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Synthesis of 5-alkylidene-2,5-dihydropyrrol-2-ones based on cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride

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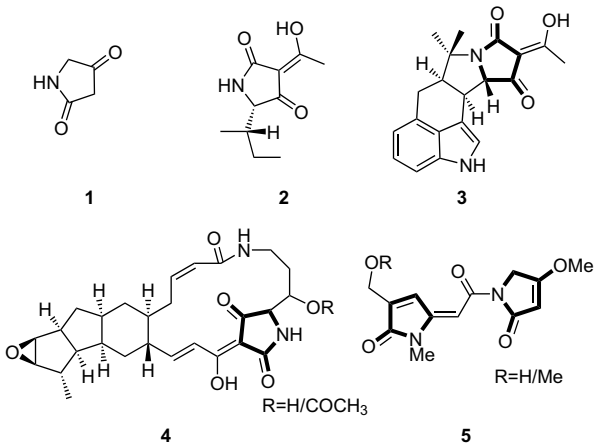
ABSTRACT

The acid-mediated reaction of amines with γ-alkylidenebutenolides, readily available by cyclization of 1,3-bis(silyloxy)-1,3-butadienes with oxalyl chloride, allows a convenient synthesis of a variety of 5-alkylidene-2,5-dihydropyrrol-2-ones. The configuration of the exocyclic double bond of the products depends on the substitution pattern of the products.

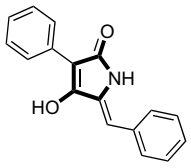
1. Introduction

Tetramic acids (pyrrolidine-2,4-diones **1**) are of considerable pharmacological relevance and occur in a variety of natural products. They occur, for example, in 3-alkylidene-3,5-dihydropyrrol-2,4-diones such as tenuazoic acid **2**, α-cyclopiazoic acid **3** or in the macrocyclic discodermides **4** (Scheme 1).[1] The related 5-alkylidene-2,5-dihydropyrrol-2-ones are also of pharmacological importance and are found in nature. This structural class includes the amaryllidacae alkaloids,[2] the pukeleimides **5**,[3] holomycin,[4] isoampullicin,[5] and linear oligopyrroles (for example, bilirubine).



Scheme 1. Tetramic acids in nature.

5-Alkylidene-3-aryltetramic acids, such as **6**, bind as antagonists at *N*-methyl-D-aspartate-receptors, which represent ion channels present in neurons (Scheme 2). Therefore, these substances are promising drugs for the treatment of epilepsis and related CNS-based diseases.[6]



6

Scheme 2. 5-Alkylidene-3-aryltetramic acid **6**.

Last but not least, 5-alkylidene-2,5-dihydropyrrol-2-ones represent versatile synthetic building blocks, which have been used as key intermediates during the synthesis of antibiotics.[1,7]

5-Alkylidene-2,5-dihydropyrrol-2-ones are synthetically available by Wittig reaction of maleimides with stabilized ylides.[8,9] They have been prepared also by hydrogenolysis of the isoxazolidines, which are available by 1,3-dipolar cycloadditions of nitrones with alkenes and alkynes.[10] An alternative approach relies on the reaction of amines with alkylidenetetronic acids[11] or dimethyl-β-oxoalkanedioates.[12] Abell and co-workers have reported an efficient two-step synthesis of cyclic enamino esters from enol lactones.[13] 5-Alkylidene-pyrrolidin-2-ones have been prepared also by reaction of protected 2,2-diethoxypyrrolidines with ketones.[14] Recently, we have developed a new approach to 5-alkylidene-3-amino-2,5-dihydropyrrol-2-ones by cyclization of 1,3-dicarbonyl dianions with oxalic acid-bis(imidoyl)chlorides.[15] However, this method is limited to the synthesis of *N*-aryl derivatives.

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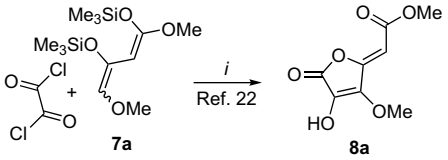
Some years ago we developed an efficient approach to γ-alkylidenebutenolides based on the cyclization of 1,3-bis(silyloxy)-1,3-butadienes with oxalyl chloride.[16] Stachel and Saalfrank were the first to report a two-step synthesis of 5-alkylidene-2,5-dihydropyrrol-2-ones by reaction of γ-alkylidenebutenolides with amines.[17] The yields of the reactions, which were carried out under basic conditions, were relatively low. Recently, we have communicated[18] an efficient and practical method for the synthesis of 5-alkylidene-2,5-dihydropyrrol-2-ones based on the reaction of γ-alkylidenebutenolides with ammonium acetates and amines in glacial acetic acid. The conditions of these reactions follow those reported[9,19] for the transformation of maleic anhydrides into maleic imides. Herein, we report full details of our methodology.

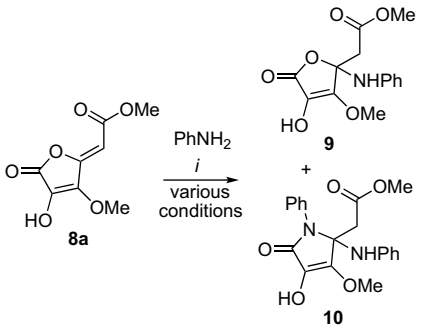
2. Results and discussion

1,3-Bis(silyloxy)-1,3-butadiene **7a** was prepared in two steps from methyl 4-methoxyacetoacetate.[20,21] Some years ago, we reported the synthesis of γ-alkylidenebutenolide **8a** by Me_3SiOTf-catalyzed cyclization of **7a** with oxalyl chloride (Scheme 3).[22] Product **8a** was formed with very good *Z*-diastereoselectivity, which can be explained by the steric effect of the methoxy group located at carbon atom C-4 of the butenolide.



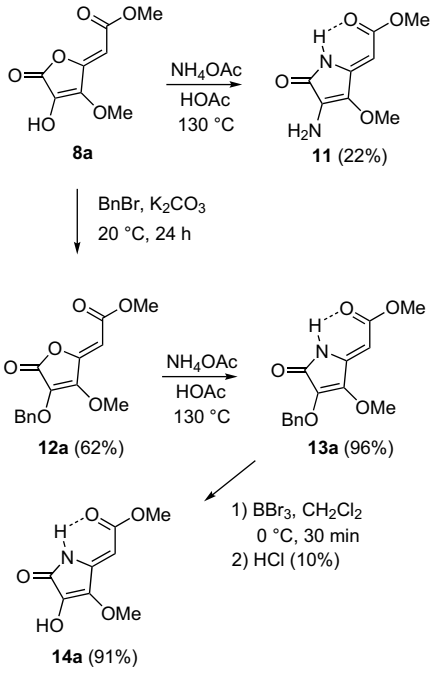
Scheme 3. Synthesis of γ-alkylidenebutenolide **8a**. Conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C.

Stirring of **8a** with aniline (neat) resulted in the formation of a complex, unseparable mixture of products containing **9** and **10** (Scheme 4). The use of different solvents (THF, MeOH, CH_2Cl_2), variation of the stoichiometry and the temperature (room temperature or reflux) did not result in an improvement.



Scheme 4. Reaction of butenolide **8a** with aniline. Conditions: (i) neat, THF, MeOH or CH_2Cl_2, 20 °C or reflux.

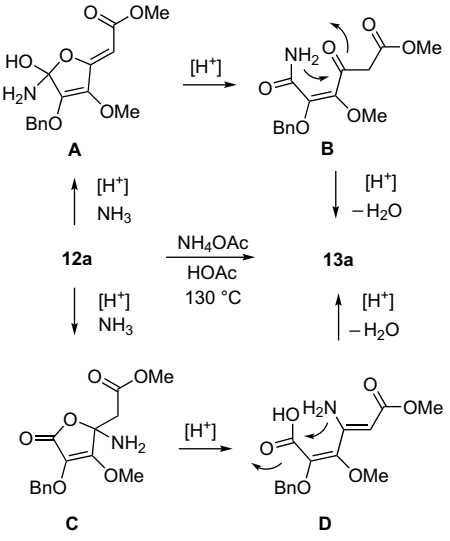
The problem could be solved by the application of acidic conditions. The reaction of **8a** with ammonium acetate in glacial acetic acid (130 °C, 2 h) resulted in the formation of a complex mixture from which product **11** could be isolated in 22% yield (Scheme 5). Although the desired transformation of the lactone into a lactam was achieved, the enolic OH group was also replaced by a NH_2 group. To solve this problem, the hydroxyl group was protected by a benzyl group (product **12a**). The reaction of **12a** with ammonium acetate afforded the desired 5-alkylidene-2,5-dihydropyrrol-2-one **13a** in excellent yield (96%). The best yields were obtained when glacial acetic acid was used as the solvent and when an excess of ammonium acetate (5.0 equiv) was used. To avoid decomposition, the reaction mixture was stirred under reflux until all starting material was converted into the product (20 h, TLC control). The deprotection of **13a** using BBr_3 proceeded smoothly and afforded product **14a** in 91% yield without cleavage of the methoxy group. During the optimization, the use of an excess of BBr_3 (3.9 equiv) and a short reaction time (30 min at 0 °C, TLC control) proved to be important.



Scheme 5. Reaction of **8a** and **12a** with ammonium acetate.

Pyrrol-2-one **13a** was formed with very good *Z*-diastereoselectivity, which can be explained by the steric effect of the methoxy group. In addition, a stable intramolecular hydrogen bond N–H···O is formed, which is not possible for the *E*-isomer. The stereochemical assignment of all products relies on NOESY experiments and detailed analysis of the chemical shifts (vide infra).

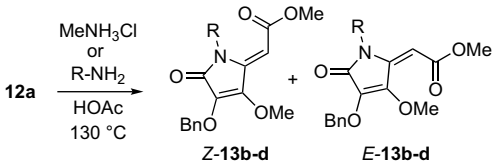
The transformation of **12a** into **13a** may proceed by acid-mediated attack of ammonia onto the lactone (intermediate **A**), ring cleavage (to give intermediate **B**) and subsequent acid-mediated recyclization by attack of the amide nitrogen atom onto the carbonyl group (Scheme 6). This mechanism has to be taken into



Scheme 6. Possible mechanisms of the formation of **12a**.

account as the related transformation of maleic anhydrides into maleic imides (under identical conditions) has been previously reported.[9,19] Alternatively, the ring-transformation may proceed by acid-mediated attack of ammonia onto the exocyclic double bond to give intermediate **C**, ring cleavage (intermediate **D**), and subsequent acid-mediated recyclization by attack of the enamine nitrogen atom onto the carboxylic acid group. The need of using glacial acetic acid can be explained by acid-mediated activation of the lactone and the ester group during the formation of intermediates **A** and **C**, respectively. In addition, the acid presumably plays an important role in the cyclization step by activation of the carbonyl and the carboxylic acid group of intermediates **B** and **D**, respectively. Last but not the least, the acid facilitates the extrusion of water in the final step of the reaction.

The reaction of **12a** with methylammonium chloride in glacial acetic acid afforded a separable mixture of *Z*-**13b** (17%) and *E*-**13b** (40%) (Scheme 7, Table 1). Starting with isobutylamine and cyclohexylamine, products **13c** and **13d** were isolated, respectively. Both products were formed as separable mixtures of *E*/*Z*-isomers. The loss of the stereoselectivity in favour of the *Z*-configured isomer can be explained (a) by the fact that an intramolecular hydrogen bond cannot be formed (due to the absence of a hydrogen atom located at the nitrogen) and (b) by the competing steric influence of the methoxy group (located at carbon C-4 of the pyrrol-2-one) and of the alkyl group attached to the nitrogen atom. Upon standing, pure *Z*-**13b** undergoes a slow isomerization to give a mixture of *E*-**13b** and *Z*-**13b** (ratio 1:3). Pure *Z*-**13c** slowly rearranges to a mixture *E*-**13c**/*Z*-**13c**=2:3. Pure *E*-**13d** slowly rearranges to a mixture *E*-**13d**/*Z*-**13d**=5:1.



Scheme 7. Synthesis of **13b–d**.

The cyclization of diene **7b**, prepared from ethyl 4-(benzyloxy)-acetoacetate, with oxalyl chloride gave butenolide **8b**,[22] which was transformed (via **12b**) into the *Z*-configured 5-alkylidene-2,5-dihydropyrrol-2-one **13e** (Scheme 8).

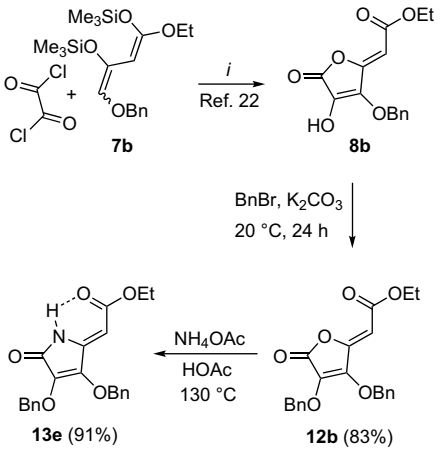
The cyclization of diene **7c**, prepared from methyl 3-oxopentanoate, with oxalyl chloride afforded butenolide **8c**,[22] which was transformed into the benzylated derivative **12c** (Scheme 9). The reaction of the latter with ammonium acetate gave the *Z*-configured 5-alkylidene-2,5-dihydropyrrol-2-one **13f**, which was subsequently transformed into the deprotected derivative **14f**. The reaction of **12c** with methylammonium chloride afforded a separable mixture of *Z*-**13g** and *E*-**13g**. Upon standing, pure *E*-**13g** undergoes a slow isomerization to give a mixture of *Z*-**13g** and *E*-**13g** (ratio 1:1).

The cyclization of diene **7d**, prepared from methyl acetoacetate, with oxalyl chloride gave butenolide **8d**,[22] which was transformed into the benzyl-protected derivative **12d** (Scheme 10). The reaction of **12d** with methylammonium chloride gave the *E*-configured 5-alkylidene-2,5-dihydropyrrol-2-one **13h**, which was subsequently

Table 1
Synthesis of **13b–d**

Compound **13**	R	% (*Z*)[a]	% (*E*)[a]
b	Me	17	40
c	*i*-Bu	25	40
d	*c*-Hex	40	30

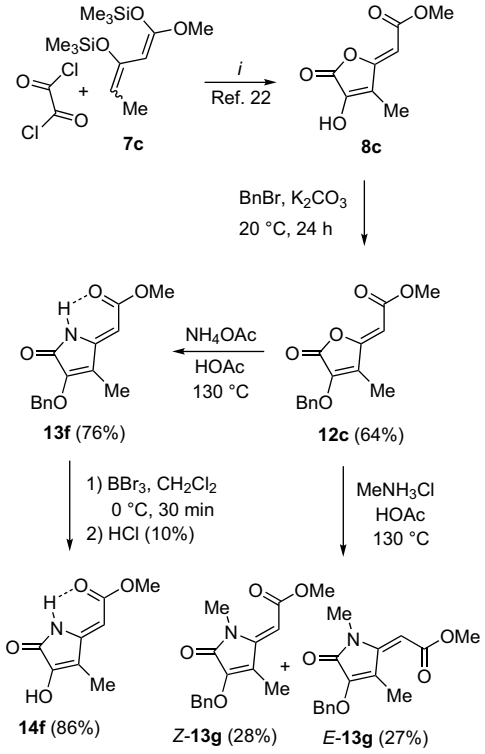
[a] Isolated yields of pure *E*/*Z*-isomers.



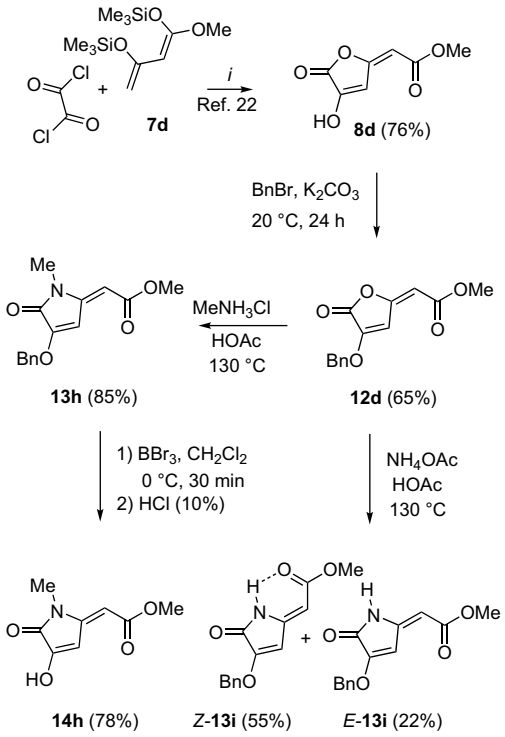
Scheme 8. Synthesis of **13e**. Conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C.

deprotected to give **14h**. The *E*-diastereoselective formation of **8d** can be explained by the higher thermodynamic stability of the *E*-compared to the *Z*-configured butenolide. The selective formation of *E*-configured pyrrol-2-one **13h** is a result of the steric effect of the methyl group located at the nitrogen atom and the absence of a substituent located at carbon C-4. The reaction of **12d** with ammonium acetate afforded a separable mixture of *Z*-**13i** and *E*-**13i**. Upon standing, the *E*-isomer underwent a slow isomerization into the *Z*-isomer. The higher stability of the latter can be explained by the presence of the intramolecular hydrogen bond N–H···O.

We have recently reported the synthesis of butenolide **16** by Suzuki reaction of triflate **15a** with phenylboronic acid (Scheme 11).[23] The reaction of **16** with NH_4OAc afforded the 5-alkylidene-2,5-dihydropyrrol-2-one **17** as a separable mixture of *E*/*Z*-isomers. Due to the formation of an N–H···O hydrogen bond, the *Z*-isomer

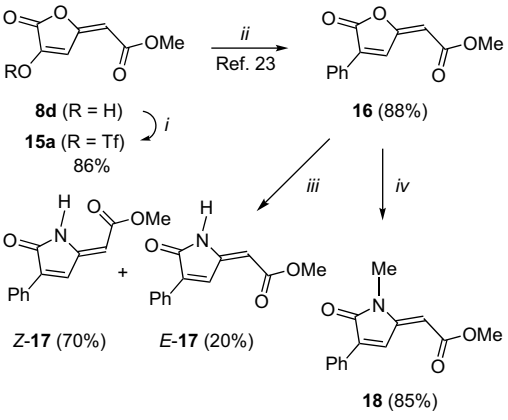


Scheme 9. Synthesis of **14f** and **13g**. Conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C.



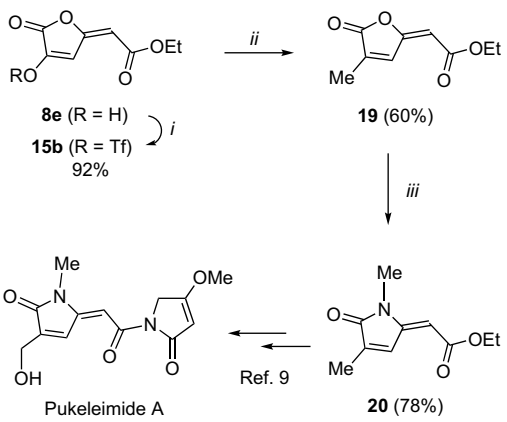
Scheme 10. Synthesis of **14h** and **13i**. Conditions: (i) Me_3SiOTf (0.3 equiv), CH_2Cl_2, −78→20 °C.

was the major product. It is worth to be noted that no isomerization of *E*-**17** was observed upon standing. This result suggests that the presence of an oxygen atom located at carbon atom C3 of the pyrrol-2-one results in a decrease of the energetic barrier of the isomerization process. Treatment of **16** with $MeNH_3Cl$ gave the *E*-configured product **18** in 85% yield. Like in the case of **13h**, the *E*-diastereoselectivity is a result of the steric effect of the methyl group located at the nitrogen atom and of the absence of a substituent located at carbon C-4.



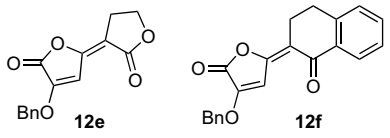
Scheme 11. Synthesis of 5-alkylidene-2,5-dihydropyrrol-2-ones **17** and **18**. Conditions (i) Tf_2O, pyridine, −78 °C→−10 °C; (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, reflux; (iii) $MeNH_3Cl$, AcOH, 130 °C, 12 h; (iv) NH_4OAc, AcOH, 130 °C, 12 h.

Triflate **15b** was prepared from butenolide **8e** (Scheme 12). The Stille reaction of **15b** with $SnMe_4$, using our recently published protocol,[24] was unsuccessful. In contrast, the Suzuki reaction of **15b** with methylboronic acid afforded the desired butenolide **19** in good yield. Treatment of **19** with $MeNH_3Cl$ afforded the *E*-configured 5-alkylidene-2,5-dihydropyrrol-2-one **20** (33% over four steps from oxalyl chloride). Pattenden and co-workers earlier reported the synthesis of this product from methylmaleic anhydride (two steps, 24% yield) and its transformation into pukeleimide A.[9]



Scheme 12. Synthesis of an intermediate of the Pattenden synthesis of pukeleimide A: (i) Tf_2O, pyridine, −78 °C→−10 °C; (ii) $MeB(OH)_2$, $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, reflux; (iii) $MeNH_3Cl$, HOAc, 140 h, 130 °C.

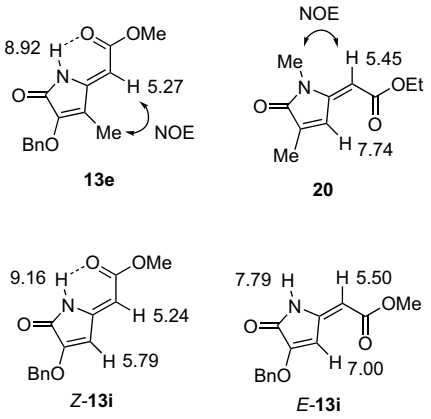
The scope of the ring-transformation seems to be limited to β-ketoester-derived butenolides containing a hydrogen atom located at the exocyclic double bond. In fact, all attempts to transform benzylated butenolide **12e** into the corresponding 5-alkylidene-2,5-dihydropyrrol-2-one (by reaction with ammonium acetate) failed (Scheme 13). Likewise, the reaction of ammonium acetate with **12f**, derived from 2-acetyltetralone, failed.



Scheme 13. Starting materials **12e**,**f**.

The configuration of the exocyclic double bond of the 5-alkylidene-2,5-dihydropyrrol-2-ones was established by spectroscopic methods (NOESY experiments and chemical shift analyses). For example, the NOSEY-spectrum of **13e** shows an interaction between the methyl group attached to carbon atom C-4 of the pyrrol-2-one and proton H-1′ located at the exocyclic double bond (Scheme 14). In case of **20**, an NOE interaction is observed between the protons located at the exocyclic double bond (H-1′) and at the pyrrol-2-one moiety (H-4).

Some general trends are observed for the chemical shifts of 5-alkylidene-2,5-dihydropyrrol-2-ones. The NH proton involved in an



Scheme 14. Characteristic NOE-interactions and chemical shifts.

Table 2
Characteristic chemical shifts

Compound	Config.	$\delta_{H\text{-}1'}$[a]	δ_{NH}[b]	$\delta_{H\text{-}4}$[c]
13a	*Z*	5.44	8.48	—
E-**13b**	*E*	5.54	—	—
Z-**13b**	*Z*	5.46	—	—
E-**13c**	*E*	5.54	—	—
Z-**13c**	*Z*	5.45	—	—
E-**13d**	*E*	5.50	—	—
Z-**13d**	*Z*	5.62	—	—
13e	*Z*	5.49	8.48	—
13f	*Z*	5.27	8.92	—
E-**13g**	*E*	5.46	—	—
Z-**13g**	*Z*	5.29	—	—
13h	*E*	5.45	—	6.98
E-**13i**	*E*	5.50	7.79	7.00
Z-**13i**	*Z*	5.24	9.16	5.79
E-**17**	*E*	5.63	br	8.24
Z-**17**	*Z*	5.43	9.18	7.12
18	*E*	5.58	—	8.25
20	*E*	5.45	—	7.74

[a] Proton located at the exocyclic double bond ($CDCl_3$).
[b] Proton NH ($CDCl_3$).
[c] Proton located at carbon C-4 of the pyrrol-2-one moiety ($CDCl_3$).

intramolecular hydrogen bond is significantly shifted downfield with respect to the signal of the NH group of the other isomer. For example, the signal of the NH group of *Z*-**13i** appears at δ=9.16 ppm whereas the respective signal of *E*-**13i** appears at δ=7.79 ppm (Scheme 14, Table 2). Proton H-4 of *E*-configured pyrrol-2-ones is considerably shifted downfield with respect to the respective signal of the *Z*-configured isomers. For example, the signal of proton H-4 of *E*-**13i** appears at δ=7.00 ppm whereas the respective signal of *Z*-**13i** appears at δ=5.79 ppm. In addition, proton H-1′ attached to the exocyclic double bond of *E*-configured pyrrol-2-ones is slightly shifted downfield with respect to the respective signal of the *Z*-configured isomers. For example, the signal of proton H-1′ of *E*-**13i** appears at δ=5.50 ppm whereas the respective signal of *Z*-**13i** appears at δ=5.24 ppm.

In conclusion, we have reported the synthesis of a variety of 5-alkylidene-2,5-dihydropyrrol-2-ones by reaction of γ-alkylidene-butenolides with amines in glacial acetic acid. The butenolides are readily available by cyclization of 1,3-bis(silyloxy)-1,3-butadienes with oxalyl chloride. The configuration of the exocyclic double bond of the products depends on the substitution pattern of the products. A *Z*-configuration is generally observed for pyrrol-2-ones containing an NH group, due to formation of an intramolecular hydrogen bond. An *E*-configured exocyclic double bond is selectively formed for products containing an alkyl group located at the nitrogen atom and a hydrogen located at carbon C-4 of the pyrrol-2-one (due to the steric effect of the *N*-alkyl group). Isomeric mixtures are formed for pyrrol-2-ones containing substituents located at both the nitrogen atom *and* at carbon C-4. In many cases, the pure minor component undergoes a slow isomerization upon standing in solution. These results suggest that the *E*/*Z*-diastereoselectivity is presumably thermodynamically controlled.

3. Experimental section

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used.

3.2. 3-Amino-4-methoxy-5-[*E*-(methoxycarbonylmethylidene)]-pyrrol-2-one (11)

A solution of **8a** (350 mg, 1.75 mmol, 1.0 equiv) and ammonium acetate (680 mg, 8.75 mmol, 5.0 equiv) in glacial acetic acid (5 mL) was heated under reflux for 10 h. The solvent was removed in vacuo and the residue was purified by chromatography (silica gel, hexanes/EtOAc=1:1) to give **11** as a yellow solid (90 mg, 23%), mp 124–126 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3416(s), 3343 (s), 2275 (s), 3199 (m), 2952 (m), 1728 (s), 1707 (s), 1676 (s), 1676 (s), 1644 (s), 1607 (s), 1439 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.69 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.95 (br s, 2H, NH_2), 5.37 (s, 1H, CH), 8.62 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.5, 59.7 (OCH_3), 90.8 (CH), 122.5, 134.2, 146.7 (C), 166.6, 167.7 (C=O). MS (EI, 70 eV): *m*/*z* (%)=198 ($[M]^+$, 95), 183 (13), 166 (62), 150 (100), 123 (26), 95 (38), 69 (49). HRMS (EI, 70 eV): calcd for $C_8H_{10}N_2O_4$: 198.0641; found: 198.0641± 2 ppm. Anal. Calcd for $C_8H_{10}N_2O_4$ (198.18): C 48.48, H 5.09, N 14.14. Found: C 48.65, H 5.19, N 12.29.

3.3. 3-Benzyloxy-4-methoxy-5-[*Z*-(methoxycarbonylmethylidene)]-2-furanone (12a)

To a suspension of K_2CO_3 (3.93 g, 28.4 mmol, 2.0 equiv) in acetone (60 mL) were added **8a** (2.84 g, 14.2 mmol, 1.0 equiv) and benzylbromide (2.41 g, 1.7 mL, 14.2 mmol, 1.0 equiv) at 20 °C. After stirring for 24 h, the solid formed was filtered off and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc=10:1→4:1) to give **12a** as a colourless solid (2.40 g, 62%), mp=126–128 °C. R_f=0.20 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2954(w), 1794 (s), 1729 (s), 1721 (s), 1673 (s), 1466 (m), 1443 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.78 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2Ph), 5.50 (s, 1H, CH), 7.40 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.9, 59.6 (OCH_3), 74.0 (CH_2Ph), 95.8 (CH), 124.2 (C), 128.8, 128.96, 128.99 (CH, Ph), 135.2, 148.5, 150.7 (C), 163.3, 163.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=290 ($[M]^+$, 12), 262 (4), 244 (1), 219 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{14}O_6$: 290.0790; found: 290.0790±2 ppm. Anal. Calcd for $C_{15}H_{14}O_6$ (290.27): C 62.07, H 4.86. Found: C 61.90, H 5.51.

3.4. 3,4-Dibenzyloxy-5-[*Z*-(ethoxycarbonylmethylidene)]-2-furanone (12b)

The reaction was carried out by application of the procedure given for the synthesis of **12a**. Starting with K_2CO_3 (760 mg, 5.5 mmol, 2.0 equiv), **8b** (760 mg, 2.75 mmol, 1 equiv) and benzylbromide (470 mg, 0.3 mL, 2.75 mmol, 1.0 equiv) in acetone (15 mL), **12b** was isolated by chromatography (silica gel, hexane/EtOAc=10:1→3:1) as a colourless oil (840 mg, 83%). R_f=0.65 (hexane/EtOAc=3:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2985(w), 1789 (s), 1721 (s), 1661 (s), 1590 (w), 1458 (m), 1416 (w). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.29 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 4.22 (q, ^3J=7.1 Hz, 2H, CH_2CH_3), 5.24 (s, 2H, CH_2Ph), 5.25 (s, 2H, CH_2Ph), 5.56 (s, 1H, CH), 7.22 (m, 5H, Ph), 7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.1 (CH_2CH_3), 60.8 (CH_2CH_3), 73.4 (CH_2Ph), 73.9 (CH_2Ph), 96.2 (CH), 124.5 (C), 127.6, 128.6, 128.73, 128.76, 128.86, 128.91 (Ph, CH), 135.01, 135.27, 147.33, 150.72 (C), 163.08, 163.20 (C=O). MS (EI, 70 eV): *m*/*z* (%)=380 ($[M]^+$, 1), 205 (4), 159 (5), 91 (100), 66 (19). HRMS (EI, 70 eV): calcd for $C_{22}H_{20}O_6$: 380.1260; found: 380.1260±2 ppm. Anal. Calcd for $C_{22}H_{20}O_6$ (380.39): C 69.46, H 5.30. Found: C 64.43, H 5.64.

3.5. 3-Benzyloxy-4-methyl-5-[*Z*-(methoxycarbonylmethylidene)]-2-furanone (12c)

The reaction was carried out by application of the procedure given for the synthesis of **12a**. Starting with K_2CO_3 (1.50 g, 10.9 mmol, 2.0 equiv), **8c** (1.00 g, 5.45 mmol, 1.0 equiv) and benzylbromide

(0.93 g, 1.1 mL, 5.45 mmol, 1 equiv) in acetone (20 mL), **12c** was isolated by chromatography (silica gel, hexane/EtOAc=1:0→4:1) as a yellow solid (0.95 g, 64%), mp=108–110 °C. R_f=0.40 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1792(s), 1696 (s), 1641 (s), 1457 (w), 1436 (m), 1405 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.90 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 5.30 (s, 1H, CH), 5.49 (s, 2H, CH_2Ph), 7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=7.5 (CH_3), 51.2 (OCH_3), 72.7 (CH_2Ph), 96.2 (CH), 128.1 (C), 128.2, 128.72, 128.73 (CH, Ph), 135.7, 144.3, 156.4 (C), 162.6, 163.8 (C=O). MS (EI, 70 eV): *m*/*z* (%)=274 ($[M]^+$, 2), 246 (1), 213 (1), 190 (2), 91 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{14}O_6$: 274.0841; found: 274.0841±2 ppm. Anal. Calcd for $C_{15}H_{14}O_6$ (274.27): C 65.69, H 5.15. Found: C 65.98, H 5.61.

3.6. 3-Benzyloxy-5-[*E*-(methoxycarbonylmethylidene)]-2-furanone (12d)

The reaction was carried out by application of the procedure given for the synthesis of **12a**. Starting with K_2CO_3 (830 mg, 6.0 mmol, 2.0 equiv), **8d** (510 mg, 3.0 mmol, 1 equiv) and benzylbromide (513 mg, 0.6 mL, 3.0 mmol, 1 equiv) in acetone (10 mL), **12d** was isolated (silica gel, hexane/EtOAc=10:1→3:1) as a yellow solid (510 mg, 65%), mp=133–135 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1812(s), 1716 (s), 1654 (s), 1617 (s), 1457 (w), 1441 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.77 (s, 3H, OCH_3), 5.16 (s, 2H, CH_2Ph), 5.75 (s, 1H, CH), 7.29 (s, 1H, ring-CH), 7.42 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.7 (CH_3), 74.2 (CH_2Ph), 99.1 (CH), 107.9 (ring-CH), 128.0, 128.8, 129.1 (CH, Ph), 133.6, 150.8, 159.1 (C), 162.3, 166.2 (C=O). MS (EI, 70 eV): *m*/*z* (%)=260 ($[M]^+$, 4), 229 (1), 204 (1), 170 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{14}H_{12}O_5$: 260.0685; found: 260.0685±2 ppm. Anal. Calcd for $C_{14}H_{12}O_5$ (260.24): C 64.61, H 4.65. Found: C 64.04, H 5.35.

3.7. 4-Benzyloxy-4′,5′-dihydro-[2,3′]bifuranylidene-5,2′-dione (12e)

The reaction was carried out by application of the procedure given for the synthesis of **12a**. Starting with K_2CO_3 (330 mg, 2.4 mmol, 2.0 equiv), 4-hydroxy-4′,5′-dihydro-[2,3′]bifuranylidene-5,2′-dione (219 mg, 1.2 mmol, 1.0 equiv) and benzylbromide (205 mg, 0.1 mL, 1.2 mmol, 1.0 equiv) in acetone (5 mL), **12e** was isolated by chromatography (silica gel, hexane/EtOAc=4:1) as a yellow solid (50 mg, 15%), mp=174–176 °C. R_f=0.25 (hexane/EtOAc=3:1). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.17 (t, ^3J=7.2 Hz, 2H, $-CH_2-$, 4-H), 4.46 (t, ^3J=7.2 Hz, 2H, $-CH_2-$, 5-H), 5.15 (s, 2H, CH_2Ph), 7.33 (s, 1H, CH), 7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.7 (C-4), 65.9 (C-5), 74.2 (CH_2Ph), 104.6 (C), 107.1 (CH), 128.0, 128.8, 129.1 (CH, Ph), 133.6, 149.4, 153.0 (C), 162.3, 170.3 (C=O). MS (EI, 70 eV): *m*/*z* (%)=272 ($[M]^+$, 1), 189 (1), 204 (2), 91 (100).

3.8. 3-Benzyloxy-5-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-2-furanone (12f)

The reaction was carried out by application of the procedure given for the synthesis of **12a**. Starting with K_2CO_3 (276 mg, 2.0 mmol, 2.0 equiv), 3-hydroxy-5-(1-oxo-3,4-dihydro-1*H*-naphthalen-2-ylidene)-2-furanone (218 mg, 0.9 mmol, 1.0 equiv) and benzylbromide (154 mg, 0.1 mL, 0.9 mmol, 1.0 equiv) in acetone (5 mL), **12f** was isolated by chromatography (silica gel, hexane/EtOAc=20:1) as a yellow solid (50 mg, 17%), mp=186–188 °C. R_f=0.25 (hexane/EtOAc=20:1). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.89 (m, 2H, $-CH_2-$, 3-H), 3.07 (m, 2H, $-CH_2-$, 4-H), 5.15 (s, 2H, CH_2Ph), 7.30 (m, 8H, Ar–H), 7.48 (dt, ^3J=7.4 Hz, ^4J=1.4 Hz, 1H, Ar–H), 7.57 (s, 1H, CH), 8.05 (dd, ^3J=7.8 Hz, ^4J=1.3 Hz, 1H, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.1 (C-3), 28.3 (C-4), 73.8 (CH_2Ph), 110.1 (CH), 116.0 (C), 127.0, 127.6, 127.9, 128.4, 128.7, 128.9, 133.5 (CH, Ar), 133.9, 143.3, 143.3, 150.6, 152.5 (C), 162.7, 187.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=332 ($[M]^+$, 3), 304 (16), 276 (5), 114 (8), 91 (100). HRMS (EI, 70 eV): calcd for $C_{21}H_{16}O_4$: 332.1049; found: 332.1049±2 ppm.

3.9. 3-Benzyloxy-4-methoxy-5-[*Z*-(methoxycarbonylmethylidene)]-pyrrol-2-one (13a)

Butenolide **12a** (292 mg, 1.0 mmol, 1.0 equiv) and ammonium acetate (385 mg, 5.0 mmol, 5.0 equiv) were dissolved in glacial acetic acid (5 mL) and the solution was stirred under reflux for 20 h. The solution was cooled to 20 °C and EtOAc was added. The mixture was washed several times with an aqueous solution of sodium bicarbonate until the organic layer was neutral. The combined aqueous layers were three times washed with EtOAc. The combined organic layers were dried (Na_2SO_4). The solution was filtered and the solvent of the filtrate was removed in vacuo to give **13a** as a colourless solid (280 mg, 96%), mp=102–104 °C. R_f=0.25 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3401(br w), 3332 (s), 3263 (w), 3257 (w), 3036 (w), 3003 (w), 2953 (m), 2928 (w), 2859 (w), 1733 (s), 1702 (s), 1674 (s), 1451 (s), 1414 (w). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.75 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2Ph), 5.44 (s, 1H, CH), 7.37 (m, 5H, Ph), 8.48 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.6, 59.4 (OCH_3), 74.2 (CH_2Ph), 92.6 (CH), 127.3 (C), 128.6, 128.6, 128.7 (CH, Ph), 136.0, 144.4, 144.5 (C), 166.3, 167.3 (C=O). MS (EI, 70 eV): *m*/*z* (%)=289 ($[M]^+$, 6), 261 (3), 170 (3), 109 (5), 91 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}NO_5$: 289.0950; found: 289.0950±2 ppm. Anal. Calcd for $C_{15}H_{15}NO_5$ (289.28): C 62.28, H 5.23, N 4.84. Found: C 62.51, H 5.60, N 4.55.

3.10. 3-Benzyloxy-4-methoxy-5-[*E*/*Z*-(methoxymethylidene)]-*N*-methylpyrrol-2-ones (*E*-13b) and (*Z*-13b)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **12a** (58 mg, 0.2 mmol, 1.0 equiv) and methylammonium chloride (68 mg, 1.0 mmol, 5.0 equiv) and AcOH (2 mL), *E*-**13b** (25 mg, 40%) and *Z*-**13b** (11 mg, 17%) were isolated by chromatography (silica gel, hexane/EtOAc=10:1→4:1) as yellow solids.

*3.10.1. Compound E-**13b***

Mp=83–85 °C. R_f=0.55 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2950(w), 1723 (s), 1679 (s), 1637 (s), 1460 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.30 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2Ph), 5.54 (s, 1H, CH), 7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=29.5 (NCH_3), 51.8 (OCH_3), 59.7 (OCH_3), 74.4 (CH_2Ph), 95.2 (CH), 125.8 (C), 128.7, 128.8, 128.9 (CH, Ph), 136.4, 143.3, 145.2 (C), 165.4, 167.5 (C=O). MS (EI, 70 eV): *m*/*z* (%)=303 ($[M]^+$, 32), 272 (5), 215 (8), 156 (6), 91 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_{17}NO_5$: 303.1107; found: 303.1107±2 ppm. Anal. Calcd for $C_{16}H_{17}NO_5$ (303.31): C 63.36, H 5.65, N 4.62. Found: C 63.04, H 5.77, N 5.44.

*3.10.2. Compound Z-**13b***

Mp 87–89 °C. R_f=0.25 (hexane/EtOAc=4:1). ^1H NMR ($CDCl_3$, 300 MHz): δ=3.02 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.28 (s, 2H, CH_2Ph), 5.46 (s, 1H, CH), 7.38 (m, 5H, CH_2Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.0 (NCH_3), 52.0 (OCH_3), 60.0 (OCH_3), 74.2 (CH_2Ph), 98.9 (CH), 128.5, 128.6, 128.7 (CH, Ph), 129.3, 136.2, 141.5, 143.7 (C), 165.1, 165.8 (C=O). MS (EI, 70 eV): *m*/*z* (%)=303 ($[M]^+$, 5), 272 (1), 243 (1), 215 (2), 91 (100). HRMS (EI, 70 eV): calcd for $C_{16}H_{17}NO_5$: 303.1107; found: 303.1107±2 ppm. Pure *Z*-**13b** rearranges to a mixture *E*-**13b**/*Z*-**13b**=1:3 upon standing.

3.11. 3-Benzyloxy-4-methoxy-5-[*E*/*Z*-(methoxycarbonylmethylidene)]-*N*-isobutyl-pyrrol-2-ones (*E*-13c) and (*Z*-13c)

To glacial acetic acid (4 mL) was slowly added isobutylamine (252 mg, 0.4 mL, 2.5 mmol, 5.0 equiv) at 0 °C. To the solution

was added **12a** (146 mg, 0.5 mmol, 1.0 equiv) and the solution was stirred for 20 h under reflux. After cooling to 20 °C, EtOAc was added and the mixture was repeatedly washed with a saturated aqueous solution of sodium bicarbonate until the organic layer was neutral. The combined aqueous layers were extracted three times with EtOAc and the combined organic layers were dried (Na_2SO_4). The solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc=5:1) to give *E*-**13c** as a yellow solid (70 mg, 40%) and *Z*-**13c** as a yellow oil (43 mg, 25%).

*3.11.1. Compound E-**13c***

Mp=69–71 °C. R_f=0.45 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2956(m), 1724 (s), 1680 (s), 1635 (s), 1456 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ=0.82 (d, ^3J=6.7 Hz, 6H, CH_3, $CH(CH_3)_2$), 1.76 (m, 1H, $CH(CH_3)_2$), 3.71 (s, 3H, OCH_3), 3.85 (d, ^3J=7.5 Hz, 2H, NCH_2), 3.89 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2Ph), 5.54 (s, 1H, CH), 7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=19.5 (CH_3), 27.7 ($CH(CH_3)_2$), 47.9 (NCH_2), 51.7, 59.4 (OCH_3), 74.1 (CH_2Ph), 95.1 (CH), 124.8 (C), 128.49, 128.50, 128.8 (CH, Ph), 136.1, 141.0, 145.1 (C), 165.1, 167.5 (C=O). MS (EI, 70 eV): *m*/*z* (%)=345 ($[M]^+$, 9), 314 (1), 302 (1), 257 (1), 226 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{19}H_{23}NO_5$: 345.1576; found: 345.1576±2 ppm. Anal. Calcd for $C_{19}H_{23}NO_5$ (345.39): C 66.07, H 6.71, N 4.06. Found: C 66.00, H 8.29, N 4.11.

*3.11.2. Compound Z-**13c***

R_f=0.25 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3065(w), 3032 (m), 2957 (s), 2872 (m), 1709 (s), 1675 (s), 1638 (s), 1496 (m), 1461 (s), 1440 (s), 1415 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ=0.90 (d, ^3J=6.7 Hz, 6H, CH_3, $CH(CH_3)_2$), 1.94 (m, 1H, $CH(CH_3)_2$), 3.32 (d, ^3J=7.6 Hz, 2H, NCH_2), 3.73 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.29 (s, 2H, CH_2Ph), 5.45 (s, 1H, CH), 7.35 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=19.6 (CH_3), 27.5 ($CH(CH_3)_2$), 46.0 (NCH_2), 51.9, 59.8 (OCH_3), 73.9 (CH_2Ph), 98.9 (CH), 124.8 (C), 128.42, 128.43, 128.6 (CH, Ph), 136.2, 140.4, 143.5 (C), 165.3, 165.8 (C=O). MS (EI, 70 eV): *m*/*z* (%)=345 ($[M]^+$, 23), 314 (1), 257 (1), 226 (1), 197 (2), 91 (100). Anal. Calcd for $C_{19}H_{23}NO_5$ (345.39): C 66.07, H 6.71, N 4.06. Found: C 66.03, H 6.93, N 3.87. Pure *Z*-**13c** slowly rearranges to *E*-**13c**/*Z*-**13c**=2:3 upon standing.

3.12. 3-Benzyloxy-4-methoxy-5-[*E*/*Z*-(methoxymethylidene)]-*N*-cyclohexyl-2-pyrrolidones (*Z*-13d) and (*E*-13d)

The reaction was carried out by application of the procedure given for the synthesis of **13c**. Starting with **12a** (116 mg, 0.4 mmol), cyclohexylamine (198 mg, 0.2 mL, 2.0 mmol) and AcOH (3.5 mL), chromatographic purification (silica gel, hexane/EtOAc=20:1→5:1) afforded *Z*-**13d** as a yellow solid (60 mg, 40%) and *E*-**13d** as a yellow oil (45 mg, 30%).

*3.12.1. Compound Z-**13d***

Mp=66–68 °C. R_f=0.65 (hexane/EtOAc=3:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2942(m), 2856 (w), 1725 (s), 1706 (s), 1684 (s), 1633 (s), 1442 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.26–2.22 (m, 10H, $-CH_2-$), 3.74 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.18 (m, 1H, NCH), 5.23 (s, 2H, CH_2Ph), 5.50 (s, 1H, CH), 7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.3, 26.3, 30.2 (CH_2), 51.7 (NCH), 57.0 (OCH_3), 59.4 (OCH_3), 74.1 (CH_2Ph), 94.4 (CH), 125.5 (C), 128.46, 128.51, 128.7 (CH, Ph), 136.2, 143.1, 144.8 (C), 165.4, 168.0 (C=O). MS (EI, 70 eV) *m*/*z* (%)=371 ($[M]^+$, 5), 340 (1), 289 (2), 280 (2), 230 (2), 91 (100). HRMS (EI, 70 eV): calcd for $C_{21}H_{25}NO_5$: 371.1733; found: 371.1733±2 ppm.

*3.12.2. Compound E-**13d***

R_f=0.4 (hexane/EtOAc=3:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2334(m), 2856 (m), 1724 (s), 1705 (s), 1642 (s), 1639 (s), 1452 (m), 1441 (m), 1406 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.28–2.07 (m, 10H, $-CH_2-$), 3.65 (m, 1H, NCH), 3.74 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.25 (s, 2H, CH_2Ph), 5.62 (s, 1H, CH), 7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.2, 26.3, 30.1 (CH_2), 52.0 (NCH), 52.5 (OCH_3), 59.8 (OCH_3), 74.0 (CH_2Ph), 99.0 (CH), 128.1 (C), 128.4, 128.5, 128.7 (CH, Ph), 136.37, 138.97, 143.32 (C), 165.30, 166.49 (C=O). MS (EI, 70 eV): *m*/*z* (%)=371 ($[M]^+$, 4), 340 (1), 315 (1), 289 (1), 252 (1), 230 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{21}H_{25}NO_5$: 371.1733; found: 371.1733±2 ppm. *E*-**13d** slowly rearranges to *Z*-**13d**/*E*-**13d**=1:5 upon standing.

3.13. 3,4-Dibenzyloxy-5-[*Z*-(ethoxycarbonylmethylidene)]-pyrrol-2-one (13e)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **12b** (540 mg, 1.40 mmol) and ammonium acetate (550 mg, 7.10 mmol), **13e** was isolated without further purification as a yellow solid (490 mg, 91%), 122–124 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3412(br), 3388 (br), 3302 (m), 1724 (s), 1697 (s), 1664 (s), 1651 (s), 1459 (m), 1416 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.28 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 4.20 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 5.16 (s, 2H, CH_2Ph), 5.27 (s, 2H, CH_2Ph), 5.49 (s, 1H, CH), 7.25–7.39 (m, 10H, Ph), 8.48 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=14.1 (CH_2CH_3), 60.8 (CH_2CH_3), 73.4, 74.3 (CH_2Ph), 93.5 (CH), 127.8 (CH, Ph), 128.1 (C), 128.7, 128.8, 128.9, 129.0 (CH, Ph), 136.1, 136.4, 143.4, 144.7 (C), 166.3, 167.2 (C=O). MS (EI, 70 eV): *m*/*z* (%)=379 ($[M]^+$, 4), 333 (1), 288 (3), 273 (3), 227 (2), 199 (3), 91 (100). HRMS (EI, 70 eV): calcd for $C_{22}H_{21}NO_5$: 379.1420; found: 379.1420±2 ppm. Anal. Calcd for $C_{22}H_{21}NO_5$ (379.41): C 69.88, H 5.58, N 3.69. Found: C 69.88, H 6.20, N 3.95.

3.14. 3-Benzyloxy-4-methyl-5-[*Z*-(methoxycarbonyl-methylidene)]-pyrrol-2-one (13f)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **12c** (250 mg, 0.90 mmol) and ammonium acetate (350 mg, 4.50 mmol), **13f** was isolated by chromatography (silica gel, hexane/EtOAc=10:1) as a yellow solid (188 mg, 76%), mp 118–120 °C. R_f=0.5 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3401(br), 3341 (s), 1732 (s), 1696 (s), 1647 (s), 1582 (w), 1447 (m), 1410 (m). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.84 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 5.27 (s, 1H, CH), 5.51 (s, 2H, CH_2Ph), 7.34 (m, 5H, Ph), 8.92 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=7.1 (CH_3), 51.6 (OCH_3), 72.5 (CH_2Ph), 93.2 (CH), 121.1 (C), 128.0, 128.4, 128.5 (CH, Ph), 136.7, 147.6, 149.6 (C), 165.5, 167.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=273 ($[M]^+$, 5), 267 (1), 244 (4), 216 (1), 195 (1), 167 (2), 91 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.1001±2 ppm.

3.15. 3-Benzyloxy-4-methyl-5-[*E*/*Z*-(methoxycarbonyl-methylidene)]-*N*-methyl-pyrrol-2-ones (*Z*-13g) and (*E*-13g)

Starting with **12c** (250 mg, 0.90 mmol) and methylammonium chloride (304 mg, 4.50 mmol), chromatographic purification (silica gel, hexane/EtOAc=10:1) afforded *Z*-**13g** (70 mg, 27%) and *E*-**13g** (72 mg, 28%) as colourless solids.

*3.15.1. Compound Z-**13g***

Mp 102–104 °C. R_f=0.60 (hexane/EtOAc=4:1). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.84 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 5.29 (s, 1H, CH), 5.46 (s, 2H, CH_2Ph), 7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=7.5 (CH_3), 29.9 (NCH_3), 51.6 (OCH_3), 72.5 (CH_2Ph), 96.3 (CH), 123.1 (C), 128.0, 128.3, 128.5 (CH, Ph), 136.8, 145.9, 148.3 (C), 165.3, 166.5 (C=O). MS (EI, 70 eV): *m*/*z* (%)=287 ($[M]^+$, 20), 258 (4), 228 (1), 196 (1), 164 (1), 91 (100).

*3.15.2. Compound E-**13g***

Mp 108–110 °C. R_f=0.55 (hexane/EtOAc=4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.11 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 5.46 (s, 1H, CH), 5.50 (s, 2H, CH_2Ph), 7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=10.7 (CH_3), 23.5 (NCH_3), 51.6 (OCH_3), 72.5 (CH_2Ph), 96.5 (CH), 121.4 (C), 128.0, 128.2, 128.5 (CH, Ph), 136.9, 149.0, 149.2 (C), 164.1, 165.7 (C=O). MS (EI, 70 eV): *m*/*z* (%)=287 ([M]$^+$, 18), 258 (3), 165 (1), 139 (1), 91 (100). Pure *E*-**13g** rearranges to *Z*-**13g**/*E*-**13g**=1:1.

3.16. 3-Benzyloxy-5-[*E*-(methoxycarbonylmethylidene)]-*N*-methyl-pyrrol-2-one (13h)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **12d** (78 mg, 0.30 mmol) and methylammonium chloride (135 mg, 1.50 mmol), **13h** was isolated by chromatography (silica gel, hexane/EtOAc=3:1) as a slightly yellow solid (70 mg, 85%), mp=117–119 °C. R_f=0.5 (hexane/EtOAc=4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.10 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 5.11 (s, 2H, CH_2Ph), 5.45 (s, 1H, CH), 6.98 (s, 1H, CH), 7.38 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=25.7 (NCH_3), 51.4 (OCH_3), 73.0 (CH_2Ph), 96.2 (CH), 100.8 (CH), 127.9, 128.61, 128.62 (CH, Ph), 134.4, 150.9, 153.4 (C), 164.1, 166.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=273 ([M]$^+$, 48), 244 (44), 241 (12), 213 (4), 195 (5), 91 (100). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}NO_4$: 273.1001; found: 273.1001±2 ppm.

3.17. 3-Benzyloxy-5-[*E*/*Z*-(methoxycarbonylmethylidene)]-pyrrol-2-ones (*Z*-13i) and (*E*-13i)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **12d** (91 mg, 0.35 mmol) and ammonium acetate (135 mg, 1.75 mmol), chromatographic purification (silica gel, hexane/EtOAc=4:1) afforded *Z*-**13i** (50 mg, 55%) and *E*-**13i** (20 mg, 22%) as colourless solids.

*3.17.1. Compound Z-**13i***

Mp=139–141 °C. R_f=0.30 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3358(br s), 2952 (w), 1752 (s), 1734 (s), 1683 (s), 1649 (s), 1620 (s), 1587 (s), 1442 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.75 (s, 3H, OCH_3), 5.10 (s, 2H, CH_2Ph), 5.24 (s, 1H, CH), 5.79 (s, 1H, CH), 7.40 (m, 5H, Ph), 9.16 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=51.8 (OCH_3), 73.5 (CH_2Ph), 96.1 (CH), 103.5 (CH-ring), 128.0, 129.96, 128.97 (CH, Ph), 134.5, 148.3, 153.9 (C), 164.8, 167.7 (C=O). MS (EI, 70 eV): *m*/*z* (%)=259 ([M]$^+$, 24), 230 (30), 227 (6), 203 (1), 169 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{14}H_{13}NO_4$: 259.0845; found: 259.0845±2 ppm.

*3.17.2. Compound E-**13i***

Mp 136–138 °C. R_f=0.2 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3307(m), 1747 (s), 1699 (s), 1639 (s), 1617 (s), 1447 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.75 (s, 3H, OCH_3), 5.13 (s, 2H, CH_2Ph), 5.50 (s, 1H, CH), 7.00 (s, 1H, CH), 7.38 (m, 5H, Ph), 7.79 (m, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.6 (OCH_3), 73.3 (CH_2Ph), 98.5 (CH), 102.3 (CH), 128.1, 128.7, 128.8 (CH, Ph), 134.3, 147.8, 154.0 (C), 165.2, 166.7 (C=O). MS (EI, 70 eV): *m*/*z* (%)=259 ([M]$^+$, 4), 230 (6), 203 (1), 167 (1), 149 (1), 91 (100). HRMS (EI, 70 eV): calcd for $C_{14}H_{13}NO_4$: 259.0845; found: 259.0845±2 ppm. *E*-**13i** slowly rearranges to *Z*-**13i**/*E*-**13i**=1:3.

3.18. 3-Phenyl-5-[*E*-(methoxycarbonylmethylidene)]-2-furanone (16)

The synthesis of **16** was carried out as previously reported.[23]

3.19. 3-Methyl-5-[*E*-(ethoxycarbonylmethylidene)]-2-furanone (19)

The synthesis was carried out by application of the procedure reported earlier.[23] Starting with **15b** (790 mg, 2.50 mmol), methylboronic acid (195 mg, 3.25 mmol), $Pd(PPh_3)_4$ (85 mg, 0.08 mmol) and potassium phosphate (850 mg, 4.00 mmol), **19** was isolated by chromatography (silica gel, hexane/EtOAc=20:1) as a colourless solid (275 mg, 60%), mp=51–53 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997(w), 1787 (s), 1742 (m), 1703 (s), 1654 (s), 1622 (s), 1439 (w). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.33 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 2.10 (d, ^4J=1.5 Hz, 3H, CH_3), 4.25 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 5.82 (s, 1H, CH), 8.02 (d, ^4J=1.5 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=11.1, 14.2 (CH_3), 60.9 (CH_2), 100.7 (CH), 135.4 (C), 135.9 (CH), 159.6 (C), 165.2, 169.0 (C=O). MS (EI, 70 eV): *m*/*z* (%)=182 ([M]$^+$, 12), 154 (16), 137 (100), 124 (4), 110 (16), 98 (8). HRMS (EI, 70 eV): calcd for $C_9H_{10}O_4$: 182.0579; found: 182.0579±2 ppm. Anal. Calcd for $C_9H_{10}O_4$ (182.17): C 59.34, H 5.53. Found: C 59.24, H 5.94.

3.20. 3-Phenyl-5-methoxycarbonylmethylidene-pyrrol-2-ones (*Z*-17) and (*E*-17)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **16** (51 mg, 0.22 mmol) and ammonium acetate (68 mg, 0.88 mmol) in glacial acetic acid (2 mL) (12 h, reflux), chromatographic purification (silica gel, hexane/EtOAc=10:1) afforded *Z*-**17** (35 mg, 70%) and *E*-**17** (10 mg, 20%) as colourless solids. The compounds were labile and readily decomposed.

*3.20.1. Compound Z-**17***

Mp=128–130 °C. R_f=0.5 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3408(br m), 3346 (s), 2952 (w), 1712 (s), 1693 (s), 1651 (s), 1443 (s), 1409 (m). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.81 (s, 3H, OCH_3), 5.43 (s, 1H, CH), 7.12 (d, ^4J=1.6 Hz, 1H, CH), 7.43 (m, 3H, Ph), 7.93 (m, 2H, Ph), 9.18 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.8 (OCH_3), 97.3 (CH), 127.1 (C), 127.7, 128.7, 129.6 (CH, Ph), 129.9 (CH), 137.4, 148.4 (C), 167.4, 170.0 (C=O). MS (EI, 70 eV): *m*/*z* (%)=229 ([M]$^+$, 100), 230 ([M+1]$^+$, 15), 231 ([M+2]$^+$, 1), 198 (64), 171 (16), 114 (6). HRMS (EI, 70 eV): calcd for $C_{13}H_{11}NO_3$: 229.0739; found: 229.0739±2 ppm.

*3.20.2. Compound E-**17***

Mp=164–166 °C. R_f=0.4 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3418(br m), 3319 (w), 3294 (w), 2923 (w), 1700 (s), 1643 (s), 1444 (w), 1412 (w). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.80 (s, 3H, OCH_3), 5.63 (d, ^4J=0.6 Hz, 1H, CH), 7.43 (m, 3H, Ph), 7.99 (m, 2H, Ph), 8.24 (d, ^4J=0.6 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=51.7 (OCH_3), 99.7 (CH), 127.8, 127.9, 128.7 (CH, Ph), 130.0 (CH), 130.2, 137.6, 148.2 (C), 166.3, 170.3 (C=O). MS (EI, 70 eV): *m*/*z* (%)=229 ([M]$^+$, 66), 198 (96), 171 (31), 148 (25), 141 (14), 128 (13), 114 (33), 102 (28), 91 (47), 77 (17). HRMS (EI, 70 eV): calcd for $C_{13}H_{11}NO_3$: 229.0739; found: 229.0739±2 ppm.

3.21. 3-Phenyl-5-[*E*-(methoxycarbonylmethylidene)]-*N*-methyl-pyrrol-2-one (18)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **16** (45 mg, 0.20 mmol) and methylammonium chloride (54 mg, 0.80 mmol) in glacial acetic acid (2 mL) (12 h, reflux), **18** was isolated by chromatography (silica gel, hexane/EtOAc=10:1) as a yellow solid (42 mg, 85%), mp=108–110 °C. The compound was unstable and readily decomposed. R_f=0.6 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2951(w), 2924 (m), 1711 (s), 1632 (s), 1441 (w). ^{1}H NMR ($CDCl_3$ $CDCl_3$, 300 MHz): δ=3.18 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 5.58 (d, ^4J=0.5 Hz, 1H, CH), 7.43 (m, 3H, Ph), 7.98 (m, 2H, Ph), 8.25 (d, ^4J=0.5 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=26.0 (NCH_3), 51.8 (OCH_3), 98.1 (CH), 127.0, 128.0, 128.9 (CH, Ph), 130.0 (ring-CH), 130.6, 136.9, 151.3 (C), 166.6, 169.4 (C=O). MS (EI, 70 eV): *m*/*z* (%)=243 ([M]$^+$, 100), 212 (75), 183 (53), 155 (20), 114 (18), 102 (14), 82 (20). HRMS (EI, 70 eV): calcd for $C_{14}H_{13}NO_3$: 243.0895; found:

243.0895±2 ppm. Anal. Calcd for $C_{14}H_{13}NO_3$ (243.26): C 69.12, H 5.39, N 5.76. Found: C 69.13, H 6.64, N 5.09.

3.22. 3-Methyl-5-[*E*-(ethoxycarbonylmethylidene)]-*N*-methyl-pyrrol-2-one (20)

The reaction was carried out by application of the procedure given for the synthesis of **13a**. Starting with **19** (50 mg, 0.28 mmol) and methylammonium chloride (74 mg 1.10 mmol) in glacial acetic acid (2 mL) (140 h, reflux), **20** was isolated by chromatography (silica gel, hexane/EtOAc=5:1) as a colourless solid (42 mg, 78%), mp 122–124 °C. R_f=0.35 (hexane/EtOAc=4:1). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3403(br w), 3072 (w), 2984 (m), 2930 (m), 2878 (m), 2854 (m), 1703 (s), 1638 (s), 1479 (m), 1443 (m), 1442 (m). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.34 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 2.02 (d, ^4J=1.8 Hz, 3H, CH_3), 3.09 (s, 3H, NCH_3), 4.24 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 5.45 (s, 1H, CH), 7.74 (d, ^4J=1.8 Hz, 1H, ring-CH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=11.3, 14.5 (CH_3), 26.0 (NCH_3), 60.6 (CH_2), 97.6 (CH), 129.3 (CH-ring), 137.6, 151.7 (C), 166.1, 171.0 (C=O). MS (EI, 70 eV): *m*/*z* (%)=195 ($[M]^+$, 100), 196 ($[M+1]^+$, 12), 180 (1), 167 (3), 150 (95), 136 (6), 123 (32). HRMS (EI, 70 eV): calcd for $C_{10}H_{13}NO_3$: 195.0895; found: 195.0895±2 ppm. Anal. Calcd for $C_{10}H_{13}NO_3$ (195.21): C 61.53, H 6.71, N 7.18. Found: C 62.76, H 6.90, N 6.44.

3.23. 3-Hydroxy-4-methoxy-5-[*Z*-(methoxycarbonyl-methylidene)]-pyrrol-2-one (14a)

To a dichloromethane solution (2 mL) of **13a** (51 mg, 0.18 mmol) was added a dichloromethane solution of boron tribromide (175 mg, 0.70 mmol) at 0 °C. After stirring for 30 min at 0 °C, hydrochloric acid (5 mL, 1 M) was added. The organic and the aqueous layers were separated and the latter was extracted three times with dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel: column size: 2.0×3.0 cm, hexane/EtOAc=1:1→1:4) to give **14a** as a yellow solid (32 mg, 91%), mp 128–130 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3313(br m), 3270 (br m), 2958 (w), 2924 (m), 1733 (s), 1692 (s), 1655 (s), 1462 (w), 1440 (m). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.76 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 5.54 (s, 1H, CH), 8.54 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=52.0, 59.3 (OCH_3), 94.3 (CH), 126.1, 136.5, 145.3 (C), 167.4, 167.6 (C=O). MS (EI, 70 eV): *m*/*z* (%)=199 ($[M]^+$, 48), 167 (100), 151 (65), 124 (26), 112 (3), 96 (9). HRMS (EI, 70 eV, ESI-HRMS): calcd for $C_8H_{10}NO_5$ $[M+H]^+$: 200.05535; found: 200.05541; calcd for $C_8H_9NO_5Na$ $[M+Na]^+$: 222.03729; found: 222.03738.

3.24. 3-Hydroxy-4-methyl-5-[*Z*-(methoxycarbonyl-methylidene)]-pyrrol-2-one (14f)

rrThe reaction was carried out by application of the procedure given for the synthesis of **14a**. Starting with **13f** (100 mg, 0.37 mmol) and boron tribromide (366 mg, 1.48 mmol), **14f** was isolated by chromatography (silica gel, column size: 2.0×3.0 cm, hexane/EtOAc=10:1→1:4) as a slightly yellow solid (58 mg, 86%), mp 117–119 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3323(s), 3241 (s), 3050 (s), 1732 (s), 1705 (s), 1690 (s), 1650 (s), 1440 (s), 1420 (s). ^{1}H NMR (acetone-d_6, 300 MHz): δ=1.90 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 5.33 (s, 1H, CH), 9.12 (br s, 1H, NH). ^{13}C NMR (acetone-d_6, 150 MHz): δ=6.7 (CH_3), 51.7 (OCH_3), 93.0 (CH), 113.6, 148.0, 152.2 (C), 166.4, 168.3 (C=O). MS (EI, 70 eV): *m*/*z* (%)=183 ($[M]^+$, 100), 184 ($[M+1]^+$, 8), 167 (1), 151 (72), 123 (12). HRMS (EI, 70 eV): calcd for $C_8H_9NO_4$: 183.0532; found: 183.0532±2 ppm. Anal. Calcd for $C_8H_9NO_4$ (183.16): C 52.46, H 4.95, N 7.65. Found: C 52.50, H 5.19, N 7.26.

3.25. 3-Trifluormethansulfonyloxy-5-[*E*-(methoxycarbonyl-methylidene)]-2-furanone (15a)

The synthesis of **15a** was carried out as previously reported.[23]

3.26. 3-Trifluormethansulfonyloxy-5-[*E*-(ethoxycarbonyl-methylidene)]-2-furanone (15b)

The synthesis was carried out by application of the procedure reported earlier.[23] Starting with **8e** (1.29 g, 7.0 mmol), pyridine (1.11 g, 1.1 mL, 14.0 mmol) and Tf_2O (2.37 g, 1.4 ml, 8.4 mmol) in dichloromethane (70 mL), **15b** was isolated (2.20 g, 92%) as a colourless solid, mp=38–40 °C. R_f=0.8 (dichloromethane). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3418(w), 3378 (w), 3326 (w), 3317 (w), 3313 (w), 3301 (w), 3264 (w), 3261 (w), 3257 (w), 3225 (w), 3144 (m), 3080 (w), 2997 (m), 2947 (w), 2913 (w), 1814 (s), 1748 (s), 1718 (s), 1661 (s), 1619 (s), 1438 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.34 (t, ^3J=7.2 Hz, 3H, CH_2CH_3), 4.29 (q, ^3J=7.2 Hz, 2H, CH_2CH_3), 6.09 (d, ^4J=0.65 Hz, 1H, CH), 8.23 (d, ^4J=0.65 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$, 150 MHz): δ=14.3 (CH_2CH_3), 61.9 (CH_2CH_3), 107.2 (CH), 118.7 (q, J=319.5 Hz, CF_3), 125.6 (CH-ring), 140.7, 155.1 (C), 159.5, 164.3 (C=O). MS (EI, 70 eV): *m*/*z* (%)=316 ($[M]^+$, 4), 288 (3), 271 (10), 247 (3), 207 (20), 180 (3), 69 (100). HRMS (EI, 70 eV): calcd for $C_9H_7F_3O_7S$: 315.9865; found: 315.9865±2 ppm. Anal. Calcd for $C_9H_7F_3O_7S$ (316.21): C 34.19, H 2.23. Found: C 33.91, H 2.27.

3.27. 3-Hydroxy-5-[*E*-(methoxycarbonylmethylidene)]-*N*-methyl-pyrrol-2-one (14h)

The reaction was carried out by application of the procedure given for the synthesis of **14a**. Starting with **13h** (109 mg, 0.40 mmol) and boron tribromide (401 mg, 1.60 mmol), **14h** was isolated by chromatography (silica gel, column size: 2.0×3.0 cm, hexane/EtOAc=10:1→1:4) as a yellow solid (57 mg, 78%), mp 88–90 °C. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3186(m), 3169 (m), 3067 (w), 2957 (w), 1735 (s), 1679 (s), 1638 (s), 1626 (s), 1447 (s). ^{1}H NMR (acetone-d_6, 300 MHz): δ=3.09 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 5.52 (s, 1H, CH), 6.86 (s, 1H, CH), 9.92 (br s, 1H, OH). ^{13}C NMR (acetone-d_6, 75 MHz): δ=26.5 (NCH_3), 52.1 (OCH_3), 96.9 (CH), 102.3 (CH), 153.2, 153.3 (C), 166.3, 167.8 (C=O). MS (EI, 70 eV): *m*/*z* (%)=183 ($[M]^+$, 56), 152 (60), 127 (8), 112 (5), 95 (8), 91 (30), 82 (100). HRMS (EI, 70 eV): calcd for $C_8H_9NO_4$: 183.0532; found: 183.0532±2 ppm. Anal. Calcd for $C_8H_9NO_4$ (183.16): C 52.46, H 4.95, N 7.65. Found: C 52.43, H 4.57, N 7.33.

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