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Synthesis of bicyclic 2,6-diketopiperazines via a three-step sequence involving an Ugi five-center, four-component reaction

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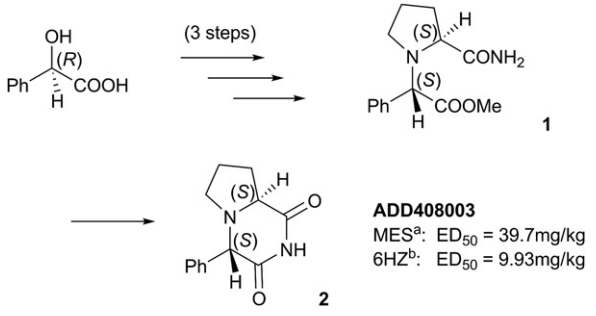
ABSTRACT

A three-step sequence involving an Ugi five-center, four-component reaction (U-5C-4CR), amide N-de-*tert*butylation and cyclocondensation has been developed for easy access to diverse bicyclic 2,6-diketopiperazine (2,6-DKP) derivatives. In the key step, aromatic aldehydes were successfully coupled with cyclic α-amino acids and isocyanides in the course of U-5C-4CR. Boron trifluoride-acetic acid complex was developed as a new N-de*tert*butylating agent effective at rt.

1. Introduction

In our recent reports we developed a straightforward synthetic route toward bicyclic 2,6-diketopiperazines (2,6-DKP) of high and stereoselective anticonvulsant activity (Scheme 1).[1] As a key intermediate, this strategy utilized a (*R*)-mandelate-derived acyclic precursor **1**, which upon treatment with base underwent a facile intramolecular cyclocondensation (Scheme 1), to furnish bioactive (*S*,*S*) isomer of **2** (ADD408003). An ongoing medicinal chemistry project required rapid access to derivatives of ADD408003 with different aryl substituents and aliphatic chains, as a first step of lead optimization. For this purpose, the present methodology proved inapplicable, due to the low availability of enantiopure (*R*)-mandelic acid derivatives.

We turned our attention to the Ugi five-center four-component reaction (U-5C-4CR), as it has proven ability to deliver quick access to structurally diverse DKP precursors.[4] The first applications of U-5C-4CR condensation in the synthesis of 2,6-DKP derivatives were reported by Ugi et al. (Scheme 2).[5] However, reaction conditions employed for the direct cyclocondensation of Ugi products would most likely cause racemization of the stereochemically labile phenylglycine fragment of **2**.[1b] Moreover, Ugi's reports did not describe



Scheme 1. Synthesis of ADD408003. [a]Maximal electroshock seizure test.[2] [b]Psychomotor test.[3]

synthesis of 2,6-DKPs lacking substituents on the imide nitrogen. Finally, to the best of our knowledge, there have been few attempts to couple aromatic aldehydes with cyclic α-amino acids (i.e., proline and pipecolic acid) in the course of U-5C-4CR.[6]

The U-5C-4CR→amide N-de*tert*butylation→intramolecular cyclocondensation sequence was examined (Scheme 3). This strategy was based on the following assumptions: (a) the U-5C-4CR condensation of a cyclic α-amino acid, aromatic aldehyde, and isocyanide would proceed with high yield and diastereoinduction toward the desired (*S*,*S*) configuration of **3**; (b) the resulting diastereomeric mixtures would be separable on a few-gram scale, at one or more

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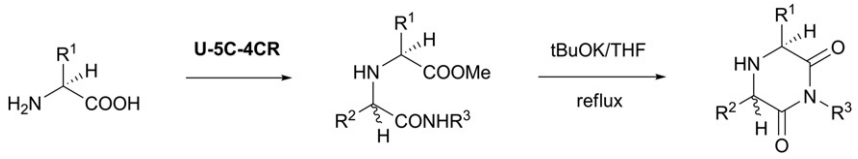
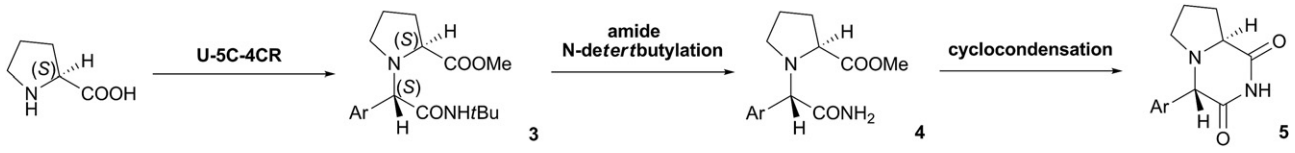


Scheme 2. U-5C-4CR reaction in synthesis of 2,6-DKPs.



Scheme 3. Possible route to desired ADD408003 derivatives.

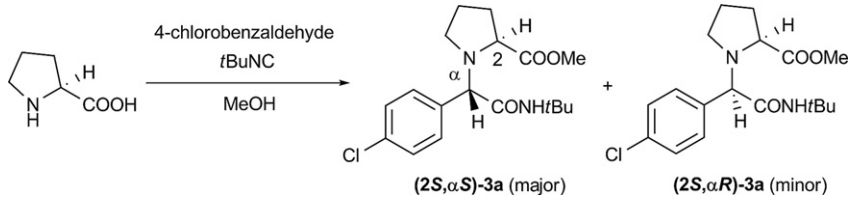
stages; (c) the use of *tert*-butyl isocyanide as a convertible isocyanide[7] would introduce a *tert*-butyl group that would be readily cleavable from N-*tert*-butylamido moiety of **3** in a mild and selective process; (d) conditions of the post-condensation reactions would not cause substantial inversion of stereocenters of **4** and **5**.

2. Results and discussion

For the U-5C-4CR condensation, cyclic α-amino acid (*S*)-proline, 4-chlorobenzaldehyde, *tert*-butyl isocyanide, and methanol were investigated as the model substrates (Table 1). We were delighted to find that these coupling partners reacted smoothly, even in catalyst-free conditions, with the diastereoinduction in favor of the desired (2*S*,α*S*)-configuration of the product **3a**. Optimization of the reaction conditions led to the conclusion that slightly higher yields were obtained when a Lewis acid was used as a promoter. In general, this was in agreement with the data presented recently by Godet et al. for U-5C-4CR condensations employing primary α-amino acids and aromatic aldehydes.[8] However, in the case of secondary α-amino acids the differences in yields between catalyzed and uncatalyzed processes were less pronounced. In contrast to Godet's findings no significant differences in chemical yields were observed upon switching between various Lewis acids (Table 1, entries 4–7). The diastereoselectivity was only slightly sensitive toward the presence and type of the catalyst. $FeCl_3$ was selected for further reactions because of the ease and safety of use compared to the more hazardous $TiCl_4$.

Other investigated aromatic aldehydes underwent U-5C-4CR condensation with L-proline and *tert*-butyl isocyanide, with chemical yields ranging from 68% to 77% (Table 2, entries 1–4). As U-5C-4CR condensation of aromatic aldehydes with secondary and cyclic α-amino acids has to date received little attention, we explored this reaction further. Changing to other secondary α-amino acids, we found that L-pipecolinic acid and *N*-phenylglycine gave lower yields (Table 2, entries 5 and 6, respectively). However, the stereoselectivity was two-fold improved in the former case. Switching from *tert*-butyl to benzyl or *tert*-octyl isocyanide (Walborsky's reagent) improved neither yield nor diastereoselectivity of the U-5C-4CR condensation (Table 2, entries 7 and 8, respectively). Importantly, with the exception of **3e**, all diastereomeric mixtures were efficiently resolved by means of column chromatography on silica gel.

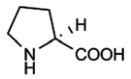
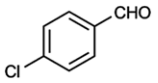
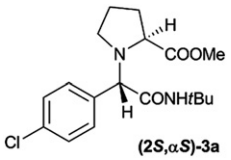
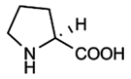
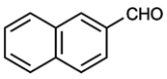
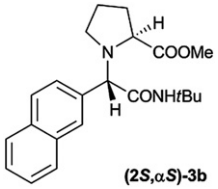
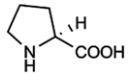
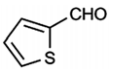
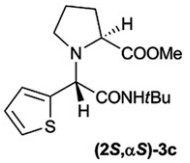
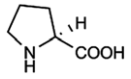
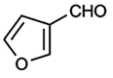
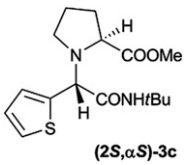
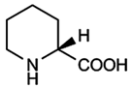
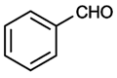
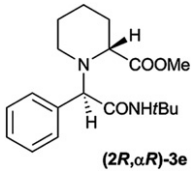
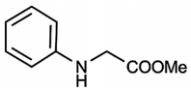
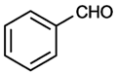
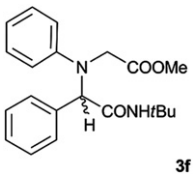
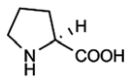
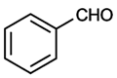
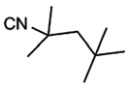
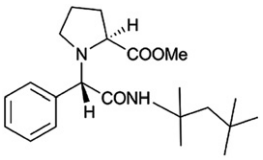
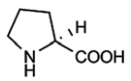
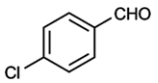
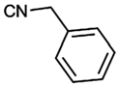
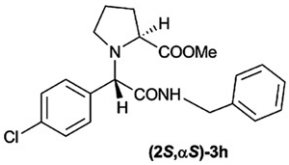
Table 1
Optimization of U-5C-4CR conditions



Entry[a]	Additive[b]	Time (h)	dr[c]	Yield[d]
1	—	24	4.5:1	77%
2	—	48	4.5:1	73%
3	TEA	24	5:1	67%
4	$BF_3 \cdot Et_2O$	24	3:1	80%
5	$FeCl_3$	24	4:1	82% (72%)[e]
6	$TiCl_4$	24	4:1	88%
7[f]	$TiCl_4$	24	4.5:1	80%

[a] Unless otherwise stated, the reactions were carried out on 0.2 mmol scale in 0.1 M solutions, at rt.
[b] 5 mol %.
[c] dr (2*S*,α*S*)-**3a**/(2*S*,α*R*)-**3a** estimated by HPLC method.
[d] Crude yields estimated by HPLC.
[e] Isolated yield on a 16.8 mmol scale.
[f] Reaction was performed at −15 °C.

Table 2
Synthesis of U-5C-4CR adducts

Entry[a]	Amino acid	Aldehyde	Isocyanide	Major diastereomer	Yield[b]	dr[c]
1				 **(2*S*,α*S*)-3a**	72% (50%)	4:1
2				 **(2*S*,α*S*)-3b**	68% (50%)	4.5:1
3				 **(2*S*,α*S*)-3c**	71% (52%)	3.5:1
4				 **(2*S*,α*S*)-3c**	77% (44%)	4:1
5				 **(2*R*,α*R*)-3e**	46%	9:1
6				 **3f**	24%	—
7				 **(2*S*,α*S*)-3g**	54% (38%)	4.5:1
8				 **(2*S*,α*S*)-3h**	52% (36%)	4:1

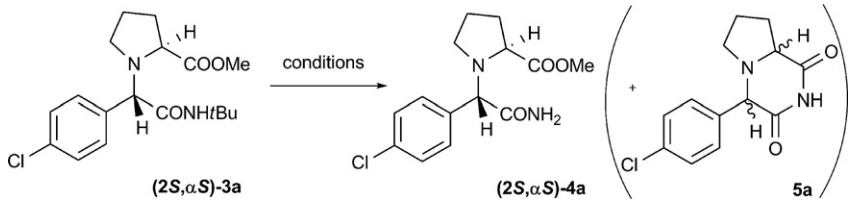
[a] The reactions were carried out on a 16.8 mmol scale in 0.17 M solutions, at rt, in the presence of 5 mol % of $FeCl_3$. With the exception of **3e** and **3f**, all stereoisomeric mixtures were efficiently resolved by column chromatography.
[b] Isolated yield, sum of diastereomers. In parentheses: isolated yield of the major isomer.
[c] Estimated by ^1H NMR of crude products.

In the next step, a mild and selective N-de*tert*butylation of Ugi adducts **3** was required to furnish acyclic DKP precursors **4**. The optimization was initiated with (2*S*,α*S*)-**3a** as a model compound and TFA as a dealkylating acid (Table 3).[9] Unfortunately, under these conditions, no anticipated product was formed and starting material was detected by HPLC. Increasing the temperature did not facilitate the process. Upon changing the acid to 2.5 equiv of TsOH, only some epimerized cyclic product **5a** was formed. $BF_3 \cdot Et_2O$ proved ineffective at rt. Interestingly, upon changing the type of the BF_3 complex to $BF_3 \cdot 2CH_3COOH$ a remarkable enhancement of N-de*tert*butylation was obtained.[10] The reaction was completed after 24 h at rt (Table 3, entry 6). When the temperature was elevated to 40 °C, full conversion was achieved after 4 h. Upon further increasing the temperature, the potentially useful dealkylation/cyclocondensation of (2*S*,α*S*)-**3a** to **5a** was observed. However, the reaction proceeded with significant level of epimerization of products **4a** and **5a**. Unfortunately, both stereocenters of product **5a** were affected and the complete cyclocondensation at 90 °C for 17 h furnished enantiomeric mixtures.[11] Thus, the practical application of this one-pot process was diminished by the formation of the inseparable enantiomeric mixtures. Analogous results were observed for $BF_3 \cdot OEt_2$ complex at 90 °C (Table 3, entry 10), however, the reaction proceeded more slowly. A considerable amount of epimerized acyclic product **4a** was still detected after 24 h.

Other derivatives of (2*S*,α*S*)-**3** were also successfully N-de*tert*-butylated at rt, with yields ranging from 57% to 81% (Table 4). The reaction was also applied to (2*S*,α*R*)-**3** stereoisomers. Of note, the dealkylation reaction of (2*S*,α*R*)-**3a** isomers, even under these mild conditions, was accompanied by a slight degree of subsequent cyclocondensation. No epimerization was detected in this case. The *tert*-octyl group of (2*S*,α*S*)-**3g** was also cleaved by $BF_3 \cdot 2CH_3COOH$ complex, at rt (Table 4, entry 6).

In the last step, the cyclocondensation of the respective stereochemically pure 2,6-DKP precursors **4** gave the final 2,6-DKPs **5** with yields ranging from 87% to 96% (Table 5). The reactions were accompanied by a slight degree of epimerization. However, the diastereomers were efficiently separated by column chromatography on silica gel.

Table 3
Optimization of amide N-de*tert*butylation conditions



Entry[a]	Conditions	Time (h)	Yield[b]	dr[c]
1	TFA, rt	24	None[d]	—
2	TFA, reflux	8	None[d]	—
3	2.5 equiv TsOH, reflux	24	None[e]	—
4	$BF_3 \cdot OEt_2$, rt,	24	None	—
5	$BF_3 \cdot 2CH_3COOH$, rt	4	23%	99:1
6	$BF_3 \cdot 2CH_3COOH$, rt	24	79% (74%)[f]	99:1
7	$BF_3 \cdot 2CH_3COOH$, 40 °C	4	70%[g]	99:1
8	$BF_3 \cdot 2CH_3COOH$, 90 °C	4	19%[g,h]	1:3
9	$BF_3 \cdot 2CH_3COOH$, 90 °C	17	None[g,i]	—
10	$BF_3 \cdot OEt_2$, 90 °C	24	30%[g,j]	1:2

[a] All reactions were carried out on 0.1 mmol scale.
[b] Crude yields estimated by HPLC method after quenching with ammonia–ice followed by a standard work-up.
[c] dr of (2*S*,α*S*)-**4a**/(2*S*,α*R*)-**4a**.
[d] No conversion.
[e] Compound **5a** (14%) (dr=1:2) was formed.
[f] Isolated yield on a 6.9 mmol scale.
[g] Conversion (100%).
[h] Compound **5a** (32%) (dr=1:1) was formed.
[i] Compound **5a** (50%) (dr=1:2.5) was formed.
[j] Compound **5a** (22%) (dr=1:2.5) was formed.

3. Conclusions

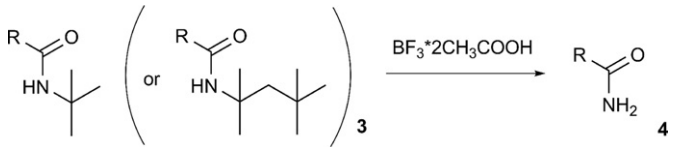
We have developed a three-step sequence leading to various bicyclic 2,6-DKPs with aromatic substituents at carbon C-4. In the key step, the U-5C-4CR condensation of secondary α-amino acids, aromatic aldehydes and *tert*-butyl isocyanide was utilized to generate the convertible N-*tert*-butylamido-esters. The novel $BF_3 \cdot 2CH_3COOH$-promoted N-de*tert*butylation at rt was developed to provide access to 2,6-DKP precursors. Application of this methodology to the synthesis of novel potential anticonvulsant agents is in progress and will be reported in due course.

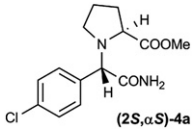
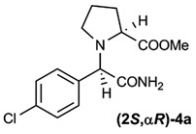
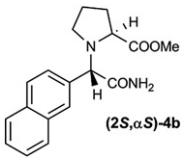
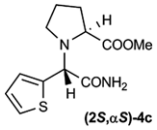
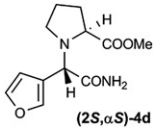
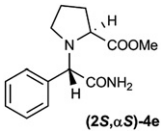
4. Experimental section

4.1. General

The NMR spectra were obtained on a 500 MHz spectrometer at rt. Chemical shifts (δ) were expressed in parts per million (ppm) relative to tetramethylsilane (TMS) or residual solvent peaks used as the internal references. The following abbreviations were used to describe the peak patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), p (pseudo-), and b (broad-). Coupling constants (J) were in hertz (Hz). The FT-IR spectra were recorded from thin film on KBr pellets. High resolution mass spectra (HRMS) were obtained using time-of-flight (TOF) spectrometer with electrospray ionization (ESI). Optical rotations were measured using a sodium lamp (589 nm). Melting points were determined in open capillary tubes. HPLC analyses were carried out on a RP-18 column.

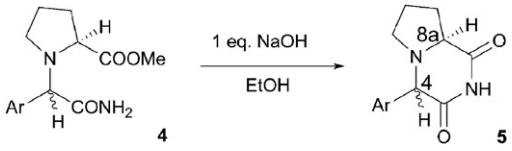
Table 4
N-Dealkylation of U-5C-4CR products

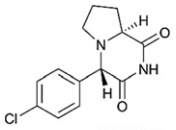
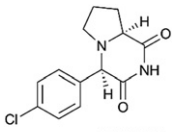
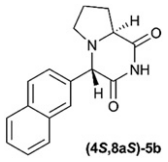
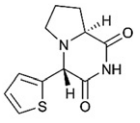
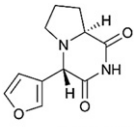
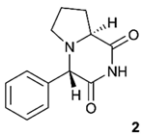


Entry[a]	Substrate	Product	Yield[b]
1	(2*S*,α*S*)-**3a**	 **(2*S*,α*S*)-4a**	74%
2	(2*S*,α*R*)-**3a**	 **(2*S*,α*R*)-4a**	76%[c]
3	(2*S*,α*S*)-**3b**	 **(2*S*,α*S*)-4b**	75%
4	(2*S*,α*S*)-**3c**	 **(2*S*,α*S*)-4c**	57%
5	(2*S*,α*S*)-**3d**	 **(2*S*,α*S*)-4d**	65%
6	(2*S*,α*S*)-**3g**	 **(2*S*,α*S*)-4e**	81%

[a] The reactions were carried out on 0.3–8.5 mmol scale with excess of $BF_3 \cdot 2CH_3COOH$ (3 mL per 1 mmol of substrate).
[b] Isolated yield of dealkylated product.
[c] (4*R*,8a*S*)-**5a** was isolated in 9% yield.

Table 5
Synthesis of 2,6-DKP derivatives **5** by intramolecular cyclocondensation of the corresponding diastereomers of **4**



Entry[a]	Substrate	Major product	Yield[b]	dr[c]
1	(2*S*,α*S*)-**4a**	 **(4*S*,8a*S*)-5a**	92% (72%)	9:1
2	(2*S*,α*R*)-**4a**	 **(4*R*,8a*S*)-5a**	88% (68%)	8.5:1
3	(2*S*,α*S*)-**4b**	 **(4*S*,8a*S*)-5b**	90% (73%)	9:1
4	(2*S*,α*S*)-**4c**	 **(4*S*,8a*S*)-5c**	87% (66%)	8.5:1
5	(2*S*,α*S*)-**4d**	 **(4*S*,8a*S*)-5d**	92% (79%)	9:1
6	(2*S*,α*S*)-**4e**	 **2**	96% (77%)	9.5:1

[a] The reactions were performed on a 0.2–4.5 mmol scale.
[b] Isolated yield, sum of diastereoisomers. In parentheses: isolated yield of the major isomer.
[c] Estimated by ^{1}H NMR of crude products.

The sample concentration was approximately 0.5 mg/mL, injection: 20 μL, flow rate 1.0 mL/min, temperature: 30 °C, detection 224 nm. Thin-layer chromatography (TLC) was run on silica gel (60-F_{254}) plates. The spots were visualized by ultraviolet light (254 nm) or iodine vapors. Flash column chromatography (FC) was carried out on silica gel 60 (particle size: 0.040–0.063 mm). Reagents were purchased from commercial sources and used as received. Solvents employed for FC were purified by passing through a short column of silica gel (Petroleum ether, PE) or by distillation (ethyl acetate). Methanol and absolute ethanol employed as reaction solvents were purchased from commercial sources and used as received. Reagent-grade DCM was used for extractions.

4.2. General procedure for the U-5C-4CR condensation

To a stirred solution of α-amino acid (1.2 equiv) and aromatic aldehyde (1.0 equiv) in MeOH (100 mL) iron (III) chloride (5 mol %) was added, followed by isocyanide (1.0 equiv). The mixture was stirred at rt for 24 h and the volatiles were removed under reduced pressure. The resulting crude diastereomeric mixtures were purified and resolved by FC.

*4.2.1. (2S,αS)- and (2S,αR)-1-(1-tert-Butyl-carbamoyl-1-(4-chlorophenyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**3a** and (2S,αR)-**3a**.* From L-proline (2.32 g, 20.16 mmol), 4-chlorobenzaldehyde (16.80 mmol, 2.36 g) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: petroleum ether/AcOEt 10:1 to 5:2): yield 4.26 g (72%): 2.94 g (50%) of (2*S*,α*S*)-**3a**, 0.40 g (7%) of (2*S*,α*R*)-**3a** and 0.92 (15%) of diastereomeric mixture. (2*S*,α*S*)-**3a**: pale-yellow oil; TLC: R_f=0.18 (petroleum ether/AcOEt 3:1); $[\alpha]_D^{20}$ −5.2 (*c* 1, $CHCl_3$); IR (KBr): 837, 1204, 1454, 1535, 1678,

1732, 2966, 3302; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (s, 9H, C(CH_3)$_3$), 1.84 (m, 2H, H-4, H′-4), 1.89 (m, 1H, H-3), 2.03 (m, 1H, H′-3), 2.68 (m, 1H, H-5), 3.20 (m, 1H, H′-5), 3.30 (dd, $^3J_1$=9.0, $^3J_2$=4.0, 1H, H-2), 3.52 (s, 3H, OCH_3), 4.07 (s, 1H, H-α), 7.21 (dt, ^3J=8.0, ^4J=2.0, 2H, H-3′, H-5′), 7.27 (dt, ^3J=8.0, ^4J=2.0, 2H, H-2′, H-6′), 7.56 (br s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.4 (C-4), 29.0 (C(*C*H$_3$)$_3$), 31.0 (C-3), 51.0 (*C*(CH$_3$)$_3$), 52.0 (O*C*H$_3$), 54.4 (C-5), 61.8 (C-2), 73.4 (C-α), 128.9 (C-3′, C-5′), 130.7 (C-2′, C-6′), 134.4 (C-4′), 136.1 (C-1′), 170.7 (*C*ONH), 176.0 (*C*OOCH$_3$); HPLC: retention time 7.5 min (MeCN/H$_2$O 60:40); HRMS (ESI$^+$) calcd for $C_{18}H_{25}{}^{15}ClN_2O_3Na$: 375.1451 (M+Na)$^+$ found 375.1460. (2*S*,α*R*)-**3a**: white wax; mp 96–98 °C; TLC: R_f=0.24 (petroleum ether/AcOEt 3:1); $[\alpha]_D^{20}$ −82.3 (*c* 1, $CHCl_3$); IR (KBr): 837, 1204, 1454, 1516, 1682, 1744, 2962, 3333; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32 (s, 9H, C(CH_3)$_3$), 1.70–1.86 (m, 2H, H-4, H′-4), 1.90 (m, 1H, H-3), 2.08 (m, 1H, H′-3), 2.47 (m, 1H, H-5), 2.90 (ddd, ^2J=9.5, $^3J_1$=7.5, $^3J_2$=4.0, 1H, H′-5), 3.50 (dd, $^3J_1$=9.0, $^3J_2$=3.0, 1H, H-2), 3.68 (s, 3H, OCH_3), 4.18 (s, 1H, H-α), 7.22 (br s, 1H, CON*H*), 7.26 (dt, ^3J=8.5, ^4J=2.5, 2H, H-3′, H-5′), 7.30 (dt, ^3J=8.5, ^4J=2.5, 2H, H-2′, H-6′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.8 (C-4), 28.6 (C(*C*H$_3$)$_3$), 29.8 (C-3), 50.7 (*C*(CH$_3$)$_3$, C-5), 51.9 (O*C*H$_3$), 63.6 (C-2), 72.3 (C-α), 128.5 (C-3′, C-5′), 130.3 (C-2′, C-6′), 133.8 (C-4′), 135.3 (C-1′), 170.1 (*C*ONH), 175.0 (*C*OOCH$_3$); HPLC: retention time 9.8 min (MeCN/H$_2$O 60:40); HRMS (ESI$^+$) calcd for $C_{18}H_{25}{}^{15}ClN_2O_3Na$: 375.1451 (M+Na)$^+$ found 375.1426.

*4.2.2. (2S,αS)- and (2S,αR)-1-(α-tert-Butyl-carbamoyl-α-(2-naphthyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**3b** and (2S,αR)-**3b**.* From L-proline (2.32 g, 20.16 mmol), 2-naphthaldehyde (16.80 mmol, 2.63 g) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: PE/AcOEt 10:1 to 3:1): yield 4.23 g (68%): 3.12 g (50%) of (2*S*,α*S*)-**3b**, 0.23 g (4%) of (2*S*,α*R*)-**3b** and 0.88 (14%) of diastereomeric mixture. (2*S*,α*S*)-**3b**: yellow oil; TLC: R_f=0.15 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ +16.9 (*c* 1, $CHCl_3$); IR (KBr): 752, 1204, 1367, 1454, 1508, 1678, 1736, 2870, 2966, 3298; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.42 (s, 9H, C(CH_3)$_3$), 1.78–1.94 (m, 3H, H-3, H-4, H′-4), 2.02 (m, 1H, H′-3), 2.76 (m, 1H, H-5), 3.26 (m, 1H, H′-5), 3.37 (dd, $^3J_1$=9.0, $^3J_2$=3.5, 1H, H-2), 3.39 (s, 3H, OCH_3), 4.26 (s, 1H, H-α), 7.38 (dd, ^3J=8.5, ^4J=1.5, 1H, H-3′), 7.46 (m, 2H, H-6′, H-7′), 7.69 (br s, 1H, CON*H*), 7.73–7.82 (m, 4H, H-1′, H-4′, H-5′, H-8′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.2 (C-4), 28.8 (C(*C*H$_3$)$_3$), 30.8 (C-3), 50.8 (*C*(CH$_3$)$_3$), 51.5 (C-5), 54.3 (O*C*H$_3$), 61.7 (C-2), 74.1 (C-α), 126.2 (C-3′), 126.2 (C-7′), 126.2 (C-6′), 127.6 (C-1′), 128.1 (C-8′), 128.2 (C-4′), 128.9 (C-5′), 133.2 (C-4a′), 133.3 (C-8a′), 134.9 (C-2′), 170.9 (*C*ONH), 175.9 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{22}H_{28}N_2O_3Na$: 391.1998 (M+Na)$^+$ found: 391.1976. (2*S*,α*R*)-**3b**: yellow oil; TLC: R_f=0.24 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −98.0 (*c* 1, $CHCl_3$); IR (KBr): 752, 1204, 1362, 1454, 1508, 1678, 1740, 2870, 2966, 3337; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34 (s, 9H, C(CH_3)$_3$), 1.75 (m, 1H, H-4), 1.83 (m, 1H, H′-4), 1.91 (m, 1H, H-3), 2.10 (m, 1H, H′-3), 2.55 (m, 1H, H-5), 2.96 (m, 1H, H′-5), 3.58 (dd, $^3J_1$=9.5, $^3J_2$=3.0, 1H, H-2), 3.66 (s, 3H, OCH_3), 4.36 (s, 1H, H-α), 7.31 (br s, 1H, CON*H*), 7.44–7.50 (m, 3H, H-3′, H-6′, H-7′), 7.76–7.83 (m, 4H, H-1′, H-4′, H-5′, H-8′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.9 (C-4), 28.6 (C(*C*H$_3$)$_3$), 29.9 (C-3), 50.8 (C-5), 51.1 (*C*(CH$_3$)$_3$), 51.8 (O*C*H$_3$), 63.8 (C-2), 73.5 (C-α), 126.0 (C-3′), 126.0 (C-7′), 126.1 (C-6′), 127.6 (C-1′), 128.0 (C-8′), 128.0 (C-4′), 128.7 (C-5′), 133.1 (C-4a′), 133.1 (C-8a′), 134.5 (C-2′), 170.5 (*C*OOCH$_3$), 175.4 (*C*ONH$_2$); HRMS (ESI$^+$) calcd for $C_{22}H_{28}N_2O_3Na$: 391.1998 (M+Na)$^+$ found: 391.2010.

*4.2.3. (2S,αS)- and (2S,αR)-1-(α-tert-Butyl-carbamoyl-α-(2-thiophene)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**3c** and (2S,αR)-**3c**.* From L-proline (2.32 g, 20.16 mmol), 2-thiophenecarboxaldehyde (16.80 mmol, 1.60 mL) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: PE/AcOEt 8:1 to 1:1): yield 3.85 g (71%): 2.84 g (52%) of (2*S*,α*S*)-**3c**, 0.44 g (8%) of (2*S*,α*R*)-**3c** and 0.57 (11%) of diastereomeric mixture. (2*S*,α*S*)-**3c**: pale-yellow solid; mp 49–50 °C; TLC: R_f=0.17 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −4.6 (*c* 1, $CHCl_3$); IR (KBr) 758, 1171, 1215, 1363, 1452, 1514, 1678, 1738, 2872, 2966, 3296; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.41 (s, 9H, C(CH_3)$_3$), 1.80–1.94 (m, 3H, H-3, H-4, H′-4), 2.04 (m, 1H, H′-3), 2.71 (m, 1H, H-5), 3.20 (m, 1H, H′-5), 3.47 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.57 (s, 3H, OCH_3), 4.37 (s, 1H, H-α), 6.93 (dd, $^3J_1$=5.0, $^3J_2$=3.5, H-4′), 6.97 (d, ^3J=3.0, 1H, H-3′), 7.23 (d, ^3J=5.0, H-5′), 7.64 (br s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.5 (C-4), 28.8 (C(*C*H$_3$)$_3$), 31.0 (C-3), 50.9 (*C*(CH$_3$)$_3$), 51.9 (O*C*H$_3$), 54.0 (C-5), 61.4 (C-2), 68.4 (C-α), 126.1 (C-3′), 126.7 (C-5′), 128.3 (C-4′), 139.5 (C-2′), 170.2 (*C*ONH), 176.0 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}N_2O_3SNa$ 347.1405 (M+Na)$^+$ found: 347.1408. (2*S*,α*R*)-**3c**: pale-yellow oil; TLC: R_f=0.24 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −63.4 (*c* 1, $CHCl_3$); IR (KBr) 701, 758, 1172, 1203, 1364, 1391, 1436, 1456, 1510, 1685, 1736, 2855, 2923, 2964, 3337; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36 (s, 9H, C(CH_3)$_3$), 1.76 (m, 1H, H-4), 1.84 (m, 1H, H′-4), 1.90 (m, 1H, H-3), 2.09 (m, 1H, H′-3), 2.65 (m, 1H, H-5), 2.91 (m, 1H, H′-5), 3.56 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.70 (s, 3H, OCH_3), 4.57 (s, 1H, H-α), 6.94 (dd, $^3J_1$=5.0, $^3J_2$=3.5, 1H, H-4′), 6.97 (d, ^3J=3.0, 1H, H-3′), 7.26 (m, 2H, H-5′, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.0 (C-4), 28.7 (C(*C*H$_3$)$_3$), 30.0 (C-3), 49.9 (C-5), 50.9 (*C*(CH$_3$)$_3$), 52.0 (O*C*H$_3$), 63.3 (C-α), 67.1 (C-2), 125.9 (C-3′), 126.3 (C-5′), 128.2 (C-4′), 138.7 (C-2′), 169.7 (*C*ONH), 175.2 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}N_2O_3SNa$ 347.1405 (M+Na)$^+$ found: 347.1399.

*4.2.4. (2S,αS)- and (2S,αR)-(α-tert-Butyl-carbamoyl-α-(3-furyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**3d** and (2S,αR)-**3d**.* From L-proline (2.32 g, 20.16 mmol), 3-furancarboxaldehyde (16.80 mmol, 1.46 mL) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: PE/AcOEt 8:1 to 1:1): yield 3.97 g (77%): 2.29 g (44%) of (2*S*,α*S*)-**3d**, 0.42 g (7%) of (2*S*,α*R*)-**3d** and 1.26 (24%) of diastereomeric mixture. (2*S*,α*S*)-**3d**: white solid; mp 57–58 °C; TLC: R_f=0.11 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −2.6 (*c* 1, $CHCl_3$); IR (KBr) 603, 758, 874, 1023, 1170, 1203, 1364, 1456, 1518, 1676, 1735, 2843, 2873, 2965, 3300; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (s, 9H, C(CH_3)$_3$), 1.80–1.94 (m, 3H, H-3, H-4, H′-4), 2.05 (m, 1H, H′-3), 2.64 (m, 1H, H-5), 3.20 (m, 1H, H′-5), 3.44 (dd, $^3J_1$=10.0, $^3J_2$=4.0, 1H, H-2), 3.58 (s, 3H, OCH_3), 4.02 (s, 1H, H-α), 6.25 (ps, 1H, H-4′), 7.33 (pt, ^4J=4.0, 1H, H-2′), 7.39 (ps, 1H, H-5′), 7.70 (br s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.6 (C-4), 28.9 (C(*C*H$_3$)$_3$), 30.9 (C-3), 50.8 (*C*(CH$_3$)$_3$), 51.9 (O*C*H$_3$), 54.2 (C-5), 61.5 (C-2), 64.9 (C-α), 110.4 (C-4′), 121.5 (C-3′), 142.2 (C-2′), 143.2 (C-2′), 170.8 (*C*ONH), 176.2 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}N_2O_4Na$ 331.1634 (M+Na)$^+$ found: 331.1623. (2*S*,α*R*)-**3d**: white solid; mp 56–57 °C; TLC: R_f=0.17 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −62.5 (*c* 1, $CHCl_3$); IR (KBr) 602, 874, 1023, 1161, 1203, 1364, 1456, 1516, 1685, 1736, 2855, 2926, 2963, 3337; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36 (s, 9H, C(CH_3)$_3$), 1.75 (m, 1H, H-4), 1.82 (m, 1H, H′-4), 1.90 (m, 1H, H-3), 2.08 (m, 1H, H′-3), 2.60 (m, 1H, H-5), 2.89 (m, 1H, H′-5), 3.48 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.70 (s, 3H, OCH_3), 4.23 (s, 1H, H-α), 6.35 (ps, 1H, H-4′), 7.32 (br s, 1H, CON*H*), 7.38 (pt, 1H, H-2′), 7.40 (ps, 1H, H-5′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.0 (C-4), 28.8 (C(*C*H$_3$)$_3$), 29.9 (C-3), 49.7 (O*C*H$_3$), 50.8 (*C*(CH$_3$)$_3$), 52.0 (C-5), 62.8 (C-α), 63.4 (C-2), 110.5 (C-4′), 120.3 (C-3′), 141.8 (C-5′), 143.1 (C-2′), 170.2 (*C*ONH), 175.3 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}N_2O_4Na$ 331.1634 (M+Na)$^+$ found: 331.1641.

*4.2.5. (2R,αR)- and (2R,αS)-1-(α-tert-Butyl-carbamoyl-α-phenyl-methyl)-piperidine-2-carboxylic acid methyl ester (2R,αR)-**3e** and (2R,αS)-**3e**.* From D-pipecolic acid (2.60 g, 20.16 mmol), benzaldehyde (16.80 mmol, 1.70 mL) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: PE/AcOEt 9:1 to 3:1): yield 2.59 g (46%) of inseparable diastereomeric mixture. White wax; mp 43–46 °C; TLC: R_f=0.39 (PE/AcOEt 3:1); ^{1}H NMR ($CDCl_3$, 500 MHz): (2*R*,α*R*)-**3e** (major): δ 1.38 (s, 9H, C(CH_3)$_3$), 1.45–1.53 (m, 2H, H-4, H′-4), 1.59 (m, 1H, H-3), 1.64–1.72 (m, 2H, H-5, H′-5), 2.02 (m, 1H, H′-3), 2.40 (dt, ^2J=12.5, $^3J_1$=$^3J_2$=3.5, 1H, H-6), 2.81 (td, ^2J=$^3J_1$=12.5,

$^3J_2$=4.5, 1H, H′-6), 3.60 (pt, ^3J=4.0, 1H, H-2), 3.68 (s, 3H, OCH_3), 4.37 (s, 1H, H-α), 7.24–7.29 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′, N*H*); (2*R*,α*S*)-**3e** (minor): δ 1.86–1.93 (m, 1H, H′-3), 2.44–2.50 (m, 1H, H-6), 3.00 (m, ^2J=12.5, $^3J_1$=10.0, $^3J_2$=2.5, 1H, H′-6), 3.27 (pt, ^3J=4.5, 1H, H-2), 3.62 (s, 3H, OCH_3), 4.33 (s, 1H, H-α), the remaining ^{1}H signals overlap with the signals of (2*R*,α*R*)-**3e** diastereomer; ^{13}C NMR ($CDCl_3$, 125 MHz): (2*R*,α*R*)-**3e** (major): δ 21.1 (C-5), 25.3 (C-4), 28.5 (C-3), 28.7 (C(CH_3)$_3$), 45.7 (C-6), 50.8 (*C*(CH_3)$_3$), 51.4 (O*C*H$_3$), 59.6 (C-2), 73.0 (C-α), 128.0 (C-4′), 128.4 (C-2′, C-6′), 129.2 (C-3′, C-5′), 137.0 (C-1′), 171.0 (*C*ONH), 173.6 (*C*OOCH$_3$); (2*R*,α*S*)-**3e** (minor): δ 21.6 (C-5), 25.7 (C-4), 47.5 (C-6), 50.5 (*C*(CH_3)$_3$), 58.8 (C-2), 71.4 (C-α), 128.1 (C-4′), 128.3 (C-2′, C-6′), 129.5 (C-3′, C-5′), 135.2 (C-1′), 170.9 (*C*ONH), 173.5 (*C*OOCH$_3$); the remaining ^{13}C signals overlap with the signals of (2*R*,α*R*)-**3e** diastereomer; HRMS (ESI$^+$) calcd for $C_{19}H_{28}N_2O_3Na$: 355.1998 (M+Na)$^+$ found 355.1987.

4.2.6. rac-N-Phenyl-N-(α-tert-butyl-carbamoyl-α-phenylmethyl)-aminoacetic acid methyl ester ***3f***. From *N*-phenylglycine (3.05 g, 20.16 mmol), benzaldehyde (16.80 mmol, 1.70 mL) and *tert*-butyl isocyanide (2.00 mL, 16.80 mmol); FC (gradient: PE/AcOEt 6:1 to 3:1): yield 1.42 g (24%). Yellow powder; mp 119–121 °C; TLC: R_f=0.44 (PE/AcOEt 3:1); IR (KBr): 696, 750, 1174, 1220, 1453, 1503, 1538, 1599, 1674, 1739, 2966, 3062, 3314; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.34 (s, 9H, C(*C*H$_3$)$_3$), 3.68 (s, 1H, H-2), 3.73 (s, 3H, OCH_3), 3.80 (m, ^2J=18.5, 1H, H′-2), 5.23 (s, 1H, H-α), 6.70 (d, ^3J=8.0, 2H, H-2″, H-6″), 6.87 (t, ^3J=8.0, 1H, H-4″), 7.24–7.30 (m, 4H, H-2′, H-6′, H-3″, H-5″), 7.30–7.39 (m, 3H, H-3′, H-4′, H-5′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.7 (C(*C*H$_3$)$_3$), 49.5 (C-2), 51.5 (*C*(CH_3)$_3$), 52.7 (O*C*H$_3$) 70.1 (C-α), 113.2 (C-2″, C-6″), 119.2 (C-4″), 128.9 (C-4′), 129.3 (C-2′, C-6′), 129.6 (C-3′, C-5′), 129.9 (C-3″,C-5″), 136.1 (C-1′), 147.5 (C-1″), 170.5 (*C*ONH), 173.9 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{21}H_{26}N_2O_3Na$: 377.1841 (M+Na)$^+$ found 377.1829.

4.2.7. (2S,αS)- and (2S,αR)-α-(1-(1,1,3,3-Tetramethylbutyl)-carbamoyl-α-phenylmethyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)- ***3g*** *and (2S,αR)-* ***3g***. From L-proline (2.32 g, 20.16 mmol), benzaldehyde (16.80 mmol, 1.70 mL) and 1,1,3,3-tetramethylbutyl isocyanide (3.10 mL, 16.80 mmol); FC (gradient: PE/AcOEt 9:1 to 3:1): yield 3.27 g (54%): 2.28 g (38%) of (2*S*,α*S*)-**3g**, 0.44 g (7%) of (2*S*,α*S*)-**3g** and 0.55 (9%) of diastereomeric mixture. (2*S*,α*S*)-**3g**: colorless oil; TLC: R_f=0.26 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −3.1 (*c* 0.667, $CHCl_3$); IR (KBr): 701, 759, 1170, 1212, 1454, 1519, 1672, 1736, 2872, 2906, 2952, 3312; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.04 (s, 9H, C(*C*H$_3$)$_3$), 1.44 (s, 3H, CCH_3), 1.50 (s, 3H, CCH_3′), 1.73 (d, ^2J=15.0, 1H, CH_2′), 1.79 (d, ^2J=15.0, 1H, CH_2′), 1.78–1.90 (m, 3H, H-3, H-4, H′-4), 2.02 (m, 1H, H′-3), 2.70 (m, 1H, H-5), 3.22 (m, 1H, H′-5), 3.31 (dd, $^3J_1$=10.0, $^3J_2$=4.0, 1H, H-2), 3.51 (s, 3H, OCH_3), 4.09 (s, 1H, H-α), 7.22–7.32 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.70 (br s, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.4 (C-4), 28.3 (C(*C*H$_3$)$_2$), 29.1 (C(*C*H$_3$′)$_2$), 30.9 (*C*(CH_3)$_3$), 31.8 (C(CH_3)$_3$), 31.7 (C-3), 51.8 (OCH_3), 53.5 (*C*H$_2$), 54.8 (C-5), 55.1 (*C*(CH_3)$_2$) 61.9 (C-2), 74.4 (C-α), 128.4 (C-4′), 128.7 (C-3′, C-5′), 129.4 (C-2′, C-6′), 137.6 (C-1′), 171.0 (*C*ONH), 176.0 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{22}H_{34}N_2O_3Na$: 397.2467 (M+Na)$^+$ found 397.2493. (2*S*,α*R*)-**3g**: colorless oil; TLC: R_f=0.30 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −62.5 (*c* 0.680, $CHCl_3$); IR (KBr): 699, 757, 1163, 1206, 1453, 1513, 1679, 1739, 2871, 2906, 2952, 3338; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.98 (s, 9H, C(*C*H$_3$)$_3$), 1.40 (s, 3H, CCH_3), 1.41 (s, 3H, CCH_3′), 1.72 (m, 3H, H-4, CH_2), 1.83 (m, 1H, H′-4), 1.89 (m, 1H, H-3), 2.04 (m, 1H, H′-3), 2.51 (m, 1H, H-5), 2.94 (m, 1H, H′-5), 3.54 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.66 (s, 3H, OCH_3), 4.25 (s, 1H, H-α), 7.24–7.38 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.9 (C-4), 28.7 (C(*C*H$_3$)$_2$), 29.1 (C(*C*H$_3$′)$_2$), 29.7 (C-3), 31.7 (C(CH_3)$_3$), 31.8 (*C*(CH_3)$_3$), 50.4 (OCH_3), 52.0 (*C*H$_2$), 52.9 (C-5), 55.0 (*C*(CH_3)$_2$) 63.4 (C-2), 72.4 (C-α), 128.1 (C-4′), 128.4 (C-2′, C-6′), 129.7 (C-3′, C-5′), 136.2 (C-1′), 170.4 (*C*ONH), 175.2 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{22}H_{34}N_2O_3Na$: 397.2467 (M+Na)$^+$ found 397.2454.

4.2.8. (2S,αS)- and (2S,αR)-1-(α-Benzyl-carbamoyl-α-(4-chlorophenyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)- ***3h*** *and (2S,αR)-* ***3h***. From L-proline (2.32 g, 20.16 mmol), benzaldehyde (16.80 mmol, 1.70 mL) and benzyl isocyanide (2.10 mL, 16.80 mmol); FC (gradient: PE/AcOEt 4:1 to 1:1): yield 3.22 g (52%): 2.20 g (36%) of (2*S*,α*S*)-**3h**, 0.69 g (11%) of (2*S*,α*S*)-**3h** and 0.33 g (6%) of diastereomeric mixture. (2*S*,α*S*)-**3h**: white solid; mp 109–111 °C; TLC: R_f=0.07 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −113.1 (*c* 0.713, $CHCl_3$); IR (KBr): 699, 756, 1015, 1090, 1170, 1202, 1490, 1517, 1660, 1730, 2847, 2932, 2950, 3030, 3064, 3293; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.78–1.87 (m, 3H, H-3, H-4, H′-4), 2.01 (m, 1H, H′-3), 2.69 (m, 1H, H-5), 3.19 (m, 1H, H′-5), 3.33 (dd, $^3J_1$=9.5, $^3J_2$=4.0, 1H, H-2), 3.45 (s, 3H, OCH_3), 4.27 (s, 1H, H-α), 4.51 (d, ^3J=6.0, 2H, H-β, H′-β), 7.19–7.36 (m, 9H, H-2′, H-3′, H-5′, H-6′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.95 (pt, ^3J=5.5, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.1 (C-4), 30.6 (C-3), 43.3 (C-β), 51.7 (O*C*H$_3$), 54.3 (C-5), 61.9 (C-2), 72.7 (C-α), 127.4 (C-4″), 127.8 (C-2′, C-6′), 128.6 (C-2″, C-6″), 128.7 (C-3″, C-5″), 130.5 (C-3′, C-5′), 134.3 (C-4′), 135.5 (C-1′), 138.4 (C-1″), 171.4 (*C*ONH), 175.6 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{21}H_{23}{}^{15}ClN_2O_3Na$: 409.1295 (M+Na)$^+$ found 409.1287. (2*S*,α*R*)-**3h**: white solid; mp 126–127 °C; TLC: R_f=0.11 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ +35.0 (*c* 1.427, $CHCl_3$); IR (KBr): 699, 756, 1014, 1090, 1159, 1204, 1491, 1515, 1661, 1730, 2844, 2950, 3029, 3317; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.73 (m, 1H, H-4), 1.80 (m, 1H, H′-4), 1.88 (m, 1H, H-3), 2.05 (m, 1H, H′-3), 2.49 (m, ^2J=9.5, $^3J_1$=$^3J_2$=8.0, 1H, H-5), 2.90 (ddd, ^2J=9.5, $^3J_1$=7.5, $^3J_2$=3.0, 1H, H′-5), 3.49 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.54 (s, 3H, OCH_3), 4.41 (dd, ^2J=15.0, ^3J=6.0, 1H, H-β), 4.42 (s, 1H, H-α), 4.50 (dd, ^2J=15.0, ^3J=6.0, 1H, H-β′), 7.23–7.34 (m, 9H, H-2′, H-3′, H-5′, H-6′, H-2″, H-3″, H-4″, H-5″, H-6″), 7.74 (pt, ^3J=5.5, 1H, CON*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.6 (C-4), 29.5 (C-3), 43.3 (C-β), 50.3 (C-5), 51.8 (O*C*H$_3$), 63.3 (C-2), 70.8 (C-α), 127.4 (C-4″), 127.7 (C-2′, C-6′), 128.6 (C-2″, C-6″), 128.7 (C-3″, C-5″), 130.6 (C-3′, C-5′), 134.0 (C-4′), 134.5 (C-1′), 138.4 (C-1″), 171.0 (*C*ONH), 174.8 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{21}H_{23}{}^{15}ClN_2O_3Na$: 409.1295 (M+Na)$^+$ found 409.1301.

4.3. General procedure for BF_3·2CH_3COOH-mediated N-de*tert*butylation

The appropriate Ugi product **3** was dissolved in BF_3·2CH_3COOH (~36% BF_3 basis, 3 mL per 1 mmol of substrate), at 40 °C. After 15 min, the mixture was allowed to reach rt and stirred until total consumption of the starting material (TLC), typically for 24 h. The resulting solution was poured onto excess of crushed ice and made alkaline with 25% aqueous solution of ammonia. The mixture was extracted with DCM (3×40 mL). The combined organic phase was washed with water (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC.

4.3.1. (2S,αS)-1-(α-Carbamoyl-α-(4-chlorophenyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)- ***4a***. From (2*S*,α*S*)-**3a** (2.44 g, 6.90 mmol) and BF_3·2CH_3COOH (21 mL); FC (gradient: petroleum ether/AcOEt 2:1 to 0:1): yield 1.51 g (74%) of (2*S*,α*S*)-**4a**. White solid; mp 114–116 °C; TLC: R_f=0.28 (AcOEt); $[\alpha]_D^{20}$ −2.9 (*c* 0.92, $CHCl_3$); IR (KBr): 818, 1204, 1489, 1678, 1732, 2851, 2955, 3190, 3306, 3431; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.88 (m, 3H, H-3, H-4, H′-4), 2.04 (m, 1H, H′-3), 2.72 (m, 1H, H-5), 3.27 (m 1H, H′-5), 3.35 (dd, $^3J_1$=9.5, $^3J_2$=5.0, 1H, H-2), 3.53 (s, 3H, OCH_3), 4.22 (s, 1H, H-α), 5.62 (br s, 1H, CON*H*) 7.27 (dt, 2H, H-3′, H-5′), 7.30 (dt, ^3J=9.0, ^4J=2.5, 2H, H-2′, H-6′), 7.59 (br s, 1H, CON*H*′); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.8 (C-4), 30.4 (C-3), 51.0 (O*C*H$_3$), 53.6 (C-5), 61.8 (C-2), 72.0 (C-α), 128.5 (C-3′, C-5′), 130.3 (C-2′, C-6′), 134.1 (C-4′), 135.2 (C-1′), 174.5

(*C*ONH), 175.4 (*C*OOCH$_3$); HPLC: retention time 24.9 min (MeCN/H$_2$O 25:75); HRMS (ESI$^+$) calcd for $C_{14}H_{17}{}^{15}ClN_2O_3Na$: 319.0826 (M+Na)$^+$ found 319.0854.

*4.3.2. (2S,αR)-1-(α-Carbamoyl-α-(4-chlorophenyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αR)-**4a**.* From (2*S*,α*R*)-**3a** (0.30 g, 0.85 mmol) and BF$_3$·2CH$_3$COOH (3 mL); FC (gradient: petroleum ether/AcOEt 4:1 to 0:1): yield 0.19 g (76%) of (2*S*,α*R*)-**4a** and 20 mg (9%) of (4*R*,8a*S*)-**5a**. Yellow oil; TLC: R_f=0.36 (AcOEt); $[\alpha]_D^{20}$ −110.3 (*c* 1.125, CHCl$_3$); IR (KBr): 821, 1204, 1489, 1682, 1732, 2847, 2951, 3202, 3333, 3437; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.76 (m, 1H, H-4), 1.85 (m, 1H, H′-4), 1.93 (m, $^2J_2$=17.5, $^3J_1$=8.0, $^3J_2$=3.5, $^3J_3$=3.5, 1H, H-3), 2.06 (m, $^2J_2$=18.0, $^3J_1$=9.0, 1H, H′-3), 2.52 (ddd, $^2J_2$=9.0, $^3J_1$=8.0, $^3J_2$=7.5, 1H, H-5), 2.96 (ddd, $^2J_2$=9.0, $^3J_1$=7.5, $^3J_2$=4.0, 1H, H′-5), 3.50 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.68 (s, 3H, OC*H*$_3$), 4.41 (s, 1H, H-α), 5.47 (br s, 1H, CON*H*) 7.26 (m, 2H, H-3′, H-5′), 7.32 (dt, ^3J=8.5, ^4J=2.0, 2H, H-2′, H-6′), 7.56 (br s, 1H, CON*H*′); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 23.4 (C-4), 29.3 (C-3), 49.8 (C-5), 51.7 (O*C*H$_3$), 62.7 (C-2), 69.8 (C-α), 128.5 (C-3′, C-5′), 130.6 (C-2′, C-6′), 133.9 (C-4′), 134.0 (C-1′), 174.3 (*C*ONH$_2$), 174.7 (*C*OOCH$_3$); HPLC: retention time 40.2 min (MeCN/H$_2$O 25:75); HRMS (ESI$^+$) calcd for $C_{14}H_{17}{}^{15}ClN_2O_3Na$: 319.0826 (M+Na)$^+$ found 319.0816.

*4.3.3. (2S,αS)-1-(α-Carbamoyl-α-(2-naphthyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**4b**.* From (2*S*,α*S*)-**3b** (1.02 g, 2.77 mmol), and BF$_3$·2CH$_3$COOH (8 mL); FC (gradient: PE/AcOEt 2:1 to 0:1): yield 0.66 g (75%) of (2*S*,α*S*)-**4b**. White solid; mp 52−54 °C; TLC: R_f=0.28 (AcOEt); $[\alpha]_D^{20}$ +25.8 (*c* 0.936, CHCl$_3$); IR (KBr): 748, 818, 1204, 1369, 1435, 1508, 1674, 1732, 2851, 2924, 3198, 3333, 3429; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.86 (m, 3H, H-3, H-4, H′-4), 2.04 (m, 1H, H′-3), 2.79 (m, 1H, H-5), 3.32 (m, 1H, H′-5), 3.41 (dd, $^3J_1$=9.5, $^3J_2$=4.0, 1H, H-2), 3.38 (s, 3H, OC*H*$_3$), 4.42 (s, 1H, H-α), 5.91 (br s, 1H, CON*H*), 7.38 (dd, ^3J=8.5, ^4J=2.0, 1H, H-3′), 7.47 (m, 2H, H-6′, H-7′), 7.67 (br s, 1H, CON*H*′), 7.76−7.83 (m, 4H, H-1′, H-4′, H-5′, H-8′); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 24.2 (C-4), 30.8 (C-3), 51.6 (C-5), 54.3 (O*C*H$_3$), 61.9 (C-2), 73.3 (C-α), 126.3 (C-3′), 126.3 (C-7′), 126.4 (C-6′), 127.6 (C-1′), 128.1 (C-8′), 128.3 (C-4′), 128.7 (C-5′), 133.2 (C-4a′), 133.2 (C-8a′), 134.1 (C-2′), 174.8 (*C*OOCH$_3$), 175.9 (*C*ONH$_2$); HRMS (ESI$^+$) calcd for $C_{18}H_{20}N_2O_3Na$: 335.1372 (M+Na)$^+$ found 335.1360.

*4.3.4. (2S,αS)-1-(α-Carbamoyl-α-(2-thiophene)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**4c**.* From (2*S*,α*S*)-**3c** (2.77 g, 8.54 mmol), and BF$_3$·2CH$_3$COOH (26 mL); FC (gradient: PE/AcOEt 2:1 to 0:1): yield 1.32 g (57%) of (2*S*,α*S*)-**4c**. Pale-yellow solid; mp 172−173 °C; TLC: R_f=0.44 (AcOEt); $[\alpha]_D^{20}$ −4.0 (*c* 1, CHCl$_3$); IR (KBr) 628, 699, 757, 1204, 1379, 1435, 1634, 1672, 1729, 2806, 2948, 3174, 3390; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.82−1.92 (m, 3H, H-3, H-4, H′-4), 2.03 (m, 1H, H′-3), 2.76 (m, 1H, H-5), 3.28 (m, 1H, H′-5), 3.51 (dd, $^3J_1$=9.5, $^3J_2$=3.5, 1H, H-2), 3.58 (s, 3H, OC*H*$_3$), 4.54 (s, 1H, H-α), 5.73 (br s, 1H, CON*H*), 6.96 (dd, $^3J_1$=5.0, $^3J_2$=3.5, H-4′), 7.03 (d, ^3J=3.0, 1H, H-3′), 7.26 (d, ^3J=4.5, H-5′), 7.66 (br s, 1H, CON*H*′); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 24.4 (C-4), 31.0 (C-3), 52.0 (O*C*H$_3$), 54.1 (C-5), 61.5 (C-2), 67.3 (C-α), 126.3 (C-3′), 126.9 (C-5′), 128.3 (C-4′), 138.5 (C-2′), 174.0 (*C*ONH$_2$), 176.1 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{12}H_{16}N_2O_3SNa$ 291.0779 (M+Na)$^+$ found: 291.0771.

*4.3.5. (2S,αS)-1-(α-Carbamoyl-α-(3-furyl)methyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**4d**.* From (2*S*,α*S*)-**3d** (2.24 g, 7.26 mmol) and BF$_3$·2CH$_3$COOH (22 mL); FC (gradient: PE/AcOEt 2:1 to 0:1): yield 1.19 g (65%) of (2*S*,α*S*)-**4d**. White solid; mp 159−161 °C; TLC: R_f=0.30 (AcOEt); $[\alpha]_D^{20}$ +1.3 (*c* 1, CHCl$_3$); IR (KBr) 874, 1022, 1159, 1205, 1677, 1729, 2802, 2924, 2952, 3152; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.80−1.95 (m, 3H, H-3, H-4, H′-4), 2.05 (m, 1H, H′-3), 2.68 (m, 1H, H-5), 3.28 (m, 1H, H′-5), 3.46 (dd, $^3J_1$=9.5, $^3J_2$=4.0, 1H, H-2), 3.58 (s, 3H, OC*H*$_3$), 4.18 (s, 1H, H-α), 5.71 (br s, 1H, CON*H*), 6.32 (ps, 1H, H-4′), 7.36 (pt, 1H, H-2′), 7.44 (ps, 1H, H-5′), 7.70 (br s, 1H, CON*H*′); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 24.5 (C-4), 30.8 (C-3), 52.0 (C-5), 54.3 (O*C*H$_3$), 61.6 (C-2), 64.0 (C-α), 110.5 (C-4′), 120.8 (C-3′), 142.3 (C-2′), 143.4 (C-2′), 174.7 (*C*ONH$_2$), 176.2 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{12}H_{16}N_2O_4Na$ 275.1008 (M+Na)$^+$ found: 275.1016.

*4.3.6. (2S,αS)-1-(α-Carbamoyl-α-phenylmethyl)-pyrrolidine-2-carboxylic acid methyl ester (2S,αS)-**4e**.* From (2*S*,α*S*)-**3g** (1.97 g, 5.46 mmol) and BF$_3$·2CH$_3$COOH (20 mL); FC (gradient: PE/AcOEt 2:1 to 0:1): yield 1.16 g (81%) of (2*S*,α*S*)-**4e**. White solid; mp 147−148 °C; TLC: R_f=0.30 (AcOEt); $[\alpha]_D^{20}$ +5.30 (*c* 1, CHCl$_3$); IR (KBr): 759, 1171, 1205, 1454, 1673, 1732, 2849, 2949, 3188; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 1.80−1.95 (m, 3H, H-3, H-4, H′-4), 2.03 (m, 1H, H′-3), 2.74 (m, 1H, H-5), 3.29 (m, 1H, H′-5), 3.36 (dd, $^3J_1$=9.5, $^3J_2$=4.0, 1H, H-2), 3.50 (s, 3H, OC*H*$_3$), 4.24 (s, 1H, H-α), 5.65 (br s, 1H, CON*H*), 7.28−7.36 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 7.64 (br s, 1H, CON*H*′); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 24.5 (C-4), 30.9 (C-3), 51.9 (O*C*H$_3$), 54.6 (C-5), 62.0 (C-2), 73.4 (C-α), 128.7 (C-4′), 128.8 (C-3′, C-5′), 129.4 (C-2′, C-6′), 136.8 (C-1′), 175.0 (*C*ONH$_2$), 176.2 (*C*OOCH$_3$); HRMS (ESI$^+$) calcd for $C_{14}H_{18}N_2O_3Na$: 285.1210 (M+Na)$^+$ found 285.1224.

4.4. General procedure for intramolecular cyclocondensation

To a stirred solution of appropriate 2,6-DKP precursor **4** in absolute EtOH (5 mL per 1 mmol of substrate), NaOH (1 equiv) was added at rt. After dissolution of the hydroxide, the mixture was quenched with saturated aqueous solution of ammonium chloride (100 mL). The resulting cloudy solution was extracted with DCM (3×30 mL). The combined organic phase was washed with water (20 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by FC.

*4.4.1. (4S,8aS)-4-(4-Chlorophenyl)-perhydropyrrolo[1,2-a]pyrazine-1,3-dione (4S,8aS)-**5a**.* From (2*S*,α*S*)-**4a** (1.23 g, 4.14 mmol) and NaOH (166 mg, 1 equiv); FC (gradient: petroleum ether/AcOEt 5:1 to 2:1): yield 1.01 (92%): 0.79 g (72%) of (4*S*,8a*S*)-**5a** and 0.22 (20%) of diastereomeric mixture. White solid; mp 146−147 °C; TLC: R_f=0.25 (petroleum ether/AcOEt 3:1); $[\alpha]_D^{20}$ −114.7 (*c* 0.935, CHCl$_3$); IR (KBr): 802, 1014, 1092, 1261, 1319, 1489, 1697, 2851, 2920, 2962, 3229; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.92 (m, 2H, H-7, H-7′), 2.26 (m, 1H, H-8), 2.32 (m, 1H, H′-8), 2.80 (pq, ^2J=$^3J_1$=7.5=$^3J_2$=8.5, 1H, H-6), 3.20 (m, ^2J=8.5, $^3J_1$=8.0, $^3J_2$=3.5, 1H, H′-6), 3.64 (dd, $^3J_1$=8.5, $^3J_2$=3.0, 1H, H-8a), 4.81 (s, 1H, H-4), 7.35 (dt, ^3J=8.5, ^4J=2.0, 2H, H-3′, H-5′), 7.40 (dt, ^3J=8.5, ^4J=2.0, 2H, H-2′, H-6′), 8.02 (br s, 1H, N*H*); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 22.4 (C-7), 27.4 (C-8), 51.8 (C-6), 57.0 (C-8a), 63.3 (C-4), 128.4 (C-3′, C-5′), 129.1 (C-2′, C-6′), 132.7 (C-4′), 134.4 (C-1′), 171.4 (C-3), 173.8 (C-1); HPLC: retention time 49.1 min (MeCN/H$_2$O 25:75); HRMS (ESI$^+$) calcd for $C_{13}H_{12}{}^{15}ClN_2O_2Na_2$: 309.0377 (M−H+2Na)$^+$ found 309.0393.

*4.4.2. (4R,8aS)-4-(4-Chlorophenyl)-perhydropyrrolo[1,2-a]pyrazine-1,3-dione (4R,8aS)-**5a**.* From (2*S*,α*R*)-**4a** (0.21 g, 0.71 mmol) and NaOH (28 mg, 1 equiv); FC (gradient: petroleum ether/AcOEt 5:1 to 2:1): yield 165 mg (88%): 128 mg (68%) of (4*R*,8a*S*)-**5a** and 37 mg (20%) of diastereomeric mixture. White solid; mp 173−175 °C; TLC: R_f=0.14 (petroleum ether/AcOEt 3:1); $[\alpha]_D^{20}$ −112.8 (*c* 0.968, CHCl$_3$); IR (KBr): 822, 1014, 1088, 1219, 1319, 1493, 1705, 2804, 2924, 2962, 3221; ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.83 (m, 2H, H-7, H-7′), 2.14 (m, 2H, H-6, H-8), 2.23 (m, 1H, H′-8), 2.82 (td, ^2J=9.0, $^3J_1$=9.0, $^3J_2$=2.0, 1H, H′-6), 3.18 (pt, $^3J_1$=8.0, 1H, H-8a), 4.03 (s, 1H, H-4), 7.31 (dt, ^3J=8.5, ^4J=2.0, 2H, H-3′, H-5′), 7.37 (dt, ^3J=8.5, ^4J=2.0, 2H, H-2′, H-6′), 7.98 (br s, 1H, N*H*); ^{13}C NMR (125 MHz, CDCl$_3$): δ 21.0 (C-7), 24.7 (C-8), 52.1 (C-6), 65.9 (C-8a), 71.0 (C-4), 129.0 (C-3′, C-5′), 130.3 (C-2′, C-6′), 134.4 (C-4′), 134.7 (C-1′), 171.0 (C-3), 171.8 (C-1); HPLC: retention time 56.3 min (MeCN/H$_2$O

25:75); HRMS (ESI^+) calcd for $C_{13}H_{13}{}^{15}ClN_2O_2Na$: 287.0563 $(M+Na)^+$ found 287.0578.

*4.4.3. (4S,8aS)-4-(2-Naphthyl)-perhydropyrrolo[1,2-a]pyrazine-1,3-dione (4S,8aS)-**5b**.* From (2*S*,α*S*)-**4b** (0.50 g, 1.60 mmol) and NaOH (64 mg, 1 equiv); FC (gradient: PE/AcOEt 5:1 to 2:1): yield 0.40 g (90%): 0.33 g (73%) of (4*S*,8a*S*)-**5b** and 76 mg (19%) of diastereomeric mixture. White solid; mp 123–124 °C (dec); TLC: R_f=0.22 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −79.4 (*c* 1.097, $CHCl_3$); IR (KBr): 752, 815, 1239, 1317, 1354, 1705, 1695, 2817, 2965, 3215; ^1H NMR (500 MHz, $CDCl_3$): δ 1.93 (m, 2H, H-7, H-7′), 2.28 (m, 2H, H-8, H′-8), 2.85 (pq, ^2J=$^3J_1$=7.5=$^3J_2$=8.5, 1H, H-6), 3.25 (td, ^2J=$^3J_1$=8.5, $^3J_2$=3.5, 1H, H′-6), 3.70 (dd, $^3J_1$=8.5, $^3J_2$=3.0, 1H, H-8a), 5.01 (s, 1H, H-4), 7.49 (m, 2H, H-6′, H-7′), 7.60 (dd, ^3J=8.5, ^4J=2.0, 1H, H-3′), 7.78–7.87 (m, 4H, H-1′, H-4′, H-5′, H-8′), 8.55 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5 (C-7), 27.4 (C-8), 51.8 (C-6), 57.2 (C-8a), 64.1 (C-4), 125.0 (C-3′), 125.8 (C-1′), 126.5 (C-7′), 126.5 (C-6′), 127.6 (C-8′), 128.1 (C-4′), 128.8 (C-5′), 131.7 (C-2′), 133.1 (C-4a′), 133.1 (C-8a′), 171.9 (C-3), 174.1 (C-1); HRMS (ESI^+) calcd for $C_{17}H_{16}N_2O_2Na$: 303.1110 $(M+Na)^+$ found 303.1138.

*4.4.4. (4S,8aS)-4-(2-Thiophene)-perhydropyrrolo[1,2-a]pyrazine-1,3-dione (4S,8aS)-**5c**.* From (2*S*,α*S*)-**4c** (1.26 g, 4.70 mmol) and NaOH (188 mg, 1 equiv); FC (gradient: PE/AcOEt 5:1 to 2:1): yield 0.97 g (87%): 0.73 g (66%) of (4*S*,8a*S*)-**5c** and 0.23 g (19%) of diastereomeric mixture. Pale-yellow solid; mp 131–132 °C; TLC: R_f=0.23 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −184.6 (*c* 1, $CHCl_3$); IR (KBr) 706, 759, 1243, 1317, 1349, 1681, 1693, 1709, 1726, 2821, 2923, 3101, 3206; ^1H NMR (500 MHz, $CDCl_3$): δ 1.84–2.00 (m, 2H, H-7, H-7′), 2.30 (m, 2H, H-8, H′-8), 2.78 (pq, ^2J=$^3J_1$=$^3J_2$=8.5, 1H, H-6), 3.23 (td, ^2J=$^3J_1$=8.5, $^3J_2$=3.5, 1H, H′-6), 3.89 (dd, ^3J=8.5, $^3J_2$=3.0, 1H, H-8a), 5.01 (s, 1H, H-4), 6.96–7.02 (m, 2H, H-3′, H-4′), 7.31 (d, 1H, ^3J=5.0, H-5′), 8.20 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.6 (C-7), 27.3 (C-8), 51.7 (C-6), 57.6 (C-8a), 60.8 (C-4), 125.4 (C-3′), 126.4 (C-5′), 127.3 (C-4′), 138.4 (C-2′), 170.6 (C-3), 171.7 (C-1); HRMS (ESI^+) calcd for $C_{11}H_{12}N_2O_2SNa$ 259.0517 $(M+Na)^+$ found: 259.0510.

*4.4.5. (4S,8aS)-4-(3-Furyl)-perhydropyrrolo[1,2-a]pyrazine-1,3-dione (4S,8aS)-**5d**.* From (2*S*,α*S*)-**4d** (0.87 g, 3.45 mmol) and NaOH (178 mg, 1 equiv); FC (gradient: PE/AcOEt 5:1 to 2:1): yield 0.72 g (92%): 0.62 (79%) of (4*S*,8a*S*)-**5d** and 0.10 g (13%) of diastereomeric mixture. White solid; mp 125–126 °C; TLC: R_f=0.14 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −99.1 (*c* 1, $CHCl_3$); IR (KBr) 602, 766, 799, 875, 901, 1023, 1159, 1243, 1259, 1319, 1353, 1698, 2806, 2969, 3113; ^1H NMR (500 MHz, $CDCl_3$): δ 1.80–1.98 (m, 2H, H-7, H-7′), 2.25 (m, 1H, H-8), 2.31 (m, 1H, H′-8), 2.74 (pq, ^2J=$^3J_1$=$^3J_2$=8.5, 1H, H-6), 3.15 (td, ^2J=$^3J_1$=8.5, $^3J_2$=3.5, 1H, H′-6), 3.77 (dd, ^3J=8.5, $^3J_2$=3.0, 1H, H-8a), 4.74 (s, 1H, H-4), 6.44 (ps, 1H, H-4′), 7.44 (m, 2H, H-2′, H-5′), 8.12 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5 (C-7), 27.2 (C-8), 51.5 (C-6), 57.6 (C-8a), 57.7 (C-4), 109.9 (C-4′), 120.1 (C-3′), 140.6 (C-2′), 143.9 (C-5′), 171.5 (C-3), 173.8 (C-1); HRMS (ESI^-) calcd for $C_{11}H_{11}N_2O_3$ 219.0770 $(M-H)^-$ found: 219.0780.

*4.4.6. (4S,8aS)-4-Phenylperhydropyrrolo[1,2-a]pyrazine-1,3-dione **2**.* From (2*S*,α*S*)-**4e** (1.09 g, 4.16 mmol) and NaOH (166 mg, 1 equiv); FC (gradient: PE/AcOEt 5:1 to 2:1): yield 0.92 g (96%): 0.77 g (77%) of **2** and 0.19 g (19%) of diastereomeric mixture. White solid; mp 122–124 °C; R_f=0.24 (PE/AcOEt 3:1); $[\alpha]_D^{20}$ −132.8 (*c* 0.621, $CHCl_3$); HRMS (ESI^-) calcd for $C_{13}H_{13}N_2O_2$: 229.0971 $(M-H)^-$ found 229.0961. Physical constants and NMR spectral data match those previously reported.[1a]

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra of all new compounds. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.07.064.

References and notes

1. (a) Herold, F.; Dawidowski, M.; Wolska, I.; Chodkowski, A.; Kleps, J.; Turło, J.; Zimniak, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2091; (b) Dawidowski, M.; Herold, F.; Wilczek, M.; Kleps, J.; Wolska, I.; Turło, J.; Widomski, P.; Bielejewska, A. *Tetrahedron: Asymmetry* **2009**, *20*, 1759; (c) Dawidowski, M.; Herold, F.; Chodkowski, A.; Kleps, J.; Szulczyk, P.; Wilczek, M. *Eur. J. Med. Chem.* **2011**, *46*, 4859; (d) Dawidowski, M.; Herold, F.; Chodkowski, A.; Kleps, J. *Eur. J. Med. Chem.* **2012**, *48*, 347.
2. Castel-Branco, M. ,M.; Alves, G. ,L.; Figueiredo, I. ,V.; Falcão, A. ,C.; Caramona, M. ,M. *Methods Find. Exp. Clin. Pharmacol.* **2009**, *31*, 101.
3. Barton, M. E.; Klein, B. ,D.; Wolf, H. H.; White, H. S. *Epilepsy Res.* **2001**, *47*, 217.
4. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (b) Demharter, A.; Hörl, W.; Eberhardt, H.; Ugi, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 173; (c) Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657; (d) Ecker, H. *Molecules* **2012**, *17*, 1074.
5. (a) Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles* **1998**, *47*, 965; (b) Ugi, I.; Ebert, B.; Hörl, W. *Chemosphere* **2001**, *43*, 75; (c) Constabel, F.; Ugi, I. *Tetrahedron* **2001**, *57*, 5785; (d) Dömling, A.; Huang, Y. *Synthesis* **2010**, *17*, 2859.
6. To the best of our knowledge there has been only one, simultaneous report: Mandai, H.; Irie, S.; Mitsudo, K.; Suga, S. *Molecules* **2011**, *16*, 8815.
7. For examples of the application of 'convertible isocyanides', see: (a) Zhou, H.; Zhang, W.; Yan, B. *J. Comb. Chem.* **2010**, *12*, 206; (b) Guchhait, S. ,K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631; (c) Gilley, C. ,B.; Buller, M. ,J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631; (d) Gilley, C.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 4198; (e) Nikulnikov, M.; Tsirulnikov, S.; Kysil, V.; Ivachtchenko, A.; Krasavin, M. *Synlett* **2009**, 260; (f) Strocker, A. ,M.; Keating, T. ,A.; Tempest, P. ,A.; Armstrong, R. ,W. *Tetrahedron Lett.* **1996**, *37*, 1149; (g) Pirrung, M. ,C.; Ghorai, S.; Ibarra-Rivera, T. ,R. *J. Org. Chem.* **2009**, *74*, 4110; (h) Hulme, C.; Ma, L.; Cherrier, M.-P.; Romano, J. ,J.; Morton, G.; Duquenne, C.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1883; (i) Dai, Q.; Xie, X.; Xu, S.; Ma, D.; Tang, S.; She, X. *Org. Lett.* **2011**, *13*, 2302.
8. Godet, T.; Bonvin, Y.; Vincent, G.; Merle, D.; Thozet, A.; Ciufolini, M. ,A. *Org. Lett.* **2004**, *19*, 3281.
9. TFA is most widely utilized for this type of reaction, also for similar substrates, see: Ref. 8. For more examples and other amide de-*tert*butylating agents, see: (a) Schleicher, K. ,D.; Jamison, T. ,F. *Org. Lett.* **2007**, *9*, 875; (b) Zhou, F.; Ding, K.; Cai, Q. *Chem.—Eur. J.* **2011**, *17*, 12268; (c) Takàcs, E.; Varga, C.; Skoda-Földes, R.; Kollàr, L. *Tetrahedron Lett.* **2007**, *48*, 2453; (d) Mahalingam, A. ,K.; Wu, X.; Alterman, M. *Tetrahedron Lett.* **2006**, *47*, 3051; (e) Lacey, R. ,N. *J. Chem. Soc.* **1960**, 1633; (f) Conover, L. ,H.; Butler, K.; Johnston, J. ,D.; Korst, J. ,J.; Woodward, R. ,B. *J. Am. Chem. Soc.* **1962**, *84*, 3222.
10. Formation of the desired product was probably enhanced due to the improved solubility of the substrate.
11. The $[\alpha]_D$ values of the purified and separated diastereomers equaled 0, which indicated the formation racemates. This was further confirmed by conducting the reaction for compound **3e**, followed by analysis of the cyclocondensation products by chiral HPLC method described in Ref. 1b.