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α-Amino acid derived enaminones and their application in the synthesis of *N*-protected methyl 5-substituted-4-hydroxypyrrole-3-carboxylates and other heterocycles

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ABSTRACT

A new and simple synthesis of novel *N*-protected methyl 5-substituted-4-hydroxypyrrole-3-carboxylates, which exist in equilibrium with their 4-oxo tautomers, has been developed in two steps starting from *N*-protected α-amino acids. The key intermediates are enaminones, which can also be isolated, characterized, and used for the construction of other functionalized heterocycles, before they spontaneously decompose to pyrrole products. 4-Hydroxypyrroles are prone to partial aerial oxidation but can be efficiently alkylated or reduced to stable polysubstituted pyrrolidine derivatives.

1. Introduction

Pyrroles represent one of the most important groups of heterocyclic compounds. For the synthesis, reactivity, physical properties, and natural occurrence of pyrroles and their numerous applications see some of the selected literature.[1–11]

Not taking into consideration the tetramic acids,[12] there are numerous ways for the synthesis of 3- (i.e., 4-)-hydroxypyrroles.[13] The parent 3-hydroxypyrrole is highly unstable and was prepared by mild methanolysis of its trimethylsilyl derivative.[14,15]

Differently substituted 4-hydroxypyrrole-3-carboxylic esters have been prepared in several ways. They can be synthesized via base-catalyzed *Dieckmann* cyclization of *Schiff* bases derived from β-keto esters and α-amino acid esters.[16] Under basic conditions, α-chloroacetyl-β-aminocrotonic esters cyclize into 4-hydroxypyrrole-3-carboxylic esters.[17,18] Enamines derived from α-amino acids react rapidly with trifluoroacetic anhydride to give the corresponding pyrrole derivatives.[19] Reaction of enamines, prepared from β-keto esters or β-keto nitriles, with α-keto aldehydes furnish 4-hydroxypyrrole-3-carboxylic esters.[20] In the same way, a three-component reaction of β-dicarbonyl compounds with arylglyoxals in the presence of ammonium acetate gives 2-alkyl-5-aryl-4-hydroxypyrrole-3-carboxylates.[21] The *Dieckmann* condensation of aminomethylenemalonate derivatives gives 3-hydroxypyrrole-2,4-dicarboxylates.[22–25] Enaminonitriles have been cyclized to 2-cyano 3-hydroxypyrrole-4-carboxylates.[26,27] Synthesis of oxopyrrolidine derivatives followed by oxidation furnished the corresponding pyrroles.[28,29] Enamines, derived from α-amino acids and dimethyl acetylenedicarboxylate, cyclize in the presence of sodium methoxide to 4-hyxroxypyrrole-2,3-dicarboxylates.[30] Similarly, 4-hyxroxypyrrole-2,3-dicarboxylates were prepared in one-step from acetylenic esters and α-amino acids with isocyanide or carbodiimide under neutral conditions,[31] or in the presence of transition-metal oxides.[32] Cyclization of α-alkoxycarbonyl-α-aminohydrazones with dialkyl acetylenedicarboxylates gave 4-hydroxy-1*H*-pyrrole-2,3-dicarboxylates.[33]

While investigating the possibility of constructing various heterocycles from protected ornithine ((*S*)-Boc-Orn(*Z*)-OH (**1k**)) via the corresponding β-keto ester **2k**, the reaction of **2k** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) yielded, upon chromatographic isolation, supposedly the expected enaminone **3k**. By chance, the product was left to stand overnight in a closed flask, which after opening smelled strongly of dimethylamine. Subsequent ^{1}H NMR investigation revealed that the desired enaminone **3k** spontaneously cyclized into 4-hydroxy-pyrrole **4k**, which is in equilibrium with the corresponding 4-oxo tautomer **4k′** with traces of enaminone **3k** as detected by mass spectrometry. A subsequent *SciFinder* literature search revealed that there are no enaminones of type **A** derived from *N*-protected α-amino acid β-

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keto esters reported in the literature. Even more, the literature search for *N*-carbamate protected 5-substituted-4-hydroxypyrrole-3-carboxylates of type **B** or its 4-oxo-4,5-dihydro tautomers of type **C** gave no hits (Fig. 1). This prompted us to investigate the subject further. Thus, herein we report the results of this research: (i) a novel and simple methodology for the construction of *N*-protected methyl 5-substituted-4-hydroxypyrrole-3-carboxylates of type **B**/**C** in a two-step synthesis starting from commercially available *N*-protected amino acid esters via enaminone intermediates, (ii) further transformations of pyrrole derivatives, and (iii) potential application of enaminone intermediates of type **A** in the construction of various heterocycles with orthogonally protected amino and carboxy groups.

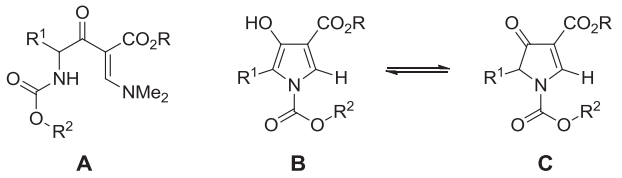
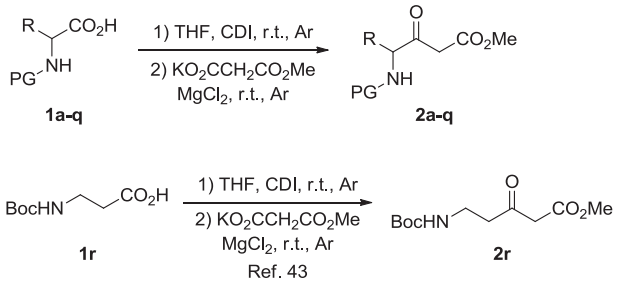


Fig. 1. *SciFinder* literature search for compounds of type **A**–**C** as of September 2013.

2. Results and discussion

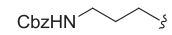
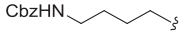
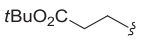
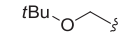
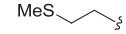
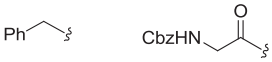
The starting β-keto esters **2a**–**r** were prepared from *N*-protected α-amino acids **1a**–**o**, dipeptide **1p**, α,β-unsaturated α-amino acid **1q**, and *N*-Boc-β-alanine (**1r**), respectively, using *Masamune*–*Claisen* condensation (Scheme 1, Table 1). The stereochemical integrity of the chiral products, derived from nonracemic starting compounds, has *not* been checked at any level of further transformations.



Scheme 1. Synthesis of β-keto esters **2a**–**r**.

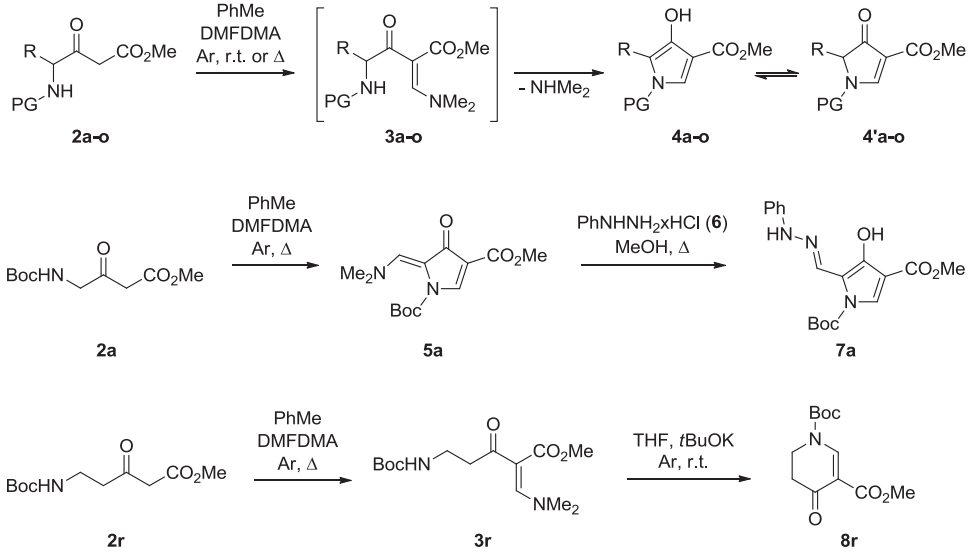
Next, β-keto esters **2a**–**q** were treated with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) (1–3 equiv) in anhydrous toluene at room temperature or at elevated temperature. The acidic methylene group of the β-keto esters **2** reacts with DMFDMA to give the corresponding enaminone intermediates[44] **3** followed by in situ cyclization into the final 4-hydroxy-pyrrole-3-carboxylates **4**, which are in equilibrium with 4-oxo-pyrrole-3-carboxylate tautomers **4′** (Scheme 2, Table 2). In principle, *N*-Cbz- or *N*-Boc-protected enaminone intermediates **3** can be isolated and characterized before they cyclize into the corresponding pyrrole derivatives **4**/**4′**. The progress of the transformation of the starting β-keto esters **2** into pyrrole derivatives **4**/**4′** via enaminone intermediates **3** can be followed by simple thin layer chromatography (TLC). As generally observed, the initially formed enaminone intermediate **3** has a much smaller retention factor (R_f) compared to the starting β-keto ester **2**. The final pyrrole derivatives **4**/**4′**, obtained upon cyclization of enaminone intermediates **3**, have a similar retention factor as the starting β-keto ester **2**, only the spot on the TLC-plate is more 'stretched' (see Fig. 2). In order to obtain

Table 1
Synthesized β-keto esters **2a**–**q**

Entry	R	PG	(*R*) or (*S*)	β-Keto ester	Yield (%)	Ref.
1	H	Boc	—	**2a**	76	34
2	Me	Boc	(*S*)	**2b**	91	35
3	Me	Cbz	(*S*)	**2c**	92	36,37
4		Boc	(*S*)	**2d**	73	38
5		Cbz	(*S*)	**2e**	62	39
6		Boc	(*R*)	**2f**	65	—
7		Boc	(*S*)	**2g**	87	35,40
8		Cbz	(*S*)	**2h**	73	35
9		Phth	(*S*)	**2i**	88	41
10	Ph	Boc	(*R*)	**2j**	78	—
11		Boc	(*S*)	**2k**	95	—
12		Boc	(*S*)	**2l**	89	—
13		Cbz	(*S*)	**2m**	85	—
14		Cbz	(*S*)	**2n**	83	—
15		Boc	(*R*)	**2o**	87	—
16			—	**2p**	84	—
17			—	**2q**	17	42

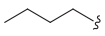
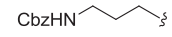
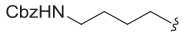
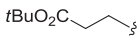
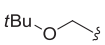
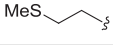
the enaminone intermediate **3**, a quick isolation (flash column chromatography) has to be done when most of the starting β-keto ester **2** transforms into enaminone intermediate **3** before the buildup of the final pyrrole product **4**/**4′**, as judging by TLC-analysis. The isolated enaminone **3** has to be characterized immediately due to the spontaneous cyclization into the respective pyrrole product **4**/**4′**. Thus, in the case of β-keto ester **2f**, beside the final pyrrole derivatives **4f**/**4f′** also the enaminone intermediate **3f** was isolated. When β-keto ester **2a** was treated with excess DMFDMA at elevated temperature, the 4-oxopyrrole-3-carboxylate **5a** was isolated in 40% yield, formed via enaminone **3a** and pyrroles **4a**/**4a′** (R=H). Reaction of **5a** with phenylhydrazine hydrochloride (**6**) gave the substitution product **7a** in 16%, the structure of which was determined by single crystal X-ray analysis (Fig. 3). Attempts to prepare the *C*5 unsubstituted pyrrole derivatives **4a**/**4a′** in one-step failed due to the formation of **5a** and other by-products. Therefore, **2a** was treated with excess DMFDMA at room temperature followed by isolation of enaminone **3a** in 76% yield. The enaminone **3a** was left to stand in an open flask overnight at room temperature to cyclize into the desired *C*5 unsubstituted pyrrole derivatives **4a**/**4a′**. The reaction of *N*-phthaloyl protected β-keto ester **2i**, as expected, stopped at the enaminone product **3i** in 73% yield due to the fully protected amino group. Transformations of **2p** and **2q** into respective pyrrole derivatives failed, complex mixture of products were formed. Finally, the reaction of *N*-Boc-β-alanine derived β-keto ester **2r** also stopped at the enaminone **3r**[45] stage. Even after prolonged heating of **3r**, the cyclization into the corresponding dihydropyridine **8r** did not take place. Upon treatment of **3r** with *t*-BuOK in anhydrous THF the desired six-membered heterocycle **8r** was obtained in 52% yield. The structure of **8r** was confirmed by

single crystal X-ray analysis (Scheme 2, Table 2, Fig. 4). In the reactions of *N*-protected β-keto esters **2** with excess DMFDMA, no *N*-methylated side products were observed.[46]



Scheme 2. Synthesis of pyrrole derivatives **4**/**4′**, **5a**, **7a**, and dihydropyridine **8r**.

Table 2
Synthesized enaminones **3** and pyrrole derivatives **4**/**4′**

Entry	R	PG	*T* (°C)	**3**, yield (%)	**4**/**4′** (solvent)	Yield (%)
1	H	Boc	rt	**3a**, 76	**4a**/**4a′**=1:0.38[a]	100[c]
2	Me	Boc	75	—	**4b**/**4b′**=1:0.54[a]	33
3	Me	Cbz	75	—	**4c**/**4c′**=1:0.62[b]	58
4		Boc	75	—	**4d**/**4d′**=0.08:1[a]	54
5		Cbz	75	—	**4e**/**4e′**=1:0.12[a]	67
6		Boc	75	**3f**, 47	**4f**/**4f′**=1:0.74[a]	41
7		Boc	75	—	**4g**/**4g′**=1:0.70[a]	84
8		Cbz	75	—	**4h**/**4h′**=1:0.66[a]	48
9		Phth	rt	**3i**, 73	—	—
10	Ph	Boc	75	—	**4j**/**4j′**=1:0.35[a]	72
11		Boc	75	—	**4k**/**4k′**=1:1[a]	96
12		Boc	75	—	**4l**/**4l′**=1:0.61[a]	55
13		Cbz	rt	—	**4m**/**4m′**=1:0.85[a]	45
14		Cbz	rt	—	**4n**/**4n′**=0.24:1[a]	66
15		Boc	75	—	**4o**/**4o'**=1:0.28[a]	71

[a] ^{1}H NMR in DMSO-d_6.
[b] ^{1}H NMR in $CDCl_3$.
[c] Prepared from **3a**.

Equilibrium between the 4-hydroxy **4** and the 4-oxo **4′** tautomeric forms in DMSO is shifted toward the 4-hydroxy form with the exception of 5-*i*-Pr (**4d**/**4d′**=0.08:1) and 5-*tert*-butoxymethyl (**4n**/**4n′**=0.24:1) substituted pyrrole derivatives. In the former case at least, this must be due to the massive 1,5-repulsion[47] between the OH and *i*-Pr groups in the 4-hydroxy tautomeric form **4d** (this strain is partially relieved in the 4-oxo tautomer **4d′**) (see Table 2).

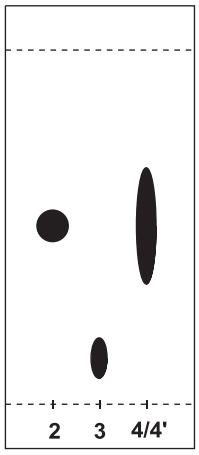


Fig. 2. TLC-follow up of the transformation of the starting β-keto esters **2** into final pyrrole products **4**/**4′** via enaminone intermediates **3**. As a mobile phase mixtures of EtOAc and petroleum ether were used.

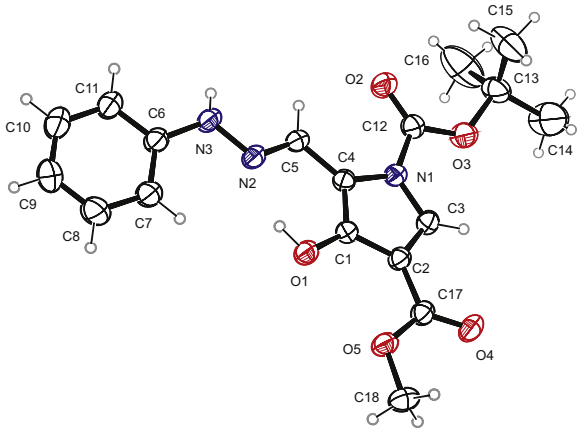


Fig. 3. Single crystal X-ray analysis of pyrrole **7a**.

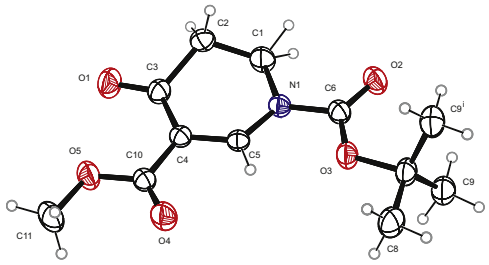
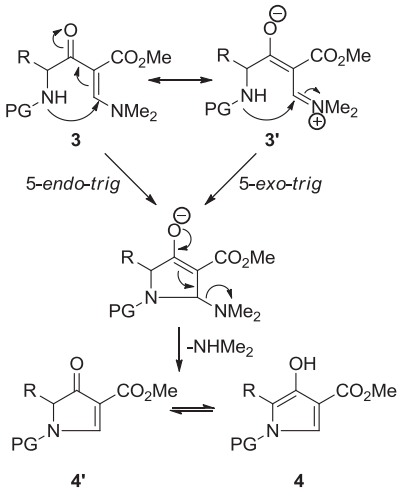


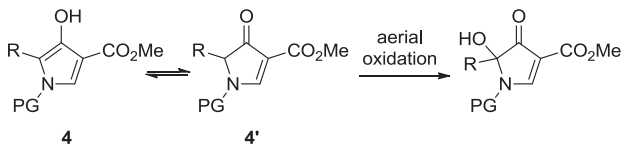
Fig. 4. Single crystal X-ray analysis of dihydropyridine derivative **8r**.

Cyclization of enaminone intermediates **3** into pyrrole products **4**/**4′** can formally take place either as a 1,4-addition followed by elimination of dimethylamine or, alternatively, via 1,2-addition of the protected amine to the imine functionality of the resonance structure **3′** (enabled by the push–pull system) followed by elimination. Considering *Baldwin's rules*,[48,49] the former is classified as 5-*endo*-*trig* cyclization and is therefore unfavorable, whereas the latter is a favorable 5-*exo*-*trig* cyclization (Scheme 3).



Scheme 3. The proposed mechanism for the cyclization considering the *Baldwin's rules*.

Although pyrrole derivatives **4**/**4′** with various substituents in position 5 could easily be prepared in low to very good yields (33–96%), most of them are subjected to partial aerial oxidation at position 5, which could not be prevented given the way the products were isolated (column chromatography) (Scheme 4). The same observation has been made previously with other *N*-substituted and *N*-unsubstituted 4-hydroxypyrroles.[20,50–54] Thus, in the worst case of pyrrole derivatives **4b**/**4b′**, after isolation, ca. 15% of the corresponding oxidation decomposition product is present (see Fig. 5). Other pyrrole derivatives are less susceptible to oxidation, in particular ornithine- **4k**/**4k′** and lysine-derived pyrroles **4l**/**4l′**, which are not oxidized even after prolonged storage (ca. 2 months).



Scheme 4. Aerial oxidation of 5-substituted-4-hydroxy/4-oxo-pyrroles **4**/**4′**.

Phenylalanine **4g**/**4g′** and ornithine **4k**/**4k′** derived 4-hydroxypyrroles have been selected for further transformations, namely alkylations and reductions. Alkylation of **4g**/**4g′** in DMF in the presence of K_2CO_3 with benzyl bromide gave the *C*5-benzylated product **9g** in 73% yield, exclusively, whereas reaction with **4k**/**4k′** furnished the major *C*-alkylated product **9k** and the minor *O*-alkylated product **10k** in 48% and 12% yields, respectively. Similarly, reaction of **4g**/**4g′** with methyl iodide furnished the major *C*-alkylated product **11g** and the minor *O*-alkylated product **12g** in 54% and 18% yields, respectively, while the same reaction with **4k**/**4k′** produced only the *O*-methylated product **12k** in 41% yield (Scheme 5, Table 3). The structure of **9g** was confirmed by single crystal X-ray analysis (Fig. 6). Alkylations of similar systems are described in the literature.[17,28,55–57]

Literature reported $NaCNBH_3$ reduction of a pyrrole structurally similar to pyrroles **4**/**4′** gave 4-hydroxypyrrolidine product as a mixture of stereoisomers.[58] Similarly, reduction of **4g**/**4g′** with 2 equiv of $NaBH_4$ in MeOH at room temperature gave four products in a ratio of **13g**/**14g**/**15g**/**16g**=1:0.67:0.67:0.73, which were chromatographically separated. Products **13g** and **14g** are diastereoisomers formed after the reduction of the endocyclic double bond and the keto group, while products **15g** and **16g** are diastereoisomers formed after the additional reduction of the ester group to the hydroxymethyl group. In the ^1H and ^{13}C NMR spectra of the isolated products, two rotamers/conformers of different ratios can be observed. HPLC analysis of each of the products on a chiral column shows they are racemic diastereoisomers. For HPLC analysis and for the NMR-observed rotamers/conformers see Supplementary data. When the same reaction was performed at −5 °C, only **13g** and **14g** were formed in a ratio of **13g**/**14g**=47:53, which makes this reduction diastereoselective (two out of four possible diastereoisomers). Single crystal X-ray analysis of **13g** and **14g** revealed their relative stereochemistry (see Figs. 7 and 8). The relative configuration of **15g** and **16g** has been confirmed by reduction of **13g** and **14g**, respectively, with large excess $NaBH_4$. In the same way, reduction of **4k**/**4k′** at −5 °C gave only two diastereoisomers **13k** and **14k** in a 1:1 ratio, which could, unfortunately, not be separated (Scheme 6, Table 4). The relative configuration of **13k** and **14k** has been assigned on the basis of ^1H NMR spectra of **13g** and **14g**, respectively.

As there are no *N*-protected-α-amino-β-keto ester derived enaminone intermediates of type **A** (see Fig. 1) reported in the literature, we wanted to show they could be useful synthons in the synthesis of various heterocyclic systems. In the case of stable fully *N*-protected enaminone **3i**, the reaction with phenylhydrazine hydrochloride (**6**) gave pyrazole **17i** in 81% yield, while reaction with 3-amino-1*H*-pyrazole-4-carboxylate (**18**) furnished compound **19i** in 32% yield. On the other hand, the partially *N*-protected (Boc, Cbz, dipeptide) enaminone intermediates **3** first had to be prepared in situ from the corresponding β-keto esters **2** and DMFDMA in CH_2Cl_2, and then cyclized in MeOH with various dinucleophiles before they cyclized into pyrroles **4**/**4′** (see Fig. 2 and the accompanying explanation). In that way, the in situ generated enaminone intermediates **3h**, **3k**, **3l**, and **3p**, prepared from the corresponding β-keto esters, gave with hydrazine **6** pyrazole products **17h**, **17k**, **17l**, and **17p**, respectively. Furthermore, reaction of enaminone intermediate **3l** with benzamidine hydrochloride (**20**), 3-amino-1*H*-pyrazole-4-carboxylate (**18**), and 5-(methylthio)-1*H*-1,2,4-triazol-3-amine (**21**) yielded pyrimidine **22l**, pyrazolo-pyrimidine **19l**, and triazolo-pyrimidine **23l**, respectively (Scheme 7, Table 5). All these reactions proceed via initial acid catalyzed substitution of the dimethylamino group by the more nucleophilic part of the dinucleophile followed by cyclization to the ketone.[44] The structure of **17i** was confirmed by single crystal X-ray analysis (Fig. 9). The structures of bicyclic heterocycles **19i**, **19l**, and **23l** were postulated on the basis of structures of related products obtained via closely related transformations.[59–61]

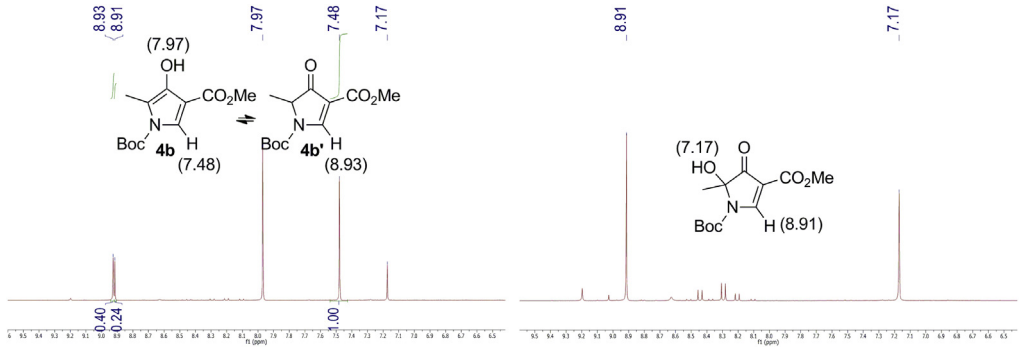
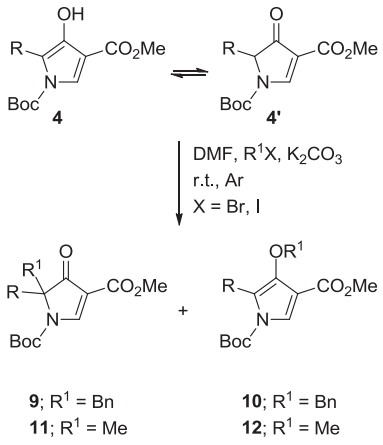


Fig. 5. Section of the ^{1}H NMR spectra of pyrrole derivatives **4b** and **4b′** (a) in DMSO-d_6 immediately after isolation; (b) after prolonged standing in DMSO-d_6.



Scheme 5. Alkylation of **4g**/**4g′** and **4k**/**4k′** with BnBr and MeI.

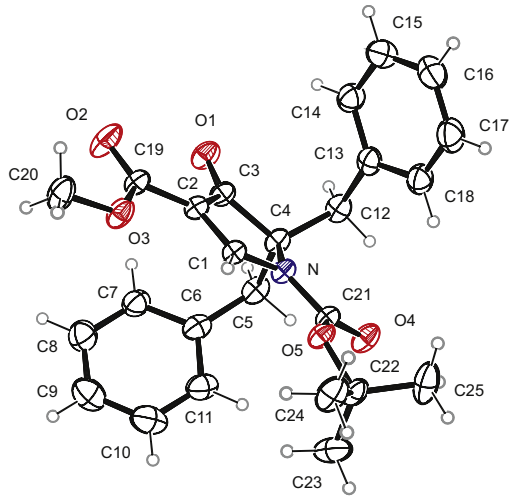


Fig. 6. Single crystal X-ray analysis of pyrrole **9g**.

Table 3
Products of alkylation of **4g**/**4g′** and **4k**/**4k′** with BnBr and MeI

Entry	Reactants	Product	R	R^1	Yield (%)
1	**4g**/**4g′**+BnBr	**9g**	Ph	Bn	73
2	**4k**/**4k′**+BnBr	**9k**	CbzHN	Bn	48
3		**10k**	CbzHN	Bn	12
4	**4g**/**4g′**+MeI	**11g**	Ph	Me	54
5		**12g**	Ph	Me	18
6	**4k**/**4k′**+MeI	**12k**	CbzHN	Me	41

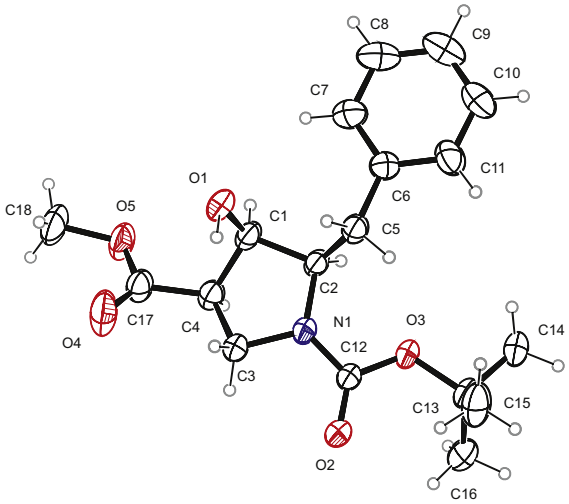


Fig. 7. Single crystal X-ray analysis of pyrrolidine **13g**.

3. Conclusions

A new methodology for the synthesis of *N*-protected methyl 5-substituted-4-hydroxypyrrole-3-carboxylates in two steps has been introduced. Starting *N*-protected α-amino acids **1** are transformed into the corresponding β-keto esters **2** using *Masamune–Claisen* homologation followed by reaction with DMFDMA thus giving enaminone intermediates **3**, which spontaneously or upon heating cyclize to 4-hydroxy-pyrrole products **4**, which are in equilibrium with their 4-oxo tautomers **4′**. Unfortunately, some pyrroles **4**/**4′** are subjected to aerial oxidation, but can nevertheless be used in further transformations, for example, alkylations and reductions. Reduction of **4**/**4′** with $NaBH_4$ yielded two out of four racemic pyrrolidine diastereoisomers, their relative configuration was determined by single crystal X-ray analysis. Pyrroles **4**/**4′** are challenging substrates for stereoselective reductions/additions to produce differently functionalized pyrrolidines. Finally, it has been shown that the until now unreported enaminone intermediates **3**

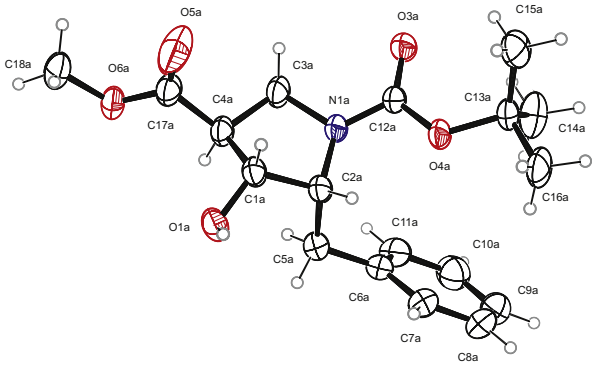
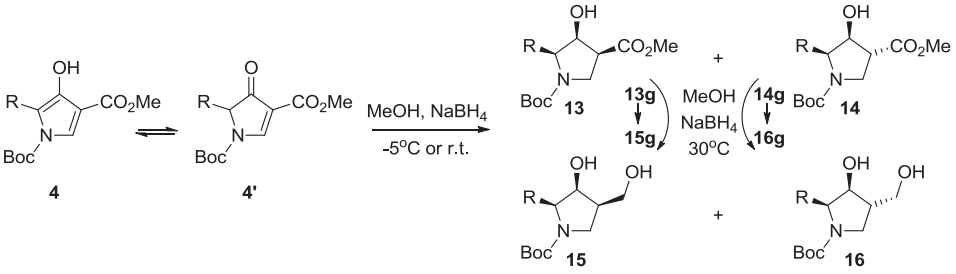


Fig. 8. Single crystal X-ray analysis of pyrrolidine **14g**.

technical grade Na_2SO_4. Melting points were determined on a Kofler micro hot stage and on SRS OptiMelt MPA100—Automated Melting Point System. The NMR spectra were obtained on a Bruker UltraShield 500 plus at 500 MHz for ^1H and 126 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS, IR spectra on a Bruker ALPHA FT-IR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyzer 2400 II. Thin layer chromatography was performed on a pre-coated Merck silica gel 60 F_{254} plates (0.25 mm). Column chromatography (CC) was performed on silica gel (Silica gel 60, particle size: 0.035–0.070 mm). Medium-pressure liquid chromatography (MPLC) was performed with Büchi Flash Chromatography System (Büchi Fraction Collector C-660, Büchi Pump Module C-605, Büchi Control Unit C-620) on silica gel (LiChrosphere® Si 60 (12 μm) and/or LiChroprep® Si 60 (15–25 μm)); column dimensions (wet



Scheme 6. $NaBH_4$ reduction of **4g**/**4g′** and **4k**/**4k′**.

Table 4
Products of reduction of **4g**/**4g′** and **4k**/**4k′** with $NaBH_4$

Entry	Reactants	R	Product ratio	Product	Yield (%)
1	**4g**/**4g′**, rt	Ph	**13g**/**14g**/**15g**/**16g**=1:0.67:0.67:0.73	**13g**	19
				14g	7
2				**15g**	18
3				**16g**	6
4					
5	**4g**/**4g′**, −5 °C	Ph	**13g**/**14g**=47:53	**13g**	33
				14g	36
6					
7	**4k**/**4k′**, −5 °C	CbzHN	**13k**/**14k**=50:50	**13k**+**14k**[a]	80
8					

[a] Could not be separated by column chromatography.

can be isolated and characterized as well as used in the construction of other α-amino acid derived heterocycles with various dinucleophiles. So formed orthogonally protected heterocycles can be, if needed, introduced into various peptide sequences. Fully *N*-protected enaminones are stable compounds.

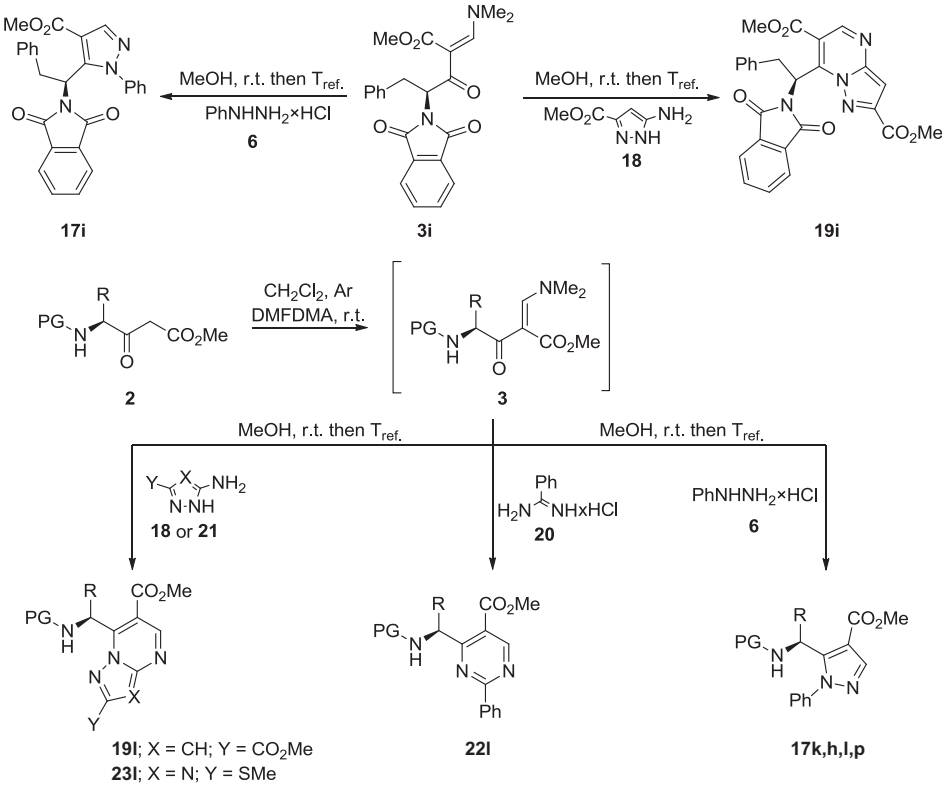
4. Experimental section

4.1. General

All reactions were performed under Argon in dried glassware using anhydrous solvents except when using aqueous reagents. Solvents for extractions and chromatography were of technical grade and were distilled prior to use. Extracts were dried over filled): 22×460 mm, 36×460 mm and 40×460 mm; backpressure: 10–20 bar; detection: UV 254 nm. HPLC analyses were performed on an Agilent 1260 Infinity LC using CHIRALPAK AD-H (0.46 cm ø×25 cm) and CHIRALCEL OD-H (0.46 cm ø×25 cm) as chiral columns. Optical rotations were recorded on a Perkin–Elmer 241MC polarimeter.

All chemicals were of reagent grade and used as supplied, unless stated otherwise. They were purchased from Sigma–Aldrich. Starting compounds **1i**,[62] **1p**,[63] **1q**,[64] and **18**[65] were prepared following the literature procedures.

The structures of novel compounds **2f**, **2j**, **2k**–**p**, **3a**, **3f**, **3i**, **4a**/**4a′**–**4h**/**4h′**, **4j**/**4j′**–**4o**/**4o′**, **5a**, **7a**, **8r**, **9g**, **9k**, **10k**, **11g**, **12g**, **12k**, **13g**–**16g**, **13k**/**14k**, **17h**, **17i**, **17k**, **17l**, **17p**, **19i**, **19l**, **22l**, and **23l** were determined by spectroscopic methods (^1H NMR, ^{13}C NMR, 2D-NMR,



Scheme 7. Synthesis of heterocyclic systems from enaminones **3**.

Table 5
Heterocycles prepared from enaminones **3**

Entry	Product	R	PG	X, Y	Yield (%)
1	**17h**	Ph	Cbz	—	11
2	**17i**	Ph	Phth	—	81
3	**17k**	CbzHN	Boc	—	45
4	**17l**	CbzHN	Boc	—	51
5	**17p**	Ph	CbzHN	—	49
6	**19i**	Ph	Phth	X=CH Y=CO_2Me	32
7	**19l**	CbzHN	Boc	X=CH Y=CO_2Me	10
8	**22l**	CbzHN	Boc	—	17
9	**23l**	CbzHN	Boc	X=N Y=SMe	9

IR, HRMS) and by elemental analyses for C, H, and N. Compounds **4a**/**4a′**–**4h**/**4h′**, **4j**/**4j′**–**4o**/**4o′**, and **13k**/**14k** were characterized as mixtures of tautomers/stereoisomers, respectively. Compounds **2k**, **2o**, **3i**, **4d**/**4d′**, **8r**, **9g**, **13g**–**16g**, **17i**, **17l**, and **22l** were obtained in analytically pure form. Identities of novel compounds, not obtained in analytically pure form, were confirmed by ^{13}C NMR and HRMS.

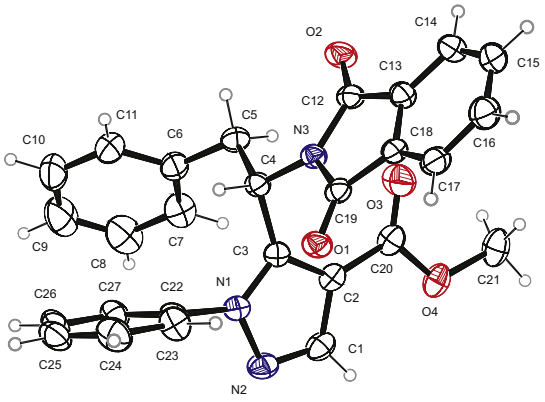


Fig. 9. Single crystal X-ray analysis of pyrazole **17i**.

4.2. Synthesis of β-keto esters from *N*-protected amino acids—general procedure 1 (GP1)

To a solution/suspension of *N*-protected amino acid (10 mmol) in anhydrous THF (50 mL) under argon was added CDI (2.01 g, 12.00 mmol) and the resulting reaction mixture was stirred at room temperature for 2 h, followed by the addition of a solid mixture of $MgCl_2$ (0.95 g, 9.80 mmol) and methyl potassium malonate (2.37 g, 15.00 mmol). The reaction mixture was stirred at room temperature for additional 24 h. Volatile components were evaporated in vacuo, the residue was dissolved in EtOAc (150 mL) and washed with $NaHSO_4$ (1 M in H_2O, 50 mL), NaCl (aq satd, 50 mL), $NaHCO_3$ (aq satd, 20 mL), and NaCl (aq satd, 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was purified by column

chromatography (CC). Fractions containing the product were combined and volatile components evaporated in vacuo.

*4.2.1. Methyl 4-((tert-butoxycarbonyl)amino)-3-oxobutanoate (**2a**).*[34] *General procedure 1 (GP1)*: Prepared from **1a** (1.75 g); CC (EtOAc/petroleum ether=1:2). Yield: 1.76 g (76%) of yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.38 (s, 9H, Boc); 3.60 (s, 2H, CH_2); 3.63 (s, 3H, CO_2Me); 3.85 (d, J=5.9 Hz, 2H, CH_2); 7.13 (t, J=5.9 Hz, 1H, NH).

*4.2.2. (S)-Methyl 4-((tert-butoxycarbonyl)amino)-3-oxopentanoate (**2b**).*[35] *General procedure 1 (GP1)*: Prepared from **1b** (1.89 g); CC (EtOAc/petroleum ether=1:2). Yield: 2.23 g (91%) of white solid; mp 48.2–50.6 °C (lit.:[35] mp 50–52 °C). $[\alpha]_D^{rt}$ −47.1 (*c* 0.25, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) for the major isomer: δ 1.36 (d, J=7.2 Hz, 3H, CH_3); 1.45 (s, 9H, Boc); 3.55 (d, J=15.8 Hz, 1H, Ha of CH_2); 3.60 (d, J=15.9 Hz, 1H, Hb of CH_2); 3.75 (s, 3H, CO_2Me); 4.34–4.42 (m, 1H, CH); 5.11 (d, J=7.0 Hz, 1H, NH). ^{1}H NMR (500 MHz, $CDCl_3$) for the minor isomer: δ 3.45(s, 2H, CH_2); 3.81 (s, 3H, CO_2Me). Isomer ratio is 5:1.

*4.2.3. (S)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-oxopentanoate (**2c**).*[36] *General procedure 1 (GP1)*: Prepared from **1c** (2.25 g); CC (EtOAc/petroleum ether=2:3). Yield: 2.57 g (92%) of brownish-orange oil. $[\alpha]_D^{rt}$ −29.9 (*c* 0.44, MeOH) (lit.:[37] $[\alpha]_D^{rt}$ −36.3 (*c* 0.69, MeOH)). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.20 (d, J=7.3 Hz, 3H, CH_3); 3.61 (s, 3H, CO_2Me); 3.65 (d, J=4.7 Hz, 2H, $H_2C(2)$); 4.13–4.20 (m, 1H, CH); 5.04 (s, 2H, CH_2 of Cbz); 7.30–7.40 (m, 5H, Ph); 7.77 (d, J=7.3 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 15.6, 45.2, 51.9, 55.5, 65.7, 127.8, 127.9, 128.4, 136.9, 155.9, 167.5, 203.4.

*4.2.4. (S)-Methyl 4-((tert-butoxycarbonyl)amino)-5-methyl-3-oxohexanoate (**2d**)..*[38] *General procedure 1 (GP1)*: Prepared from **1d** (2.17 g); CC (EtOAc/petroleum ether=1:2). Yield: 1.99 g (73%) of orange oil. $[\alpha]_D^{rt}$ +11.3 (*c* 0.29, CH_2Cl_2) (lit.:[38] $[\alpha]_D^{20}$ +28.2 (*c* 0.62, $CHCl_3$)). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.80 (d, J=6.8 Hz, 3H, Me); 0.85 (d, J=6.9 Hz, 3H, Me); 1.40 (s, 9H, Boc); 2.05–2.13 (m, 1H, CH); 3.60 (s, 2H, CH_2); 3.61 (s, 3H, CO_2Me); 3.88 (dd, J=6.4; 8.3 Hz, 1H, CH); 7.29 (d, J=8.3 Hz, 1H, NH).

*4.2.5. (S)-Methyl 4-(((benzyloxy)carbonyl)amino)-6-methyl-3-oxoheptanoate (**2e**).*[39] *General procedure 1 (GP1)*: Prepared from **1e** (2.65 g); CC (EtOAc/petroleum ether=1:2). Yield: 1.99 g (62%) of orange oil. $[\alpha]_D^{rt}$ −8.8 (*c* 0.30, $CHCl_3$) (lit.:[39] $[\alpha]_D^{rt}$ −6.8° (*c* 1.0, $CHCl_3$)). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (d, J=6.6 Hz, 3H, $H_3C(7)$); 0.88 (d, J=6.6 Hz, 3H, $H_3C(7')$); 1.39–1.50 (m, 2H, $H_2C(5)$); 1.57–1.66 (m, 1H, H–C(6)); 3.61 (s, 3H, CO_2Me); 3.63 (s, 2H, $H_2C(2)$); 4.08–4.14 (m, 1H, H–C(4)); 5.05 (s, 2H, CH_2 of Cbz); 7.28–7.41 (m, 5H, Ph); 7.76 (d, J=7.9 Hz, 1H, NH).

*4.2.6. (R)-Methyl 4-((tert-butoxycarbonyl)amino)-3-oxooctanoate (**2f**). General procedure 1 (GP1)*: Prepared from **1f** (2.31 g); CC (EtOAc/petroleum ether=1:3). Yield: 1.87 g (65%) of white solid; mp 46–49 °C. $[\alpha]_D^{rt}$ −1.7 (*c* 0.18, CH_2Cl_2). ν_{max} 3365, 2982, 2953, 2931, 2860, 1749, 1719, 1686, 1518, 1466, 1439, 1394, 1367, 1321, 1288, 1268, 1247, 1161, 1140, 1107, 1077, 1048, 1034, 1007, 944, 929, 856, 826, 779, 758, 730, 628 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, J=6.5 Hz, 3H, CH_3); 1.19–1.31 (m, 4H, 2×CH_2); 1.39 (s, 9H, Boc); 1.42–1.49 (m, 1H, 1H of CH_2); 1.58–1.68 (m, 1H, 1H of CH_2); 3.59 (s, 2H, CH_2); 3.61 (s, 3H, CO_2Me); 3.90–3.97 (m, 1H, CH); 7.32 (d, J=7.6 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.8, 21.7, 27.5, 28.1, 28.8, 45.3, 51.8, 59.7, 78.4, 155.6, 167.5, 203.7; EI-HRMS: m/z=188.1282 (MH^+–Boc); $C_9H_{18}NO_3$ requires: m/z=188.1281 (MH^+–Boc).

*4.2.7. (S)-Methyl 4-((tert-butoxycarbonyl)amino)-3-oxo-5-phenylpentanoate (**2g**).*[35] *General procedure 1 (GP1)*: Prepared from **1g** (2.65 g); CC (EtOAc/petroleum ether=1:2). Yield: 3.09 g (87%) of white solid; mp 84.5–87.0 °C (lit.:[35] mp 85–87 °C). $[\alpha]_D^{rt}$ −53.1 (*c* 0.4, MeOH) (lit.:[40] $[\alpha]_D^{rt}$ −64.8 (*c* 0.68, MeOH)). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.31 (s, 9H, Boc); 2.69 (dd, J=10.4; 13.9 Hz, 1H, Ha of $H_2C(5)$); 3.05 (dd, J=4.6; 13.9 Hz, 1H, Hb of $H_2C(5)$); 3.62 (s, 3H, CO_2Me); 3.66 (d, J=3.0 Hz, 2H, $H_2C(2)$); 4.20–4.26 (m, 1H, H–C(4)); 7.17–7.30 (m, 5H, Ph); 7.35 (d, J=8.1 Hz, 1H, NH).

*4.2.8. (S)-Methyl 4-(((benzyloxy)carbonyl)amino)-3-oxo-5-phenylpentanoate (**2h**).*[35] *General procedure 1 (GP1)*: Prepared from **1h** (3.02 g); CC (EtOAc/petroleum ether=1:2). Yield: 2.60 g (73%) of pink solid; mp 75.4–76.7 °C (lit.:[35] mp 78–80 °C). $[\alpha]_D^{rt}$ −48.0 (*c* 0.27, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.70 (dd, J=10.6; 13.9 Hz, 1H, Ha of $H_2C(5)$); 3.11 (dd, J=4.3; 13.9 Hz, 1H, Hb of $H_2C(5)$); 3.62 (s, 3H, CO_2Me); 3.71 (s, 2H, $H_2C(2)$); 4.33–4.39 (m, 1H, H–C(4)); 4.98 (s, 2H, CH_2 of Cbz); 7.19–7.37 (m, 10H, 2×Ph); 7.82 (d, J=8.2 Hz, 1H, NH).

*4.2.9. (S)-Methyl 4-(1,3-dioxoisoindolin-2-yl)-3-oxo-5-phenylpentanoate (**2i**).*[41] *General procedure 1 (GP1)*: Prepared from **1i** (2.95 g); CC (EtOAc/petroleum ether=1:1). Yield: 3.10 g (88%) of white solid; mp 123–128 °C. $[\alpha]_D^{rt}$ −2.4 (*c* 0.26, CH_2Cl_2). ν_{max} 2945, 1748, 1711, 1604, 1495, 1466, 1456, 1442, 1383, 1338, 1306, 1287, 1257, 1208, 1187, 1149, 1096, 1067, 1029, 997, 976, 948, 878, 826, 779, 757, 720, 706, 655, 639, 620 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.25 (dd, J=11.4; 13.9 Hz, 1H, Ha of H_2–C(5)); 3.51 (dd, J=4.8; 13.9 Hz, 1H, Hb of H_2–C(5)); 3.60 (s, 3H, CO_2Me); 3.83 (d, J=16.7 Hz, 1H, Ha of H_2–C(2)); 3.89 (d, J=16.7 Hz, 1H, Hb of H_2–C(2)); 5.32 (dd, J=4.8; 11.4 Hz, 1H, H–C(4)); 7.07–7.22 (m, 5H, Ph); 7.80–7.84 (m, 4H, indoline). ^{13}C NMR (126 MHz, DMSO-d_6): δ 32.7, 45.9, 52.0, 59.7, 123.4, 126.6, 128.3, 128.8, 130.8, 134.9, 136.9, 167.1, 167.2, 198.2; EI-HRMS: m/z=352.1179 (MH^+); $C_{20}H_{18}NO_5$ requires: m/z=352.1179 (MH^+).

*4.2.10. (R)-Methyl 4-((tert-butoxycarbonyl)amino)-3-oxo-4-phenylbutanoate (**2j**). General procedure 1 (GP1)*: Prepared from **1j** (2.51 g); CC (EtOAc/petroleum ether=1:2). Yield: 2.42 g (78%) of yellow-orange solid; mp 93–96 °C. $[\alpha]_D^{rt}$ +1.1 (*c* 0.38, CH_2Cl_2). ν_{max} 3380, 2980, 2907, 1734, 1720, 1686, 1518, 1456, 1439, 1392, 1366, 1352, 1321, 1301, 1280, 1253, 1209, 1159, 1072, 1044, 1025, 1011, 954, 923, 883, 864, 829, 805, 779, 753, 719, 701, 666 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.39 (s, 9H, Boc); 3.49 (d, J=16.5 Hz, 1H, Ha-C(2)); 3.55 (s, 3H, CO_2Me); 3.67 (d, J=16.5 Hz, 1H, Hb-C(2)); 5.39 (d, J=8.2 Hz, 1H, H–C(3)); 7.29–7.42 (m, 5H, Ph); 7.79 (d, J=8.1 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 28.1, 45.8, 51.8, 63.8, 78.7, 128.1, 128.4, 128.6, 136.0, 155.2, 167.1, 200.1; EI-HRMS: m/z=208.0962 (MH^+–Boc); $C_{11}H_{14}NO_3$ requires: m/z=208.0968 (MH^+–Boc).

*4.2.11. (S)-Methyl 7-(((benzyloxy)carbonyl)amino)-4-((tert-butoxycarbonyl)amino)-3-oxoheptanoate (**2k**). General procedure 1 (GP1)*: Prepared from **1k** (3.66 g); CC (EtOAc/petroleum ether=1:1). Yield: 4.01 g (95%) of yellowish solid; mp 79.6–83.9 °C. $[\alpha]_D^{rt}$ −4.3 (*c* 0.26, CH_2Cl_2). $C_{21}H_{30}N_2O_7$ requires: C, 59.70; H, 7.16; N, 6.63. Found C, 59.46; H, 7.39; N, 6.66. ν_{max} 3353, 2987, 2938, 2856, 1748, 1718, 1695, 1683, 1516, 1449, 1439, 1403, 1393, 1369, 1319, 1299, 1248, 1158, 1128, 1071, 1053, 1019, 955, 940, 919, 858, 791, 773, 751, 731, 694, 641 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.34–1.52 (m, 3H, 3H of CH_2); 1.40 (s, 9H, Boc); 1.63–1.74 (m, 1H, 1H of CH_2); 2.95–3.05 (m, 2H, 2H of CH_2); 3.60 (d, J=2.2 Hz, 2H, $H_2C(2)$); 3.62 (s, 3H, CO_2Me); 3.95–4.01 (m, 1H, CH); 5.02 (s, 2H, CH_2 of Cbz); 7.27 (t, J=5.7 Hz, 1H, NH); 7.29–7.40 (m, 6H, Ph, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 25.9, 26.4, 28.1, 39.8, 45.3, 51.8, 59.4, 65.2, 78.4, 127.73, 127.75, 128.3, 137.3, 155.6, 156.1, 167.5, 203.4; EI-HRMS: m/z=323.1598 (MH^+–Boc); $C_{16}H_{23}N_2O_5$ requires: m/z=323.1601 (MH^+–Boc).

*4.2.12. (S)-Methyl 8-(((benzyloxy)carbonyl)amino)-4-((tert-butoxycarbonyl)amino)-3-oxooctanoate (**2l**). General procedure 1 (GP1)*:

Prepared from **1l** (3.80 g); CC (EtOAc/petroleum ether=1:1). Yield: 3.88 g (89%) of white solid; mp 76.7–78.2 °C. $[\alpha]_D^{rt}$ −24.9 (*c* 0.27, MeOH). ν_{max} 3351, 3065, 3033, 2985, 2953, 2931, 2867, 1748, 1718, 1685, 1522, 1478, 1454, 1438, 1402, 1368, 1329, 1268, 1244, 1226, 1161, 1140, 1092, 1078, 1062, 1025, 1008, 940, 921, 905, 886, 856, 779, 757, 739, 727, 695, 626 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.20–1.49 (m, 5H, 5H of CH_2); 1.39 (s, 9H, Boc); 1.58–1.68 (m, 1H, 1H of CH_2); 2.94–3.01 (m, 2H, 2H of CH_2); 3.58–3.65 (m, 2H, $H_2C(2)$); 3.61 (s, 3H, CO_2Me); 3.90–3.95 (m, 1H, H–C(4)); 5.00 (s, 2H, CH_2 of Cbz); 7.24 (t, *J*=5.5 Hz, 1H, NH); 7.28–7.39 (m, 6H, Ph, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 22.7, 28.2, 28.7, 29.0, 40.0, 41.4, 45.3, 51.9, 59.8, 65.1, 78.5, 127.7, 128.4, 137.3, 155.6, 156.0, 167.5, 203.6; EI-HRMS: *m*/*z*=337.1753 (MH^+–Boc); $C_{17}H_{25}N_2O_5$ requires: *m*/*z*=337.1758 (MH^+–Boc).

*4.2.13. (S)-7-tert-Butyl 1-methyl 4-(((benzyloxy)carbonyl)amino)-3-oxoheptanedioate (**2m**). General procedure 1 (GP1)*: Prepared from **1m** (3.37 g); CC (EtOAc/petroleum ether=1:4). Yield: 3.35 g (85%) of orange oil. $[\alpha]_D^{rt}$ +5.5 (*c* 0.87, CH_2Cl_2). ν_{max} 3342, 3066, 3033, 2977, 2955, 1714, 1587, 1519, 1453, 1438, 1393, 1367, 1320, 1237, 1149, 1043, 1028, 1003, 946, 914, 845, 810, 776, 736, 697, 655 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.39 (s, 9H, *t*-Bu); 1.61–1.70 (m, 1H, Ha of $H_2C(5)$); 1.92–2.02 (m, 1H, Hb of $H_2C(5)$); 2.24 (t, *J*=7.5 Hz, 2H, $H_2C(6)$); 3.61 (d, 1H, *J*=16.4 Hz, Ha of $H_2C(2)$); 3.61 (s, 3H, CO_2Me); 3.67 (d, 1H, *J*=16.4 Hz, Hb of $H_2C(2)$); 4.09–4.16 (m, 1H, CH); 5.05 (s, 2H, CH_2 of Cbz); 7.27–7.42 (m, 5H, Ph); 7.78 (d, *J*=7.9 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 24.5, 27.7, 31.0, 45.4, 51.9, 59.2, 65.8, 79.8, 127.8, 127.9, 128.4, 136.8, 156.2, 167.4, 171.5, 202.7; EI-HRMS: *m*/*z*=394.1865 (MH^+); $C_{20}H_{28}NO_7$ requires: *m*/*z*=394.1860 (MH^+).

*4.2.14. (S)-Methyl 4-(((benzyloxy)carbonyl)amino)-5-(tert-butoxy)-3-oxopentanoate (**2n**). General procedure 1 (GP1)*: Prepared from **1n** (2.95 g); CC (EtOAc/petroleum ether=1:2). Yield: 2.92 g (83%) of light orange oil. $[\alpha]_D^{rt}$ +20.2 (*c* 0.26, $CHCl_3$). ν_{max} 3339, 2973, 2877, 1714, 1499, 1455, 1437, 1393, 1364, 1322, 1218, 1192, 1086, 1057, 1025, 1002, 912, 879, 845, 775, 738, 697 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.11 (s, 9H, *t*-Bu); 3.53 (dd, *J*=5.2; 9.4 Hz, 1H, Ha of $H_2C(5)$); 3.58–3. 64 (m, 1H, Hb of $H_2C(5)$); 3.62 (s, 3H, CO_2Me); 3.64 (d, 1H, *J*=16.6 Hz, Ha of $H_2C(2)$); 3.70 (d, 1H, *J*=16.6 Hz, Hb of $H_2C(2)$); 4.27–4.32 (m, 1H, H–C(4)); 5.07 (s, 2H, CH_2 of Cbz); 7.31–7.40 (m, 5H, Ph); 7.63 (d, *J*=7.7 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.0, 46.7, 51.8, 60.3, 60.9, 65.7, 73.0, 127.8, 127.9, 128.3, 136.9, 156.1, 167.3, 201.9; EI-HRMS: *m*/*z*=352.1758 (MH^+); $C_{18}H_{26}NO_6$ requires: *m*/*z*=352.1755 (MH^+).

*4.2.15. (R)-Methyl 4-((tert-butoxycarbonyl)amino)-6-(methylthio)-3-oxohexanoate (**2o**). General procedure 1 (GP1)*: Prepared from **1o** (2.49 g); CC (EtOAc/petroleum ether=1:2). Yield: 2.67 g (87%) of yellow solid; mp 55.1–57.6 °C. $[\alpha]_D^{rt}$ +17.4 (*c* 0.30, CH_2Cl_2). $C_{13}H_{23}NO_5S$ requires: C, 51.13; H, 7.59; N, 4.59. Found C, 51.10; H, 7.79; N, 4.60. ν_{max} 3361, 2981, 2913, 1748, 1718, 1685, 1516, 1460, 1438, 1393, 1369, 1324, 1285, 1267, 1245, 1221, 1159, 1138, 1089, 1054, 1028, 1008, 942, 923, 891, 854, 806, 779, 762, 735, 691, 650, 617 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.39 (s, 9H, Boc); 1.68–1.78 (m, 1H, 1H of CH_2); 1.88–1.97 (m, 1H, 1H of CH_2); 2.03 (s, 3H, SMe); 2.38–2.50 (m, 2H, 2H of CH_2); 3.61 (s, 3H, CO_2Me); 3.57–3.69 (m, 2H, $H_2C(2)$); 4.07–4.14 (m, 1H, CH); 7.41 (d, *J*=7.6 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 14.5, 28.1, 28.8, 29.7, 45.4, 51.9, 58.7, 78.6, 155.6, 167.5, 203.3; EI-HRMS: *m*/*z*=206.0848 (MH^+–Boc); $C_8H_{16}NO_3S$ requires: *m*/*z*=206.0845 (MH^+–Boc).

*4.2.16. Methyl 4-(2-(((benzyloxy)carbonyl)amino)acetamido)-3-oxo-5-phenylpentanoate (**2p**). General procedure 1 (GP1)*: Prepared from **1p** (3.56 g); CC (EtOAc/petroleum ether=2:1). Yield: 3.49 g (84%) of yellow oil. ν_{max} 3308, 3063, 3031, 2952, 1714, 1662, 1515, 1498, 1454, 1437, 1401, 1321, 1233, 1149, 1047, 1028, 1001, 932, 738, 698 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.82 (dd, *J*=9.6; 14.0 Hz, 1H, Ha of CH_2); 3.13 (dd, *J*=4.8; 14.0 Hz, 1H, Hb of CH_2); 3.55–3.75 (m, 4H, 2×CH_2); 3.64 (s, 3H, CO_2Me); 4.52–4.59 (m, 1H, CH); 5.05 (s, 2H, CH_2 of Cbz); 7.12–7.41 (m, 10H, 2×Ph); 7.51 (t, *J*=6.1 Hz, 1H, NH); 8.43 (d, *J*=7.7 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 34.7, 43.3, 45.8, 51.9, 59.6, 65.6, 126.4, 127.8, 127.8, 128.2, 128.4, 129.2, 137.0, 137.6, 156.5, 167.6, 169.6, 202.1; EI-HRMS: *m*/*z*=413.1706 (MH^+); $C_{22}H_{25}N_2O_6$ requires: *m*/*z*=413.1707 (MH^+).

*4.2.17. (Z)-Methyl 4-acetamido-3-oxo-5-phenylpent-4-enoate (**2q**).*[42] *General procedure 1 (GP1)*: Prepared from **1q** (2.05 g); CC (EtOAc/petroleum ether=1:1). Yield: 445 mg (17%) of yellow oil. ν_{max} 3212, 3002, 2957, 1746, 1697, 1646, 1625, 1521, 1487, 1436, 1363, 1328, 1289, 1272, 1219, 1185, 1142, 1054, 1008, 995, 978, 944, 925, 880, 846, 808, 756, 687, 659, 630, 615 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.03 (s, 3H, COMe); 3.64 (s, 3H, CO_2Me); 3.76 (s, 2H, CH_2); 7.19 (s, 1H, CH); 7.37–7.49 (m, 3H, 3H of Ph); 7.63–7.67 (m, 2H, 2H of Ph); 9.76 (s, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 22.4, 45.0, 51.9, 128.7, 129.7, 130.2, 131.4, 132.9, 133.4, 167.9, 170.0, 192.1; EI-HRMS: *m*/*z*=262.1071 (MH^+); $C_{14}H_{16}NO_4$ requires: *m*/*z*=262.1074 (MH^+).

*4.2.18. Methyl 5-((tert-butoxycarbonyl)amino)-3-oxopentanoate (**2r**).*[43] *General procedure 1 (GP1)*: Prepared from **1r** (1.89 g); CC (EtOAc/petroleum ether=1:2). Yield: 1.94 g (79%) of yellow oil. ^1H NMR (500 MHz, DMSO-d_6): δ 1.37 (s, 9H, Boc); 2.66 (t, *J*=6.8 Hz, 2H, CH_2); 3.11 (q, *J*=6.7 Hz, 2H, CH_2); 3.62 (s, 2H, CH_2); 3.62 (s, 3H, CO_2Me); 6.79 (t, *J*=4.9 Hz, 1H, NH).

4.3. Synthesis of 4-hydroxypyrrole derivatives and/or enaminone intermediates from β-keto esters—general procedure 2 (GP2)

To a solution of β-keto ester (1 equiv) in anhydrous toluene (V_1) under argon was added DMFDMA (1.0–3.0 equiv) and the resulting reaction mixture was stirred at room temperature or at elevated temperature (T_1) for t_1 h till completion of the reaction judging by TLC-analysis (see Fig. 2 and the accompanying discussion). Volatile components were evaporated in vacuo and the residue was as quickly as possible purified/separated by column chromatography (CC). Fractions containing the isolated/separated product(s) were combined, respectively, and volatile components evaporated in vacuo. The products were characterized as soon as isolated and stored under argon.

*4.3.1. Methyl 4-((tert-butoxycarbonyl)amino)-2-((dimethylamino)methylene)-3-oxobutanoate (**3a**). General procedure 2 (GP2)*: Prepared from **2a** (432 mg, 1.868 mmol), PhMe (V_1=10 mL), DMFDMA (827 μL, 5.60 mmol), room temperature, t_1=3 h, CC (EtOAc). The isolation and characterization must be done as quick as possible because of the decomposition of **3a** into **4a**! Yield: 407 mg (76%) of orange oil. ν_{max} 3412, 2977, 2933, 1694, 1644, 1581, 1489, 1425, 1386, 1365, 1275, 1248, 1209, 1164, 1113, 1098, 1039, 1006, 977, 946, 869, 767 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.37 (s, 9H, Boc); 2.74 (s, 3H, NMe); 3.25 (s, 3H, NMe); 3.64 (s, 3H, CO_2Me); 3.96 (d, *J*=5.9 Hz, 2H, CH_2); 6.66 (t, *J*=5.8 Hz, 1H, NH); 7.75 (s, 1H, CH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 28.2, 41.7, 46.9, 48.5, 50.7, 77.7, 98.3, 155.8, 157.5, 167.4, 191.7; EI-HRMS: *m*/*z*=287.1600 (MH^+); $C_{13}H_{23}N_2O_5$ requires: *m*/*z*=287.1601 (MH^+).

*4.3.2. 1-tert-Butyl 3-methyl 4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4a**) and 1-tert-butyl 3-methyl 4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4a′**).* Enaminone **3a** (300 mg, 1.05 mmol) was left to stand in an open flask for 20 h to cyclize into **4a**/**4a′**. Afterward, the residue was dissolved in anhydrous PhMe (50 mL) and rotated

on rotary evaporator (P=80 mbar) for 30 min at 40 °C followed by removal of volatile components. The residue was re-dissolved in anhydrous PhMe (50 mL) and the procedure on the rotary evaporator was repeated. This was done twice more followed by drying on high vacuum. The residue was characterized without any additional purification and stored under argon. Yield: 223 mg (93%; 100% conversion) of orange oil; **4a**/**4a**′=1:0.38 (in DMSO-d_6). ν_{max} 3400, 2980, 1732, 1695, 1579, 1524, 1476, 1444, 1392, 1369, 1341, 1299, 1239, 1145, 1122, 1088, 1034, 979, 953, 912, 845, 762, 733, 716, 631 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) for **4a**: δ 1.55 (s, 9H, Boc); 3.73 (s, 3H, CO_2Me); 6.63 (d, J=2.6 Hz, 1H, H–C(5)); 7.51 (d, J=2.6 Hz, 1H, H–C(2)); 8.98 (s, 1H, OH). ^{1}H NMR (500 MHz, DMSO-d_6) for **4a**′: δ 1.51 (s, 9H, Boc); 3.69 (s, 3H, CO_2Me); 4.24 (s, 2H, H_2C(5)); 8.91 (s, 1H, OH). ^{13}C NMR (126 MHz, DMSO-d_6) for **4a** and **4a**′: δ 27.4, 27.5, 51.0, 51.1, 55.9, 83.9, 84.6, 102.3, 110.1, 111.5, 122.3, 144.8, 147.5, 161.5, 163.1, 163.5, 191.9; EI-HRMS: m/z=242.1021 (MH$^+$); $C_{11}H_{16}NO_5$ requires: m/z=242.1023 (MH$^+$).

*4.3.3. 1-tert-Butyl 3-methyl 5-((dimethylamino)methylene)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**5a**). General procedure 2 (GP2)*: Prepared from **2a** (448 mg, 1.937 mmol), PhMe (V_1=10 mL), DMFDMA (858 μL, 5.81 mmol), T_1=90 °C, t_1=3 h, CC (EtOAc/MeOH=10:1). Yield: 230 mg (40%) of brown semisolid. ν_{max} 2930, 1724, 1650, 1568, 1482, 1432, 1389, 1348, 1299, 1248, 1219, 1185, 1148, 1102, 1011, 987, 934, 897, 848, 785, 757, 733, 708, 650 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.54 (s, 9H, Boc); 3.29 (s, 6H, NMe_2); 3.66 (s, 3H, CO_2Me); 8.03 (s, 1H, CH); 8.23 (s, 1H, CH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.5, 43.9, 46.6, 50.7, 84.5, 111.1, 112.2, 142.4, 146.9, 147.9, 162.6, 171.5; EI-HRMS: m/z=297.1445 (MH$^+$); $C_{14}H_{21}N_2O_5$ requires: m/z=297.1445 (MH$^+$).

*4.3.4. 1-tert-Butyl 3-methyl 4-hydroxy-5-methyl-1H-pyrrole-1,3-dicarboxylate (**4b**) and 1-tert-butyl 3-methyl 5-methyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4b**′). General procedure 2 (GP2)*: Prepared from **2b** (1.23 g, 5.00 mmol), PhMe (V_1=15 mL), DMFDMA (1.48 mL, 10 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 431 mg (33%) of orange oil; **4b**/**4b**′=1:0.54 (in DMSO-d_6). ν_{max} 3398, 3003, 2984, 2956, 2936, 1727, 1692, 1579, 1541, 1477, 1455, 1370, 1303, 1283, 1248, 1188, 1144, 1080, 1044, 939, 869, 846, 795, 766, 743, 703, 633 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) for **4b**: δ 1.55 (s, 9H, Boc); 2.22 (s, 3H, Me); 3.73 (s, 3H, CO_2Me); 7.48 (s, 1H, H–C(2)); 7.97 (s, 1H, OH). ^{1}H NMR (500 MHz, DMSO-d_6) for **4b**′: δ 1.38 (d, J=7.1 Hz, 3H, Me); 1.52 (s, 9H, Boc); 3.69 (s, 3H, CO_2Me); 4.25 (q, J=7.1 Hz, 1H, H–C(5)); 8.93 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, $CDCl_3$) for **4b** and **4b**′: δ 10.5, 16.5, 28.06, 28.10, 51.6, 51.9, 63.0, 84.7, 85.1, 106.5, 111.0, 112.0, 120.5, 142.4, 149.2, 162.6, 163.2, 166.7, 195.9; EI-HRMS: m/z=256.1179 (MH$^+$); $C_{12}H_{18}NO_5$ requires: m/z=256.1179 (MH$^+$).

*4.3.5. 1-Benzyl 3-methyl 4-hydroxy-5-methyl-1H-pyrrole-1,3-dicarboxylate (**4c**) and 1-benzyl 3-methyl 5-methyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4c**′). General procedure 2 (GP2)*: Prepared from **2c** (140 mg, 0.5 mmol), PhMe (V_1=2 mL), DMFDMA (0.148 mL, 1.0 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 85 mg (58%) of orange oil; **4c**/**4c**′=1:0.62 (in DMSO-d_6). ν_{max} 3412, 2953, 2925, 1731, 1698, 1580, 1538, 1498, 1448, 1401, 1367, 1298, 1215, 1183, 1099, 1037, 976, 941, 912, 806, 753, 729, 696, 652, 632 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) for **4c**: δ 2.33 (s, 3H, Me); 3.85 (s, 3H, CO_2Me); 5.36 (s, 2H, CH_2 of Cbz); 7.05 (s, 1H, H–C(2)); 7.34–7.46 (m, 5H, Ph); 7.58 (s, 1H, OH). ^{1}H NMR (500 MHz, $CDCl_3$) for **4c**′: δ 1.54 (d, J=7.0 Hz, 3H, Me); 3.82 (s, 3H, CO_2Me); 4.22 (q, J=7.0 Hz, 1H, H–C(5)); 5.31 (d, J=12.4 Hz, 2H, CH_2 of Cbz); 7.34–7.46 (m, 5H, Ph); 9.03 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, $CDCl_3$) for **4c** and **4c**′: δ 10.3, 16.4, 51.6, 51.9, 62.9, 69.4, 69.6, 107.4, 111.9, 112.3, 120.5, 128.7, 128.82, 128.86, 128.95, 128.99, 129.2, 134.2, 134.5, 142.5, 150.5, 162.2, 162.7, 166.5, 195.4; EI-HRMS: m/z=290.1018 (MH$^+$); $C_{15}H_{16}NO_5$ requires: m/z=290.1023 (MH$^+$).

*4.3.6. 1-tert-Butyl 3-methyl 4-hydroxy-5-isopropyl-1H-pyrrole-1,3-dicarboxylate (**4d**) and 1-tert-butyl 3-methyl 5-isopropyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4d**′). General procedure 2 (GP2)*: Prepared from **2d** (273 mg, 1 mmol), PhMe (V_1=5 mL), DMFDMA (0.295 mL, 2.0 mmol), T_1=75 °C, t_1=3 h, CC (EtOAc/petroleum ether=1:3). Yield: 154 mg (54%) of white solid; mp 94–97.0 °C; **4d**/**4d**′=0.08:1 (in DMSO-d_6). $C_{14}H_{21}NO_5$ requires: C, 59.35; H, 7.47; N, 4.94. Found C, 59.34; H, 7.45; N, 4.95. ν_{max} 2972, 2878, 1747, 1721, 1697, 1575, 1465, 1439, 1371, 1323, 1306, 1230, 1215, 1191, 1139, 110.4, 1073, 1032, 965, 930, 904, 840, 825, 798, 767, 736, 702, 620 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) for **4d**: δ 1.25 (d, J=7.0 Hz, 6H, 2×Me); 1.55 (s, 9H, Boc); 2.46–2.53 (m, 1H, CH); 3.75 (s, 3H, CO_2Me); 7.45 (s, 1H, H–C(2)), 7.72 (s, 1H, OH). ^{1}H NMR (500 MHz, DMSO-d_6) for **4d**′: δ 0.76 (d, J=6.9 Hz, 3H, Me); 1.07 (d, J=7.0 Hz, 3H, Me); 1.51 (s, 9H, Boc); 2.46–2.53 (m, 1H, CH); 3.68 (s, 3H, CO_2Me); 4.16 (d, J=3.4 Hz, 1H, H–C(5)); 8.98 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4d**′: δ 16.0, 17.0, 27.5, 29.5, 51.1, 69.8, 84.2, 111.1, 147.7, 161.4, 164.1, 194.6; EI-HRMS: m/z=284.1494 (MH$^+$); $C_{14}H_{22}NO_5$ requires: m/z=284.1492 (MH$^+$).

*4.3.7. 1-Benzyl 3-methyl 4-hydroxy-5-isobutyl-1H-pyrrole-1,3-dicarboxylate (**4e**) and 1-benzyl 3-methyl 5-isobutyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4e**′). General procedure 2 (GP2)*: Prepared from **2e** (225 mg, 0.7 mmol), PhMe (V_1=2.5 mL), DMFDMA (0.207 mL, 1.4 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 157 mg (67%) of yellow oil; **4e**/**4e**′=1:0.12 (in DMSO-d_6). ν_{max} 3446, 3168, 3067, 3042, 2955, 2866, 1753, 1688, 1621, 1584, 1536, 1499, 1456, 1438, 1396, 1369, 1332, 1287, 1256, 1204, 1185, 1175, 1120, 1098, 1052, 1030, 1004, 971, 919, 826, 744, 718, 695, 677, 647 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) for **4e**: δ 0.76 (d, J=6.7 Hz, 6H, 2×CH_3); 1.69–1.78 (m, 1H, $(CH_3)_2CHCH_2$); 2.57 (d, J=7.1 Hz, 2H, $(CH_3)_2CHCH_2$); 3.74 (s, 3H, CO_2Me); 5.36 (s, 2H, CH_2 of Cbz); 7.34–7.46 (m, 3H, 3H of Ph); 7.48–7.53 (m, 2H, 2H of Ph); 7.56 (s, 1H, H–C(2)), 7.96 (s, 1H, OH). ^{1}H NMR (500 MHz, DMSO-d_6) for **4e**′: δ 1.45–1.53 (m, 1H, $(CH_3)_2CHCH_2$); 3.68 (s, 3H, CO_2Me); 4.35 (dd, J=3.9, 7.2 Hz, 1H, H–C(5)); 9.03 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4e**: δ 21.9, 28.2, 32.3, 51.1, 69.1, 109.2, 117.5, 121.7, 128.6, 128.7, 128.8, 134.7, 141.8, 149.6, 163.6; EI-HRMS: m/z=332.1491 (MH$^+$); $C_{18}H_{22}NO_5$ requires: m/z=332.1492 (MH$^+$).

*4.3.8. (R)-Methyl 4-((tert-butoxycarbonyl)amino)-2-((dimethylamino) methylene)-3-oxooctanoate (**3f**) and 1-tert-butyl 3-methyl 5-butyl-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4f**), and 1-tert-butyl 3-methyl 5-butyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4f**′). General procedure 2 (GP2)*: Prepared from **2f** (330 mg, 1.15 mmol), PhMe (V_1=10 mL), DMFDMA (0.678 mL, 4.59 mmol), T_1=75 °C, t_1=3 h, CC ((1) EtOAc/petroleum ether=1:2 to elute **4f**/**4f**′; (2) EtOAc to elute **3f**).

*4.3.8.1. Compounds **4f**/**f4**′*. Elutes first from the column. Yield: 142 mg (41%) of yellowish oil; **4f**/**4f**′=1:0.74 (in DMSO-d_6). ν_{max} 3401, 2956, 2932, 2872, 2862, 1734, 1695, 1627, 1582, 1535, 1459, 1438, 1393, 1370, 1315, 1277, 1251, 1145, 1095, 1069, 1049, 968, 932, 848, 751, 711, 619 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) for **4f**: δ 0.88 (t, J=7.3 Hz, 3H, Me); 1.22–1.31 (m, 2H, 2H of CH_2); 1.41–1.44 (m, 2H of CH_2); 1.56 (s, 9H, Boc); 2.71 (t, J=7.4 Hz, 2H, 2H of CH_2); 3.74 (s, 3H, CO_2Me); 7.48 (s, 1H, H–C(2)); 7.91 (s, 1H, OH). ^{1}H NMR (500 MHz, DMSO-d_6) for **4f**′: δ 0.82 (t, J=7.3 Hz, 3H, Me); 0.97–1.06 (m, 1H, 1H of CH_2); 1.07–1.14 (m, 1H, 1H of CH_2); 1.52 (s, 9H, Boc); 1.85–1.93 (m, 1H, 1H of CH_2); 2.01–2.07 (m, 1H, 1H of CH_2); 3.69 (s, 3H, CO_2Me); 4.31 (dd, J=3.0; 6.5 Hz, 1H, H–C(5)); 9.00 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4f** and **4f**′: δ 13.7, 13.8, 21.8, 21.9, 23.2, 24.3, 27.4, 27.5, 28.8, 31.5, 51.0, 51.1, 66.0, 84.1, 84.6,

108.6, 110.7, 118.1, 121.5, 141.0, 147.6, 148.3, 161.5, 163.7, 163.9, 194.9; EI-HRMS: m/z=298.1649 (MH^+); $C_{15}H_{24}NO_5$ requires: m/z=298.1649 (MH^+).

*4.3.8.2. Compound **3f**.* Elutes second from the column. Yield: 188 mg (47%) of yellowish oil. ν_{max} 3349, 2955, 2932, 2872, 1696, 1639, 1576, 1488, 1455, 1423, 1363, 1281, 1244, 1206, 1165, 1094, 1042, 1003, 969, 915, 870, 915, 870, 836, 777, 731, 638, 608 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.81–0.87 (m, 3H, Me); 1.18–1.32 (m, 5H, 5H of CH_2); 1.36 (s, 9H, Boc); 1.56–1.65 (m, 1H, 1H of CH_2); 2.73 (br s, 3H, NMe_2); 3.25 (br s, 3H, NMe_2); 3.63 (s, 3H, CO_2Me); 4.72 (*td*, J=3.6; 9.1 Hz, 1H, H–C(3)); 6.52 (d, J=8.6 Hz, 1H, NH); 7.74 (s, 1H, CH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.9, 21.9, 28.0, 28.2, 31.7, 41.4, 46.9, 50.7, 56.2, 77.5, 98.6, 155.3, 157.6, 167.5, 195.2; EI-HRMS: m/z=343.2226 (MH^+); $C_{17}H_{31}N_2O_5$ requires: m/z=343.2227 (MH^+).

*4.3.9. 1-tert-Butyl 3-methyl 5-benzyl-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4g**) and 1-tert-butyl 3-methyl 5-benzyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4g**′). General procedure 2 (GP2)*: Prepared from **2g** (186 mg, 0.58 mmol), PhMe (V_1=3 mL), DMFDMA (0.177 mL, 1.2 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 161 mg (84%) of yellow oil; **4g**/**4g**′=1:0.70 (in DMSO-d_6). ν_{max} 3401, 2979, 2952, 2934, 1732, 1695, 1627, 1579, 1534, 1495, 1456, 1439, 1392, 1370, 1278, 1254, 1192, 1143, 1047, 981, 846, 753, 729, 703, 630 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4g**: δ 1.34 (s, 9H, Boc); 3.76 (s, 3H, CO_2Me); 4.14 (s, 2H, CH_2); 7.00–7.03 (m, 2H, 2H of Ph); 7.12–7.28 (m, 3H, 3H of Ph); 7.58 (s, 1H, H–C(2)), 8.27 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4g**′: δ 1.55 (s, 9H, Boc); 3.23 (dd, J=2.6; 13.8 Hz, 1H, Ha of CH_2); 3.39 (dd, J=6.4; 13.9 Hz, 1H, Hb of CH_2); 3.62 (s, 3H, CO_2Me); 4.59 (dd, J=2.6; 6.3 Hz, 1H, H–C(5)); 6.93–6.97 (m, 2H, 2H of Ph); 7.12–7.28 (m, 3H, 3H of Ph); 8.71 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4g** and **4g**′: δ 27.1, 27.5, 28.9, 34.9, 51.09, 51.12, 66.4, 84.4, 84.7, 108.8, 111.0, 115.5, 122.3, 125.7, 127.08, 127.45, 128.21, 128.26, 129.1, 134.3, 140.3, 142.2, 147.6, 148.2, 161.2, 163.5, 163.8, 194.4; EI-HRMS: m/z=332.1490 (MH^+); $C_{18}H_{22}NO_5$ requires: m/z=332.1492 (MH^+).

*4.3.10. 1-Benzyl 3-methyl 5-benzyl-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4h**) and 1-benzyl 3-methyl 5-benzyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4h**′). General procedure 2 (GP2)*: Prepared from **2h** (249 mg, 0.7 mmol), PhMe (V_1=2 mL), DMFDMA (0.207 mL, 1.4 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 123 mg (48%) of orange oil; **4h**/**4h**′=1:0.66 (in DMSO-d_6). ν_{max} 3402, 3151, 3086, 3063, 3030, 2952, 2859, 1732, 1694, 1629, 1581, 1535, 1495, 1454, 1440, 1399, 1367, 1312, 1253, 1218, 1189, 1162, 1107, 1044, 979, 913, 878, 847, 823, 779, 750, 735, 698, 645 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4h**: δ 3.76 (s, 3H, CO_2Me); 4.14 (s, 2H, CH_2); 5.26 (s, 2H, CH_2 of Cbz); 7.01–7.05 (m, 2H, 2H of Ph); 7.11–7.17 (m, 1H, 1H of Ph); 7.19–7.24 (m, 2H, 2H of Ph); 7.31–7.38 (m, 3H, 3H of Ph); 7.41–7.48 (m, 2H, 2H of Ph); 7.60 (s, 1H, H–C(2)); 8.40 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4h**′: δ 3.22 (dd, J=2.7; 13.9 Hz, 1H, 1H of CH_2); 3.34 (dd, J=6.3; 14.1 Hz, 1H, 1H of CH_2); 3.62 (s, 3H, CO_2Me); 4.65 (dd, J=2.7; 6.2 Hz, 1H, H–C(5)); 5.40 (s, 2H, CH_2 of Cbz); 6.80–6.83 (m, 2H, 2H of Ph); 7.11–7.17 (m, 2H, 2H of Ph); 7.31–7.38 (m, 4H, 4H of Ph); 7.51–7.54 (m, 2H, 2H of Ph); 8.81 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4h** and **4h**′: δ 28.9, 34.8, 51.16, 51.17, 66.4, 68.8, 68.9, 109.6, 111.8, 116.5, 122.2, 125.7, 127.0, 127.7, 128.1, 128.2, 128.49, 128.53, 128.58, 128.63, 128.67, 128.70, 129.1, 134.1, 134.7, 135.0, 140.0, 142.3, 149.0, 149.3, 161.0, 163.3, 163.6, 194.2; EI-HRMS: m/z=366.1337 (MH^+); $C_{21}H_{20}NO_5$ requires: m/z=366.1336 (MH^+).

*4.3.11. (S)-Methyl 2-((dimethylamino)methylene)-4-(1,3-dioxoisoindolin-2-yl)-3-oxo-5-phenylpentanoate (**3i**). General procedure 2 (GP2)*: Prepared from **2i** (416 mg, 1.18 mmol), PhMe (V_1=10 mL), DMFDMA (0.354 mL, 2.4 mmol), T_1=rt, t_1=12 h, the product precipitated from the reaction mixture and was collected by filtration under reduced pressure and washed with petroleum ether. Yield: 350 mg (73%) of white solid; mp 187.0–190.0 °C. $[\alpha]_D^{rt}$ +5.8 (c 0.27, CH_2Cl_2). $C_{23}H_{22}N_2O_5$ requires: C, 67.97; H, 5.46; N, 6.89. Found C, 68.19; H, 5.44; N, 6.96. ν_{max} 2947, 2936, 1769, 1706, 1676, 1639, 1611, 1580, 1496, 1466, 1434, 1417, 1376, 1322, 1278, 1212, 1188, 1165, 1113, 1097, 1077, 1059, 1044, 969, 918, 889, 868, 808, 795, 771, 749, 729, 701, 653 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.92 (s, 3H, 3H of NMe_2); 3.27 (s, 3H, 3H of NMe_2); 3.43 (dd, J=11.7; 14.1 Hz, 1H, Ha of $H_2C(5)$); 3.55 (dd, J=4.4; 14.0 Hz, 1H, Hb of $H_2C(5)$); 3.70 (s, 3H, CO_2Me); 5.95 (dd, J=4.3; 11.7 Hz, 1H, H–C(4)); 7.07–7.12 (m, 1H, 1H of Ph); 7.13–7.22 (m, 4H, 4H of Ph); 7.63 (dd, J=3.0; 5.5 Hz, 2H, indoline); 7.72 (dd, J=3.1; 5.4 Hz, 2H, indoline); 7.76 (s, 1H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 35.2, 42.8, 48.2, 51.5, 60.7, 123.2, 126.5, 128.5, 129.0, 131.9, 133.8, 138.2, 159.1, 167.9, 168.2, 192.9; EI-HRMS: m/z=407.1590 (MH^+); $C_{23}H_{23}N_2O_5$ requires: m/z=407.1601 (MH^+).

*4.3.12. 1-tert-Butyl 3-methyl 4-hydroxy-5-phenyl-1H-pyrrole-1,3-dicarboxylate (**4j**) and 1-tert-butyl 3-methyl 4-oxo-5-phenyl-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4j**′). General procedure 2 (GP2)*: Prepared from **2j** (361 mg, 1.17 mmol), PhMe (V_1=5 mL), DMFDMA (0.518 mL, 3.51 mmol), T_1=75 °C, t_1=2 h, CC (EtOAc/petroleum ether=1:2). Yield: 270 mg (72%) of orange oil; **4j**/**4j**′=1:0.35 (in DMSO-d_6). ν_{max} 3400, 2980, 2952, 1736, 1691, 1619, 1578, 1531, 1497, 1476, 1455, 1436, 1392, 1369, 1322, 1282, 1244, 1207, 1142, 1101, 1075, 1032, 995, 962, 939, 844, 812, 773, 756, 739, 705, 695, 636 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4j**: δ 1.29 (s, 9H, Boc); 3.78 (s, 3H, CO_2Me); 7.27–7.31 (m, 2H, 2H of Ph); 7.35–7.41 (m, 3H, 3H of Ph); 7.66 (s, 1H, H–C(2)); 8.19 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4j**′: δ 1.28 (br s, 9H, Boc); 3.70 (s, 3H, CO_2Me); 5.33 (s, 1H, H–C(5)), 7.19–7.22 (m, 2H, 2H of Ph); 7.27–7.31 (m, 2H, 2H of Ph); 7.35–7.41 (m, 1H, 1H of Ph); 9.20 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4j** and **4j**′: δ 27.0, 27.2, 51.19, 51.25, 69.4, 84.0, 84.6, 108.7, 109.2, 123.4, 126.5, 126.7, 127.5, 128.1, 128.7, 129.7, 130.9, 142.2, 147.3, 148.2, 161.6, 163.7, 164.8, 192.5; EI-HRMS: m/z=318.1332 (MH^+); $C_{17}H_{20}NO_5$ requires: m/z=318.1336 (MH^+).

*4.3.13. 1-tert-Butyl 3-methyl 5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4k**) and 1-tert-butyl 3-methyl 5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4k**′). General procedure 2 (GP2)*: Prepared from **2k** (6.77 g, 16.03 mmol), PhMe (V_1=70 mL), DMFDMA (3.56 mL, 24.1 mmol), T_1=75 °C, t_1=2 h, CC (EtOAc/petroleum ether=1:1). Yield: 6.65 g (96%) of yellow oil; **4k**/**4k**′=1:1 (in DMSO-d_6). ν_{max} 3367, 2950, 2872, 1698, 1578, 1529, 1440, 1395, 1370, 1280, 1240, 1196, 1143, 1070, 1043, 1027, 967, 915, 845, 752, 697, 609 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4k**: δ 1.46–1.64 (m, 2H, 2H of CH_2); 1.56 (s, 9H, Boc); 2.72 (t, J=7.4 Hz, 2H of CH_2); 2.90–3.03 (m, 2H, 2H of CH_2); 3.74 (s, 3H, CO_2Me); 5.01 (s, 2H, CH_2 of Cbz); 7.23 (t, J=5.7 Hz, 1H, NH); 7.27–7.39 (m, 5H, Ph); 7.51 (s, 1H, H–C(2)); 8.03 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4k**′: δ 1.10–1.20 (m, 1H, Ha of CH_2); 1.23–1.34 (m, 1H, Hb of CH_2); 1.51 (s, 9H, Boc); 1.84–1.92 (m, 1H, Ha of CH_2); 2.01–2.07 (m, 1H, Hb of CH_2); 2.90–3.03 (m, 2H, 2H of CH_2); 3.70 (s, 3H, CO_2Me); 4.33 (dd, J=3.1; 6.5 Hz, 1H, H–C(5)); 4.99 (s, 2H, CH_2 of Cbz); 7.27–7.39 (m, 6H, 5H of Ph, NH); 9.00 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4k** and **4k**′: δ 21.1, 23.1, 26.8, 27.4, 27.5, 29.7, 40.0, 51.08, 51.14, 65.1, 65.2, 65.8, 84.2, 84.8, 108.7, 110.7, 117.3, 121.8, 127.7, 127.8, 128.3, 137.2, 137.3, 141.1, 147.6, 148.3, 156.0, 156.1, 161.5, 163.6, 164.0, 194.8; EI-HRMS: m/z=433.1967 (MH^+); $C_{22}H_{29}N_2O_7$ requires: m/z=433.1969 (MH^+).

*4.3.14. 1-tert-Butyl 3-methyl 5-(4-(((benzyloxy)carbonyl)amino)butyl)-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4l**) and 1-tert-butyl 3-*

*methyl 5-(4-(((benzyloxy)carbonyl)amino)butyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4l′**). General procedure 2 (GP2)*: Prepared from **2l** (218 mg, 0.5 mmol), PhMe (V_1=2 mL), DMFDMA (0.148 mL, 1.0 mmol), T_1=75 °C, t_1=1 h, CC (EtOAc/petroleum ether=1:2). Yield: 123 g (55%) of orange oil; **4l**/**4l′**=1:0.61 (in DMSO-d_6). ν_{max} 3368, 3160, 3089, 3065, 3032, 2976, 2936, 2865, 1694, 1626, 1579, 1530, 1455, 1439, 1394, 1370, 1278, 1242, 1191, 1143, 1046, 1027, 9670, 847, 751, 697, 609 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4l**: δ 1.28–1.46 (m, 4H, 4H of CH_2); 1.54 (s, 9H, Boc); 2.67–2.74 (m, 2H, CH_2); 2.96–3.02 (m, 2H, CH_2); 3.74 (s, 3H, CO_2Me); 4.99 (s, 2H, CH_2 of Cbz); 7.23 (t, J=5.8 Hz, 1H, NH); 7.28–7.39 (m, 5H, Ph); 7.49 (s, 1H, H–C(2)); 7.95 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4l′**: δ 0.97–1.08 (m, 1H, Ha of CH_2); 1.09–1.20 (m, 1H, Hb of CH_2); 1.28–1.46 (m, 2H, 2H of CH_2); 1.51 (s, 9H, Boc); 1.84–1.93 (m, 1H, Ha of CH_2); 1.98–2.08 (m, 1H, Hb of CH_2); 2.90–2.96 (m, 2H, CH_2); 3.69 (s, 3H, CO_2Me); 4.31 (dd, J=3.1; 6.5 Hz, 1H, H–C(5)); 4.99 (s, 2H, CH_2 of Cbz); 7.28–7.39 (m, 6H, 5H of Ph, NH); 8.99 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4l** and **4l′**: δ 19.7, 23.2, 26.7, 27.4, 27.5, 29.0, 29.2, 29.3, 40.2, 51.07, 51.12, 65.1, 66.0, 84.2, 84.7, 108.7, 110.6, 117.8, 121.6, 127.72, 127.74, 128.3, 137.2, 137.3, 141.1, 147.6, 148.3, 156.0, 156.1, 161.5, 163.6, 164.0, 194.8; EI-HRMS: m/z=447.2119 (MH^+); $C_{23}H_{31}N_2O_7$ requires: m/z=447.2126 (MH^+).

*4.3.15. 1-Benzyl 3-methyl 5-(3-(tert-butoxy)-3-oxopropyl)-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4m**) and 1-benzyl 3-methyl 5-(3-(tert-butoxy)-3-oxopropyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4m′**). General procedure 2 (GP2)*: Prepared from **2m** (433 mg, 1.1 mmol), PhMe (V_1=3 mL), DMFDMA (0.325 mL, 2.2 mmol), T_1=rt, t_1=15 h, CC (EtOAc/petroleum ether=1:2). Yield: 200 g (45%) of orange-yellow oil; **4m**/**4m′**=1:0.85 (in DMSO-d_6). ν_{max} 3423, 3411, 3034, 2977, 2953, 2934, 1722, 1697, 1629, 1582, 1537, 1498, 1456, 1440, 1400, 1366, 1317, 1218, 1187, 1148, 1111, 1067, 1027, 981, 952, 913, 846, 751, 698, 645 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4m**: δ 1.37 (s, 9H, *t*-Bu); 2.34–2.40 (m, 2H, 2H of CH_2); 2.93–2.99 (m, 2H, 2H of CH_2); 3.73 (s, 3H, CO_2Me); 5.38 (s, 2H, CH_2 of Cbz); 7.36–7.45 (m, 3H, 3H of Ph); 7.46–7.52 (m, 2H, 2H of Ph); 7.55 (s, 1H, H–C(2)), 8.18 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4m′**: δ 1.36 (s, 9H, *t*-Bu); 2.05–2.29 (m, 4H, 4H of CH_2); 3.70 (s, 3H, CO_2Me); 4.45 (dd, J=3.3, 6.3 Hz, 1H, H–C(5)); 5.30 (d, J=12.3 Hz, 1H, Ha of Cbz); 5.35 (d, J=12.4 Hz, 1H, Hb of Cbz); 7.36–7.45 (m, 3H, 3H of Ph); 7.46–7.52 (m, 2H, 2H of Ph); 9.01 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4m** and **4m′**: δ 19.4, 24.7, 27.6, 27.7, 28.6, 34.5, 51.1, 51.2, 65.0, 68.7, 69.1, 79.6, 80.0, 109.4, 111.2, 116.4, 121.9, 128.2, 128.50, 128.53, 128.54, 128.6, 128.7, 134.8, 135.0, 141.5, 149.0, 149.4, 161.3, 163.3, 164.1, 171.1, 171.4, 194.4; EI-HRMS: m/z=348.1076 (MH–*t*-Bu^+); $C_{17}H_{18}NO_7$ requires: m/z=348.1078 (MH–*t*-Bu^+).

*4.3.16. 1-Benzyl 3-methyl 5-(tert-butoxymethyl)-4-hydroxy-1H-pyrrole-1,3-dicarboxylate (**4n**) and 1-benzyl 3-methyl 5-(tert-butoxymethyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4n′**). General procedure 2 (GP2)*: Prepared from **2n** (282 mg, 0.8 mmol), PhMe (V_1=5 mL), DMFDMA (0.148 mL, 1.0 mmol), T_1=rt, t_1=12 h, CC (EtOAc/petroleum ether=1:2). Yield: 193 g (66%) of orange oil; **4n**/**4n′**=0.24:1 (in DMSO-d_6). ν_{max} 2973, 2875, 1722, 1582, 1535, 1440, 1404, 1364, 1307, 1270, 1225, 1187, 1158, 1118, 1094, 1035, 975, 915, 890, 832, 755, 698, 643 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4n**: δ 1.12 (s, 9H, *t*-Bu); 3.74 (s, 3H, CO_2Me); 4.48 (s, 2H, 2H of *t*-BuOCH_2); 5.38 (s, 2H, CH_2 of Cbz); 7.35–7.44 (m, 3H, 3H of Ph); 7.49–7.52 (m, 2H, 2H of Ph); 7.62 (s, 1H, H–C(2)); 8.41 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4n′**: δ 0.94 (s, 9H, *t*-Bu); 3.69 (s, 3H, CO_2Me); 3.71–3.76 (m, 1H, Ha of *t*-BuOCH_2); 3.97 (dd, J=3.2; 10.0 Hz, 1H, Hb of *t*-BuOCH_2); 4.45 (dd, J=1.7; 3.3 Hz, 1H, H–C(5)); 5.32 (d, J=12.2 Hz, 1H, Ha of Cbz); 5.35 (d, J=12.4 Hz, 1H, Hb of Cbz); 7.35–7.44 (m, 3H, 3H of Ph); 7.45–7.48 (m, 2H, 2H of Ph); 9.08 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4n** and **4n′**: δ 26.9, 27.4, 51.2, 51.9, 59.3, 66.6, 68.3, 68.5, 69.0, 72.4, 72.7, 109.0, 111.6, 115.6, 123.3, 128.28, 128.32, 128.41, 128.52, 128.54, 128.55, 134.9, 135.1, 143.4, 149.0, 149.2, 161.3, 163.3, 164.2, 193.4; EI-HRMS: m/z=362.1590 (MH^+); $C_{19}H_{24}NO_6$ requires: m/z=362.1598 (MH^+).

*4.3.17. 1-tert-Butyl 3-methyl 4-hydroxy-5-(2-(methylthio)ethyl)-1H-pyrrole-1,3-dicarboxylate (**4o**) and 1-tert-butyl 3-methyl 5-(2-(methylthio)ethyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**4o′**). General procedure 2 (GP2)*: Prepared from **2o** (410 mg, 1.34 mmol), PhMe (V_1=10 mL), DMFDMA (0.594 mL, 4.02 mmol), T_1=75 °C, t_1=2 h, CC (EtOAc/petroleum ether=1:3). The product has an unpleasant smell! Yield: 300 g (71%) of yellow oil; **4o**/**4o′**=1:0.28 (in DMSO-d_6). ν_{max} 3410, 2978, 2951, 2918, 1738, 1693, 1626, 1580, 1533, 1459, 1437, 1390, 1370, 1276, 1246, 1188, 1142, 1109, 1066, 961, 847, 750 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) for **4o**: δ 1.56 (s, 9H, Boc); 2.08 (s, 3H, SMe); 2.54–2.62 (m, 2H, 2H of CH_2); 2.97–3.04 (m, 2H, 2H of CH_2); 3.74 (s, 3H, CO_2Me); 7.50 (s, 1H, H–C(2)); 8.12 (s, 1H, OH). ^1H NMR (500 MHz, DMSO-d_6) for **4o′**: δ 1.52 (s, 9H, Boc); 2.01 (s, 3H, SMe); 2.17–2.46 (m, 4H, 2×CH_2); 3.69 (s, 3H, CO_2Me); 4.40 (dd, J=3.5; 6.6 Hz, 1H, H–C(5)); 8.96 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6) for **4o** and **4o′**: δ 14.6, 14.63, 23.7, 27.3, 27.4, 27.5, 28.7, 32.9, 51.07, 51.12, 65.1, 84.3, 84.9, 108.7, 110.6, 116.3, 122.0, 141.7, 147.6, 148.2, 161.5, 163.5, 163.9, 194.3; EI-HRMS: m/z=316.1212 (MH^+); $C_{14}H_{22}NO_5S$ requires: m/z=316.1213 (MH^+).

*4.3.18. Methyl 5-((tert-butoxycarbonyl)amino)-2-((dimethylamino)methylene)-3-oxopentanoate (**3r**).*[45] *General procedure 2 (GP2)*: Prepared from **2r** (310 mg, 1.26 mmol), PhMe (V_1=7 mL), DMFDMA (0.524 mL, 3.55 mmol), T_1=75 °C, t_1=4 h, volatile components were evaporated in vacuo and the residue dried in high vacuum. Yield: 100% conversion; yellow oil. ^1H NMR (500 MHz, DMSO-d_6): δ 1.36 (s, 9H, Boc); 2.66 (t, J=7.2 Hz, 2H, 2H of CH_2); 2.73 (br s, 3H, NMe_2); 3.11 (q, J=7.0 Hz, 2H, 2H of CH_2); 3.19 (br s, 3H, NMe_2); 3.63 (s, 3H, CO_2Me); 6.63 (s, 1H, NH); 7.64 (s, 1H, CH).

4.4. (*E*)-1-*tert*-Butyl 3-methyl 4-hydroxy-5-((2-phenylhydrazono)methyl)-1*H*-pyrrole-1,3-dicarboxylate (7a)

To a solution of **5a** (403 mg, 1.36 mmol) in MeOH (10 mL) was added $PhNHNH_2$·HCl (**6**) (197 mg, 1.36 mmol) and the resulting reaction mixture was stirred at room temperature for 2 h and under reflux for 2 h. The reaction mixture was cooled to 0 °C and the resulting precipitate collected by filtration and washed with cold MeOH (1 mL, 0 °C). Yield: 80 mg (16%) of yellow-orange solid; mp 128–142 °C. ν_{max} 3283, 3166, 2977, 1754, 1682, 1593, 1541, 1496, 1450, 1434, 1371, 1330, 1302, 1259, 1245, 1199, 1152, 1076, 1061, 994, 979, 935, 912, 869, 852, 814, 745, 703, 689, 617 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.60 (s, 9H, Boc); 3.77 (s, 3H, CO_2Me); 6.77 (t, J=7.4 Hz, 1H of Ph); 6.88 (d, J=7.8 Hz, 2H, 2H of Ph); 7.24 (t, J=7.9 Hz, 2H, 2H of Ph); 7.60 (s, 1H, CH); 8.60 (s, 1H, H–C(2)); 9.95 (br s, 1H); 10.39 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.4, 51.3, 85.8, 108.1, 111.4, 112.6, 118.9, 124.0, 129.4, 133.7, 144.5, 146.3, 147.8, 162.3; EI-HRMS: m/z=360.1549 (MH^+); $C_{18}H_{22}N_3O_5$ requires: m/z=360.1554 (MH^+).

4.5. Synthesis of 1-*tert*-butyl 3-methyl 4-oxo-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (8r)

To a solution of **3r** (317 mg, 1.055 mmol) in anhydrous THF (5 mL) under argon was added *t*-BuOK (118 mg, 1.055 mmol) and the resulting reaction mixture was stirred under argon at room temperature for 30 min. Then HCl (1 mL, 1 M in H_2O) was added and the mixture was stirred for additional 5 min at room temperature. The reaction mixture was poured into EtOAc (150 mL) and washed

with NaCl (aq sat, 2×30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was purified by column chromatography [(1) EtOAc/petroleum ether=1:2 to elute the nonpolar impurities; (2) EtOAc/petroleum ether=2:1 to elute the product]. Fractions containing the product **6r** were combined and volatile components evaporated in vacuo. Yield: 140 mg (52%) of yellowish solid; mp 88.9–91.3 °C. $C_{12}H_{17}NO_5$ requires: C, 56.46; H, 6.71; N, 5.49. Found C, 56.26; H, 6.82; N, 5.53. ν_{max} 2977, 2949, 1736, 1683, 1587, 1454, 1438, 1396, 1369, 1345, 1316, 1269, 1247, 1210, 1193, 1141, 1047, 1037, 1004, 970, 887, 837, 793, 761, 690, 653 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.58 (s, 9H, Boc); 2.60–2.65 (t, J=7.4 Hz, 2H, 2H of CH_2); 3.81 (s, 3H, CO_2Me); 3.98–4.03 (t, J=7.4 Hz, 2H, 2H of CH_2); 8.81 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.4, 35.6, 42.2, 51.3, 84.4, 106.8, 150.3, 150.9, 163.9, 188.1; EI-HRMS: m/z=256.1190 (MH^+); $C_{12}H_{18}NO_5$ requires: m/z=256.1185 (MH^+).

4.6. Alkylation of 4-hydroxypyrrole derivatives—general procedure 3 (GP3)

To a solution of 4-hydroxypyrrole derivative (1 equiv) in anhydrous DMF (V_1) under argon were added RX (X=Br, I) and K_2CO_3 (2 equiv). The resulting reaction mixture was stirred at room temperature for t_1. Volatile components were evaporated in vacuo, the residue was dissolved/suspended in EtOAc (150 mL), and washed with NaCl (aq satd, 2×30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was purified/separated by column chromatography (CC). Fractions containing the isolated/separated product(s) were combined, respectively, and volatile components evaporated in vacuo.

*4.6.1. 1-tert-Butyl 3-methyl 5,5-dibenzyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**9g**). General procedure 3 (GP3)*: Prepared from **4g** (463 mg, 1.40 mmol), DMF (V_1=10 mL), BnBr (0.221 mL, 1.82 mmol), K_2CO_3 (390 mg, 2.80 mmol), 48 h, CC (EtOAc/petroleum ether=1:5). Yield: 434 mg (73%) of white solid; mp 124.5–128.0 °C. $C_{25}H_{27}NO_5$ requires: C, 71.24; H, 6.46; N, 3.32. Found C, 71.41; H, 6.18; N, 3.31. ν_{max} 3104, 3083, 3064, 3029, 3006, 2984, 2968, 2947, 2932, 2860, 1742, 1720, 1689, 1573, 1494, 1476, 1455, 1442, 1387, 1368, 1340, 1332, 1311, 1297, 1257, 1224, 1185, 1171, 1139, 1086, 1069, 1037, 1014, 982, 957, 917, 880, 854, 837, 808, 791, 767, 756, 726, 700, 638, 622 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.59 (br s, 9H, Boc); 3.26 (d, J=13.4 Hz, 2H, 2H of CH_2); 3.47 (m, 2H, 2H of CH_2); 3.52 (s, 3H, CO_2Me); 6.95 (d, J=5.6 Hz, 4H, 4H of Ph); 7.16–7.28 (m, 6H, 6H of Ph); 8.39 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.6, 41.2, 51.1, 76.7, 84.8, 111.3, 127.3, 128.3, 129.1, 134.0, 147.4, 160.5, 163.6, 196.6; EI-HRMS: m/z=422.1958 (MH^+); $C_{25}H_{28}NO_5$ requires: m/z=422.1962 (MH^+).

*4.6.2. 1-tert-Butyl 3-methyl 4-(benzyloxy)-5-(3-(((benzyloxy)carbonyl)amino)propyl)-1H-pyrrole-1,3-dicarboxylate (**10k**) and 1-tert-butyl 3-methyl 5-benzyl-5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**9k**). General procedure 3 (GP3)*: Prepared from **4k** (480 mg, 1.11 mmol), DMF (V_1=12 mL), BnBr (0.175 mL, 1.44 mmol), K_2CO_3 (307 mg, 2.22 mmol), 48 h, CC (EtOAc/petroleum ether=1:2).

*4.6.2.1. Compound **10k***. Elutes first from the column. Yield: 72 mg (12%) of yellowish oil. ν_{max} 3363, 2948, 2872, 1749, 1713, 1596, 1528, 1454, 1440, 1421, 1367, 1273, 1255, 1146, 1092, 987, 914, 847, 752, 733, 696 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.46–1.58 (m, 2H, 2H of CH_2); 1.56 (s, 9H, Boc); 2.60–2.68 (m, 2H, 2H of CH_2); 2.95 (q, J=6.7 Hz, 2H of CH_2); 3.76 (s, 3H, CO_2Me); 4.89 (s, 2H, CH_2); 4.99 (s, 2H, CH_2); 7.25 (d, J=5.6 Hz, 1H, NH); 7.27–7.40 (m, 8H, 8H of Ph); 7.41–7.47 (m, 2H, 2H of Ph); 7.63 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.4, 27.3, 29.8, 40.2, 51.3, 65.1, 76.1, 85.4, 110.6, 123.5, 125.0, 127.71, 127.74, 128.0, 128.29, 128.32, 128.5, 137.1, 137.2, 142.4, 147.9, 156.0, 162.6; EI-HRMS: m/z=523.2432 (MH^+); $C_{29}H_{35}N_2O_7$ requires: m/z=523.2439 (MH^+).

*4.6.2.2. Compound **9k***. Elutes second from the column. Yield: 280 mg (48%) of yellowish oil. ν_{max} 3366, 3031, 2976, 2950, 2933, 2872, 1711, 1578, 1523, 1496, 1440, 1391, 1370, 1282, 1224, 1199, 1138, 1072, 1040, 992, 852, 841, 760, 731, 696, 627 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.95–1.05 (m, 1H, Ha of CH_2); 1.06–1.16 (m, 1H, Hb of CH_2); 1.58 (s, 9H, Boc); 1.87 (dt, J=4.6; 12.8 Hz, 1H, Ha of CH_2); 2.17 (dt, J=4.3; 13.3 Hz, 1H, Hb of CH_2); 2.86–2.99 (m, 2H, 2H of CH_2); 3.05 (d, J=13.3 Hz, 1H, Ha of CH_2); 3.24 (d, J=13.4 Hz, 1H, Hb of CH_2); 3.60 (s, 3H, CO_2Me); 4.97 (d, J=12.5 Hz, 1H, Ha of CH_2); 5.01 (d, J=12.5 Hz, 1H, Hb of CH_2); 6.87–6.91 (m, 2H, 2H of Ph); 7.12–7.23 (m, 3H, 3H of Ph); 7.28–7.39 (m, 6H, 5H of Ph, NH); 8.76 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.4, 27.5, 33.3, 41.7, 51.1, 65.2, 75.8, 85.0, 111.0, 127.2, 127.7, 127.8, 128.2, 128.3, 129.0, 133.9, 137.2, 147.4, 156.1, 160.9, 164.0, 196.7; EI-HRMS: m/z=523.2434 (MH^+); $C_{29}H_{35}N_2O_7$ requires: m/z=523.2439 (MH^+).

*4.6.3. 1-tert-Butyl 3-methyl 5-benzyl-4-methoxy-1H-pyrrole-1,3-dicarboxylate (**12g**) and 1-tert-butyl 3-methyl 5-benzyl-5-methyl-4-oxo-4,5-dihydro-1H-pyrrole-1,3-dicarboxylate (**11g**). General procedure 3 (GP3)*: Prepared from **4g** (441 mg, 1.33 mmol), DMF (V_1=10 mL), MeI (0.335 mL, 5.32 mmol), K_2CO_3 (368 mg, 2.66 mmol), 24 h, CC (EtOAc/petroleum ether=1:5).

*4.6.3.1. Compound **12g***. Elutes first from the column. Yield: 83 mg (18%) of yellowish oil. ν_{max} 3159, 3085, 3063, 3029, 2981, 2937, 2837, 1744, 1720, 1599, 1530, 1495, 1455, 1436, 1366, 1332, 1275, 1256, 1191, 1144, 1112, 1071, 1012, 971, 926, 896, 846, 806, 754, 726, 698 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.34 (s, 9H, Boc); 3.70 (s, 3H, OMe); 3.77 (s, 3H, CO_2Me); 4.15 (s, 2H, CH_2); 7.01 (d, J=7.8 Hz, 2H, 2H of Ph); 7.14–7.19 (m, 1H, 1H of Ph); 7.26 (t, J=7.6 Hz, 2H, 2H of Ph); 7.68 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.0, 29.0, 51.23, 62.2, 85.3, 110.5, 122.2, 123.9, 125.9, 127.4, 128.3, 139.7, 145.3, 147.8, 162.4; EI-HRMS: m/z=346.1645 (MH^+); $C_{19}H_{24}NO_5$ requires: m/z=346.1649 (MH^+).

*4.6.3.2. Compound **11g***. Elutes second from the column. Yield: 250 mg (54%) of yellowish oil. ν_{max} 3088, 3064, 3031, 2979, 2950, 2935, 1712, 1577, 1496, 1477, 1452, 1438, 1385, 1369, 1298, 1283, 1225, 1195, 1143, 1097, 1074, 996, 945, 917, 898, 876, 854, 838, 794, 761, 729, 702, 690, 637, 609 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.50 (s, 3H, Me); 1.58 (s, 9H, Boc); 3.08 (d, J=13.5 Hz, 1H, Ha of CH_2); 3.29 (d, J=13.5 Hz, 1H, Hb of CH_2); 3.62 (s, 3H, CO_2Me); 6.88–6.92 (m, 2H, 2H of Ph); 7.16–7.24 (m, 3H, 3H of Ph); 8.68 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 21.9, 27.6, 41.2, 51.1, 72.5, 84.7, 109.4, 127.2, 128.2, 128.9, 134.5, 147.3, 161.2, 163.1, 197.0; EI-HRMS: m/z=346.1645 (MH^+); $C_{19}H_{24}NO_5$ requires: m/z=346.1649 (MH^+).

*4.6.4. 1-tert-Butyl 3-methyl 5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-methoxy-1H-pyrrole-1,3-dicarboxylate (**12k**). General procedure 3 (GP3)*: Prepared from **4k** (444 mg, 1.027 mmol), DMF (V_1=12 mL), MeI (0.194 mL, 3.081 mmol), K_2CO_3 (284 mg, 2.054 mmol), 48 h, CC (EtOAc/petroleum ether=1:3). Yield: 190 mg (41%) of yellowish oil. ν_{max} 3368, 2976, 2936, 2874, 1708, 1597, 1529, 1454, 1409, 1367, 1274, 1254, 1194, 1146, 1122, 1091, 1071, 1009, 847, 753, 697 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.56 (s, 9H, Boc); 1.58–1.64 (m, 2H, 2H of CH_2); 2.67–2.73 (m, 2H, 2H of CH_2); 2.97–3.03 (m, 2H, 2H of CH_2); 3.68 (s, 3H, OMe); 3.74 (s, 3H, CO_2Me); 5.01 (s, 2H, CH_2 of Cbz); 7.27–7.40 (m, 6H, 5H of Ph, NH); 7.59 (s, 1H, H–C(2)). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 28.0, 29.1, 39.9, 51.4, 62.7, 66.4, 85.2, 110.9, 124.29, 124.33, 128.0, 128.5, 136.9,

144.9, 148.4, 156.5, 163.5; EI-HRMS: m/z=447.2128 (MH^+); $C_{23}H_{31}N_2O_7$ requires: m/z=447.2126 (MH^+).

4.7. Reduction of 4-hydroxypyrrole derivatives—general procedure 4 (GP4)

To a solution of 4-hydroxypyrrole derivative (1 equiv) in MeOH (V_1) under argon at T_1 was added $NaBH_4$ (2 equiv, added portion wise) and the resulting mixture was vigorously stirred for t_1. The reaction was quenched with the addition of $NaHCO_3$ (aq satd, 15 mL). After stirring of the reaction mixture for an additional 10 min at room temperature, volatile components were evaporated in vacuo (mainly MeOH), the residue was dissolved/suspended in EtOAc (150 mL), and washed with NaCl (aq satd, 2×20 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was purified/separated by column chromatography (CC). Fractions containing the isolated/separated product(s) were combined, respectively, and volatile components evaporated in vacuo.

*4.7.1. rel-(3S,4S,5S)-1-tert-Butyl 3-methyl 5-benzyl-4-hydroxypyrrolidine-1,3-dicarboxylate (**13g**), rel-(3R,4S,5S)-1-tert-butyl 3-methyl 5-benzyl-4-hydroxypyrrolidine-1,3-dicarboxylate (**14g**), rel-(2S,3S,4R)-tert-butyl 2-benzyl-3-hydroxy-4-(hydroxymethyl)pyrrolidine-1-carboxylate (**15g**), and rel-(2S,3S,4S)-tert-butyl 2-benzyl-3-hydroxy-4-(hydroxymethyl)pyrrolidine-1-carboxylate (**16g**). General procedure 4 (GP4)*: Prepared from **4g** (516 mg, 1.56 mmol), MeOH (V_1=8 mL), $NaBH_4$ (118 mg, 3.12 mmol), T_1=rt, 1 h, ratio of products: **13g**/**14g**/**15g**/**16g**=1:0.67:0.67:0.73, CC [(1) EtOAc/petroleum ether=1:3 to elute/separate products **13g** and **14g**; (2) EtOAc/petroleum ether=3:1 to elute/separate products **15g** and **16g**].

*4.7.1.1. Compound **13g**.* Elutes first from the column. Yield: 100 mg (19%) of white solid; mp 85–90 °C. $C_{18}H_{25}NO_5$ requires: C, 64.46; H, 7.51; N, 4.18. Found C, 64.25; H, 7.84; N, 4.18. ν_{max} 3434, 2975, 1737, 1671, 1603, 1495, 1477, 1454, 1438, 1394, 1366, 1308, 1253, 1212, 1159, 1114, 1091, 1049, 1028, 982, 949, 924, 865, 834, 751, 699, 666, 607 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.44 (s, 9H, Boc); 2.78–3.02 (m, 1H, Ha of CH_2Ph); 3.05–3.20 (m, 1.5H, 0.5 Hb of CH_2Ph, H–C(3)); 3.31–3.41 (m, 0.5H, 0.5 Hb of CH_2Ph); 3.44–3.57 (m, 1H, Ha of H_2C(2)); 3.60 (s, 3H, CO_2Me); 3.60–3.76 (m, 1H, Hb of H_2–C(2)); 3.80 (dt, J=3.8; 10.6 Hz, 1H, H–C(5)); 4.09 (d, J=8.5 Hz, 1H, H–C(4)); 5.50 (d, J=20.5 Hz, 1H, OH); 7.16–7.23 (m, 1H, 1H of Ph); 7.24–7.34 (m, 4H, 4H of Ph) (two conformers). ^{13}C NMR (126 MHz, DMSO-d_6): δ 28.2, 32.23, 33.6, 45.9, 46.2, 47.8, 47.9, 51.4, 64.2, 64.4, 70.4, 71.1, 78.6, 79.0, 125.9, 128.2, 129.2, 139.4, 154.3, 170.3 (two conformers); EI-HRMS: m/z=236.1280 ($MH-Boc^+$); $C_{13}H_{18}NO_3$ requires: m/z=236.1281 ($MH-Boc^+$). HPLC analysis: CHIRALPAK AD-H, *n*-hexane/*i*-PrOH=93:7, flow rate: 1.0 mL/min, 25 °C, UV: λ=210 nm, t_1 (first enantiomer)=8.8 min, t_2 (second enantiomer)=9.9 min.

*4.7.1.2. Compound **14g**.* Elutes second from the column. Yield: 40 mg (7%) of white solid; mp 87–89 °C. $C_{18}H_{25}NO_5$ requires: C, 64.46; H, 7.51; N, 4.18. Found C, 64.26; H, 7.90; N, 4.18. ν_{max} 3416, 2975, 1735, 1664, 1495, 1477, 1454, 1394, 1366, 1337, 1251, 1201, 1164, 1127, 1081, 1028, 948, 858, 750, 700, 666 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.17 and 1.39 (s, 9H, Boc); 2.58–2.75 (m, 1H, 0.5H of H–C(3), 0.5H of CH_2Ph); 2.80–2.99 (m, 2H, 1.5H of CH_2Ph, 0.5H of H–C(3)); 3.23–3.46 (m, 2H, H_2C(2)); 3.55–3.68 (br s, 3H, CO_2Me); 3.90–4.02 (m, 1H, H–C(5)); 4.23–4.31 (m, 1H, H–C(4)), 5.67 (br s, 1H, OH), 7.13–7.31 (m, 5H, 5H of Ph) (two conformers). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.7, 28.1, 33.3, 34.1, 45.5, 46.3, 47.6, 48.7, 51.9, 60.9, 61.3, 72.6, 73.5, 78.4, 78.6, 125.8, 127.9, 128.0, 129.8, 139.3, 153.5, 172.6, 173.2 (two conformers). HPLC analysis: CHIRALPAK AD-H, *n*-hexane/*i*-PrOH=93:7, flow rate: 1.0 mL/min, 25 °C, UV: λ=210 nm, t_1 (first enantiomer)=9.5 min, t_2 (second enantiomer)=12.2 min; EI-HRMS: m/z=336.1795 (MH^+); $C_{18}H_{26}NO_5$ requires: m/z=336.1805 (MH^+).

*4.7.1.3. Compound **15g**.* Elutes third from the column. Yield: 90 mg (18%) of white solid; mp 128–129 °C. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56. Found C, 66.71; H, 8.50; N, 4.55. ν_{max} 3419, 3324, 2971, 2897, 1657, 1476, 1453, 1413, 1364, 1249, 1223, 1168, 1120, 1083, 1051, 1028, 997, 941, 917, 868, 826, 780, 769, 734, 699, 614 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.43 (s, 9H, Boc); 1.94–2.06 (m, 1H, H–C(3)); 2.77–3.19 (m, 2.5H, 1.5H of CH_2Ph, Ha of H_2C(2)); 3.31–3.45 (m, 1.5H, 0.5H of CH_2Ph, Ha of CH_2OH); 3.51–3.66 (m, 2H, Hb of H_2C(2), Hb of CH_2OH); 3.71 (dt, J=3.7; 10.3 Hz, 1H, H–C(5)); 3.79–3.91 (m, 1H, H–C(4)); 4.41 (t, J=5.2 Hz, 1H, CH_2OH); 4.79–4.94 (m, 1H, CHO*H*); 7.13–7.21 (m, 1H, 1H of Ph); 7.23–7.35 (m, 4H, 4H of Ph) (two conformers). ^{13}C NMR (126 MHz, DMSO-d_6): δ 28.2, 32.4, 33.8, 45.5, 48.3, 48.8, 58.9, 64.9, 69.3, 70.0, 78.3, 78.7, 125.8, 128.1, 129.2, 139.8, 154.5 (two conformers); EI-HRMS: m/z=208.1333 ($MH-Boc^+$); $C_{12}H_{18}NO_2$ requires: m/z=208.1332 ($MH-Boc^+$). HPLC analysis: CHIRALCEL OD-H, *n*-hexane/*i*-PrOH=90:10, flow rate: 1.0 mL/min, 25 °C, UV: λ=210 nm, t_1 (first enantiomer)=15.0 min, t_2 (second enantiomer)=30.0 min.

*4.7.1.4. Compound **16g**.* Elutes fourth from the column. Yield: 30 mg (6%) of white solid; mp 133–134 °C. $C_{17}H_{25}NO_4$ requires: C, 66.43; H, 8.20; N, 4.56. Found C, 66.58; H, 8.40; N, 4.56. ν_{max} 3351, 3320, 2932, 1644, 1604, 1495, 1474, 1416, 1367, 1335, 1308, 1244, 1166, 1139, 1104, 1080, 1050, 1008, 956, 879, 853, 821, 777, 741, 724, 694 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.17 and 1.39 (s, 9H, Boc); 1.84–1.96 and 1.97–2.10 (m, 1H, H–C(3)); 2.54–2.64 and 2.76–2.86 and 3.01–3.09 (m, 1H); 2.92–2.99 (m, 1H); 3.16 (deg t, J=8.9; 9.7 Hz, 1H); 3.25 (deg t, J=9.3; 10.0 Hz, 1H); 3.31–3.41 (m, 1H); 3.41–3.57 (m, 1H); 3.86–3.95 (m, 2H, H–C(4), H–C(5)); 4.54–4.64 (m, 1H, CH_2OH); 5.13–5.21 (m, 1H, CHO*H*); 7.12–7.31 (m, 5H, 5H of Ph) (two conformers). ^{13}C NMR (126 MHz, DMSO-d_6): δ 27.8, 28.2, 33.7, 34.6, 44.5, 45.6, 45.9, 46.8, 60.4, 60.9, 61.4, 70.4, 70.9, 77.9, 78.1, 125.6, 127.8, 127.9, 129.8, 129.9, 139.9, 153.7 (two conformers); EI-HRMS: m/z=208.1333 ($MH-Boc^+$); $C_{12}H_{18}NO_2$ requires: m/z=208.1332 ($MH-Boc^+$). HPLC analysis: CHIRALCEL OD-H, *n*-hexane/*i*-PrOH=93:7, flow rate: 1.0 mL/min, 25 °C, UV: λ=210 nm, t_1 (first enantiomer)=7.7 min, t_2 (second enantiomer)=9.0 min.

*4.7.2. rel-(3S,4S,5S)-1-tert-Butyl 3-methyl 5-benzyl-4-hydroxypyrrolidine-1,3-dicarboxylate (**13g**) and rel-(3R,4S,5S)-1-tert-butyl 3-methyl 5-benzyl-4-hydroxypyrrolidine-1,3-dicarboxylate (**14g**). General procedure 4 (GP4)*: Prepared from **4g** (216 mg, 0.65 mmol), MeOH (V_1=2 mL), $NaBH_4$ (49 mg, 1.30 mmol), T_1=−5 °C, 1 h, ratio of products: **13g**/**14g**=47:53, CC (EtOAc/petroleum ether=1:3 to separate products **13g** and **14g**).

*4.7.2.1. Compound **13g**.* Elutes first from the column. Yield: 73 mg (33%) of white solid.

*4.7.2.2. Compound **14g**.* Elutes second from the column. Yield: 80 mg (36%) of white solid.

*4.7.3. rel-(3S,4S,5S)-1-tert-Butyl 3-methyl 5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-hydroxypyrrolidine-1,3-dicarboxylate (**13k**) and rel-(3R,4S,5S)-1-tert-butyl 3-methyl 5-(3-(((benzyloxy)carbonyl)amino)propyl)-4-hydroxypyrrolidine-1,3-dicarboxylate (**14k**). General procedure 4 (GP4)*: Prepared from **4k** (925 mg, 2.14 mmol), MeOH (V_1=10 mL), $NaBH_4$ (162 mg, 4.28 mmol), T_1=−5 °C, 1 h, CC (EtOAc/petroleum ether=1:2).

*4.7.3.1. Diastereoisomers **13k** and **14k**.* Elute together, could not be separated by CC. Yield: 753 mg (80%) of colorless oil; **13k**/**14k**=1:1. ν_{max} 3352, 2972, 2952, 1689, 1672, 1528, 1476, 1454, 1398,

1366, 1309, 1245, 1212, 1164, 1130, 1025, 941, 912, 867, 773, 737, 697 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.29–1.64 (m, 4H); 1.38 (s, 9H, Boc); 2.86–3.13 (m, 3H); 3.35–3.54 (m, 2H); 3.57–3.70 (m, 1H); 3.61 (s, 1.5H, CO_2Me); 3.64 (s, 1.5H, CO_2Me); 4.23–4.28 (m, 0.5H, CH); 4.32 (br s, 0.5H, CH); 5.00 (s, 2H, CH_2 of Cbz); 5.32 (br s, 0.5H, OH); 5.50 (br s, 0.5H, OH); 7.20–7.39 (m, 6H, 5H of Ph, NH) (two conformers). ^{13}C NMR (126 MHz, DMSO-d_6): δ 24.3, 25.4, 26.1, 26.2, 26.7, 28.1, 39.8, 40.7, 45.6, 46.0, 47.8, 48.0, 48.7, 51.4, 51.9, 54.9, 59.1, 59.4, 62.2, 62.4, 65.07, 65.10, 70.9, 71.6, 72.9, 73.5, 78.4, 78.6, 78.7, 127.69, 127.73, 128.3, 137.31, 137.35, 153.8, 154.1, 156.07, 156.09, 170.3, 172.8, 173.1 (two conformers); EI-HRMS: m/z=437.2278 (MH^+); $C_{22}H_{33}N_2O_7$ requires: m/z=437.2282 (MH^+). HPLC analysis: CHIRALCEL OD-H, *n*-hexane/*i*-PrOH=90:10, flow rate: 1.0 mL/min, 25 °C, UV: λ=210 nm, t_1 (first isomer)=18.8 min, t_2 (second isomer)=22.6 min, t_3 (third isomer)=27.2 min, t_4 (fourth isomer)=29.4 min.

4.8. Synthesis of *rel*-(2*S*,3*S*,4*R*)-*tert*-butyl 2-benzyl-3-hydroxy-4-(hydroxymethyl)pyrrolidine-1-carboxylate (15g) and *rel*-(2*S*,3*S*,4*S*)-*tert*-butyl 2-benzyl-3-hydroxy-4-(hydroxymethyl) pyrrolidine-1-carboxylate (16g)

To a solution of **13g** or **14g** (30 mg, 0.09 mmol) in MeOH (2 mL) at 30 °C was added $NaBH_4$ (76 mg, 2 mmol) and the resulting reaction mixture was stirred at 30 °C for 1 h, followed by addition of $NaHCO_3$ (aq satd, 5 mL). The resulting mixture was stirred at rt for 0.5 h, followed by extraction with EtOAc (3×20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and volatile components evaporated in vacuo. The residue was purified by column chromatography (EtOAc/petroleum ether=3:1). Fractions containing the product **15g** (from **13g**) or **16g** (from **14g**) were combined and volatile components evaporated in vacuo.

*4.8.1. Compound **15g**.* Prepared from **13g**. Yield: 13 mg (47%) of white solid.

*4.8.2. Compound **16g**.* Prepared from **14g**. Yield: 11 mg (40%) of white solid.

4.9. Cyclization of enaminone intermediates with dinucleophiles—general procedure 5 (GP5)

To a solution of β-keto ester (1 equiv) in anhydrous CH_2Cl_2 or toluene (V_1) under Argon was added DMFDMA (1.1 equiv) and the resulting reaction mixture was stirred at room temperature till most of the starting β-keto ester **A** reacted into enaminone intermediate **B** judging by TLC-analysis (see Fig. 2 and the accompanying discussion). If the reaction is left for too long, the enaminone intermediate **B** cyclizes into pyrrole product **C**. Volatile components were evaporated in vacuo and the residue was dissolved in MeOH (V_2) followed by addition of dinucleophile hydrochloride (0.9 equiv) or dinucleophile (0.9 equiv) and HCl (0.9 equiv). Reactions with stable isolated enaminone **3i** were carried out in the same manner with the addition of 1 equiv of dinucleophile and HCl. The resulting reaction mixture was stirred for 30 min at room temperature, t_1 under reflux, and additional 12 h at room temperature. Volatile components were evaporated in vacuo and the residue was purified/separated by column chromatography (CC) and/or MPLC. Fractions containing the isolated/separated product(s) were combined, respectively, and volatile components evaporated in vacuo. Products that precipitated from the reaction mixture were collected by filtration and washed with cold MeOH (2 mL, 0 °C).

*4.9.1. (S)-Methyl 5-(1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)-1-phenyl-1H-pyrazole-4-carboxylate (**17h**). General procedure 5 (GP5)*: Prepared from **2h** (355 mg, 1.0 mmol), CH_2Cl_2 (V_1=2 mL), DMFDMA (0.162 mL, 1.1 mmol), MeOH (V_2=2 mL), $PhNHNH_2 \cdot HCl$ (**6**) (131 mg, 0.9 mmol), t_1=3 h, CC (EtOAc/petroleum ether=1:3). Yield: 53 mg (11%) of orange oil. $[\alpha]_D^{rt}$ +25.8 (*c* 0.59, CH_2Cl_2). ν_{max} 3380, 3063, 3030, 2951, 1697, 1597, 1548, 1499, 1453, 1437, 1415, 1375, 1336, 1265, 1242, 1226, 1183, 1154, 1101, 1076, 1039, 1020, 971, 942, 911, 878, 846, 808, 765, 733, 695 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.07 (dd, J=6.1; 13.1 Hz, 1H, Ha of CH_2); 3.16 (dd, J=10.1; 13.0 Hz, 1H, Hb of CH_2); 3.93 (s, 3H, CO_2Me); 5.02 (d, J=12.3 Hz, 1H, Ha of Cbz); 5.15 (dd, J=12.3 Hz, 1H, Hb of Cbz); 5.23–5.31 (m, 1H, NHC*H*); 6.71 (d, J=7.2 Hz, 2H, 2H of Ph); 6.92 (d, J=7.4 Hz, 2H, 2H of Ph); 7.03–7.10 (m, 2H, 2H of Ph); 7.11–7.16 (m, 1H, 1H of Ph); 7.20 (d, J=10.2 Hz, 1H, NH); 7.27–7.40 (m, 8H, Ph 8H of Ph); 8.02 (s, 1H, H–C(3)). ^{13}C NMR (126 MHz, $CDCl_3$): δ 41.2, 49.2, 52.0, 66.8, 111.7, 126.5, 126.8, 128.0, 128.1, 128.5, 128.6, 129.0, 129.2, 129.3, 136.3, 136.5, 138.0, 142.5, 147.4, 155.9, 165.0; EI-HRMS: m/z=456.1912 (MH^+); $C_{27}H_{26}N_3O_4$ requires: m/z=456.1918 (MH^+).

*4.9.2. (S)-Methyl 5-(1-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl)-1-phenyl-1H-pyrazole-4-carboxylate (**17i**). General procedure 5 (GP5)*: Prepared from **3i** (128 mg, 0.315 mmol), MeOH (V_2=2 mL), $PhNHNH_2 \cdot HCl$ (**6**) (46 mg, 0.315 mmol), t_1=3 h, CC (EtOAc/petroleum ether=1:3). Yield: 116 mg (81%) of white solid; mp 108–111 °C. $[\alpha]_D^{rt}$ +5.6 (*c* 0.09, CH_2Cl_2). $C_{27}H_{21}N_3O_4$ requires: C, 71.83; H, 4.69; N, 9.31. Found C, 71.91; H, 4.63; N, 9.11. ν_{max} 3062, 3030, 2950, 1776, 1710, 1597, 1546, 1500, 1467, 1454, 1436, 1416, 1380, 1330, 1261, 1227, 1192, 1174, 1125, 1085, 1071, 1031, 1004, 983, 967, 947, 921, 874, 846, 772, 714, 695, 639 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.71 (dd, J=7.3; 13.8 Hz, 1H, Ha of CH_2); 3.86 (s, 3H, CO_2Me); 3.99 (dd, J=9.0; 13.9 Hz, 1H, Hb of CH_2); 6.05 (dd, J=7.2; 9.0 Hz, 1H, CH); 7.05–7.19 (m, 7H, 7H of Arl); 7.18–7.33 (m, 3H, 3H of Arl); 7.59–7.69 (m, 4H, 4H of Arl); 8.06 (s, 1H, H–C(3)). ^{13}C NMR (126 MHz, $CDCl_3$): δ 36.9, 51.2, 51.8, 112.9, 123.2, 126.9, 127.4, 128.6, 129.0, 129.3, 129.4, 131.5, 134.0, 137.1, 139.1, 142.4, 144.5, 163.6, 167.8; EI-HRMS: m/z=452.1588 (MH^+); $C_{27}H_{22}N_3O_4$ requires: m/z=452.1605 (MH^+).

*4.9.3. (S)-Methyl 5-(12,12-dimethyl-3,10-dioxo-1-phenyl-2,11-dioxa-4,9-diazatridecan-8-yl)-1-phenyl-1H-pyrazole-4-carboxylate (**17k**). General procedure 5 (GP5)*: Prepared from **2k** (425 mg, 1.006 mmol), CH_2Cl_2 (V_1=5 mL), DMFDMA (0.164 mL, 1.107 mmol), MeOH (V_2=5 mL), $PhNHNH_2 \cdot HCl$ (**6**) (132 mg, 0.905 mmol), t_1=4 h, CC (EtOAc/petroleum ether=1:4). Yield: 250 mg (45%) of yellow oil. $[\alpha]_D^{rt}$ +19.0 (*c* 0.32, CH_2Cl_2). ν_{max} 3366, 2976, 2950, 2872, 1697, 1597, 1549, 1499, 1454, 1414, 1366, 1341, 1263, 1163, 1101, 1044, 1016, 971, 917, 868, 807, 766, 694 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.10–1.38 (m, 2H, 2H of CH_2); 1.33 (s, 9H, Boc); 1.65–1.74 (m, 1H, Ha of CH_2); 1.75–1.88 (m, 1H, Hb of CH_2); 2.79–2.97 (m, 2H, 2H of CH_2); 3.83 (s, 3H, CO_2Me); 4.75–4.86 (m, 1H, CH); 4.98 (s, 2H, CH_2 of Cbz); 6.78 (d, J=8.7 Hz, 1H, NH); 7.18 (br s, 1H, NH); 7.27–7.39 (m, 5H, 5H of Ph); 7.39–7.51 (m, 2H, 2H of Ph); 7.53–7.63 (m, 3H, 3H of Ph); 8.07 (s, 1H, H–C(3)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 26.2, 28.0, 31.4, 46.7, 51.8, 65.1, 78.7, 110.8, 126.4, 127.70, 127.75, 128.3, 129.4, 129.5, 137.3, 138.4, 142.0, 148.3, 154.7, 156.0, 163.8; EI-HRMS: m/z=523.2546 (MH^+); $C_{28}H_{35}N_4O_6$ requires: m/z=523.2551 (MH^+).

*4.9.4. (S)-Methyl 5-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-9-yl)-1-phenyl-1H-pyrazole-4-carboxylate (**17l**). General procedure 5 (GP5)*: Prepared from **2l** (436 mg, 1.0 mmol), CH_2Cl_2 (V_1=2 mL), DMFDMA (0.162 mL, 1.1 mmol), MeOH (V_2=2 mL), $PhNHNH_2 \cdot HCl$ (**6**) (131 mg, 0.9 mmol), t_1=4 h, CC (EtOAc/petroleum ether=1:2). Yield: 274 mg (51%) of white solid; mp 143–145 °C. $[\alpha]_D^{rt}$ −23.0 (*c* 0.27, CH_2Cl_2). $C_{29}H_{36}N_4O_6$ requires: C, 64.91; H, 6.76; N, 10.44. Found C, 64.73; H, 6.64; N, 10.33. ν_{max} 3385, 3299, 3108, 3070, 3036, 3001, 2981, 2930, 2904, 2866, 2847, 1711, 1593, 1546, 1494, 1470, 1453, 1434, 1413, 1388, 1367, 1339, 1315, 1286, 1262, 1238, 1227, 1167, 1142, 1124, 1101, 1089, 1069, 1056, 1041, 1020, 989, 974, 946, 925, 912, 891, 872, 863, 812, 800, 785, 766, 756,

741, 706, 695, 657, 626 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.96–1.08 (m, 1H, Ha of CH_2); 1.09–1.39 (m, 3H, 3H of CH_2); 1.33 (s, 9H, Boc); 1.64–1.75 (m, 1H, Ha of CH_2); 1.75–1.85 (m, 1H, Hb of CH_2); 2.82–2.96 (m, 2H, 2H of CH_2); 3.84 (s, 3H, CO_2Me); 4.82 (dt, J=5.4; 8.6 Hz, 1H, CH); 5.00 (s, 2H, CH_2 of Cbz); 6.76 (d, J=8.8 Hz, 1H, NH); 7.18 (t, J=5.6 Hz, 1H, NH); 7.29–7.40 (m, 5H, 5H of Ph); 7.41–7.53 (m, 2H, 2H of Ph); 7.54–7.63 (m, 3H, 3H of Ph); 8.07 (s, 1H, H–C(3)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 22.9, 28.0, 28.7, 33.5, 39.8, 46.6, 51.8, 65.1, 78.7, 110.8, 126.4, 127.7, 127.8, 128.3, 129.39, 129.45, 137.3, 138.4, 142.0, 148.5, 154.7, 156.1, 163.9; EI-HRMS: m/z=537.2707 (MH^+); $C_{29}H_{37}N_4O_6$ requires: m/z=537.2708 (MH^+).

*4.9.5. Methyl 5-(1-(2-(((benzyloxy)carbonyl)amino)acetamido)-2-phenylethyl)-1-phenyl-1H-pyrazole-4-carboxylate (**17p**). General procedure 5 (GP5)*: Prepared from **2p** (1.63 g, 3.95 mmol), CH_2Cl_2 (V_1=20 mL), DMFDMA (0.641 mL, 4.345 mmol), MeOH (V_2=30 mL), $PhNHNH_2 \cdot HCl$ (**6**) (514 mg, 3.555 mmol), t_1=1 h, CC [(1) EtOAc/petroleum ether=1:2 to elute the nonpolar impurities; (2) EtOAc/petroleum ether=1:1 to elute the product]. Yield: 1.0 g (49%) of orange semisolid. ν_{max} 3338, 3030, 2951, 1699, 1676, 1598, 1547, 1498, 1454, 1437, 1415, 1375, 1347, 1264, 1230, 1153, 1112, 1093, 1046, 1029, 1002, 971, 940, 918, 882, 808, 785, 738, 693, 659 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.03 (dd, J=6.8; 13.2 Hz, 1H, Ha of CH_2); 3.21 (dd, J=8.9; 13.2 Hz, 1H, Hb of CH_2); 3.54 (dd, J=6.0; 17.1 Hz, 1H, Ha of CH_2); 3.63 (dd, J=6.3; 16.8 Hz, 1H, Hb of CH_2); 3.86 (s, 3H, CO_2Me); 5.04 (d, J=12.5 Hz, 1H, Ha of CH_2); 5.09 (d, J=12.6 Hz, 1H, Hb of CH_2); 5.23 (q, J=8.4 Hz, 1H, CH); 6.76–6.82 (m, 2H, 2H of Ph); 6.97–7.01 (m, 2H, 2H of Ph); 7.10–7.27 (m, 4H, 4H of Ph); 7.29–7.44 (m, 6H, 6H of Ph); 7.45–7.51 (m, 1H, 1H of Ph); 7.65 (t, J=6.1 Hz, 1H, NH); 8.07 (s, 1H, H–C(3)); 8.39 (d, J=8.5 Hz, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 39.3, 43.7, 46.8, 51.8, 65.7, 111.3, 126.3, 126.6, 127.7, 127.8, 128.3, 128.4, 128.9, 129.0, 129.2, 136.5, 136.9, 137.9, 142.0, 146.7, 156.5, 163.7, 168.6; EI-HRMS: m/z=513.2127 (MH^+); $C_{29}H_{29}N_4O_5$ requires: m/z=513.2132 (MH^+).

*4.9.6. (S)-Dimethyl 7-(1-(1,3-dioxoisoindolin-2-yl)-2-phenylethyl) pyrazolo[1,5-a]pyrimidine-2,6-dicarboxylate (**19i**). General procedure 5 (GP5)*: Prepared from **3i** (338 mg, 0.83 mmol), MeOH (V_2=10 mL), methyl 3-amino-1*H*-pyrazole-4-carboxylate (**18**) (118 mg, 0.83 mmol), HCl (37% in H_2O, three drops, ca. 0.07 mL), t_1=18 h, CC (EtOAc/petroleum ether=1:2). Yield: 130 mg (32%) of white solid; mp 68–78 °C. $[\alpha]_D^{rt}$ +11.1 (c 0.09, CH_2Cl_2). ν_{max} 2951, 1777, 1709, 1607, 1560, 1517, 1467, 1454, 1433, 1369, 1328, 1278, 1199, 1173, 1155, 1121, 1090, 1011, 987, 962, 926, 910, 872, 790, 718, 698, 672, 639 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 3H, CO_2Me); 3.96 (s, 3H, CO_2Me); 3.98 (dd, J=7.7; 14.1 Hz, 1H, Ha of CH_2); 4.50 (dd, J=8.6; 13.9 Hz, 1H, Hb of CH_2); 7.14–7.24 (m, 6H, 5H of Ph, CH); 7.64–7.69 (m, 2H, 2H of Arl); 7.73–7.77 (m, 2H, 2H of Arl); 8.63 (s, 1H, CH); 9.08 (s, 1H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.3, 52.0, 53.0, 53.3, 103.6, 113.7, 123.3, 127.1, 128.4, 129.3, 131.5, 134.2, 136.4, 148.4, 149.1, 149.8, 152.9, 162.5, 164.1, 168.2; EI-HRMS: m/z=485.1454 (MH^+); $C_{26}H_{21}N_4O_6$ requires: m/z=485.1456 (MH^+).

*4.9.7. (S)-Dimethyl 7-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-9-yl)pyrazolo[1,5-a]pyrimidine-2,6-dicarboxylate (**19l**). General procedure 5 (GP5)*: Prepared from **2l** (524 mg, 1.2 mmol), CH_2Cl_2 (V_1=2 mL), DMFDMA (0.192 mL, 1.3 mmol), MeOH (V_2=3 mL), 3-amino-1*H*-pyrazole-4-carboxylate (**18**) (152 mg, 1.08 mmol), HCl (0.540 mL, 1.08 mmol, 2 M in EtOAc), t_1=4 h, CC (EtOAc) then MPLC (EtOAc/petroleum ether=1:2). Yield: 73 mg (10%) of orange oil. $[\alpha]_D^{rt}$ +16.4 (c 0.42, CH_2Cl_2). ν_{max} 3369, 3065, 3032, 2976, 2951, 2866, 1704, 1608, 1519, 1495, 1455, 1435, 1391, 1367, 1283, 1241, 1215, 1203, 1158, 1099, 1044, 1013, 985, 934, 910, 861, 824, 794, 775, 747, 697, 678, 637 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 9H, Boc); 1.38–1.53 (m, 1H, 1H of CH_2); 1.53–1.71 (m, 3H, 3H of CH_2); 1.87–1.99 (m, 1H, Ha of CH_2); 2.19–2.31 (m, 1H, Hb of CH_2); 3.14–3.26 (m, 2H, 2H of CH_2); 3.98 (s, 3H, CO_2Me); 4.02 (s, 3H, CO_2Me); 4.89–4.96 (m, 1H, CH); 5.08 (s, 2H, CH_2 of Cbz); 6.40–6.64 (m, 2H, 2×NH); 7.29–7.38 (m, 5H, 5H of Ph); 8.67 (s, 1H, CH); 9.19 (s, 1H, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.0, 28.3, 29.1, 31.9, 40.8, 48.8, 52.0, 53.4, 66.6, 80.2, 103.7, 111.7, 128.1, 128.2, 128.5, 136.7, 148.4, 148.9, 153.7, 155.4, 156.5, 162.5, 164.1; EI-HRMS: m/z=570.2552 (MH^+); $C_{28}H_{36}N_5O_8$ requires: m/z=570.2558 (MH^+).

*4.9.8. (S)-Methyl 4-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-9-yl)-2-phenylpyrimidine-5-carboxylate (**22l**). General procedure 5 (GP5)*: Prepared from **2l** (524 mg, 1.2 mmol), CH_2Cl_2 (V_1=2 mL), DMFDMA (0.192 mL, 1.3 mmol), MeOH (V_2=3 mL), benzamidine hydrochloride (**20**) (173 mg, 1.10 mmol), t_1=4 h, precipitates from the reaction mixture. Yield: 95 mg (17%) of white solid; mp 153.5–155.1 °C. $[\alpha]_D^{rt}$ −50.0 (c 0.33, CH_2Cl_2). $C_{30}H_{36}N_4O_6$ requires: C, 65.68; H, 6.61; N, 10.21. Found C, 65.92; H, 6.52; N, 10.22. ν_{max} 3357, 3091, 3068, 3036, 2988, 2970, 2950, 2920, 2861, 1729, 1683, 1571, 1525, 1456, 1425, 1383, 1364, 1343, 1325, 1308, 1268, 1247, 1213, 1167, 1149, 1107, 1090, 1073, 1050, 1032, 1005, 988, 958, 918, 880, 857, 843, 827, 814, 778, 766, 754, 705, 692, 678, 647, 623 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.32 (s, 9H, Boc); 1.34–1.54 (m, 4H, 4H of CH_2); 1.62–1.75 (m, 2H, 2H of CH_2); 2.94–3.06 (m, 2H, 2H of CH_2); 3.92 (s, 3H, CO_2Me); 5.00 (s, 2H, CH_2 of Cbz); 5.35 (dt, J=5.6; 8.1 Hz, 1H, CH); 7.23–7.42 (m, 7H, 7H of Ph); 7.54–7.63 (m, 3H, 3H of Ph); 8.52–8.59 (m, 2H, 2×NH); 9.19 (s, 1H, H–C(5)). ^{13}C NMR (126 MHz, DMSO-d_6): δ 23.4, 27.7, 28.2, 29.1, 33.7, 40.1, 52.7, 52.8, 65.1, 78.0, 119.8, 127.7, 128.3, 128.6, 128.8, 131.9, 136.2, 137.3, 155.7, 156.1, 159.3, 164.6, 164.7, 171.9; EI-HRMS: m/z=549.2703 (MH^+); $C_{30}H_{37}N_4O_6$ requires: m/z=549.2708 (MH^+).

*4.9.9. (S)-Methyl 7-(13,13-dimethyl-3,11-dioxo-1-phenyl-2,12-dioxa-4,10-diazatetradecan-9-yl)-2-(methylthio)-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (**23l**). General procedure 5 (GP5)*: Prepared from **2l** (524 mg, 1.2 mmol), CH_2Cl_2 (V_1=2 mL), DMFDMA (0.192 mL, 1.3 mmol), MeOH (V_2=3 mL), 5-(methylthio)-1*H*-1,2,4-triazol-3-amine (**21**) (140 mg, 1.08 mmol), HCl (0.540 mL, 1.08 mmol, 2 M in EtOAc), t_1=4 h, CC (EtOAc) then MPLC (EtOAc/petroleum ether=1:2). Yield: 66 mg (9%) of orange oil. $[\alpha]_D^{rt}$ +1.7 (c 0.37, CH_2Cl_2). ν_{max} 3341, 3090, 3065, 3033, 2977, 2933, 2868, 1709, 1634, 1597, 1497, 1455, 1435, 1366, 1315, 1277, 1237, 1202, 1158, 1093, 1044, 1003, 916, 860, 811, 794, 737, 698, 677, 631, 606 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 0.99–1.13 (m, 1H, 1H of CH_2); 1.25–1.52 (m, 2H, 2H of CH_2); 1.29 (s, 9H, Boc); 1.50–1.64 (m, 1H, 1H of CH_2); 1.82–1.93 (m, 1H, 1H of CH_2); 2.05–2.18 (m, 1H, 1H of CH_2); 2.72 (s, 3H, SMe); 3.01 (dd, J=6.5; 12.7 Hz, 2H, 2H of CH_2); 3.94 (s, 3H, CO_2Me); 5.01 (s, 2H, CH_2 of Cbz); 5.67 (s, 1H, CH); 7.27 (t, J=5.8 Hz, 1H, NH); 7.29–7.39 (m, 5H, 5H of Ph); 7.4 (br d, J=5.7 Hz, 1H, NH); 9.01 (s, 1H, CH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 13.4, 23.1, 27.7, 28.0, 28.9, 29.9, 39.8, 53.2, 65.1, 78.8, 112.7, 127.8, 128.3, 137.3, 152.2, 154.8, 155.1, 155.9, 156.1, 164.4, 169.1; EI-HRMS: m/z=559.2313 (MH^+); $C_{26}H_{35}N_6O_6S$ requires: m/z=559.2333 (MH^+).

4.10. Single crystal X-ray structure analysis for compounds 7a, 8r, 9g, 13g, 14g, and 17i

Single crystal diffraction data for compounds **8r**, **13g**, **14g**, and **17i** have been collected on an Agilent SuperNova dual source diffractometer with an Atlas detector at room temperature with Mo Kα radiation (0.71073 Å) for **8r** and **17i** and Cu Kα radiation (1.54184 Å) for **13g** and **14g**, respectively. These data were processed using CrysAlis PRO software.[66] Single crystal diffraction data for compounds **7a** and **9g**, have been collected on a Nonius Kappa CCD diffractometer at room temperature with Mo Kα radiation (0.71073 Å) and graphite monochromator using the Nonius Collect

Software.[67] These reflection data were processed using DENZO software.[68] All structures were solved by direct methods, using SIR97.[69] A full-matrix least-squares refinement on F^2 was employed with anisotropic displacement parameters for all non-hydrogen atoms. H atoms were placed at calculated positions and treated as riding. SHELXL97 software[70] was used for structure refinement and interpretation. Drawings of the structures were produced using ORTEP-3.[71] Structural and other crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 954147–CCDC 954152, for **7a**, **8r**, **9g**, **13g**, **14g**, and **17i**, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra of the products and HPLC data are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.008. These data include MOL files and InChiKeys of the most important compounds described in this article.

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