Preparation of precursors for the synthesis of analogues of rhazinilam

Inga Kholod, Olivier Vallat, Ana-Maria Buciumas, and Reinhard Neier*

Institute of Chemistry, University of Neuchâtel, Avenue de Bellevaux 51, CH-2000 Neuchâtel, Switzerland
E-mail: reinhard.neier@unine.ch

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

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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

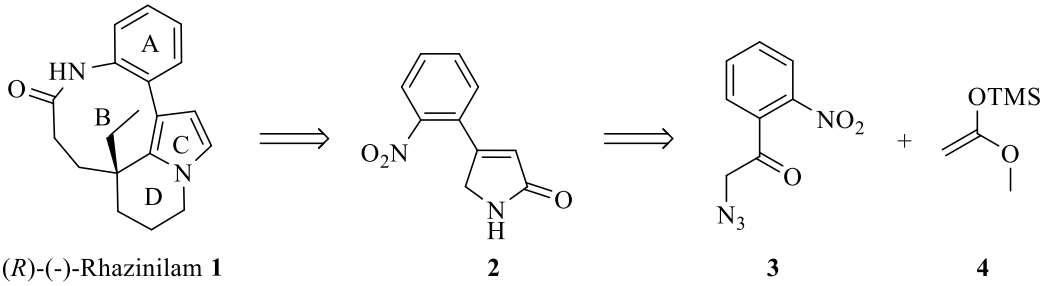
Introduction

(*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 transformations[6] 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.[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,[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[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.[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).



(*R*)-(-)-Rhazinilam **1** **2** **3** **4**

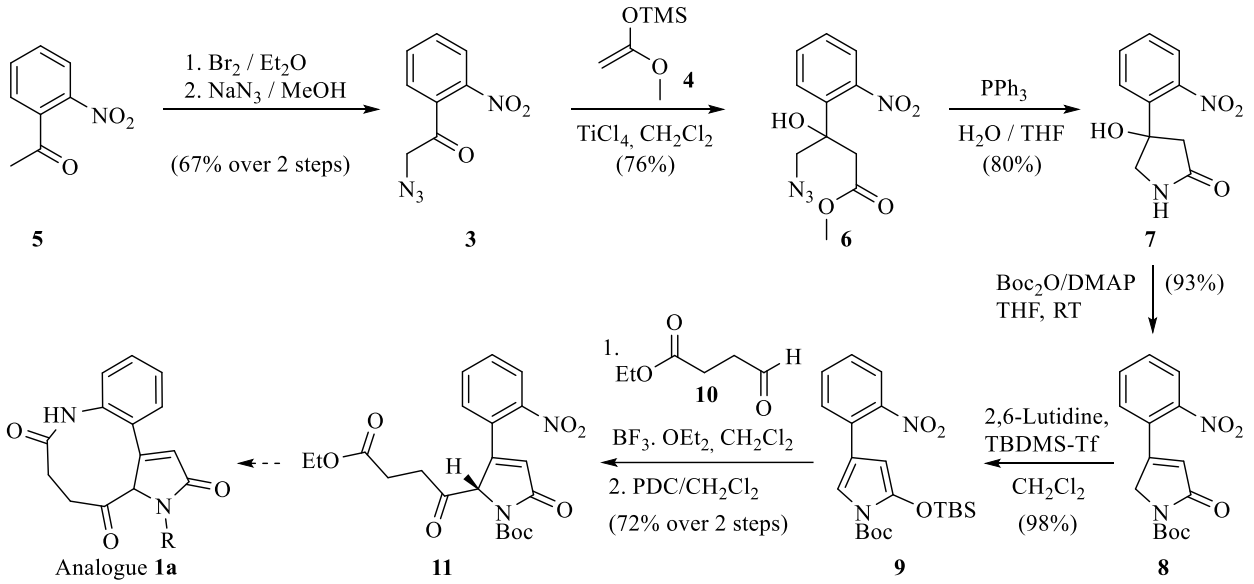
Scheme 1. Retrosynthetic analysis based on the Mukaiyama – Staudinger tandem sequence

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,[18,19] whereas the D-ring seemed to influence the *in vitro* activity only slightly.[20-22]



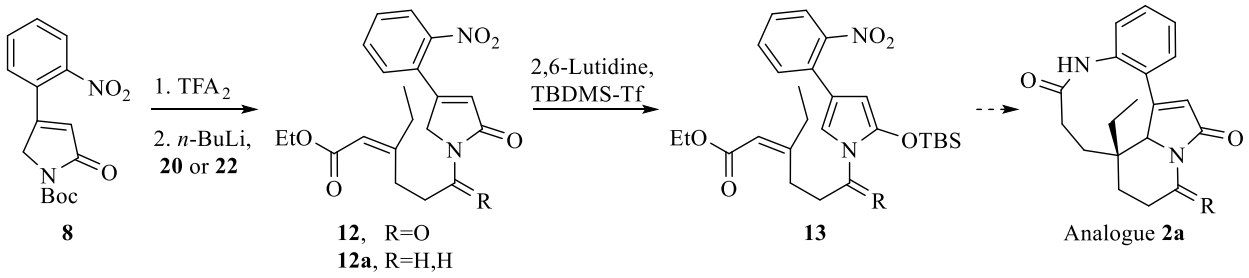
Scheme 2. Synthetic pathway to the formation of lactam B-ring[15]

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 $TiCl_4$ 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 $TiCl_4$ 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 Boc_2O 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.[15] 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 un-wanted 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. Peparation of **11** and its tentative transformation to **1a** are described in an another paper: Vallat,

O.; Buciumas, A.-M.; Neier, R, under submission.[23] 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.

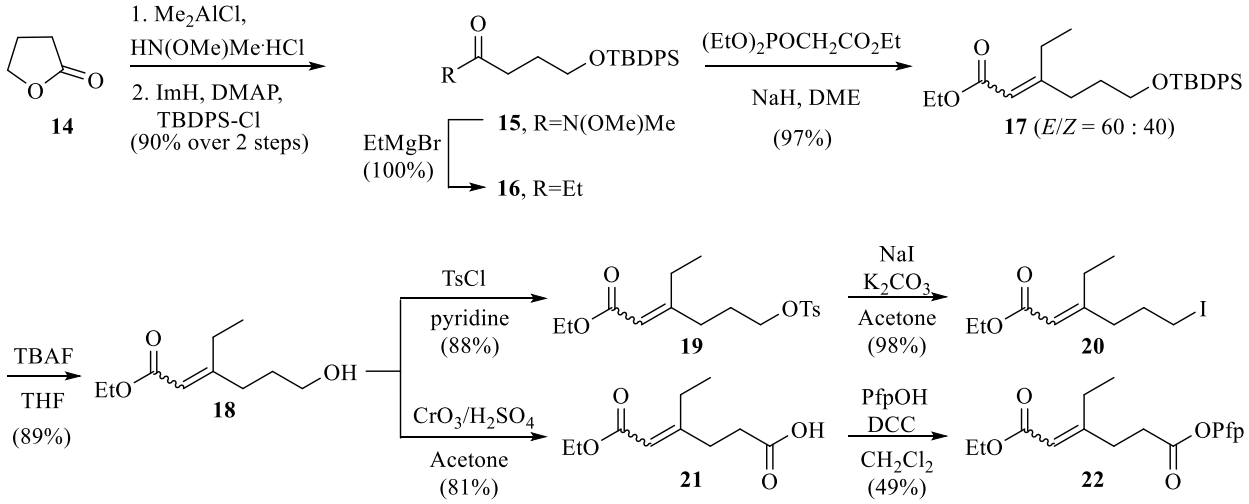
Synthesis of the building blocks 20 and 22

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 attractivity of this strategy was the fact that the intramolecular Michael addition reaction has been successfully applied[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. 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.



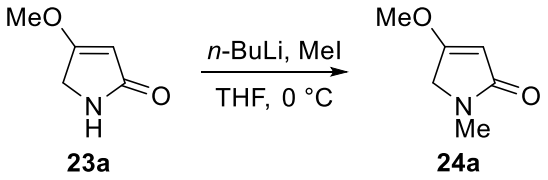
Scheme 4. Synthesis of acrylates **20** and **22**

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*.[25,26] in 90% yield over the two steps (Scheme 4). Reaction of amide **15** with ethylmagnesium bromide afforded the alkynone **16**[27] in nearly quantitative yield. Compound **16** underwent a Wadsworth-Horner-Emmons (WHE)[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**[29] in 78% yield over the two steps. Finally **19** was converted into the desired iodo acrylate **20**[30] in excellent 67% overall yield over seven steps starting from the lactone **14**.

In parallel, the alcohol **18** was oxidized with Jones' reagent[31,32] (1.9 M, acetone/H_2O, 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**[33] in moderate yield. However, the activated acrylate **22** could be obtained from γ-butyrolactone **14** in seven steps and 31% overall yield.

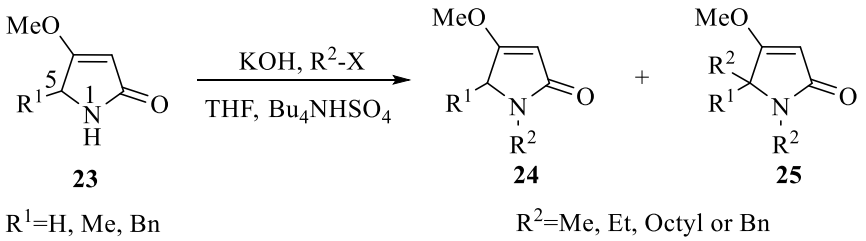
N-alkylation of 4-(2-nitrophenyl)-1*H*-pyrrol-2(5*H*)-one 2

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



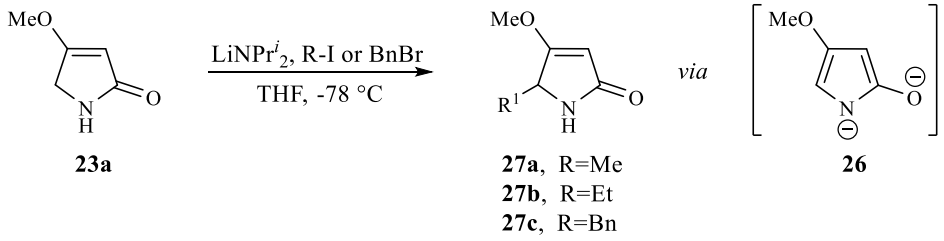
Scheme 5. Reported N-alkylation of *O*-metyl tetramate **23a** using *n*-BuLi.[34]

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.[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]

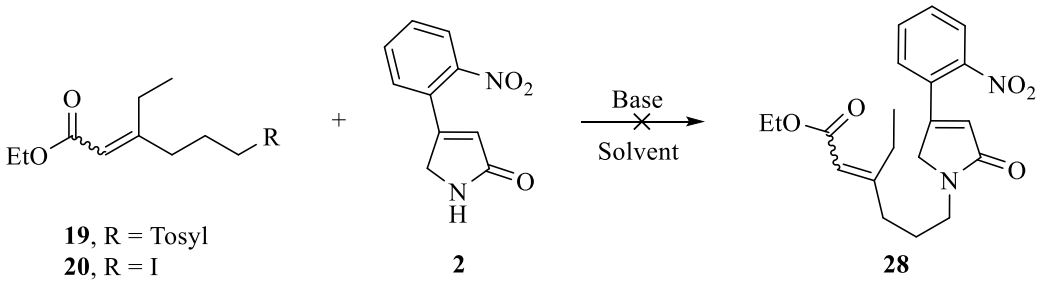
As an alternative the authors investigated the alkylation at C-5 of the *N*-unsubstituted tetramates using at least two equivalents of a strong base under low temperature conditions (Scheme 7). The resulting dianion of 4-*O*-methyl tetramate **26** underwent preferential *C*-alkylation in moderate to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



19, R = Tosyl
20, R = I

2 **28**

Entry	Electrophile (equiv.)	Base (equiv.)	PTS [a] (equiv.)	Solvent	T, °C	t, h	Product [b]
1[15,34]	**20** (1.13)	*n*-BuLi (1.12)	-	THF	0-20	3.5	**20**
2[34,35]	**20** (1.25)	KOH (6.00)/ K_2CO_3 (1.25)	Bu_4NHSO_4 (0.10)	Toluene	60	5	**20** + **2** decomposed
3[35]	**20** (3.00)	KOH (1.40)	Bu_4NHSO_4 (0.10)	THF	0-20	18	**20** + **2** decomposed
4[35, c]	**BnBr** (3.00)	KOH (1.40)	Bu_4NHSO_4 (0.10)	THF	0-20	18	BnBr + **2**
5[37]	**19** (1.1)	KHMDS (1.1)	-	THF	70	2	**19** + **2** decomposed
6[37]	**20** (1.1)	KHMDS (1.1)	-	THF	70	3	**20** + **2** decomposed
7[38]	**19** (1.10)	NaH (1.10)	TBAI (0.22)	THF DMF	20	27	**19** + **2** decomposed
8[39]	**20** (1.10)	NaH (1.10)	-	DMF	20	24	**20** + **2** decomposed
9[39]	**20** (1.10)	NaH (1.10)	-	DMF	0-20	24	**20** + **2** decomposed

[a] Phase transfer catalyst was added. [b] According to NMR and/or GC. [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 $CHCl_3$, δ 3.31 ppm (^{1}H NMR) or δ 49.00 ppm (^{13}C NMR) for CH_3OH, δ 2.50 ppm (^{1}H NMR) or δ 39.52 ppm (^{13}C NMR) for DMSO-d_6, δ 2.05 ppm (^{1}H NMR) or δ 29.84 and 206.26 ppm (^{13}C NMR) for acetone-d_6. 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**).[15] To a stirred mixture of 2′-nitroacetophenone **5** (20 g, 121 mmol) and $AlCl_3$ (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 $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/petroleum ether, 70:30) to afford 31.7 g of 2-bromo-1-(2-nitrophenyl)ethanone as a yellow solid. The product was crystallised from MeOH to give 26.1 g of pure product. Yield: 88%. Colorless micro-needles; TLC: R_f (CH_2Cl_2/petroleum ether, 70:30) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): 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 (ddd, ^3J 8.1 Hz, ^3J 7.5 Hz, ^4J 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, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2).

To a mechanically stirred solution of sodium azide (3.68 g, 56.55 mmol) in water (55 mL) at 6 °C was added a solution of 2-bromo-2′-nitroacetophenone (9.20 g, 37.70 mmol) in MeOH (190 mL). The reaction mixture was stirred for 48 h at 6 °C and then extracted with Et_2O (4 × 200 mL). The organic layer was washed with water (1 × 200 mL), dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel using CH_2Cl_2 as eluent to afford 6.17 g of **3** as a brown solid. The product was crystallised from Et_2O/hexane to give 5.83 g of pure **3**. Yield: 75%. Yellow-brown micro-needles; TLC: R_f (CH_2Cl_2, 100%) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, ^{3}J 8.0 Hz, ^4J 1.5 Hz, 1 H, Ar-H), 7.80 (td, 2 × ^3J 7.4 Hz, ^4J 1.5 Hz, 1 H, Ar-H'), 7.70 (ddd, ^3J 8.0 Hz, ^3J 7.4 Hz, ^4J 1.6 Hz, 1 H, Ar-H'), 7.43 (dd, ^3J 7.4 Hz, ^4J 1.6 Hz, 1 H, Ar-H), 4.32 (s, 2 H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2).

[(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: R_f (CH_2Cl_2, 100%) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (s, 3 H, OCH_3'), 3.22 and 3.11 (AB system, ^2J 2.6 Hz, 2 H, CH_2), 0.25 (s, 9 H, Si-CH_3'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (C), 59.9 (CH_2), 55.1 (OCH_3'), 2.5 (Si-CH_3).

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 CH_2Cl_2 (60 mL) at -30 °C and under argon. A solution of freshly distilled $TiCl_4$ (0.84 mL, 7.28 mmol) in dry CH_2Cl_2 (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 $CHCl_3$ (4 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was

purified by flash chromatography on silica gel using CH_2Cl_2 as eluent to afford 3.39 g of **6** as a clear, slightly yellowish oil which solidified on standing. The product was crystallised from Et_2O/hexane to give pure **6** (3.10 g., 76%). White solid; TLC: R_f (CH_2Cl_2, 100%) 0.3; Mp: 77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.52 (m, 4 H, 4 Ar-CH), 4.83 (s, 1 H, OH), 3.66 (s, 3 H, CH_3), 3.80 and 3.59 (AB system, ^2J 12.7 Hz, 2 H, N_3-CH_2), 3.17 and 3.06 (AB system, ^2J 16.7 Hz, 2 H, CH_2-CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8 (COO), 150.4 (Ar-C′), 134.6 (Ar-C′), 131.1 (Ar-CH), 129.4 (Ar-CH), 128.1 (Ar-CH), 124.5 (Ar-CH), 76.2 (C), 59.2 (CH_2-N_3), 52.5 (OCH_3), 41.0 (CH_2-CO_2CH_3).

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): ν_{max} 3403 (s), 3227 (m), 1673 (vs), 1525 (s), 1373 (s) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): 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, CH_2-NH), 2.96 and 2.42 (AB system, ^2J 16.6 Hz, 2 H, CH_2-CONH); ^{13}C NMR (100 MHz, DMSO-d_6): 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 (C_q), 55.4 (CH_2-NH), 45.7 (CH_2-CONH); MS-ESI: 245.2 (100, [M+Na]$^+$).

***tert*-Butyl 4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1*H*-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 Boc_2O (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 (CH_2Cl_2/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 Et_2O/petroleum ether to give 0.97 g of pure **8**. Yield: 71%. White solid; TLC: R_f (CH_2Cl_2/MeOH, 99:1= 0.2; IR (KBr): ν_{max} 3105 (vw), 2981 (w), 2924 (w), 1781 (vs), 1693 (m), 1520 (vs), 1368 (s), 1357 (vs) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, ^3J 8.1 Hz, ^4J 1.2 Hz, 1 H, Ar-CH), 7.74 (td, 2 × ^3J 7.5 Hz, ^4J 1.1 Hz, 1 H, Ar-CH), 7.65 (td, 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, CH_2), 1.58 (s, 9 H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$): 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 (CH_2-NH), 28.5 (CH_3); MS-ESI: 326.9 (100, [M+Na]$^+$). Anal. Calcd for $C_{11}H_{12}N_4O_5$: 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_2Cl_2 (50 mL) under argon. The solution was cooled to 0 °C and Me_2AlCl (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_2Cl_2 (3 × 10 mL). Aqueous phase was diluted with saturated Rochelle's salt (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated to afford the crude alcohol (1.42 g) as a clear, colourless oil. R_f (CH_2Cl_2/MeOH, 95:5) 0.2. GC (method IZ): t_R 6.67 min.

Under argon, imidazole (728 mg, 10.69 mmol) was added to a solution of the crude alcohol in dry CH_2Cl_2 (50 mL) and the solution was cooled to 0 °C. *tert*-Butyldiphenylchlorosilane (2.32 mL, 9.75 mmol) and 4-DMAP (58 mg, 0.47 mmol) were added and the resulting mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with water (20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_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, $CDCl_3$): δ 7.66 (≈ td, ^3J 6.1 Hz, 2 × ^4J 1.5 Hz, 4 H, Ar-CH), 7.44-7.35 (m, 6 H, Ar-CH), 3.73 (t, ^3J 6.1 Hz, 2 H, CH_2-OSi), 3.67 (s, 3 H, H_3C-O), 3.18 (s, 3 H, H_3C-N), 2.56 (t, ^3J 7.5 Hz, 2 H, CH_2-CO), 1.89 (tt, ^3J 7.5 Hz, ^3J 6.1 Hz, 2 H, C-CH_2-C), 1.05 (s, 9 H, CH_3-C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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_3C-O), 32.3 (H_3C-N), 28.4 (C-*C*H_2-C), 27.6 (*C*H_2-CO), 26.9 (H_3*C*-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 ethyl-magnesium 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_4Cl (40 mL). The mixture was poured into Et_2O (60 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over Na_2SO_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, $CDCl_3$): δ 7.65 (≈ td, ^3J 6.1 Hz, 2 × ^4J 1.5 Hz, 4 H, Ar-CH), 7.45-7.35 (m, 6 H, Ar-CH), 3.66 (t, ^3J 6.1 Hz, 2 H, CH_2-OSi), 2.52 (t, ^3J 7.4 Hz, 2 H, CH_2-CO), 2.41 (q, ^3J 7.3 Hz, 2 H, CH_3-C*H*$_2$-CO), 1.83 (tt, ^3J 7.4 Hz, ^3J 6.1 Hz, 2 H, C-CH_2-C), 1.04 (t, ^3J 7.3 Hz, 3 H, C*H*$_3$-CH_2), 1.04 (s, 9 H, CH_3-C); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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

(CH_2-*C*H_2-CO), 35.9 (CH_3-*C*H_2-CO), 26.9 (CH_3-C), 26.7 (C-*C*H_2-C), 19.2 (C-Si), 7.8 (H_3*C*-CH_2-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 $MgSO_4$, 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: R_f (Petroleum ether/EtOAc, 95:5) 0.2; GC: t_R 17.06 min (*Z*) and 17.33 min (*E*); IR (KBr, film): ν_{max} 3072 (w), 3050 (w), 2959 (s), 2933 (vs), 2897 (s), 2859 (s), 1741 (m), 1716 (vs), 1645 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*E*)-isomer: δ 7.66 (ddd, ^3J 7.7 Hz, ^4J 2.7 Hz, ^4J 1.5 Hz, 4 H, Ar-CH), 7.35-7.446 (m, 6 H, Ar-CH), 5.61 (s, 1 H, CH), 4.14 (q, ^3J 7.2 Hz, 2 H, CH_3-CH_2-O), 3.67 (t, ^3J 6.2 Hz, 2 H, CH_2-OSi), 2.60 (q, ^3J 7.5 Hz, 2 H, CH_3-CH_2-C), 2.25 (≈t, ^3J 7.3 Hz, 2 H, -CH_2-CH_2-C), 1.72 (≈quint, 2 × ^3J 6.2 Hz, 2 H, -CH_2-CH_2-C), 1.28 (t, ^3J 7.2 Hz, 3 H, CH_3-CH_2-O), 1.06 (t, ^3J 7.5 Hz, 3 H, CH_3-CH_2-C), 1.05 (s, 9 H, CH_3-C); ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*)-isomer: δ 7.66 (ddd, ^3J 7.7 Hz, ^4J 2.7 Hz, ^4J 1.5 Hz, 4 H, Ar-CH), 7.35-7.446 (m, 6 H, Ar-CH), 5.61 (s, 1 H, CH), 4.11 (q, ^3J 7.1 Hz, 2 H, CH_3-CH_2-O), 3.71 (t, ^3J 6.4 Hz, 2 H, CH_2-OSi), 2.67 (≈t, ^3J 7.8 Hz, 2 H, -CH_2-CH_2-C), 2.17 (dq, ^3J 7.4 Hz, ^4J 1.0 Hz, 2 H, CH_3-CH_2-C), 1.70 (≈quint, 2 × ^3J 6.2 Hz, 2 H, -CH_2-CH_2-C), 1.25 (t, ^3J 7.1 Hz, 3 H, CH_3-CH_2-O), 1.05 (t, ^3J 7.3 Hz, 3 H, CH_3-CH_2-C), 1.05 (s, 9 H, CH_3-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 166.6 (COO), 165.7 (C_q), 135.7 (Ar-CH), 134.0 (Ar-C), 129.8 (Ar-CH), 127.8 (Ar-CH), 115.0 (CH), 63.4 (-CH_2-OSi), 59.6 (CH_3-*C*H_2-O), 34.4 (CH_2-*C*H_2-C), 30.8 (CH_2-*C*H_2-CH_2), 27.0 (*C*H_3-C), 25.4 (CH_3-*C*H_2-C), 19.4 (C-Si), 14.5 (*C*H_3-CH_2-O), 13.1 (*C*H_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 166.7 (COO), 165.6 (C_q), 135.8 (Ar-CH), 134.2 (Ar-C), 129.7 (Ar-CH), 127.7 (Ar-CH), 114.6 (CH), 64.1 (-CH_2-OSi), 59.6 (CH_3-*C*H_2-O), 31.8 (CH_2-*C*H_2-C), 31.4 (CH_2-*C*H_2-CH_2), 28.9 (CH_2-*C*H_2-C), 27.0 (*C*H_3-C), 19.4 (C-Si), 14.5 (*C*H_3-CH_2-O), 12.2 (*C*H_3-CH_2-C); MS-ESI: 447.6 (100, $[M+Na]^+$); HR-MS (ESI): 447.23192 ($[M+Na]^+$; $C_{26}H_{36}O_3SiNa^+$; 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 $MgSO_4$, 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: R_f (Petroleum ether/EtOAc, 50:50) 0.4; GC: t_R 12.72 min (*Z*) and 13.21 min

(*E*); IR (KBr, film): ν_{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, $CDCl_3$) (*E*)-isomer: δ 5.63 (s, 1 H, CH), 4.14 (q, ^3J 7.0 Hz, 2 H, CH_3-CH_2-O), 3.67 (t, ^3J 6.4 Hz, 2 H, CH_2-OH), 2.62 (q, ^3J 7.5 Hz, 2 H, CH_3-CH_2-C), 2.24 (≈t, ^3J 7.2 Hz, 2 H, -CH_2-CH_2-C), 1.77-1.70 (m (partially resolved), ^3J 7.2 Hz, ^3J 6.4 Hz, 2 H, -CH_2-CH_2-C), 1.27 (t, ^3J 7.1 Hz, 3 H, CH_3-CH_2-O), 1.08 (t, ^3J 7.5 Hz, 3 H, CH_3-CH_2-C); ^1H NMR (400 MHz, $CDCl_3$) (*Z*)-isomer: δ 5.74 (s, 1 H, CH), 4.15 (q, ^3J 7.0 Hz, 2 H, CH_3-CH_2-O), 3.56 (t, ^3J 5.6 Hz, 2 H, CH_2-OH), 2.71 (t, ^3J 7.0 Hz, 2 H, -CH_2-CH_2-C), 2.18 (dq, ^3J 7.4 Hz, ^4J 1.0 Hz, 2 H, CH_3-CH_2-C), 1.77-1.70 (m (partially resolved), ^3J 7.2 Hz, ^3J 5.7 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 7.5 Hz, 3 H, CH_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 166.4 (COO), 165.0 (C_q), 115.1 (CH), 62.2 (-CH_2-OH), 59.5 (CH_3-*C*H_2-O), 34.1 (CH_2-*C*H_2-C), 30.5 (CH_2-*C*H_2-CH_2), 25.3 (CH_3-*C*H_2-C), 14.3 (*C*H_3-CH_2-O), 13.0 (*C*H_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 166.4 (COO), 164.9 (C_q), 115.5 (CH), 60.7 (-CH_2-OH), 60.0 (CH_3-*C*H_2-O), 30.6 (CH_3-*C*H_2-C), 30.5 (CH_2-*C*H_2-CH_2), 27.7 (CH_2-*C*H_2-C), 14.2 (*C*H_3-CH_2-O), 12.1 (*C*H_3-CH_2-C); MS-ESI: 209.3 (100, $[M+Na]^+$); HR-MS (ESI): 209.11464 ($[M+Na]^+$; $C_{10}H_{18}O_3Na^+$; calc. 209.11536).

(*E*/*Z*)-Ethyl 3-ethyl-6-(tosyloxy)hex-2-enoate (**19**). To a solution of alcohol **18** (1.00 g, 5.37 mmol) in dry CH_2Cl_2 (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 Et_2O. The phases were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with 1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, 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: R_f (Petroleum ether/EtOAc, 80:20) 0.3; GC: t_R 15.70; IR (KBr, film): ν_{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, $CDCl_3$) (*E*)-isomer: δ 7.80 (d, ^3J 8.1 Hz, 2 H, A_2B_2, Ar-CH), 7.35 (d, ^3J 8.1 Hz, 2 H, A_2B_2, Ar-CH), 5.51 (s, 1 H, CH), 4.13 (q, ^3J 7.1 Hz, 2 H, CH_3-CH_2-O), 4.04 (t, ^3J 6.4 Hz, 2 H, CH_2-OS), 2.54 (q, ^3J 7.5 Hz, 2 H, CH_3-CH_2-C), 2.45 (s, 3 H, CH_3-C), 2.17 (≈t, ^3J 7.3 Hz, 2 H, -CH_2-CH_2-C), 1.84 (≈quint, 2 × ^3J 6.2 Hz, 2 H, -CH_2-CH_2-C), 1.27 (t, ^3J 7.1 Hz, 3 H, CH_3-CH_2-O), 1.02 (t, ^3J 7.5 Hz, 3 H, CH_3-CH_2-C); ^1H NMR (400 MHz, $CDCl_3$) (*Z*)-isomer: δ 7.80 (d, ^3J 8.1 Hz, 2 H, A_2B_2, Ar-CH), 7.34 (d, ^3J 8.1 Hz, 2 H, A_2B_2, Ar-CH), 5.63 (s, 1 H, CH), 4.11 (q, ^3J 7.1 Hz, 2 H, CH_3-CH_2-O), 4.06 (t, ^3J 6.4 Hz, 2 H, CH_2-OS), 2.58 (≈t, ^3J 7.8 Hz, 2 H, -CH_2-CH_2-C), 2.45 (s, 3 H, CH_3-C), 2.13 (dq, ^3J 7.4 Hz, ^4J 1.3 Hz, 2 H, CH_3-CH_2-C), 1.80 (≈quint, 2 × ^3J 6.2 Hz, 2 H, -CH_2-CH_2-C), 1.25 (t, ^3J 7.1 Hz, 3 H, CH_3-CH_2-O), 1.04 (t, ^3J 7.4 Hz, 3 H, CH_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 166.1 (COO), 163.2 (C_q), 144.8 (Ar-C), 133.1 (Ar-C), 129.9 (Ar-CH), 127.9 (Ar-CH), 115.7 (CH), 69.6 (-CH_2-OS), 59.6 (CH_3-*C*H_2-O), 33.3 (CH_2-*C*H_2-C), 26.9 (CH_2-*C*H_2-CH_2),

25.1 (CH_3-CH_2-C), 21.6 (CH_3-C), 14.3 (CH_3-CH_2-O), 12.9 (CH_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 166.4 (COO), 163.7 (C_q), 144.7 (Ar-C), 133.2 (Ar-C), 129.8 (Ar-CH), 127.9 (Ar-CH), 115.3 (CH), 70.5 (-CH_2-OS), 59.6 (CH_3-CH_2-O), 31.2 (CH_3-CH_2-C), 28.4 (CH_2-CH_2-C), 27.9 (CH_2-CH_2-CH_2), 21.6 (CH_3-C), 14.3 (CH_3-CH_2-O), 11.9 (CH_3-CH_2-C); MS-ESI: 363.3 (100, $[M+Na]^+$); HR-MS (ESI): 363.12288 ($[M+Na]^+$; $C_{17}H_{24}O_5SNa^+$; calc. 363.12421).

(*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_2CO_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): ν_{max} 2964 (s), 2929 (s), 2873 (m), 1715 (vs), 1645 (s), 1460 (m), 1379 (m), 1314 (m), 1272 (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: δ 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 (≈t, ^3J 6.9 Hz, 2 H, -CH_2-CH_2-C), 1.99 (≈quint, 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: δ 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 (≈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 ((≈quint, 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); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 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-CH_2), 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); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 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, $[M+K+H_2O]^+$), 319.1 (100, $[M+Na]^+$), 304.5 (33, $[(M+Na)-15]^+$); HR-MS (ESI): 319.01666 ($[M+Na]^+$; $C_{10}H_{17}IO_2Na^+$; 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 dropewise a freshly prepared Jones reagent (1.9 M, *ca*. 2 mL). The addition of the oxadant 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 *i*PrOH (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_2O) and concentrated *in vacuo*. The organic residue was taken up in Et_2O (100 mL) and washed with brine (40 mL), dried over Na_2SO_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): ν_{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: δ 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,

CH_3-C*H*$_2$-C), 2.58-2.48 (m, 2 H, CH_2-COOH), 2.53 (≈t, ^3J 6.7 Hz, 2 H, -CH_2-C*H*$_2$-C), 1.27 (t, ^3J 7.1 Hz, 3 H, C*H*$_3$-CH_2-O), 1.09 (t, ^3J 7.5 Hz, 3 H, C*H*$_3$-CH_2-C); ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*)-isomer: δ 5.69 (s, 1 H, CH), 4.16 (q, ^3J 7.2 Hz, 2 H, CH_3-C*H*$_2$-O), 2.88 (≈t, ^3J 7.6 Hz, 2 H, -CH_2-C*H*$_2$-C), 2.58-2.48 (m, 2 H, CH_2-COOH), 2.21 (dq, ^3J 7.4 Hz, ^4J 1.3 Hz, 2 H, CH_3-C*H*$_2$-C), 1.28 (t, ^3J 7.1 Hz, 3 H, C*H*$_3$-CH_2-O), 1.08 (t, ^3J 7.4 Hz, 3 H, C*H*$_3$-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 177.6 (COOH), 166.2 (COO), 162.7 (C_q), 115.4 (CH), 59.7 (CH_3-*C*H_2-O), 32.2 (*C*H_2-COOH), 31.7 (CH_2-*C*H_2-C), 25.4 (CH_3-*C*H_2-C), 14.3 (*C*H_3-CH_2-O), 12.9 (*C*H_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 177.9 (COOH), 166.4 (COO), 162.9 (C_q), 115.7 (CH), 59.8 (CH_3-*C*H_2-O), 32.8 (*C*H_2-COOH), 31.4 (CH_3-*C*H_2-C), 27.5 (CH_2-*C*H_2-C), 14.1 (*C*H_3-CH_2-O), 11.9 (*C*H_3-CH_2-C); MS-ESI: 223.1 (100, $[M+Na]^+$); HR-MS (ESI): 223.09407 ([M+Na]+; $C_{10}H_{16}O_4Na$+; calc. 223.09463).

(*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_2Cl_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_2Cl_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): ν_{max} 2932 (s), 2857 (m), 2669 (vw), 2461 (vw), 2120 (m), 1791 (vs), 1717 (vs), 1649 (s), 1521 (vs), 1466 (m), 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: δ 5.67 (s, 1 H, CH), 4.16 (q, ^3J 7.1 Hz, 2 H, CH_3-C*H*$_2$-O), 2.86 (≈t, ^3J 8.0 Hz, 2 H, -CH_2-C*H*$_2$-C), 2.67 (q, ^3J 7.5 Hz, 2 H, CH_3-C*H*$_2$-C), 2.63 (t, ^3J 7.8 Hz, 2 H, CH_2-COOPfp), 1.28 (t, ^3J 7.1 Hz, 3 H, C*H*$_3$-CH_2-O), 1.12 (t, ^3J 7.5 Hz, 3 H, C*H*$_3$-CH_2-C); ^{1}H NMR (400 MHz, $CDCl_3$) (*Z*)-isomer: δ 5.75 (s, 1 H, CH), 4.17 (q, ^3J 7.1 Hz, 2 H, CH_3-C*H*$_2$-O), 3.01 (t, ^3J 8.0 Hz, 2 H, -CH_2-C*H*$_2$-C), 2.88 (≈t, ^3J 8.0 Hz, 2 H, CH_2-COOPfp), 2.26 (dq, ^3J 7.4 Hz, ^4J 1.4 Hz, 2 H, CH_3-C*H*$_2$-C), 1.29 (t, ^3J 7.1 Hz, 3 H, C*H*$_3$-CH_2-O), 1.11 (t, ^3J 7.5 Hz, 3 H, C*H*$_3$-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*E*)-isomer: δ 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-*C*H_2-O), 32.1 (*C*H_2-COOPfp), 31.3 (CH_2-*C*H_2-C), 25.3 (CH_3-*C*H_2-C), 14.2 (*C*H_3-CH_2-O), 12.9 (*C*H_3-CH_2-C); ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*)-isomer: δ 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-*C*H_2-O), 32.1 (*C*H_2-COOPfp), 31.4 (CH_3-*C*H_2-C), 27.5 (CH_2-*C*H_2-C), 14.2 (*C*H_3-CH_2-O), 11.9 (*C*H_3-CH_2-C); ^{19}F NMR (376 MHz, $CDCl_3$): (*E*)-isomer: δ -151.5 (d, ^3J 19.4 Hz, 2 F, A_2B_2, Ar-CF), -156.7 (≈t, ^3J 19.1 Hz, 1 F, A_2B_2, Ar-CF), -161.1 (≈t, ^3J 20.1 Hz, 2 F, A_2B_2, Ar-CF); ^{19}F NMR (376 MHz, CDCl3): (*Z*)-isomer: δ -151.5 (d, ^3J 17.4 Hz, 2 F, A_2B_2, Ar-CF), -157.1 (≈t, ^3J 19.0 Hz, 1 F, A_2B_2, Ar-CF), -161.4 (≈t, ^3J 20.7 Hz, 2 F, A_2B_2, Ar-CF); MS-ESI: 389.1 (100, $[M+Na]^+$); HR-MS (ESI): 389.07832 ($[M+Na]^+$; $C_{16}H_{15}F_5O_4Na^+$; calc. 389.07882).

4-(2-Nitrophenyl)-1*H*-pyrrol-2(5*H*)-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 CH_2Cl_2 (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 $NaHCO_3$ (30 mL). The organic and aqueous layers were separated and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and evaporated. 131 mg of deprotected 3-pyrrolin-2-one **2** were recovered. Yield: 98%. Yellow solid; TLC: R_f (EtOAc, 100%) 0.3; GC : t_R 15.71 min; ^{1}H NMR (400 MHz, CD_3OD): δ 8.03 (dd, ^3J 8.1 Hz, ^4J 1.3 Hz, 1 H, Ar-CH), 7.76 (td, 2 × ^3J 7.5 Hz, ^4J 1.3 Hz, 1 H, Ar-CH), 7.66 (td, 2 × ^3J 7.5 Hz, ^4J 1.3 Hz, 1 H, Ar-CH), 7.59 (dd, ^3J 7.6 Hz, ^4J 1.5 Hz, 1 H, Ar-CH), 6.12 (t, ^4J 1.6 Hz, 1 H, CH), 4.35 (d, ^4J 1.6 Hz, 2 H, CH_2); ^{13}C NMR (100 MHz, CD_3OD): δ 176.0 (C=O), 158.3 (C), 149.6 (Ar-C), 134.4 ($C^{5'}$), 131.6 (Ar-CH), 131.6 (Ar-CH), 129.4 (Ar-C), 126.6 (Ar-CH), 125.3 (CH), 51.6 (CH_2); MS-ESI: 227.2 (100, $[M+Na]^+$); HR-MS (ESI): 227.04317 ($[M+Na]^+$; $C_{10}H_8N_2O_3Na^+$; calc. 227.04326).

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