Preparation of precursors for the synthesis  
of analogues of rhazinilam

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Dedicated to Professor Pierre Vogel on the occasion of his 70th birthday

Abstract
Rhazinilam a structurally relatively simple tetracyclic natural product exerts interesting  
anticancer activities in vitro, which are difficult to reproduce in vivo. Based on the findings  
accumulated during the synthetic efforts and on the known metabolic sensitivity towards  
oxidation and acids a modified structural analogue of rhazinilam is proposed. A novel  
convergent approach towards the heterocyclic biaryl unit is described. The key sequence for the  
construction of 7 is the Mukaiyama crossed aldol reaction followed by the Staudinger reaction.  
Using known N-alkylation procedures the introduction of the side chains onto the 3-pyrrolin-2-
one intermediate 2 needed for the construction of the tetracycle could not be achieved.

Keywords: Rhazinilam, Mukaiyama crossed aldol, Staudinger reaction, 3-pyrrolin-2-one

Introduction
(R)-(−)-Rhazinilam 1 and some of its congeners manifest a remarkable in vitro activity on the  
tubulin-microtubules equilibrium involved in the formation of mitotic spindle.1-4 These  
tetracyclic compounds were identified as promising targets for developing of a new generation of  
anticancer agents. The scientific challenge of this relatively simple natural product is disclosing  
and explaining in structural terms its activity. Transferring the knowledge from in vitro studies to  
in vivo experiments has proved to be quasi impossible.5 The combination of the findings on the  
chemical reactivity, with the well-known sensitivity of rhazinilam towards oxidative metabolic  
transformations6 was used as a guideline for proposing and designing novel rhazinilam  
analogues. The retrosynthetic approach chosen is conceived so as to avoid the notorious  
sensitivity of non-stabilized pyrroles towards oxidation and/or acid conditions avoiding  
protecting groups as much as possible. However, two syntheses published during the preparation
of our manuscript succeeded to avoid the use of protecting groups.\textsuperscript{7,8} Our group envisaged in parallel with the above mentioned publications that avoiding protecting groups would broaden our understanding of the metabolism and of the mode of interaction of these compounds with tubulin by structure-activity relationship (SAR) studies.

Despite the diversity and efficiency of the known total syntheses of rhazinilam and its natural occurring analogues,\textsuperscript{9,10} to the best of our knowledge none of them has been utilised to obtain modified analogues for biological screening.

Our group has developed a convergent synthesis of the phenyl-pyrrolic core of rhazinilam involving a tandem Mukaiyama aldol-type condensation – Staudinger cyclisation sequence\textsuperscript{11-16} (Scheme 1). The chosen convergent strategy allows a short and efficient synthesis of many derivatives. The new approach complements the classical Knorr pyrrole synthesis.\textsuperscript{17} The key intermediate is the 3-pyrrolin-2-one 2 serving two goals: facilitating the introduction of the substituents needed for the construction of rings B and D and reducing the sensitivity the pyrrole ring precursor (ring C).

\begin{scheme}
\centering
\includegraphics[width=0.8\textwidth]{Scheme1.png}
\caption{Retrosynthetic analysis based on the Mukaiyama – Staudinger tandem sequence}
\end{scheme}

Having this key intermediate 2 in hand, the challenge is finding a reproducible and efficient sequence for the introduction of the B-ring and the D-ring.

**Results and Discussion**

**Previous studies**
The first studies pursued the goal of introducing a side chain needed for the creation of the B-ring (Scheme 2). The realisation of this goal would be the preparation of analogue 1a of the general form depicted in Scheme 2. Earlier structure activity studies had clearly indicated the importance of the B-ring,\textsuperscript{18,19} whereas the D-ring seemed to influence the \textit{in vitro} activity only slightly.\textsuperscript{20-22}
Scheme 2. Synthetic pathway to the formation of lactam B-ring

The synthetic pathway exploited the protocols established for the preparation of 3-pyrrolin-2-one 8 involving the Mukaiyama crossed aldol condensation - Staudinger cyclisation sequence as a key reaction. The synthesis started with the commercially available 2-nitroacetophenone 5 which is brominated and subsequently treated with sodium azide to give the 2-azido-1-(2-nitrophenyl)-ethanone 3. The Mukaiyama crossed aldol reaction has proved to be sensitive to temperatures above -10 °C because the starting materials and products were unstable at higher temperatures. Accelerating the reaction by the use of large excess of a Lewis acid such as TiCl₄ diminished the yield dramatically because of problems during the work-up. Under optimized conditions compound 3 was treated with 3 equivalents of ketene acetal 4 and 0.5 equivalents of TiCl₄ keeping the temperature between -30 °C and -15 °C, the desired aldol product 6 was obtained in very good 76% yield. The Staudinger cyclisation using 1.5 equivalent of triphenylphosphine proceeded smoothly to afford the 2-pyrrolidinone 7 in 80% yield. The subsequent elimination of the tertiary alcohol was achieved treating the 2-pyrrolidinone 7 with 2.1 equivalents of Boc₂O in the presence of catalytic amount of DMAP and resulted in the formation of Boc-protected 2-3-pyrrolin-2-one 8 in excellent yield. As expected the side-chain was introduced to compound 8 at C-5 position of 3-pyrrolin-2-one ring in a sequence of three steps: silylation of 8, second enamine aldol type condensation of silyloxypyrrole 9 with aldehyde 10 and finally Swern oxidation of the resulting product yielding product 11 in good yield. Compound 11 contains all the carbons required to form the nine-membered lactam ring B. However, this intermediate has proved to be very sensitive, probably due to the ease of deprotonation followed by unwanted side reactions. As a result, our efforts to introduce the missing fragment necessary to obtain the D-ring have often failed or have been inconclusive. Preparation of 11 and its tentative transformation to 1a are described in an another paper: Vallat,
Alternative strategies avoiding this problem had to be developed. Inverting the proposed sequence by constructing the D ring at first might bring a solution to the observed problem.

**Synthesis of the building blocks 20 and 22**

A strategy introducing a side chain containing all the carbon atoms of ring D and the appropriate functionality for the ring closure and the introduction of ring B on the 3-pyrrolin-2-one ring was chosen. The attractiveness of this strategy was the fact that the intramolecular Michael addition reaction has been successfully applied\(^\text{24}\) in former syntheses of rhazinilam. The activation of the pyrrole through the O-silyl group in the 2-position should facilitate the ring-closing process (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Synthetic pathway to the formation of D-ring via an intramolecular Michael addition.

To realize this strategy the corresponding iodo acrylate 20 or the pentafluorophenyl ester 22 had to be prepared.

![Scheme 4](image)

**Scheme 4.** Synthesis of acrylates 20 and 22.
The synthesis of these acrylates started with γ-butyrolactone 14 which was converted into the Weinreb amide 15 according to the procedure described by Fukuda et al.\textsuperscript{25,26} in 90% yield over the two steps (Scheme 4). Reaction of amide 15 with ethylmagnesium bromide afforded the alkynone 16\textsuperscript{27} in nearly quantitative yield. Compound 16 underwent a Wadsworth-Horner-Emmons (WHE)\textsuperscript{24,28} olefination to give the unsaturated ester 17 as a 60:40 mixture of E/Z-isomers in excellent yield. After desilylation of 17 with TBAF, treatment of the resulting alcohol 18 with tosyl chloride produced the tosyl acrylate 19\textsuperscript{29} in 78% yield over the two steps. Finally 19 was converted into the desired iodo acrylate 20\textsuperscript{30} in excellent 67% overall yield over seven steps starting from the lactone 14.

In parallel, the alcohol 18 was oxidized with Jones' reagent\textsuperscript{31,32} (1.9 M, acetone/H\textsubscript{2}O, 0 °C) to provide the acid 21 in 81% yield. Activation of acid 21 using pentafluorophenol and N,N'-dicyclohexylcarbodiimide provided the pentafluorophenyl ethyl ester 22\textsuperscript{33} in moderate yield. However, the activated acrylate 22 could be obtained from γ-butyrolactone 14 in seven steps and 31% overall yield.

### N-alkylation of 4-(2-nitrophenyl)-1H-pyrrol-2(5H)-one 2

In the literature only a few examples of N-alkylation of tetramates have been reported.\textsuperscript{34,35} Thus, Jones and Bates\textsuperscript{34} accomplished the alkylation of NH-3-pyrrolin-2-one by two procedures. N-methylated 4-O-methyltetramate 24\textsubscript{a} was obtained from 3-pyrrolin-2-one 23\textsubscript{a} using a strong base such as n-BuLi at low temperature (Scheme 5).

![Scheme 5. Reported N-alkylation of O-methyl tetramate 23\textsubscript{a} using n-BuLi.\textsuperscript{34}](image)

However, the most effective reported N-alkylation procedure used phase-transfer (PT) conditions for promoting N-1 deprotonation and alkyl iodides or benzyl bromides as electrophiles (Scheme 6). Under these conditions double alkylation products 25 were often co-isolated in minor amounts. A more recent systematic study of the reaction of 4-O-methyl tetramate was reported by Jones and Patience.\textsuperscript{35} The amount of N-1, C-5 or multiple alkylations could be influenced by the stoichiometry of the reagents. Di- and trialkyl derivatives were obtained using 10 mol equivalents of base and alkyl halide. In many cases increasingly large excess of these reagents and/or longer reaction times led to extensive decomposition of 3-pyrrolin-2-one. In some cases even O-alkylated by-products were isolated. However, the normal sequence of deprotonation of tetramates was brought to light.
Scheme 6. Reported N-alkylation of O-methyl tetramates under phase transfer conditions \(^{34,35}\)

As an alternative the authors investigated the alkylation at C-5 of the N-unsubstituted tetramates using at least two equivalents of a strong base under low temperature conditions (Scheme 7). The resulting dianion of 4-O-methyl tetramate 26 underwent preferential C-alkylation in moderate to good yields using benzyl bromide or alkyl iodides as electrophiles.

Scheme 7. Reported C-5-alkylation of the N-unsubstituted O-methyl tetramates via the intermediate dianion 26\(^ {35}\)

Based on the encouraging results reported in the literature, we focused our attention on the N-alkylation with alkyl iodide 20 of 3-pyrrolin-2-one 2 quantitatively prepared from compound 8 by deprotection using TFA. Despite numerous efforts varying the approach and the reaction parameter the N-alkylation of 3-pyrrolin-2-one 2 using olefin 20 could not be achieved in our hands (Table 1). Often starting material could be re-isolated or degradation of 3-pyrrolin-2-one was observed as evidenced by the poor mass-balance after work-up and purification. Using n-BuLi as a strong base at low temperatures and then warming the solution to room temperature led to recovery of the iodide 20 whereas the 3-pyrrolin-2-one 2 was degraded (Entry 1). Using different variants of the phase transfer alkylation did not lead to product formation either. Under these milder conditions both starting materials could be partially recovered (Entry 2 – 4). Using strong bases like potassium hexamethyldisilazane or sodium hydride in THF or in DMF did not allow detection of product formation (Entry 5 and 6 for KHMDS and 7 to 9 for NaH).
Table 1. Attempts to N-alkylate the 3-pyrrolin-2-one 2

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (equiv.)</th>
<th>Base (equiv.)</th>
<th>PTS (^a) (equiv.)</th>
<th>Solvent</th>
<th>(T, ^\circ C)</th>
<th>(t, h)</th>
<th>Product (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{15,34})</td>
<td>20 (1.13)</td>
<td>(n)-BuLi (1.12)</td>
<td>-</td>
<td>THF</td>
<td>0-20</td>
<td>3.5</td>
<td>20</td>
</tr>
<tr>
<td>2(^{34,35})</td>
<td>20 (1.25)</td>
<td>KOH (6.00)/K(_2)CO(_3) (1.25)</td>
<td>Bu(_4)NHSO(_4) (0.10)</td>
<td>Toluene</td>
<td>60</td>
<td>5</td>
<td>20 + 2 decomposed</td>
</tr>
<tr>
<td>3(^{35})</td>
<td>20 (3.00)</td>
<td>KOH (1.40)</td>
<td>Bu(_4)NHSO(_4) (0.10)</td>
<td>THF</td>
<td>0-20</td>
<td>18</td>
<td>20 + 2 decomposed</td>
</tr>
<tr>
<td>4(^{35,\text{c}})</td>
<td>BnBr (3.00)</td>
<td>KOH (1.40)</td>
<td>Bu(_4)NHSO(_4) (0.10)</td>
<td>THF</td>
<td>0-20</td>
<td>18</td>
<td>BnBr + 2</td>
</tr>
<tr>
<td>5(^{37})</td>
<td>19 (1.1)</td>
<td>KHMDS (1.1)</td>
<td>-</td>
<td>THF</td>
<td>70</td>
<td>2</td>
<td>19 + 2 decomposed</td>
</tr>
<tr>
<td>6(^{37})</td>
<td>20 (1.1)</td>
<td>KHMDS (1.1)</td>
<td>-</td>
<td>THF</td>
<td>70</td>
<td>3</td>
<td>20 + 2 decomposed</td>
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<td>7(^{38})</td>
<td>19 (1.10)</td>
<td>NaH (1.10)</td>
<td>TBAI (0.22)</td>
<td>THF</td>
<td>20</td>
<td>27</td>
<td>19 + 2 decomposed</td>
</tr>
<tr>
<td>8(^{39})</td>
<td>20 (1.10)</td>
<td>NaH (1.10)</td>
<td>-</td>
<td>DMF</td>
<td>20</td>
<td>24</td>
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<tr>
<td>9(^{39})</td>
<td>20 (1.10)</td>
<td>NaH (1.10)</td>
<td>-</td>
<td>DMF</td>
<td>0-20</td>
<td>24</td>
<td>20 + 2 decomposed</td>
</tr>
</tbody>
</table>

\(^a\) Phase transfer catalyst was added. \(^b\) According to NMR and/or GC. \(^\text{c}\) Benzyl bromide was used as electrophile.

Conclusions

The synthesis of an advanced precursor for the planned synthesis of the rhazinilam analogue could be achieved using the tandem process Mukaiyama aldol condensation – Staudinger cyclisation. The pyrrolidinone 7 was transformed in two steps into the 2-silyloxypyrrole 9. This electron-rich pyrrole was transformed in two steps, reaction with the aldehyde followed by oxidation, into compound 11. Further transformation of this advanced intermediate was
hampered by its sensitivity to acids and to oxygen. As an alternative we studied the N-alkylation of the 3-pyrrolin-2-one 2. This process is attractive because the product of the N-alkylation could contain all the atoms and the functionality needed for the formation of the ring D via Michael addition. In this process the substituent for the elaboration of ring B could be introduced simultaneously. We report the synthesis of this building block. The side chain needed for the construction of the ring B could be introduced. Under the conditions reported in the literature and under the conditions tested in our laboratory, the introduction of a side chain by nucleophilic N-alkylation could not be achieved. Further studies are required which will be reported in due time.

**Experimental Section**

**General.** Reactions employing air- and/or moisture-sensitive reagents and intermediates were carried out under nitrogen or argon using dry solvents. Thin layer chromatography TLC: The retention factor (R_f) quoted is rounded to the nearest 0.01. Column chromatography: Flash silica gel (Silica 32-63, 60 Å; Chemie Brunschwig AG, Basel, Switzerland). Gas chromatography: performed on Agilent 6850 Series chromatograph using high resolution gas chromatography HP-5 column (30 m × 0.32 mm × 0.25 μm; polysiloxane (crosslinked 5% Ph, Me siloxane), gas: He, 1.1 mL/min. Injection temperature 245 °C, detector temperature (FID) 300 °C. Temperature program: 100 °C (3 min), 100-280 °C 15 °C/min, 280 °C (4 min). IR spectra: Perkin–Elmer Spectrum One version B FT-IR unit. Absorption maxima (ν_{max}) are reported in wave numbers (cm\(^{-1}\)). The intensity of spectrum was divided into five equal parts vs (very strong – the maximum intensity), s (strong), m (medium), w (weak), vw (very weak) and br (broad). NMR spectra: Bruker Avance-400 spectrometer at 400 (\(^1\)H NMR), 376 (\(^19\)F NMR) or 100 (\(^13\)C NMR) at 298 K. Referenced to the residual protonated NMR solvent, defined as δ 7.26 ppm (\(^1\)H NMR) or δ 77.00 ppm (\(^13\)C NMR) for CHCl₃, δ 3.31 ppm (\(^1\)H NMR) or δ 49.00 ppm (\(^13\)C NMR) for CH₃OH, δ 2.50 ppm (\(^1\)H NMR) or δ 39.52 ppm (\(^13\)C NMR) for DMSO-d₆, δ 2.05 ppm (\(^1\)H NMR) or δ 29.84 and 206.26 ppm (\(^13\)C NMR) for acetone-d₆. Spectra are reported as: Chemical shifts (δ) [multiplicity, number of protons, coupling constant(s) J (Hz) and assignment (where possible)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; br = broad; m = multiplet or combinations of the above. The sign “≈” denotes for the average value of J varying from 0.2 to 0.4 Hz. MS: ESI (electro-spray ionisation) or APCI (atmospheric pressure chemical ionisation) were recorded on a ThermoFinnigan LCQ instrument (San José, California, USA). High resolution mass spectrometry (HR-MS) was carried out at the University of Fribourg (Switzerland), recorded on a Brucker BioAPEX II Daltonics instrument by ESI.

**2-Azido-1-(2-nitrophenyl)ethanone (3).**° To a stirred mixture of 2′-nitroacetophenone 5 (20 g, 121 mmol) and AlCl₃ (500 mg, 3.75 mmol) in dry ether (600 mL) at 0 °C and under argon was added dropwise bromine (6.2 mL, 121 mmol) over 1 h. The reaction mixture was allowed to
warm to room temperature and stirred for 3 h (reaction progress monitored by TLC). The organic layer was washed with water (3 × 200 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel (CH₂Cl₂/petroleum ether, 70:30) to afford 31.7 g of 2-bromo-1-(2-nitrophenyl)ethanone as a yellow solid. The product was crystallized from MeOH to give 26.1 g of pure product. Yield: 88%. Colorless micro-needles; TLC: Rf (CH₂Cl₂/petroleum ether, 70:30) 0.4; ¹H NMR (400 MHz, CDCl₃): δ 8.21 (dd, ³J 8.1 Hz, ⁴J 1.2 Hz, 1 H, Ar-H), 7.79 (td, 2 × ³J 7.5 Hz, ⁴J 1.3 Hz, 1 H, Ar-H), 7.68 (dd, ³J 8.1 Hz, ⁴J 7.5 Hz, ³J 1.6 Hz, 1 H, Ar-H), 7.50 (dd, ³J 7.5 Hz, ⁴J 1.6 Hz, 1 H, Ar-H), 4.30 (s, 2 H, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 194.3 (C=O), 145.4 (Ar-C), 134.9 (Ar-C), 134.8 (Ar-CH), 131.3 (Ar-CH), 129.1 (Ar-CH), 124.5 (Ar-CH), 33.9 (CH₂) 

To a mechanically stirred solution of sodium azide (3.0 g, 14.55 mmol) was added portionwise to a solution of methyl 4-bromomethoxyvinyl)oxy(trimethyl)silane (3.68 g, 43.66 mmol) in water (55 mL). The mixture was stirred for 48 h at 6 °C and then extracted with Et₂O (4 × 200 mL). The organic layer was washed with water (1 × 200 mL), dried over MgSO₄, filtered and evaporated. The residue was purified by column chromatography on silica gel using CH₂Cl₂ as eluent to afford 6.17 g of 3 as a brown solid. The product was crystallized from Et₂O/hexane to give 5.83 g of pure 3. Yield: 75%. Yellow-brown micro-needles; TLC: Rf (CH₂Cl₂, 100%) 0.5; ¹H NMR (400 MHz, CDCl₃): δ 8.23 (dd, ³J 8.0 Hz, ⁴J 1.5 Hz, 1 H, Ar-H), 7.80 (td, 2 × ³J 7.4 Hz, ³J 1.5 Hz, 1 H, Ar-H), 7.70 (ddd, ³J 8.0 Hz, ⁴J 7.4 Hz, ³J 1.6 Hz, 1 H, Ar-H), 7.43 (dd, ³J 7.4 Hz, ³J 1.6 Hz, 1 H, Ar-H), 4.32 (s, 2 H, CH₂); ¹³C NMR (100 MHz, CDCl₃): δ 197.2 (C=O), 145.9 (Ar-C), 135.2 (Ar-C), 135.0 (Ar-CH), 131.5 (Ar-CH), 127.9 (Ar-CH), 124.6 (Ar-CH), 57.8 (CH₂) 

[(1-Methoxyvinyl)oxy]trimethylsilane (4).¹⁵ To a stirred solution of LHMDS (1.0 M in THF, 100 mL, 100 mmol) in dry THF (30 mL) was added dropwise a solution of methyl acetate (6.17 g, 83.33 mmol) in dry THF (37 mL) at -78 °C and under argon. After 30 min at -78 °C, TMSCl (10.86 g, 100 mmol) was added dropwise over 20 min. The mixture was allowed to stir at -78 °C for 1.5 h. The solvent was removed in vacuo and the excess salts were precipitated by the addition of dry pentane (30 mL). After filtration through a plug of Celite and evaporation of solvent, the residue was purified by distillation (48-50 °C/45 mmHg) to afford 11.68 g of 4. Yield: (96%). Clear, colourless oil; TLC: Rf (CH₂Cl₂, 100%) 0.4; ¹H NMR (400 MHz, CDCl₃): δ 3.55 (s, 3 H, OCH₃), 3.22 and 3.11 (AB system, ²J 2.6 Hz, 2 H, CH₂), 0.25 (s, 9 H, Si-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 162.1 (C), 59.9 (CH₂), 55.1 (OCH₃), 2.5 (Si-CH₃). 

Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)butanoate (6).¹⁵ 2-Azido-1-(2-nitrophenyl)ethanone 3 (3.0 g, 14.55 mmol) was added portionwise to a stirred solution of ((1-methoxyvinyl)oxy)trimethylsilane 4 (6.39 g, 43.66 mmol) in dry CH₂Cl₂ (60 mL) at -30 °C and under argon. A solution of freshly distilled TiCl₄ (0.84 mL, 7.28 mmol) in dry CH₂Cl₂ (10 mL) was added dropwise over 15 min. The resulting mixture was stirred at -30 °C for 15 min and then allowed to reach -15 °C over a period of 30 min. The dark red solution was quenched with NaOH (2.0 M, 15 mL) and extracted with CHCl₃ (4 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over MgSO₄, filtered and concentrated. The residue was
purified by flash chromatography on silica gel using CH₂Cl₂ as eluent to afford 3.39 g of 6 as a clear, slightly yellowish oil which solidified on standing. The product was crystallised from Et₂O/hexane to give pure 6 (3.10 g, 76%). White solid; TLC: Rf (CH₂Cl₂, 100%) 0.3; Mp: 77 °C; ¹H NMR (400 MHz, CDCl3): δ 7.45-7.52 (m, 4 H, 4 Ar-CH), 4.83 (s, 1 H, OH), 3.66 (s, 3 H, CH₃), 3.80 and 3.59 (AB system, ²J 12.7 Hz, 2 H, N₃-CH₂), 3.17 and 3.06 (AB system, ²J 16.7 Hz, 2 H, CH₂-CO₂CH₃); ¹³C NMR (100 MHz, CDCl3): δ 125.4 (CH), 83.7 (C₁), 131.2 (Ar-C'), 131.1 (Ar-CH), 129.4 (Ar-CH), 128.1 (Ar-CH), 124.5 (Ar-CH), 76.2 (C), 59.2 (CH₂-N₃), 52.5 (OCH₃), 41.0 (CH₂-CO₂CH₃).

4-Hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (7),¹⁵ Methyl 4-azido-3-hydroxy-3-(2-nitrophenyl)butanoate 6 (8.42 g, 30.05 mmol) and triphenylphosphine (12.00 g, 45.07 mmol) were dissolved in THF (126 mL) at room temperature. After 10 min, deionized water (1%, 1.26 mL) was added. The resulting mixture was stirred at room temperature for 3 days and then the solvents were evaporated in vacuo. The crude product was crystallised from MeOH and washed with EtOAc to give 5.43 g of pure 7. Yield: 81%. White solid; MP: 223 °C; IR (KBr): νmax 3403 (s), 3227 (m), 1673 (vs), 1525 (s), 1373 (s) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 7.77 (br s, 1 H, Ar-CH), 7.66 (dd, ³J 7.8 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 7.65 (dd, ³J 7.9 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 7.59 (m (partially resolved), ³J 7.9 Hz, ³J 7.3 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 7.50 (m partially resolved), ³J 7.8 Hz, ³J 7.3 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 6.06 (s, 1 H, OH), 3.65 and 3.46 (AB system, ²J 10.6 Hz, 2 H, CH₂-NH), 2.96 and 2.42 (AB system, ²J 16.6 Hz, 2 H, CH₂-CONH); ¹³C NMR (100 MHz, DMSO-d₆): δ 173.8 (C=O), 150.1 (Ar-C), 137.0 (Ar-C), 131.2 (Ar-CH), 128.7 (Ar-CH), 127.4 (Ar-CH), 123.9 (Ar-CH), 76.3 (C₉), 55.4 (CH₂-NH), 45.7 (CH₂-CONH); MS-ESI: 245.2 (100, [M+Na]⁺).

tert-Butyl 4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (8).¹⁵ To a stirred suspension of pyrrolidinone 7 (1.0 g, 4.50 mmol) in dry THF (100 mL) at room temperature and under argon was added DMAP (222 mg, 1.80 mmol) followed by Boc₂O (2.06 g, 9.45 mmol). The resulting solution was stirred at room temperature for 5 days, then was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH₂Cl₂/MeOH, 99:1) to afford 1.39 g (100%) of Boc-protected 3-pyrrolin-2-one 8 as a viscous, brownish red oil. The product was crystallised from Et₂O/petroleum ether to give 0.97 g of pure 8. Yield: 71%. White solid; TLC: Rf (CH₂Cl₂/MeOH, 99:1= 0.2; IR (KBr): νmax 3105 (vw), 2981 (w), 2924 (w), 1781 (vs), 1693 (m), 1520 (vs), 1369 (s), 1357 (vs) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.12 (dd, ³J 8.1 Hz, ⁴J 1.2 Hz, 1 H, Ar-CH), 7.74 (tt, 2 × ³J 7.5 Hz, ⁴J 1.1 Hz, 1 H, Ar-CH), 7.65 (tt, 2 × ³J 7.7 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 7.43 (dd, ³J 7.5 Hz, ⁴J 1.4 Hz, 1 H, Ar-CH), 6.15 (t, ⁴J 1.5 Hz, 1 H, CH), 4.56 (d, ⁴J 1.5 Hz, 2 H, CH₂), 1.58 (s, 9 H, Si-CH₃); ¹³C NMR (400 MHz, CDCl₃): δ 168.4 (C=O), 155.7 (Ar-C), 149.6 (Ar-C), 147.8 (C), 134.0 (Ar-CH), 131.1 (Ar-CH), 130.7 (Ar-CH), 128.7 (Ar-C), 125.4 (Ar-CH), 125.3 (CH), 83.7 (C-Si), 53.4 (CH₂-NH), 28.5 (CH₃); MS-ESI: 326.9 (100, [M+Na]⁺). Anal. Calcd for C₁₁H₁₂N₂O₅: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.23; H, 5.39; N, 9.11.
4-(tert-Butyldiphenylsilyloxy)-N-methoxy-N-methylbutanamide (15) \(^{25}\)  

\(N,O\)-dimethylhydroxylamine hydrochloride (1.03 g, 10.31 mmol) was dissolved in dry CH\(_2\)Cl\(_2\) (50 mL) under argon. The solution was cooled to 0 °C and Me\(_2\)AlCl (1.0 M solution in \(n\)-hexane, 10.3 mL, 10.31 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. Neat γ-butyrolactone 14 (0.72 mL, 93.8 mmol) was then added slowly and the resulting mixture was stirred at room temperature for 21 h. The reaction mixture was quenched with water (10 mL). The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 10 mL). Aqueous phase was diluted with saturated Rochelle’s salt (10 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 40 mL). The combined organic phases were dried over MgSO\(_4\), filtered and concentrated. The crude alcohol (1.42 g) as a clear, colourless oil. \(R_f\) (CH\(_2\)Cl\(_2\)/MeOH, 95:5) 0.2. GC (method IZ): \(t_f\) 6.67 min.

Under argon, imidazole (728 mg, 10.69 mmol) was added to a solution of the crude alcohol in dry CH\(_2\)Cl\(_2\) (50 mL) and the solution was cooled to 0 °C. tert-Butyldiphenylchlorosilane (2.32 mL, 9.75 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with water (20 mL). The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 40 mL). The combined organic phases were dried over MgSO\(_4\), filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 70:30) to afford 15 (3.25 g, 90%). Clear, colourless oil; TLC: \(R_f\) (Petroleum ether/EtOAc, 50:50) 0.6; GC: \(t_R\) 16.28 min. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.66 (≈ td, \(^3\)J 6.1 Hz, 2 × \(^2\)J 1.5 Hz, 4 H, Ar-CH), 7.44-7.35 (m, 6 H, Ar-CH), 3.73 (t, \(^3\)J 7.5 Hz, 2 H, CH\(_2\)-CO), 1.83 (tt, \(^3\)J 7.5 Hz, \(^3\)J 6.1 Hz, 2 H, C(CH\(_2\))\(_2\)-C), 1.05 (s, 9 H, CH\(_3\)-C); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 174.4 (C=O) visible on HMBC spectrum, 135.5 (Ar-CH), 133.9 (Ar-C), 129.6 (Ar-CH), 127.6 (Ar-CH), 63.2 (CH\(_2\)-OSi), 61.2 (H\(_2\)-C=O), 32.3 (H\(_3\)-C-N), 28.4 (C(CH\(_2\))\(_2\)-C), 27.6 (CH\(_2\)-CO), 26.9 (H\(_3\)-C), 19.2 (C); MS-ESI: 408.5 (100, [M+Na]\(^+\)).

6-(tert-Butyldiphenylsilyloxy)hexan-3-one (16) \(^{27,40}\) Weinreb amide 15 (3.25 g, 8.41 mmol) was dissolved in dry THF (17 mL) under argon. The solution was cooled to 0 °C and ethylmagnesium bromide (1.0 M solution in THF, 16.83 mL, 16.83 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 45 min and quenched with saturated aqueous NH\(_4\)Cl (40 mL). The mixture was poured into Et\(_2\)O (60 mL) and the phases were separated. The aqueous phase was extracted with Et\(_2\)O (3 × 100 mL). The combined organic phases were dried over Na\(_2\)SO\(_4\), filtered and concentrated. The solvent was removed in vacuo to afford spectroscopically pure ketone 16 (2.98 g). The product was taken to the next step without further purification. Yield: 100%. Clear, colourless oil; TLC: \(R_f\) (Petroleum ether/EtOAc, 80:20) 0.6; GC: \(t_R\) 5.01 min; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.65 (≈ td, \(^3\)J 6.1 Hz, 2 × \(^2\)J 1.5 Hz, 4 H, Ar-CH), 7.45-7.35 (m, 6 H, Ar-CH), 3.66 (t, \(^3\)J 6.1 Hz, 2 H, CH\(_2\)-OSi), 2.52 (t, \(^3\)J 7.4 Hz, 2 H, CH\(_2\)-CO), 2.41 (q, \(^3\)J 7.3 Hz, 2 H, CH\(_3\)-CH\(_2\)-CO), 1.83 (tt, \(^3\)J 7.4 Hz, \(^3\)J 6.1 Hz, 2 H, C(CH\(_2\))\(_2\)-C), 1.04 (t, \(^3\)J 7.3 Hz, 3 H, CH\(_3\)-CH\(_2\)\(_2\)), 1.04 (s, 9 H, CH\(_3\)-C); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 211.5 (C=O), 135.5 (Ar-CH), 133.8 (Ar-C), 129.6 (Ar-CH), 127.6 (Ar-CH), 63.1 (CH\(_2\)-OSi), 38.7
(CH₂-CH₂-CO), 35.9 (CH₃-CH₂-CO), 26.9 (CH₃-C), 26.7 (C-CH₂-C), 19.2 (C-Si), 7.8 (H₃C-CH₂-CO); MS-ESI: 377.6 (100, [M+Na]+).

(E/Z)-Ethyl 6-(tert-butyldiphenylsilyloxy)-3-ethylhex-2-enoate (17). A flame-dried 250 mL two-necked round bottom flask was charged with NaH (864 mg of 95%, 34.21 mmol) and 100 mL of dry DME. Neat triethyl phosphonoacetate (7.62 mL, 37.25 mmol) was then added slowly to the suspension at room temperature. After the addition was completed (~15 min), the ketone 16 (2.70 g, 7.60 mmol) in dry DME (25 mL) was added. The homogeneous mixture was refluxed overnight then cooled to room temperature. The reaction mixture was diluted with 70 mL of water and 100 mL of EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (80 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 99:1 to 96:4) to afford an E/Z mixture (60:40) of 17 (3.13 g, 97%). Clear, slightly yellowish oil; TLC: Rf (Petroleum ether/EtOAc, 95:5) 0.2; GC: t_R 17.06 min (Z) and 17.33 min (E); IR (KBr, film): vmax 3072 (w), 3050 (w), 2959 (s), 2933 (vs), 2897 (s), 2859 (s), 1714 (m), 1716 (vs), 1645 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) (E)-isomer: δ 7.66 (dd, 3J 7.7 Hz, 4J 2.7 Hz, 4J 1.5 Hz, 4H, Ar-CH), 7.35-7.446 (m, 6H, Ar-CH), 5.61 (s, 1H, CH), 4.14 (q, 3J 7.2 Hz, 2H, CH₃-CH₂-O), 3.67 (t, 3J 6.2 Hz, 2H, CH₂-O), 2.60 (q, 3J 7.5 Hz, 2H, CH₃-CH₂-C), 2.25 (=t, 3J 7.3 Hz, 2H, -CH₂-CH₂-C), 1.72 (=quint, 2 × 3J 6.2 Hz, 2H, -CH₂-CH₂-C), 1.28 (t, 3J 7.2 Hz, 3H, CH₃-CH₂-O), 1.06 (t, 3J 7.5 Hz, 3H, CH₃-CH₂-C), 1.05 (s, 9H, CH₃-C), 1H NMR (400 MHz, CDCl₃) (Z)-isomer: δ 7.66 (dd, 3J 7.7 Hz, 4J 2.7 Hz, 4J 1.5 Hz, 4H, Ar-CH), 7.35-7.446 (m, 6H, Ar-CH), 5.61 (s, 1H, CH), 4.11 (q, 3J 7.1 Hz, 2H, CH₃-CH₂-O), 3.71 (t, 3J 6.4 Hz, 2H, CH₂-O), 2.67 (=t, 3J 7.8 Hz, 2H, -CH₂-CH₂-C), 2.17 (dq, 3J 7.4 Hz, 4J 1.0 Hz, 2H, CH₃-CH₂-C), 1.70 (=quint, 2 × 3J 6.2 Hz, 2H, -CH₂-CH₂-C), 1.25 (t, 3J 7.1 Hz, 3H, CH₃-CH₂-O), 1.05 (t, 3J 7.3 Hz, 3H, CH₃-CH₂-C), 1.05 (s, 9H, CH₃-C); ¹³C NMR (100 MHz, CDCl₃) (E)-isomer: δ 166.6 (COO), 165.7 (C₀), 135.7 (Ar-CH), 134.0 (Ar-C), 129.8 (Ar-CH), 127.8 (Ar-CH), 115.0 (CH), 63.4 (-CH₂-O), 59.6 (CH₃-CH₂-O), 34.4 (CH₂-CH₂-C), 30.8 (CH₂-CH₂-C), 27.0 (CH₃-C), 25.4 (CH₃-CH₂-C), 19.4 (C-Si), 14.5 (CH₃-CH₂-O), 13.1 (CH₃-CH₂-C); ¹³C NMR (100 MHz, CDCl₃) (Z)-isomer: δ 166.7 (COO), 165.6 (C₀), 135.8 (Ar-CH), 134.2 (Ar-C), 129.7 (Ar-CH), 127.7 (Ar-CH), 114.6 (CH), 64.1 (-CH₂-O), 59.6 (CH₂-CH₂-O), 31.8 (CH₂-CH₂-C), 31.4 (CH₂-CH₂-C), 28.9 (CH₂-CH₂-C), 27.0 (CH₃-C), 19.4 (C-Si), 14.5 (CH₃-CH₂-O), 12.2 (CH₃-CH₂-C); MS-ESI: 447.6 (100, [M+Na]+); HR-MS (ESI): 447.23192 ([M+Na]+); C₂₆H₃₆O₅SiNa⁺; calc. 447.23259.

(E/Z)-Ethyl 3-ethyl-6-hydroxyhex-2-enoate (18). At 0°C and under argon, TBAF (1.0 M solution in THF, 6.65 mL, 6.65 mmol) was added to a solution of acrylate 17 (2.57 g, 6.04 mmol) in 35 mL of dry THF. The resulting solution was stirred at room temperature for 3 h then concentrated. The residue was diluted with water (40 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (40 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 50:50) to afford an E/Z mixture (60:40) of 18 (1.00 g, 89%). Clear, slightly yellowish oil; TLC: Rf (Petroleum ether/EtOAc, 50:50) 0.4; GC: t_R 12.72 min (Z) and 13.21 min...
(E); IR (KBr, film): v_max 3415 (br s), 2938 (vs), 2876 (s), 1715 (vs), 1644 (s), 1463 (s), 1421 (m), 1380 (s), 1304 (s), 1275 (s), 1209 (vs), 1148 (vs), 1097 (s), 1038 (vs), 920 (w), 870 (m), 809 (vw), 736 (w), 628 (w) cm⁻¹; 1H NMR (400 MHz, CDCl₃) (E)-isomer: δ 5.63 (s, 1 H, CH), 4.14 (q, 3J 7.0 Hz, 2 H, CH₂-CH₂-O), 3.67 (t, 3J 6.4 Hz, 2 H, CH₂-OH), 2.62 (q, 3J 7.5 Hz, 2 H, CH₃-CH₂-C), 2.24 (2H CH₂, -CH₂-CH₂-C), 1.77-1.89 (m partially resolved), 1H 7.2 Hz, 3J 4.13 (q, 80:20) 0.3; phases were separated and the aqueous phase was extracted with Et₂O. The product was identified by comparison of IR and 1H NMR spectra with literature values.

Issue in Honor of Prof. Pierre Vogel

(E/Z)-Ethyl 3-ethyl-6-(tosyloxy)hex-2-enolate (19). To a solution of alcohol 18 (1.00 g, 5.37 mmol) in dry CH₂Cl₂ (5 mL) at 0 °C and under argon was added p-toluene sulfonyl chloride (1.56 g, 8.16 mmol), followed by pyridine (0.93 mL, 11.60 mmol). The reaction mixture was stirred at room temperature overnight then diluted with 50 mL of water and 50 mL of Et₂O. The phases were separated and the aqueous phase was extracted with Et₂O (2 × 50 mL). The combined organic phases were washed with 1M HCl (50 mL), saturated aqueous NaHCO₃ (50 mL), brine (50 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 80:20) to afford an E/Z mixture (60:40) of 19. (1.60 g, 88%). Clear, colourless oil; TLC: Rf 15.70; IR (KBr, film): v_max 2974 (m), 2934 (m), 1713 (vs), 1645 (m), 1599 (w), 1496 (vw), 1463 (m), 1363 (vs), 1308 (w), 1274 (w), 1209 (s), 1189 (vs), 1177 (vs), 1149 (s), 1098 (m), 1037 (m), 1009 (w), 967 (m), 929 (s), 870 (w), 836 (m), 816 (m), 785 (w), 738 (w), 706 (vw), 690 (vw), 665 (s), 577 (w), 555 (s) cm⁻¹; 1H NMR (400 MHz, CDCl₃) (E)-isomer: δ 7.80 (d, 3J 8.1 Hz, 2 H, A₂B₂, Ar-CH), 7.35 (d, 3J 8.1 Hz, 2 H, A₂B₂, Ar-CH), 5.51 (s, 1 H, CH), 4.13 (q, 3J 7.1 Hz, 2 H, CH₃-CH₂-O), 4.04 (t, 3J 6.4 Hz, 2 H, CH₂-OS), 2.54 (q, 3J 7.5 Hz, 2 H, CH₃-CH₂-C), 2.45 (s, 3 H, CH₃-C), 2.17 (=t, 3J 7.3 Hz, 2 H, -CH₂-CH₂-C), 1.84 (=quint, 2 × 3J 6.2 Hz, 2 H, -CH₂-CH₂-C), 1.27 (t, 3J 7.1 Hz, 3 H, CH₃-CH₂-O), 1.02 (t, 3J 7.5 Hz, 3 H, CH₃-CH₂-C); 1H NMR (400 MHz, CDCl₃) (Z)-isomer: δ 7.80 (d, 3J 8.1 Hz, 2 H, A₂B₂, Ar-CH), 7.34 (d, 3J 8.1 Hz, 2 H, A₂B₂, Ar-CH), 5.63 (s, 1 H, CH), 4.11 (q, 3J 7.1 Hz, 2 H, CH₃-CH₂-O), 4.06 (t, 3J 6.4 Hz, 2 H, CH₂-OS), 2.58 (=t, 3J 7.8 Hz, 2 H, -CH₂-CH₂-C), 2.45 (s, 3 H, CH₃-C), 2.13 (dq, 3J 7.4 Hz, 4J 1.3 Hz, 2 H, CH₃-CH₂-C), 1.80 (=quint, 2 × 3J 6.2 Hz, 2 H, -CH₂-CH₂-C), 1.25 (t, 3J 7.1 Hz, 3 H, CH₃-CH₂-O), 1.04 (t, 3J 7.4 Hz, 3 H, CH₃-CH₂-C); 1H NMR (100 MHz, CDCl₃) (E)-isomer: δ 166.1 (COO), 163.2 (C₀), 144.8 (Ar-C), 133.1 (Ar-C), 129.9 (Ar-CH), 127.9 (Ar-CH), 115.7 (CH), 69.6 (-CH₂-OS), 59.6 (CH₃-CH₂-O), 33.3 (CH₂-CH₂-C), 26.9 (CH₂-CH₂-CH₂),
(E/Z)-Ethyl 3-ethyl-6-iodohex-2-enoate (20). To a solution of tosylate 19 (700 mg, 2.06 mmol) in acetone (70 mL) was added sodium iodide (925 mg, 6.17 mmol), followed by K$_2$CO$_3$ (853 mg, 6.17 mmol). The reaction mixture was refluxed for 5 h then concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to afford an E/Z mixture (60:40) of 20 (594 mg, 98%). Clear, colourless oil; TLC: $R_f$ (Petroleum ether/EtOAc, 80:20) 0.6; GC: $t_R$ 10.10; IR (KBr, film): $\nu_{\text{max}}$ 2964 (s), 2929 (s), 2873 (m), 1715 (vs), 1645 (s), 1460 (m), 1379 (m), 1314 (m), 1205 (vs), 1151 (vs), 1096 (w), 1078 (w), 1037 (m), 948 (vw), 870 (w), 810 (vw), 726 (vw), 594 (vw), 502 (vw) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (E)-isomer: $\delta$ 5.63 (s, 1 H, CH), 4.14 (q, $^3J$ 7.1 Hz, 2 H, CH$_3$-CH$_2$O), 3.18 (t, $^3J$ 6.9 Hz, 2 H, CH$_2$-I), 2.61 (q, $^3J$ 7.5 Hz, 2 H, CH$_3$-CH$_2$-C), 2.27 ($\approx$ t, $^3J$ 6.9 Hz, 2 H, -CH$_2$-CH$_2$-C), 1.99 ($\approx$ quin, 2 × $^3J$ 6.9 Hz, 2 H, -CH$_2$-CH$_2$-C), 1.28 (t, $^3J$ 7.2 Hz, 3 H, CH$_3$-CH$_2$-O), 1.08 (t, $^3J$ 7.5 Hz, 3 H, CH$_3$-CH$_2$-C); $^1$H NMR (400 MHz, CDCl$_3$) (Z)-isomer: $\delta$ 5.67 (s, 1 H, CH), 4.14 (q, $^3J$ 7.1 Hz, 2 H, CH$_3$-CH$_2$-O), 3.22 (t, $^3J$ 7.2 Hz, 2 H, CH$_2$-I), 2.68 ($\approx$ t, $^3J$ 7.7 Hz, 2 H, -CH$_2$-CH$_2$-C), 2.19 (dq, $^3J$ 7.4 Hz, $^4J$ 1.2 Hz, 2 H, CH$_3$-CH$_2$-C), 1.99 ($\approx$ quin, 2 × $^3J$ 6.9 Hz, 2 H, -CH$_2$-CH$_2$-C), 1.28 (t, $^3J$ 7.1 Hz, 3 H, CH$_3$-CH$_2$-O), 1.08 (t, $^3J$ 7.4 Hz, 3 H, CH$_3$-CH$_2$-C); $^1$C NMR (100 MHz, CDCl$_3$) (E)-isomer: $\delta$ 166.4 (COO), 163.4 (C$_q$), 116.0 (CH), 59.8 (CH$_3$-CH$_2$-O), 38.5 (CH$_2$-CH$_2$-C), 31.3 (CH$_2$-CH$_2$-C), 25.3 (CH$_3$-CH$_2$-C), 14.5 (CH$_3$-CH$_2$-O), 13.1 (CH$_3$-CH$_2$-C), 5.8 (-CH$_2$-I); $^1$C NMR (100 MHz, CDCl$_3$) (Z)-isomer: $\delta$ 166.6 (COO), 163.6 (C$_q$), 115.5 (CH), 59.8 (CH$_3$-CH$_2$-O), 33.6 (CH$_2$-CH$_2$-C), 32.8 (CH$_2$-CH$_2$-CH$_2$), 31.5 (CH$_3$-CH$_2$-C), 14.4 (CH$_3$-CH$_2$-O), 12.1 (CH$_3$-CH$_2$-O), 6.4 (-CH$_2$-I); MS-ESI: 353.4 (10, [M+K+H$^+$]), 319.1 (100, [M+Na$^+$]), 304.5 (33, [(M+Na)-15]); HR-MS (ESI): 319.01666 ([M+Na]$^+$); C$_{10}$H$_{17}$O$_2$Na$^+$; calc. 319.01654.

(E/Z)-6-Ethoxy-4-ethyl-6-oxohex-4-enoic acid (21). To a stirred solution of alcohol 18 (200 mg, 1.07 mmol) in acetone (4.5 mL) at 0 °C was added dropwise a freshly prepared Jones reagent (1.9 M, ca. 2 mL). The addition of the oxidant was continued until the starting material was consumed as determined by TLC analysis (ca. 0.5 h). The resulting yellow-brown reaction mixture was stirred for an additional 2 h at 0 °C, before it was quenched with iPrOH (2 mL) and warmed to room temperature for 10 min. The crude reaction mixture was then filtered through a plug of Celite (eluting with 30 mL of Et$_2$O) and concentrated in vacuo. The organic residue was taken up in Et$_2$O (100 mL) and washed with brine (40 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 50:50) to afford an E/Z mixture (60:40) of 21 (175 mg, 81%). Clear, slightly yellowish oil; TLC: $R_f$ (Petroleum ether/EtOAc, 50:50) 0.2; IR (KBr, film): $\nu_{\text{max}}$ 2976 (vs), 2934 (vs), 1715 (vs), 1646 (vs), 1447 (s), 1422 (s), 1381 (s), 1276 (vs), 1209 (vs), 1148 (vs), 1096 (m), 1040 (s), 920 (m), 870 (s), 759 (w), 666 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (E)-isomer: $\delta$ 5.61 (s, 1 H, CH), 4.15 (q, $^3J$ 7.1 Hz, 2 H, CH$_3$-CH$_2$-O), 2.63 (q, $^3J$ 7.5 Hz, 2 H,
(E/Z)-1-Ethyl 6-perfluorophenyl 3-ethylhex-2-enedioate (22). To a stirred solution of acid 21 (110 mg, 0.55 mmol) in dry CH$_2$Cl$_2$ (1.0 mL) at 0 °C and under argon was added pentafluorophenol (111 mg, 0.60 mmol) followed by N,N'-dicyclohexylcarbodiimide (127 mg, 0.62 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 days, then was filtered through a plug of Celite (eluting with 40 mL of CH$_2$Cl$_2$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10) to afford an E/Z mixture (60:40) of 22 (98 mg, 49%). Clear, slightly yellowish oil; TLC: $R_f$ (Petroleum ether/EtOAc, 80:20) 0.6; IR (KBr, film): $\nu_{\text{max}}$ 2932 (s), 2857 (m), 2669 (vw), 2461 (vw), 2120 (m), 1791 (vs), 1717 (vs), 1649 (s), 1466 (s), 1380 (m), 1314 (m), 1275 (m), 1207 (vs), 1150 (vs), 1100 (vs), 1042 (s), 1004 (vs), 873 (m), 741 (m), 729 (vw), 618 (vw), 553 (vw) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (E)-isomer: $\delta$ 5.67 (s, 1 H, CH), 4.16 (q, $^3$J 7.1 Hz, 2 H, CH$_3$-CH$_2$-O), 2.86 ($\approx$ t, $^3$J 8.0 Hz, 2 H, -CH$_2$-CH$_2$-C), 2.67 (q, $^3$J 7.5 Hz, 2 H, CH$_3$-CH$_2$-C), 2.63 (t, $^3$J 7.8 Hz, 2 H, CH$_2$-COOPfp), 1.28 (t, $^3$J 7.1 Hz, 3 H, CH$_3$-CH$_2$-O), 1.12 (t, $^3$J 7.5 Hz, 3 H, CH$_3$-CH$_2$-C); $^1$H NMR (400 MHz, CDCl$_3$) (Z)-isomer: $\delta$ 5.75 (s, 1 H, CH), 4.17 (q, $^3$J 7.1 Hz, 2 H, CH$_3$-CH$_2$-O), 3.01 (t, $^3$J 8.0 Hz, 2 H, -CH$_2$-CH$_2$-C), 2.88 ($\approx$ t, $^3$J 8.0 Hz, 2 H, CH$_2$-COOPfp), 2.26 (dq, $^3$J 7.4 Hz, $^4$J 1.4 Hz, 2 H, CH$_3$-CH$_2$-C), 1.29 (t, $^3$J 7.1 Hz, 3 H, CH$_3$-CH$_2$-O), 1.11 (t, $^3$J 7.5 Hz, 3 H, CH$_3$-CH$_2$-C); $^{13}$C NMR (100 MHz, CDCl$_3$) (E)-isomer: $\delta$ 168.4 (COOPfp), 165.9 (COO), 165.9 (2 × Ar-C), 161.5 (C$_q$), 142.4 (Ar-C), 139.8 (Ar-C), 138.9 (Ar-C.), 125.0 (Ar-C), 116.0 (CH), 59.7 (CH$_3$-CH$_2$-O), 32.1 (CH$_2$-COOPfp), 31.3 (CH$_2$-CH$_2$-C), 25.3 (CH$_3$-CH$_2$-C), 14.2 (CH$_3$-CH$_2$-O), 12.9 (CH$_3$-CH$_2$-C); $^{13}$C NMR (100 MHz, CDCl$_3$) (Z)-isomer: $\delta$ 168.9 (COOPfp), 166.2 (COO), 165.9 (2 × Ar-C.), 161.8 (C$_q$), 142.3 (Ar-C), 139.8 (Ar-C), 138.9 (Ar-C.), 125.0 (Ar-C), 116.3 (CH), 59.9 (CH$_3$-CH$_2$-O), 32.1 (CH$_2$-COOPfp), 31.4 (CH$_3$-CH$_2$-C), 27.5 (CH$_2$-CH$_2$-C), 14.2 (CH$_3$-CH$_2$-O), 11.9 (CH$_3$-CH$_2$-C); $^{19}$F NMR (376 MHz, CDCl$_3$) (E)-isomer: $\delta$ -151.5 (d, $^3$J 19.4 Hz, 2 F, A$_2$B$_2$, Ar-CF), -156.7 ($\approx$ t, $^3$J 19.1 Hz, 1 F, A$_2$B$_2$, Ar-CF), -161.1 ($\approx$ t, $^3$J 20.1 Hz, 2 F, A$_2$B$_2$, Ar-CF); $^{19}$F NMR (376 MHz, CDCl$_3$) (Z)-isomer: $\delta$ -151.5 (d, $^3$J 17.4 Hz, 2 F, A$_2$B$_2$, Ar-CF), -157.1 ($\approx$ t, $^3$J 19.0 Hz, 1 F, A$_3$B$_2$, Ar-CF), -161.4 ($\approx$ t, $^3$J 20.7 Hz, 2 F, A$_2$B$_2$, Ar-CF); MS-ESI: 389.1 (100, [M+Na]$^+$); HR-MS (ESI): 389.07832 ([M+Na]$^+$); C$_{16}$H$_{15}$F$_3$O$_4$Na$^+$; calc. 389.07882.
4-(2-Nitrophenyl)-1H-pyrrol-2(5H)-one (2). Trifluoroacetic acid (1.60 mL) was added dropwise to a solution of Boc-protected 3-pyrrolin-2-one 8 (200 mg, 0.66 mmol) in dry CH₂Cl₂ (8.0 mL) at room temperature. The mixture was stirred at room temperature for 40 min (reaction progress monitored by TLC) and then quenched with saturated aqueous NaHCO₃ (30 mL). The organic and aqueous layers were separated and the organic layer was washed with brine (20 mL), dried over MgSO₄, filtered and evaporated. 131 mg of deprotected 3-pyrrolin-2-one 2 were recovered. Yield: 98%. Yellow solid; TLC: Rf(EtOAc, 100%) 0.3; GC: tR 15.71 min; ¹H NMR (400 MHz, CD₃OD): δ 8.03 (dd, 3J 8.1 Hz, 4J 1.3 Hz, 1H, Ar-CH), 7.76 (td, 2 × 3J 7.5 Hz, 4J 1.3 Hz, 1H, Ar-CH), 7.66 (td, 2 × 3J 7.5 Hz, 4J 1.3 Hz, 1H, Ar-CH), 7.62 (t, 4J 1.6 Hz, 1H, CH), 4.35 (d, 4J 1.6 Hz, 2H, CH₂); ¹³C NMR (100 MHz, CD₃OD): δ 176.0 (C=O), 158.3 (C), 149.6 (Ar-C), 134.4 (C⁵), 131.6 (Ar-CH), 131.6 (Ar-CH), 129.4 (Ar-C), 126.6 (Ar-CH), 125.3 (CH), 51.6 (CH₂); MS-ESI: 227.2 (100, [M+Na]⁺); HR-MS (ESI): 227.04317 ([M+Na]⁺; C₁₀H₈N₂O₃Na⁺; calc. 227.04326).

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    [http://doc.rero.ch/record/9611](http://doc.rero.ch/record/9611)


23. Selected data for compound 11: HR-MS (ESI): 455.1427 ([M+Na]+; C_{21}H_{24}N_{2}O_{8}Na^{+}; calc. 455.1430).


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