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Synthetic Strategies for the Synthesis and Transformation of Substituted Pyrrolinones as Advanced Intermediates for Rhazinilam Analogues

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

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The biaryl core structure of rhazinilam with its fixed dihedral angle is a pivotal element for its unique in vitro cytotoxic activity. Most of the related natural products are oxidized versions of rhazinilam. Replacing the sensitive pyrrole ring by a pyrrolinone ring is the basis of our initial strategy towards rhazinilam analogues. With this goal, variants of the sequence crossed Mukaiyama aldol reaction followed by the Staudinger reaction were studied. Reacting a suitably substituted acetophenone with *O*-methyl *O*-trimethylsilyl ketene acetal gave pyrrolinones **8a** and **8b** in good to excellent yields. These intermediates could be transformed in four high-yielding steps into the pyrrolic precursors **7a–c** containing all the atoms necessary for the construction of rings A, B, and C of rhazinilam. Our studies illustrate a lack of stability of these intermediates. Alternative synthetic approaches towards this central biaryl core structure are described.

Introduction

Since its discovery fifty years ago, (*R*)-(–)-rhazinilam (**1**) and some of its congeners have been the subject of intense studies because of their relatively simple but fascinating structure and original in vitro cytotoxic activity (Figure 1).[1]

Transferring the knowledge from in vitro studies to in vivo experiments has, however, proven to be almost impossible.[2] The SAR understanding of this promising spindle toxin is clearly a scientific challenge, as testified by the inability to design more active compounds. Despite a number of previous efforts to obtain potent analogues, none have succeeded in producing a more cytotoxic compound than the natural product. Even worse, no analogues showed in vivo activity. Three reasons have been proposed to account for the in vivo inactivity of rhazinilam and its analogues: lack of transport, solubility issues, or its biotransformation by cytochromes.[3] Recent in-depth studies have ruled out the first two factors. On the other hand it was found that rhazinilam is easily oxidized and transformed into less active, mostly inactive, metabolites. The combination of the findings on the chemical reactivity, with the sensitivity of rhazinilam towards oxidative metabolic transformations, was used by our group as a guideline for proposing and designing novel rhazinilam analogues (Scheme 1).

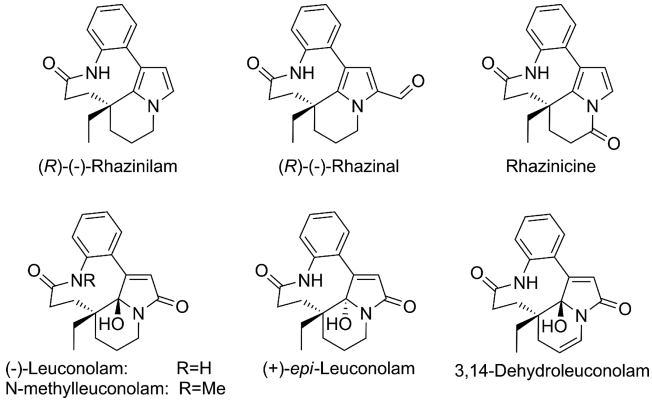

Figure 1. Bioactive (*R*)-(–)-rhazinilam (**1**) and some of its natural occurring analogues.

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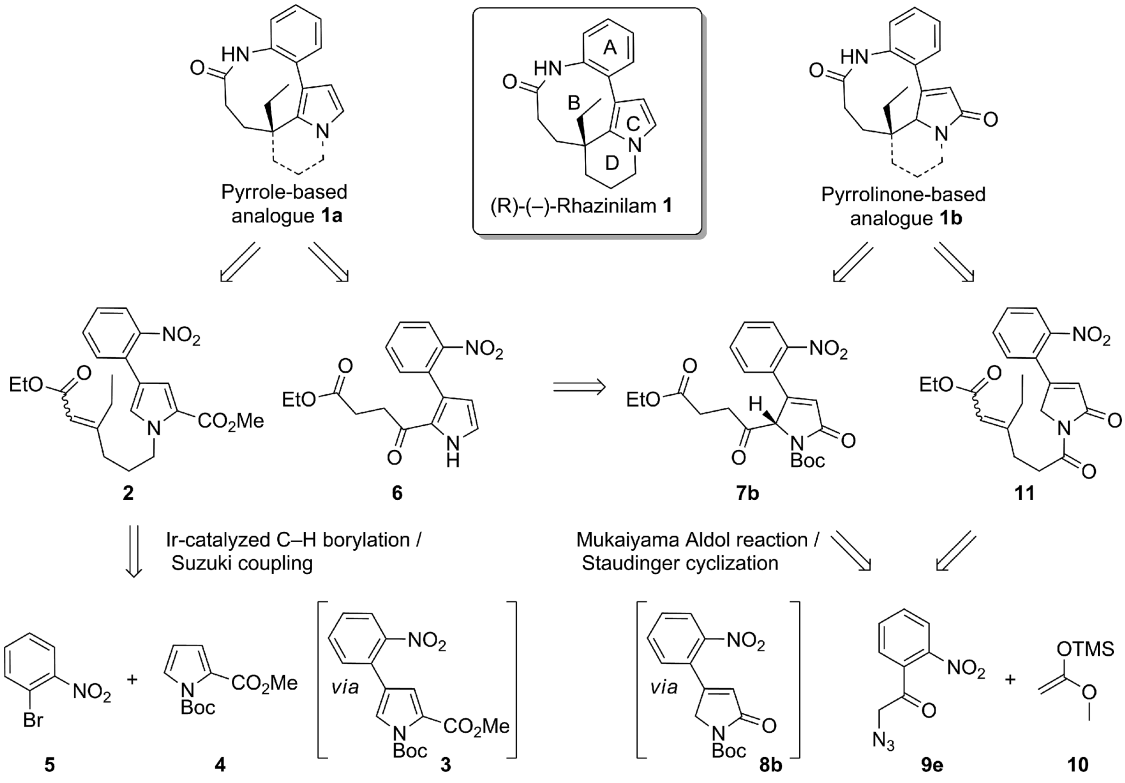


Scheme 1. Synthetic pathway to pyrrole- and pyrrolinone-based analogues of rhazinilam.

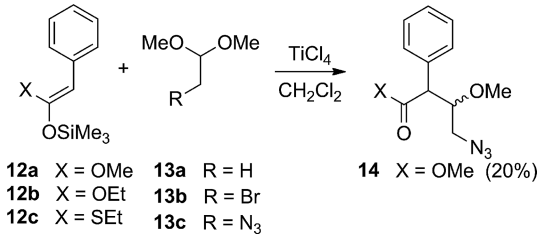
Two approaches to the synthesis of rhazinilam analogues **1a** and **1b** have been investigated by our group.[4] The starting point of our first approach is a convergent synthesis of the phenyl-pyrrolic core of rhazinilam involving a tandem Mukaiyama aldol-type condensation – Staudinger cyclization sequence.[5] The key intermediate is 3-pyrrolin-2-one **8b**, which can help to achieve two goals: facilitating the introduction of the substituents needed for construction of rings B and D, and reducing the sensitivity of the pyrrole ring precursor (ring C). The second approach involves construction of the biaryl core of **3** by a one-pot Ir-catalyzed C–H borylation[6] followed by Suzuki coupling.[7]

Having key intermediate **8b** and **3** in hand, the important challenges are to find good and efficient methodologies to introduce rings B and D.

Results and Discussion

The first task was the elaboration of an efficient methodology for the synthesis of pyrrolinone-containing precursors of type **8b**. Once a reliable access to precursors of this type was available, more advanced studies focused on introducing the side chain needed for the creation of rings B and D via intermediates **7** and **11** (Scheme 1). To realize this goal, we embarked on a synthetic effort to prepare 3-pyrroline-2-one derivatives by using a Mukaiyama aldol addition reaction followed by Staudinger reaction.

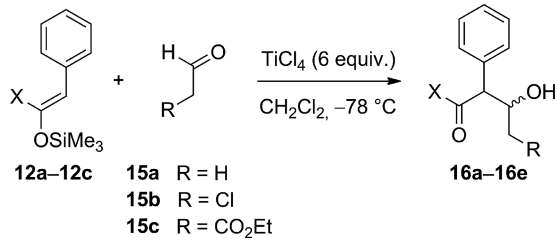
In our initial trials we tried to use silyl enol ethers derived from phenylacetaldehyde as nucleophiles, however, we were unable to control the reaction conditions sufficiently. We mostly isolated polymeric materials, probably due to the high reactivity of the substituted phenylacetaldehyde obtained after the crossed aldol reaction. To avoid this problem the nucleophile was modified by using *O*-alkylketene *O*-silyl acetals of the type **12** instead of the silyl enol ether (Scheme 2).



Scheme 2. Mukaiyama reaction involving *O*-alkylketene *O*-silyl acetals of type **12a**–**c** as nucleophile and acetals **13a**–**c**.

By using ketene-acetal **12a** and acetal **13c** it was possible to isolate small amounts of the aldol product **14** as reported by Mukaiyama in his previous work.[8] By using aldehydes **15a**–**c** instead of acetals **13a**–**c**, considerably improved yields of the products **16a**–**e** were obtained (Scheme 3 and Table 1).

The yields of aldol products **16a**–**d** obtained under these optimized conditions were satisfactory to excellent. Only the Mukaiyama reaction between ketene acetal **12c** and aldehyde **15c** was unsatisfactory. Compound **15c** was difficult to obtain in anhydrous form, and the enolization of the β-aldehydo ester occurs easily, diminishing the yield of product obtained under the reaction conditions.

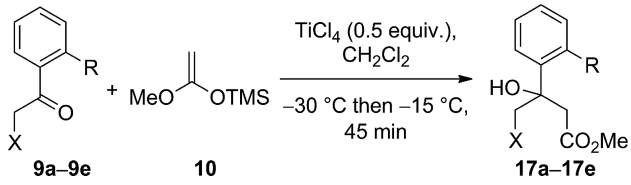


Scheme 3. Mukaiyama reaction involving *O*-alkylketene *O*-silyl acetals of type **12** as nucleophile and aldehydes **15a**–**c**.

Table 1. Synthesis of aldol products **16a**–**e** from *O*-alkylketene *O*-silyl acetals **12a**–**c** and aldehydes **15a**–**c**.

Entry	Substrates		Product	Isolated yield [%]
1	**12a**	**15a**	**16a**	51
2	**12b**	**15a**	**16b**	34
3	**12c**	**15a**	**16c**	70
4	**12c**	**15b**	**16d**	51
5	**12c**	**15c**	**16e**	13

In view of these results, we decided to invert the roles of the two fragments needed for the pyrrole synthesis (Scheme 4 and Table 2).



Scheme 4. Mukaiyama reaction involving ketene acetal **10** as nucleophile and phenylacetophenones **9a**–**e**.

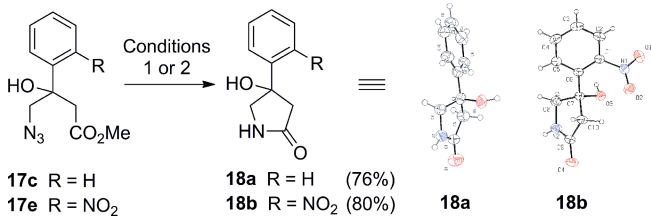
Table 2. Synthesis of aldol products **17a**–**e** from ketene acetal **10** and phenylacetophenones **9a**–**e**.

Entry	9	X	R	Isolated yield of **17** [%]
1	**9a**	Cl	H	20
2	**9b**	Br	H	87
3	**9c**	N_3	H	74
4	**9d**	Br	NO_2	48
5	**9e**	N_3	NO_2	80

We initially used 6 equiv. of $TiCl_4$ and near stoichiometric amounts of **10**. The reaction was initiated at –78 °C and then warmed slowly to room temperature; under these conditions, moderate yields of the condensation products **17a** and **17b** were isolated.

Detailed studies indicated the formation of side products and a corresponding reduction of the yield at temperatures above –10 °C. The presence of large quantities of the strong Lewis acid $TiCl_4$, which had to be neutralized, rendered the work-up more difficult and this led to lower yield. In a systematic study, the amount of $TiCl_4$ was reduced from 6 to 0.5 equiv. The amount of ketene acetal was increased to 3 equiv., and the reaction temperature was kept between –30 and –15 °C. Under these conditions, the reaction time could be kept to just under 1 h, allowing the isolation of the products in excellent yields of up to 87% (Table 2, entry 2). The reaction was allowed to run for 2 h without significant change in the yield.

The Staudinger reaction transforming the aldol products **17c** and **17e** into pyrrolidinones **18a** and **18b** occurred without any problems, in good yields by using 1.5 equiv. of tri(*n*-butyl)phosphine for **18a** and triphenylphosphine for **18b** (Scheme 5).



Scheme 5. Staudinger-type reductive cyclization. Conditions 1 for **18a**: P(*n*Bu)$_3$, H_2O, THF, room temp.; Conditions 2 for **18b**: PPh_3, H_2O, THF, room temp.

The isolation of **18b** was very expedient because the product is not soluble in tetrahydrofuran (THF). Simple filtration allowed the pure product to be isolated. X-ray crystallographic analysis of **18b** revealed that all functional groups are implicated in a dense network of hydrogen bonds (Figure 2 and Table S1 in the Supporting Information for details).

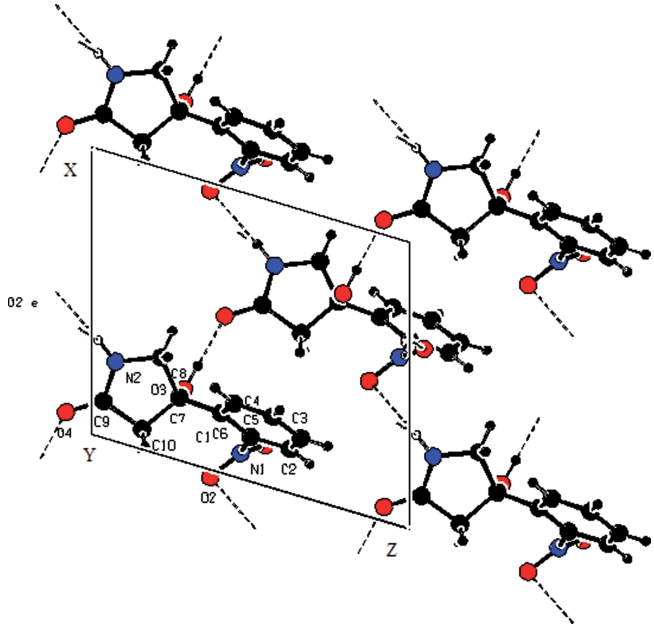


Figure 2. Packing diagram of compound **18b**. Hydrogen bonds are indicated by dashed lines.

The solubility of **18a** in organic solvents was sufficient and did not complicate further transformations. X-ray analysis of **18a** revealed that the molecules are associated as dimers. A third hydrogen bond links these dimers together into a one-dimensional chain (Figure 3).

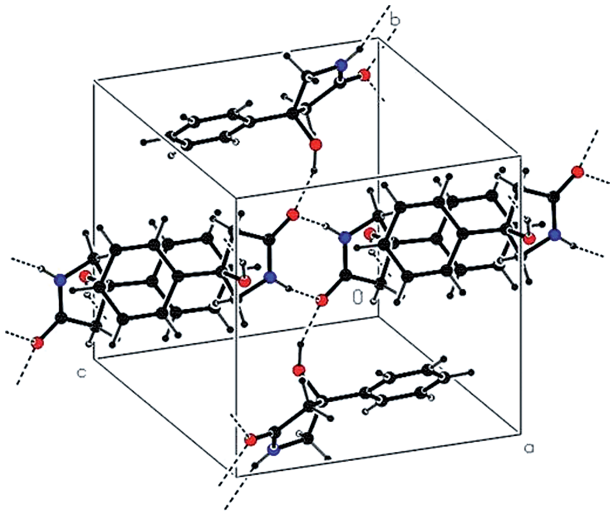
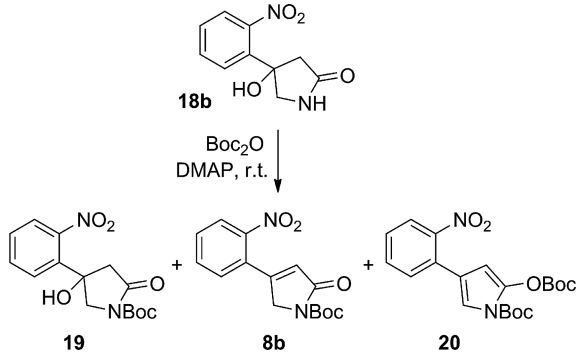


Figure 3. Packing diagram of compound **18a**. Hydrogen bonds are indicated by dashed lines.

Whereas **18b** makes six hydrogen bonds per molecule, the absence of the nitro group in **18a** reduces this number of hydrogen bonds to four. In the crystals, **18b** forms sheets, whereas **18a** forms one-dimensional chains, which probably contributes to the difference in solubility.

The elimination of the tertiary alcohol was more difficult than anticipated. The alcohol reacted only sluggishly, if at all, with many of the reagents tried. Part of the problem was the low solubility of **18b**. However, treating **18b** with 2 equiv. Boc-anhydride in the presence of 4-(dimethylamino)pyridine (DMAP) using THF as a solvent, introduced the Boc-protecting group on the lactam nitrogen and effected at the same time the elimination of the tertiary alcohol in almost quantitative yield to give the product **8b** (Scheme 6).[9] This one-pot procedure was an elegant solution to the problem of solubility and associated low reactivity. A systematic study of this reaction revealed that three different products could be isolated with satisfactory selectivity by changing the amount of Boc_2O (Table 3).



Scheme 6. One-pot Boc-protection and tertiary alcohol elimination.

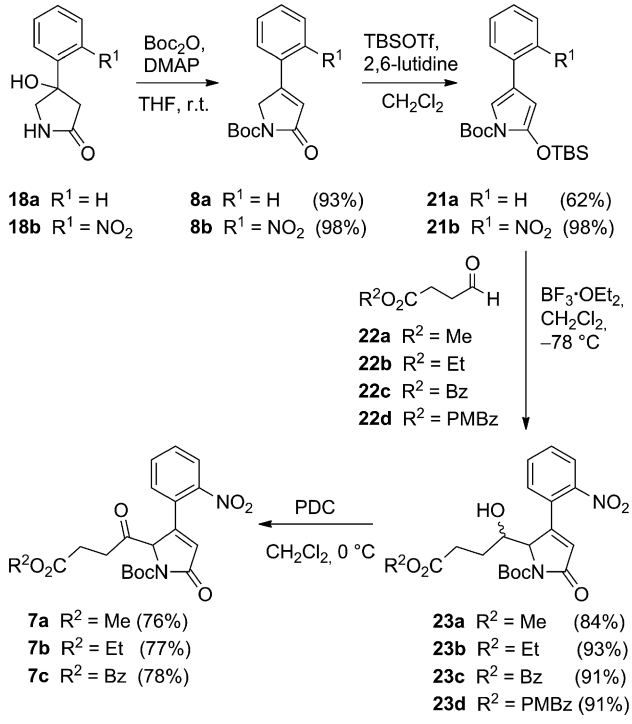
With one equivalent of Boc_2O, a mixture of **19** and **8b** was isolated (conditions were not optimized). When **18b** was treated with 3 equiv. Boc_2O, pyrrolic tautomer **20** was isolated in almost quantitative yield. We initially conducted

Table 3. One-pot bocylation of **18b** and tertiary alcohol elimination.

Entry	Boc_2O [equiv.]	Solvent	Time [h]	Ratio [%]			Yield [%]
				19	**8b**	**20**	
1	1	DMF	1	75	25	–	–
2	2.1	THF	24	–	98	2	98
3	3	DMF	2	–	–	100	93
4	3	THF	2	–	–	100	82–98

this reaction in *N*,*N*-dimethylformamide (DMF) because of the low solubility of **18b**. However, by using THF as solvent, the reaction was found to proceed with the same efficiency and it simplified purification. This study suggests that the first step is *N*-Boc protection followed by *O*-Boc protection. Elimination with the help of the third equivalent of Boc_2O produced aromatic compound **20** (Scheme 6).

To introduce the four-carbon side chain, the pyrrolinone was first silylated to form **21a** and **21b** (Scheme 7).[10] We were able to purify **21b** by flash chromatography on silica gel but **21a** was not stable under these conditions and was instead purified by distillation to prevent hydrolysis. The side chain was introduced by using aldehyde **22a**–**d** as electrophile and BF_3 etherate as catalyst.[11] Aldehyde **22a** was obtained by using a previously described procedure,[12] whereas compounds **22b**–**d** were prepared by hydrolysis and esterification of γ-butyrolactone followed by Swern oxidation.



Scheme 7. Synthesis of advanced precursor **7b**.

The aldol products **23a**–**d** were obtained in 84 to 94% yield starting from **21b**. The diastereoselectivity of the reaction controlling the two newly formed chiral centers was low. In the next step, alcohols **23a**–**c** were oxidized by using

pyridinium dichromate (PDC) in the presence of molecular sieves (Table 4).

Table 4. Oxidation of alcohols **23a**–**c** with pyridinium dichromate (PDC).

Entry	R	PDC [equiv.]	Conc. [m]	Temp. [°C]	Time [h]	MS 4 Å [g]	Yield [%]
1	Me	3.4	2.4 10^{-2}	r.t.	1	2	23
2	Me	2.5	1.6 10^{-2}	r.t.	3	2	76
3	Et	1.8	1.6 10^{-2}	r.t.	3	2	43
4	Et	1.1	1.6 10^{-2}	0	3	2.5	35
5	Et	1.1	1.4 10^{-2}	0	6	2	45
6	Et	2	9 10^{-3}	0	7	2	77
7	Bz	2	1 10^{-2}	0	7	2	78

The synthetic sequence towards the first advanced intermediate developed in our group is summarized in Scheme 7. The resulting compound **7b** contains all the carbons required to form the nine-membered lactam ring B. However, this intermediate has proven to be very sensitive to pH changes due to the acidic proton at C-5 of 3-pyrrolin-2-one ring. This proton can easily be deprotonated due to the keto-enol equilibrium between the pyrrolinone and the aromatic hydroxy-pyrrole tautomeric form (Figure 4).

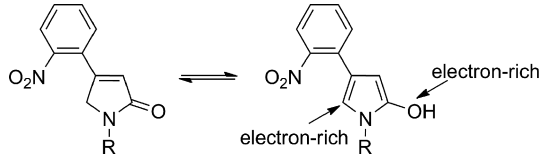
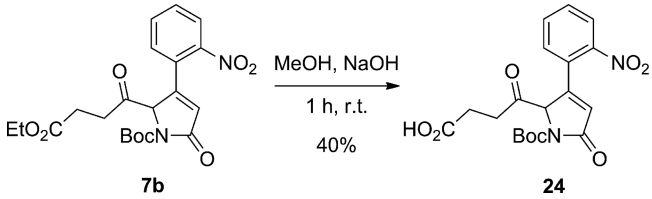


Figure 4. Keto-enol equilibrium in 3-pyrrolin-2-ones.

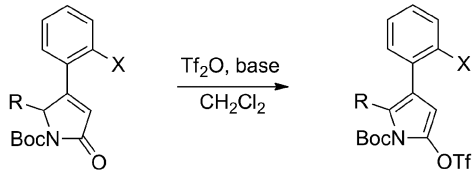
The ease of tautomerization makes this position particularly sensitive to unwanted side reactions. All efforts to saponify or to reduce these intermediates and thereby increase their stability have either been inconclusive or have failed. We summarize in the following our efforts.

The hydrolysis of **7b** under basic conditions gave the corresponding acid **24** but only in moderate yield (Scheme 8). We were not able to improve this result by changing the parameters of this procedure. The best conditions for basic hydrolysis found were the treatment of **7b** with an excess of aqueous sodium hydroxide and MeOH at room temperature. The hydrolysis under acidic conditions was even less convincing. Other procedures such as enzymatic hydrolysis or hydrogenation of **7c** were tried in an attempt to optimize this step but without success.



Scheme 8. Hydrolysis of intermediate **7b**.

In a second approach we tried to reduce pyrrolinone **7b** to the pyrrole ring. For this purpose, a two-step procedure was developed in which the pyrrolinones were first transformed into the corresponding triflate derivatives and then reduced by Pd^0-catalyzed reductive elimination. Taking into account that the α-ketopyrrole are more stable and less sensitive than the pyrrolinone, four different triflate derivatives **25a**–**d** were prepared in good to moderate yields (Scheme 9).



8a X = H, R = H
8b X = NO_2, R = H
7a X = NO_2, R = $MeCO_2(CH_2)_2CO$
7b X = NO_2, R = $EtCO_2(CH_2)_2CO$

25a X = H, R = H (82%)
25b X = NO_2, R = H (61%)
25c X = NO_2, R = $MeCO_2(CH_2)_2CO$ (21%)
25d X = NO_2, R = $EtCO_2(CH_2)_2CO$ (74%)

Scheme 9. Preparation of triflate derivatives **25a**–**d**.

The use of 2,6-lutidine as base for the nonsubstituted pyrrolinones **8a** and **8b** gave the corresponding triflate **25a** and **25b** in good yield. However, in the presence of the side chain, this base gave only moderate yield of **25c**. The use of Et_3N instead improved the reaction and gave **25d** in good yield.

We observed for all compounds **25a**–**d** an unusual ^6J coupling in the ^1H NMR spectra between H-3 and the fluorines of the triflate group (Figure 5). The ^1H NMR signal of H-3 appeared as a doublet of quadruplets. The coupling constant of the doublet is a classical ^4J for pyrrole rings between H-3 and H-5 with a typical coupling constant of 2.3 Hz. The coupling constant of the quadruplet is much smaller (0.8 Hz) and is correlated with the coupling constant of the doublet (0.7 Hz) observed in ^{19}F NMR spectroscopy. X-ray analysis of derivative **25a** showed the trifluoromethyl group to be in the vicinity of the pyrrolic hydrogen, reinforcing the argument of a through-space interaction (Figures S1 and S2 in the Supporting Information).

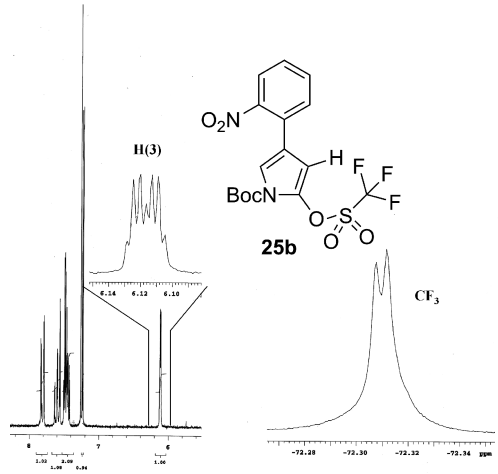
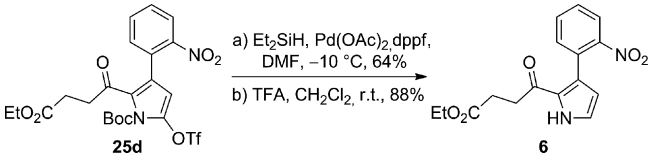


Figure 5. ^1H NMR spectrum of **25b**: ^6J coupling between H-3 and the fluorine atoms of the triflate group.

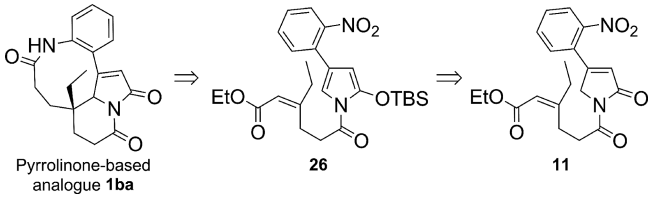
The reduction of **25d** using Et_3SiH in the presence of $Pd(OAc)_2$ and 1,1′-bis(diphenylphosphino)ferrocene (dppf) as catalyst afforded the expected pyrrole in good yield (Scheme 10). This reduction was very fast at room temperature (less than 1 min) and lower temperatures were required to control the reaction. Finally, deprotection of the Boc group under standard conditions using trifluoroacetic acid (TFA) in CH_2Cl_2 gave the advanced intermediate **6** in 88% yield. However, introducing the additional carbon atoms needed for the introduction of the D-ring proved difficult.



Scheme 10. Preparation of precursor **6** by Pd^0-catalyzed reductive elimination.

Thus, alternative strategies that either avoided or reduced the problem of stability of substituted 3-pyrrolin-2-one were needed. We wondered whether inverting the proposed sequence by constructing the D-ring first might bring a solution to the observed problem.

A strategy that introduced 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. Intramolecular Michael addition reactions have been successfully applied[13] in earlier syntheses of Rhazinilam. The activation of the pyrrole **26** through the *O*-silyl group in the 2-position should facilitate the ring-closing process (Scheme 11).



Scheme 11. Retrosynthetic pathway to formation of the D-ring through intramolecular Michael addition reaction.

To realize this strategy, the corresponding iodoacrylate **33** and the pentafluorophenyl ester **35** were prepared accordingly to a previously described procedure.[14] Synthesis of these acrylates started with commercially available γ-butyrolactone **27**, which was converted into the Weinreb amide **28** according to the procedure described by Fukuda et al.[15] in 90% yield over the two steps (Scheme 12). Reaction of amide **28** with ethylmagnesium bromide afforded alkynone **29**[16] in nearly quantitative yield. Compound **29** underwent a Wadsworth–Horner–Emmons (WHE)[13,17] olefination to give the unsaturated ester **30** as a 60:40 mixture of *E*/*Z* isomers in excellent yield. After desilylation of **30** with tetrabutylammonium fluoride (TBAF), treatment of the resulting alcohol **31** with tosyl chloride produced tosyl acrylate **32**[18] in 78% yield over the two steps. Finally, **32** was converted into the desired iodo acrylate **33**[19] in excellent 67% overall yield over seven steps starting from the commercial lactone **27**.

The structure of **31** was determined by spectral analyses, and the stereochemistry was confirmed by NOE experiments (Figure 6).

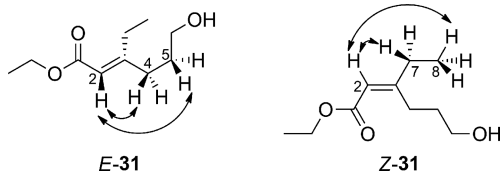
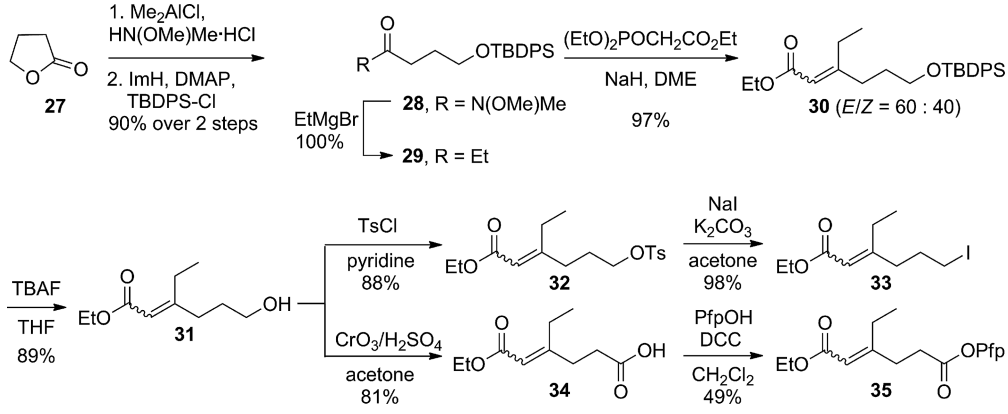


Figure 6. NOE experiments of (*E*)-**31** and (*Z*)-**31**.

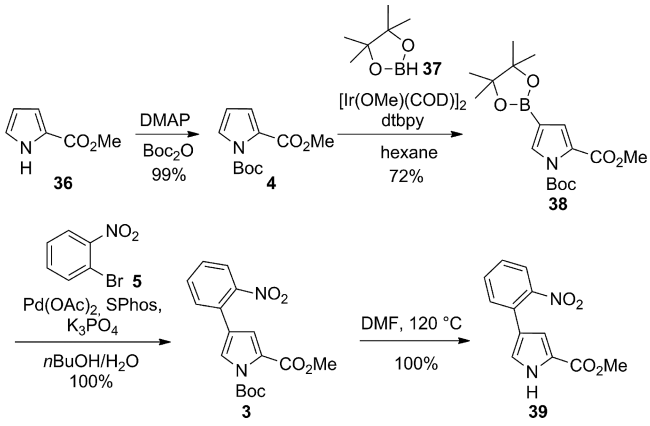
In parallel, alcohol **31** was oxidized with Jones' reagent[20] (1.9 M, acetone/H_2O, 0 °C) to provide acid **34** in 81% yield. Activation of acid **34** using pentafluorophenol and *N*,*N*′-dicyclohexylcarbodiimide provided the pentafluorophenylethyl ester **35**[21] in moderate yield. The activated acrylate **35** could be obtained from the commercially available γ-butyrolactone **27** in seven-steps and in 31% overall yield.

Our previous studies demonstrated that the nucleophilicity of the 3-pyrrolin-2-one substrate is not sufficiently high for an optimal further transformation through *N*-alkylation.[14] We envisaged the use of more nucleophilic arylpyrrole **40** (Scheme 13). The synthesis started with pyrrole



Scheme 12. Synthesis of acrylates **33** and **35**.

36 containing a temporary blocking group at C2 position. In most of the reported rhazinilam syntheses[4b,22] a carboxymethyl group at the C2 position of the pyrrole ring had to be used as temporary protecting group. This protection probably prevents competing oxidative pyrrole dimerization reactions.



Scheme 13. Synthesis of biaryl **39**.

The key structural elements of **39** could be directly installed starting from a simple pyrrole nucleus by a metal-catalyzed C–H bond arylation to produce the heterobiaryl framework.

The Ir^{I}-catalyzed C–H borylation, developed by the groups of Smith–Malezcka and Hartwig–Miyaura,[6] was adopted to furnish the desired pyrrole nucleus, which was followed by a Suzuki coupling. The *tert*-butylcarboxy (Boc) group is known to be a protector and director for Ir-catalyzed borylations.[23] Pyrrole **36** was converted into *N*-Boc-pyrrole **4** in excellent yield. Compound **4** underwent an Ir-catalyzed borylation under Smith–Malezcka conditions to give 4-borylated pyrrole **38** in 72% yield with complete regioselectivity at C-4. The Pd-catalyzed Suzuki cross-coupling reaction of **38** with 2-bromo-nitrobenzene **5** was achieved quantitatively by following the procedure described by Morrison and co-workers.[7] Alternatively, biaryl **3** could be obtained in 96% yield by one-pot Ir^{I}-catalyzed C–H borylation and Suzuki coupling on **4** (see in the Supporting Information). Removal of the Boc group under thermal conditions[23,24] furnished **39** in quantitative yield.

Having sufficient quantities of the required aryl-pyrrole **39** available, we tested the alkylation reaction with the corresponding olefin (Table 5).

Nucleophilic substitution of the tosyl group by the potassium salt of pyrrole **39** was unsuccessful. The *N*-alkylated pyrrole **2** was isolated in moderate yield by using the sodium salt of the pyrrole precursor. Gratifyingly *N*-alkylation of pyrrole **39** preceded smoothly and quantitatively by using iodo-alkyl **33** as electrophile and NaH as base. The structure of **2** was determined by spectral analyses, and the stereochemistry was confirmed by NOE experiments (Figure 7).

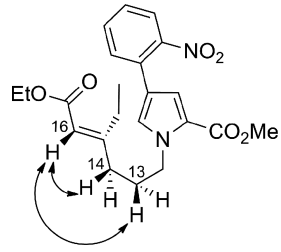
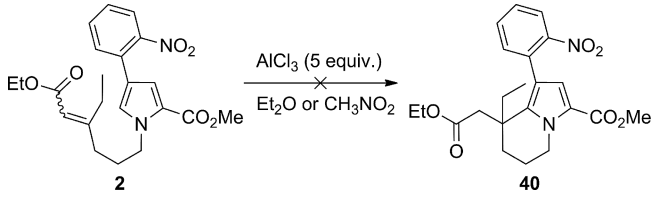


Figure 7. NOE experiments with (*E*)-**2**.

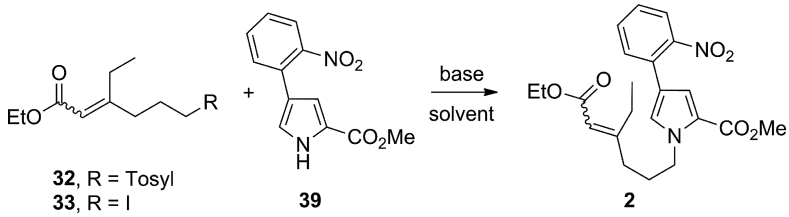
Unfortunately, all our attempts to obtain the cyclic adduct **40** from acrylate **2** by using aluminum chloride in diethyl ether or nitromethane failed (Scheme 14).



Scheme 14. Attempts to cyclize acrylate **2** into tetrahydroindolizine **40**.

The presence of both a methyl ester substituent on the pyrrole ring and a 2-nitro group on the phenyl ring deactivates the pyrrole ring sufficiently, preventing the Michael

Table 5. *N*-Alkylation of pyrrole **39**.



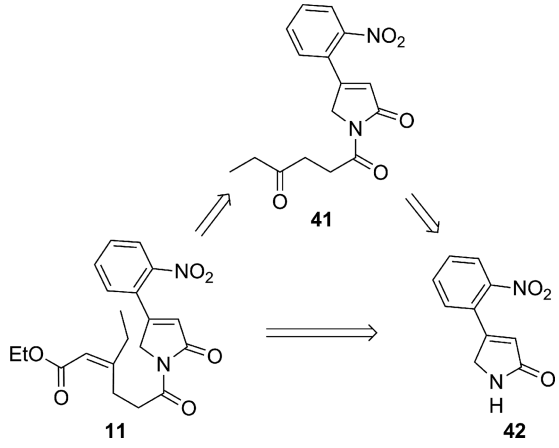
32, R = Tosyl
33, R = I

Entry	Electrophile	Base	Solvent	Temp. [°C]	Time [h]	Yield [%]
1	**32**	KHMDS	THF	85	20	–[a]
2	**32**	NaH	DMF	0–20	20	63[b]
3	**33**	NaH	DMF	0–20	6	quant.

[a] Only starting materials were recovered. [b] According to NMR spectroscopic analysis.

addition from occurring. The synthesis of a more nucleophilic pyrrole was a logical solution that could overcome this problem. Therefore we decided not to pursue this approach further.

Given the poor nucleophilic nature of 3-pyrrolin-2-one substrate, it was decided to investigate the *N*-acylation instead of the *N*-alkylation on the model series involving sterically less demanding substrates (Scheme 15). *N*-Acylation of sterically hindered chiral cyclic amides has previously been described, and oxazolidinones especially have attracted much interest because of their use as chiral auxiliaries.[25] Similar 3-pyrrolin-2-ones have been *N*-acylated by using an *n*BuLi protocol with electrophiles such as acid chlorides[26] and pentafluorophenyl (Pfp) esters.[27]



Scheme 15. Retrosynthetic pathways for the preparation of **11** through *N*-acylation of 3-pyrrolin-2-one **42**.

Two retrosynthetic pathways were envisaged and experimentally tested. The *N*-acylation could be successfully executed by using activated esters derived from levulinic acid, but attempts to extend the chain were not successful (see the Supporting Information for more details).

Treating the more complex aryl-3-pyrrolin-2-one **42** with the activated acrylate **35**, which was specifically synthesized for this purpose, and *n*BuLi under low temperature was successful (Scheme 16). Compound **11** was easily silylated by using *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine to give the pyrrole **26** in good yield. Compound **11** and **26** contain all essential elements needed for the construction of the Rhazinilam skeleton through a simple homologation step.[13,28]

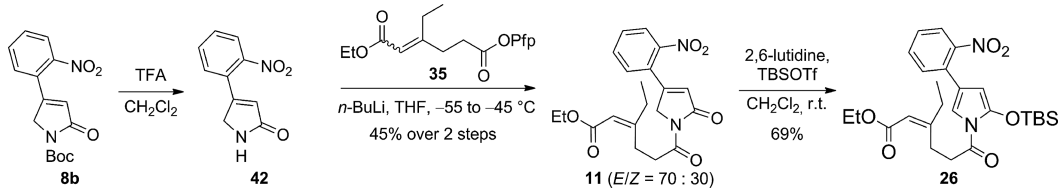
Conclusions

We have described the evolution of our synthetic strategies towards the preparation of advanced intermediates of pyrrole- and pyrrolinone-based analogues of rhazinilam, a potent mitotic spindle toxin. The retrosynthetic approach focused on the synthesis of the heterobiarylic core, attaching the chains and functional groups needed for the formation of rings C and D in a later stage. Building on the known sensitivity of pyrrole rings lacking electronic or steric stabilization, the synthetic intermediates were designed to contain at least one stabilizing element: either the well-known methoxycarbonyl ester group or the novel pyrrolinone element. Each successive generation of our synthetic approaches implemented new chemistry or modified existing methods, broadening the substrate scope. The focus on stable and resistant pyrrole derivatives facilitated the isolation but posed its own unique challenges for the later-stage transformations. The reported approaches make advanced intermediates readily available through two efficient and flexible syntheses. The most promising approach to the desired rhazinilam analogues is based on the elegant tandem Mukaiyama–Staudinger reaction sequence.

Studies on the further transformations disclosed a disturbing tendency of these advanced intermediates to undergo a panoply of uncharacterized side reactions. This statement is especially true for the intermediates of type **7** containing the pyrrolinone unit. This, from the synthetic standpoint, obstructive inclination for oxidative side reactions has a significance in the context of the metabolism of the natural product. (–)-Leuconolam and (+)-*epi*-leuconolam are products obtained through oxidative pathways from (–)-rhazinilam. Both products are known to be inactive in vivo. No plausible proposal for this remarkable difference in the biological effect compared with rhazinilam has been proposed so far. Our synthetic observation on the lack of stability of the pyrrolinone class of derivatives may be relevant in this context. The observed chemical instability of compounds of this type under hydrolytic conditions and in the presence of oxygen might be the reason for the inactivity of (–)-leuconolam and (+)-*epi*-leuconolam. This important message is taken into consideration in our ongoing studies, which are focused on the preparation of newly designed analogues of rhazinilam.

Experimental Section

Materials and Methods: All chemicals were used as received unless otherwise noted. Reagent-grade solvents were distilled prior to use.



Scheme 16. Preparation of precursors **11** and **26** by *N*-acylation of 3-pyrrolin-2-one **42**.

All reported NMR spectra were recorded in appropriated solvent (Cambridge Isotope Laboratories) at 298 K either with a Bruker Avance-400 spectrometer at 400 (^{1}H NMR) or 100 (^{13}C NMR) MHz or with a Varian Gemini XL-200 spectrometer at 200 (^{1}H NMR) and 50 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to TMS, defined as $CDCl_3$, δ = 7.26 ppm; CD_3OD, δ = 4.87 ppm; DMSO, δ = 3.33 ppm for ^{1}H NMR and $CDCl_3$, δ = 77.00 ppm; CD_3OD, δ = 49.00 ppm; DMSO, δ = 39.52 ppm for ^{13}C NMR spectroscopy. ^{1}H NMR spectroscopic data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), number of protons] 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 symbol "≈" denotes for the average value of J varying from 0.2 to 0.4 Hz. Infrared spectra were obtained with a Perkin–Elmer Spectrum One version B FTIR unit using KBr pressed films or KBr disks. Mass spectra were obtained with a ThermoFinnigan PolarisQ instrument by EI (70 eV) or with a ThermoFinnigan LCQ instrument by the ESI or APCI technique. HRMS were recorded with a Bruker BioAPEX II Daltonics instrument. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh ASTM). TLC analyses were performed on silica gel plates (0.2 mm) 60 F254 (Merck). Detection was first by UV (254 nm) then charring with a basic aqueous solution of $KMnO_4$. The isomer ratios were determined by gas chromatography (Agilent 6850 Series chromatograph) on a high-resolution gas chromatography HP-5 column (30 m × 0.32 mm × 0.25 μm) and the configuration was assigned by comparison of the retention time with the reported values. The following temperature programs were employed: (1) 100 °C (3 min), 15 °C/min to 280 °C, 280 °C (4 min); (2) 220 °C (2 min), 5 °C/min to 300 °C, 300 °C (10 min).

CCDC-813048 (for **18a**), -813047 (for **18b**), -813045 (for **20**), and -813046 (for **25a**) contain 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.

(1-Methoxyvinyloxy)trimethylsilane (10). A solution of LHMDS (1 M in THF, 16.20 mL, 16.2 mmol) was diluted in anhydrous THF (10 mL) and cooled to –78 °C, and a solution of methyl acetate (1.00 g, 13.5 mmol) in THF (6 mL) was added dropwise. After 30 min, TMSCl (1.75 g, 16.2 mmol) was added and the resulting mixture was stirred for 1.5 h at –78 °C. The solvent was evaporated and the salts were precipitated with pentane. The solution was filtered through Celite and the solvent was evaporated. The crude product was purified by distillation (P = 45 Torr, T = 48–50 °C) to give a pure **9** (1.81 g, 92%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.54 (s, 3 H), 3.21 and 3.11 (2× d, J = 2.6 Hz, 2 H), 0.22 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 162.1, 59.9, 55.1, 2.5 ppm.

General Procedure for 17c,e: A solution of **9c**,**e** (2.4 mmol) in anhydrous CH_2Cl_2 (15 mL) was added to a solution of keten acetal **10** (7.3 mmol) in anhydrous CH_2Cl_2 (15 mL) at –30 °C under argon. A solution of $TiCl_4$ (1.2 mmol), freshly distilled from polyvinylpyridine, in anhydrous CH_2Cl_2 (4 mL) was added slowly. The solution became red immediately and then dark-red. The reaction mixture was stirred at –30 °C for 15 min and then at –15 °C for 30 min. The cold mixture was poured into an aqueous solution of NaOH (2 N, 2.4 mL) and was extracted with chloroform. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel; CH_2Cl_2) followed by crystallization (diethyl ether/hexane) afforded **17c**,**e** as a white solid.

Methyl 4-Azido-3-hydroxy-3-phenylbutyrate (17c): Yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.43 (m, 2 H), 7.41–7.36 (m, 2 H), 7.33–7.29 (m, 1 H), 4.64 (d, J ≈ 1.4 Hz, 1 H), 3.62 (s, 3 H), 3.51 and 3.27 [AB system, J = 12.7 Hz, (B part) × d, J = 1.3 Hz, 2 H], 3.10 and 3.00 (AB system, J = 16.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 142.7, 128.6, 127.8, 125.0, 75.7, 60.7, 52.0, 41.2 ppm. IR (KBr): $\tilde{\nu}$ = 3522, 3435, 3024, 2987, 2962, 2918, 2852, 2473, 2097, 1721, 1697, 1434, 1356, 1297, 1286, 1217, 1161, 1006, 700, 587 cm^{-1}. ESI-MS: m/z = 258.1 $[M + Na]^+$. $C_{11}H_{13}N_3O_3$ (235.24): calcd. C 56.16, H 5.57, N 17.86; found C 55.69, H 5.57, N 17.81.

Methyl 4-Azido-3-hydroxy-3-(2-nitrophenyl)butyrate (17e): Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.56 (m, 4 H), 4.86 (s, 1 H), 3.67 (s, 3 H), 3.82 and 3.59 (AB system, J = 12.8 Hz, 2 H), 3.18 and 3.08 (AB system, J = 16.7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 150.7, 134.8, 131.4, 129.7, 128.3, 124.7, 76.4, 59.4, 52.8, 41.2 ppm. IR (KBr): $\tilde{\nu}$ = 3600–2800 (br.), 3445, 3075, 3009, 2959, 2924, 2853, 2198, 2109, 1716, 1532, 1436, 1419, 1365, 1303, 1276, 1244, 1200, 1168, 1044, 1008, 950, 911, 771, 554 cm^{-1}. ESI-MS: m/z = 303.0 $[M + Na]^+$. $C_{11}H_{12}N_4O_5$ (280.24): calcd. C 47.15, H 4.32, N 19.99; found C 47.15, H 4.39, N 19.76.

4-Hydroxy-4-(2-nitrophenyl)pyrrolidin-2-one (18b): PPh_3 (1.4 g, 5.4 mmol) was added to a solution of azido **17e** (3.6 mmol) in THF (15 mL). Water (1%, 0.15 mL) was added and the mixture was stirred at room temperature for 3 d. The solution was concentrated and MeOH (10 mL) was added. The mixture was stirred and heated to reflux for 30 min, then the suspension was cooled to –20 °C overnight, filtered, and the white powder was washed with EtOAc and dried to afford **18b** (80% yield). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.79 (br. s, 1 H), 7.49–7.67 (m, 4 H), 6.08 (s, 1 H), 3.66 and 3.46 (AB system, J = 10.7 Hz, 2 H), 2.97 and 2.42 (AB system, J = 16.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 174.7, 151.0, 137.8, 132.1, 129.6, 128.3, 124.8, 77.2, 56.3, 46.5 ppm. IR (KBr): $\tilde{\nu}$ = 3500–2800 (br.), 3402, 3225, 1672, 1526, 1481, 1440, 1406, 1373, 1321, 1284, 1104, 781, 752, 725, 712, 645, 632 cm^{-1}. ESI-MS: m/z = 688.7 $[3M + Na]^+$, 466.9 $[2M + Na]^+$. $C_{10}H_{10}N_2O_4$ (222.20): calcd. C 54.06, H 4.54, N 12.61; found C 54.00, H 4.63, N 12.50.

***tert*-Butyl 4-(2-Nitrophenyl)-2oxo-2,5-dihydropyrrole-1-carboxylate (8b):** DMAP (22.7 mg, 0.18 mmol) and Boc_2O (206 mg, 0.95 mmol) were added to a suspension of lactam **18**–**b** (0.45 mmol) in anhydrous THF (10 mL) under argon. The solution became clear immediately. The solution was stirred at room temperature for a minimum of 2 h. After removal of the solvent, the residue was purified by flash chromatography (silica gel; MeOH/CH_2Cl_2, 1%) to afford **8b** (98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (dd, J = 8.1, 1.3 Hz, 1 H), 7.72 (dt, J = 7.6, 1.3 Hz, 1 H), 7.63 (td, J = 8.1, 7.6, 1.5 Hz, 1 H), 7.41 (dd, J = 7.6, 1.5 Hz, 1 H), 6.13 (t, J = 1.6 Hz, 1 H), 4.55 (d, J = 1.6 Hz, 2 H), 1.56 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 155.3, 149.2, 147.4, 133.7, 130.7, 130.3, 128.3, 125.0, 124.9, 83.3, 53.0, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 3359, 3081, 2984, 2971, 2933, 2857, 1780, 1524, 1365, 1356, 1344, 1323, 1288, 1256, 1153, 1072, 846 cm^{-1}. ESI-MS: m/z = 303.1 $[M – H]^-$. $C_{11}H_{12}N_4O_5$ (280.24): calcd. C 59.21, H 5.30, N 9.21; found C 59.23, H 5.39, N 9.11.

***tert*-Butyl 4-Hydroxy-4-(2-nitrophenyl)-2-oxopyrrolidine-1-carboxylate (19):** DMAP (0.023 g, 0.2 mmol) and Boc_2O (0.1 mg, 0.5 mmol) were added to a solution of 4-hydroxy-4-(2-nitrophenyl)pyrrolidine-2-one (**18b**; 0.10 g, 0.5 mmol) in DMF (2 mL) under Ar. After 24 h at room temp., the solvent was evaporated and the crude product was purified by chromatography (EtOAc/CH_2Cl_2, 8:2). ^{1}H

NMR (200 MHz, CD_3OD): δ = 7.65–7.47 (m, 4 H), 4.11 and 5.05 (2× d AB system, J = 12.6 Hz, 2 H), 3.43 and 2.75 (1× d and 1× dd AB system, J = 17.0, 0.9 Hz, 2 H), 1.54 (s, 9 H) ppm.

***tert*-Butyl 2-(*tert*-Butoxycarbonyloxy)-4-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate (20):** DMAP (0.023 g, 0.2 mmol) and Boc_2O (0.30 g, 1.4 mmol) were added to a suspension of 4-hydroxy-4-(2-nitrophenyl)pyrrolidine-2-one (**18b**; 0.10 g, 0.5 mmol) in anhydrous THF (3 mL) under Ar. The solution became clear. After 1 h at room temp., the solvent was evaporated and the crude product was purified by chromatography (hexane/EtOAc, 7:3) to give **20** (169 mg, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (ddd, J = 8.1, 1.3, 0.5 Hz, 1 H), 7.64 (ddd, J = 7.8, 7.1, 1.3 Hz, 1 H), 7.60 (ddd, J = 7.8, 1.8, 0.5 Hz, 1 H), 7.49 (ddd, J = 8.1, 7.1, 1.8 Hz, 1 H), 7.16 (d, J = 2.3 Hz, 1 H), 5.97 (d, J = 2.3 Hz, 1 H), 1.62 (s, 9 H), 1.55 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 149.6, 147.7 and 137.9, 132.2, 131.1, 128.2, 128.0, 123.6, 119.3, 114.5, 100.6, 85.2, 84.7, 27.1, 26.8 ppm. ESI-MS: m/z = 426.9 $[M + Na]^+$. $C_{20}H_{24}N_2O_7$ (404.42): calcd. C 59.40, H 5.98, N 6.93; found C 59.66, H 6.16, N 6.89.

General Procedure for 21a–b: 2,6-Lutidine (0.2 mL) and TBSOTf (127 mg, 0.48 mmol) were added at room temperature under argon to a solution of pyrrolidinone **8a**–**b** (0.48 mmol) in anhydrous CH_2Cl_2 (5 mL), and the mixture was stirred for 1 h. After removal of the solvent, purification of the residual oil by filtration through silica gel (EtOAc/hexane, 20%) afforded silyl enol **21a**–**b** as an orange oil.

***tert*-Butyl 2-(*tert*-Butyldimethylsilanyloxy)-4-phenylpyrrole-1-carboxylate (21a):** Yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2 H), 7.36 (m, 2 H), 7.23 (m, 1 H), 7.04 (d, J = 2.3 Hz, 1 H), 5.63 (d, J = 2.3 Hz, 1 H), 1.63 (s, 9 H), 1.06 (s, 9 H), 0.31 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 144.1, 134.6, 128.5, 126.2, 125.0, 123.3, 108.6, 91.2, 83.0, 28.1, 25.7, 18.4, –4.7 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2931, 2859, 1757, 1595, 1575, 1552, 1473, 1452, 1386, 1369, 1353, 1301, 1288, 1255, 1210, 1162, 1113, 895, 841, 785 cm^{-1}.

***tert*-Butyl 2-(*tert*-Butyldimethylsilanyloxy)-4-(2-nitrophenyl)pyrrole-1-carboxylate (21b):** Yield 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, J = 8.1, 1.2 Hz, 1 H), 7.53 (td, J = 7.8, 6.9, 1.3 Hz, 1 H), 7.50 (dd, J = 7.8, 2.0 Hz, 1 H), 7.37 (ddd, J = 8.1, 6.9, 1.9 Hz, 1 H), 6.91 (d, J = 2.3 Hz, 1 H), 5.31 (d, J = 2.3 Hz, 1 H), 1.61 (s, 9 H), 1.02 (s, 9 H), 0.27 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1, 147.8, 144.0, 131.8, 130.8, 129.3, 127.2, 123.6, 118.7, 111.1, 92.4, 83.5, 28.1, 25.7, 18.4, –4.8 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 2931, 2859, 1761, 1736, 1595, 1553, 1530, 1386, 1370, 1351, 1257, 1160, 1118, 896, 842, 785 cm^{-1}.

***tert*-Butyl 2-(3-Ethoxycarbonylpropionyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydropyrrole-1-carboxylate (23b):** To a solution of silyl enol **21b** (2.3 mmol) in anhydrous CH_2Cl_2 (20 mL) at –78 °C and under argon were added aldehyde **22b** (3.0 mmol) and dropwise $BF_3{\cdot}OEt_2$ (2.3 mmol). The color of the solution changed from yellow to pale-yellow. The mixture was stirred at –78 °C for 1 h, then the reaction was quenched at –78 °C with a saturated aqueous solution of $NaHCO_3$ (15 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (silica gel; EtOAc/Et_2O, 30%) afforded the aldol products **23b** (93% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (**isomer 1**) = 8.05 (dd, J = 8.1, 1.2 Hz, 1 H), 7.69 (dt, J = 7.6, 1.3 Hz, 1 H), 7.59 (ddd, J = 8.1, 7.5, 1.5 Hz, 1 H), 7.47 (dd, J = 7.7, 1.4 Hz, 1 H), 6.21 (d, J = 1.2 Hz, 1 H), 5.15 (dd, J = 3.8, 1.2 Hz, 1 H), 4.12 (m, 1 H), 4.05 (q, J = 7.2 Hz, 2 H), 2.78 (d, J = 5.7 Hz, 1 H, OH), 2.35 (m, 2 H), 1.71–1.65 (m, 1 H), 1.57 (s, 9 H), 1.50–1.42 (m, 1 H), 1.19 (t, J = 7.2 Hz, 3 H) ppm; δ (**isomer 2**) = 8.14 (dd, J = 8.2, 1.2 Hz, 1 H), 7.73 (dt, J = 7.6, 1.3 Hz, 1 H), 7.64 (ddd, J = 8.2, 7.5, 1.5 Hz, 1 H), 7.53 (dd, J = 7.6, 1.4 Hz, 1 H), 6.05 (d, J = 1.3 Hz, 1 H), 5.09 (t, J = 1.2 Hz, 1 H), 4.40–4.20 (br. s, 1 H, OH), 4.02 (q, J = 7.1 Hz, 2 H), 3.93 (m, 1 H), 2.34 (m, 2 H), 1.57 (s, 9 H), 1.52–1.44 (m, 1 H), 1.26–1.20 (m, 1 H), 1.16 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (**isomer 1**) = 173.9, 168.2, 159.0, 149.5, 148.0, 133.6, 131.3, 130.5, 129.3, 125.9, 124.9, 83.8, 70.5, 65.9, 60.7, 31.4, 28.1, 26.4, 14.1 ppm; δ (**isomer 2**) = 173.1, 167.9, 157.9, 150.8, 147.1, 134.0, 131.7, 130.7, 128.7, 125.5, 125.0, 84.2, 69.1, 60.3, 30.6, 28.6, 26.9, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3468, 3102, 2982, 2934, 1777, 1733, 1605, 1572, 1528, 1478, 1443, 1371, 1350, 1323, 1256, 1229, 1156, 1077, 965, 869, 845, 789, 773, 759, 716, 690, 641, 530 cm^{-1}. ESI-MS: m/z = 457.0 $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{21}H_{26}N_2O_8$ $[M + Na]^+$ 457.1587; found 457.1584.

***tert*-Butyl 2-(4-Ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (7b):** To a solution of aldol product **23b** (0.52 mmol) in anhydrous CH_2Cl_2 (60 mL) was added MS 4 Å (2 g) and pyridinium dichromate (PDC) (1.04 mmol) at 0 °C. The progress of the reaction was monitored by TLC until the starting material disappeared (ca. 6 h). The mixture was then filtered through a pad of Celite and silica gel and, after concentration, the residue was purified by flash chromatography (silica gel; CH_2Cl_2/Et_2O, 30%) to afford the products **7b** (77% yield) as a slightly yellow paste. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.1, 1.4 Hz, 1 H), 7.70 (dt, J = 7.5, 1.4 Hz, 1 H), 7.63 (td, J = 8.0, 7.6, 1.5 Hz, 1 H), 7.34 (dd, J = 7.5, 1.5 Hz, 1 H), 6.20 (d, J = 1.7 Hz, 1 H), 5.44 (d, J = 1.7 Hz, 1 H), 4.05 (q, J = 7.1 Hz, 2 H), 2.84 [(A part of AB system)× t, $J \approx$ 19.0 Hz, 1 H], 2.55 [(B part of AB system)× dd, $J \approx$ 19.0, 7.1, 5.7 Hz, 1 H], 2.41 and 2.40 [(AB system)× dd, $J \approx$ 17.2, 7.1, 5.7 Hz, 2 H], 1.55 (s, 9 H), 1.19 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 171.8, 167.3, 153.8, 148.7, 147.2, 133.8, 131.3, 131.1, 126.7, 125.8, 125.2, 84.7, 71.9, 60.7, 32.9, 27.9, 27.1, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3102, 2982, 2930, 1787, 1728, 1635, 1605, 1572, 1530, 1396, 1371, 1348, 1329, 1258, 1208, 1155, 1126, 1070, 843, 755 cm^{-1}. ESI-MS: m/z = 454.9 $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{21}H_{24}N_2O_8$ $[M + Na]^+$ 455.1430; found 455.1427.

4-[1-(*tert*-Butoxycarbonyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]-4-oxobutanoic Acid (24): To a solution of *tert*-butyl 2-(4-ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**7b**; 0.70 g, 1.6 mmol) was added a solution of NaOH 50% (3 mL). The solution became red and then dark-brown. After 1 h, the reaction mixture was diluted with Et_2O, the phases were separated, and the aqueous phase was acidified with HCl (3.5*N*) to pH ca. 1 and extracted three times with Et_2O. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by chromatography (CH_2Cl_2/MeOH, 95:5) to afford the acid **24** (40%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dd, J = 8.0, 1.4 Hz, 1 H), 7.68 (dt, J = 7.4, 1.5 Hz, 1 H), 7.63 (ddd, J = 8.0, 7.6, 1.6 Hz, 1 H), 7.29 (dd, J = 7.5, 1.6 Hz, 1 H), 6.22 (d, J = 1.7 Hz, 1 H), 5.46 (d, J = 1.7 Hz, 1 H), 1.55 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 177.1, 167.3, 153.9, 148.7, 147.2, 133.9, 131.3, 131.3, 126.5, 125.8, 125.3, 84.8, 71.6, 32.7, 27.9, 26.7 ppm. IR (KBr): $\tilde{\nu}$ = 3276, 3104, 2981, 2932, 1784, 1726, 1605, 1572, 1529, 1478, 1458, 1396, 1370, 1347, 1258, 1154, 1129, 1074, 871, 844, 788, 756, 691 cm^{-1}. ESI-MS: m/z = 403.1 $[M – H]^-$.

***tert*-Butyl 2-(4-Ethoxy-4-oxobutanoyl)-3-(2-nitrophenyl)-5-(trifluoromethylsulfonyloxy)-1*H*-pyrrole-1-carboxylate (25d):** To a solution of pyrrolinone **7b** or **8a**–**b** (3.52 mmol) in anhydrous CH_2Cl_2

(80 mL) was added Et_3N (7.04 mmol) followed by Tf_2O (4.93 mmol) at –10 °C. The reaction was monitored by TLC until complete disappearance of the starting material was observed, then it was quenched with a saturated solution of $NaHCO_3$ (40 mL). The organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel; EtOAc/hexane, 40%) afforded triflate **25d** (71% yield) as a slightly orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (ddd, J = 8.1, 1.4, 0.3 Hz, 1 H), 7.65 (td, J = 7.5, 1.4 Hz, 1 H), 7.57 (ddd, J = 8.1, 7.5, 1.6 Hz, 1 H), 7.43 (ddd, J = 7.5, 1.6, 0.3 Hz, 1 H), 5.99 (m, 1 H), 4.02 (q, J = 7.2 Hz, 2 H), 2.58–2.54 (m, 2 H), 2,48–2.45 (m, 2 H), 1.60 (s, 9 H), 1.16 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0, 172.0, 148.9, 146.2, 135.1, 133.0, 132.8, 129.9, 127.9, 126.7, 124.5, 124.5, 118.6 [q, $J_{C,F}$ = 321.1 Hz, CF_3], 101.9, 88.1, 60.5, 36.3, 28.1, 27.3, 14.1 ppm. ESI-MS: m/z = 586.8 $[M + Na]^+$.

Ethyl 4-[3-(2-Nitrophenyl)-1*H*-pyrrol-2-yl]-4-oxobutanoate (6): Compound **25d** (1.37 g, 2.43 mmol) was dissolved in DMF (15 mL), then $Pd(OAc)_2$ (27.3 mg, 0.12 mmol) and dppf (67.3 mg, 0.12 mmol) were added and the temperature was decreased to –10 °C. Et_3SiH (0.96 mL, 6.08 mmol) was then added and the mixture was stirred at this temperature for 30–40 min (reaction followed by ^{1}H NMR spectroscopic analysis). The solution was diluted with diethyl ether and first washed with water, then with a saturated solution of $NaHCO_3$ and finally with brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (silica gel; Et_2O/hexane, 50%) afforded the reduced product, yield 649 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, J = 8.1, 1.3 Hz, 1 H), 7.60 (dt, J = 7.6, 1.4 Hz, 1 H), 7.51 (ddd, J = 8.1, 7.5, 1.5 Hz, 1 H), 7.42 (dd, J = 7.6, 1.5 Hz, 1 H), 7.29 (d, J = 3.3 Hz, 1 H), 6.16 (d, J = 3.2 Hz, 1 H), 4.06 (q, J = 7.1 Hz, 2 H), 2.86 (t, $J \approx$ 7.2 Hz, 2 H), 2.55 (t, $J \approx$ 7.2 Hz, 2 H), 1.61 (s, 9 H), 1.20 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 172.4, 149.3, 148.3, 133.9, 132.3, 130.2, 128.9, 128.7, 127.0, 124.1, 123.7, 112.2, 85.6, 60.4, 38.0, 28.6, 27.7, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3149, 3071, 2983, 2937, 1740, 1681, 1615, 1563, 1530, 1492, 1478, 1459, 1436, 1413, 1372, 1345, 1280, 1260, 1215, 1149, 1071, 1038, 995, 943, 931, 877, 851, 844, 787, 752, 703, 651, 605 cm^{-1}. ESI-MS: m/z = 454.9 $[M + K]^+$, 438.9 $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{21}H_{24}N_2O_7$ $[M + Na]^+$ 439.1481; found 439.1475.

The resulting reduced product (374 mg, 0.90 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (2 mL) was added to the mixture at room temperature. The progress of the reaction was followed by ^{1}H NMR spectroscopy. After 20 min, the mixture was treated with a saturated solution of $NaHCO_3$ (10 mL) and the organic phase was washed with brine, dried with $MgSO_4$, filtered, and concentrated to give the pure product **6**, yield 251 mg (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.73 (s, 1 H), 7.95 (dd, J = 8.1, 1.3 Hz, 1 H), 7.64 (dt, J = 7.5, 1.4 Hz, 1 H), 7.55 (d × tripletoid, J = 8.1, 7.5, 1.6 Hz, 1 H), 7.50 (dd, J = 7.5, 1.6 Hz, 1 H), 7.02 (tripletoid, J = 3.0, 2.6 Hz, 1 H), 6.20 (t, J = 2.7 Hz, 1 H), 4.07 (q, J = 7.1 Hz, 2 H), 2.57–2.51 (m, 4 H), 1.20 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5, 172.7, 149.7, 132.8, 132.3, 130.9, 128.9, 128.8, 125.8, 124.0, 123.0, 112.8, 60.5, 33.7, 28.0, 14.1 ppm. IR (KBr): $\tilde{\nu}$ = 3289, 3130, 3115, 2975, 2929, 2903, 2868, 2610, 2554, 1998, 1964, 1886, 1847, 1734, 1629, 1571, 1529, 1494, 1481, 1412, 1372, 1353, 1308, 1291, 1276, 1259, 1221, 1202, 1183, 1162, 1121, 1100, 1075, 1032, 1012, 976, 965, 938, 896, 884, 852, 791, 771, 758, 715, 701, 647, 621, 588, 529 cm^{-1}. ESI-MS: m/z = 339.1 $[M + Na]^+$. HRMS (ESI): m/z calcd. for $C_{16}H_{16}N_2O_5$ $[M + Na]^+$ 339.0957; found 339.0952.

1-*tert*-Butyl 2-Methyl 4-(2-Nitrophenyl)-1*H*-pyrrole-1,2-dicarboxylate (3). Method A: In an over-dried glass microwave flask, the solid starting materials *N*-(Boc)pyrrole pinacol boronate **38** (450 mg, 1.28 mmol), 2-bromo-nitrobenzene **5** (216 mg, 1.07 mmol), palladium acetate (12 mg, 0.05 mmol), 2-dicyclohexyl-phosphino-2′,6′-dimethoxybiphenyl (44 mg, 0.11 mmol), and K_3PO_4 (453 mg, 2.14 mmol) were combined. The vial was sealed with a Teflon®-coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. The solvent system (2.56 mL, 2.0 mL/mmol 2-bromo-nitrobenzene), consisting of degassed *n*-butanol (1.83 mL) and degassed deionized water (0.73 mL) in the ratio of 2.5:1 was added. The resulting mixture was heated at 35 °C for 16 h. The crude reaction mixture was then filtered through a plug of silica gel (eluting with 35 mL of EtOAc) and concentrated in vacuo. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 90:10) to provide the desired Boc-protected phenylpyrrole **3** (380 mg, 100%) as a yellow oil.

Method B. One-Pot Synthesis from Pyrrole 4: A glass microwave flask was initially charged with $[Ir(OMe)(COD)]_2$ (20 mg, 0.03 mmol, 3 mol-% Ir) and 4,4′-di-*tert*-butyl-2,2′-bipyridine (16 mg, 0.06 mmol, 3 mol-%). The vial was sealed with a Teflon®-coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. Anhydrous and degassed hexane (3 mL) was added at room temperature. To the resulting mixture was added dropwise pinacolborane (0.35 mL, 2.40 mmol) followed by pyrrole **4** (450 mg, 2.00 mmol). The resulting mixture was heated at 80 °C for 6 h, and then stirred at room temperature overnight. The screwcap was removed and the solid starting materials were added to a crude mixture of 2-bromo-nitrobenzene **5** (403 mg, 2.00 mmol), palladium acetate (19 mg, 0.04 mmol), SPhos (68 mg, 0.08 mmol), and K_3PO_4 (706 mg, 1.66 mmol). The vial was sealed with a Teflon®-coated screwcap, a needle was inserted through the cap and the vial was then evacuated and backfilled with argon. The solvent system (2.56 mL, 1.0 mL/mmol 2-bromo-nitrobenzene), consisting of degassed *n*-butanol (1.83 mL) and degassed deionized water (0.73 mL) in a ratio of 2.5:1 was added. The resulting mixture was heated at 35 °C for 16 h. The crude reaction mixture was then filtered through a plug of silica gel (eluting with 30 mL of EtOAc) and concentrated in vacuo. The crude material so obtained was purified by flash chromatography on silica gel (petroleum ether and then petroleum ether/EtOAc gradually to 90:10) to give the desired Boc-protected phenylpyrrole **3** (661 mg, 96% starting from pyrrole **4**) as a yellow oil. R_f = 0.30 (petroleum ether/EtOAc, 80:20). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 7.87 (dd, J = 8.1, 1.0 Hz, 1 H), 7.72 (ddd, J = 7.9, 6.9, 1.2 Hz, 1 H), 7.68 (dd, J = 7.7, 1.8 Hz, 1 H), 7.60 (d, J = 1.9 Hz, 1 H), 7.59 (ddd, J = 8.0, 6.9, 1.9 Hz, 1 H), 6.90 (d, J = 1.9 Hz, 1 H), 3.84 (s, 3 H), 1.60 (s, 9 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 161.4, 150.1, 148.9, 133.2, 132.3, 129.4, 128.0, 126.8, 125.2, 124.6, 121.8, 119.9, 86.3, 52.4, 27.7 ppm. IR (KBr, film): $\tilde{\nu}$ = 3134, 2983, 2954, 1732, 1613, 1569, 1529, 1459, 1436, 1395, 1371, 1344, 1284, 1246, 1155, 1078, 1037, 954, 929, 849, 802, 776, 748, 704, 648, 634, 596, 527 cm^{-1}. MS-ESI: m/z = 369.3 (100) $[M + Na]^+$, 269.2 (17) [M – 77]. HRMS (ESI): m/z calcd. for $C_{17}H_{18}N_2O_6$ $[M + Na]^+$ 369.10626; found 369.10566.

Methyl 4-(2-Nitrophenyl)-1*H*-pyrrole-2-carboxylate (39): Under argon, a solution of Boc-protected phenylpyrrole **3** (330 mg, 0.95 mmol) in anhydrous DMF (3 mL) was heated at 120 °C for 3 h. The reaction mixture was cooled to room temperature and poured into water (100 mL). The aqueous layer was extracted with EtOAc (3× 60 mL) and the combined organic extracts were

washed with water (2 × 50 mL), brine (60 mL), dried with $MgSO_4$, filtered, and the solvents evaporated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 90:10 to 70:30) to afford the deprotected phenylpyrrole **39** (243 mg, 100%) as a yellow solid. R_f = 0.15 (petroleum ether/EtOAc, 80:20). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 11.28 (br. s, 1 H, NH), 7.75 (dd, J = 7.9, 0.9 Hz, 1 H), 7.68 (dd, J = 7.6, 1.8 Hz, 1 H), 7.65 (ddd, J = 7.8, 6.6, 1.2 Hz, 1 H), 7.49 (ddd, J = 8.1, 6.8, 1.9 Hz, 1 H), 7.30 (dd, J = 3.0, 1.8 Hz, 1 H), 6.93 (t, J = 1.9 Hz, 1 H), 3.81 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 161.5, 150.3, 132.7, 131.7, 129.1, 128.3, 124.5, 124.1, 123.1, 121.1, 114.6, 51.6 ppm. IR (KBr): $\tilde{\nu}$ = 3282, 3128, 2956, 2925, 2855, 1967, 1926, 1697, 1608, 1568, 1516, 1438, 1393, 1367, 1309, 1292, 1251, 1217, 1174, 1151, 1048, 992, 943, 929, 854, 834, 807, 764, 741, 703, 648, 611, 543, 503, 459, 438, 419 cm^{-1}. MS-ESI: m/z = 245.3 (100) [M – H]$^-$. HRMS (ESI): m/z calcd. for $C_{12}H_{10}N_2O_4$ [M + Na]$^+$ 269.05383; found 269.05355.

Methyl (*E*/*Z*)-1-(6-Ethoxy-4-ethyl-6-oxohex-4-enyl)-4-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylate (2): To a solution of phenylpyrrole **39** (20 g, 0.08 mmol) in anhydrous DMF (0.3 mL) at 0 °C was added 95% NaH (2 mg, 0.09 mmol) under argon. After 10 min at 0 °C, the solution was stirred at room temperature for 1 h. The mixture was cooled to 0 °C, and a solution of iodo acrylate **33** (26 mg, 0.09 mmol) in anhydrous DMF (0.1 mL) was added dropwise. The flask containing **39** was rinsed with additional anhydrous DMF (0.2 mL) and the resulting solution was stirred at room temperature for 6 h, and then poured into water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), brine (15 mL), dried with $MgSO_4$, filtered, and concentrated. The product was purified by column chromatography (petroleum ether and then petroleum ether/EtOAc, 90:10) to afford an *E*/*Z* mixture (70:30) of **2** (36 mg, 100%) as a yellowish oil. R_f = 0.33 (petroleum ether/EtOAc, 80:20). GC: t_R = 21.27 [(*E*)-**2**], 20.55 [(*Z*)-**2**] min. ^{1}H NMR (400 MHz, [D$_6$]acetone): δ [(*E*)-**2**] = 7.75 (dd, J = 7.9, 2.4 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.49 (ddd, J = 8.8, 8.1, 4.3 Hz, 1 H), 7.35 (d, J = 2.1 Hz, 1 H), 6.99 (d, J = 2.1 Hz, 1 H), 5.63 (s, 1 H), 4.45 (t, J = 7.1 Hz, 2 H), 4.08 (q, J = 7.1 Hz, 2 H), 3.81 (s, 3 H), 2.64 (q, J = 7.5 Hz, 2 H), 2.23 (app. t, J = 7.5 Hz, 2 H), 2.00 (app. quint, J = 7.3 Hz, 2 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.5 Hz, 3 H) ppm; δ [(*Z*)-**2**] = 7.75 (dd, J = 7.9, 2.4 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.49 (ddd, J = 8.8, 8.1, 4.3 Hz, 1 H), 7.37 (d, J = 2.1 Hz, 1 H), 6.98 (d, J = 2.1 Hz, 1 H), 5.66 (s, 1 H), 4.44 (t, J = 7.2 Hz, 2 H), 4.10 (q, J = 7.0 Hz, 2 H), 3.80 (s, 3 H), 2.67 (app. t, J = 7.7 Hz, 2 H), 2.22 (dq, J = 7.5, 1.2 Hz, 2 H), 1.97 (app. quint, J = 7.4 Hz, 2 H), 1.22 (t, J = 7.1 Hz, 3 H), 1.05 (t, J = 7.4 Hz, 3 H) ppm. ^{1}H NOE diff: (*E*)-**2**: irrad H^{16} (5.63 ppm)→enhanced H^{14} (2.23 ppm) and H^{13} (2.00 ppm). ^{13}C NMR (100 MHz, [D$_6$]acetone): δ [(*E*)-**2**] = 166.4, 165.1, 161.6, 150.2, 132.7, 131.6, 128.9, 128.6, 128.3, 124.2, 123.3, 119.0, 117.5, 116.0, 59.8, 51.5, 49.5, 35.2, 30.2, 25.3, 14.6, 13.3 ppm; δ [(*Z*)-**2**] = 166.4, 164.9, 161.6, 150.2, 132.7, 131.6, 128.9, 128.6, 128.2, 124.2, 123.3, 118.9, 117.4, 115.8, 60.0, 51.5, 49.9, 31.5, 30.9, 29.6, 14.3, 12.3 ppm. IR (KBr, film): $\tilde{\nu}$ = 3065, 2956, 2874, 1713, 1645, 1609, 1563, 1531, 1495, 1476, 1446, 1394, 1368, 1259, 1206, 1148, 1105, 1038, 959, 933, 853, 812, 779, 749, 696, 674, 651, 561, 509, 445 cm^{-1}. MS-ESI: m/z = 437.5 (100) [M + Na]$^+$, 453.3 (13) [M + K]$^+$. HRMS (ESI): m/z calcd. for $C_{22}H_{26}N_2O_6$ [M + Na]$^+$ 437.16886; found 437.16802.

4-(2-Nitrophenyl)-1*H*-pyrrol-2(5*H*)-one (42): Trifluoroacetic acid (1.60 mL) was added dropwise to a solution of Boc-protected pyrrolinone **8b** (200 mg, 0.66 mmol) in anhydrous 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 the reaction was 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 with $MgSO_4$, filtered, and the solvents evaporated. Deprotected pyrrolinone **42** (131 mg, 98%) was recovered as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 8.03 (dd, J = 8.1, 1.3 Hz, 1 H), 7.76 (td, J = 7.5, 1.3 Hz, 1 H), 7.66 (td, J = 7.5, 1.3 Hz, 1 H), 7.59 (dd, J = 7.6, 1.5 Hz, 1 H), 6.12 (t, J = 1.6 Hz, 1 H), 4.35 (d, J = 1.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 176.0, 158.3, 149.6, 134.4, 131.6, 131.6, 129.4, 126.6, 125.3, 51.6 ppm. MS (ESI): m/z (%) = 227.2 (100) [M + Na]$^+$. HRMS (ESI): m/z calcd. for $C_{10}H_8N_2O_3$ [M + Na]$^+$ 227.04326; found. 227.04317.

Ethyl (*E*/*Z*)-3-Ethyl-6-[4-(2-nitrophenyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl]-6-oxohex-2-enoate (11): To a solution of pyrrolinone **42** (50 mg, 0.25 mmol) in anhydrous THF (3.0 mL) was added dropwise BuLi (2.0 M in cyclohexane, 0.13 mL, 0.25 mmol) at –55 °C and under argon. After 10 min at –54 °C, a solution of activated ester **35** (98 mg, 0.27 mmol) in anhydrous THF (2.0 mL) was added dropwise over 15 min. The mixture was stirred for an additional 5 min. Over this 30 min period, the temperature had been allowed to reach –45 °C. The mixture was quenched with AcOH (0.1 mL) and evaporated with 5 mL of silica. The product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 70:30 to 50:50) to afford an *E*/*Z* mixture (70:30) of **11** (43 mg, 45%) as an orange oil. R_f = 0.45 (petroleum ether/EtOAc, 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ [(*E*)-**11**] = 8.11–8.08 (m, 1 H), 7.73 (td, J = 7.3, 2.4 Hz, 1 H), 7.67–7.62 (m, 1 H), 7.41 (dd, J = 7.2, 2.3 Hz, 1 H), 6.15 (t, J = 1.5 Hz, 1 H), 5.71 (s, 1 H), 4.64 (d, J = 1.5 Hz, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.21–3.13 (m, 2 H), 2.68 (q, J = 7.5 Hz, 2 H), 2.23 (td, J = 7.6, 0.8 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.12 (t, J = 7.5 Hz, 3 H) ppm; δ [(*Z*)-**11**] = 8.11–8.08 (m, 1 H), 7.73 (td, J = 7.3, 2.4 Hz, 1 H), 7.67–7.62 (m, 1 H), 7.41 (dd, J = 7.2, 2.3 Hz, 1 H), 6.13 (t, J = 1.5 Hz, 1 H), 5.69 (s, 1 H), 4.64 (d, J = 1.5 Hz, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.21–3.13 (m, 2 H), 2.97 (app. t, J = 7.9 Hz, 2 H), 2.26 (q, J = 7.3 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.11 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ [(*E*)-**11**] = 171.8, 168.7, 166.3, 163.5, 156.8, 147.6, 133.6, 130.9, 130.1, 128.0, 125.1, 124.5, 115.5, 59.6, 52.3, 34.7, 31.8, 25.5, 14.3, 13.0 ppm; δ [(*Z*)-**11**] = 172.2, 168.7, 166.4, 163.5, 156.5, 147.6, 133.5, 130.8, 130.1, 128.1, 125.0, 124.6, 115.6, 59.6, 52.3, 35.4, 31.4, 26.9, 14.3, 11.9 ppm. IR (KBr, film): $\tilde{\nu}$ = 3079, 2979, 2924, 1744, 1713, 1683, 1646, 1601, 1570, 1531, 1478, 1446, 1373, 1349, 1319, 1259, 1239, 1208, 1190, 1172, 1152, 1085, 1048, 984, 897, 882, 866, 796, 755, 726, 697, 688, 646, 629, 574, 533 cm^{-1}. HPLC-MS (EI, 70 eV): t_R = 6.94 [(*E*)-**11**], 7.08 [(*Z*)-**11**] min; m/z (%) = 425.1 (11) [M + K]$^+$, 409.2 (100) [M + Na]$^+$, 387.2 (14) [M + H]$^+$. HRMS (ESI): m/z calcd. for $C_{20}H_{22}N_2O_6$ [M + Na]$^+$ 409.13756; found 409.13695.

Ethyl (*E*/*Z*)-6-{2-[(*tert*-Butyldimethylsilyl)oxy]-4-(2-nitrophenyl)-1*H*-pyrrol-1-yl}-3-ethyl-6-oxohex-2-enoate (26): To a stirred solution of pyrrolinone **11** (40 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (1 mL) at room temperature and under argon was added 2,6-lutidine (0.04 g, 0.31 mmol) followed by TBSOTf (0.02 mL, 0.11 mmol). The reaction mixture was stirred at room temperature for 15 min (reaction progress monitored by TLC) then concentrated in vacuo. The residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 90:10) to afford an *E*/*Z* mixture (60:40) of **26** (36 mg, 69%) as a yellow oil. R_f = 0.39 (cyclohexane/EtOAc, 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ [(*E*)-**26**] = 7.70 (ddd, J = 8.0, 4.2, 1.2 Hz, 1 H), 7.54 (ddd, J = 7.8, 2.7, 1.2 Hz, 1 H), 7.51–7.47 [m (partially solved), J = 7.8, 4.2 Hz, 1 H], 7.40–7.35 [m (partially solved), J = 8.0 Hz, 1 H], 7.17 (d, J = 2.3 Hz, 1 H), 5.66 (s, 1 H), 5.28 (d, J = 2.3 Hz, 1 H), 4.15 (q, J = 7.2 Hz, 2 H),

3.13–3.08 (m, 2 H), 2.66 (q, J = 7.5 Hz, 2 H), 2.62 (dd, J = 7.7, 6.4 Hz, 2 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.11 (t, J = 7.5 Hz, 3 H), 1.00 (s, 9 H), 0.32 (s, 6 H) ppm; δ [(*Z*)-**26**] = 7.70 (ddd, J = 8.0, 4.2, 1.2 Hz, 1 H), 7.54 (ddd, J = 7.8, 2.7, 1.2 Hz, 1 H), 7.51–7.47 [m (partially solved), J = 7.8, 4.2 Hz, 1 H], 7.40–7.35 [m (partially solved), J = 8.0 Hz, 1 H], 7.20 (d, J = 2.3 Hz, 1 H), 5.71 (s, 1 H), 5.25 (d, J = 2.3 Hz, 1 H), 4.13 (q, J = 7.1 Hz, 2 H), 3.13–3.08 (m, 2 H), 2.96 (dd, J = 9.0, 6.7 Hz, 2 H), 2.23 (qd, J = 7.4, 1.3 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.10 (t, J = 7.4 Hz, 3 H), 0.95 (s, 9 H), 0.28 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ [(*E*)-**26**] = 169.9, 166.1, 163.4, 149.0, 143.0, 132.1, 130.8, 129.0, 127.7, 123.8, 120.4, 115.6, 109.7, 91.8, 59.6, 35.3, 31.7, 25.7, 25.6, 18.3, 14.3, 13.0 ppm; δ [(*Z*)-**26**] = 170.4, 166.2, 163.8, 149.1, 143.1, 132.0, 130.8, 129.2, 127.5, 123.7, 120.1, 115.6, 109.7, 91.5, 59.7, 36.4, 31.8, 27.1, 25.7, 18.1, 14.1, 12.0 ppm. MS-ESI: *m*/*z* (%) = 539.4 (7) [M + K]$^+$, 423.5 (100) [M + Na]$^+$, 501.5 (8) [M + H]$^+$. HRMS (ESI): *m*/*z* calcd. for $C_{26}H_{36}N_2O_6Si$ [M + Na]$^+$ 523.22403; found 523.22399.

Supporting Information (see footnote on the first page of this article): X-ray crystallographic analysis of **18b** and **25a**, studies on *N*-acylation of 1*H*-pyrrol-2(5*H*)-one, detailed experimental procedures, full characterization, and copies of ^{1}H and ^{13}C NMR spectra of newly reported compounds.

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