolved in chloroform. Subsequently mesyl chloride (1.1 equiv) and triethylamine (4 equiv) were added portionwise. After heating under reflux for 30 min the reaction mixture was diluted with 5% HCl solution. The aqueous mixture was extracted with $CH_2Cl_2$. The combined organic phases were washed with 5% HCl solution, saturated $NaHCO_3$ solution until neutral, water and finally dried with magnesium sulfate. The solvents were evaporated under reduced

pressure and the residue was chromatographed on silica gel (ethyl acetate/petroleum ether 50:50) to furnish the pure oxopyrroles **2**.

Product **2f** (1.96 g, 40%) was prepared as described in the general procedure A (GP A) and was obtained as a red powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.06 (t, 3H, $J$=7.3 Hz), 2.86 (s, 3H), 3.46 (s, 2H), 4.02 (q, 2H, $J$=7.3 Hz), 7.31–7.34 (m, 2H), 7.46–7.48 (m, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=14.3, 28.2, 37.5, 60.1, 105.5, 128.7, 129.1, 130.1, 130.3, 155.4, 163.5, 176.4; LRMS (CI): 246 $MH^+$; mp: 35 °C.

**4.3.1. 5-(4-(Dimethylamino)phenyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2g).** Product **2g** (220 mg, 40%) was prepared as described in the GP A and was obtained as a red powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.14 (t, 3H, $J$=7.3 Hz), 2.92 (s, 3H), 3.02 (s, 6H), 3.43 (s, 2H), 4.06 (q, 2H, $J$=7.3 Hz), 6.74 (d, 2H, $J$=8.2 Hz), 7.22 (d, 2H, $J$=8.2 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=14.6, 28.5, 37.7, 40.5, 60.0, 104.1, 111.5, 116.5, 130.7, 151.5, 156.6, 163.9, 176.9; LRMS (CI): 289 $MH^+$; mp: 87–88 °C.

**4.3.2. 1-Allyl-2-oxo-5-(thien-2-yl)-4,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2i).** Product **2i** (7.02 g, 51%) was prepared as described in the GP A and was obtained as a red powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.12 (t, 3H, $J$=7.3 Hz), 3.49 (s, 2H), 4.02–4.10 (m, 4H), 4.97 (d, 1H, $J$=14.6 Hz), 5.09 (d, 1H, $J$=10.1 Hz), 5.62–5.75 (m, 1H), 7.10 (dd, 1H, $J$=5.5 Hz), 7.16 (d, 1H, $J$=3.7 Hz), 7.52 (d, 1H, $J$=6.4 Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=14.4, 37.8, 43.4, 60.4, 108.8, 117.4, 127.3, 128.9, 130.6, 132.7, 148.1, 163.2, 175.3; LRMS (CI): 278 $MH^+$; mp: 58 °C.

**4.3.3. 1,5-Bis(4-chlorophenyl)-2-oxo-4,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2j).** Product **2j** (7.44 g, 66%) was prepared as described in the GP A and was obtained as a brownish powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.13 (t, 3H, $J$=7.3 Hz), 3.49 (s, 2H), 4.09 (q, 2H, $J$=7.3 Hz), 6.88 (d, 2H, $J$=8.2 Hz), 7.13 (d, 2H, $J$=8.2 Hz), 7.18–7.27 (m, 4H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$=14.4, 37.9, 60.6, 106.9, 127.8, 128.5, 129.1, 129.6, 131.3, 132.8, 134.0, 136.1, 152.8, 163.2, 174.9; LRMS (CI): 376–378 $MH^+$; mp: 70 °C.

**4.3.4. Diethyl 2-(4-nitrobenzoyl)succinate (4a).** To a solution of ethyl 4-nitrobenzoylacetate (2.0 g, 8.4 mmol), NaH (202 mg, 8.4 mmol), and NaI (100 mg) in THF (100 mL) was added ethyl chloroacetate (2.8 g, 16.8 mmol). After stirring the mixture at 50 °C for 1 h it was cooled and diluted with ether (50 mL) and acidified with aqueous 5% HCl solution. After extraction with ether, drying over $MgSO_4$ and evaporation under reduced pressure, the product **4a** (1.6 g, 58%) was isolated as a yellow oil after column chromatography of the residue on silica gel ($CH_2Cl_2$). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.13–1.27 (m, 6H), 3.04 (dd, 1H, $J$=6.5 Hz, $J$=23.4 Hz), 3.22 (dd, 1H, $J$=9.2 Hz, $J$=26.0 Hz), 4.09–4.16 (m, 4H), 4.85 (q, 1H, $J$=9.1 Hz), 5.30 (s, 1H), 8.19 (d, 2H, $J$=8.8 Hz), 8.34 (d, 2H, $J$=8.8 Hz); LRMS (CI): 324 $MH^+$.

**4.3.5. Diethyl 2-benzoylsuccinate (4b).** A suspension of ethyl benzoylacetate **3b** (20.2 g, 18.3 mL, 105 mmol), $K_2CO_3$ (15.2 g, 110 mmol), NaI (2.0 g), and ethyl chloroacetate (13.2 g, 11.6 mL, 108 mmol) in acetone/DME 120 mL: 80 mL was heated under reflux for 24 h. After cooling to room temperature the salts were filtered and washed with acetone. The combined filtrates were evaporated to dryness under reduced pressure affording **4b** (9.40 g, 71%) as a red brown oil with sufficient purity. A sample was extra purified by column chromatography on silica gel ($CH_2Cl_2$) affording **4b** as a colorless to green oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.2 (m, 6H), 3.13–3.16 (m, 2H), 4.12–4.17 (m, 4H), 4.84 (t, 1H, $J$=7.7 Hz), 7.51 (t, 2H, $J$=7.7 Hz), 7.60 (t, 1H, $J$=7.7 Hz), 8.04 (d, 2H, $J$=8.4 Hz); LRMS (CI): 279 $MH^+$.

### 4.4. General procedure B: synthesis of 4-carbethoxy-2,3-dioxopyrrolidines 5 in acetic acid

To a solution of sodium diethyl oxalacetate (1 equiv) in acetic acid was added portionwise with constant stirring, amine (1 equiv) followed by aldehyde (1 equiv). After heating the mixture until everything dissolved, it was kept overnight at room temperature. On dilution with water and stirring, a yellow solid separated, which was filtered, washed with water, dried under reduced pressure, and recrystallized from toluene. After drying under reduced pressure the 2,3-dioxopyrrolidines **5** were obtained with sufficient purity.

**4.4.1. 1,5-Bis-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5a).** Product **5a** was prepared as described in the GP B and was obtained as a white powder (2.79 g, 71%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.20 (t, 3H, $J$=7.3 Hz), 4.20 (q, 2H, $J$=7.3 Hz), 5.68 (s, 1H), 7.19 (m, 6H), 7.41 (d, 2H, $J$=8.8 Hz), 8.99 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.3, 61.2, 61.9, 113.3, 123.6, 129.2, 129.4, 129.6, 131.8, 133.8, 134.9, 156.7, 163.1, 165.2; LRMS (CI): 392 $MH^+$; mp: 172 °C.

**4.4.2. 1-Benzyl-5-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5b).** Product **5b** (1.190 g, 32%) was prepared as described in the GP B and was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.10 (t, 3H, $J$=7.3 Hz), 4.10 (q, 2H, $J$=7.3 Hz), 4.38 (dd, 2H), 4.86 (s, 1H), 7.03–7.35 (m, 9H), 8.71 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=13.8, 44.0, 59.0, 61.1, 112.9, 128.0, 128.4, 128.9, 129.1, 129.2, 133.2, 134.6, 136.0, 157.4, 163.5, 165.0; LRMS (CI): 372 $MH^+$; mp: 195 °C.

**4.4.3. 5-(4-Chlorophenyl)-1-cyclohexyl-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5c).** Product **5c** (671 mg, 31%) was prepared as described in the GP B and was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.20 (t, 3H), 1.40 (m, 10H), 3.71 (m, 1H), 4.11 (q, 2H), 5.13 (s, 1H), 7.18 (d, 2H, $J$=6.6 Hz), 7.31 (d, 2H, $J$=7.3 Hz), 8.30 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=13.9, 25.1, 25.7, 30.9, 54.3, 59.5, 60.9, 112.8, 128.6, 129.0, 134.2, 134.9, 156.9, 163.9, 164.6; LRMS (CI): 364 $MH^+$; mp: >350 °C.

**4.4.4. 3-Hydroxy-1-(4-methoxybenzyl)-5-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5d).** Product **5d** (1.59 g, 40%) was prepared as described in the GP B and was obtained as a white

powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.07 (t, 3H, $J$=7.3 Hz), 3.48 (d, 1H, $J$=14.6 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.06 (q, 2H, $J$=7.3 Hz), 4.82 (s, 1H), 5.12 (d, 1H, $J$=14.6 Hz), 6.82 (d, 2H, $J$=8.8 Hz), 6.86 (d, 2H, $J$=8.8 Hz), 7.02 (d, 2H, $J$=8.1 Hz), 7.04 (d, 2H, $J$=8.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.3, 43.6, 55.6, 59.4, 60.9, 114.3, 114.4, 128.9, 129.4, 130.1, 130.2, 159.5, 160.0, 165.8; LRMS (CI): 398 $MH^+$; mp: 174 °C.

**4.4.5. 5-(4-Chlorophenyl)-3-hydroxy-1-(4-methoxybenzyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5e).** Product **5e** (2.58 g, 64%) was prepared as described in the GP B and was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.00 (t, 3H, $J$=7.3 Hz), 3.66 (d, 1H, $J$=15.3 Hz), 3.83 (s, 3H), 3.90–4.06 (m, 2H), 4.76 (d, 1H, $J$=15.3 Hz), 4.91 (s, 1H), 6.83 (d, 2H, $J$=8.8 Hz), 6.98 (d, 2H, $J$=8.1 Hz), 7.11 (d, 2H, $J$=8.1 Hz), 7.37 (d, 2H, $J$=8.1 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.9, 44.1, 56.0, 60.2, 60.5, 112.2, 115.0, 129.2, 129.5, 130.1, 133.7, 136.0, 154.8, 159.5, 162.8, 165.6; LRMS (CI): 402 $MH^+$; mp: 180–181 °C.

**4.4.6. 3-Hydroxy-5-(3-hydroxyphenyl)-2-oxo-1-(3,4,5-trimethoxyphenyl)-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5f).** Product **5e** (851 mg, 38%) was prepared as described in the GP B and was obtained as a white powder. $^1$H NMR (300 MHz, DMSO): $\delta$=1.07 (t, 3H, $J$=7.3 Hz), 3.57 (s, 3H), 3.69 (s, 6H), 3.99–4.06 (m, 2H), 5.99 (s, 1H), 6.56 (d, 2H, $J$=8.1 Hz), 6.63 (s, 1H), 6.74 (d, 2H, $J$=8.1 Hz), 6.93 (s, 2H), 7.03 (t, 1H, $J$=8.1 Hz), 9.38 (s, 1H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=14.9, 56.8, 60.6, 60.9, 61.6, 101.2, 112.7, 115.1, 115.9, 119.6, 130.1, 133.3, 135.7, 139.1, 153.4, 153.6, 158.0, 162.9, 164.9; LRMS (CI): 430 $MH^+$; mp: 205 °C.

### 4.5. General procedure C: synthesis of 2,3-dioxopyrrolidines 5 in ethanol

A suspension of sodium diethyl oxalacetate (1 equiv), amine (1 equiv), and aldehyde (1 equiv) in ethanol was heated at reflux toward complete solution (30 min) or until completion (TLC). After cooling the mixture was added on ice-water and then acidified with $H_2SO_4$ or $H_3PO_4$ until pH 2. The precipitate was filtered, washed with water, and dried under reduced pressure. The powder was washed with petroleum ether in order to remove traces of aldehyde or if necessary recrystallized with toluene. After drying under reduced pressure the 2,3-dioxopyrrolidines **5** were obtained with sufficient purity.

**4.5.1. 5-(4-Dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5i).** Product **5i** (7.4 g, 48%) was prepared as described in the GP C and was obtained as a white powder. Heating at reflux for 3 days was necessary and acidification was unnecessary. $^1$H NMR (300 MHz, DMSO): $\delta$=0.95 (s, 3H), 2.56 (s, 3H), 2.84 (s, 6H), 3.80 (q, 2H, $J$=7.3 Hz), 4.78 (s, 1H), 6.63 (d, 2H, $J$=8.8 Hz), 6.94 (d, 2H, $J$=8.8 Hz); $^{13}$C NMR (75 MHz, DMSO): $\delta$=15.3, 28.0, 41.1, 57.8, 62.5, 99.9, 112.9, 128.9, 129.1, 129.8, 150.5, 166.1, 169.9, 170.6; LRMS (CI): 305 $MH^+$; mp: 186 °C.

**4.5.2. 3-Hydroxy-1-methyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5j).** Product **5j** (7.7 g, 59%) was prepared as described in the GP C and was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=corresponding with data literature;[31] LRMS (CI): 262 $MH^+$; mp: 133 °C (lit. 164–165 °C).

**4.5.3. 3-Hydroxy-5-(2-hydroxy-phenyl)-1-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5k).** Product **5k** (3.58 g, 52%) was prepared as described in the GP C and was obtained as a white powder. $^1$H NMR (300 MHz, DMSO): $\delta$=1.02 (t, 3H, $J$=7.3 Hz), 2.63 (s, 3H), 3.94–3.99 (m, 2H), 5.43 (s, 1H), 6.73 (t, 1H, $J$=7.3 Hz), 6.82 (d, 2H, $J$=7.3 Hz), 7.10 (t, 1H, $J$=8.8 Hz), 9.58 (s, 1H), 11.31 (s, 1H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=14.9, 28.0, 60.1, 111.5, 116.6, 120.1, 122.7, 129.9, 155.2, 157.0, 163.1, 165.6; LRMS (CI): 305 $MH^+$; mp: 196–197 °C.

**4.5.4. 1-Allyl-3-hydroxy-2-oxo-5-thiophen-2-yl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5l).** Product **5l** (17.3 g, 62%) was prepared as described in the GP C and was obtained as a white powder. $^1$H NMR (300 MHz, DMSO): $\delta$=1.12 (t, 3H, $J$=7.3 Hz), 3.49 (s, 2H), 4.02–4.11 (m, 4H), 5.00 (d, 1H, $J$=16.4 Hz), 5.10 (d, 1H, $J$=10.1 Hz), 5.62–5.75 (m, 1H), 7.11 (t, 1H, $J$=5.49 Hz), 7.17 (d, 1H, $J$=3.7 Hz), 7.52 (d, 1H, $J$=6.4 Hz); $^{13}$C NMR (75 MHz, DMSO): $\delta$=14.3, 43.0, 55.6, 61.4, 112.9, 119.2, 126.5, 127.1, 128.3, 132.4, 138.5, 157.6, 163.1, 165.3; LRMS (CI): 294 $MH^+$; mp: 119 °C.

### 4.6. General procedure D: synthesis of alcohols 9

A suspension of enol **5** (1 equiv), zinc powder (6 equiv), and a few drops of sulfuric acid in acetic acid 150 mL was vigorously stirred at 100 °C for 2 h. A second portion of zinc powder (6 equiv) was added and the reaction mixture was then stirred at 100 °C until completion of the reaction (followed by TLC). After cooling to room temperature the excess of zinc and the inorganic salts were filtered off. The filtrate was then diluted with water (300 mL). The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic phases were washed with saturated $NaHCO_3$ solution until neutral and finally dried with magnesium sulfate. The solvents were evaporated under reduced pressure and the residue used directly in the next step or was chromatographed on silica gel (EtOAc) to furnish the pure alcohol **9**.

**4.6.1. (3*S*,4*R*,5*S*)-5-(4-Dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9c*trans–trans*) and (3*R*,4*S*,5*S*)-5-(4-dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9c*trans–cis*).** Products **9c***trans–trans* and **9c***trans–cis* were prepared as described in the GP D. Product **9c***trans–trans* (560 mg, 36%) was obtained as a white powder and **9c***trans–cis* (83 mg, 5.4%) was obtained as a viscous colorless oil. Product **9c***trans–trans* $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=1.22 (t, 3H, $J$=7.3 Hz), 2.62 (s, 3H), 2.96 (s, 6H), 3.06 (t, 1H, $2\times{}^3J$=8.4 Hz), 4.18 (q, 2H, $J$=7.3 Hz), 4.53 (d, 1H, $J$=8.1 Hz), 4.66 (d, 1H, $J$=8.8 Hz), 6.71 (d, 2H, $J$=8.8 Hz), 7.13 (d, 2H, $J$=8.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$=14.1, 28.1, 40.3, 56.1, 61.3, 62.9, 72.6, 112.5, 124.6, 128.3, 150.8, 171.5, 173.0; LRMS (CI): 307 $MH^+$; mp: 45 °C.

Product **9c***trans–cis* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.94 (t, 3H, $J$=7.3 Hz), 2.74 (s, 3H), 2.94 (s, 6H), 3.59 (t, 1H, 2×$^3J$=7.4 Hz), 3.78–3.88 (m, 2H), 4.08–4.17 (m, 1H), 4.55 (d, 1H, $J$=7.3 Hz), 4.68 (d, 1H, $J$=7.3 Hz), 6.67 (d, 2H, $J$=8.8 Hz), 7.11 (d, 2H, $J$=8.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=13.6, 28.6, 40.2, 49.4, 60.7, 62.7, 70.4, 112.0, 121.8, 128.6, 151.0, 169.6, 173.2; LRMS (CI): 307 $MH^+$.

**4.6.2. (3*S*,4*R*,5*S*)-1-Benzyl-5-(4-chloro-phenyl)-3-hydroxy-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9d*trans–trans*) and (3*R*,4*S*,5*S*)-1-benzyl-5-(4-chlorophenyl)-3-hydroxy-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9d*trans–cis*).** Products **9d***trans–trans* (6.4 g, 64%) and **9d***trans–cis* (520 mg, 5.2%) were prepared as described in the GP D and were obtained as white powders. Product **9d***trans–trans* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.15 (t, 3H, $J$=7.3 Hz), 3.06 (t, 1H, $J$=8.1 Hz), 3.52 (d, 1H, $J$=14.6 Hz), 4.13 (q, 2H, $J$=7.3 Hz), 4.44 (d, 1H, $J$=7.3 Hz), 4.71 (d, 1H, $J$=8.1 Hz), 5.05 (d, 2H, $J$=14.6 Hz), 6.95–6.99 (m, 2H), 7.15 (d, 2H, $J$=8.8 Hz), 7.25–7.27 (m, 3H), 7.36 (d, 2H, $J$=8.8 Hz); LRMS (CI): 374–376 $MH^+$; mp: 99 °C.

Product **9d***trans–cis* $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.92 (t, 3H, $J$=7.3 Hz), 3.50 (t, 1H, $J$=8.1 Hz), 3.61 (d, 1H, $J$=14.6 Hz), 3.67–3.81 (m, 3H), 4.56 (t, 2H, $J$=6.6 Hz), 5.16 (d, 1H, $J$=14.6 Hz), 6.98–7.02 (m, 2H), 7.23 (d, 2H, $J$=8.8 Hz), 7.26–7.28 (m, 3H), 7.30 (s, 2H, $J$=8.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.0, 45.2, 48.7, 60.2, 61.6, 70.9, 128.4, 128.9, 129.2, 129.3, 130.1, 133.9, 135.2, 135.6, 169.7, 173.1; LRMS (CI): 374–376 $MH^+$; mp: 117–118 °C.

### 4.7. General procedure E: synthesis of benzylidene-5-aryl-2-oxopyrroles 10

To a solution of oxopyrrole **2** (1 equiv) in ethanol was added aromatic aldehyde (1 equiv). A catalytic amount of concentrated HCl was added and the mixture was heated under reflux for 2 h. During cooling to room temperature orange crystals precipitated. The solid was filtered and washed with cold ethanol. After drying under reduced pressure, compound **10** was obtained as orange powder.

**4.7.1. 4-(4-Carboxy-benzylidene)-2-(4-methoxy-phenyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (10a).** Product **10a** (1.09 g, 69%) was prepared as described in the GP E and was obtained as an orange powder. $^1$H NMR (300 MHz, DMSO): $\delta$=1.1 (t, 3H), 3.8 (s, 1H), 4.1 (q, 2H), 7.0 (d, 2H, $J$=8.8 Hz), 7.5 (d, 2H, $J$=8.8 Hz), 7.9 (d, 2H, $J$=8.1 Hz), 8.0 (s, 1H), 8.1 (d, 2H, $J$=8.8 Hz), 10.9 (s, 1H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=14.6, 56.2, 60.3, 102.9, 114.1, 122.7, 129.6, 131.6, 131.8, 131.9, 137.9, 139.3, 152.6, 161.8, 164.3, 167.3, 167.7; LRMS (CI): 394 $MH^+$; mp: 282 °C.

**4.7.2. 4-(4-Methoxy-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (10b).** Product **10b** (1.24 g, 89%) was prepared as described in the GP E and was obtained as a yellow powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.13 (t, 3H, $J$=7.3 Hz), 3.90 (s, 3H), 4.23 (q, 2H, $J$=7.3 Hz), 6.94 (dd, 2H, $J$=8.8 Hz), 7.45–7.49 (m, 3H), 7.55–7.59 (m, 2H), 8.21 (s, 1H), 8.31 (d, 2H, $J$=8.78 Hz), 8.61 (br s, 1H); LRMS (CI): 350 $MH^+$; mp: 188 °C.

**4.7.3. 4-(Ethoxycarbonyl-hydroxy-methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (16).** To a suspension of **2c** (462 mg, 2.00 mmol) in (5 mL) was added diethyl oxalate (0.55 mL, 4.00 mmol) and sodium ethoxide (5 mmol from sodium (115 mg) dissolved in 3 mL ethanol). The mixture was heated at reflux for 2 h, partially concentrated under reduced pressure, diluted with water and acidified with acetic acid affording a white precipitate. After filtering and drying under reduced pressure compound **16** (250 mg, 40%) was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.03 (t, 3H, $J$=6.9 Hz), 1.37 (t, 3H, $J$=7.3 Hz), 4.17 (q, 2H, $J$=7.3 Hz), 4.39 (t, 3H, $J$=7.3 Hz), 7.45 (s, 5H), 9.75 (br s, 1H), 14.41 (br s, 1H); LRMS (CI): 332 $MH^+$; mp: 178 °C.

**4.7.4. 3-(4-Methoxyphenyl)-2*H*-pyrrolo[3,4-*c*]benzoxepine-1,4-dione (13) and 2-(4-methoxyphenyl)chromeno[2,3-*b*]pyrrole-3-carboxylic acid ethyl ester (14).** A solution of methoxyphenylpyrrolinone **2d** (512 mg, 2.00 mmol), salicylaldehyde (244 mg, 2.00 mmol) in acetic acid (2 mL) was stirred and heated in a monomode microwave oven at 120 °C for 30 min. After cooling to room temperature the mixture was poured on water and extracted with ether. The organic phase was washed with water and finally dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel ($CH_2Cl_2$/EtOAc 95:5) to furnish the pure **14** (87 mg, 13%) as an orange powder. Washing the slightly impure fractions containing product **13** with $CH_2Cl_2$ furnished pure **13** (50 mg, 8%) as yellow-orange powder. Compound **13** $^1$H NMR (300 MHz, DMSO): $\delta$=3.85 (s, 3H), 7.04 (d, 2H, $J$=8.8 Hz), 7.16 (d, 1H, $J$=8.8 Hz), 7.28 (t, 1H, $J$=7.3 Hz), 7.39 (s, 1H), 7.48 (t, 1H, $J$=7.3 Hz), 7.64 (d, 1H, $J$=7.3 Hz), 7.74 (d, 2H, $J$=8.8 Hz), 11.41 (br s, 1H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=56.3, 99.0, 114.2, 120.3, 122.8, 124.9, 126.3, 128.5, 130.7, 132.8, 133.7, 134.1, 150.7, 156.5, 159.0, 162.3, 166.7; UV ($CH_2Cl_2$): $\lambda_{max}$ (log ε)=427 nm (4.230), 310 (4.072); LRMS (CI): 320 $MH^+$; mp: 287 °C.

Compound **14** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.42 (t, 3H, $J$=7.3 Hz), 3.88 (s, 3H), 4.41 (q, 2H, $J$=7.3 Hz), 6.99 (d, 2H, $J$=8.8 Hz), 7.48 (t, 1H, $J$=7.3 Hz), 7.69 (t, 1H, $J$=7.3 Hz), 7.76 (d, 1H, $J$=7.3 Hz), 7.85 (d, 1H, $J$=7.3 Hz), 8.25 (d, 1H, $J$=8.8 Hz), 8.65 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.8, 55.7, 60.3, 103.4, 113.5, 118.2, 120.9, 125.4, 127.5, 128.8, 129.7, 132.0, 133.3, 136.4, 151.3, 161.8, 163.4, 164.5, 164.9; LRMS (CI): 348 $MH^+$; mp: 134 °C.

**4.7.5. 5-Oxo-2-phenyl-4-(phenyl-hydrazono)-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (18).** To a suspension of **2c** (924 mg, 4.00 mmol) in ethanol (10 mL) was added freshly prepared phenyldiazonium chloride (560 mg, 4.00 mmol). The mixture was refluxed for 1 h. After 5–6 min compound **18** started to precipitate. After cooling, the precipitate was filtered and dried affording **18** (804 mg, 60%) as bright orange crystals. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=0.98 (t, 3H, $J$=6.9 Hz), 4.11 (q, 2H, $J$=6.6 Hz), 7.01–7.57 (m, 10H), 9.04 (br s, 1H), 13.34 (br s, 1H); LRMS (CI): 366 $MH^+$; mp: 199 °C.

**4.7.6. 4-(Bis(methylthio)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (19).** To a solution of **2c** (462 mg, 2.00 mmol) in DMSO (10 mL) was added triethylamine (0.55 mL, 4.00 mmol). After 3 min, $CS_2$ (0.132 mL, 2.00 mmol) was added and methyl iodide was added after the color change. The reaction mixture was stirred at room temperature for 4 h and then poured on ice-water and acidified with acetic acid (1 mL). The aqueous mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the viscous residue was chromatographed on silica gel ($CH_2Cl_2$/EtOAC 4:1) to furnish the pure **19** (400 mg, 60%) as yellow crystals. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.25 (t, 3H, $J$=7.3 Hz), 2.50 (s, 3H), 2.63 (s, 3H), 4.23 (q, 2H, $J$=7.0 Hz), 7.38–7.43 (m, 3H), 7.58–7.62 (m, 2H), 9.17 (br s, 1H); LRMS (CI): 336 $MH^+$; mp: 118 °C.

**4.7.7. 5-Chloro-4-formyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20a).** To pyrrolinone **2c** (5.00 g, 21.0 mmol) in DMF (3.40 mL, 43.0 mmol) was added $POCl_3$ (16.1 mL, 173 mmol) in a dropswise manner at $T$<10 °C. The mixture was heated overnight at 100 °C and then poured on ice (800 mL). After 2 h stirring the suspension was extracted with ethyl acetate (4×100 mL). The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was filtered over silica gel ($CH_2Cl_2$) to furnish the pure **20a** (4.82 g, 80%) as brownish powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.20 (t, 3H, $J$=7.1 Hz), 4.23 (q, 2H, $J$=7.2 Hz), 7.40 (m, 5H), 9.17 (s, 1H), 10.32 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.0, 60.9, 112.8, 119.6, 122.0, 128.4, 128.9, 129.3, 130.1, 136.4, 163.8, 186.9; LRMS (CI): 278: $MH^+$; mp: 160 °C.

### 4.8. General procedure F: synthesis of *N*-substituted pyrroles 20 via alkylation

To pyrrole aldehyde **20a** (1 equiv) in acetonitrile was added alkylating agent (1.4 equiv) and $K_2CO_3$ (1.6 equiv). The mixture was heated overnight at 60 °C and then poured on ice. The suspension was extracted with ethyl acetate. The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was chromatographed over silica gel ($CH_2Cl_2$/EtOAc) to furnish the pure *N*-substituted pyrroles **20**.

### 4.9. General procedure G: synthesis of *N*-substituted pyrroles 20 via chloroformylation

To *N*-substituted oxopyrrole **2** (1 equiv) in DMF (2 equiv) was added $POCl_3$ (8 equiv) in a dropswise manner at $T$<10 °C. The mixture was heated overnight at 120 °C and then poured on ice. After 2 h stirring the suspension was extracted with ethyl acetate. The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was filtered over silica gel ($CH_2Cl_2$) to furnish the pure *N*-substituted pyrrole **20**.

**4.9.1. 1-Benzyl-5-chloro-4-formyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20b).** Product **20b** (3.97 g, 99%) was prepared as described in the GP F and was obtained as an orange-brown powder.

The same product **20b** (76 mg, 66%) was also prepared as described in the GP G. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.01 (t, 3H, $J$=7.1 Hz), 4.10 (q, 2H, $J$=7.2 Hz), 5.05 (s, 2H), 6.82 (m, 2H), 7.26 (m, 8H), 10.49 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=13.7, 48.0, 60.3, 114.3, 119.1, 123.3, 126.1, 127.8, 128.1, 128.7, 129.3, 130.2, 130.5, 135.4, 139.2, 163.3, 186.7; LRMS (CI): 368: $MH^+$; mp: 82–84 °C.

**4.9.2. 5-Chloro-4-formyl-1-(2-oxo-2-phenyl-ethyl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20c).** Product **20c** (300 mg, 76%) was prepared as described in the GP F and was obtained as an orange-brown powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.03 (t, 3H, $J$=7.1 Hz), 4.11 (q, 2H, $J$=7.1 Hz), 5.18 (s, 2H), 7.40–7.53 (m, 10H), 10.50 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=13.8, 50.8, 60.4, 114.0, 119.1, 123.4, 127.3, 128.4, 129.1, 129.5, 130.2, 130.4, 133.8, 134.5, 139.5, 163.2, 187.0, 190.8; LRMS (CI): 396: $MH^+$; mp: 79–81 °C.

**4.9.3. 5-Chloro-1,2-bis-(4-chlorophenyl)-4-formyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20d).** Product **20d** (740 mg, 66%) was prepared as described in the GP G and was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.13 (t, 3H, $J$=7.3 Hz), 4.19 (q, 2H, $J$=7.3 Hz), 7.03 (d, 2H, $J$=8.2 Hz), 7.08 (d, 2H, $J$=8.2 Hz), 7.22 (d, 2H, $J$=9.1 Hz), 7.34 (d, 2H, $J$=9.1 Hz), 10.43 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.3, 61.2, 115.1, 119.7, 124.8, 128.4, 128.6, 130.0, 130.1, 133.4, 135.5, 136.1, 138.1, 163.5, 186.8; LRMS (CI): 422 $MH^+$; mp: 199 °C.

**4.9.4. 6-Benzyl-5-chloro-7-phenyl-2,6-dihydro-pyrrolo[3,4-*d*]pyridazin-1-one (21a).** To a solution of **20b** (183 mg, 0.50 mmol) in ethanol (10 mL) was added hydrazine monohydrate (50 μL, 1.00 mmol). The reaction mixture was heated at reflux for 4 h. On cooling **21a** precipitated. The precipitate was filtered and washed with cold ethanol furnishing **21a** (108 mg, 64%) as yellow crystals. $^1$H NMR (300 MHz, DMSO): $\delta$=5.35 (s, 2H), 6.84 (d, 2H, $J$=6.6 Hz), 7.23–7.28 (m, 3H), 7.40–7.46 (m, 5H), 8.09 (s, 1H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=48.5, 111.3, 112.1, 115.9, 126.1, 127.9, 128.4, 129.1, 129.3, 129.4, 131.2, 132.7, 136.3, 157.9; LRMS (CI): 336 $MH^+$; mp: 249–251 °C.

**4.9.5. 6-Benzyl-5-chloro-2-methyl-7-phenyl-2,6-dihydro-pyrrolo[3,4-*d*]pyridazin-1-one (21b).** To a solution of **20b** (877 mg, 2.40 mmol) in ethanol (40 mL) was added methyl hydrazine (190 μL, 3.60 mmol). The reaction mixture was heated at reflux overnight. The solvent was evaporated in vacuo and the residue was chromatographed over silica gel ($CH_2Cl_2$/EtOAc 9:1) to furnish the pure **21b** (352 mg, 42%) as orange crystals. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=3.69 (s, 3H), 5.31 (s, 2H), 6.86 (m, 2H), 7.26 (m, 3H), 7.37 (m, 5H), 8.00 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=38.1, 48.7, 111.2, 112.4, 116.2, 126.0, 127.9, 128.2, 128.9, 129.2, 130.9, 132.9, 135.8, 157.6; LRMS (CI): 350 $MH^+$; mp: 77 °C.

**4.9.6. Diethyl 6-benzyl-5-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,4-dicarboxylate (24).** To a solution of **20b** (741 mg, 2.00 mmol) in ethanol (20 mL) was added mercapto ethyl

acetate (0.333 mL, 3.00 mmol). The reaction mixture was refluxed overnight. On standing **24** precipitated. The precipitate was filtered and washed with water. After drying under reduced pressure product **24** (323 mg, 37%) was obtained as a white powder. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.24 (t, 3H, $J$=7.1 Hz), 1.36 (t, 3H, $J$=7.1 Hz), 4.22 (q, 2H, $J$=7.1 Hz), 4.33 (q, 2H, $J$=7.1 Hz), 5.01 (s, 2H), 7.05 (m, 2H), 7.29 (m, 3H), 7.45 (m, 5H), 8.06 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.3, 14.4, 59.8, 61.1, 77.2, 126.3, 127.1, 127.5, 128.2, 128.4, 128.6, 128.9, 129.3, 129.5, 130.6, 130.7, 134.4, 139.5, 146.4, 163.4, 163.8; LRMS (CI): 434: ($MH^+$); mp: 137 °C.

### 4.10. General procedure H: synthesis of azepines 25, 26, and 27

To *N*-benzylated pyrrole aldehyde **20b** (1 equiv) in ethanol was added the *ortho* functionalized aniline (1 equiv) and a few drops of piperidine. The reaction mixture was heated at reflux for 4 h. After partial evaporation of the solvent under reduced pressure the mixture was diluted with diethyl ether. The precipitated piperidine salts were filtered. The filtrate was evaporated in vacuo. The residue was chromatographed over silica gel ($CH_2Cl_2$/EtOAc) to furnish the pure azepines as brown viscous oils.

**4.10.1. 8-Benzyl-10-ethoxycarbonyl-9-phenylpyrrolo[7,6-*b*]-1,4-benzoxazepine (25).** Product **25** (81 mg, 38%) was prepared as described in the GP H and was obtained as a brown viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.12 (t, 3H, $J$=7.1 Hz), 4.13 (q, 2H, $J$=7.1 Hz), 7.26 (m, 14H), 4.96 (s, 2H), 8.75 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.0, 46.3, 59.9, 103.9, 108.6, 120.3, 126.2, 126.3, 127.7, 128.0, 128.1, 128.8, 128.9, 130.2, 130.5, 134.5, 136.4, 140.7, 148.0, 151.7, 157.3, 163.6; LRMS (CI): 423 $MH^+$.

**4.10.2. 8-Benzyl-10-ethoxycarbonyl-9-phenylpyrrolo[7,6-*b*]-1,4-benzothiazepine (26).** Product **26** (100 mg, 45%) was prepared as described in the GP H and was obtained as a brown viscous oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=1.09 (t, 3H, $J$=7.1 Hz), 4.10 (q, 2H, $J$=7.1 Hz), 6.79 (m, 2H), 5.08 (s, 2H), 7.09 (m, 4H), 7.22 (m, 3H), 7.32 (m, 5H), 9.12 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$=14.0, 48.3, 60.0, 112.3, 121.7, 126.2, 126.8, 127.3, 127.4, 127.6, 128.0, 128.7, 128.8, 129.0, 129.3, 130.4, 130.8, 132.1, 136.8, 141.4, 150.8, 158.5, 163.3; LRMS (CI): 439 $MH^+$.

**4.10.3. 1-Benzyl-2-phenyl-1,10-dihydro-benzo[*b*]pyrrolo[2,3-*e*][1,4]diazepine-3-carboxylic acid ethyl ester (27).** Product **27** (67 mg, 36%) was prepared as described in the GP H and was obtained as a brown viscous oil. $^1$H NMR (300 MHz, DMSO): $\delta$=1.17 (t, 3H, $J$=7.1 Hz), 4.02 (q, 2H, $J$=7.1 Hz), 5.15 (s, 2H), 7.32 (m, 14H); $^{13}$C NMR (75 MHz, DMSO): $\delta$=14.2, 53.1, 60.9, 93.1, 113.9, 116.3, 123.3, 123.8, 126.7, 127.0, 127.7, 128.0, 129.0, 131.4, 136.3, 136.9, 139.2, 153.5, 157.5; LRMS (CI): 422 $MH^+$.

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