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Convenient synthesis of 4-*tert*-butyl 2-ethyl 3-amino-1-benzyl-5-dialkylamino-1*H*-pyrrole-2,4-dicarboxylate derivatives

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ABSTRACT

Optimization details and limitations of a novel synthetic method of 4-*tert*-butyl 2-ethyl 3-amino-1-benzyl-5-dialkylamino-1*H*-pyrrole-2,4-dicarboxylate derivatives are herein disclosed. This synthesis consists of four steps that include a highly selective cyclization, and can be carried out from starting materials to target compounds without column chromatography purification. The high selectivity is controlled by lithium coordination and steric hindrance caused by *tert*-butyl ester.

1. Introduction

Dipeptidyl peptidase IV (DPP-4) inhibitors have recently been the focus of new treatment for type 2 diabetes.[1] DPP-4 is a serine protease distributed throughout the body, and is known to cleave a variety of peptides and modulate their biological activity. One of the peptides cleaved by DPP-4 is Glucagon-like peptide 1, which plays an important role in maintaining normal blood glucose level.[2,3] Based on this mechanism of action, a number of DPP-4 inhibitors have already been approved for the treatment of diabetes, while others are under clinical or preclinical investigation.[4–7] We have previously reported a series of new chemotype DPP-4 inhibitors, including the pyrolo[3,2-*d*]pyrimidine structure **1** and the deazahypoxanthine structure **2** (Fig. 1). These compounds showed potent in vitro DPP-4 inhibitory activity, good pharmacokinetic profile, and considerable in vivo efficacy.[8] To prepare structures **1** and **2**, we have shown that the α-amino pyrrole derivative **3** is an important synthetic intermediate.

Efficient methods to make α-amino pyrrole structures have rarely been reported. Indeed, it is difficult to introduce an amine at the α-position of the pyrrole by traditional methods, such as Knorr pyrrole synthesis.[9] Conventionally, pyrroles are synthesized by cyclodehydration between primary amines and 1,4-dicarbonyl compounds or α-aminoketones and β-ketoesters. However, using amide derivatives instead of 1,4-dicarbonyl compounds requires a microwave reaction,[10] and the use of diaminoketone derivatives

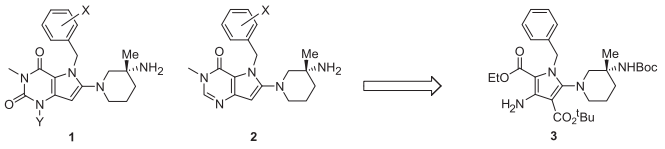

Fig. 1. Structures of new chemotype DPP-4 inhibitors.

instead of α-aminoketones has never been reported. Other reported methods for the preparation of α-amino pyrrole derivatives are difficult to apply to our intermediate **3** due to starting materials and products limitations.[11] Although amination of α-bromo pyrrole has been reported as an alternative method to prepare α-amino pyrrole derivatives,[12] our attempt to use amination of α-bromo pyrrolo[3,2-*d*]pyrimidine in the synthesis of compound **1** resulted in no reaction or desorption of the bromo. Under these circumstances, we tried to look for a new way to make the target pyrrole compound **3**, and could produce it by selective cyclization, as disclosed briefly in our previous work.[8] In that report, compound **3** was synthesized in moderate yield in a step-by-step reaction, although the scope and limitations of this reaction have not been investigated. Preparation of DPP-4 inhibitors from intermediate **3** included elimination of protecting benzyl and benzylation steps. These steps needed harsh hydrogenation conditions, gave low yields, and were consequently considered unnecessary manipulations. As it was imperative to prepare appropriate pyrrole derivatives for the synthesis of DPP-4 inhibitors, a more convenient method, and its scope and limitations were required. Here, we report in details our optimizations of a novel method for preparation of appropriate pyrrole derivatives. In addition, we show an improved method, which can be carried

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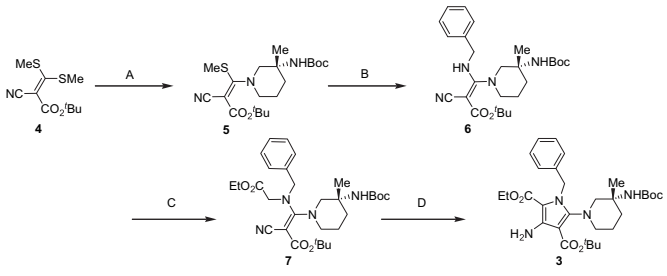
out from starting material to target pyrroles without column chromatography, and its scope and limitations. Finally, as this novel synthetic method includes a highly selective cyclization, we consider here the effects of *tert*-butyl ester and lithium coordination on this cyclization.

2. Optimization of reaction conditions

As shown in Scheme 1, the synthetic method for the preparation of pyrrole derivatives consists of four steps. Our goal was to carry out the synthesis from starting materials to the target pyrroles without column chromatography purification. First, details of the optimization of each step (A–D) are given below.



Scheme 1. Synthetic route to the intermediate **3**.

The reaction from **4** to **5** (A) proceeded smoothly at 50 °C in various solvents without the use of a base and gave a quantitative yield. To reduce the number of steps involved, we attempted the reaction between the intermediate **5** and *N*-benzyl glycine ethyl ester to make **7** directly. Unfortunately, the reaction did not proceed even under various conditions, i.e. different bases, solvents, and temperatures. Therefore, the conditions of the reaction from **5** to **6** (B) were investigated (Table 1).

Table 1
Reaction conditions for the second step (**5**–**6**) (B)

Entry	Base	Solvent	Temp °C	Yield[a] (%)
1	—	EtOH	50	—
2	—	EtOH	80	—
3	K_2CO_3 (1.5 equiv)	EtOH	50	Trace
4	K_2CO_3 (1.5 equiv)	DMF	50	37
5	DBU (1.5 equiv)	CH_3CN	50	69
6	Et_3N (1.5 equiv)	CH_3CN	50	Trace
7	DBU (2.0 equiv)	CH_3CN	50	76 (66)[b]
8	DBU (1.5 equiv)	Dioxane	50	42
9	DBU (2.0 equiv)	CH_3CN	80[c]	72[b]

[a] LC yield. All reactions were performed for 8 h.
[b] Isolated yield.
[c] Reaction was performed for 5 h.

In the absence of a base, the second step (B) did not proceed at 50 °C or 80 °C (entries 1 and 2). With potassium carbonate, only a trace amount of **6** was detected by LC/MS (entry 3). At the same time, it was revealed that the use of EtOH was not appropriate for this step due to production of a by-product obtained by reaction between **5** and the ethoxide, which displaces the methylthiol. Using DMF instead of EtOH gave the target molecule in low yield (entry 4), but the use of K_2CO_3 in other solvents, such as toluene, THF and CH_3CN, did not work well (data not shown). These findings suggest that this step needs a base, however, inorganic bases are usually inefficient in low polar solvents, such as those described above. Therefore, we focused our search on organic bases. The use of 1,8-diazabicyclo[5,4,0]undeca-7-ene (DBU) in CH_3CN gave **6** in good yield, but Et_3N afforded only a trace amount of the target product (entries 5 and 6). As for DBU equivalent, 2.0 equiv gave the best yield (entries 5 and 7). When more than 2.0 equiv DBU was used, no improvement was observed (data not shown). Regarding the solvent, CH_3CN was the most suitable (entries 5 and 8). Finally, investigation of the reaction temperature and time indicated that 80 °C and 5 h are the most suitable conditions (entry 9).

As alkylation of **6** to obtain **7** (C) proceeded smoothly under a set of 1.2 equiv of K_2CO_3 and 1.1 equiv of ethyl bromoacetate in DMF at 50 °C, conditions of the selective cyclization from **7** to **3** (D) were investigated. The most important step of this new method is this selective cyclization, which occurs between the generated carbanion at the α-position of the ethyl ester and the nitril. A similar selective cyclization to produce pyrimidine structures by reaction of amidines with an ethyl ester or nitril has already been reported in the literature.[13] Its selectivity was controlled by a combination of reagents and solvents, i.e., NaOEt/EtOH, *p*-TSA/benzene or HCl/dioxane. However, in the case of our compound strong acids can cleave the *tert*-butoxycarbonyl (Boc) protection and *tert*-butyl ester at C3-position of the pyrrole. Therefore, we decided to search for other conditions using any bases to control selectivity in our reaction (Table 2).

Table 2
Reaction conditions for cyclization (**7**–**3**) (D)

Entry	Base	Solvent	Temp °C	Yield[a] (%)
1[b]	K_2CO_3 (1.2 equiv)	DMF	50/120	—
2[b]	NaH (2.0 equiv)	DMF	50/120	—
3[b]	*t*-BuOK (1.2 equiv)	THF	50	Trace
4[b]	*t*-BuOK (1.2 equiv)	*t*-BuOH	50	14
5[b]	*t*-BuONa (1.2 equiv)	*t*-BuOH	50	21
6[c]	*t*-BuOLi[d] (1.2 equiv)	*t*-BuOH	50	32
7[c]	*t*-BuOLi[d] (1.2 equiv)	CH_3CN	30	64
8[c]	*t*-BuOLi[d] (2.0 equiv)	CH_3CN	30	72

[a] Isolated yield.
[b] Reaction was conducted at 1.0 mmol scale.
[c] Reaction was conducted at 5.0 mmol scale.
[d] Reagent was generated in situ from $LiNH_2$ and *t*-BuOH.

The use of K_2CO_3 and NaH was not effective in DMF at 50 °C and 120 °C (entries 1 and 2, respectively). Other bases, such as KHMDS, gave undesired products or no products (data not shown). On the other hand, the use of potassium *tert*-butoxide produced a trace amount of the target **3** as indicated by LC/MS (entry 3). When the reaction was conducted in *tert*-butanol, the target pyrrole **3** was obtained in low yield (entry 4). To examine the effects of various alkoxides on the reaction, sodium *tert*-butoxide and lithium *tert*-butoxide, which was generated in situ from lithium amide and *tert*-butanol, were used. Both alkoxides gave even better results than potassium *tert*-butoxide (entries 5 and 6).The use of other solvents with *tert*-butanol improved the yield, and the combination of CH_3CN and *tert*-butanol afforded the best result (entry 7). In addition, it was possible to reduce the reaction temperature from 50 °C to 30 °C (entry 7). Finally, investigation into the base equivalent revealed 2.0 equiv of $LiNH_2$ as the most appropriate (entry 8). As for by-products, the reaction gave a *tert*-butyl ester instead of ethyl ester at the 2-position of the pyrrole, which could be separated by column chromatography, with a yield less than 5% compared to the target product **3**.

Based on the findings above, we tried to examine the continuous reactions from step A to step D without purification. Unfortunately, except for the first step, all other steps of the reaction needed to be modified. In the second step (B), the reaction proceeded slowly, and finally 10 h was needed to consume **5** completely. As for the alkylation step (C), the remaining benzylamine used in the second step seemed to prevent the reaction from completion probably due to reaction of the benzylamine with ethyl bromacetate. Finally, 3.0 equiv of K_2CO_3 and 1.3 equiv of ethyl bromacetate were necessary for the smooth progression of this step. Regarding the cyclization step (D), the reaction was stopped under the optimum

conditions, (entry 8, Table 2), probably due to generation of by-products from the former reactions. Therefore, the appropriate amount of *t*-BuOLi was investigated, and 2.5 equiv of $LiNH_2$ was found to be necessary. Based on these results, we explored the scope and limitations of this modified synthesis.

3. Scope and limitations

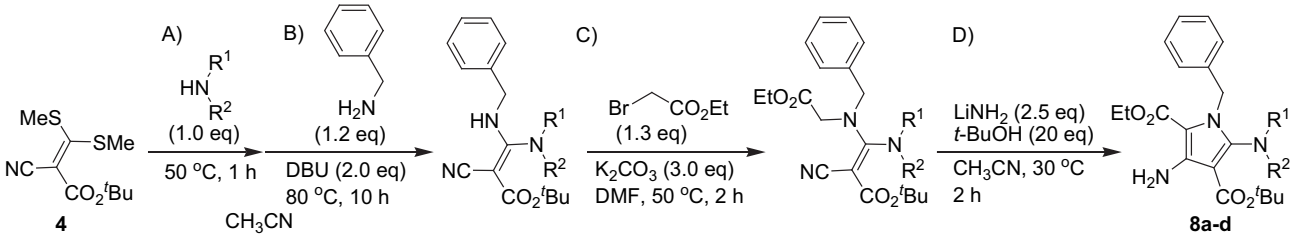
As shown in Table 3, we first investigated the R^1R^2 limitation in the first step (A). A benzylamine was selected as reagent in the second step (B), and the use of a secondary amine was examined. Cycloalkylamines were preferable for this step, and *N*-methylbenzylamine was also accepted (entries 1–4). However, other alkylamines could not be used (entries 5–7). *N*-Ethylbutylamine afforded the intermediate in the second step (B), but in the third step (C) the reaction did not proceed to completion, and gave a complex mixture (entry 5). What prevented the reaction from completion in the third step (C) is not clear. However, when a dipropylamine was used as R^1R^2NH, even the first step (A) did not proceed (entry 6). Among a series of *N*-methylalkylamines, *N*-methylcyclohexylamine was also inappropriate (entry 7). These results suggest that R^1R^2 steric hindrance has an impact on the first step (A) and that cycloalkylamines and *N*-methylalkylamines are suitable.

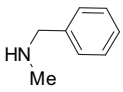
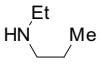
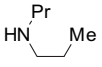
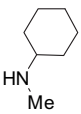
To explore limitations of the primary amines (Z-NH_2) in the second step (B), a piperidine was chosen as R^1R^2NH, and the use of primary amines was investigated (Table 4). A benzylamine was acceptable, but α-methyl benzylamine was not appropriate (entries 1 and 2). When a cyclohexylmethylamine or a cyclohexylamine was used, the desired intermediate was obtained in the second step (B). However, the third step (C) did not proceed to completion (entry 3). A phenetylamine gave the same result (entry 4), and the use of aniline prevented progression even of the second step (B) (entry 5). These results suggest that steric hindrance around NH_2 and basicity of the reagents are important in the second step (B) and that benzylamines are appropriate as primary amines (Z-NH_2).

The results described above led us to investigate the scope of substituents of R^1R^2NH and R^3-$PhCH_2NH_2$ (Table 5). The modified synthesis gave almost the same yield as the basic step-by-step reaction (entry 1). A number of substituents of R^1R^2NH and R^3 were accepted in this synthetic method. An ester substituent was tolerated under basic conditions of cyclization (D). However, there was a significant difference between R^1R^2 and R^3. An ethyl ester for R^1R^2 gave a good yield, but a methyl ester for R^3 afforded modest yield (entries 3 and 8). When ethyl isonipecotate was used in the first step (A), no by-products were obtained in the whole step (entry 3). However, in the cyclization step (D), the use of methyl (4-aminomethyl)benzoate for R^3-$PhCH_2NH_2$ produced by-products, which were difficult to isolate by SiO_2-column chromatography due to the presence of other close by-products.

LC/MS analysis suggested that one of the by-products was an ester exchange product, and ester exchange was occurred at the methyl ester of R^3. While a series of carbamates were accepted, amines afforded complex mixtures in the third step (C) (entries 1, 4, 6, and 9). The reason for this limitation was assumed to be reaction

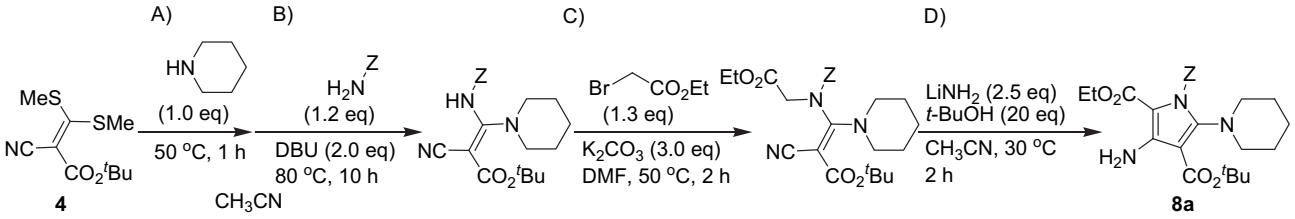
Table 3
Limitations of R^1R^2 in the first step (A)

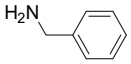
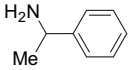
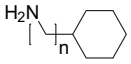
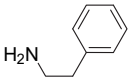


Entry	R^1R^2NH	(A)	(B)	(C)	(D)	Yield[a] (%)
1 (**8a**)		→	→	→	→	55
2 (**8b**)		→	→	→	→	48
3 (**8c**)		→	→	→	→	69
4 (**8d**)		→	→	→	→	63
5		→	→	Not finish	—	—
6		Not proceed	—	—	—	—
7		Not proceed	—	—	—	—

[a] Isolated yield.

Table 4
Limitations of primary amines in the second step (B)



Entry	*Z*-NH_2	(A)	(B)	(C)	(D)	Yield[a] (%)
1 (**8a**)		→	→	→	→	55
2		→	Not finish	—	—	—
3		→	→	Not finish	—	—
4		→	→	Not finish	—	—
5		→	Not proceed	—	—	—

[a] Isolated yield.

of amines with ethyl bromacetate. As for the results of R^3, strong electron withdrawing groups seemed to decrease the yield (entries 5, 7, and 8). This synthetic method afforded compound **8i**, an important intermediate in the preparation of our DPP-4 inhibitor, DSR-12727, in moderate yield and gave almost the same yield in a larger preparation (entry 6). DSR-12727 is one of our compounds in preclinical development and its biological activity data will be discussed in future reports.

4. Effects of lithium coordination and *tert*-butyl ester on the cyclization step (D)

As our new synthesis resulted in a highly selective cyclization (D), we decided to examine factors that affect this selectivity. Based on the fact that nucleophilic addition produced pyrrole structures, we assumed that the stereochemistry (*E* and *Z* isomers) of the third intermediate **7** is the most important aspect of the selectivity. Accordingly, we presumed that the nucleophilic attack was controlled by the position of the ethyl ester. However, NMR analysis did not confirm the configuration of intermediate **7**. In fact, ^1H NMR of **7** measured in both DMSO and $CDCl_3$ with or without heat showed no clear peak, and ^{13}C NMR gave no detectable peaks. The third structure **7** seems to be in a fast equilibrium between *E* and *Z* isomers. Based on these findings, we thought that the selectivity in our synthesis is controlled only by conditions of the final step (D). Therefore, we paid attention to two factors that apparently relate to control of selectivity. One is the steric hindrance caused by *tert*-butyl ester, and the other is coordination between the lithium and carbonyl group of the *tert*-butyl ester or nitril. To confirm our hypothesis, two additional experiments were conducted.

To investigate the influence of the *tert*-butyl ester methyl 2-cyano-3,3-bis(methylthio)acrylate was used as starting material instead of **4** (Scheme 2). First, we had to eliminate any surplus effects caused by unknown by-products from former steps. For that, once intermediate **9** was isolated, it was subjected to cyclization. The yield of the target product **10** was half that of the undesired product **11**. This finding indicates that the lithium enolate attack the carbonyl carbon of the ester group faster than the nitril, however, steric hindrance of the *tert*-butyl ester prevents this attack.

Next, to examine the effect of coordination, HMPA, which can prevent coordination between the lithium enolate and the nitril or the *tert*-butyl ester (1.0 equiv or 3.0 equiv to lithium) was added to the reaction (Scheme 3). The target pyrrole **3** and by-product **11** were obtained in almost the same yield, which means that coordination also influences the selectivity. These results suggest that both steric hindrance and coordination have effects on the selectivity in the cyclization step (D). However, *tert*-butyl ester seems to be more important than lithium *tert*-butoxide.

5. Conclusion

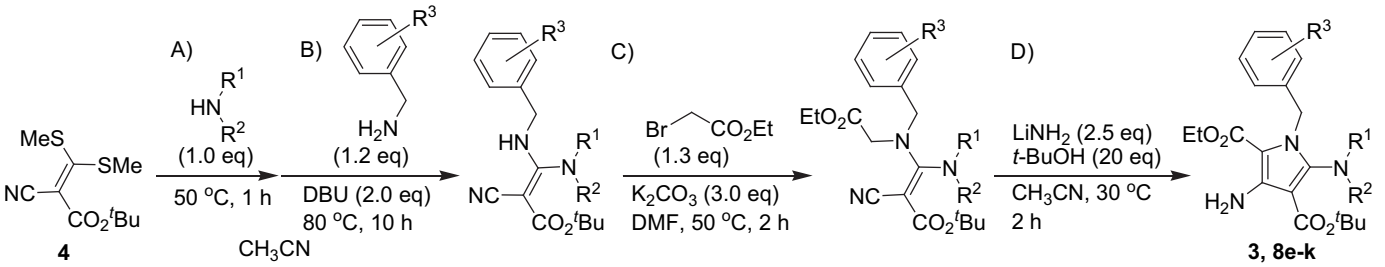
In conclusion, we herein report details of our optimization and the modification, as well as the scope and limitations, of a novel synthetic method of 4-*tert*-butyl 2-ethyl 3-amino-1-benzyl-5-dialkylamino-1*H*-pyrrole-2,4-dicarboxylate derivatives. This synthesis afforded new α-amino pyrrole derivatives that are difficult to be synthesized by conventional methods.

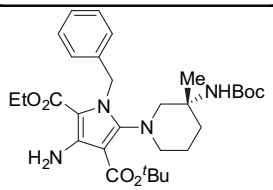
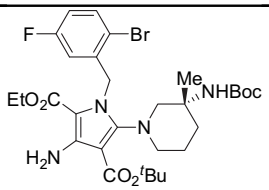
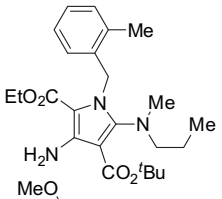
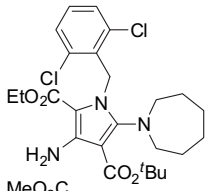
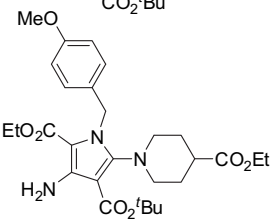
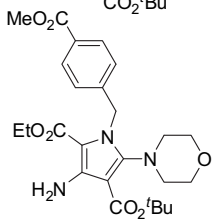
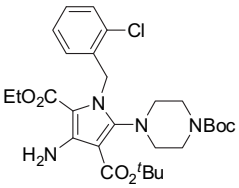
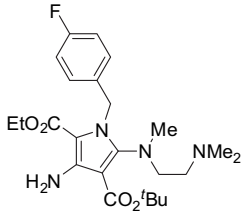
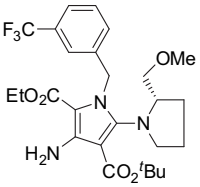
6. Experimental section

6.1. General

All reagents and solvents were obtained from commercial suppliers and used without further drying or purification. All reactions were performed under nitrogen atmosphere. Normal-phase column chromatography was performed using Yamazen W-prep

Table 5
Applications of the reaction

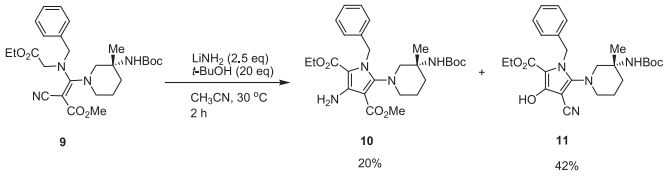


Entry	Product	Yield[a] (%)	Entry	Product	Yield[a] (%)
1 (**3**)		49 (45)[b]	6 (**8i**)		46 (44)[c]
2 (**8e**)		43	7 (**8j**)		36
3 (**8f**)		65	8 (**8k**)[d]		31
4 (**8g**)		64	9		—[e]
5 (**8h**)		35			

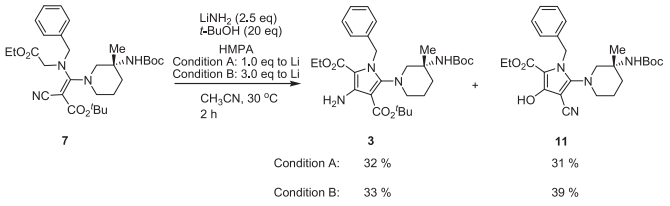
[a] Isolated yield.
[b] Yield of step-by-step method.
[c] Reaction was performed at 20 mmol scale.
[d] HCl (1.2 equiv) salt and 3.1 equiv of DBU were used.
[e] Complex mixture was given in the third reaction (C).

system with pre-packed SiO_2 columns. Visualization was done by UV light (254 nm). ^1H NMR spectra at 400 MHz and ^{13}C NMR spectra at 100 MHz were recorded on a Brucker AVANCE 400 spectrometer with all chemical shift (δ) values referenced to $CDCl_3$ as an internal standard and reported as shift (proton count, multiplicity, coupling constant (J)). Proton assignments were based on COSY, and Carbon assignments were based on HMQC and/or HMBC. IR spectra were recorded on a JEOL JIR-SPX60 spectrometer as ATR. High-resolution mass spectra (HRMS) were recorded on a Thermo Fischer Scientific LTQ Orbitrap Discovery MS equipment. Melting points were determined on a Stanford Research Systems OptiMelt MPA100. Each compound form was based on appearance, microscopic observations and melting points. Measurement of purity of compounds was done by Ultra Fluent Liquid chromatography (UFLC) with Shim-pack XR-ODC 75 mm×3.0. Samples were dissolved in MeOH/0.1%TFA and the eluent volume was 1.0 ml/min with 10 min-gradient (from 10%B to 90%B), where solvent A is H_2O/0.1%TFA and solvent B is CH_3CN/0.1%TFA. Purity of compounds was determined by UFLC and averaged 95%.

6.1.1. General procedure. To a solution of *tert*-butyl 2-cyano-3,3-bis (methylthio) acrylate (**4**) (245 mg; 1.0 mmol) in CH_3CN (3.0 ml) was



Scheme 2. Effect of the *tert*-butyl ester on the selectivity.



Scheme 3. Effect of lithium on the selectivity.

added R^1R^2NH (1.0 mmol), and the mixture was stirred at 50 °C for 1 h. DBU (0.3 ml; 2.0 mmol) and R^3-$PhCH_2NH_2$ (1.2 mmol) were then added to the mixture, and the new mixture was stirred for 10 h at 80 °C. The mixture was next diluted with EtOAc, washed with H_2O, 1 N HCl aq, satd $NaHCO_3$ aq and brine, and dried over Na_2SO_4, and the filtrate was concentrated in vacuo. To the residue in DMF (3.0 ml) was added K_2CO_3 (415 mg; 3.0 mmol) and then ethyl bromoacetate (0.13 ml; 1.3 mmol) dropwise, and the reaction mixture was stirred for 2 h at 50 °C. The resulting slurry was diluted with EtOAc, washed with satd NH_4Cl aq and brine and dried over Na_2SO_4, and the filtrate was concentrated in vacuo. To *tert*-butanol (1.5 ml) was added $LiNH_2$ (58 mg; 2.5 mmol) and the mixture was stirred for 10 min at 80 °C and then cooled to room temperature, and CH_3CN (2.0 ml) was added. To the prepared slurry was added dropwise the alkylated intermediate in toluene (1.0 ml), and the resulting mixture was stirred for 2 h at 30 °C. The slurry was diluted with EtOAc, washed with satd NH_4Cl aq, and brine and dried over Na_2SO_4, and the filtrate was concentrated in vacuo. Finally, the residue was purified by column chromatography (hexane/EtOAc=8/1 to 3/1).

*6.1.2. tert-Butyl 3-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-2-cyano-3-(methylthio)acrylate (**5**).* The product was obtained as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, s, C(NHBoc)(*Me*)), 1.43 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$), 1.50–1.60 (2H, m, $CH_2NCH_2CH_2CH_2CH_2$), 1.60–1.72 (1H, m, $CH_2NCH_2CH_2CH_2CH_2$), 1.73–1.88 (1H, m, $CH_2NCH_2CH_2CH_2CH_2$), 2.59 (3H, s, *SMe*), 3.35–3.48 (2H, m, $CH_2NCH_2CH_2CH_2CH_2$), 3.70 (1H, br s, $CH_2NCH_2CH_2CH_2CH_2$), 4.10 (1H, br s, $CH_2NCH_2CH_2CH_2CH_2$), 4.55 (1H, br s, N*H*Boc). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.5 (CH_3, *SMe*), 21.7 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 23.7 (CH_3, C(NHBoc)(*Me*)), 28.3 (CH_3, C(CH_3)$_3$), 28.4 (CH_3, C(CH_3)$_3$), 35.5 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 52.1 (C, *C*(NHBoc)(Me)), 54.5 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 61.1 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 76.2 (C), 79.6 (C, *C*(CH_3)$_3$), 80.6 (C, *C*(CH_3)$_3$), 119.9 (C), 154.3 (C), 163.4 (C), 178.9 (C). HRMS (ESI$^+$): *m*/*z* 412.2259 (calcd *m*/*z* 412.2265 for $C_{20}H_{33}N_4O_3S$+H). Mp 128–137 °C.

*6.1.3. tert-Butyl 3-(benzylamino)-3-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-2-cyanoprop-2-enoate (**6**).* The product was obtained as a white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.29 (3H, s, C(NHBoc)(*Me*)), 1.37 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3$), 1.40–1.50 (2H, m, $CH_2NCH_2CH_2CH_2CH_2$), 1.55–1.68 (2H, m, $CH_2NCH_2CH_2CH_2CH_2$), 1.88 (2H, br s, $CH_2NCH_2CH_2CH_2CH_2$), 2.98 (2H, br s, $CH_2NCH_2CH_2CH_2CH_2$), 3.47 (1H, br s, *NH*CH_2Ph), 4.39 (2H, s, CH_2Ph), 4.49 (1H, s, N*H*Boc), 7.25–7.38 (5H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.6 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 24.2 (CH_3, C(NHBoc)(*Me*)), 28.1 (CH_3, C(CH_3)$_3$), 28.4 (CH_3, C(CH_3)$_3$), 35.9 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 49.5 (CH_2 CH_2, $CH_2NCH_2CH_2CH_2CH_2$, $CH_2NCH_2CH_2CH_2CH_2$), 51.5 (CH_2, CH_2Ph), 56.3 (C, *C*(NHBoc)(Me)), 79.7 (CH_2, CH_2Ph), 121 (C), 127.3 (CH, Ph), 127.7 (CH, Ph), 128.7 (CH, Ph), 137 (C, Ph), 155.3 (C), 168.2 (C), 168.8 (C). HRMS (ESI$^+$): *m*/*z* 471.2955 (calcd *m*/*z* 471.2966 for $C_{26}H_{38}N_4O_4$+H). Mp 80–88 °C.

*6.1.4. tert-Butyl 3-[benzy(2-ethoxy-2-oxoethyl)lamino]-3-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-2-cyanoprop-2-enoate (**7**).* The product was obtained as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.0–1.70 (27H, m), 2.1–2.7 (1H, m), 3.0–4.0 (4H, m), 4.0–4.4 (5H, m), 4.81 (1H, s), 7.18–7.23 (1H, m), 7.27–7.40 (4H, m). IR (ATR): 3318, 2975, 2192, 1789, 1688 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 557.3324 (calcd *m*/*z* 557.3334 for $C_{30}H_{44}N_4O_6$+H). Mp 83–89 °C.

*6.1.5. 4-tert-Butyl 2-ethyl 3-amino-1-benzyl-5-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidin-1-yl}-1H-pyrrole-2,4-dicarboxylate(**3**).* The product was obtained as a pale-yellow amorphous solid (270 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, t, *J*=6.8 Hz, OCH_2CH_3), 1.25 (3H, s, C(NHBoc)(*Me*)), 1.41 (9H, s, C(CH_3)$_3$), 1.60 (9H, s, C(CH_3)$_3$), 1.40–1.60 (3H, m, $CH_2NCH_2CH_2CH_2CH_2$), 2.19 (1H, s, $CH_2NCH_2CH_2CH_2CH_2$), 2.49 (1H, s, $CH_2NCH_2CH_2CH_2$), 2.72 (1H, s, $CH_2NCH_2CH_2CH_2$), 3.14 (1H, t, *J*=11 Hz, $CH_2NCH_2CH_2CH_2CH_2$), 3.33 (1H, d, *J*=12 Hz, $CH_2NCH_2CH_2CH_2$), 4.16 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 4.56 (1H, s, N*H*Boc), 5.54–5.57 (2H, m, CH_2Ph), 6.95 (2H, d, *J*=7.0 Hz, H-2′, and H-6′), 7.15–7.31 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3, OCH_2CH_3), 21.5 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 25.0 (CH_3, C(NHBoc)(*Me*)), 28.5 (CH_3, C(CH_3)$_3$), 28.9 (CH_3, C(CH_3)$_3$), 32.8 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 47.2 (CH_2, CH_2Ph), 49.6 (CH_2, $CH_2NCH_2CH_2CH_2CH_2$), 51.1 (CH_2, $CH_2NCH_2CH_2CH_2$), 58.8 (C, *C*(Me)(NHBoc)), 59.2 (CH_2, OCH_2CH_3), 78.6 (C, *C*(CH_3)$_3$), 80.8 (C, *C*(CH_3)$_3$), 98.5 (C), 100.7 (C), 125.3 (CH, 2′, and 6′-Ph), 126.7 (CH, 4′-Ph), 128.5 (CH, 3′, and 5′-Ph), 139.1 (C, Ph), 145.9 (C), 147.6 (C), 154.5 (CO), 161.6 (CO), 164 (CO). IR (ATR): 3506, 3372, 2973, 2931, 1677 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 557.3322 (calcd *m*/*z* 557.3334 for $C_{30}H_{44}N_4O_6$+H). Mp 61–72 °C.

*6.1.6. 4-tert-Butyl 2-ethyl 3-amino-1-benzyl-5-(piperidin-1-yl)-1H-pyrrole-2,4-dicarboxylate (**8a**).* The product was obtained as a white solid (235 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.47 (6H, m, $NCH_2(CH_2)_3$), 1.61 (9H, s, C(CH_3)$_3$), 2.50–3.50 (4H, m, NCH_2), 4.16 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.46 (2H, s, CH_2Ph), 6.97 (2H, d, *J*=7.2 Hz, H-2′, and H-6′), 7.15–7.26 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4 (CH_3, OCH_2CH_3), 23.8 (CH_2, $NCH_2(CH_2)_3$), 26.3 (CH_2, $NCH_2(CH_2)_3$), 28.9 (CH_3, C(CH_3)$_3$), 47.3 (CH_2, CH_2Ph), 50.2 (CH_2 NCH_2), 59.0 (CH_2, OCH_2CH_3), 80.6 (C, *C*(CH_3)$_3$), 97.7 (C), 100.4 (C), 125.8 (CH, 2′, and 6′-Ph), 126.4 (CH, 4′-Ph), 128.2 (CH, 3′, and 5′-Ph), 139.5 (C, Ph), 146.2 (C), 149.4 (C), 161.7 (CO), 164.3 (CO). IR (ATR): 3482, 3367, 2937, 2848, 1675, 1643 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 428.2538 (calcd *m*/*z* 428.2544 for $C_{24}H_{33}N_3O_4$+H). Mp 97–100 °C.

*6.1.7. 4-tert-Butyl 2-ethyl 3-amino-1-benzyl-5-(pyrrolidin-1-yl)-1H-pyrrole-2,4-dicarboxylate (**8b**).* The product was obtained as a pale-yellow oil (201 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, t, *J*=6.9 Hz, OCH_2CH_3), 1.57 (9H, s, C(CH_3)$_3$), 1.85–1.89 (4H, m, $NCH_2(CH_2)_2$), 3.10 (4H, s, NCH_2), 4.15 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.41 (2H, s, CH_2Ph), 6.96 (2H, d, *J*=7.1 Hz, H-2′, and H-6′), 7.17–7.26 (3H, m, H-3′, H-4′, and H-5′). ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 14.4 (CH_3, OCH_2CH_3), 25.6 (CH_2, $NCH_2(CH_2)_2$), 28.7 (CH_3, $C(CH_3)_3$), 47.4 (CH_2, CH_2Ph), 51.0 (CH_2, NCH_2), 59.0 (CH_2, OCH_2CH_3), 80.2 (C, $C(CH_3)_3$), 97.2 (C), 100.4 (C), 125.8 (CH, 2′, and 6′-Ph), 126.4 (CH, 4′-Ph), 128.2 (CH, 3′, and 5′-Ph), 139.6 (C, Ph), 146.3 (C), 147.1 (C), 161.6 (CO), 164.0 (CO). IR (ATR): 3506, 3372, 2973, 2867, 1675 cm^{-1}. HRMS (ESI^+): m/z 414.2390 (calcd m/z 414.2387 for $C_{23}H_{31}N_3O_4$+H).

*6.1.8. 4-tert-Butyl 2-ethyl 3-amino-1-benzyl-5-(azepan-1-yl)-1H-pyrrole-2,4-dicarboxylate (**8c**).* The product was obtained as a yellow oil (302 mg, 69%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.44–1.60 (8H, m, $NCH_2(CH_2)_4$), 1.60 (9H, s, $C(CH_3)_3$), 2.80–3.50 (4H, m, NCH_2), 4.11 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.52 (2H, s, CH_2Ph), 6.90 (2H, d, J=7.1 Hz, H-2′, and H-6′), 7.14–7.26 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4 (CH_3, OCH_2CH_3), 27.3 (CH_2, $NCH_2(CH_2)_4$), 28.8 (CH_3, $C(CH_3)_3$), 30.1 (CH_2, $NCH_2(CH_2)_4$), 46.9 (CH_2, CH_2Ph), 53.8 (CH_2, NCH_2), 58.9 (CH_2, OCH_2CH_3), 80.2 (C, $C(CH_3)_3$), 96.6 (C), 99.9 (C), 124.9 (CH, 2′, and 6′-Ph), 126.3 (CH, 4′-Ph), 128.1 (CH, 3′, and 5′-Ph), 139.6 (C, Ph), 146.3 (C), 150.9 (C), 161.5 (CO), 164.3 (CO). IR (ATR): 3488, 3375, 2927, 2852, 1675 cm^{-1}. HRMS (ESI^+): m/z 442.2700 (calcd m/z 442.2700 for $C_{25}H_{35}N_3O_4$+H).

*6.1.9. 4-tert-Butyl 2-ethyl 3-amino-1-benzyl-5-[benzyl(methyl)amino]-1H-pyrrole-2,4-dicarboxylate (**8d**).* The product was obtained as a pale-yellow oil (294 mg, 63%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t, J=7.0 Hz, OCH_2CH_3), 1.67 (9H, s, $C(CH_3)_3$), 2.60 (3H, s, N*Me*), 4.13 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.19 (2H, br s, $MeNCH_2Ph$), 5.49 (2H, s, CH_2Ph), 6.92 (2H, d, J=7.3 Hz, H-2′, and H-6′), 7.10–7.30 (8H, m, 2Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3, OCH_2CH_3), 28.8 (CH_3, $C(CH_3)_3$), 39.8 (CH_3, N*Me*), 47.2 (CH_2, CH_2Ph), 59.1 (CH_2, $MeNCH_2Ph$), 59.2 (CH_2, OCH_2CH_3), 80.7 (C, $C(CH_3)_3$), 97.8 (C), 100.3 (C), 125.4 (CH, 6′-Ph), 126.4 (CH, Ph), 127.1 (CH, Ph), 128.3 (CH,CH, Ph), 128.8 (CH, Ph), 138.5 (C), Ph, 139.3 (C, Ph), 146.2 (C), 149.3 (C), 161.6 (CO), 164.2 (CO). IR (ATR): 3506, 3372, 2975, 2931, 1675 cm^{-1}. HRMS (ESI^+): m/z 464.2534 (calcd m/z 464.2544 for $C_{27}H_{33}N_3O_4$+H).

*6.1.10. 4-tert-Butyl 2-ethyl 3-amino-1-(2-methylbenzyl)-5-[methyl(propyl)amino]-1H-pyrrole-2,4-dicarboxylate (**8e**).* The product was obtained as a pale-yellow oil (184 mg, 43%).

^1H NMR (400 MHz, $CDCl_3$) δ: 0.72 (3H, t, J=7.4 Hz, OCH_2CH_3), 1.02 (3H, s, $MeNCH_2CH_2CH_3$), 1.25–1.40 (2H, m, $MeNCH_2CH_2CH_3$), 1.60 (9H, s, $C(CH_3)_3$), 2.34 (3H, s, *Me*), 2.63 (3H, s, N*Me*), 2.93 (2H, t, J=7.2 Hz, $MeNCH_2CH_2CH_3$), 4.07 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.40 (2H, s, CH_2Ph), 6.39 (1H, d, J=7.4 Hz, H-6′), 6.90–7.13 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3 (CH_3, $MeNCH_2CH_2CH_3$), 14.1 (CH_3, OCH_2CH_3), 18.9 (CH_3, *Me*), 21.8 (CH_2, $MeNCH_2CH_2CH$), 28.7 (CH_3, $C(CH_3)_3$), 40.2 (CH_3, N*Me*), 45.3 (CH_2, CH_2Ph), 57.1 (CH_2, $MeNCH_2CH_2CH_3$), 58.9 (CH_2, OCH_2CH_3), 80.4 (C, $C(CH_3)_3$), 97.3 (C), 100.3 (C), 124.2 (CH, Ph), 125.9 (CH, Ph), 126.0 (CH, Ph), 129.5 (CH, Ph), 133.5 (C, Ph), 137.7 (C, Ph), 146.2 (C), 149.6 (C), 161.5 (CO), 164.2 (CO). IR (ATR): 3486, 3372, 2971, 2871, 1677 cm^{-1}. HRMS (ESI^+): m/z 430.2690 (calcd m/z 430.2700 for $C_{24}H_{35}N_3O_4$+H).

*6.1.11. 4-tert-Butyl 2-ethyl 3-amino-5-[4-(ethoxycarbonyl)piperidin-1-yl]-1-(4-methoxybenzyl)-1H-pyrrole-2,4-dicarboxylate (**8f**).* The product was obtained as a pale-yellow oil (344 mg, 65%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.59 (9H, s, $C(CH_3)_3$), 1.50–1.70 (2H, m, NCH_2CH_2CH), 1.80–1.90 (2H, m, NCH_2CH_2CH), 2.34 (1H, br s, NCH_2CH_2CH), 2.74 (2H, br s, NCH_2CH_2CH), 3.35 (2H, br s, NCH_2CH_2CH), 3.75 (3H, s, O*Me*), 4.12 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.18 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.39 (2H, s, CH_2Ph), 6.77 (2H, d, J=8.7 Hz, H-3′, and H-5′), 6.90 (2H, d, J=8.6 Hz, H-2′, and H-6′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (CH_3, OCH_2CH_3), 14.4 (CH_3, OCH_2CH_3), 28.8 (CH_3, CH_2, $C(CH_3)_3$, NCH_2CH_2CH), 40.9 (CH, NCH_2CH_2CH), 46.6 (CH_2, CH_2Ph), 48.8 (CH_2, NCH_2CH_2CH), 55.1 (CH_3, O*Me*), 59.0 (CH_2, OCH_2CH_3), 60.3 (CH_2, OCH_2CH_3), 80.5 (C, $C(CH_3)_3$), 97.8 (C), 100.5 (C), 113.5 (CH, 3′, and 5′-Ph), 126.9 (CH, 2′, and 6′-Ph), 131.3 (C, Ph), 145.9 (C), 148.3 (C), 158.2 (C, Ph), 161.6 (CO), 164 (CO), 175 (CO). IR (ATR): 3506, 3374, 2975, 1729, 1675 cm^{-1}. HRMS (ESI^+): m/z 530.2846 (calcd m/z 530.2861 for $C_{28}H_{39}N_3O_7$+H).

*6.1.12. 4-tert-Butyl 2-ethyl 3-amino-5-[4-(tert-butoxycarbonyl)piperadin-1-yl]-1-(2-chlorobenzyl)-1H-pyrrole-2,4-dicarboxylate (**8g**).* The product was obtained as a pale-yellow oil (362 mg, 64%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.58 (9H, s, $C(CH_3)_3$), 2.41–2.60 (2H, br s, NCH_2CH_2NBoc), 2.73 (2H, br s, NCH_2CH_2NBoc), 3.43 (2H, br s, NCH_2CH_2NBoc), 3.94 (2H, br s, NCH_2CH_2NBoc), 4.20 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.50 (2H, s, CH_2Ph), 6.84 (1H, apparent d, J=6.6 Hz, H-6′), 6.98 (1H, s, H-3′), 7.17–7.21 (2H, m, H-4′, and 5′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3, OCH_2CH_3), 28.3 (CH_3, $C(CH_3)_3$), 28.7 (CH_3, $C(CH_3)_3$), 43.4 (CH_2, NCH_2CH_2NBoc), 44.5 (CH_2, NCH_2CH_2NBoc), 46.7 (CH_2, CH_2Ph), 48.7 (CH_2, CH_2, NCH_2CH_2NBoc), 59.3 (CH_2, OCH_2CH_3), 79.6 (C, $C(CH_3)_3$), 81.1 (C, $C(CH_3)_3$), 98.4 (C), 100.6 (C), 123.8 (C, Ph), 125.8 (CH, 6′-Ph), 126.9 (CH, 3′-Ph), 129.6 (CH, Ph), 134.2 (CH, Ph), 141.4 (C, Ph), 145.9 (C), 146.9 (C), 154.3 (CO), 161.5 (CO), 163.9 (CO). IR (ATR): 3506, 3376, 2975, 2931, 1675 cm^{-1}. HRMS (ESI^+): m/z 563.2623 (calcd m/z 563.2631 for $C_{28}H_{39}ClN_4O_6$+H).

*6.1.13. 4-tert-Butyl 2-ethyl 3-amino-5-[(2S)-2-(methoxymethyl)pyrrolidine-1-yl]-1-[3-(trifluoromethyl)benzyl]-1H-pyrrole-2,4-dicarboxylate (**8h**).* The product was obtained as a pale-yellow oil (181 mg, 35%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.11 (3H, t, J=6.6 Hz, OCH_2CH_3), 1.58 (9H, s, $C(CH_3)_3$), 1.70–1.90 (3H, m, $NCH_2CH_2CH_2$), 2.10–2.19 (1H, s, $NCH_2CH_2CH_2$), 2.77 (1H, br s, NCH_2), 3.05–3.18 (3H, m, $CH_2NCH(CH_2OMe)$), 3.17 (3H, s, OMe), 3.79–3.84 (1H, m, N*CH*), 4.08–4.20 (2H, m, OCH_2CH_3), 5.45–5.60 (2H, m, CH_2Ph), 7.12 (1H, d, J=7.7 Hz, H-2′), 7.32–7.46 (3H, m, H-4′, H-5′, and H-6′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2 (CH_3, OCH_2CH_3), 24.7 (CH_2, NCH_2CH_2), 28.7 (CH_3, $C(CH_3)_3$), 46.8 (CH_2, CH_2Ph), 53.1 (CH_2, NCH_2CH_2), 58.6 (CH_3, O*Me*), 59.1 (CH_2, OCH_2CH_3), 61.4 (CH_2, CH_2OMe), 75.9 (CH, N*CH*), 80.5 (C, $C(CH_3)_3$), 97.4 (C), 100.6 (C), 122.8 (^3J(C,F)=4.0 Hz) (CH, 2′-Ph), 123.3 (^3J(C,F)=3.7 Hz) (CH, 4′-Ph), 124.1 (C, ^1J(C,F)=270 Hz) (C, CF_3), 128.7 (CH, Ph), 129.1 (CH, Ph), 130.4 (^2J(C,F)=32 Hz) (C, 3′-Ph), 140.9 (C, Ph), 146 (C), 146.9 (C), 161.4 (CO), 163.7 (CO). IR (ATR): 3507, 3376, 2975, 2871, 1675 cm^{-1}. HRMS (ESI^+): m/z 526.2513 (calcd m/z 526.2523 for $C_{26}H_{34}F_3N_3O_5$+H).

*6.1.14. 4-tert-Butyl 2-ethyl 3-amino-1-(2-bromo-5-fluorobenzyl)-5-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidin-1-yl}-1H-pyrrole-2,4-dicarboxylate(**8i**).* The product was obtained as a pale-yellow amorphous solid (301 mg, 46%).

^1H NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.26 (3H, s, C(NHBoc)(*Me*)), 1.39 (9H, s, $C(CH_3)_3$), 1.40–1.60 (3H, m, $CH_2NCH_2CH_2CH_2$), 1.62 (9H, s, $C(CH_3)_3$), 2.27 (1H, br s, $CH_2NCH_2CH_2CH_2$), 2.58 (1H, br s, $CH_2NCH_2CH_2$), 2.80 (1H, s, $CH_2NCH_2CH_2$), 3.08 (1H, br s, $CH_2NCH_2CH_2$), 3.33 (1H, br s, $CH_2NCH_2CH_2$), 4.13 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.34–5.60 (2H, m, CH_2Ph), 6.22 (1H, d, J=8.0 Hz, H-6′), 6.83 (1H, td, J=8.2, 2.9 Hz, H-3′), 7.51 (1H, dd, J=8.9, 3.6 Hz, H-4′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (CH_3, OCH_2CH_3), 21.6 (CH_2, $CH_2NCH_2CH_2CH_2$), 25 (CH_3, C(NHBoc)(*Me*)), 28.4 (CH_3, $C(CH_3)_3$), 28.8 (CH_3, $C(CH_3)_3$), 32.8 (CH_2, $CH_2NCH_2CH_2CH_2$), 48.0 (CH_2, $PhCH_2$), 50.2 (CH_2, $CH_2NCH_2CH_2CH_2$), 51.1 (CH_2, $CH_2NCH_2CH_2CH_2$), 59.2 (CH_2, C, OCH_2CH_3, C(Me)(NHBoc)), 78.7 (C, $C(CH_3)_3$), 81.1 (C, $C(CH_3)_3$), 98.5 (C), 100.2 (C), 113.7 (^2J(C,F)=24 Hz) (CH, Ph), 114.6 (C, Ph), 115.3 (^2J(C,F)=22 Hz), (CH, Ph), 133.8 (^3J

(C,F)=7.0 Hz) (CH, 3′-Ph), 140.9 (C, Ph), 146 (C), 148 (C), 154.5 (CO), 161.3 (CO), 162.4 (^1J(C,F)=245 Hz) (C, 5′-Ph), 163.8 (CO). IR (ATR): 3496, 3371, 2973, 2921, 1679 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 653.2344 (calcd *m*/*z* 653.2345 for $C_{30}H_{42}BrFN_4O_6$+H). Mp 74–84 °C.

*6.1.15. 4-tert-Butyl 2-ethyl 3-amino-5-(azepan-1-yl)-1-(2,6-dichlorobenzyl)-1H-pyrrole-2,4-dicarboxylate (**8j**).* The product was obtained as a yellow solid (184 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.08 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.59 (9H, s, $C(CH_3)_3$), 1.61 (8H, br s, $NCH_2(CH_2)_4$), 2.98 (2H, br s, NCH_2), 3.35 (2H, br s, NCH_2), 4.07 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.65 (2H, s, CH_2Ph), 7.06 (1H, t, *J*=8.0 Hz, H-4′), 7.22 (2H, d, *J*=8.0 Hz, H-3′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.4 (CH_3, OCH_2CH_3), 27.5 (CH_2, $NCH_2(CH_2)_4$), 28.8 (CH_3, $C(CH_3)_3$), 30.2 (CH_2, $NCH_2(CH_2)_4$), 44.5 (CH_2, $PhCH_2$), 53.5 (CH_2, NCH_2), 58.8 (CH_2, OCH_2CH_3), 80.1 (C, $C(CH_3)_3$), 96.4 (C), 100.4 (C), 127.8 (CH, 4′-Ph), 128.8 (CH, 3′, and 5′-Ph), 133.2 (C, Ph), 134.6 (C, 2′, and 6′-Ph), 146.9 (C), 151.9 (C), 161.6 (CO), 164.2 (CO). IR (ATR): 3488, 3372, 2927, 2852, 1675 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 510.1911 (calcd *m*/*z* 510.1921 for $C_{25}H_{33}Cl_2N_3O_4$+H). Mp 100–106 °C.

*6.1.16. 4-tert-Butyl 2-ethyl 3-amino-1-[4-(methoxycarbonyl)benzyl]-5-(morpholin-4-yl)-1H-pyrrole-2,4-dicarboxylate(**8k**).* The product was obtained as a yellow oil (137 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.17 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.62 (9H, s, $C(CH_3)_3$), 3.57 (8H, br s, NCH_2CH_2O), 3.89 (3H, s, O*Me*), 4.17 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 5.59 (2H, s, CH_2Ph), 7.03 (2H, d, *J*=8.4 Hz, H-2′, and H-6′), 7.94 (2H, d, *J*=8.3 Hz, H-3′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.3 (CH_3, OCH_2CH_3), 28.8 (CH_3, $C(CH_3)_3$), 47.1 (CH_2, CH_2Ph), 49.1 (CH_2, NCH_2CH_2O), 52.0 (CH_2, NCH_2CH_2O), 59.3 (CH_2, OCH_2CH_3), 67.2 (CH_3, O*Me*), 81.2 (C, $C(CH_3)_3$), 98.4 (C), 100.7 (C), 125.5 (CH, 3′, and 5′-Ph), 128.6 (C, Ph), 129.7 (CH, 2′, and 6′-Ph), 144.6 (C, Ph), 145.9 (C), 146.9 (C), 161.5 (CO), 164 (CO), 166.7 (CO). IR (ATR): 3504, 3374, 2975, 2854, 1720, 1675 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 488.2391 (calcd *m*/*z* 488.2386 for $C_{25}H_{33}N_3O_7$+H).

*6.1.17. Methyl 3-[benzy(2-ethoxy-2-oxoethyl)lamino]-3-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-2-cyanoprop-2-enoate (**9**).* The product was obtained as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.0–1.70 (21H, m), 3.0–3.3 (1H, m), 3.5–3.8 (4H, m), 4.0–4.4 (6H, m), 4.81 (1H, s), 7.18–7.23 (1H, m), 7.27–7.40 (4H, m). IR (ATR): 3330, 2975, 2192, 1737, 1685 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 515.2860 (calcd *m*/*z* 515.2864 for $C_{27}H_{38}N_4O_6$+H). Mp 78–87 °C.

*6.1.18. 2-Ethyl 4-methyl 3-amino-1-benzyl-5-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-1H-pyrrole-2,4-dicarboxylate (**10**).* The product was obtained as a pale-yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.16 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.25 (3H, s, C(NHBoc)(*Me*)), 1.42 (9H, s, $C(CH_3)_3$), 1.20–1.40 (3H, m, $CH_2NCH_2CH_2CH_2$), 2.17 (1H, br s, $CH_2NCH_2CH_2CH_2$), 2.49 (1H, br s, $CH_2NCH_2CH_2$), 2.80 (1H, br s, $CH_2NCH_2CH_2$), 3.10 (1H, t, *J*=9.7 Hz, $CH_2NCH_2CH_2$), 3.22 (1H, d, *J*=12 Hz, $CH_2NCH_2CH_2$), 3.86 (3H, s, O*Me*), 4.16 (2H, q, *J*=8.2 Hz, OCH_2CH_3), 4.56 (1H, s, N*H*Boc), 5.44–5.67 (2H, m, CH_2Ph), 5.92 (2H, s, NH_2), 6.95 (2H, d, *J*=6.8 Hz, H-2′, and H-6′), 7.17–7.28 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.4 (CH_3, OCH_2CH_3), 21.5 (CH_2, $CH_2NCH_2CH_2CH_2$), 25.0 (CH_3, C(*Me*)(NHBoc)), 28.5 (CH_3, $C(CH_3)_3$), 33.4 (CH_2, $CH_2NCH_2CH_2CH_2$), 47.3 (CH_2, CH_2Ph), 49.8 (CH_2, $CH_2NCH_2CH_2$), 50.8 (CH_3, O*Me*), 51.1 (CH_2, $CH_2NCH_2CH_2$), 59.0 (C, *C*(Me)(NHBoc)), 59.3 (CH_2, OCH_2CH_3), 78.7 (C, $C(CH_3)_3$), 96.8 (C), 100.8 (C), 125.3 (CH, 2′, and 6′-Ph), 126.8 (CH, 4′-Ph), 128.5 (CH, 3′, and 5′-Ph), 139 (C, Ph), 145.7 (C), 148.4 (C), 154.6 (CO), 161.6 (CO), 164.7 (CO). IR (ATR): 3506, 3376, 2975, 2935, 1681 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 515.2857 (calcd *m*/*z* 515.2864 for $C_{27}H_{38}N_4O_6$+H). Mp 43–58 °C.

*6.1.19. Ethyl 1-benzyl-5-{(3R)-3-[(tert-butoxycarbonyl)amino]-3-methylpiperidine-1-yl}-4-cyano-3-hydroxy-1H-pyrrole-2-carboxylate (**11**).* The product was obtained as a pale-yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.18 (3H, t, *J*=7.1 Hz, OCH_2CH_3), 1.30–1.40 (1H, m, $CH_2NCH_2CH_2CH_2$), 1.33 (3H, s, C(*Me*)(NHBoc)), 1.39 (9H, s, $C(CH_3)_3$), 1.50–1.70 (2H, m, $CH_2NCH_2CH_2CH_2$), 1.97 (1H, apparent d, *J*=13 Hz, $CH_2NCH_2CH_2CH_2$), 2.92–3.00 (2H, m, $CH_2NCH_2CH_2CH_2$), 3.10 (1H, d, *J*=12 Hz, $CH_2NCH_2CH_2CH_2$), 3.28 (1H, d, *J*=12 Hz, $CH_2NCH_2CH_2CH_2$), 4.23 (2H, q, *J*=7.12 Hz, OCH_2CH_3), 4.53 (1H, s, *OH*), 5.31 (2H, s, CH_2Ph), 6.94 (2H, d, *J*=7.1 Hz, H-2′, and H-6′), 7.20–7.40 (3H, m, H-3′, H-4′, and H-5′). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.2 (CH_3, OCH_2CH_3), 21.6 (CH_2, $CH_2NCH_2CH_2CH_2$), 24.1 (CH_3, C(*Me*)(NHBoc)), 28.4 (CH_3, $C(CH_3)_3$), 34.2 (CH_2, $CH_2NCH_2CH_2CH_2$), 48.0 (CH_2, CH_2Ph), 51.1 (CH_2, $CH_2NCH_2CH_2CH_2$), 52.1 (CH_2, $CH_2NCH_2CH_2CH_2$), 60.2 (C, *C*(Me)(NHBoc)), 60.7 (CH_2, OCH_2CH_3), 79.2 (C, $C(CH_3)_3$), 101.9 (C), 113.4 (C), 125.6 (CH, 2′, and 6′-Ph), 127.4 (CH, 4′-Ph), 128.7 (CH, 3′, and 5′-Ph), 137.4 (C, Ph), 149.7 (C), 154.5 (C), 156.5 (CO), 162.0 (CO). IR (ATR): 3417, 2975, 2221, 1704, 1648 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 483.2601 (calcd *m*/*z* 483.2602 for $C_{26}H_{34}N_4O_5$+H). Mp 44–53 °C.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.02.071.

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