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Synthesis of Hetero Atom Modified Pyrromethenones

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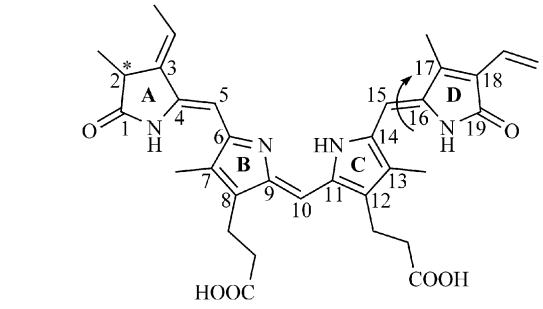
A series of six heteroaromatic compounds, ethyl-/methyl- and dimethylfuranones, thiophenones, and cyclopentenones, was synthesized and condensed with a methyl methylpropionate substituted pyrrole, yielding the "right" half of open-chain tetrapyrroles. These compounds serve as light-inducible chromophores in the plant photoreceptor phytochrome. Three-dimensional structure analysis of the 10-oxapyrromethen-1-one **25** revealed a planar conformation, similar to the dipyrromethenone parent compound, stabilized by a hydrogen bond formed between the pyrrole proton and the furanone oxygen atom. All six pyrrole-substituted heteroaromatic derivatives **25**–**30** show absorbances in the visible spectrum with high molar extinction coefficients.

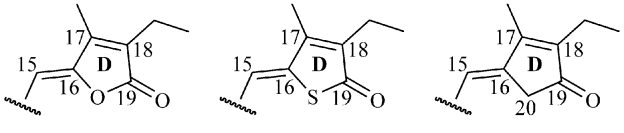
Introduction

Abbreviations: BR: bilirubin, BV: biliverdin, PCB: phycocyanobilin, PEB: phycoerythrobilin, PΦB: Phytochromobilin, P_r, P_{fr}: red-, far-red absorbing forms of plant photoreceptor phytochrome.

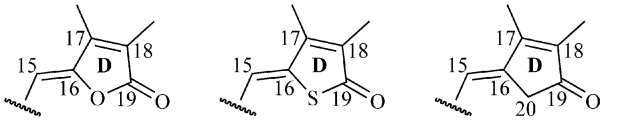
Bile pigments like biliverdin and bilirubin and their derivatives, e.g. phycocyanobilin, phycoerythrobilin or phytochromobilin (PΦB, **1**) are compounds which are ubiquitous in all living organisms (see Figure 1). On the one hand, they represent intermediates in the metabolism of heme groups[1] and on the other hand, they are important light-detecting chromophores in many biological photoreceptors. In particular their photobiological importance as chromophores of light-harvesting antenna in photosynthetic organisms[2] and their role as chromophores in the plant and bacterial light-sensing phytochromes[3,4] has raised much interest in modified bilin compounds. In contrast to their biochemical generation (via oxidative cleavage of heme groups), the highly variable substitution pattern represents great challenge for chemists working in the field of synthesis. Many efforts have been reported to synthesize the original compounds as well as some substitutent-modified open-chain tetrapyrroles.[5–9] We are mainly interested in the role of these compounds as chromophores in phytochromes.[10,11] Recently, a three-dimensional structure of the chromophore-binding domain of a bacterial phytochrome has been reported which demonstrates the stunning number of interactions between chromophore and protein.[12] This network of hydrogen bonds and polar and electrostatic interactions keeps the tetrapyrrole moiety in a bent conformation and allows one to understand why ring D of the chromophore (see Figure 1) selectively undergoes a *Z*/*E* double bond photoisomerization as the primary response to incident light ("P_r-to-P_{fr}" photoconversion).[13,14] Since the D-ring is not substituted by very polar groups, but only



1 (PΦB)



2 **4** **6**



3 **5** **7**

Figure 1. Kekulé formula of phytochromobilin (PΦB, **1**) in its *ZZZ*,*asa* state. The photoisomerization of the C(15)–C(16) double bond is indicated by an arrow. Additionally, the novel, structurally modified chromophores **2**–**7** are mapped.

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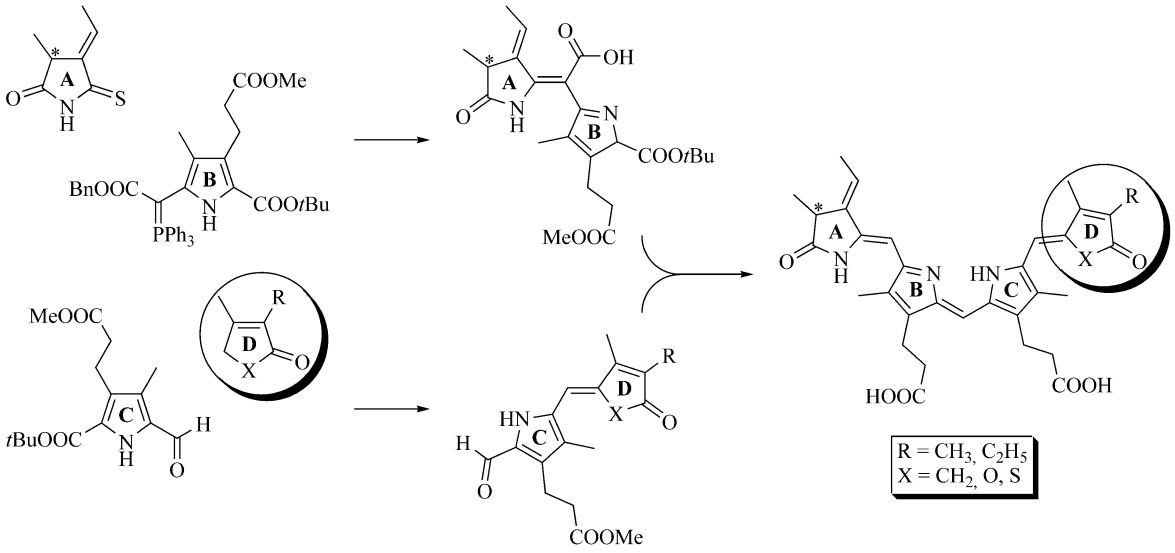

Figure 2. Preparation of novel ring-D-modified chromophores **2**–**7** following the convergent synthesis-strategy of open-chain tetrapyrroles established by Gossauer et al.[6;15]

by a methyl, a vinyl (or ethyl) and the carbonyl function, the pyrrole nitrogen atom might play an important role in fixing the conformation of this ring in both P_r- and P_{fr}-form. We therefore report here on the synthesis of modified pyrromethenones as ring-C,D building blocks for open-chain tetrapyrroles in which the N atom of ring D (N10 in pyrromethene; nomenclature according to the complete bilin chromophores) is replaced by an oxygen or a sulfur atom, or a methylene group (see Figure 2). Since according to the established convergent synthesis[6,15] the "left" and the "right" half of an open-chain tetrapyrrole are synthesized separately, and as the final reaction the central coupling is performed, we report here on the hetero atom-modified "right halves" of novel tetrapyrroles.

Results and Discussion

Syntheses

Synthesis of 3-Ethyl-4-methyl- (10) and 3,4-Dimethylfuranones (11):[16] Ethyl (*R*,*S*)-2-bromobutyrate was converted by Reformatsky reaction into its Zn derivative and allowed to react with acetoxyacetone to yield lactone **8** in 38%. Elimination of acetic acid upon the addition of TosH·H_2O gave furanone **10** in an overall yield of 22%. The same reaction, using ethyl (*R*,*S*)-2-bromopropionate led to furanone **9** (26%, Figure 3).

Synthesis of 3-Ethyl-4-methyl- (14) and 3,4-Dimethylthiophenones (15):[17] Thiophenones **14** and **15** were synthesized (Figure 4) from the same starting material (3-methylthiophene). Oxidation yielded a mixture of methyl thiophenones **12** and **13** in a ratio of 22.5:77.5 (yield of 18 and 62%, respectively). Both compounds could be separated by chromatography. Treatment of **13** with either ethyl or methyl iodide yielded the target compounds **14** and **15** in 33 and 37%, respectively.

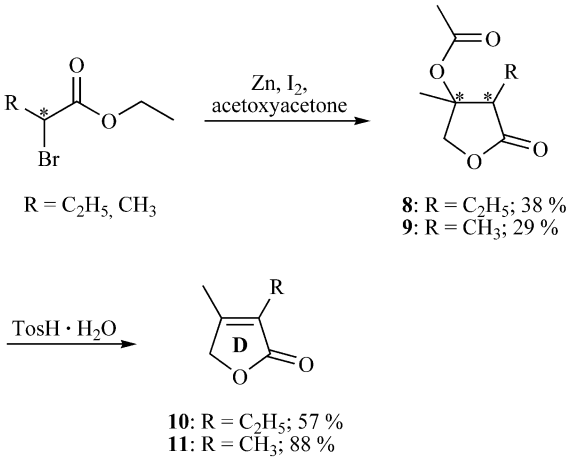

Figure 3. Synthesis of the furanones **10** and **11** according to DeGraw.[16]

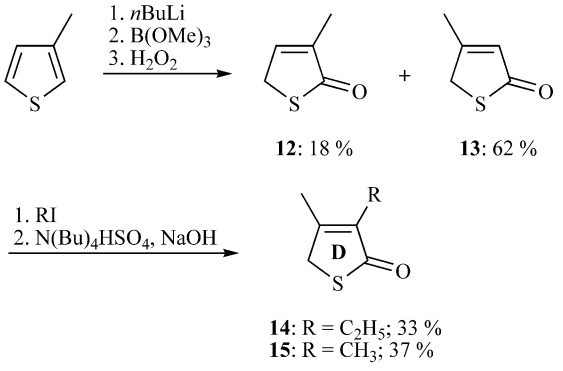

Figure 4. Synthesis of the thiophenones **14** and **15** according to Kiesewetter et al.[17]

Synthesis of 3-Ethyl-2-methyl-4-(diethoxyphosphoryl)- (22) and 2,3-Dimethyl-4-(diethoxyphosphoryl)cyclopentenones (23): 2-Ethyl-4-hydroxy-3-methylcyclopent-2-en-1-

one (**18**) and its 2,3-dimethyl derivative **19** were synthesized starting from ethyl 3-oxohexanoate or methyl 3-oxopentanoate (Figure 5). Each of these compounds was allowed to react with pyruvaldehyde, yielding racemic 3-hydroxy-2,5-dioxooctane (**16**) or -heptane (**17**), respectively.[18–20] Intramolecular condensation reaction to the hydroxycyclopentenones **18** and **19**, respectively, was successful in 47 and 50% yield. The hydroxy substituents were transiently converted into the chlorides **20** and **21**, from which phosphonates **22** and **23** were obtained in an Michaelis–Arbuzov reaction with triethyl phosphite. The generation of phosphonates was assumed to be required in order to direct reactivity to the 4-position of the novel cyclopentenones. While the furanones **10**, **11** and the thiophenones **14**, **15** are supposed to react with the C-ring building block utilizing the acidic protons in the unsubstituted α-position, in the case of the cyclopentenones the α-position with respect to the carbonyl group (C-5) is considered the most reactive part in the molecule for the anticipated Knoevenagel reaction.

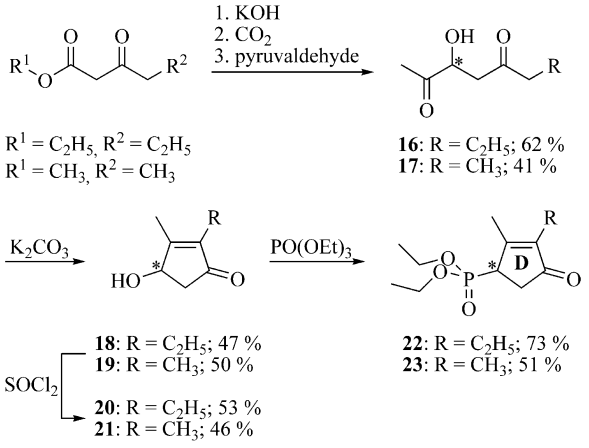

Figure 5. Synthesis of the cyclopentenones **22** and **23**.

Condensation of Furanones, Thiophenones, and Cyclopentenones 10, 11, 14, 15, 22, and 23 with the C-Ring Building Block 24: The generation of the "right" half of the tetrapyrrole derivatives was accomplished by condensation of the novel furanones, thiophenones, and cyclopentenones with the C-ring building block **24**. As mentioned above, the furanones and thiophenones reacted via their acidic proton at the unsubstituted α-position with the aldehyde function of ring C (Figure 6),[21] whereas the condensation of the cyclopentenones could be performed in a Horner–Emmons reaction. In all six cases, excellent to moderate yields were observed for the remarkably stable products **25**–**30**.

Three-Dimensional Structure of 25

The three-dimensional structure of some of the novel structures **25**–**30** could be determined. Compound **25**, for example, forms highly defracting crystals that allow three-dimensional structure determination (Figure 7). The crystal structure (resolution 0.7 Å) reveals a nearly planar arrangement of both rings. The small torsion angle C(6)–C(5)–N–H of –3.39° is probably the result of a hydrogen bond that is formed between the pyrrole N–H atom and the lone electron pair of the furan oxygen. Both atoms show a distance of 2.24 Å which is considerably smaller than the sum of their van der Waals radii (2.60 Å) and thereby a strong argument for the assumed hydrogen bond. Additional evidence for a direct interaction between these two atoms can be deduced from the IR and the ^{1}H NMR spectra. The position of the N–H stretching vibration band for an unsubstituted pyrrole building block is found at 3324 cm^{-1}, whereas for **25** in which, as proposed, a hydrogen bond for-

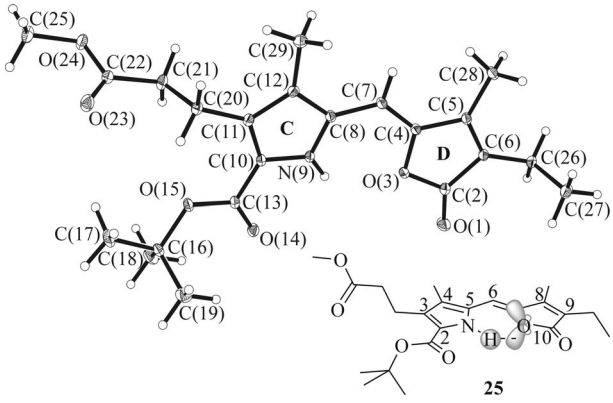

Figure 7. X-ray crystal structure (resolution 0.7 Å) and Kekulé formula of the pyrromethen-furanone **25**. Due to the intramolecular hydrogen bond between the 1s orbital of the pyrrole hydrogen atom and the sp^3 hybrid orbital of the furanone oxygen atom the C(6)–C(7) double bond shows *Z* configuration while the C(5)–C(6) single bond shows *syn* conformation.

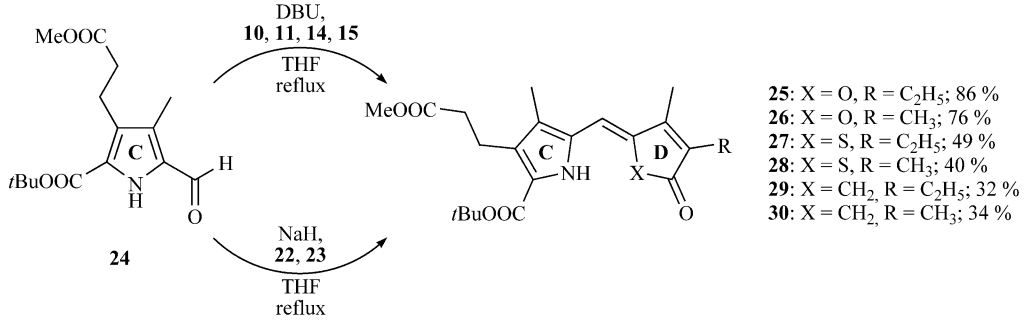

Figure 6. Synthesis of the ring-C,D units **25**–**30** by Knoevenagel[21] or Horner–Emmons reaction.

mation would be possible, this band shifts to higher energy (3448 cm^{-1}), indeed indicative of the formation of a hydrogen bond. A similar conclusion can be drawn from the ^1H NMR spectroscopic data: whereas the signal of the pyrrole hydrogen atom in the unformylated precursor of **24** is found at 8.8 ppm, it is shifted upon formylation (compound **24**) to lower field (δ = 9.4 ppm), and experiences an additional downfield shift in the furanone **25** to 9.7 ppm. All these NMR measurements were performed under identical conditions, allowing a direct comparison of the chemical shifts obtained (see also Exp. Section).

UV/Vis Absorption Properties of Compounds 25–30

Condensation of the novel five-membered ring compounds with the pyrrole **24** generates an extended π-electron system. Comparison of the absorbance maxima for **25**–**30** reveals the effect of the oxygen, sulfur, or carbon (as methylene group) on the π-electron system compared to the parent pyrromethenone (Figure 6, X = NH). All novel compounds show characteristic absorption spectra with a peak in the UV region and a more intense, structured band in the visible range. The highest extinction coefficients for this long-wavelength band is found for both furanones **25** and **26** with 48100 $M^{-1} cm^{-1}$ (389 nm) and 44400 $M^{-1} cm^{-1}$ (387 nm). The thiophenones and also the cyclopentenone derivatives show lower extinction coefficients: 21800 $M^{-1} cm^{-1}$ (401 nm) and 29300 $M^{-1} cm^{-1}$ (400 nm) for the thiophenones **27** and **28**, respectively, and 27800 $M^{-1} cm^{-1}$ (369 nm) and 21400 $M^{-1} cm^{-1}$ (368 nm) for the cyclopentenone derivatives **29** and **30** (see Table 1) (Figure 8). Compared to the data from the dipyrromethenone (Figure 6, X = NH), 25500 $M^{-1} cm^{-1}$ (393 nm), the auxochromic effect of the hetero atom is clearly seen by a monotonous increase of the absorption maxima (369–389–393–401 nm).

Table 1. UV/Vis absorption parameters for the compounds **25**–**30** (all values were determined in *n*-hexane).

Substance	λ_{max} [nm] (ε [$M^{-1} cm^{-1}$])		
25	254 (32000)	389 (48100)	409 (45200)
26	254 (30400)	387 (44400)	407 (41100)
27	267 (12900)	401 (21800)	419 (21300)
28	267 (16700)	400 (29300)	418 (29100)
29	253 (23500)	369 (27800)	388 (19600)
30	252 (15500)	368 (21400)	387 (17700)

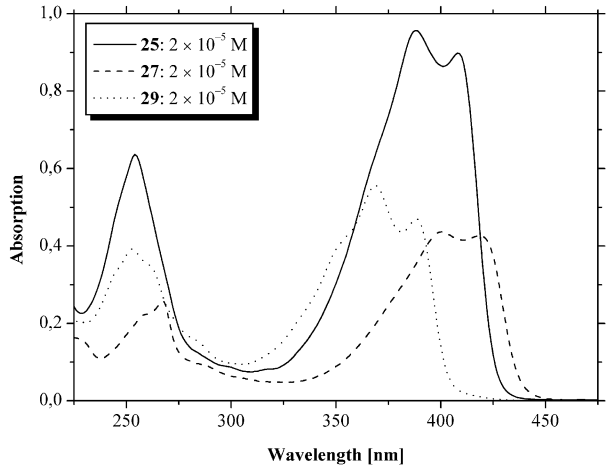

Figure 8. UV/Vis absorption spectra of selected furanone- (**25**), thiophenone- (**27**), and cyclopentenone-substituted (**29**) ring-C,D building blocks (*n*-hexane).

Conclusion

Aza-, thia- and carba-analogues of pyrromethenone were synthesized in order to serve as building blocks for the planned construction of open-chain tetrapyrroles with different hetero atoms in the D-ring moiety. Crystal structure analysis revealed that the two-ring building blocks adapt the same configuration and conformation as the all-N parent compound. Since bilins serve as chromophores in plant photoreceptor phytochrome, the changed reactivity of D-ring-modified systems will reveal new insight into the chromophore-protein interactions that are essential for the function of biological photoreceptors.

Experimental Section

General Methods: Column chromatographical purifications were performed on Merck silica gel 60 (230–400 mesh) under slightly increased pressure. HPLC: Purifications were carried out on Kromasil C18 ODS-5–100 columns (RP-C_{18}, 5 μm, 250 mm × 21 mm) at a flow rate of 0.8 mL min^{-1}. NMR: Spectra were recorded on Bruker ARX 250, DRX 400, or DRX 500 spectrometers in $CDCl_3$; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. The solvent signals were used as references and the chemical shifts converted into the TMS scale ($CDCl_3$: δ_C = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δ_H = 7.24 ppm). IR: Perkin–Elmer System 2000 spectrometer; wavenumbers $\tilde{\nu}$ are given. UV/Vis: Shimadzu UV-2401 PC spectrometers; the solvents applied were of appropriated quality (Uvasol). MS (EI): Finnigan MAT 8200, or MAT 8400 (70 eV). ESI-MS: Bruker Esquire 3000, or HP Quadrupol MS Engine; accurate mass determinations (HRMS): Finnigan MAT 95. Melting points: Reichert melting point microscope (uncorrected).

Although the nomination of the ring-C,D building blocks **25**–**30** correlates to the IUPAC rules, for prudential reasons, the assignment of the hydrogen and carbon atoms for NMR analysis follows the Kekulé formula displayed in Figure 7.

4-Ethyl-3-methyl-5-oxotetrahydrofuran-3-yl Acetate (8): A suspension of acetoxyacetone (27.5 mL, 254.6 mmol), zinc powder (20.0 g, 305.9 mmol) and a catalytic amount of iodine in benzene (300 mL) was refluxed under argon with vigorous stirring. Within 45 min ethyl (*R*,*S*)-2-bromobutyrate (41.4 mL, 280.2 mmol) was added in such a way that simmering was maintained. The dispersion was refluxed for additional 45 min, cooled externally with ice, then mixed with ice/water (200 mL). After addition of hydrochloric acid (60 mL, 6 M), the slurry was stirred until two almost clear phases had formed. These were separated and the aqueous phase was extracted with diethyl ether (2 × 75 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (100 mL) and dried with Na_2SO_4. Evaporation of the solvent yielded the

crude product (28.53 g) which was purified by fractional distillation in vacuo. The product **8** was obtained as a mixture of its stereoisomers (17.90 g, 96.1 mmol, 38%) in the form of a yellowish liquid, b.p. 124–126 °C (4.4 mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.12 (m, 3 H, 4^2-CH_3), 1.54–1.82 (m, 2 H, 4^1-CH_2), 1.48 (s, 1.1 H, 3^1-CH_3), 1.64 (s, 1.9 H, 3^1-CH_3), 1.98 (s, 1.7 H, acetoxy CO_2CH_3), 1.99 (s, 1.3 H, acetoxy CO_2CH_3), 2.21 (t, ^3J = 6.83 Hz, 1.9 H, 4-C*H*), 2.65 (t, ^3J = 7.20 Hz, 1.1 H, 4-C*H*), 4.06 (d, A′B′ system, $J_{A'B'}$ = 10.82 Hz, 0.6 H, 2-C$H_{A'}$), 4.26 (d, A′′B′′ system, $J_{A''B''}$ = 9.96 Hz, 0.4 H, 2-C$H_{A''}$), 4.42 (d, A′′B′′ system, $J_{A''B''}$ = 9.98 Hz, 0.4 H, 2-C$H_{B''}$), 4.72 (d, A′B′ system, $J_{A'B'}$ = 10.83 Hz, 0.6 H, 2-C$H_{B'}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 11.94 (d, $^1J_{C,H}$ = 59.49 Hz, C-4^2), 17.58 (d, $^1J_{C,H}$ = 44.71 Hz, C-4^1), 18.57 (acetoxy CO_2CH_3), 21.44 (d, $^1J_{C,H}$ = 15.65 Hz, C-3^1), 51.02 (d, $^1J_{C,H}$ = 159.81 Hz, C-4), 73.29 (C-2), 83.49 (d, $J_{C,H}$ = 6.29 Hz, C-3), 170.06 (d, $J_{C,H}$ = 4.75 Hz, acetoxy CO_2CH_3), 175.98 (d, $J_{C,H}$ = 129.88 Hz, C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2972, 2940, 2881, 1783, 1740, 1458, 1371, 1258, 1231, 1149, 1133, 1023, 946 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 158 (3), 144 (5), 126 (14), 113 (2), 99 (3), 98 (3), 86 (4), 71 (8), 70 (9), 67 (5), 58 (2), 45 (3), 43 (100), 41 (22), 40 (3), 39 (12).

3-Ethyl-4-methylfuran-2(5*H*)-one (10): A mixture of the lactone **8** (7.46 g, 51.7 mmol) and 4-toluenesulfonic acid monohydrate (0.29 g, 1.5 mmol) was heated under argon at 150 °C for 19 h such that slight reflux was observable. The accrued dark brown mixture was purified by fractional distillation in vacuo. Thereby, the reaction product **10** (3.70 g, 29.3 mmol, 57%) was obtained as slightly yellow liquid, b.p. 51–54 °C (0.010 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7.57 Hz, 3 H, 3^2-CH_3), 1.97 (s, 3 H, 4^1-CH_3), 2.23 (q, ^3J = 7.56 Hz, 2 H, 3^1-CH_2), 4.56 (s, 2 H, 5-CH_2) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 11.99 (C-3^2), 12.51 (C-3^1), 16.66 (C-4^1), 72.32 (C-5), 128.57 (C-3), 155.82 (C-4), 174.88 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 2973, 2936, 2877, 1758, 1744, 1679, 1453, 1390, 1341, 1190, 1093, 1065, 1035, 948, 773 cm^{-1}. MS (EI, –15 °C): *m*/*z* (%) = 126 (60) [M$^+$], 97 (38), 80 (4), 79 (8), 77 (2), 69 (52), 68 (6), 67 (20), 63 (2), 59 (2), 51 (7), 50 (4), 43 (11), 41 (100), 40 (8), 39 (38), 38 (5), 29 (16). HRMS (EI): *m*/*z*: calcd. for $C_7H_{10}O_2$: 126.068080; found: 126.068038.

3,4-Dimethyl-5-oxotetrahydrofuran-3-yl Acetate (9): A dispersion consisting of acetoxyacetone (25.0 mL, 226.8 mmol), zinc powder (18.8 g, 287.6 mmol) and a catalytic amount of iodine in benzene (270 mL) was refluxed under argon with vigorous stirring. Within 75 min ethyl (*R*,*S*)-2-bromopropionate (32.8 mL, 250.0 mmol) was added such that simmering was afforded. The dispersion was refluxed for additional 60 min, cooled on ice, and mixed with ice-water (380 mL). After addition of hydrochloric acid (80 mL, 6 M) the slurry was stirred until two almost clear phases occurred. They were separated from each other and the aqueous phase was extracted with diethyl ether (3 × 120 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (300 mL) and dried with Na_2SO_4. Evaporation of the solvent yielded the crude product (17.57 g) which was purified by fractional distillation in vacuo. The product **9** of the reaction was obtained as a mixture of its stereoisomers (11.27 g, 65.5 mmol, 29%) in form of a yellowish oil, b.p. 76–78 °C (0.23 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.17 (d, ^3J = 2.99 Hz, 1.4 H, 4^1-CH_3), 1.20 (d, ^3J = 2.77 Hz, 1.6 H, 4^1-CH_3), 1.44 (s, 1.4 H, 3^1-CH_3), 1.61 (s, 1.6 H, 3^1-CH_3), 1.97 (s, 1.6 H, acetoxy CO_2CH_3), 1.99 (s, 1.4 H, acetoxy CO_2CH_3), 2.40 (q, J = 7.26 Hz, 0.5 H, 4-C*H*), 2.83 (q, J = 7.42 Hz, 0.5 H, 4-C*H*), 4.04 (d, A′B′ system, $J_{A'B'}$ = 10.90 Hz, 0.6 H, 2-C$H_{A'}$), 4.29 (d, A′′B′′ system, $J_{A''B''}$ = 10.04 Hz, 0.4 H, 2-C$H_{A''}$), 4.44 (d, A′′B′′ system, $J_{A''B''}$ = 10.03 Hz, 0.4 H, 2-C$H_{B''}$), 4.80 (d, A′B′ system, $J_{A'B'}$ = 10.91 Hz, 0.6 H, 2-C$H_{B'}$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 17.96 (C-4^1), 20.50 (acetoxy CO_2CH_3), 21.90 (d, $^1J_{C,H}$ = 15.85 Hz, C-3^1), 45.43 (d, $^1J_{C,H}$ = 91.12 Hz, C-4), 73.35 (d, $^1J_{C,H}$ = 54.19 Hz, C-2), 83.69 (d, $J_{C,H}$ = 12.60 Hz, C-3), 170.54 (d, $J_{C,H}$ = 3.99 Hz, acetoxy CO_2CH_3), 177.08 (d, $J_{C,H}$ = 61.30 Hz, C-5) ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2945, 2909, 1786, 1741, 1452, 1372, 1235, 1149, 1133, 1098, 1032, 1014, 942, 857, 817, 668, 610, 557, 543 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 130 (17), 114 (2), 112 (30), 99 (8), 84 (7), 83 (9), 72 (8), 68 (3), 67 (2), 56 (17), 55 (9), 45 (2), 43 (100), 39 (6), 27 (10), 26 (2).

3,4-Dimethylfuran-2(5*H*)-one (11): A mixture of the lactone **9** (11.27 g, 65.5 mmol) and 4-toluenesulfonic acid monohydrate (0.56 g, 2.9 mmol) was heated under argon at 150 °C for 19 h such that slight reflux was observable. The accrued dark brown mixture was purified by fractional distillation in vacuo. Thereby, the reaction product **11** (6.43 g, 57.4 mmol, 88%) was obtained as colourless crystals, m.p. 28 °C, b.p. 71–72 °C (0.22 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.75–1.76 (m, 3 H, 3^1-CH_3), 1.94–1.96 (m, 3 H, 4^1-CH_3), 4.54–4.57 (m, 2 H, 5-CH_2) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 8.68 (C-3^1), 12.61 (C-4^1), 72.92 (C-5), 123.56 (C-3), 156.58 (C-4), 175.77 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2928, 2865, 1752, 1682, 1449, 1385, 1351, 1326, 1188, 1081, 1031, 887, 760, 660, 577, 480 cm^{-1}. MS (EI, –10 °C): *m*/*z* (%) = 112 (80) [M$^+$], 83 (80), 82 (3), 55 (100), 54 (11), 53 (11), 52 (3), 51 (5), 50 (4), 39 (16), 38 (2), 29 (12), 27 (11), 26 (2). HRMS (EI): *m*/*z*: calcd. for $C_6H_8O_2$: 112.052430; found: 112.052443.

4-Methylthiophen-2(5*H*)-one (13): A solution of *n*-butyllithium in *n*-hexane (69.8 mL, 111.7 mmol, 1.6 M) was added to a solution of 3-methylthiophene (10.0 mL, 102 mmol) in absolute diethyl ether (100 mL) under argon. After refluxing for 30 min, the solution was cooled down to –63 °C. Within 30 min a solution consisting of trimethyl borate (12.8 mL, 111.0 mmol) and absolute diethyl ether (100 mL) was added. The resulting mixture was stirred for 4 h at –67 °C. Warming up to ambient temperature induced the formation of a colourless precipitation. Within 30 min an aqueous solution of hydrogen peroxide (17.6 mL, 204.7 mmol, 35%) was added to the dispersion which was refluxed for 1 h afterwards. The layers were separated from each other, and the aqueous phase was extracted with diethyl ether (4 × 50 mL). After combining, the organic layers were dried with Na_2SO_4. Evaporation of the solvent yielded the raw material (10.02 g) which was purified by fractional distillation in vacuo. Subsequent column chromatography of the remaining mixture of the regioisomers 4-methyl-2(5*H*)-thiophenone (**13**) and 3-methyl-2(5*H*)-thiophenone (**12**) with *n*-pentane und ethyl acetate (4:1) yielded the desired reaction product **13** (7.22 g, 63.2 mmol, 62%) as a slight yellow-brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (m, 3 H, 4^1-CH_3), 3.92–3.93 (m, 2 H, 5-CH_2), 6.05–6.06 (m, 1 H, 3-C*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 18.94 (C-4^1), 40.90 (C-5), 129.19 (C-3), 167.55 (C-4), 199.73 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3073, 2982, 2946, 2915, 1678, 1659, 1634, 1434, 1404, 1378, 1310, 1228, 1156, 1098, 1017, 881, 833, 766, 656, 566, 484, 437 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 114 (100) [M$^+$], 86 (26), 85 (34), 82 (2), 71 (26), 69 (17), 58 (4), 53 (24), 51 (5), 50 (6), 47 (2), 46 (11), 45 (23), 41 (12), 40 (8), 39 (28), 38 (7), 37 (4), 27 (10).

Additionally, the byproduct **12** (2.04 g, 17.9 mmol, 18%) was obtained in the form of yellow-brown coloured crystals, m.p. 35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89–1.91 (m, 3 H, 3^1-CH_3), 3.90–3.92 (m, 2 H, 5-CH_2), 7.16–7.18 (m, 1 H, 4-C*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 11.78 (C-3^1), 34.93 (C-5), 141.50 (C-3), 147.04 (C-4), 200.57 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3053, 2986, 2951, 2919, 2871, 1794, 1666, 1638, 1432, 1412, 1404, 1370, 1300, 1191, 1041, 1024, 988, 897, 811, 748, 678, 670, 592, 476, 423 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 114 (100) [M$^+$], 113 (2), 88 (2), 87 (6), 86

(54), 85 (78), 82 (2), 81 (2), 69 (13), 58 (7), 53 (41), 52 (5), 51 (11), 50 (11), 49 (2), 47 (3), 46 (19), 45 (29), 41 (19), 39 (27), 38 (4), 27 (20), 26 (6).

3-Ethyl-4-methylthiophen-2(5*H*)-one (14): Ethyl iodide (3.35 mL, 41.0 mmol) was added to a solution consisting of the thiophenone **13** (3.00 g, 26.3 mmol) and chloroform (27.3 mL) under argon and exclusion of light. After addition of a solution of tetrabutylammonium hydrogen sulfate (8.97 g, 26.4 mmol) and sodium hydroxide (2.14 g, 53.5 mmol) in water (27.3 mL), the resulting slurry was stirred at ambient temperature for 70 h. The reaction was quenched by addition of hydrochloric acid (25.7 mL, 2 M), the aqueous layer was extracted with chloroform (3 × 20 mL), and the solvent of the combined organic phases was removed by evaporation in vacuo. Upon addition of diethyl ether (200 mL) to the remaining brown oil, the ammonium salt formed, which was separated from the solution by filtration. After drying the filtrate over Na_2SO_4, the solvent was evaporated in vacuo. The residue was purified by fractional distillation in vacuo and subsequently by column chromatography with *n*-pentane and ethyl acetate (9:1). The product **14** (1.21 g, 8.5 mmol, 33%) was obtained as an orange, clear liquid, b.p. 54–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.00 (t, ^3J = 7.56 Hz, 3 H, 3^2-CH_3), 2.11 (s, 3 H, 4^1-CH_3), 2.29 (q, ^3J = 7.53 Hz, 2 H, 3^1-CH_2), 3.80 (q, ^4J = 0.80 Hz, 2 H, 5-CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.75 (C-3^2), 17.28 (C-3^1), 18.33 (C-4^1), 38.74 (C-5), 140.75 (C-3), 158.37 (C-4), 200.16 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 2970, 2934, 2875, 1675, 1651, 1456, 1409, 1380, 1334, 1297, 1222, 1155, 1112, 1023, 916, 847, 761, 707, 658, 623, 543, 472 cm^{-1}. MS (EI, 10 °C): *m*/*z* (%) = 142 (100) [M$^+$], 127 (17), 114 (6), 109 (8), 101 (2), 99 (39), 97 (6), 86 (2), 81 (23), 79 (9), 77 (3), 69 (10), 66 (2), 65 (7), 58 (2), 50 (2), 45 (10), 41 (18), 39 (15), 38 (2), 29 (2). HRMS (EI): *m*/*z*: calcd. for $C_7H_{10}OS$: 142.045238; found: 142.045368.

Additionally, the byproduct 3-ethyl-4-methyl-2(3*H*)-thiophenone (0.13 g, 0.9 mmol, 4%) was isolated in the form of a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 1.25 Hz, 3 H, 3^2-CH_3), 1.64–1.75 (m, 1 H, 3^1-CH_2), 2.05–2.15 (m, 1 H, 3^1-CH_2), 2.09 (dd, ^4J_d = 1.25, ^4J_d = 0.47 Hz, 3 H, 4^1-CH_3), 4.24 (dq, ^4J_d = 3.58, ^4J_q = 0.67 Hz, 0.5 H, 3-C*H*), 4.26 (dq, ^3J_d = 3.47, ^4J_q = 0.73 Hz, 0.5 H, 3-C*H*), 6.00 (q, ^4J = 1.30 Hz, 1 H, 5-C*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 10.85 (C-3^2), 17.13 (C-3^1), 25.71 (C-4^1), 57.82 (C-3), 129.80 (C-5), 170.36 (C-4), 198.79 (C-2) ppm. MS (GC-EI): *m*/*z* (%) = 142 (100) [M$^+$], 127 (6), 113 (48), 109 (6), 99 (15), 85 (57), 81 (22), 79 (11), 73 (10), 69 (32), 65 (8), 59 (7), 53 (13), 45 (33), 39 (34), 27 (14). HRMS (EI): *m*/*z*: calcd. for $C_7H_{10}OS$: 142.045238; found: 142.045472.

3,4-Dimethylthiophen-2(5*H*)-one (15): Methyl iodide (3.45 mL, 54.9 mmol) was added to a solution consisting of the thiophenone **13** (3.00 g, 26.3 mmol) and chloroform (27.0 mL) under argon and exclusion of light. After addition of a solution composed of tetrabutylammonium hydrogen sulfate (8.93 g, 25.8 mmol) and sodium hydroxide (2.12 g, 52.4 mmol) in water (27.0 mL), the resulting slurry was stirred at ambient temperature for 76 h. The reaction was quenched by addition of hydrochloric acid (25.0 mL, 2 M). The aqueous layer was extracted with chloroform (3 × 20 mL), and the solvent of the combined organic phases was removed by evaporation in vacuo. Upon addition of diethyl ether (200 mL) to the residue, the ammonium salt formed, which was separated from the solution by filtration. After drying the filtrate over $MgSO_4$, the solvent was evaporated in vacuo. The residue was purified by fractional distillation in vacuo and subsequently by column chromatography with *n*-pentane and ethyl acetate (9:1). The product **15** (1.14 g, 8.9 mmol, 34% isolated yield, 37% concerning converted thiophenone **13**) was obtained as an orange, clear liquid. Also, some thiophenone **13** (0.27 g, 2.38 mmol, 9% of the starting material) was recovered, m.p. 38–39 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.81 (m, 3 H, 3^1-CH_3), 2.09–2.10 (m, 3 H, 4^1-CH_3), 3.80–3.82 (m, 2 H, 5-CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 10.12 (C-3^1), 17.51 (C-4^1), 38.78 (C-5), 135.13 (C-3), 158.45 (C-4), 200.47 (C-2) ppm. IR (KBr): $\tilde{\nu}$ = 2980, 2943, 2923, 2856, 1678, 1655, 1437, 1409, 1377, 1297, 1231, 992, 936, 827, 766, 677, 632, 536, 474, 430 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 128 (100) [M$^+$], 113 (3), 99 (25), 85 (56), 83 (7), 71 (3), 67 (34), 65 (9), 59 (12), 55 (16), 45 (15), 41 (14), 39 (25), 29 (3), 27 (13). HRMS (EI): *m*/*z*: calcd. for C_6H_8OS: 128.029588; found: 128.029781.

3-Hydroxyoctane-2,5-dione (16): Ethyl butyrylacetate (20.0 mL, 123.9 mmol) cooled down to 0 °C was dosed with a chilled solution of potassium hydroxide (8.33 g, 137.3 mmol) in water (50 mL). The resulting slurry was stirred for 30 min and subsequently stored at 5 °C for 8 d. At ambient temperature carbon dioxide was passed into for 2 h. Afterwards a solution of pyruvaldehyde in water (22.3 mL, 40%) was added, the mixture was stirred for 24 h and extracted with diethyl ether (5 × 70 mL). The combined organic layers were washed with brine (170 mL) and dried with Na_2SO_4. Evaporation of the solvent yielded 18.04 g of the crude material which was purified by fractional distillation under reduced pressure. The product **16** of the reaction was obtained (12.05 g, 76.2 mmol, 62%) as a yellowish, clear, and slightly viscous oil, b.p. 77–79 °C. ^{1}H NMR (400 MHz, ^{1}H/^{1}H-COSY, $CDCl_3$): δ = 0.85 (t, ^3J = 7.42 Hz, 3 H, 8-CH_3), 1.54 (tq, ^3J_t = 7.26, ^3J_q = 7.35 Hz, 2 H, 7-CH_2), 2.20 (s, 3 H, 1-CH_3), 2.39 (t, ^3J = 7.27 Hz, 2 H, 6-CH_2), 2.76 (dd, ABX system, J_{AB} = 17.12, $^3J_{AX}$ = 6.38 Hz, 1 H, 4-CH_A), 2.88 (dd, ABX system, J_{AB} = 17.12, $^3J_{BX}$ = 3.85 Hz, 1 H, 4-CH_B), 3.45 (br. s, 1 H, O*H*), 4.29 (dd, ABX system, $^3J_{AX}$ = 6.37, $^3J_{BX}$ = 3.85 Hz, 1 H, 3-CH_X) ppm. ^{13}C NMR (101 MHz, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 13.47 (C-8), 16.81 (C-7), 25.28 (C-2), 45.19 (C-4), 45.46 (C-6), 73.72 (C-3), 209.30 (C-2,-5) ppm. IR (KBr): $\tilde{\nu}$ = 3458, 2965, 2937, 2878, 1713, 1459, 1407, 1359, 1248, 1181, 1128, 1106, 1017, 967, 904, 617, 529 cm^{-1}. MS (EI, –2 °C): *m*/*z* (%) = 158 (1) [M$^+$], 143 (1), 115 (37), 97 (9), 87 (1), 71 (95), 55 (5), 43 (100), 41 (13), 27 (11). HRMS (CI, isobutane): *m*/*z*: calcd. for $C_8H_{15}O_3$ [M + H]$^+$: 159.102292; found: 159.102117.

2-Ethyl-4-hydroxy-3-methylcyclopent-2-enone (18): A solution of the dione **16** (12.05 g, 76.2 mmol) in methanol (55 mL, 1.4 mol) was cooled to 0 °C. Within 2 h an aqueous solution of K_2CO_3 (332 mL, 20%) was added such that the temperature of the resulting mixture did not exceed 5 °C. It was stirred for 2 h at 0 °C, for additional 24 h at ambient temperature, and afterwards was neutralised by addition of hydrochloric acid (2 M). The solution was extracted with dichloromethane (4 × 440 mL) and the combined organic layers were dried with Na_2SO_4. Removal of the solvent by evaporation in vacuo yielded 9.22 g of the crude material which was purified by column chromatography with chloroform and methanol (99:1). The product **18** (5.00 g, 35.7 mmol, 47%) was obtained as an auburn coloured, clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.60 Hz, 3 H, 2^2-CH_3), 2.06 (s, 3 H, 3^1-CH_3), 2.16 (q, ^3J = 7.56 Hz, 2 H, 2^1-CH_2), 2.23 (dd, ABX system, $^3J_{AX}$ = 1.76, J_{AB} = 18.35 Hz, 1 H, 5-CH_A), 2.57 (br. s, 1 H, O*H*), 2.72 (dd, ABX system, J_{AB} = 18.35, $^3J_{BX}$ = 6.12 Hz, 1 H, 5-CH_B), 4.67 (d, ABX system, $^3J_{BX}$ = 5.94 Hz, 1 H, 4-CH_X) ppm. ^{13}C NMR (126 MHz, BB, $CDCl_3$): δ = 12.37 (C-2^2), 13.18 (C-3^1), 15.94 (C-2^1), 44.18 (C-5), 71.25 (C-4), 143.22 (C-2), 168.07 (C-3), 205.31 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 3411, 2971, 2936, 2876, 1694, 1646, 1463, 1384, 1348, 1311, 1262, 1238, 1192, 1148, 1095, 1048, 1012, 938, 918, 849, 777, 616, 579 cm^{-1}. MS (EI, 14 °C): *m*/*z* (%) = 40 (100) [M$^+$], 125 (50), 111 (59), 107 (6), 97 (70), 95 (19), 93 (7), 83 (17), 79 (41), 77 (18), 67 (38), 55 (54), 53 (33), 43 (90), 41 (75), 39 (47), 29 (20), 27 (30).

HRMS (EI): *m*/*z*: calcd. for $C_8H_{12}O_2$: 140.083733; found: 140.083832.

4-Chloro-2-ethyl-3-methylcyclopent-2-enone (20): Thionyl chloride (2.5 mL, 33.2 mmol) was slowly added under argon to the alcohol **18** (1.98 g, 14.1 mmol) at 0 °C. The solution was stirred for 15 min at ambient temperature and the excess of thionyl chloride was removed by distillation under reduced pressure (27–4 mbar). Purification of the residual solution by fractional distillation in vacuo yielded the product **20** (1.18 g, 7.5 mmol, 53%) in the form of a clear, yellow and slightly viscous oil, b.p. 51 °C (0.76 mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, ^3J = 7.60 Hz, 3 H, 2^2-CH_3), 2.09 (s, 3 H, 3^1-CH_3), 2.21 (q, ^3J = 7.61 Hz, 2 H, 2^1-CH_2), 2.60 (dd, ABX system, J_{AB} = 19.05, $^3J_{AX}$ = 1.65 Hz, 1 H, 5-CH_A), 2.94 (dd, ABX system, J_{AB} = 19.03, $^3J_{BX}$ = 6.45 Hz, 1 H, 5-CH_2), 4.81 (dd, ABX system, $^3J_{AX}$ = 1.83, $^3J_{BX}$ = 6.47 Hz, 1 H, 4-CH_X) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.42 (C-2^2), 14.24 (C-3^1), 16.50 (C-2^1), 45.03 (C-5), 57.85 (C-4), 145.07 (C-2), 165.36 (C-3), 203.46 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 2973, 2936, 2877, 1712, 1647, 1461, 1386, 1346, 1249, 1222, 1183, 1086, 1057, 930, 899, 781, 718, 658, 587 cm^{-1}. MS (EI, –7 °C): *m*/*z* (%) = 158 (52) [M$^+$], 138 (2), 123 (85), 115 (2), 107 (2), 95 (100), 93 (8), 79 (17), 67 (30), 65 (8), 55 (19), 39 (21), 27 (13). HRMS (EI): *m*/*z*: calcd. for $C_8H_{11}ClO$: 158.049956; found: 158.049842.

Diethyl (3-Ethyl-2-methyl-4-oxocyclopent-2-enyl)phosphonate (22): A mixture of the chloride **20** (1.18 g, 7.5 mmol) and triethyl phosphite (1.4 mL, 7.7 mmol) was heated under argon to 75–80 °C for 45 min and was subsequently refluxed at 160 °C for 5 h. Purification of the resulting solution by fractional distillation in vacuo yielded the product **22** (0.86 g, 3.3 mmol, 44% isolated yield, 73% concerning converted chloride **20**) as a yellow, clear liquid. Additionally, some chloride **20** (0.46 g, 2.9 mmol, 39% of the starting material) was recovered, b.p. 123–124 °C (0.76–0.82 mbar). ^{1}H NMR (400 MHz, ^{1}H/^{1}H-COSY, $CDCl_3$): δ = 0.93 (t, ^3J = 7.57 Hz, 3 H, 3^2-CH_3), 1.21 [t, ^3J = 7.05 Hz, 3 H, PO(OCH$_2$-CH_3)$_2$], 1.26 [t, ^3J = 7.05 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 2.17 (s, 3 H, 2^1-CH_3), 2.17 (q, ^3J = 7.48 Hz, 2 H, 3^1-CH_2), 2.48–2.63 (m, 2 H, 5-CH_2), 3.03 (m, 0.5 H, 1-C*H*), 3.09 (m, 0.5 H, 1-C*H*), 3.95–4.14 [m, 4 H, PO(OCH_2CH$_3$)$_2$] ppm. ^{13}C NMR (101 MHz, DEPT 135, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 12.54 (d, $^1J_{C,H}$ = 4.25 Hz, C-3^2), 16.35 [d, ^3J = 5.78 Hz, PO(OCH$_2$CH_3)$_2$], 16.45 (C-2^1), 16.45 (C-3^1), 36.60 (d, $^2J_{C,P}$ = 3.97 Hz, C-5), 41.62 (d, $^1J_{C,P}$ = 144.47 Hz, C-1), 62.04 [d, $^2J_{C,P}$ = 6.83 Hz, PO(OCH$_2$CH$_3$)$_2$], 62.54 [d, $^2J_{C,P}$ = 6.99 Hz, PO(OCH$_2$CH$_3$)$_2$], 144.30 (d, $^1J_{C,H}$ = 9.99 Hz, C-3), 164.28 (d, $^2J_{C,P}$ = 8.99 Hz, C-2), 206.05 (d, $^1J_{C,H}$ = 2.32 Hz, C-4). IR (KBr): $\tilde{\nu}$ = 2978, 2935, 2876, 1702, 1641, 1445, 1387, 1348, 1256, 1233, 1209, 1164, 1052, 1024, 966, 800, 615, 570, 534, 489 cm^{-1}. MS (EI, 45 °C): *m*/*z* (%) = 260 (99) [M$^+$], 245 (8), 232 (34), 217 (7), 204 (77), 189 (15), 175 (6), 150 (12), 139 (21), 122 (100), 107 (38), 95 (36), 79 (30), 67 (18), 55 (21), 41 (18), 29 (25). HRMS (ESI pos, methanol + dichloromethane): *m*/*z*: calcd. for $C_{12}H_{21}O_4NaP$ [M + Na]$^+$: 283.107312; found: 283.106969.

3-Hydroxyheptane-2,5-dione (17): Methyl propionylacetate (20.0 mL, 158.3 mmol) was cooled down to 0 °C and was dosed with a chilled solution of potassium hydroxide (9.80 g, 174.7 mmol) in water (63 mL). The resulting slurry was stirred for 35 min and subsequently stored at 5 °C for 6 d. Carbon dioxide was passed into it at ambient temperature for 2 h. Afterwards, a solution of pyruvaldehyde in water (28.5 mL, 40%) was added, the mixture was stirred for 24 h, stored at 5 °C for 17 h, and extracted with diethyl ether (5 × 90 mL). The combined organic layers were washed with brine (230 mL) and dried with Na_2SO_4. Evaporation of the solvent yielded 14.14 g of the crude material which was purified by fractional distillation in vacuo. The product **17** was obtained (9.25 g, 64.2 mmol, 41%) as a colourless, clear, and slightly viscous oil, b.p. 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, ^3J = 7.29 Hz, 3 H, 7-CH_3), 2.22 (s, 3 H, 1-CH_3), 2.45 (q, ^3J = 7.31 Hz, 2 H, 6-CH_2), 2.78 (dd, ABX system, J_{AB} = 17.02, $^3J_{AX}$ = 6.39 Hz, 1 H, 4-CH_A), 2.91 (dd, ABX system, J_{AB} = 17.01, $^3J_{BX}$ = 3.82 Hz, 1 H, 4-CH_B), 3.70 (br. s, 1 H, O*H*), 4.31 (dd, ABX system, $^3J_{AX}$ = 6.32, $^3J_{BX}$ = 3.87 Hz, 1 H, 3-C*H*) ppm. ^{13}C NMR (101 MHz, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 7.45 (C-7), 25.30 (C-1), 36.87 (C-6), 44.88 (C-4), 73.81 (C-3), 209.24 (C-2), 209.72 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3450, 2979, 2941, 1714, 1460, 1411, 1359, 1242, 1183, 1114, 1003, 967, 616 cm^{-1}. MS (GC-EI): *m*/*z* (%) = 126 (1), 108 (1), 101 (20), 83 (7), 79 (1), 73 (9), 69 (7), 57 (100), 55 (10), 43 (45), 29 (20), 27 (4). HRMS (CI, isobutane): *m*/*z*: calcd. for $C_7H_{13}O_3$ [M + H]$^+$: 145.086470; found: 145.086323.

4-Hydroxy-2,3-dimethylcyclopent-2-enone (19): A solution of the dione **17** (4.02 g, 27.9 mmol) in methanol (20 mL, 0.49 mol) was cooled to 0 °C. An aqueous solution of K_2CO_3 (121 mL, 20%) was added within 1 h such that the temperature of the resulting mixture did not exceed 3 °C. It was stirred for 2 h at 0 °C for additional 24 h at ambient temperature, and was afterwards neutralised by addition of hydrochloric acid (2 M). The solution was extracted with dichloromethane (4 × 110 mL) and the combined organic layers were dried with Na_2SO_4. Removal of the solvent by evaporation in vacuo yielded 2.47 g of the raw material which was purified by column chromatography with chloroform and methanol (99:1). The product **19** (1.74 g, 13.8 mmol, 50%) was obtained as an auburn, clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 3 H, 3^1-CH_3), 2.06 (s, 3 H, 2^1-CH_3), 2.19 (br. s, 1 H, O*H*), 2.25 (d, ABX system, J_{AB} = 18.38 Hz, 1 H, 5-CH_A), 2.75 (dd, ABX system, J_{AB} = 18.38, $^3J_{BX}$ = 6.09 Hz, 1 H, 5-CH_B), 4.70 (d, 4-CH_X, $^3J_{BX}$ = 5.50 Hz, 1 H, ABX system) ppm. ^{13}C NMR (126 MHz, BB, $CDCl_3$): δ = 7.67 (C-3^1), 13.39 (C-2^1), 44.00 (C-5), 71.40 (C-4), 137.90 (C-2), 168.00 (C-3), 205.41 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 3411, 2978, 2923, 1699, 1648, 1437, 1386, 1327, 1242, 1195, 1149, 1085, 1050, 1006, 946, 903, 836, 717, 661, 590, 508 cm^{-1}. MS (EI, 15 °C): *m*/*z* (%) = 126 (94) [M$^+$], 111 (89), 98 (100), 93 (5), 83 (85), 81 (20), 79 (31), 71 (5), 69 (16), 65 (10), 55 (86), 53 (39), 43 (89), 41 (44), 39 (56), 29 (28), 27 (47). HRMS (EI): *m*/*z*: calcd. for $C_7H_{10}O_2$: 126.068082; found: 126.068227.

4-Chloro-2,3-dimethylcyclopent-2-enone (21): Thionyl chloride (3.8 mL, 50.5 mmol) was slowly added under argon to the alcohol **19** (1.75 g, 13.9 mmol) at 0 °C. The solution was stirred for 1 h at 0 °C and for another 1 h at ambient temperature. Subsequently, the excess of thionyl chloride was removed by distillation under reduced pressure (11–8 mbar). Purification of the residual solution by fractional distillation in vacuo yielded the product **21** (0.93 g, 6.4 mmol, 46%) in form of a clear, yellow and slightly viscous oil, b.p. 36–40 °C (0.11–0.13 mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (s, 3 H, 2^1-CH_3), 2.07 (s, 3 H, 3^1-CH_3), 2.60 (dd, ABX system, J_{AB} = 19.06, $^3J_{AX}$ = 1.74 Hz, 1 H, 5-CH_A), 2.94 (dd, ABX system, J_{AB} = 19.06, $^3J_{BX}$ = 6.45 Hz, 1 H, 5-CH_B), 4.81 (dd, ABX system, $^3J_{AX}$ = 0.75, $^3J_{BX}$ = 6.40 Hz, 1 H, 4-CH_X) ppm. ^{13}C NMR (101 MHz, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 8.20 (C-3^1), 14.43 (C-2^1), 44.85 (C-5), 57.77 (C-4), 139.68 (C-2), 165.60 (C-3), 203.68 (C-1) ppm. IR (KBr): $\tilde{\nu}$ = 2983, 2924, 2860, 1709, 1652, 1439, 1387, 1326, 1294, 1254, 1225, 1186, 1107, 1071, 925, 872, 725, 690, 659, 560, 537, 478 cm^{-1}. MS (EI, –15 °C): *m*/*z* (%) = 144 (46) [M$^+$], 129 (1), 109 (100), 101 (1), 81 (67), 79 (28), 65 (8), 53 (23), 39 (19), 27 (13). HRMS (EI): *m*/*z*: calcd. for C_7H_9ClO: 144.034192; found: 144.034146.

Diethyl (2,3-Dimethyl-4-oxocyclopent-2-enyl)phosphonate (23): A mixture of the chloride **21** (0.78 g, 5.4 mmol) and triethyl phosphite

(0.95 mL, 5.4 mmol) was heated under argon to 75–80 °C for 45 min and subsequently refluxed at 160–170 °C for 5.5 h. Purification of the resulting solution by fractionating distillation in vacuo, followed by column chromatography with *n*-hexane, ethyl acetate, and 2-propanol (49:49:2) as eluent yielded the product **23** (0.68 g, 2.8 mmol, 51%) as a yellow, clear liquid, b.p. 86 °C (0.032–0.035 mbar). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 [t, ^3J = 7.03 Hz, 3 H, $PO(OCH_2CH_3)_2$], 1.27 [t, ^3J = 7.07 Hz, 3 H, $PO(OCH_2CH_3)_2$], 1.68 (dq, J_d = 4.91, J_q = 0.93 Hz, 3 H, 3^1-CH_3), 2.16 (d, J = 3.33 Hz, 3 H, 2^{1}CH_3), 2.50–2.65 (m, 2 H, 5-CH_2), 3.03–3.06 (m, 0.5 H, 1-C*H*), 3.09–3.12 (m, 0.5 H, 1-C*H*), 3.97–4.13 [m, 4 H, $PO(OCH_2CH_3)_2$] ppm. ^{13}C NMR (101 MHz, DEPT 135, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 8.29 (d, $^1J_{C,H}$ = 1.92 Hz, C-3^1), 16.40 [d, $^3J_{C,P}$ = 5.49 Hz, $PO(OCH_2CH_3)_2$], 16.84 (C-2^1), 36.44 (d, $^2J_{C,P}$ = 3.83 Hz, C-5), 41.72 (d, $^1J_{C,P}$ = 144.99 Hz, C-1), 62.12 [d, $^2J_{C,P}$ = 6.89 Hz, $PO(OCH_2CH_3)_2$], 62.60 [d, $^2J_{C,P}$ = 6.98 Hz, $PO(OCH_2CH_3)_2$], 138.84 (d, $^1J_{C,H}$ = 9.94 Hz, C-3), 164.53 (d, $^1J_{C,H}$ = 8.79 Hz, C-2), 206.37 (d, $^1J_{C,H}$ = 2.82 Hz, C-4) ppm. IR (KBr): $\tilde{\nu}$ = 2985, 2931, 1702, 1644, 1445, 1388, 1329, 1258, 1236, 1210, 1164, 1027, 967, 888, 797, 731, 693, 655, 600, 532, 491 cm^{-1}. MS (EI, 50 °C): *m*/*z* (%) = 246 (74) [M$^+$], 231 (1), 218 (22), 203 (1), 190 (72), 173 (14), 162 (5), 136 (12), 108 (100), 92 (15), 81 (37), 65 (9), 53 (16), 41 (15), 29 (13). HRMS (ESI pos, methanol + dichloromethane): *m*/*z*: calcd. for $C_{11}H_{19}NaO_4P$ [M + Na]$^+$: 269.091319; found: 269.091189.

***tert*-Butyl 5-{[4-Ethyl-3-methyl-5-oxofuran-2(5*H*)-ylidene]methyl}-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (25):** A solution of the pyrrole **24** (0.31 g, 1.1 mmol), the furanone **10** (0.13 g, 1.0 mmol), and DBU (0.36 mL, 2.4 mmol) in absolute THF (1.4 mL), to which a small amount of molecular sieves (3 Å) was added, was refluxed for 19 h in the dark and under argon. The reaction mixture was decanted from the molecular sieves which was repeatedly washed with chloroform as long as the solvent showed colour. The combined organic phases were washed with a solution of Na_2CO_3 (2 M, 3 × 100 mL), with a solution of saturated KH_2PO_4 (3 × 100 mL), and with a solution of saturated $NaHCO_3$ (3 × 100 mL). After drying over Na_2SO_4, the solvent was evaporated. Column chromatography of the remaining crude material (0.46 g) with dichloromethane and ethyl acetate (49:1) as eluent yielded the expected reaction product **25** (0.36 g, 0.9 mmol, 86%) as yellow crystals, m.p. 134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.61 Hz, 3 H, 9^2-CH_3), 1.57 [s, 9 H, $CO_2C(CH_3)_3$], 2.09 (s, 3 H, 4^1-CH_3), 2.11 (s, 3 H, 8^1-CH_3), 2.37 (q, ^3J = 7.66 Hz, 2 H, 9^1-CH_2), 2.52 (t, ^3J = 7.87 Hz, 2 H, 3^2-CH_2), 2.99 (t, ^3J = 8.00 Hz, 2 H, 3^1-CH_2), 3.65 (s, 3 H, CO_2CH_3), 5.88 (s, 1 H, 6-C*H*), 9.70 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 9.64 (C-4^1), 12.77 (C-9^2), 17.28 (C-9^1), 20.51 (C-8^1), 28.36 [C(*C*H$_3$)$_3$], 31.20 (C-3^1), 34.85 (C-3^2), 51.47 (CO_2CH_3), 81.35 [*C*(CH$_3$)$_3$], 95.90 (C-6), 123.15 (C-3), 125.55, 126.45, 128.37, 128.40 (C-2,-4,-5,-9), 146.59, 146.80 (C-7,-8), 160.07 [*C*O$_2$C(CH$_3$)$_3$], 168.96 (C-10), 173.61 (*C*O$_2$CH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3066, 2978, 2878, 1759, 1735, 1680, 1622, 1445, 1394, 1367, 1298, 1278, 1268, 1256, 1193, 1172, 1161, 1138, 1131, 1115, 1097, 1006, 944, 848, 673, 613 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 254 (32000), 389 (48100), 409 nm (45200). MS (EI, 130 °C): *m*/*z* (%) = 403 (18) [M$^+$], 347 (100), 316 (7), 303 (10), 287 (20), 286 (2), 274 (9), 272 (3), 270 (3), 269 (2), 256 (5), 254 (2), 244 (7), 241 (3), 230 (5), 228 (3), 226 (2), 200 (3), 135 (3). HRMS (EI): *m*/*z*: calcd. for $C_{22}H_{29}NO_6$: 403.199489; found: 403.199617.

***tert*-Butyl 5-{[3,4-Dimethyl-5-oxofuran-2(5*H*)-ylidene]methyl}-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (26):** A solution of the pyrrole **24** (0.30 g, 1.0 mmol), the furanone **11** (0.11 g, 1.0 mmol), and DBU (0.35 mL, 2.3 mmol) in absolute THF (1.4 mL), to which a small amount of molecular sieves (3 Å) was added, was refluxed for 19 h in the dark and under argon. The reaction mixture was decanted from the molecular sieves which was repeatedly washed with chloroform as long as the solvent showed colour. The combined organic phases were washed with a solution of Na_2CO_3 (2 M, 3 × 100 mL), with a solution of saturated KH_2PO_4 (3 × 100 mL), and with a solution of saturated $NaHCO_3$ (3 × 100 mL). After drying over Na_2SO_4, the solvent was evaporated. Column chromatography of the remaining raw material (0.49 g) with dichloromethane and ethyl acetate (49:1) as eluent yielded the expected reaction product **26** (0.30 g, 0.8 mmol, 76%) as yellow crystals, m.p. 151–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $CO_2C(CH_3)_3$], 1.93 (s, 3 H, 9^1-CH_3), 2.09 (s, 3 H, 8^1-CH_3), 2.09 (s, 3 H, 4^1-CH_3), 2.52 (t, ^3J = 8.00 Hz, 2 H, 3^2-CH_2), 2.99 (t, ^3J = 7.80 Hz, 2 H, 3^1-CH_2), 3.65 (s, 3 H, CO_2CH_3), 5.88 (s, 1 H, 6-C*H*), 9.69 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.91 (C-9^1), 9.87 (C-4^1), 20.52 (C-8^1), 28.37 [$CO_2C(CH_3)_3$], 29.69 (C-3^1), 34.90 (C-3^2), 51.48 (CO_2CH_3), 81.47 [$CO_2C(CH_3)_3$], 95.81 (C-6), 122.89, 123.08, 126.40, 128.36 (C-2,-4,-5,-9), 123.17 (C-3), 146.86 (C-7), 147.11 (C-8), 160.11 [*C*O$_2$C(CH$_3$)$_3$], 169.03 (C-10), 173.60 (*C*O$_2$CH$_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3447, 3067, 3007, 2974, 2953, 2930, 1758, 1736, 1682, 1653, 1625, 1449, 1367, 1272, 1252, 1192, 1171, 1137, 1096, 1007, 946, 845, 809, 753, 712, 678, 603, 571 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 254 (30400), 387 (44400), 407 nm (41100). MS (EI, 130 °C): *m*/*z* (%) = 389 (19) [M$^+$], 333 (100), 302 (9), 289 (11), 288 (11), 273 (24), 272 (2), 260 (11), 258 (2), 256 (4), 255 (4), 242 (7), 230 (9), 227 (5), 216 (7), 214 (3), 186 (4), 144 (2), 128 (4), 57 (2). HRMS (EI): *m*/*z*: calcd. for $C_{21}H_{27}NO_6$: 389.183839; found: 389.183447.

***tert*-Butyl 5-{[4-Ethyl-3-methyl-5-oxothiophen-2(5*H*)-ylidene]methyl}-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (27):** A solution of the pyrrole **24** (0.30 g, 1.0 mmol), the thiophenone **14** (0.15 g, 1.1 mmol), and DBU (0.35 mL, 2.3 mmol) in absolute THF (1.4 mL), to which a small amount of molecular sieves (3 Å) was added, was refluxed for 19 h in the dark and under argon. The reaction mixture was decanted from the molecular sieves which was repeatedly washed with chloroform, as long as the solvent showed colour. The combined organic phases were washed with a solution of Na_2CO_3 (2 M, 3 × 100 mL), with a solution of saturated KH_2PO_4 (3 × 100 mL), and with a solution of saturated $NaHCO_3$ (3 × 100 mL). After drying over Na_2SO_4, the solvent was evaporated. Column chromatography of the remaining crude material (0.58 g) with dichloromethane and ethyl acetate (19:1) as eluent yielded the expected reaction product **27** (0.21 g, 0.5 mmol, 49%) as a yellow-orange solid, m.p. 67–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.58 Hz, 3 H, 9^2-CH_3), 1.56 [s, 9 H, $CO_2C(CH_3)_3$], 2.12 (s, 3 H, 8^1-CH_3), 2.27 (s, 3 H, 4^1-CH_3), 2.42 (q, ^3J = 7.60 Hz, 2 H, 9^1-CH_2), 2.52 (t, ^3J = 7.87 Hz, 2 H, 3^2-CH_2), 2.99 (t, ^3J = 7.89 Hz, 2 H, 3^1-CH_2), 3.64 (s, 3 H, CO_2CH_3), 6.93 (s, 1 H, 6-C*H*), 8.98 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 9.07 (C-4^1), 12.66 (C-9^1), 13.11 (C-9^2), 18.97 (C-8^1), 20.35 (C-3^1), 28.33 [$CO_2C(CH_3)_3$], 34.64 (C-3^2), 51.48 (CO_2CH_3), 81.69 [$CO_2C(CH_3)_3$], 114.31 (C-6), 124.28, 125.66, 127.87, 129.07, 131.21 (C-2,-3,-4,-5,-7), 139.59 (C-9), 153.09 (C-8), 159.82 [*C*O$_2$C(CH$_3$)$_3$], 173.44 (*C*O$_2$CH$_3$), 192.32 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3429, 2974, 2952, 2934, 2875, 1740, 1675, 1608, 1583, 1537, 1437, 1383, 1368, 1276, 1197, 1165, 1140, 1054, 985, 961, 884, 847, 816, 778, 741, 708, 649, 545, 514, 473 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 267 (12900), 401 (21800), 419 nm (21300). MS (EI, 120 °C): *m*/*z* (%) = 419 (26) [M$^+$], 363 (100), 317 (13), 303 (24), 290 (6), 244 (3), 216 (2), 166 (1), 129 (2), 91 (1), 73 (1), 57 (3). HRMS (ESI pos, methanol + dichloromethane): *m*/*z*: calcd. for $C_{22}H_{29}NNaO_5S$ [M + Na]$^+$: 442.166415; found: 442.16614.

***tert*-Butyl 5-[3,4-Dimethyl-5-oxothiophen-2(5*H*)-ylidenemethyl]-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (28):** A solution of the pyrrole **24** (0.30 g, 1.0 mmol), the thiophenone **15** (0.13 g, 1.0 mmol), and DBU (0.35 mL, 2.3 mmol) in absolute THF (1.4 mL), to which a small amount of molecular sieves (3 Å) was added, was refluxed for 19 h in the dark and under argon. The reaction mixture was decanted from the molecular sieves which was repeatedly washed with chloroform as long as the solvent showed colour. The combined organic phases were washed with a solution of Na_2CO_3 (2 M, 3 × 100 mL), with a solution of saturated KH_2PO_4 (3 × 100 mL), and with a solution of saturated $NaHCO_3$ (3 × 100 mL). After drying over Na_2SO_4, the solvent was evaporated. Column chromatography of the remaining raw material (0.62 g) with dichloromethane and ethyl acetate (19:1) as eluent yielded the expected reaction product **28** (0.14 g, 0.3 mmol, 34% isolated yield, 40% concerning converted pyrrole **24**) as a yellow-orange solid as well as some pyrrole **24** (50 mg, 0.17 mmol, 17% of the starting material), m.p. 67–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 [s, 9 H, $CO_2C(CH_3)_3$], 1.97 (s, 3 H, 2^1-CH_3), 2.13 (s, 3 H, 3^1-CH_3), 2.27 (s, 3 H, 7^1-CH_3), 2.53 (t, ^3J = 7.89 Hz, 2 H, 8^2-CH_2), 3.00 (t, ^3J = 7.91 Hz, 2 H, 8^1-CH_2), 3.65 (s, 3 H, CO_2CH_3), 6.94 (s, 1 H, 5-C*H*), 8.99 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 9.11 (C-4^1), 10.89 (C-9^1), 13.03 (C-8^1), 20.37 (C-3^1), 28.37 [$CO_2C(CH_3)_3$], 34.67 (C-3^2), 51.51 (CO_2CH_3), 81.74 [$CO_2C(CH_3)_3$], 114.21 (C-6), 124.31, 125.73, 127.87, 129.11, 131.11 (C-2,-3,-4,-5,-7), 133.98 (C-9), 153.37 (C-8), 159.84 [$CO_2C(CH_3)_3$], 173.48 (CO_2CH_3), 192.60 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2968, 2952, 2930, 1737, 1694, 1678, 1610, 1587, 1537, 1438, 1384, 1367, 1274, 1255, 1162, 1138, 1056, 1010, 906, 852, 808, 776, 689, 541, 490, 473 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 267 (16700), 400 (29300), 418 nm (29100). MS (EI, 125 °C): *m*/*z* (%) = 405 (28) [M$^+$], 349 (100), 303 (11), 289 (24), 276 (6), 258 (4), 229 (4), 202 (4), 168 (2), 136 (2), 115 (1), 91 (1), 77 (1), 57 (5), 41 (3). HRMS (EI): *m*/*z*: calcd. for $C_{21}H_{27}NO_5S$: 405.160996; found: 405.161075.

***tert*-Butyl 5-[(3-Ethyl-2-methyl-4-oxocyclopent-2-enylidene)methyl]-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (29):** The coupling-reaction was performed in the dark and under argon. A dispersion of NaH in mineral oil (0.10 g, 55–65%) was dispersed at ambient temperature in THF (8.0 mL) and mixed with a solution of the phosphonate **22** (0.59 g, 2.3 mmol) in THF (6.0 mL). When the mixture was stirred at 60–62 °C for 1 h development of hydrogen was observed. After cooling to ambient temperature, a solution of the pyrrole **24** (0.35 g, 1.2 mmol) and THF (8.0 mL) was added, and the mixture was stirred for another hour. Thereafter, a dark brown solution was formed which was refluxed for 21 h. After addition of a saturated aqueous solution of NH_4Cl (2.4 mL), the resulting slurry was diluted with 90 mL of ethyl acetate and 90 mL of water. The phases were separated, the aqueous phase was extracted with ethyl acetate (5 × 90 mL), and the combined organic phases were washed with brine (4 × 90 mL). After drying over Na_2SO_4, evaporation of the solvent yielded the crude product (0.67 g) which was purified by HPLC with methanol and water (5:1) as eluent. Evaporation of the methanol and freeze-drying of the remaining aqueous dispersion resulted in the reaction product **29** (0.14 g, 0.34 mmol, 29% isolated yield, 32% concerning converted pyrrole **24**) as a yellow-orange, clear, and viscous oil. Additionally, some pyrrole **24** (37 mg, 0.12 mmol, 10% of the starting material) was recovered. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7.59 Hz, 3 H, 9^2-CH_3), 1.56 [s, 9 H, $CO_2C(CH_3)_3$], 2.09 (s, 3 H, 4^1-CH_3), 2.17 (s, 3 H, 8^1-CH_3), 2.33 (q, ^3J = 7.65 Hz, 2 H, 9^1-CH_2), 2.51 (t, ^3J = 7.98 Hz, 2 H, 3^2-CH_2), 2.99 (t, ^3J = 8.00 Hz, 2 H, 3^1-CH_2), 3.15 (s, 2 H, 11-CH_2), 3.65 (s, 3 H, CO_2CH_3), 6.47 (s, 1 H, 6-C*H*), 8.67 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, BB, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 8.69 (C-4^1), 11.47 (C-8^1), 12.75 (C-9^2), 16.69 (C-9^1), 20.31 (C-3^1), 28.15 [$CO_2C(CH_3)_3$], 34.62 (C-3^2), 38.27 (C-11), 51.25 (CO_2CH_3), 81.19 [$CO_2C(CH_3)_3$], 109.81 (C-6), 121.95 (C-2), 122.62 (C-4), 128.46 (C-3), 129.11 (C-5), 133.48 (C-7), 144.10 (C-9), 160.16 [$CO_2C(CH_3)_3$], 163.32 (C-8), 173.29 (CO_2CH_3), 202.68 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3471, 2974, 2933, 2875, 1739, 1691, 1619, 1439, 1394, 1368, 1275, 1254, 1166, 1137, 1098, 1057, 983, 962, 929, 855, 809, 777, 697, 649 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 253 (23500), 369 (27800), 388 nm (19600). MS (EI, 150 °C): *m*/*z* (%) = 401 (27) [M$^+$], 379 (2), 359 (5), 345 (100), 285 (24), 242 (5), 182 (3), 115 (1), 91 (1), 77 (1), 57 (4), 41 (2). HRMS (ESI pos, methanol + dichloromethane): *m*/*z*: calcd. for $C_{23}H_{31}NNaO_5$ [M + Na]$^+$ 424.209440; found: 424.209631.

***tert*-Butyl 5-[(2,3-Dimethyl-4-oxocyclopent-2-enylidene)methyl]-3-[2-(methoxycarbonyl)ethyl]-4-methyl-1*H*-pyrrole-2-carboxylate (30):** The coupling-reaction was performed in the dark and under argon. At ambient temperature, a dispersion of NaH in mineral oil (0.07 g, 55–65%) was dispersed in THF (4.9 mL) and was mixed with a solution of phosphonate **23** (0.38 g, 1.6 mmol) in THF (3.7 mL). When the mixture was stirred at 60–70 °C for 1 h, development of hydrogen was observed. After cooling to ambient temperature, a solution of the pyrrole **24** (0.24 g, 0.8 mmol) and THF (4.8 mL) was added, and the mixture was stirred for another hour. Thereby a dark brown solution was formed which was refluxed for 21 h. After addition of a saturated aqueous solution of NH_4Cl (1.8 mL), the resulting slurry was diluted with 60 mL of ethyl acetate and water at a time. The phases were separated, the aqueous phase was extracted with ethyl acetate (5 × 60 mL), and the combined organic phases were washed with brine (4 × 60 mL). After drying over Na_2SO_4, evaporation of the solvent yielded the crude product (0.56 g) which was purified by HPLC with methanol and water (5:1) as eluent. Evaporation of the methanol and freeze-drying of the remaining aqueous dispersion resulted in the reaction product **30** (0.11 g, 0.28 mmol, 34%) as a yellow-orange solid, m.p. 111–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 [s, 9 H, $CO_2C(CH_3)_3$], 1.86 (s, 3 H, 9^1-CH_3), 2.09 (s, 3 H, 4^1-CH_3), 2.17 (s, 3 H, 8^1-CH_3), 2.52 (t, ^3J = 7.99 Hz, 2 H, 3^2-CH_2), 2.99 (t, ^3J = 8.01 Hz, 2 H, 3^1-CH_2), 3.16 (s, 2 H, 11-CH_2), 3.66 (s, 3 H, CO_2CH_3), 6.47 (s, 1 H, 6-C*H*), 8.67 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (126 MHz, BB, ^{1}H/^{13}C-COSY, $CDCl_3$): δ = 8.52 (C-9^1), 8.70 (C-4^1), 11.75 (C-8^1), 20.30 (C-3^1), 28.16 [$CO_2C(CH_3)_3$], 34.62 (C-3^2), 38.08 (C-11), 51.24 (CO_2CH_3), 81.19 [$CO_2C(CH_3)_3$], 109.64 (C-6), 121.95 (C-2), 122.65 (C-4), 128.46 (C-3), 129.07 (C-5), 133.40 (C-7), 138.54 (C-9), 160.17 [$CO_2C(CH_3)_3$], 163.76 (C-8), 173.28 (CO_2CH_3), 202.94 (C-10) ppm. IR (KBr): $\tilde{\nu}$ = 3473, 2975, 2953, 2929, 1737, 1676, 1624, 1595, 1439, 1393, 1368, 1331, 1275, 1256, 1165, 1138, 1091, 1056, 962, 942, 882, 848, 808, 777, 655, 545, 470, 452 cm^{-1}. UV/Vis (*n*-hexane): λ_{max} (ε) = 252 (15500), 368 (21400), 387 nm (17700). MS (EI, 125 °C): *m*/*z* (%) = 387 (25) [M$^+$], 331 (100), 300 (9), 271 (24), 258 (7), 228 (5), 212 (4), 184 (4),127 (3), 91 (2), 77 (2), 57 (7), 41 (5). HRMS (ESI pos, methanol + dichloromethane): *m*/*z*: calcd. for $C_{22}H_{29}NNaO_5$ [M + Na]$^+$ 410.193795; found: 410.193322.

X-ray Crystal Structure Analysis of 25: $C_{22}H_{29}NO_6$, M_r = 403.46, yellow opaque parallelepiped, crystal size 0.34 × 0.26 × 0.10 mm, triclinic, space group P-1, a = 8.4299(3), b = 10.0423(4), c = 13.7683(6) Å, α = 74.765(3), β = 77.259(3), γ = 73.333(3)°, V = 1063.98(8) Å^3, T = 100 K, Z = 2, $\delta_{calcd.}$ = 1.259 g × cm^{-3}, λ = 0.71073 Å, μ(Mo-K_α) = 0.091 mm^{-1}, Bruker–Nonius Kappa-CCD, $3.69 < \theta < 30.99$, 14387 measured reflections, 6735 independent reflections, structure solved by direct methods and refined by full-matrix least-squares on F^2 to R_1 = 0.0492 [$I > 2\sigma(I)$], wR_2 = 0.1254,

262 parameters, S = 1.034, residual electron density +0.577/–0.650 e ×Å^{-3}.

CCDC-654307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Bond lenghts and angles of compound **25**.

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[1] S. I. Beale, *Plant Physiol.* **1990**, *93*, 1273–1279.
[2] A. N. Glazer, *Ann. Rev. Biophys. Biophys. Chem.* **1985**, *14*, 47–77.
[3] J. Cornejo, S. I. Beale, M. J. Terry, J. C. Lagarias, *J. Biol. Chem.* **1992**, *267*, 14790–14798.
[4] C. Kami, K. Mukougawa, T. Muramoto, A. Yokota, T. Shinomura, J. C. Lagarias, T. Kohchi, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 1099–1104.
[5] K. Kohori, M. Hashimoto, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3088–3093.
[6] A. Gossauer, W. Hirsch, *Justus Liebigs Ann. Chem.* **1974**, 1496–1513.
[7] H. Hanzawa, K. Inomata, H. Kinoshita, T. Kakiuchi, K. P. Jayasundera, D. Sawamoto, A. Ohta, K. Uchida, K. Wada, M. Furuya, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 3612–3617.
[8] P. A. Jacobi, I. M. A. Odeh, S. C. Buddhu, G. L. Cai, S. Rajeswari, D. Fry, W. J. Zheng, R. W. Desimone, J. S. Guo, L. D. Coutts, S. I. Hauck, S. H. Leung, I. Ghosh, D. Pippin, *Synlett* **2005**, 2861–2885.
[9] S. E. Boiadjiev, D. A. Lightner, *Org. Prep. Proced. Int.* **2006**, *38*, 347–400.
[10] I. Lindner, B. Knipp, S. E. Braslavsky, W. Gärtner, K. Schaffner, *Angew. Chem. Int. Ed.* **1998**, *37*, 1843–1846.
[11] U. Robben, I. Lindner, W. Gärtner, K. Schaffner, *Angew. Chem. Int. Ed.* **2001**, *40*, 1048–1050.
[12] J. R. Wagner, J. S. Brunzelle, K. T. Forest, R. D. Vierstra, *Nature* **2005**, *438*, 325–331.
[13] S. E. Braslavsky, W. Gärtner, K. Schaffner, *Plant Cell Environ.* **1997**, *20*, 700–706.
[14] M. A. Mroginski, D. H. Murgida, P. Hildebrandt, *Acc. Chem. Res.* **2007**, *40*, 258–266.
[15] A. Gossauer, R.-P. Hinze, *J. Org. Chem.* **1978**, *43*, 283–285.
[16] J. I. DeGraw, *Tetrahedron* **1972**, *28*, 967–972.
[17] R. Kiesewetter, P. Margaretha, *Helv. Chim. Acta* **1985**, *68*, 2350–2354.
[18] S. Andersen, N. B. Das, R. D. Jørgensen, G. Kjeldsen, J. S. Knudsen, S. C. Sharma, K. B. G. Torssell, *Acta Chem. Scand., Ser. B* **1982**, *36*, 1–14.
[19] F. B. LaForge, H. L. Haller, *J. Am. Chem. Soc.* **1936**, *58*, 1777–1780.
[20] M. Matsui, F. B. LaForge, N. Green, M. S. Schechter, *J. Am. Chem. Soc.* **1952**, *74*, 2181–2182.
[21] F. P. Montforts, U. M. Schwartz, *Liebigs Ann. Chem.* **1985**, 1228–1253.

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