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Diastereoselective Ugi reaction without chiral amines: the synthesis of chiral pyrroloketopiperazines

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Abstract—The three-component Ugi reaction with chiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acids prepared from natural L-aminoacids was investigated. The reaction opens a new route to chiral substituted pyrroloketopiperazines. One of the first examples of an asymmetric Ugi reaction without chiral amines is described. The reaction proceeds with moderate diastereoselectivity to give the target compounds in good yields. The scope and limitation of the approach are discussed.

1. Introduction

The four-component Ugi reaction is of considerable interest owing to its exceptional synthetic efficiency and is widely used, especially in the field of modern combinatorial and medical chemistry.[1] This is most evident in the application towards multicomponent heterocyclisations. The three-component Ugi reaction wherein one component is a bifunctional building blocks is an effective strategy for the one-pot synthesis of various heterocyclic systems and the efficiency of bifunctional blocks containing various combinations of the four functional groups acting in the Ugi reaction has been shown.[2]

It is noteworthy that there is, to date, no general solution for the problem of the stereocontrol in the Ugi reaction. The only way to achieve an appropriate stereoinduction for the new stereocentre is to use a chiral amine.[3] In contrast, chiral acids, isocyanides and carbonyl compounds give poor[4] induction or even epimerisation[5] of the starting chiral stereocentre. Bifunctional chiral amines have been reported as stereoselective precursors for the Ugi synthesis of α-aminoacids[6] and substituted diketopiperazines.[7] We proposed that chiral bifunctional amine-free blocks would also be effective in an asymmetric Ugi reaction. Reaction of chiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acids obtained from enantiomerically pure natural aminoacids with isocyanides and amines would provide a novel route to chiral substituted 3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines. These compounds are of interest because 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines can serve as effective aldol protease inhibitors.[8]

2. Results and discussion

Chiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acids were prepared from natural L-aminoacids: alanine, phenylalanine, leucine, valine and isoleucine (Scheme 1). The hydrochloride salts of α-aminoacid ethyl esters reacted with 2,5-diMeO-THF to afford the corresponding chiral pyrroles (**1**–**5**) in good yields. Subsequent Vilsmeier-type formylation and basic hydrolysis under mild conditions led to the desired formylacids **11**–**15** in high yields. The optical rotatory power of acid **13** was identical to that described in literature.[9] In addition, the absence of racemisation during the ester hydrolysis was confirmed by an alternative transformation using TMSI.[10] The optical rotations for formylacids **11**, **12** and **14** were identical for the two independent methods.

Model acid **11** has been chosen to study the influence of the isocyanide and amine component on yield and diastereoselectivity of the Ugi reaction (Scheme 2). Recently, it was reported that achiral, unsubstituted 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acid **16** gives the corresponding substituted pyrroloketopiperazines in moderate to good yields when reacted with isocyanides and primary amines.[11] We found that optimal conditions for the reaction of **11** with isocyanides and primary amines require the use of MeOH as solvent at 40 °C. In contrast, aprotic polar and non-polar solvents (PhH, CH_3CN, $CHCl_3$) gave unsatisfactory, low yields of the desired products.

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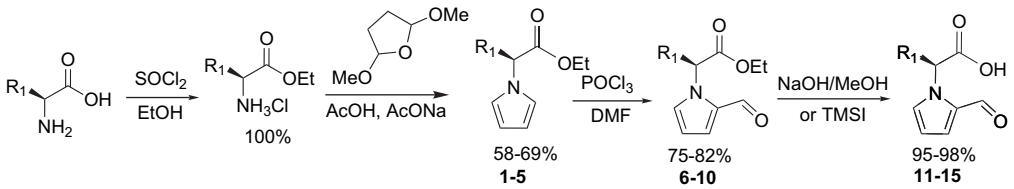
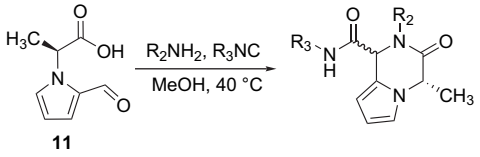


Scheme 1.



Scheme 2.

We have found that the reaction is general and applicable for various amines and isocyanides (Table 1). The only exception is the sterically hindered *tert*-butylamine. For the other examples, target products were obtained in good yields; unfortunately, low diastereoselectivity was observed in all cases. Thus, the reaction appears almost insensitive to the nature of amine and isocyanide components.

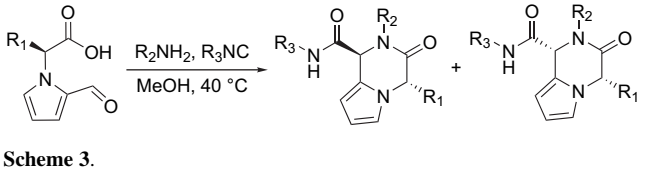
We proposed that the use of 2-(2-formyl-1*H*-pyrrol-1-yl)-acetic acids with more sterically hindered substituents should improve the diastereoselectivity of the reaction. Thus, we were delighted to find that the diastereoselectivity of the reaction is sensitive to the nature of substituent in the molecule of the formylacid (Table 2). 2-(2-Formyl-1*H*-pyrrol-1-yl)acetic acids bearing bulky substituents such as *i*-Pr or *s*-Bu could serve as most efficient asymmetric inductors for this reaction. The diastereoselectivity obtained (d.r.∼3:1) represents first examples of asymmetric Ugi reaction without a chiral amine. It is noteworthy that the target heterocycles were separated by column chromatography and could be isolated as single diastereomers in most cases (Scheme 3).

Table 1

Entry	R_2	R_3	No.	Yield, %	d.r.
1	4-MeOPh	*t*-Bu	**17**	62	1.7:1
2	2-Furylmethyl	*t*-Bu	**18**	58	1.9:1
3	*i*-Pr	*t*-Bu	**19**	59	1.7:1
4	*t*-Bu	*t*-Bu	—	0	—
5	Bn	Bn	**20**	68	1.8:1
6	Bn	*t*-Bu	**21**	70	1.7:1
7	4-MeOPh	4-BrPh	**22**	74	1.6:1

Table 2

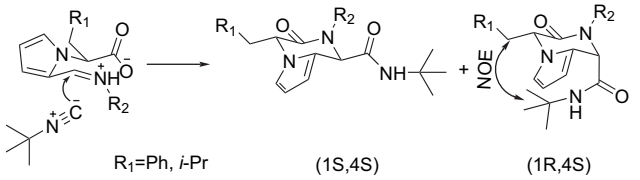
Entry	R_1	R_2	R_3	No.	Yield, %	d.r.
1	Bn	4-MeOPh	*t*-Bu	**23**	62	1.9:1
2	*i*-Bu	4-MeOPh	*t*-Bu	**24**	59	2.2:1
3	*i*-Pr	4-MeOPh	*t*-Bu	**25**	68	2.9:1
4	*s*-Bu	4-MeOPh	*t*-Bu	**26**	67	3.2:1
5	Bn	Bn	*t*-Bu	**27**	66	2.2:1
6	*i*-Bu	Bn	*t*-Bu	**28**	68	2.3:1
7	*i*-Pr	Bn	*t*-Bu	**29**	60	2.8:1
8	*s*-Bu	Bn	*t*-Bu	**30**	70	3.1:1
9	Bn	2-Furylmethyl	*t*-Bu	**31**	63	2.1:1
10	*i*-Bu	Bn	Et	**32**	68	2.3:1
11	*s*-Bu	Bn	Et	**33**	61	3.1:1



Scheme 3.

The reaction is quite general and we found no other restriction on the structure of the reagents participating in the process. A number of substituted heterocycles were prepared using benzylamine as the amine moiety; this allows the possibility of subsequent removal of the amine protecting group. The influence of amine structure on the diastereoselectivity is very low and the most important factor effecting the ratio of diastereomers is the structure of starting formylacids.

In spite of the high effectiveness of Ugi reaction this four-component transformation is really a complex process. It is known that multicomponent reactions proceed through a number of reversible steps. In the case of the Ugi reaction the final step, the formation of amide, is irreversible. The general scheme of the Ugi process includes the initial formation of an iminium salt.[12,13] Subsequent reaction of iminium salt (Scheme 4) with isocyanide then gives a diastereomeric mixture of the target pyrroloketopiperazines. We proposed that if the reaction is a thermodynamically controlled process the energy of final products will play critical role in the diastereoselectivity of the process.



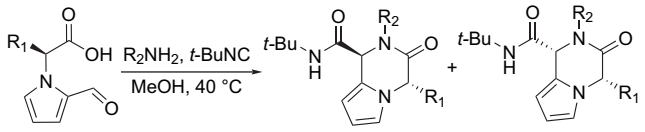
Scheme 4.

This statement can be illustrated by semiempirical calculations for both diastereoisomers of compound **19**. PM3 calculations showed that the major trans-isomer **19a** is only 0.6 kcal/mol more stable than minor cis-isomer. Such small differences in the stability of cis- and trans-isomer of target products can be explained to be due to structural peculiarities of substituted pyrroloketopiperazines. Due to the condensed nature of target heterocycle and the presence of an amide component, the piperazine ring is almost planar. As a result of this, low difference in energies of two diastereomers leads to moderate diastereoselectivity of the reaction.

The absolute configuration of the target pyrroloketopiperazines was established via NOESY ^{1}H NMR analysis of both stereoisomers of compounds **24** and **27**. Interaction between *tert*-butyl and CH-protons of benzyl or isobutyl group,

observed in minor stereoisomers (**24b** and **27a**, respectively) illustrates that more stable (1*S*,4*S*)-isomer is the major product of the Ugi reaction (Scheme 4).

To confirm our proposal that structural motif of pyrroloketopiperazines is responsible for moderate diastereoselectivity of Ugi reaction we decided to investigate the influence of chiral amines as asymmetric inductors. As it was noted previously, the use of chiral amines is still the only ability to obtain an appropriate induction (up to 90% ee) in the Ugi reaction. Achiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acid **16** (derivative of glycine) reacted with chiral (1*R*)-1-phenylethylamine to give the corresponding heterocycle **34** with the lowest diastereoselectivity observed from the variety of reactions we have investigated. In the case of reaction with substituted formylacids **11** and **13** no significant improvement in diastereoselectivity was observed. The *R*-enantiomer of phenylethylamine is more effective asymmetric inductor than *S*-enantiomer (matched stereochemistry (Table 3)). However, chiral amines do not change the diastereoselectivity dramatically, as observed in the traditional variant of the Ugi reaction. We believe that this is due to the almost flat geometry of the target pyrroloketopiperazines (Scheme 5).



Scheme 5.

Table 3

Entry	R_1	R_2	No.	Yield, %	d.r.
1	H	(1*R*)-PhEt	**34**	67	1.3:1
2	CH_3	(1*R*)-PhEt	**35**	66	1.9:1
3	CH_3	(1*S*)-PhEt	**36**	64	1.8:1
4	*i*-Bu	(1*R*)-PhEt	**37**	65	2.7:1
5	*i*-Bu	(1*S*)-PhEt	**38**	63	2.4:1
6	*s*-Bu	(1*R*)-PhEt	**39**	65	4.0:1
7	*s*-Bu	(1*S*)-PhEt	**40**	62	3.6:1

3. Conclusion

In conclusion, we have described a novel effective approach to chiral substituted pyrroloketopiperazines via a three-component Ugi reaction with chiral 2-(2-formyl-1*H*-pyrrol-1-yl)acetic acids. The reaction proceeds smoothly to give the products as a mixture of diastereomers (d.r., up to 4:1), which can be easily separated and isolated in individual form in most cases. The low diastereoselectivity observed can be explained by the almost planar structure of the heterocyclic fragment in the target molecules. The use of chiral amines does not improve the diastereoselectivity significantly due to the structural peculiarities of pyrroloketopiperazines.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker VRX-400 at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts are recorded relative to TMS as an internal standard and are given in δ values. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Merck $60F_{254}$ plates were used for analytical TLC. Column chromatography was performed on a silica gel (60–230 mesh, Merck). All starting materials are commercially available.

2-(2-Formyl-1*H*-pyrrol-1-yl)acetic acid **16** was prepared according to the literature procedure.[14]

4.1.1. Ethyl (1*H*-pyrrol-1-yl)acetates. To a stirred suspension of 1.0 mol α-aminoacid in 700 mL of ethanol, $SOCl_2$ (110 mL, 1.5 mol) was added dropwise and the mixture was stirred under reflux for 5 h. The solvent was removed in vacuo, the residue was suspended in a solution of NaOAc (150 g, 1.1 mol) and 2,5-dimethoxytetrahydrofuran (140 mL, 1.0 mol) in 800 mL of AcOH added. The mixture was stirred at 80 °C for an appropriate time (0.5–1.5 h, TLC monitoring) before the solvent was evaporated, the residue was dissolved in water (1 L) and extracted with ether (2×200 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and the residue was purified by vacuum distillation or by flash chromatography on silica gel (CH_2Cl_2).

4.1.1.1. Ethyl (2*S*)-2-(1*H*-pyrrol-1-yl)propionate (1). Yield 57%, colourless oil. R_f 0.80 (CH_2Cl_2). Bp 70–74 °C (1 Torr). $[\alpha]_D^{20}$ 22.4 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 2920, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.76–6.74 (m, 2H), 6.19–6.17 (m, 2H), 4.74 (q, *J*=7.2 Hz, 1H), 4.17 (q, *J*=7.2 Hz, 2H, OCH_2), 1.71 (d, *J*=7.2 Hz, 3H, CH_3), 1.24 (t, *J*=7.2 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 171.2, 119.6, 108.4, 61.5, 57.0, 18.2, 14.0. Anal. Calcd: C, 64.65; H, 7.84. Found: C, 64.85; H, 7.88%.

4.1.1.2. Ethyl (2*S*)-2-(1*H*-pyrrol-1-yl)-3-phenylpropanoate (2). Yield 67%, yellow oil. R_f 0.83 (CH_2Cl_2). $[\alpha]_D^{20}$ 42.9 (*c* 0.16, $CHCl_3$). ν_{max} (Nujol): 2940, 1745 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.27–7.21 (m, 3H), 7.06–7.04 (m, 2H), 6.76–6.74 (m, 2H), 6.16–6.14 (m, 2H), 4.75 (t, *J*=7.8 Hz, CH), 4.18–4.13 (m, 2H, CH_2), 3.42 (dd, J_1=13.9 Hz, J_2=6.8 Hz, 1H), 3.26 (dd, J_1=3.9 Hz, J_2=6.8 Hz, 1H), 1.20 (t, *J*=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.0, 136.3, 128.8, 128.4, 126.9, 120.0, 108.5, 63.6, 61.5, 39.5, 13.9. Anal. Calcd: C, 69.12; H, 5.39. Found: C, 69.04; H, 5.31%.

4.1.1.3. Ethyl (2*S*)-4-methyl-2-(1*H*-pyrrol-1-yl)pentanoate (3). Yield 62%, colourless oil. R_f 0.82 (CH_2Cl_2). Bp 91–96 °C (1 Torr). $[\alpha]_D^{20}$ 9.4 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 2920, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.76–6.74 (m, 2H), 6.18–6.16 (m, 2H), 4.64 (dd, J_1=9.9 Hz, J_2=6.1 Hz, 1H), 4.17 (q, *J*=7.8 Hz, 2H, OCH_2), 2.02–1.86 (m, 2H, CH_2), 1.45–1.38 (m, 1H, CH), 1.25 (t, *J*=7.8 Hz, 3H, CH_3), 0.94 (d, *J*=6.8 Hz, 3H, CH_3), 0.91 (d, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 171.1 (COO), 120.0, 108.3, 61.4, 60.2, 41.5, 24.5, 22.7, 21.6, 14.0. Anal. Calcd: C, 68.87; H, 9.15. Found: C, 68.95; H, 9.20%.

4.1.1.4. Ethyl (2*S*)-3-methyl-2-(1*H*-pyrrol-1-yl)butanoate (4). Yield 68%, yellow oil. R_f 0.82 (CH_2Cl_2). Bp 90–94 °C (1 Torr). $[\alpha]_D^{20}$ 8.2 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 2920, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.79–6.77 (m, 2H),

6.16–6.14 (m, 2H), 4.23–4.13 (m, 2H, CH_2), 4.09 (d, J=10.2 Hz, 1H, CH), 2.45–2.36 (m, 1H, CH), 1.26 (t, J=7.1 Hz, 3H, CH_3), 0.99 (d, J=6.5 Hz, 3H, CH_3), 0.74 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.5, 120.3, 108.2, 67.5, 61.2, 37.7, 24.6, 15.5, 15.0. Anal. Calcd: C, 67.66; H, 8.78. Found: C, 67.93; H, 8.70%.

4.1.1.5. Ethyl (2*S*,3*R*)-3-methyl-2-(1*H*-pyrrol-1-yl)-pentanoate (5). Yield 68%, yellow oil. R_f 0.82 (CH_2Cl_2). Bp 115–118 °C (1 Torr). $[\alpha]_D^{20}$ 9.7 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 2940, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.79–6.77 (m, 2H), 6.16–6.14 (m, 2H), 4.23–4.13 (m, 3H, CH_2, CH), 2.25–2.15 (m, 1H, CH), 1.27 (t, J=7.1 Hz, 3H, CH_3), 1.19–1.10 (m, 1H, CH), 0.96 (d, J=6.8 Hz, 3H, CH_3), 0.82 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.5, 120.3, 108.2, 67.5, 61.2, 37.8, 24.7, 15.5, 14.0, 10.5. Anal. Calcd: C, 68.87; H, 9.15. Found: C, 68.93; H, 9.22%.

4.1.2. Ethyl (2-formyl-1*H*-pyrrol-1-yl)acetates. $POCl_3$ (50 mL, 0.55 mol) was added dropwise to a stirred DMF (150 mL, 1.5 mol) at 0 °C. The reaction mixture was then stirred for a further 0.5 h at 0 °C. A solution of 0.5 mol of the corresponding ethyl (1*H*-pyrrol-1-yl)acetate in 100 mL CH_2Cl_2 was added dropwise at 0 °C. The mixture was stirred 4 h at rt then poured into a solution of NaOAc (270 g, 2 mol) in water (500 mL). The mixture was stirred for 3 h, then diluted with water (1 L) and extracted with CH_2Cl_2 (3×200 mL). The combined extracts were dried (Na_2SO_4), the solvent was removed in vacuo and the residue was purified with flash chromatography (CH_2Cl_2).

4.1.2.1. Ethyl (2*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propionate (6). Yield 57%, colourless oil. R_f 0.11 (CH_2Cl_2). $[\alpha]_D^{20}$ −74.0 (c 0.19, $CHCl_3$). ν_{max} (Nujol): 2920, 1740, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.49 (s, 1H, CHO), 7.17–7.15 (m, 1H), 6.97–6.95 (m, 1H), 6.29 (t, J=3.2 Hz, 1H), 5.85 (q, J=7.3 Hz, 1H, CH), 4.17 (q, J=7.1 Hz, 2H, CH_2), 1.72 (d, J=7.3 Hz, 3H, CH_3), 1.23 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 179.6 (CHO), 171.1 (CO_2), 131.5, 128.7, 125.4, 110.1, 61.5, 55.3, 17.7, 14.0. Anal. Calcd: C, 61.53; H, 6.71. Found: C, 61.74; H, 6.82%.

4.1.2.2. Ethyl (2*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropionate (7). Yield 67%, yellow needle crystals. R_f 0.13 (CH_2Cl_2). Mp 42 °C. $[\alpha]_D^{20}$ 0.8 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 2950, 1740, 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.42 (s, 1H, CHO), 7.21–7.16 (m, 3H), 7.05–6.99 (m, 3H), 6.89–6.87 (m, 1H), 6.19 (t, J=3.1 Hz, 1H), 6.10–6.03 (m, 1H, CH), 4.19 (q, J=7.1 Hz, 2H, OCH_2), 3.51 (dd, J_1=14.2 Hz, J_2=5.7 Hz, 1H), 3.27 (dd, J_1=14.2 Hz, J_2=9.6 Hz, 1H), 1.21 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 179.4 (CHO), 169.8 (CO_2), 136.0, 131.3, 130.5, 128.9, 128.7, 128.3, 126.8, 125.5, 110.1, 61.7 (OCH_2), 39.1 (CH_2), 14.00 (CH_3). Anal. Calcd: C, 70.83; H, 6.32. Found: C, 71.05; H, 6.51%.

4.1.2.3. Ethyl (2*S*)-4-methyl-2-(2-formyl-1*H*-pyrrol-1-yl)pentanoate (8). Yield 62%, colourless oil. R_f 0.11 (CH_2Cl_2). $[\alpha]_D^{20}$ 12.2 (c 0.07, $CHCl_3$). ν_{max} (Nujol): 2930, 1750, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.49 (s, 1H, CHO), 7.19–7.17 (m, 1H), 6.93–6.91 (m, 1H), 6.29 (t, J=3.2 Hz, 1H), 6.05 (t, J=7.1 Hz, 1H, CH), 4.15 (q, J=7.1 Hz, 2H, OCH_2), 1.95 (m, 2H, CH_2), 1.43–1.33 (m, 1H, CH), 1.22 (t, J=7.3 Hz, 3H, CH_3), 0.90 (d, J=6.6 Hz, 3H, CH_3), 0.88 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 179.6 (CHO), 171.0 (CO_2), 131.6, 129.5, 125.4, 110.3, 61.4, 57.5, 41.2, 24.6, 22.8, 21.3, 14.0. Anal. Calcd: C, 65.80; H, 8.07. Found: C, 66.05; H, 8.15%.

4.1.2.4. Ethyl (2*S*)-3-methyl-2-(2-formyl-1*H*-pyrrol-1-yl)butanoate (9). Yield 65%, yellow oil. R_f 0.11 (CH_2Cl_2). $[\alpha]_D^{20}$ 10.1 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 2950, 1740, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.51 (s, 1H, CHO), 7.40–7.38 (m, 1H), 6.91–6.89 (m, 1H), 6.29 (t, J=3.1 Hz, 1H), 5.95 (d, J=9.4 Hz, 1H, CH), 4.25–4.12 (m, 2H, OCH_2), 2.42–2.35 (m, 1H, CH), 1.25 (t, J=7.2 Hz, 3H, CH_3), 0.99 (d, J=6.7 Hz, 3H, CH_3), 0.77 (d, J=6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 179.8 (CHO), 170.6 (CO_2), 131.9, 130.0, 125.3, 110.6, 63.8, 61.3, 33.0, 19.1, 18.5, 14.0. Anal. Calcd: C, 64.55; H, 7.67. Found: C, 64.59; H, 7.56%.

4.1.2.5. Ethyl (2*S*,3*R*)-3-methyl-2-(2-formyl-1*H*-pyrrol-1-yl)pentanoate (10). Yield 68%, yellow oil. R_f 0.12 (CH_2Cl_2). $[\alpha]_D^{20}$ 38.5 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 2930, 1740, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 9.49 (s, 1H, CHO), 7.39–7.37 (m, 1H), 6.90–6.88 (m, 1H), 6.27 (t, J=3.1 Hz, 1H), 5.99 (d, J=9.6 Hz, 1H, CH), 4.25–4.09 (m, 2H, OCH_2), 2.18–2.11 (m, 1H, CH), 1.24 (t, J=7.0 Hz, 3H, CH_3), 1.18–1.10 (m, 1H), 1.07–0.99 (m, 1H), 0.95 (d, J=6.7 Hz, 3H, CH_3), 0.79 (t, J=7.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 179.8 (CHO), 170.8 (COO), 132.0, 130.0, 125.4, 110.6, 62.9, 61.3, 39.0, 24.9, 15.4, 14.1, 10.6. Anal. Calcd: C, 65.80; H, 8.07. Found: C, 65.93; H, 8.00%.

4.1.3. (2-Formyl-1*H*-pyrrol-1-yl)acetic acids. To a stirred solution of corresponding ethyl (2-formyl-1*H*-pyrrol-1-yl)-acetate (0.2 mol) in methanol (200 mL), a solution of NaOH (8.8 g, 0.22 mol) in water (100 mL) was added dropwise. The reaction mixture was stirred 4–6 h at rt (TLC monitoring). The reaction mixture was then diluted with water (200 mL), acidified with HCl (5%) to pH 3–4 and the product was extracted with ether (2×100 mL). The combined organic extracts were dried (Na_2SO_4) and the ether was removed in vacuo to give the target acid.

4.1.3.1. (2*S*)-2-(2-Formyl-1*H*-pyrrol-1-yl)propionic acid (11). Yield 97%, yellow needle crystals. R_f 0.41 (CH_3OH–CH_2Cl_2 1:4). Mp 81–84 °C. $[\alpha]_D^{20}$ 67.1 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 3100–3300, 1720, 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 12.9 (br s, 1H, COOH), 9.45 (s, CHO), 7.44–7.42 (m, 1H), 7.07–7.05 (m, 1H), 6.26 (t, J=3.1 Hz, 1H), 5.61 (q, J=7.3 Hz, 1H), 1.63 (d, J=7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 180.1 (CHO), 175.9 (CO_2), 131.4, 129.2, 126.1, 110.5, 55.3, 17.5. Anal. Calcd: C, 57.48; H, 5.43. Found: C, 57.51; H, 5.39%.

4.1.3.2. (2*S*)-2-(2-Formyl-1*H*-pyrrol-1-yl)-3-phenylpropionic acid (12). Yield 97%, yellow needle crystals. R_f 0.45 (CH_3OH–CH_2Cl_2 1:4). Mp 89 °C. $[\alpha]_D^{20}$ 11.5 (c 0.10, $CHCl_3$). ν_{max} (Nujol): 3100–3300, 1720, 1680 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 10.7 (br s, 1H, COOH), 9.40 (s, 1H, CHO), 7.21–7.16 (m, 3H), 7.00–6.92 (m, 4H), 6.19 (t, J=3.1 Hz, 1H), 6.07–5.97 (m, 1H, CH), 3.59 (dd, J_1=14.4 Hz, J_2=4.8 Hz, 1H), 3.31 (dd, J_1=14.4 Hz, J_2=10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 179.9 (CHO), 174.3

(CO_2), 135.8, 131.6, 131.0, 128.8, 128.4, 126.9, 126.5, 110.4, 38.3 (CH_2). Anal. Calcd: C, 69.12; H, 5.39. Found: C, 69.51; H, 5.56%.

4.1.3.3. (2*S*)-4-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-pentanoic acid (13). Yield 98%, yellow needle crystals. R_f 0.43 (CH_3OH–CH_2Cl_2 1:4). Mp 76–78 °C. $[\alpha]_D^{20}$ 12.2 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 3100–3300, 1710, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 10.7 (br s, 1H, COOH), 9.48 (s, 1H, CHO), 7.17–7.15 (m, 1H), 6.98–6.96 (m, 1H), 6.31 (t, *J*=3.1 Hz, 1H), 6.08–6.02 (m, 1H, CH), 2.01 (t, *J*=7.4 Hz, 2H, CH_2), 1.45–1.38 (m, 1H, CH), 0.92–0.88 (m, 6H, $2CH_3$). Optical rotatory power and ^1H NMR are similar to that described in literature.[9]

4.1.3.4. (2S)-3-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-butanoic acid (14). Yield 98%, yellow needle crystals. R_f 0.43 (CH_3OH–CH_2Cl_2 1:4). Mp 90 °C. $[\alpha]_D^{20}$ 8.2 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 3100–3300, 1720, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 9.6 (br s, 1H, COOH), 9.49 (s, 1H, CHO), 7.34–7.32 (m, 2H), 6.97–6.95 (m, 1H), 6.31 (t, *J*=3.1 Hz, 1H), 5.91 (d, *J*=9.1 Hz, 1H), 2.48–2.39 (m, 1H), 1.04 (d, *J*=6.7 Hz, 3H, CH_3), 0.81 (d, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 180.2 (CHO), 174.7 (CO_2), 131.9, 130.8, 126.1, 110.9, 64.2, 32.3, 19.2 (CH_3), 18.6 (CH_3). Anal. Calcd: C, 76.55; H, 8.57. Found: C, 76.21; H, 8.39%.

4.1.3.5. (2*S*,3*R*)-3-Methyl-2-(2-formyl-1*H*-pyrrol-1-yl)-pentanoic acid (15). Yield 96%, white needle crystals. R_f 0.42 (CH_3OH–CH_2Cl_2 1:4). Mp 67–68 °C. $[\alpha]_D^{20}$ 4.0 (*c* 0.10, $CHCl_3$). ν_{max} (Nujol): 3100–3300, 1720, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 10.8 (br s, 1H, COOH), 9.48 (s, 1H, CHO), 7.34–7.32 (m, 2H), 6.97–6.95 (m, 1H), 6.31 (t, *J*=3.1 Hz, 1H), 6.01 (d, *J*=9.1 Hz, 1H), 2.26–2.15 (m, 1H), 1.27–1.18 (m, 1H), 1.12–1.01 (m, 4H), 0.83 (t, *J*=7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 180.2 (CHO), 175.0 (CO_2), 131.8, 130.8, 126.3, 110.9, 63.2, 38.3, 25.0, 15.5 (CH_3), 10.8 (CH_3). Anal. Calcd: C, 63.14; H, 7.23. Found: C, 62.91; H, 7.39%.

4.1.4. 3-Oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamides. A solution of (2-formyl-1*H*-pyrrol-1-yl)acetic acid (1 mmol), amine (1 mmol) and isocyanide (1 mmol) in methanol (2 mL) was stirred at 40 °C for an appropriate time (12–20 h, TLC monitoring). The solvent was then evaporated in vacuo and the residue was purified by column chromatography (CH_2Cl_2–CH_3CN).

4.1.4.1. (4*S*)-2-(4-Methoxyphenyl)-*N*-(*tert*-butyl)-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (17). Mixture of (1*R*)/(1*S*) isomers 1.9:1. Yield 62%, yellow oil. R_f 0.16 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^1H NMR ($CDCl_3$) signals of major isomer δ: 7.20 (d, *J*=9.0 Hz, 2H), 6.89 (d, *J*=9.0 Hz, 2H), 6.79–6.77 (m, 1H), 6.22 (t, *J*=3.0 Hz, 1H), 6.08–6.06 (m, 1H), 5.46 (br s, 1H, NH), 5.06 (s, 1H), 4.98 (q, *J*=6.7 Hz, 1H), 3.79 (s, 3H, OCH_3), 1.81 (d, *J*=6.7 Hz, 3H), 1.23 (s, 9H, *t*-Bu), signals of minor isomer δ: 6.68–6.66 (m, 1H), 6.25 (t, *J*=3.0 Hz, 1H), 6.03–6.01 (m, 1H), 5.52 (br s, 1H, NH), 5.10 (s, 1H), 4.84 (q, *J*=6.7 Hz, 1H), 1.85 (d, *J*=6.7 Hz, 3H), other signals are observed by the signals of the major isomer. ^{13}C NMR ($CDCl_3$) δ: 169.1, 169.0, 167.7, 167.5, 158.9, 158.8, 158.8, 134.4, 134.0, 128.6, 128.2, 123.3, 121.6, 118.6, 117.7, 109.8, 109.0, 104.2, 103.7, 64.0, 63.7, 55.7, 55.4, 54.5, 51.9, 28.4, 22.3, 15.79. Anal. Calcd: C, 67.58; H, 7.09. Found: C, 67.74; H, 7.22%.

4.1.4.2. (4*S*)-2-(2-Furylmethyl)-*N*-(*tert*-butyl)-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (18). Mixture of (1*R*)/(1*S*) isomers 1.6:1. Yield 58%, yellow oil. R_f 0.16 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1705 cm^{-1}. ^1H NMR ($CDCl_3$) signals of major isomer δ: 7.31–7.29 (m, 1H), 6.70–6.68 (m, 1H), 6.29–6.26 (m, 2H), 6.16 (t, *J*=3.0 Hz, 1H), 6.06–6.04 (m, 1H), 5.69 (br s, 1H, NH), 5.16 (d, *J*=15.7 Hz, 1H), 4.93 (s, 1H), 4.74 (q, *J*=6.8 Hz, 1H), 4.30 (d, *J*=15.7 Hz, 1H), 1.79 (d, *J*=6.7 Hz, 3H), 1.25 (s, 9H, *t*-Bu), signals of minor isomer δ: 6.61–6.59 (m, 1H), 6.70–6.68 (m, 1H), 6.29–6.26 (m, 2H), 6.19 (t, *J*=3.0 Hz, 1H), 6.02–6.00 (m, 1H), 5.78 (br s, 1H, NH), 5.39 (d, *J*=15.7 Hz, 1H), 4.97 (s, 1H), 4.21 (d, *J*=15.7 Hz, 1H), 1.69 (d, *J*=6.7 Hz, 3H), 1.27 (s, 9H, *t*-Bu), other signals are overlapped by signals of major isomer. ^{13}C NMR ($CDCl_3$) δ: 168.6, 168.4, 167.3, 149.5, 149.4, 142.7, 142.6, 110.5, 110.4, 109.8, 109.7, 109.6, 109.1, 104.5, 104.3, 58.8, 58.2, 55.3, 53.8, 51.8, 51.7, 42.6, 42.3, 28.5, 28.4, 21.8, 21.83, 16.1. Anal. Calcd: C, 65.63; H, 7.04. Found: C, 67.74; H, 7.22%.

4.1.4.3. (1*S*,4*S*)-*N*-(*tert*-Butyl)-2-isopropyl-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (19a). Yield 37%, yellow oil. R_f 0.20 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 56.47 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.71–6.69 (m, 1H), 6.15 (t, *J*=3.0 Hz, 1H), 6.08–6.06 (m, 1H), 5.75 (br s, 1H, NH), 4.91 (s, 1H), 4.84–4.78 (m, 2H), 1.77 (d, *J*=7.1 Hz, 3H), 1.26 (s, 9H, *t*-Bu), 1.18 (d, *J*=6.8 Hz, 3H), 1.15 (d, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 168.7, 168.5, 123.9, 117.3, 108.8, 103.8, 54.9, 54.2, 51.7, 46.3, 28.5, 19.9, 19.5, 15.3. Anal. Calcd: C, 65.95; H, 8.65. Found: C, 70.90; H, 7.62%.

4.1.4.4. (1*R*,4*S*)-*N*-(*tert*-Butyl)-2-isopropyl-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (19b). Yield 22%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 38.2 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1695 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 6.58–6.56 (m, 1H), 6.17 (t, *J*=3.0 Hz, 1H), 6.11 (br s, 1H, NH), 6.05–6.03 (m, 1H), 5.02 (s, 1H), 4.78–4.66 (m, 2H), 1.77 (d, *J*=7.1 Hz, 3H), 1.27 (s, 9H, *t*-Bu), 1.18 (d, *J*=6.8 Hz, 3H), 1.17 (d, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 168.7, 168.6, 122.2, 118.1, 109.5, 103.4, 55.6, 55.4, 51.5, 46.7, 28.3, 22.0, 19.8, 19.4. Anal. Calcd: C, 65.95; H, 8.65. Found: C, 70.90; H, 7.62%.

4.1.4.5. (4*S*)-*N*,2-Dibenzyl-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (20). Mixture of (1*R*)/(1*S*) isomers 1.8:1. Yield 68%, white amorphous solid. R_f 0.18 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^1H NMR ($CDCl_3$) signals of major isomer δ: 7.29–7.11 (m, 10H), 6.78–6.72 (m, 2H), 6.23 (t, *J*=3.0 Hz, 1H), 6.04–6.02 (m, 1H), 5.32 (d, *J*=15.1 Hz, 1H), 5.03 (s, 1H), 4.82 (q, *J*=6.8 Hz, 1H), 4.39–4.28 (m, 2H), 4.08 (d, *J*=15.1 Hz, 1H), 1.77 (d, *J*=6.8 Hz, 3H), signals of minor isomer δ: 6.64–6.62 (m, 1H), 6.02–6.00 (m, 1H), 5.48 (d, *J*=15.1 Hz, 1H), 5.04 (s, 1H), 4.67 (q,

J=6.8 Hz, 1H), 3.97 (d, J=15.1 Hz, 1H), 1.72 (d, J=6.8 Hz, 3H), other signals are observed by the signals of the major isomer. ^{13}C NMR ($CDCl_3$) δ: 169.3, 169.1, 168.4, 168.2, 137.51, 137.47, 135.5, 135.4, 128.61, 128.57, 128.3, 128.2, 127.74, 127.70, 127.50, 127.46, 127.41, 127.37, 122.2, 120.6, 118.5, 117.6, 109.8, 109.2, 104.7, 104.4, 57.9, 57.6, 55.1, 53.9, 53.9, 49.7, 49.3, 43.7, 43.6, 22.0, 16.3. Anal. Calcd: C, 73.97; H, 6.21. Found: C, 73.90; H, 6.32%.

4.1.4.6. (4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (21). Mixture of (1*R*)/(1*S*) isomers 1.7:1. Yield 70%, yellow oil. R_f 0.18 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) signals of major isomer δ: 7.32–7.21 (m, 5H), 6.75–6.73 (m, 1H), 6.17 (t, J=3.0 Hz, 1H), 5.96–5.94 (m, 1H), 5.31 (d, J=15.2 Hz, 1H), 5.82 (br s, 1H, NH), 4.77 (q, J=6.7 Hz, 1H), 4.71 (s, 1H), 4.17 (d, J=15.2 Hz, 1H), 1.72 (d, J=6.7 Hz, 3H), 1.23 (s, 9H, *t*-Bu), signals of minor isomer δ: 6.66–6.64 (m, 1H), 6.20 (t, J=3.0 Hz, 1H), 5.94–5.92 (m, 1H), 5.62 (d, J=15.7 Hz, 1H), 5.49 (br s, 1H, NH), 4.82 (q, J=6.7 Hz, 1H), 4.76 (s, 1H), 4.10 (d, J=15.7 Hz, 1H), 1.84 (d, J=6.7 Hz, 3H, CH_3), 1.26 (s, 9H, *t*-Bu), other signals are observed by the signals of the major isomer. ^{13}C NMR ($CDCl_3$) δ: 169.0, 168.9, 167.4, 167.3, 135.8, 135.6, 128.7, 128.3, 127.7, 122.6, 121.2, 118.5, 117.5, 109.8, 109.1, 104.4, 104.2, 58.6, 58.0, 55.3, 53.9, 49.7, 49.4, 28.44, 21.92, 16.4. Anal. Calcd: C, 70.77; H, 7.42. Found: C, 70.90; H, 7.62%.

4.1.4.7. (1*S*,4*S*)-*N*-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-1-carboxamide (22a). Yield 46%, yellow oil. R_f 0.20 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 24.6 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.30 (d, 2H, J=8.6 Hz), 7.18 (d, 2H, J=8.6 Hz), 7.10 (d, 2H, J=9.2 Hz), 6.79 (t, J=3.0 Hz, 1H), 6.74 (d, 2H, J=9.2 Hz), 6.25–6.23 (m, 2H), 5.37 (s, 1H), 5.01 (q, 1H, J=6.9 Hz), 3.69 (s, 3H, OCH_3), 1.79 (d, J=6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 170.0, 166.7, 159.0, 136.4, 134.1, 131.8, 128.1, 122.5, 121.4, 118.1, 117.3, 114.7, 109.4, 105.1, 63.5, 55.4, 54.6, 15.5. Anal. Calcd: C, 58.16; H, 4.44. Found: C, 57.90; H, 4.47%.

4.1.4.8. (1*R*,4*S*)-*N*-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-methyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazine-1-carboxamide (22b). Yield 28%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ −12.0 (c 0.04, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 6.58–6.56 (m, 1H), 6.17 (t, J=3.0 Hz, 1H), 6.11 (br s, 1H, NH), 6.05–6.03 (m, 1H), 5.02 (s, 1H), 4.78–4.66 (m, 2H), 1.77 (d, J=7.1 Hz, 3H), 1.27 (s, 9H, *t*-Bu), 1.18 (d, J=6.8 Hz, 3H), 1.17 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 169.9, 166.6, 159.1, 136.5, 133.7, 131.7, 128.4, 121.4, 120.7, 119.0, 114.7, 110.2, 104.5, 63.8, 55.9, 55.4, 22.3. Anal. Calcd: C, 58.16; H, 4.44. Found: C, 58.03; H, 4.30%.

4.1.4.9. (1*R*,4*S*)-4-Benzyl-*N*-(*tert*-butyl)-2-(4-methoxyphenyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (23a). Yield 21%, yellow oil. R_f 0.31 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 18.27 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.25 (m, 5H), 7.09–7.06 (m, 2H), 6.92 (d, J=9.1 Hz, 2H), 6.08–6.06 (m, 1H), 5.99 (t, J=3.0 Hz, 1H), 5.78–5.76 (m, 1H), 5.55 (br s, 1H, NH), 4.18 (s, 1H), 4.8, 7 (dd, J_1=10.8 Hz, J_2=3.7 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.59 (dd, J_1=13.7 Hz, J_2=3.7 Hz, 1H), 3.39 (dd, J_1=13.7 Hz, J_2=10.8 Hz, 1H), 1.29 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 168.1, 158.8, 137.4, 134.1, 129.8, 128.4, 126.8, 121.6, 120.4, 114.5, 108.4, 63.5, 62.5, 55.3, 51.7, 42.0, 28.3. Anal. Calcd: C, 72.37; H, 6.77. Found: C, 72.09; H, 6.47%.

4.1.4.10. (1*S*,4*S*)-4-Benzyl-*N*-(*tert*-butyl)-2-(4-methoxyphenyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (23b). Yield 41%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 22.4 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.28–7.25 (m, 1H), 7.21–7.17 (m, 2H), 6.84–6.80 (m, 5H), 6.76–6.72 (m, 2H), 6.29 (t, J=3.0 Hz, 1H), 5.91–5.89 (m, 1H), 5.34 (br s, 1H, NH), 5.23–5.21 (m, 1H), 4.27 (s, 1H), 3.76 (s, 3H, OCH_3), 3.47 (dd, J_1=13.9 Hz, J_2=3.9 Hz, 1H), 3.37 (dd, J_1=13.9 Hz, J_2=11.1 Hz, 1H), 1.04 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 167.2, 166.7, 158.6, 135.0, 132.3, 129.5, 128.2, 128.0, 127.3, 122.7, 117.7, 114.1, 110.2, 103.7, 63.2, 55.3, 51.3, 41.0, 28.0. Anal. Calcd: C, 72.37; H, 6.77. Found: C, 72.29; H, 6.54%.

4.1.4.11. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-2-(4-methoxyphenyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (24a). Yield 40%, yellow oil. R_f 0.35 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 12.6 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.27 (d, J=8.9 Hz, 2H), 7.89 (d, J=8.9 Hz, 2H), 6.68–6.66 (m, 1H), 6.23 (t, J=3.0 Hz, 1H), 6.12–6.10 (m, 1H), 5.65 (br s, 1H, NH), 5.17 (s, 1H), 4.75 (dd, J_1=8.4 Hz, J_2=6.3 Hz, 1H), 3.79 (s, 1H, OCH_3), 1.98–1.92 (m, 2H, CH_2), 1.90–1.82 (m, 1H), 1.24 (s, 9H, *t*-Bu), 1.02 (d, J=6.5 Hz, 3H, CH_3), 0.96 (d, J=6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.7, 167.3, 158.7, 134.5, 128.6, 122.4, 119.6, 114.4, 109.4, 104.5, 63.2, 59.1, 55.4, 51.7, 44.4, 28.4, 24.8, 23.0, 21.6. Anal. Calcd: C, 69.49; H, 7.86. Found: C, 69.90; H, 7.98%.

4.1.4.12. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-2-(4-methoxyphenyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (24b). Yield 18%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 21.3 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J=8.9 Hz, 2H), 6.90 (d, J=8.9 Hz, 2H), 6.75–6.73 (m, 1H), 6.22 (t, J=3.1 Hz, 1H), 6.06–6.04 (m, 1H), 5.37 (br s, 1H, NH), 5.21 (s, 1H), 4.80 (t, J=5.5 Hz, 1H), 3.79 (s, 1H, OCH_3), 2.16–2.01 (m, 2H, CH_2), 1.86–1.76 (m, 1H), 1.17 (s, 9H, *t*-Bu), 0.93 (d, J=6.7 Hz, 3H, CH_3), 0.90 (d, J=6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.9, 167.3, 158.7, 133.5, 128.1, 122.6, 118.4, 114.4, 109.2, 104.4, 63.7, 57.7, 55.4, 51.7, 40.9, 28.3, 28.4, 24.9, 22.8, 22.5. Anal. Calcd: C, 69.49; H, 7.86. Found: C, 64.86; H, 7.95%.

4.1.4.13. (1*R*,4*S*)-2-(4-Methoxyphenyl)-*N*-(*tert*-butyl)-4-isopropyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (25a). Yield 60%, yellow amorphous solid. Mp 68–70 °C. R_f 0.28 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 5.3 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.34 (d, J=8.8 Hz, 2H), 6.93 (d,

J=8.8 Hz, 2H), 6.71–6.69 (m, 1H), 6.24 (t, J=3.0 Hz, 1H), 6.19–6.17 (m, 1H), 5.80 (br s, 1H, NH), 5.26 (s, 1H), 4.29 (d, J=9.2 Hz, 1H), 3.81 (s, 3H, CH_3), 2.28–2.19 (m, 1H), 1.25 (s, 9H, *t*-Bu), 1.21 (d, J=6.7 Hz, 3H, CH_3), 0.98 (d, J=6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.6, 167.3, 134.9, 128.7, 122.9, 121.1, 114.4, 109.0, 105.0, 67.5, 62.8, 55.4, 51.6, 32.9, 28.9 (*t*-Bu), 20.1, 19.9. Anal. Calcd: C, 68.90; H, 7.62. Found: C, 68.96; H, 7.74%.

4.1.4.14. (1*S*,4*S*)-2-(4-Methoxyphenyl)-*N*-(*tert*-butyl)-4-isopropyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (25b). Yield 18%, yellow amorphous solid. Mp 78–79 °C. R_f 0.19 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 29.14 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.19 (d, J=8.8 Hz, 2H), 6.92 (d, J=8.8 Hz, 2H), 6.70–6.68 (m, 1H), 6.24 (t, J=3.0 Hz, 1H), 6.07–6.05 (m, 1H), 5.43 (s, 1H), 5.80 (br s, 1H, NH), 5.26 (d, J=9.2 Hz, 1H), 4.74 (s, 1H), 3.79 (s, 3H, CH_3), 2.55–2.44 (m, 1H), 1.09 (s, 9H, *t*-Bu), 1.05 (d, J=6.7 Hz, 3H, CH_3), 0.98 (d, J=6.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.1, 167.6, 158.6, 132.3, 128.7, 122.5, 120.4, 113.5, 108.6, 104.7, 67.0, 64.3, 54.8, 51.5, 34.6, 28.7 (*t*-Bu), 18.5, 17.3. Anal. Calcd: C, 68.90; H, 7.62. Found: C, 68.99; H, 7.56%.

4.1.4.15. (1*S*,4*S*)-*N*-(*tert*-Butyl)-2-(4-methoxyphenyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-1-carboxamide (26a). Yield 51%, yellow oil. R_f 0.31 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 10.25 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.31 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.9 Hz, 2H), 6.69–6.67 (m, 1H), 6.22 (t, J=3.0 Hz, 1H), 6.17–6.15 (m, 1H), 5.79 (br s, 1H, NH), 5.25 (s, 1H), 4.34 (d, J=9.0 Hz, 1H), 3.79 (s, 3H, OCH_3), 2.04–1.95 (m, 1H), 1.59–1.52 (m, 1H), 1.23 (s, 9H, *t*-Bu), 1.14 (d, J=6.7 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.6, 167.0, 158.5, 134.7, 128.6, 122.8, 120.6, 114.2, 109.0, 104.9, 65.7, 62.7, 55.3, 51.4, 39.0, 28.2, 25.8, 15.6, 10.5. Anal. Calcd: C, 69.49; H, 7.86. Found: C, 69.48; H, 8.07%.

4.1.4.16. (1*R*,4*S*)-*N*-(*tert*-Butyl)-2-(4-methoxyphenyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-1-carboxamide (26b). Yield 16%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 37.03 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, J=8.8 Hz, 2H), 6.91 (d, J=8.9 Hz, 2H), 6.71–6.69 (m, 1H), 6.24 (t, J=3.0 Hz, 1H), 6.06–6.05 (m, 1H), 5.40 (s, 1H), 5.32 (br s, 1H, NH), 4.81 (d, J=3.0 Hz, 1H), 3.79 (s, 3H, OCH_3), 2.25–2.17 (m, 1H), 1.67–1.61 (m, 1H), 1.31–1.25 (m, 1H), 1.10 (s, 9H, *t*-Bu), 0.99 (d, J=6.7 Hz, 3H), 0.93 (t, J=7.0 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.8, 166.8, 158.7, 132.5, 128.1, 122.5, 119.0, 114.3, 109.5, 104.4, 63.8, 63.4, 55.5, 51.6, 42.3, 28.2, 25.3, 15.4, 11.9. Anal. Calcd: C, 69.49; H, 7.86. Found: C, 69.34; H, 8.17%.

4.1.4.17. (1*R*,4*S*)-2,4-Dibenzyl-*N*-(*tert*-butyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (27a). Yield 21%, yellow oil. R_f 0.35 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 12.74 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.21 (m, 8H), 7.04–7.01 (m, 2H), 5.99–5.97 (m, 1H), 5.94 (t, J=3.0 Hz), 5.75–5.73 (m, 1H), 5.71 (br s, 1H, NH), 5.64 (d, J=15.2 Hz, 1H), 4.85 (s, 1H), 4.81 (dd, 1H, J_1=11.1 Hz, J_2=3.5 Hz), 4.24 (d, 1H, J=15.2 Hz), 3.50 (dd, 1H, J_1=13.6 Hz, J_2=11.1 Hz), 1.32 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 167.8, 167.5, 137.0, 135.7, 129.7, 128.8, 128.5, 128.3, 127.7, 127.0, 121.2, 120.6, 108.5, 104.7, 62.3, 57.6, 51.8, 49.9, 42.5, 28.5. Anal. Calcd: C, 75.15; H, 7.03. Found: C, 75.32; H, 7.14%.

4.1.4.18. (1*S*,4*S*)-2,4-Dibenzyl-*N*-(*tert*-butyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (27b). Yield 45%, yellow oil. R_f 0.15 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 33.14 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.26–7.15 (m, 4H), 7.08–7.04 (m, 2H), 6.83–6.78 (m, 3H), 6.70–6.67 (m, 2H), 6.24 (t, J=3.0 Hz, 1H), 5.87–5.85 (m, 1H), 5.36 (d, J=15.2 Hz, 1H), 5.26 (br s, 1H, NH), 5.17–5.14 (m, 1H), 3.71 (d, J=15.2 Hz, 1H), 3.55–3.43 (m, 2H), 1.23 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 167.2, 167.9, 135.4, 135.1, 129.4, 128.5, 128.3, 128.2, 127.5, 126.9, 121.9, 117.8, 110.1, 103.9, 59.5, 58.7, 51.8, 48.3, 40.1, 28.3. Anal. Calcd: C, 75.15; H, 7.03. Found: C, 75.41; H, 7.10%.

4.1.4.19. (1*S*,4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-isobutyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (28a). Yield 52%, yellow oil. R_f 0.32 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 40.74 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.25 (m, 3H), 7.21–7.19 (m, 2H), 6.64–6.62 (m, 1H), 6.17 (t, J=3.0 Hz, 1H), 6.00–5.98 (m, 1H), 5.65 (br s, 1H, NH), 5.63 (d, J=15.3 Hz, 1H), 4.81 (s, 1H), 4.73 (dd, J_1=9.1 Hz, J_2=4.9 Hz, 1H), 4.29 (d, J=15.3 Hz, 1H), 1.86–1.75 (m, 2H, CH_2), 1.73–1.68 (m, 1H), 1.25 (s, 9H, *t*-Bu), 1.02 (d, J=5.8 Hz, 3H, CH_3), 0.94 (d, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.5, 167.4, 135.9, 128.7, 128.2, 127.6, 119.6, 109.4, 104.9, 58.6, 57.2, 51.6, 49.9, 44.2, 28.4, 24.6, 22.9, 21.5. Anal. Calcd: C, 72.41; H, 8.19. Found: C, 72.40; H, 8.28%.

4.1.4.20. (1*R*,4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-isobutyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (28b). Yield 23%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 31.2 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.33–7.23 (m, 5H), 6.69–6.67 (m, 1H), 6.16 (t, J=3.1 Hz, 1H), 5.96–5.94 (m, 1H), 5.50 (d, J=15.1 Hz, 1H), 5.37 (br s, 1H, NH), 4.78–4.73 (m, 2H), 4.00 (d, J=15.1 Hz, 1H), 2.12–2.02 (m, 2H, CH_2), 1.81–1.70 (m, 1H), 1.27 (s, 9H, *t*-Bu), 0.90 (d, J=6.7 Hz, 3H, CH_3), 0.83 (d, J=6.7 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.7, 167.3, 135.9, 128.7, 128.5, 127.8, 121.8, 118.1, 109.2, 104.3, 59.2, 57.0, 51.8, 48.9, 41.1, 28.4, 24.8, 22.9, 22.3. Anal. Calcd: C, 72.41; H, 8.19. Found: C, 72.45; H, 8.30%.

4.1.4.21. (4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-isopropyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (29). Mixture of (1*R*)/(1*S*) isomers 2.8:1. Yield 60%, yellow oil. R_f 0.18 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) signals of major isomer δ: 7.35–7.24 (m, 5H), 6.65–6.63 (m, 1H), 6.19 (t, J=3.0 Hz, 1H), 6.01–5.99 (m, 1H), 5.57 (d, J=14.7 Hz, 1H), 5.34 (br s, 1H, NH), 4.83 (s, 1H), 4.53 (d, J=2.7 Hz, 1H), 3.98 (d, J=14.7 Hz, 1H), 2.54–2.45 (m, 1H), 1.32 (s,

9H, *t*-Bu), 0.95 (d, *J*=7.1 Hz, 3H, CH_3), 0.76 (d, *J*=6.8 Hz, 3H, CH_3), signals of minor isomer δ: 7.22–7.19 (m, 2H), 6.67–6.65 (m, 1H), 6.03–6.01 (m, 1H), 5.83 (br s, 1H, NH), 5.68 (d, *J*=15.7 Hz, 1H), 4.44 (d, *J*=15.7 Hz, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 2.15–2.07 (m, 1H), 1.25 (s, 9H, *t*-Bu), 1.15 (d, *J*=6.8 Hz, 3H, CH_3), 0.91 (d, *J*=6.8 Hz, 3H, CH_3), other signals observed by the signals of the major isomer. ^{13}C NMR ($CDCl_3$) δ: 168.0, 167.54, 167.45, 167.2, 136.0, 135.9, 129.1, 128.6, 128.2, 127.9, 127.6, 122.3, 121.9, 120.9, 119.0, 109.3, 109.1, 105.3, 104.4, 66.6, 63.7, 60.3, 56.8, 51.8, 51.5, 50.2, 48.2, 35.5, 33.0, 28.4, 28.2, 19.9, 19.6, 19.3, 17.3. Anal. Calcd: C, 71.90; H, 7.95. Found: C, 71.90; H, 8.01%.

4.1.4.22. (1*S*,4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (30a). Yield 53%, yellow oil. R_f 0.30 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 8.11 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.23 (m, 3H), 7.21–7.17 (m, 2H), 6.64–6.62 (m, 1H), 6.17 (t, *J*=3.0 Hz, 1H), 6.00–5.98 (m, 1H), 5.82 (br s, 1H, NH), 5.64 (d, *J*=15.3 Hz, 1H), 4.84 (s, 1H), 4.45–4.40 (m, 2H), 1.92–1.84 (m, 1H), 1.54–1.47 (m, 1H), 1.24 (s, 9H, *t*-Bu), 1.18–1.11 (m, 1H), 1.08 (d, *J*=6.8 Hz, 3H, CH_3), 0.87 (t, *J*=7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.42, 167.40, 136.1, 128.7, 128.2, 127.6, 122.3, 120.6, 109.2, 105.3, 65.3, 57.0, 51.5, 50.2, 39.4, 28.3, 25.6, 15.7, 10.8. Anal. Calcd: C, 72.41; H, 8.19. Found: C, 72.18; H, 7.99%.

4.1.4.23. (1*R*,4*S*)-2-Benzyl-*N*-(*tert*-butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (30b). Yield 16%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 44.85 (*c* 0.04, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.33–7.28 (m, 5H), 6.63–6.61 (m, 1H), 6.17 (t, *J*=3.0 Hz, 1H), 5.98–5.96 (m, 1H), 5.55 (d, *J*=14.7 Hz, 1H), 5.37 (br s, 1H, NH), 4.80 (s, 1H), 4.71 (d, *J*=2.9 Hz, 1H), 3.93 (d, *J*=14.7 Hz, 1H), 2.20–2.14 (m, 1H), 1.52–1.54 (m, 1H), 1.30 (s, 9H, *t*-Bu), 1.14–1.06 (m, 1H), 0.86 (t, *J*=7.3 Hz, 3H, CH_3), 0.82 (d, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.7, 167.3, 136.0, 129.0, 128.6, 127.9, 121.9, 118.5, 109.5, 104.2, 62.6, 60.3, 51.8, 48.3, 42.5, 28.4, 25.2, 15.3, 12.0. Anal. Calcd: C, 72.41; H, 8.19. Found: C, 72.48; H, 8.07%.

4.1.4.24. (1*R*,4*S*)-4-Benzyl-*N*-(*tert*-butyl)-2-(2-furylmethyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (31a). Yield 20%, yellow oil. R_f 0.30 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ −18.30 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.32–7.30 (m, 1H), 7.27–7.23 (m, 3H), 7.01–6.98 (m, 2H), 6.32–6.28 (m, 2H), 6.06–6.04 (m, 1H), 5.94 (t, *J*=3.1 Hz, 1H), 5.83 (br s, 1H, NH), 5.72–5.70 (m, 1H), 5.43 (d, *J*=15.7 Hz, 1H), 5.02 (s, 1H), 4.77–4.73 (m, 1H), 4.36 (d, *J*=15.7 Hz, 1H), 3.48–3.44 (m, 1H), 3.05–3.00 (m, 1H), 1.34 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 167.5, 167.4, 149.5, 142.7, 136.9, 129.6, 128.5, 127.0, 121.2, 120.6, 110.4, 109.8, 108.5, 104.9, 62.2, 57.9, 51.8, 42.8, 41.5, 28.5. Anal. Calcd: C, 71.09; H, 6.01. Found: C, 71.25; H, 6.19%.

4.1.4.25. (1*S*,4*S*)-4-Benzyl-*N*-(*tert*-butyl)-2-(2-furylmethyl)-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (31b). Yield 43%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 29.16 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.33–7.28 (m, 5H), 6.63–6.61 (m, 1H), 6.17 (t, *J*=3.0 Hz, 1H), 5.98–5.96 (m, 1H), 5.55 (d, *J*=14.7 Hz, 1H), 5.37 (br s, 1H, NH), 4.80 (s, 1H), 4.71 (d, *J*=2.9 Hz, 1H), 3.93 (d, *J*=14.7 Hz, 1H), 2.20–2.14 (m, 1H), 1.52–1.54 (m, 1H), 1.30 (s, 9H, *t*-Bu), 1.14–1.06 (m, 1H), 0.86 (t, *J*=7.3 Hz, 3H, CH_3), 0.82 (d, *J*=6.8 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 167.3, 149.4, 142.3, 134.9, 129.1, 128.1, 126.9, 121.9, 117.8, 110.5, 110.1, 109.8, 103.9, 60.0, 58.8, 51.9, 41.3, 40.5, 28.4. Anal. Calcd: C, 71.09; H, 6.01. Found: C, 71.21; H, 6.09%.

4.1.4.26. (1*S*,4*S*)-2-Benzyl-*N*-ethyl-4-isobutyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (32a). Yield 47%, yellow oil. R_f 0.30 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 26.08 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.29–7.18 (m, 5H), 6.64–6.62 (m, 1H), 6.17 (t, *J*=3.0 Hz, 1H), 6.04–6.00 (m, 2H), 5.61 (d, *J*=15.2 Hz, 1H), 4.90 (s, 1H), 4.74–4.70 (m, 1H), 4.22 (d, *J*=15.2 Hz, 1H), 3.24–3.17 (m, 2H), 1.87–1.72 (m, 3H), 1.06–1.01 (m, 6H), 0.92 (d, *J*=5.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.5, 168.2, 135.7, 128.7, 128.3, 127.7, 121.3, 119.7, 109.3, 105.0, 58.4, 56.7, 49.7, 44.3, 34.8, 24.6, 22.9, 21.4, 14.6. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.18; H, 7.65%.

4.1.4.27. (1*R*,4*S*)-2-Benzyl-*N*-ethyl-4-isobutyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (32b). Yield 21%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 19.50 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.30–7.20 (m, 5H), 6.69–6.67 (m, 1H), 6.16 (t, 1H, *J*=3.0 Hz), 5.98–5.96 (m, 1H), 5.86 (br s, 1H, NH), 5.47 (d, *J*=15.2 Hz, 1H), 4.89 (s, 1H), 4.77–4.75 (m, 1H), 4.00 (d, *J*=15.2 Hz, 1H), 3.23–3.13 (m, 2H), 2.14–2.03 (m, 2H), 1.79–1.72 (m, 1H), 1.04 (t, *J*=7.3 Hz, 3H, CH_3), 0.89 (d, *J*=5.9 Hz, 3H, CH_3), 0.81 (d, *J*=5.9 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.7, 168.2, 135.8, 128.7, 128.5, 127.8, 121.7, 118.2, 109.3, 104.6, 58.5, 57.0, 49.1, 40.8, 34.8, 25.0, 22.8, 22.3, 14.5. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.21; H, 7.60%.

4.1.4.28. (1*S*,4*S*)-2-Benzyl-*N*-ethyl-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (33a). Yield 46%, yellow oil. R_f 0.30 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 22.4 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.28–7.23 (m, 3H), 7.21–7.16 (m, 2H), 6.65–6.63 (m, 1H), 6.18 (t, *J*=3.0 Hz, 1H), 6.02–6.00 (m, 1H), 5.96 (br s, 1H, NH), 5.69 (d, *J*=15.3 Hz, 1H), 4.89 (s, 1H), 4.43–4.39 (m, 2H), 3.24–3.17 (m, 2H), 1.87–1.80 (m, 1H), 1.51–1.42 (m, 1H), 1.16–1.01 (m, 7H), 0.85 (t, *J*=7.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.4, 167.4, 136.0, 128.7, 128.3, 127.6, 121.9, 120.9, 109.2, 105.5, 65.3, 56.2, 50.0, 39.5, 34.7, 25.6, 15.8, 14.6, 10.9. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.19; H, 7.79%.

4.1.4.29. (1*R*,4*S*)-2-Benzyl-*N*-ethyl-4-[(1*R*)-1-methylpropyl]-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (33b). Yield 15%, yellow oil. R_f 0.11 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 34.92 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ:

7.33–7.27 (m, 5H), 6.65–6.63 (m, 1H), 6.18 (t, J=3.0 Hz, 1H), 5.99–5.97 (m, 1H), 5.63 (br s, 1H, NH), 5.52 (d, J=15.3 Hz, 1H), 4.94 (s, 1H), 4.70 (d, J=3.0 Hz, 1H), 3.95 (d, J=15.3 Hz, 1H), 3.28–3.20 (m, 2H), 2.21–2.14 (m, 1H), 1.51–1.45 (m, 1H), 1.16–1.10 (m, 1H), 1.06 (t, 3H, J=7.2 Hz, CH_3), 0.87 (t, 3H, J=7.6 Hz, CH_3), 0.81 (d, 3H, J=7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.3, 167.5, 135.8, 129.0, 128.6, 128.0, 121.7, 118.5, 109.6, 104.5, 62.5, 59.6, 48.5, 42.5, 34.7, 25.3, 15.2, 14.4, 12.0. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.28; H, 7.75%.

4.1.4.30. (4*S*)-*N*-(*tert*-Butyl)-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (34). Mixture of (1*R*)/(1*S*) isomers 1.3:1. Yield 67%, white amorphous solid. Mp 80 °C. R_f 0.14 (CH_3CN–CH_2Cl_2 1:20). ν_{max} (Nujol): 3100–3200, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$) signals of major isomer δ: 7.44–7.40 (m, 2H), 7.35–7.22 (m, 3H), 6.61–6.59 (m, 1H), 6.11 (t, J=3.0 Hz, 1H), 6.04 (q, J=7.1 Hz, 1H), 5.84–5.82 (m, 1H), 5.43 (br s, 1H, NH), 4.95 (d, J=16.4 Hz), 4.62 (d, J=16.4 Hz), 1.56 (d, J=7.1 Hz, 3H, CH_3), 1.27 (s, 9H, *t*-Bu), signals of minor isomer δ: 6.60–6.58 (m, 1H), 5.97–5.95 (m, 1H), J=6.8 Hz, 1H), 4.94 (d, J=16.4 Hz), 4.71 (br s, 1H, NH), 4.68 (s, 1H), 4.58 (d, J=16.4 Hz), 1.49 (d, J=7.1 Hz, 3H, CH_3), 0.92 (s, 9H, *t*-Bu), other signals are observed by the signals of the major isomer. ^{13}C NMR ($CDCl_3$) δ: 168.7, 167.6, 166.6, 166.3, 139.8, 139.4, 138.3, 129.2, 128.8, 128.7, 128.2, 127.7, 127.3, 123.8, 123.0, 119.5, 109.1, 103.4, 103.3, 55.8, 55.7, 51.8, 51.7, 51.4, 51.2, 50.1, 49.7, 28.5, 28.2, 16.5, 15.8. Anal. Calcd: C, 70.77; H, 7.42. Found: C, 70.70; H, 7.44%.

4.1.4.31. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-methyl-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (35a). Yield 44%, yellow oil. R_f 0.33 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 26.75 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ: 7.47–7.44 (m, 2H), 7.33–7.29 (m, 3H), 6.64–6.62 (m, 1H), 6.20 (t, J=3.2 Hz, 1H), 6.00 (q, J=7.1 Hz, 1H), 6.00–5.98 (m, 1H), 4.87 (br s, 2H), 4.81 (q, J=7.3 Hz, 1H), 1.84 (d, J=7.1 Hz, 3H, CH_3), 1.58 (d, J=7.3 Hz, 3H, CH_3), 0.98 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 169.0, 167.5, 138.5, 128.9, 128.6, 128.1, 127.2, 124.4, 117.2, 108.6, 103.7, 55.6, 54.4, 52.1, 51.2, 28.2, 16.4, 14.9. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.45; H, 7.68%.

4.1.4.32. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-methyl-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (35b). Yield 22%, yellow oil. R_f 0.24 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 43.25 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.47–7.44 (m, 2H), 7.37–7.32 (m, 3H), 6.62–6.60 (m, 1H), 6.20 (t, J=3.2 Hz, 1H), 6.00 (q, J=7.1 Hz, 1H), 5.99–5.97 (m, 1H), 4.87–4.78 (m, 3H), 1.84 (d, J=7.1 Hz, 3H, CH_3), 1.56 (d, J=7.3 Hz, 3H, CH_3), 0.98 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 169.0, 167.3, 138.3, 129.2, 128.6, 128.2, 127.5, 122.4, 118.2, 109.6, 103.5, 56.5, 55.9, 53.1, 51.2, 28.2, 21.9, 16.9. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.39; H, 7.67%.

4.1.4.33. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-methyl-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (36a). Yield 41%, yellow oil. R_f 0.33 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 46.74 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.47–7.44 (m, 2H), 7.33–7.29 (m, 3H), 6.64–6.62 (m, 1H), 6.19 (t, J=3.2 Hz, 1H), 6.00 (q, J=7.1 Hz, 1H), 6.00–5.98 (m, 1H), 4.87 (br s, 2H), 4.81 (q, J=7.3 Hz, 1H), 1.83 (d, J=7.1 Hz, 3H, CH_3), 1.58 (d, J=7.2 Hz, 3H, CH_3), 0.98 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ: 169.0, 167.5, 138.5, 128.9, 128.6, 128.1, 127.2, 124.4, 117.2, 108.6, 103.6, 55.8, 54.2, 52.0, 51.2, 28.2, 16.4, 14.9. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.32; H, 7.80%.

4.1.4.34. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-methyl-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (36b). Yield 23%, yellow oil. R_f 0.24 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 19.3 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.47–7.44 (m, 2H), 7.37–7.32 (m, 3H), 6.62–6.60 (m, 1H), 6.20 (t, J=3.2 Hz, 1H), 6.00 (q, J=7.1 Hz, 1H), 5.99–5.97 (m, 1H), 4.87–4.78 (m, 3H), 1.84 (d, J=7.1 Hz, 3H, CH_3), 1.56 (d, J=7.3 Hz, 3H, CH_3), 0.98 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$): 169.0, 167.3, 138.3, 129.2, 128.6, 128.2, 127.5, 122.4, 118.2, 109.6, 103.5, 56.5, 55.9, 53.1, 51.2, 28.2, 21.9, 16.9. Anal. Calcd: C, 71.36; H, 7.70. Found: C, 71.34; H, 7.85%.

4.1.4.35. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (37a). Yield 47%, yellow oil. R_f 0.33 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 37.3 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.43–7.40 (m, 2H), 7.35–7.29 (m, 3H), 6.57–6.55 (m, 1H), 6.16 (t, J=3.1 Hz, 1H), 6.08–6.06 (m, 1H), 5.83 (q, J=7.0 Hz, 1H), 5.05 (br s, 1H, NH), 4.93 (s, 1H), 4.68 (t, J=7.0 Hz, 1H), 1.88–1.83 (m, 2H, CH_2), 1.58 (d, J=7.0 Hz, 3H, CH_3), 1.04 (d, J=6.0 Hz, 3H, CH_3), 0.98 (s, 9H, *t*-Bu), 0.91 (d, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.1, 167.1, 138.8, 128.8, 128.7, 128.2, 122.8, 119.0, 109.3, 104.5, 59.0, 56.7, 54.6, 51.2, 44.5, 28.1, 24.9, 23.0, 21.4, 17.1. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.65; H, 8.30%.

4.1.4.36. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (37b). Yield 18%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 35.14 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1710 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.32–7.21 (m, 5H), 6.73–6.71 (m, 1H), 6.10 (t, J=3.1 Hz, 1H), 5.94 (q, J=7.0 Hz, 1H), 5.82–5.80 (m, 1H), 5.28 (br s, 1H, NH), 4.86 (t, J=4.7 Hz, 1H), 4.45 (s, 1H), 2.33–2.26 (m, 1H), 2.21–2.15 (m, 1H), 1.96–1.89 (m, 1H), 1.57 (d, J=7.0 Hz, 3H, CH_3), 1.25 (s, 9H, *t*-Bu), 0.96 (d, J=6.7 Hz, 3H, CH_3), 0.99 (d, J=6.5 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.0, 168.7, 139.7, 128.7, 127.6, 127.3, 123.5, 118.0, 108.7, 103.5, 57.3, 56.1, 52.6, 51.7, 38.8, 28.4, 25.4, 22.8, 22.7, 15.9. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.60; H, 8.26%.

4.1.4.37. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (38a). Yield 44%, yellow oil. R_f 0.33 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 40.6 (c 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.31–7.19 (m, 5H), 6.58–6.56 (m, 1H), 6.16 (t, J=3.3 Hz, 1H), 6.97 (q, J=7.3 Hz, 1H), 5.85–6.83 (m, 1H), 5.49

(br s, 1H, NH), 4.70 (t, J=7.0 Hz, 1H), 4.57 (s, 1H), 1.96–1.86 (m, 3H), 1.59 (d, J=7.3 Hz, 3H, CH_3), 1.26 (s, 9H, *t*-Bu), 1.02 (d, J=6.3 Hz, 3H, CH_3), 0.95 (d, J=6.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.0, 168.1, 139.7, 128.6, 127.7, 127.4, 122.7, 119.2, 109.1, 103.7, 58.7, 55.8, 52.8, 51.5, 44.7, 28.3, 24.8, 23.0, 21.5, 16.6. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.55; H, 8.44%.

4.1.4.38. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-isobutyl-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (38b). Yield 19%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 110.3 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.45–7.42 (m, 2H), 7.35–7.28 (m, 3H), 6.71–6.69 (m, 1H), 6.12 (t, J=3.1 Hz, 1H), 6.00–5.93 (m, 2H), 4.83 (t, J=5.1 Hz, 1H), 4.75 (br s, 1H, NH), 4.45 (s, 1H), 2.32–2.25 (m, 1H), 2.10–2.03 (m, 1H), 1.98–1.92 (m, 1H), 1.51 (d, J=7.1 Hz, 3H, CH_3), 0.97–0.92 (m, 15H). ^{13}C NMR ($CDCl_3$) δ: 169.0, 168.1, 139.7, 128.6, 127.7, 127.4, 122.7, 119.2, 109.1, 103.7, 58.7, 55.8, 52.8, 51.5, 44.7, 28.3, 24.8, 23.0, 21.5, 16.6. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.65; H, 8.38%.

4.1.4.39. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-1-carboxamide (39a). Yield 52%, yellow oil. R_f 0.29 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 20.1 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.35–7.26 (m, 2H), 7.24–7.20 (m, 3H), 6.62–6.64 (m, 1H), 6.12 (t, J=3.1 Hz, 1H), 5.96 (q, J=7.0 Hz, 1H), 5.88–5.86 (m, 1H), 5.65 (br s, 1H, NH), 4.63 (s, 1H), 4.30 (d, J=7.5 Hz, 1H), 2.01–1.91 (m, 1H, CH), 1.60 (d, J=7.0 Hz, 3H, CH_3), 1.57–1.47 (m, 1H), 1.28 (s, 9H, *t*-Bu), 1.22–1.12 (m, 4H), 0.86 (t, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.2, 167.0, 138.9, 128.5, 128.6, 128.3, 122.4, 118.6, 109.4, 104.5, 59.0, 56.7, 54.6, 51.2, 44.5, 28.1, 24.9, 23.2, 21.4, 17.0. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.71; H, 8.36%.

4.1.4.40. (1*R*,4*S*)-*N*-(*tert*-Butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-1-carboxamide (39b). Yield 13%, yellow oil. R_f 0.14 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 46.25 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.22 (m, 2H), 7.25–7.19 (m, 3H), 6.62–6.64 (m, 1H), 6.13 (t, J=3.1 Hz, 1H), 5.90 (q, J=7.0 Hz, 1H), 5.98–5.96 (m, 1H), 5.35 (br s, 1H, NH), 4.63 (s, 1H), 4.30 (d, J=7.5 Hz, 1H), 2.01–1.91 (m, 1H, CH), 1.55 (d, J=7.0 Hz, 3H, CH_3), 1.55–1.46 (m, 1H), 1.22–1.12 (m, 4H), 1.14 (s, 9H, *t*-Bu), 0.87 (t, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.1, 168.9, 134.0, 128.7, 127.5, 127.4, 123.7, 118.0, 108.2, 103.8, 56.9, 56.5, 52.6, 52.0, 39.0, 28.3, 25.0, 22.8, 22.7, 16.0. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.62; H, 8.34%.

4.1.4.41. (1*S*,4*S*)-*N*-(*tert*-Butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazine-1-carboxamide (40a). Yield 47%, yellow oil. R_f 0.31 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 11.0 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.35–7.26 (m, 2H), 7.24–7.20 (m, 3H), 6.62–6.64 (m, 1H), 6.12 (t, J=3.1 Hz, 1H), 5.96 (q, J=7.0 Hz, 1H), 5.88–5.86 (m, 1H), 5.65 (br s, 1H, NH), 4.63 (s, 1H), 4.30 (d, J=7.5 Hz, 1H), 2.01–1.91 (m, 1H, CH), 1.60 (d, J=7.0 Hz, 3H, CH_3), 1.57–1.47 (m, 1H), 1.28 (s, 9H, *t*-Bu), 1.22–1.12 (m, 4H), 0.86 (t, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.1, 167.1, 138.8, 128.8, 128.7, 128.2, 122.8, 119.0, 109.3, 104.5, 59.0, 56.7, 54.6, 51.2, 44.5, 28.1, 24.9, 23.0, 21.4, 17.1. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.69; H, 8.37%.

4.1.4.42. (1*R*,4*S*)-*N*,*N*-(*tert*-Butyl)-4-[(1*R*)-1-methylpropyl]-3-oxo-2-[(1*S*)-1-phenylethyl]-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-1-carboxamide (40b). Yield 14%, yellow oil. R_f 0.13 (CH_3CN–CH_2Cl_2 1:20). $[\alpha]_D^{20}$ 28.64 (*c* 0.05, $CHCl_3$). ν_{max} (Nujol): 3100–3200, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.37–7.22 (m, 2H), 7.25–7.19 (m, 3H), 6.62–6.64 (m, 1H), 6.13 (t, J=3.1 Hz, 1H), 5.90 (q, J=7.0 Hz, 1H), 5.98–5.96 (m, 1H), 5.35 (br s, 1H, NH), 4.63 (s, 1H), 4.30 (d, J=7.5 Hz, 1H), 2.01–1.91 (m, 1H, CH), 1.55 (d, J=7.0 Hz, 3H, CH_3), 1.55–1.46 (m, 1H), 1.22–1.12 (m, 4H), 1.14 (s, 9H, *t*-Bu), 0.87 (t, J=6.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 169.1, 168.9, 134.0, 128.7, 127.5, 127.2, 123.7, 118.0, 108.2, 104.0, 56.9, 56.1, 52.6, 51.7, 38.8, 28.3, 24.9, 22.8, 22.7, 16.0. Anal. Calcd: C, 72.88; H, 8.41. Found: C, 72.79; H, 8.30%.

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