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Ribose conversion with amino acids into pyrraline platform chemicals – expeditious synthesis of diverse pyrrole-fused alkaloid compounds†

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One-pot conversion of sustainable D-ribose with L-amino acid, methyl esters produced pyrrole-2-carbaldehydes **5** in reasonable yields (32–63%) under pressurized conditions of 2.5 atm at 80 °C. The value-added pyrraline compounds **5** as platform chemicals were utilized for quick installation of poly-heterocyclic cores for the development of pyrrole-motif natural and artificial therapeutic agents. A pyrrole-fused piperazin-2-one scaffold **6** was prepared by reductive amination of pyrralines **5** with benzylamine. While further cyclization of pyrralines **5** with ethane-1,2-diamine produced pyrrolo-piperazin-2-ones **7** with an extra imidazolidine ring, the reaction with 2-amino alcohols derived from natural L-amino acids, alanine, valine, and phenylalanine, respectively provided pyrrolo-piperazin-2-ones **8**, **9**, and **10** with oxazolidine as the third structural core. Cell viability and an anti-inflammatory effect of the synthesized compounds were briefly tested by the MTT method and the Griess assay, among which **8h** and **10g** exhibited significant anti-inflammatory effects with negligible cell toxicity.

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Introduction

Pyrrole is an interesting five-membered heterocyclic compound with the nitrogen lone-pair electrons being delocalized within the ring for aromaticity. It is therefore non-basic contrary to the six-membered ring homologue, pyridine. Alkaloid natural products containing pyrrole as a pharmacophore exhibit various biological activities such as sedative, anti-inflammatory, anti-biotic, anti-cancer, anti-hypertensive, anti-convulsant, anti-malarial, and many more.[1–6] The organic synthesis of pyrrole was reported in the late 19th century,[7–9] among which the Paal–Knorr method utilizing a 1,4-dicarbonyl compound and primary amine was the first (Fig. 1).[10–12] The Hantzsch method by the reaction of α-haloketone and β-ketoester with a primary amine is useful for the preparation of 3-carboxylated pyrroles.[13,14] In 1948, Clauson-Kaas reported furan conversion into 2,5-dimethoxytetrahydrofuran for the efficient preparation of pyrroles.[15] Many others then modified the above original methods for the syntheses of various pyrrole compounds.[16–33]

Transformation of D-glucose as sustainable biomass into 5-hydroxymethyl-2-furfural (5-HMF) as a value-added platform chemical has been well documented in the literature in recent years.[34–36] Utilization of reducing sugars for the preparation of pyrroles would also be beneficial and providential. In 1912, Maillard reported the reaction between D-glucose and amino acids at high temperature (>140°) to produce hundreds of small chemicals for flavouring in food chemistry,[37] which was later known to include pyrraline **1**, the nitrogen analogue of 5-HMF, in a very small quantity.[38] Pyrraline **1** would be a useful platform

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† Electronic supplementary information (ESI) available: Cell viability assays, nitric oxide concentration (Griess assay), picture demonstration for the pressure reaction, and $^{1}H/^{13}C$ NMR spectra for compounds **5**, **6**, **7**, **8**, **9**, and **10**. See DOI: 10.1039/d1ra06110k

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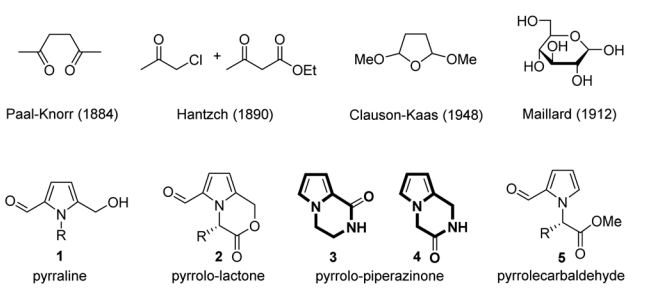


Fig. 1 The original synthetic methods of pyrrole and structures of some pyrrole derivatives.

chemical for the development of pyrrole-motif natural and artificial therapeutic agents by further reactions.[39–43]

The first chemical synthesis of pyrralines **1** by Kato from the reaction of D-glucose and primary amines either at 100 °C in H_2O for 1 h or at 70 °C in MeOH for 3 h both with acetic acid just confirmed the formation of pyrralines **1**.[44] Monnier reported the synthesis of butyl pyrraline **1** (R = Bu) in only 3.4% yield by the reaction of D-glucose and butylamine in aqueous acetic acid at 100 °C for 2 h.[38] We believed that the low yield of pyrraline **1** was ascribed to the unstable imine intermediates under the aqueous acidic condition. We recently studied the reaction conditions of D-glucose and primary amines, and significantly improved the yield of pyrralines **1** (20–50%) under non-aqueous condition by use of oxalic acid in DMSO at 90 °C for 30 min.[45] Anti-inflammatory and pain-relieving pyrrolo-lactones **2**, which could be isolated from *Celastrus orbiculatus* (R = Bn) and *Capparis spinosa* (R = Me), were synthesized in 27% and 32% yields, respectively when methyl esters of amino acids, phenylalanine and alanine, were used as primary amines in the above one-pot reaction condition.[45] Nonetheless, it was still necessary to improve the one-pot reaction conditions of sugars and amino acids for reasonable yields of the pyrrole platform chemicals, which might be realized by reducing the formation of tar by-product under a pressurized reaction condition.

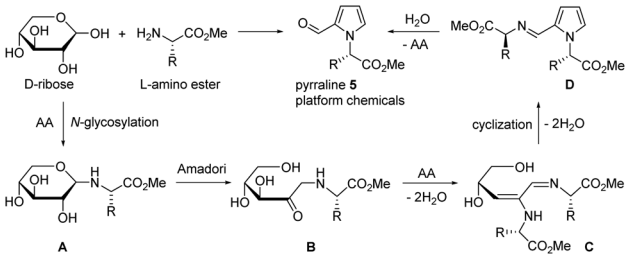
Piperazin-2-one is a privileged structural unit in drug discovery because many of the biologically active natural products and the approved drug molecules contain the above scaffold,[46–49] which exhibit opiate,[50] antiviral,[51] anti-cancer,[52] and anti-diabetes activities[53] as well as treatment effects for immunological disorder[54] and non-Hodgkin's lymphoma.[55] Pyrrole-fused piperazin-2-ones (**3** and **4** in Fig. 1) would thus be a very promising structural unit for the discovery of new therapeutic agents. In fact, the structure of pyrrolo-piperazinone **3** has been found in numerous antibiotic and cytotoxic alkaloid natural products, such as agelastatins,[56,57] longamide,[58] hanishin,[59] and agesamides.[60]

We envisioned that the structure of pyrrolo-piperazinone **4** would be obtainable from pyrrole-2-carbaldehyde **5**, which might be prepared by the one-pot "Maillard-type" reaction between D-ribose and α-amino acids. Amination of the formyl group and subsequent lactam formation with the carboxylic ester in pyrrole-2-carbaldehyde **5** would form the core structure of pyrrolo-piperazinone **4**. In this paper, we described one-pot conversion of D-ribose with various α-amino acids under a pressurized condition to obtain reasonable yields of pyrrole-2-carbaldehydes **5** as platform chemicals and their further cyclization reactions to pyrrolo-piperazinone derivatives **6–10** as new potential therapeutic agents. Finally, cell viability and anti-inflammatory effect of the synthesized pyrrolo-piperazinones were briefly tested for RAW264.7 cells by the MTT method and the Griess assay.

Results and discussion

One-pot ribose conversion with amino acid

D-Ribose was first reacted with L-valine methyl ester in DMSO with oxalic acid at 90 °C for 30 min to produce pyrraline **5** (R = i-Pr) in 24% yield, which was the previous optimized condition for D-glucose.[45] Unlike D-glucose case providing pyrrololactones,

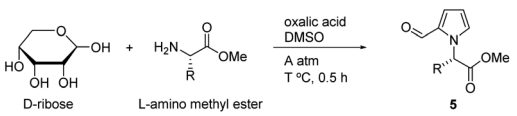


Scheme 1 Ribose conversion with amino ester through *N*-glycosylation, Amadori reaction, and cyclization to produce pyrraline **5** as platform chemicals.

pyrrole-2-carbaldehyde **5** with intact methyl ester was obtained. Pyrroles as the glycosylation end products were believed to be formed through 3-deoxyglucosone intermediate after *N*-glycosylation and Amadori reaction.[38,61,62] The reaction of D-ribose was thus speculated to follow *N*-glycosylation (**A**) and Amadori reaction (**B**) in sequence (Scheme 1). Second amino ester was introduced to give the structure **C** by imine tautomerization and dehydration, which is the adduct of amino esters to the 3-deoxyglucosone homologue from D-ribose. Cyclization of enamine and dehydration produced pyrrole ring **D**. Finally, hydrolysis of the imine provided pyrraline **5** and regenerated amino ester. D-Ribose reaction with other amino esters from L-phenylalanine and L-methionine also produced the corresponding pyrralines **5** in 37% (R = Bn) and 30% (R = CH_2CH_2SMe) yields, respectively, but it was imperative to improve the ribose conversion reaction to utilize pyrralines **5** as sustainable platform chemicals for the discovery of potent therapeutic agents.

The ribose conversion reaction with α-amino methyl esters under the above condition produced pyrralines **5** in 24–37% yields as the only isolable product together with dark-brown tarry materials, which suggested that reducing the amount of tar would improve the yield of pyrralines **5**. The ribose conversion was thus studied for the above three amino esters under pressurized conditions (1–4 atm) at 90 °C to reduce the tar formation (Table 1). We found gradual yield improvements of **5** as pressure was increased with the maximum value at 2.5 atm. The yield of **5** was maintained or slowly fell after 3.0 atm.

Table 1 Optimization of D-ribose conversion (%yield of **5**) with L-amino acid, methyl ester at 90 °C under various pressure conditions



	Yield of **5** (%) under each pressure (atm)						
AA[a]	1	1.5	2	2.5	3	3.5	4
Val	**24**	29	30	**38**	36	36	33
Phe	**37**	38	39	**48**	47	46	46
Met	**30**	35	36	**42**	37	37	37

[a] Amino acid: valine (R = i-Pr), phenylalanine (R = Bn), methionine (R = CH_2CH_2SMe).

Table 2 Optimization of D-ribose conversion (% yield of **5**) with L-amino acid, methyl ester at 2.5 atm under various temperature conditions

	Yield of **5** (%) at each temperature (°C)					
AA[a]	60	70	75	80	85	90
Val	29	31	38	**42**	39	38
Phe	35	41	45	**54**	48	48
Met	32	35	37	**46**	43	42

[a] Amino acid: valine (R = i-Pr), phenylalanine (R = Bn), methionine (R = CH_2CH_2SMe).

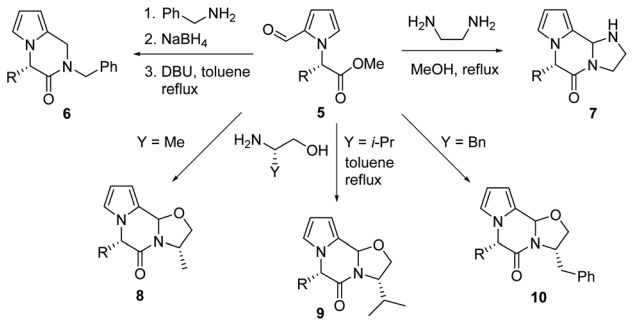
Reaction temperature was then screened from 60 °C to 90 °C at the optimal pressure of 2.5 atm (Table 2). The yield of **5** was progressively improved as temperature was raised up to 80 °C and fell slowly down since then. The best yields of pyrralines **5** were obtained at 80 °C (2.5 atm) for all three amino esters, which were approximately 150% of those at the previous optimal condition for glucose (90 °C, 1 atm).[45]

Generality of the ribose conversion with α-amino methyl esters and improvement of the yields of pyrralines **5** under the pressure condition (2.5 atm, 80 °C) compared to the original one (1 atm, 90 °C) were summarized in Table 3, in which 150–300% yield increases for pyrralines **5** were notified for eleven natural L-α-amino acids. Amino esters reacted with D-ribose as nucleophile and the yields of pyrralines **1** were reflected by the nucleophilicity of each amino ester, which was differentiated by the α-substituent R in this case. It was initially predicted that R would provide steric hinderance to the amino group, thereby lower yield of **1** could be obtained as the size of R was increased. Surprisingly, it was L-glycine (R = H), however, which gave the lowest yield (32%) of pyrraline **1**, and the highest yield of **1** (63%) was obtained for L-leucine (R = i-Bu).

Table 3 Improvement of D-ribose conversion (% yield of **5**) with L-amino acid, methyl ester at 2.5 atm and 80 °C compared at 1.0 atm and 90 °C

		Yield of **5** (%)	
Amino Acid[a]	Compound **5**	1.0 atm, 90 °C	2.5 atm, 80 °C
Gly	**5a**	10	32
Ala	**5b**	23	38
Val	**5c**	24	42
Leu	**5d**	43	63
Ile	**5e**	20	40
Phe	**5f**	37	54
Bn	**5g**	20	53
Asp	**5h**	18	47
Glu	**5i**	16	37
Met	**5j**	30	46
Trp	**5k**	34	55

[a] Amino acid (R): glycine (H), alanine (Me), valine (i-Pr), leucine (i-Bu), isoleucine (*s*-Bu), phenylalanine (CH_2Ph), benzylalanine (CH_2CH_2Ph), aspartic acid (CH_2CO_2Me), glutamic acid ($CH_2CH_2CO_2Me$), methionine (CH_2CH_2SMe), tryptophane (3-indole).



Scheme 2 Further cyclization of pyrraline platform chemicals **5** to pyrrolo-piperazin-2-one derivatives **6–10**.

It seemed that the hydrogen bonding between primary amino and ester groups would reduce the nucleophilicity of amino esters. L-Glycine with no α-substituent may participate in the hydrogen bonding, which reduces the nucleophilicity of the amino group. Primary alkyl or aryl substituents R (*e.g.*, Leu, Phe, Bn) would be good enough to maintain the nucleophilicity of amino group by interrupting the hydrogen bonding without providing steric hinderance to the amino group. Pyrralines **5** can now be obtained in 32–60% yield by one-pot conversion from D-ribose with L-amino acid methyl esters and certainly be flatform chemicals for the syntheses of pyrrole-based poly heterocyclic compounds as potential therapeutic agents.

Cyclization of the platform pyrralines 5 to pyrrolo-piperazinones 6–10

We demonstrated three different methods for further cyclization of pyrralines **5**, derived from eight different L-amino acids – glycine (**a**), alanine (**b**), valine (**c**), isoleucine (**d**), phenylalanine (**e**), benzylalanine (**f**), aspartic acid (**g**), and methionine (**h**) – with five different nitrogen reagents to produce the 2-piperazin-2-one skeleton as the second pharmacophore with the basic pyrrole scaffold (Scheme 2 and Table 4). The 1,5-relationship between the carbonyl carbons of formyl and ester groups in pyrralines **5** allowed δ-lactam formation with primary amines by reductive amination and cyclization. Benzylamine was utilized for the reductive amination with pyrralines **5**, which was carefully carried out first by imine formation in MeOH at 25 °C, followed by selective $NaBH_4$ reduction at 0 °C due to the presence of the sensitive α-amino ester group. The resulting secondary amine underwent lactam formation with the ester group in the presence

Table 4 Yields (%) of the reactions in Scheme 2

Entry	R	**6**	**7**	**8**	**9**	**10**
a	H	36	58	12	4	6
b	Me	66	87	41	27	32
c	i-Pr	73	94	73	61	41
d	*s*-Bu	86	91	77	50	31
e	$PhCH_2$	41	86	52	71	62
f	$PhCH_2CH_2$	64	88	22	51	57
g	MeO_2CCH_2	84	72	27	10	14
h	$MeSCH_2CH_2$	47	87	24	24	22

of DBU at the reflux temperature of toluene to produce pyrrolo-piperazin-2-ones **6** in 36–84% yields (Table 4).

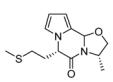
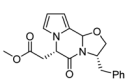
α,ω-Alkanediamine (*e.g.*, 1,2-ethanediamine) can be utilized in lactam formation with pyrralines **5**, where initially formed imine may react with the second amine by cyclization.[40,41] One of the resulting two symmetrical secondary amines participated in further cyclization with the ester group to form pyrrolo-piperazinones **7** with an imidazolidine ring as the third core in 58–94% yields (Table 4). The conversion of pyrralines **5** with norephedrine was reported,[42] where the initially formed imine was reacted with the alcohol group by cyclization to form an oxazolidine unit, which underwent further cyclization with the ester group to produce pyrrolo-piperazinones with the oxazolidine unit. In a similar manner, 2-amino alcohols derived from natural α-amino acids, alanine (Y = Me), valine (i-Pr), and phenylalanine (Bn), can be utilized for the syntheses of oxazolidine-fused pyrrolo-piperazinones **8**, **9**, and **10**, respectively. Even though somewhat lower yields were notified for the pyrralines **5** from Gly (**a**, R = H), Asp (**g**, $CH_2CO_2CH_3$), and Met (**h**, $CH_2CH_2SCH_3$), fare yields of poly heterocyclic products **8–10** were obtained for the pyrralines **5** derived from α-amino acids with a simple alkyl substituent (Table 4).

Cell viability (MTT test) and anti-inflammation assays (Griess method)

All the synthesized pyrrolo-piperazinones **6–10** (**a–h**) were briefly screened for cytotoxicity to RAW264.7 cells (Murine macrophages) at a fixed concentration at 20 μg mL^{-1}. Four compounds **7a**, **7c**, **8h**, and **10g** showed 80% or higher cell viability by Formazan formation in MTT {3-(4,5-dimetnythiazol-2-yl)-2,5-diphenyl-thetazolium bromide} assay (see ESI†).[63] The other regents might still be good candidates for antibiotics.

Anti-inflammatory activities to RAW264.7 cells were then tested for the above four samples at five different concentrations (0, 1, 5, 10, 20 μg mL^{-1} each) in 24 h after triggering by 1 μg mL^{-1} of LPS (lipopolysaccharides). Nitric oxide concentration, which is correlated with the inflammation level, was determined by the Griess method.[64] The measurements were repeated three times. The mean and standard deviation values of the NO concentration (μg mL^{-1}) for the cell treated by each compound at each concentration are listed in Table 5. Pyrrolo-piperazinones **8h** and **10g** containing oxazolidine as the third core exhibited significant anti-inflammation activities, in which IC_{50} values were estimated to be 20 μg mL^{-1} and 10 μg mL^{-1}, respectively. For comparison, IC_{50} of NIL {L-N^6-(1-iminoethyl) lysine} as a positive control was measured as 10.17 mM, which is converted as 2.64 μg mL^{-1} (see ESI†).

Table 5 Nitric oxide concentration (μM) by Griess assay for RAW264.7 cells after treatment of each reagent (μg mL^{-1}) and lipopolysaccharides (LPS, 1 μg mL^{-1})

Conc. (μg mL^{-1})	 **7a**	 **7c**	 **8h**	 **10g**
0[a]	3.21 ± 0.15	3.21 ± 0.15	3.21 ± 0.15	3.21 ± 0.15
0	25.54 ± 2.60	25.54 ± 2.60	25.54 ± 2.60	25.54 ± 2.60
1	26.23 ± 2.60	25.03 ± 2.13	22.23 ± 2.13	17.31 ± 1.31
5	22.31 ± 1.65	24.32 ± 1.31	21.32 ± 1.31	15.32 ± 2.60
10	20.30 ± 2.65	23.51 ± 1.10	16.31 ± 1.10	**14.31 ± 2.11**
20	20.02 ± 3.64	21.65 ± 2.51	**14.32 ± 2.51**	11.10 ± 1.31

[a] Without LPS treatment.

Experimental

General experimental

Reactions were performed in a well-dried flask under argon atmosphere unless noted otherwise. A mini-clave steel reactor (100 mL, up to 15 bar) made from büchiglasuster (Switzerland) was used for the pressurized reactions. The pressure was controlled by argon gas (see ESI† for picture demonstration). Solvents used as reaction media were dried over pre-dried molecular sieve (4 Å) by microwave oven. Solvents for extraction and chromatography were reagent grade and used as received. The flash column chromatography was performed by the method of Still (*J. Org. Chem.*, 1978, **43**, 2923) with silica gel 60 (70–230 mesh) using a mixture of EtOAc/hexane as gradient eluent. ^1H and ^{13}C NMR spectra were respectively recorded on a 400 MHz and 100 MHz NMR spectrometer in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference unless noted otherwise.

Cell viability assay (MTT method)[63]

RAW264.7 cells (Murine macrophages) were cultured using Dulbecco's modified Eagle medium (DMEM) (Welgene, Seoul, Korea) containing 10% fetal bovine serum (FBS), 2 mM glutamine, and 100 unit/mL of antibiotics (Gibco BRL, Rockville, MD). Cells were incubated at 37 °C incubators, which maintained a humidified atmosphere of 5% (v/v) air/CO_2. The incubated RAW264.7 cells (5×10^3/well) were seeded to a 96-cell culture plate to conduct a cell viability assay. The RAW264.7 cells prepared for the viability assay went through 18 h of attachment and stabilization. The growth medium was removed and replaced by a fresh medium without FBS. The synthetic compounds were treated to the cells at a concentration of 20 μg mL^{-1} and the resulting cells were incubated for 24 h. The sample-treated culture medium was removed and 100 μg mL^{-1} of 3-(4,5-dimetnythiazol-2-yl)-2,5-diphenyl-thetazolium bromide (MTT) was added to each well. In 1 h, purple formazan produced by cellular respiration was dissolved in a 200 μL DMSO solution and the absorbance at 560 nm was measured using a multi-plate reader. The analyses were repeated three times. The results were expressed as means of three independent experiments.

Measurement of nitric oxide concentration (Griess assay)[64]

RAW264.7 cells were transferred into 3×10^5 cells per well in a 96-cell culture plate and incubated for 24 h in a 5% CO_2 incubator at 37 °C. Four different concentrations (1, 5, 10, and 20 μg mL^{-1}) of synthetic compounds was treated to the incubated RAW264.7 cells. Simultaneously, 1 μg mL^{-1} of

lipopolysaccharides (LPS) (Sigma-Aldrich, St. Louis, MO) was added and the resulting cells were incubated for 24 h. The same amount of Griess reagent (Sigma-Aldrich) equal to 100 μL of the culture solution was added according to the manufacturer's recommendations, and the absorbance was measured at 540 nm with a multi-plate reader. The NO concentration in the culture medium was determined using a standard curve for each concentration of sodium nitrite.

General procedure for D-ribose conversion with L-amino acids for the synthesis of pyrraline 5

Methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (5a). To a stirred solution of glycine (10.0 g, 0.133 mol, 1 equiv.) in MeOH (7 mL) at 0 °C under argon atmosphere was slowly added thionyl chloride (9.73 mL, 0.133 mol, 1 equiv.) through a syringe. The mixture was then heated at 65 °C for 8 h and cooled to room temperature. The mixture was triturated with Et_2O to give glycine methyl ester, ammonium chloride salt as white crystalline salt (16.57 g, 0.133 mol).

Under ambient pressure. To a stirred solution of the above glycine methyl ester, ammonium chloride salt (8.35 g, 66.5 mmol, 1 equiv.) in DMSO (20 mL) were added Et_3N (18.4 mL, 0.133 mol, 2 equiv.) and D-ribose (10.0 g, 66.6 mmol, 1 equiv.). After complete dissolution, oxalic acid (12.0 g, 0.133 mol, 2 equiv.) was added and the resulting mixture was heated at 90 °C for 30 min. Upon cooling to room temperature, the mixture was filtered through a short pad of SiO_2 with EtOAc rinsing. The filtrate was concentrated and purified by SiO_2 flash column chromatography to give **5a** (1.08 g, 6.45 mmol) in 10% yield as light-yellow liquid.

Under pressure bottle at 2.5 bar. A mixture of glycine methyl ester, ammonium chloride salt (2.00 g, 15.9 mmol) and Et_3N (2.18 mL, 15.9 mmol) in dry DMSO (10 mL) was stirred in a mini-clave steel reactor and then D-ribose (4.73 g, 31.8 mmol) and oxalic acid (1.41 g, 15.9 mmol) were added. The mixture was pressurized to 2.5 bar with argon and heated at 80 °C for 0.5 h. The mixture was then cooled to room temperature and depressurized. The resulting viscous mixture was filtered through a short pad of SiO_2 rinsing with EtOAc. The filtrate was concentrated and purified by SiO_2 flash column chromatography (eluent 7 : 1 EtOAc/hexane) to give **5a** (0.85 g, 5.09 mmol) in 32% yield as light-yellow liquid.

*Data for **5a**.* $R_f = 0.50$ (4 : 6 EtOAc/hexane); ^{1}H NMR $\delta = 3.77$ (s, 3H), 5.08 (s, 2H), 6.31 (dd, $J = 2.4$, 1.6 Hz, 1H), 6.92 (dd, $J = 4.0$, 2.4 Hz, 1H), 7.00 (dd, $J = 4.0$, 1.6 Hz, 1H), 9.54 (s, 1H) ppm; ^{13}C NMR $\delta = 50.0$, 52.5, 110.2, 124.6, 124.6, 132.0, 168.7, 179.8 ppm; IR $\nu = 3111$, 2941, 2904, 2840, 1740, 1650, 1528, 1480, 1403, 1359, 1321, 1216, 1081, 1031, 999, 761 cm^{-1}; HRMS (EI) calcd for $C_8H_9NO_3$ 167.0582, found 167.0582.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (5b). The mixture of L-alanine methyl ester, ammonium chloride salt (2.00 g, 14.3 mmol), Et_3N (2.0 mL, 14.3 mmol), D-ribose (4.35 g, 28.6 mmol), and oxalic acid (1.27 g, 14.3 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5b** (985 mg, 5.4 mmol) in 38% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5b**.* $R_f = 0.53$ (4 : 6 EtOAc/hexane); ^{1}H NMR $\delta = 1.73$ (d, $J = 7.6$ Hz, 3H), 3.71 (s, 3H), 5.86 (q, $J = 7.6$ Hz, 1H), 6.30 (dd, $J = 4.0$, 2.0 Hz, 1H), 6.98 (dd, $J = 4.0$, 1.6 Hz, 1H), 7.18 (ddd, $J = 2.0$, 1.6, 1.2 Hz, 1H), 9.50 (d, $J = 1.2$ Hz, 1H) ppm; ^{13}C NMR $\delta = 17.6$, 52.2, 55.1, 110.0, 125.1, 128.7, 131.3, 171.2, 179.3 ppm; IR $\nu = 3116$, 2999, 2954, 2851, 2809, 1729, 1608, 1517, 1470, 1406, 1364, 1339, 1313, 1211, 1090, 1066, 1033, 983, 743 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}NO_3$ + Na 204.0631, found 204.0636.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (5c). The mixture of L-valine methyl ester, ammonium chloride salt (2.00 g, 11.9 mmol), Et_3N (1.7 mL, 11.9 mmol), D-ribose (3.59 g, 23.8 mmol), and oxalic acid (1.07 g, 11.9 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5c** (1.05 g, 5.0 mmol) in 42% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5c**.* $R_f = 0.76$ (4 : 6 EtOAc/hexane); ^{1}H NMR $\delta = 0.78$ (d, $J = 6.4$ Hz, 3H), 1.01 (d, $J = 6.4$ Hz, 3H), 2.40 (m, 1H), 3.75 (s, 3H), 5.99 (d, $J = 10.4$ Hz, 1H), 6.31 (ddd, $J = 4.0$, 2.8, 1.2 Hz, 1H), 6.93 (ddd, $J = 4.0$, 1.6, 1.6 Hz, 1H), 7.39 (ddd, $J = 2.8$, 1.6, 1.2 Hz, 1H), 9.54 (dd, $J = 1.6$, 1.2 Hz, 1H) ppm; ^{13}C NMR $\delta = 18.5$, 19.2, 33.0, 52.2, 63.8, 110.7, 125.3, 129.9, 131.9, 171.2, 179.9 ppm; IR $\nu = 3126$, 2952, 2874, 2846, 2813, 1729, 1655, 1523, 1460, 1408, 1373, 1338, 1258, 1201, 1147, 1062, 1033, 1000, 877, 825, 743 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NO_3$ + Na 232.0944, found 232.0942.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-methylpentanoate (5d). The mixture of L-leucine methyl ester, ammonium chloride salt (2.00 g, 11.0 mmol), Et_3N (1.6 mL, 11.0 mmol), D-ribose (3.32 g, 22.0 mmol), and oxalic acid (0.99 g, 11.0 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5d** (1.55 g, 6.93 mmol) in 63% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5d**.* $R_f = 0.76$ (4 : 6 EtOAc/hexane); ^{1}H NMR $\delta = 0.90$ (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 1.40 (m, 1H), 1.99 (dd, $J = 8.0$, 6.8 Hz, 2H), 3.72 (s, 3H), 6.10 (t, $J = 8.0$ Hz, 1H), 6.32 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.96 (dd, $J = 4.0$, 1.6 Hz, 1H), 7.21 (ddd, $J = 2.8$, 1.6, 1.2 Hz, 1H), 9.52 (d, $J = 1.2$ Hz, 1H) ppm; ^{13}C NMR $\delta = 21.3$, 22.8, 24.6, 41.3, 52.4, 57.4, 110.4, 125.5, 129.5, 131.6, 171.5, 179.6 ppm; IR $\nu = 3119$, 2963, 2873, 2810, 2773, 2729, 1750, 1657, 1534, 1473, 1411, 1373, 1348, 1273, 1203, 1164, 1132, 1080, 1029, 1001, 911, 878, 832, 778, 753 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1207.

Methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (5e). The mixture of L-isoleucine methyl ester, ammonium chloride salt (2.00 g, 11.0 mmol), Et_3N (1.5 mL, 11.0 mmol), D-ribose (3.31 g, 22.0 mmol), and oxalic acid (0.88 g, 11.0 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5e** (982 mg, 4.4 mmol) in 40% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5e**.* $R_f = 0.80$ (4 : 6 EtOAc/hexane); ^{1}H NMR $\delta = 0.83$ (t, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H), 1.00–1.24 (m, 2H), 2.18 (m, 1H), 3.74 (s, 3H), 6.06 (d, $J = 9.6$ Hz, 1H), 6.31 (dd, $J =$

3.2, 2.4 Hz, 1H), 6.93 (dd, J = 3.2, 1.6 Hz, 1H), 7.41 (ddd, J = 2.4, 1.6, 1.2 Hz, 1H), 9.53 (s, 1H) ppm; ^{13}C NMR δ = 10.5, 15.3, 24.7, 38.8, 52.0, 62.6, 110.5, 125.2, 129.7, 131.8, 171.0, 179.6 ppm; IR ν = 3116, 2961, 2862, 2703, 1735, 1655, 1530, 1468, 1410, 1375, 1343, 1250, 1202, 1151, 1070, 1026, 991, 750 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{17}NO_3$ 223.1208, found 223.1207; HRMS (ESI) calcd for $C_{12}H_{17}NO_3$ + Na 246.1101, found 246.1105.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (5f). The mixture of L-phenylalanine methyl ester, ammonium chloride salt (2.00 g, 9.3 mmol), Et_3N (1.3 mL, 9.3 mmol), D-ribose (2.80 g, 18.6 mmol), and oxalic acid (0.84 g, 9.3 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5f** (1.29 g, 5.02 mmol) in 54% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5f**.* R_f = 0.88 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 3.27 (dd, J = 14.0, 10.0 Hz, 1H), 3.54 (dd, J = 14.0, 5.6 Hz, 1H), 3.74 (s, 3H), 6.06 (br s or dd, J = 10.0, 5.6 Hz, calcd. 1H), 6.21 (dd, J = 4.0, 2.8 Hz, 1H), 6.91 (dd, J = 4.0, 1.6 Hz, 1H), 6.98–7.03 (m, 3H), 7.15–7.23 (m, 3H), 9.43 (d, J = 0.8 Hz, 1H) ppm; ^{13}C NMR δ = 39.0, 52.6, 61.1, 110.2, 125.6, 126.9, 128.4, 128.9, 130.6, 131.2, 136.0, 170.3, 179.5 ppm; IR ν = 3114, 3067, 3029, 2955, 2845, 2812, 1740, 1654, 1530, 1500, 1472, 1409, 1373, 1343, 1277, 1215, 1079, 1032, 1002, 744, 698 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_3$ + Na 280.0944, found 280.0948.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (5g). The mixture of L-homophenylalanine methyl ester, ammonium chloride salt (2.00 g, 8.7 mmol), Et_3N (1.2 mL, 8.7 mmol), D-ribose (2.62 g, 17.4 mmol), and oxalic acid (0.79 g, 8.7 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5g** (1.25 g, 4.6 mmol) in 53% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **5g**.* R_f = 0.71 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 2.26–2.36 (m, 1H), 2.45–2.60 (m, 3H), 3.70 (s, 3H), 5.89 (br d, J = 8.0 Hz, 1H), 6.34 (dd, J = 4.0, 2.8 Hz, 1H), 6.98 (dd, J = 4.0, 1.6 Hz, 1H), 7.07–7.12 (m, 2H), 7.15–7.20 (m, 2H), 7.22–7.28 (m, 2H), 9.51 (d, J = 1, 2 Hz, 1H) ppm; ^{13}C NMR δ = 31.8, 34.0, 52.5, 58.9, 110.5, 125.5, 126.2, 128.2, 128.4, 129.7, 131.6, 140.0, 170.8, 179.6 ppm; IR ν = 3114, 3067, 3027, 2955, 2847, 2810, 1735, 1644, 1532, 1502, 1472, 1413, 1375, 1340, 1254, 1209, 1179, 1087, 1031, 1008, 734, 686 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{18}NO_3$ 272.1287, found 272.1284.

Dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (5h). The mixture of L-aspartic acid dimethyl ester, ammonium chloride salt (2.00 g, 10.1 mmol), Et_3N (1.4 mL, 10.1 mmol), D-ribose (3.04 g, 20.2 mmol), and oxalic acid (0.92 g, 10.1 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5h** (1.14 g, 4.76 mmol) in 47% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5h**.* R_f = 0.45 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 3.06 (dd, J = 17.2, 8.4 Hz, 1H), 3.39 (dd, J = 17.2, 4.8 Hz, 1H), 3.66 (s, 3H), 3.74 (s, 3H), 5.42 (d, J = 14.8 Hz, 1H), 5.87 (br s, 1H), 6.29 (dd, J = 4.0, 2.8 Hz, 1H), 7.01 (dd, J = 4.0, 1.6 Hz, 1H), 7.13 (ddd, J = 2.8, 1.6, 1.2 Hz, 1H), 9.48 (d, J = 1.2 Hz, 1H) ppm; ^{13}C NMR δ = 37.1, 52.1, 52.9, 57.5, 110.2, 125.9, 131.0, 131.9, 169.2, 170.7, 179.3 ppm; IR ν = 3116, 3002, 2952, 2848, 2817, 1737, 1652, 1533, 1474, 1433, 1413, 1370, 1339, 1276, 1221, 1166, 1084, 1039, 1008, 755 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{13}NO_5$ 239.0794, found 239.0797.

Dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)pentanedioate (5i). The mixture of L-glutamic acid dimethyl ester, ammonium chloride salt (2.00 g, 9.45 mmol), Et_3N (1.3 mL, 9.45 mmol), D-ribose (2.84 g, 18.9 mmol), and oxalic acid (0.86 g, 9.45 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5i** (885 mg, 3.50 mmol) in 37% yield as light-brown liquid after purification by SiO_2 column chromatography.

*Data for **5i**.* R_f = 0.46 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 2.19–2.37 (m, 3H), 2.55–2.65 (m, 1H), 3.65 (s, 3H), 3.74 (s, 3H), 5.95 (br s, 1H), 6.33 (dd, J = 4.0, 2.8 Hz, 1H), 6.99 (dd, J = 4.0, 1.6 Hz, 1H), 7.15 (ddd, J = 2.8, 1.6, 1.2 Hz, 1H), 9.51 (d, J = 1.2 Hz, 1H) ppm; ^{13}C NMR δ = 27.8, 30.0, 51.8, 52.7, 58.6, 110.7, 125.6, 130.1, 131.6, 170.4, 172.6, 179.7 ppm; IR ν = 3120, 2996, 2960, 2927, 2857, 2811, 2727, 1744, 1664, 1535, 1478, 1443, 1417, 1368, 1337, 1268, 1211, 1181, 1097, 1036, 1017, 887, 849, 834, 765 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{15}NO_5$ 253.0950, found 253.0948.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio) butanoate (5j). The mixture of L-methionine methyl ester, ammonium chloride salt (2.00 g, 10.0 mmol), Et_3N (1.4 mL, 10.1 mmol), D-ribose (3.01 g, 20.0 mmol), and oxalic acid (0.90 g, 10.0 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5j** (1.11 g, 4.60 mmol) in 46% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **5j**.* R_f = 0.59 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 2.07 (s, 3H), 2.21–2.36 (m, 2H), 2.36–2.44 (m, 1H), 2.48–2.58 (m, 1H), 3.74 (s, 3H), 5.91 (br s, 1H), 6.33 (dd, J = 4.0, 2.8 Hz, 1H), 7.00 (dd, J = 4.0, 1.6 Hz, 1H), 7.16 (dd, J = 2.8, 1.6 Hz, 1H) ppm; ^{13}C NMR δ = 16.2, 30.1, 31.4, 52.7, 58.7, 110.5, 110.0, 125.7, 130.5, 131.5, 170.5, 179.5 ppm; IR ν = 3112, 2946, 2918, 2843, 2817, 1741, 1650, 1532, 1472, 1407, 1373, 1342, 1272, 1226, 1208, 1085, 1031, 1003, 750 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{15}NO_3S$ 241.0773, found 241.0771.

Methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-(1*H*-indol-3-yl) propanoate (5k). The mixture of L-tryptophan methyl ester, ammonium chloride salt (2.00 g, 7.85 mmol), Et_3N (1.1 mL, 7.85 mmol), D-ribose (2.36 g, 15.7 mmol), and oxalic acid (0.71 g, 7.85 mmol) in dry DMSO (10 mL) was pressurized to 2.5 bar by argon and reacted at 80 °C for 30 min to give **5k** (1.28 g, 4.32 mmol) in 55% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **5k**.* R_f = 0.40 (4 : 6 EtOAc/hexane); ^{1}H NMR δ = 3.47 (dd, J = 14.4, 9.2 Hz, 1H), 3.71 (dd, J = 14.4, 5.6 Hz, 1H), 3.73 (s, 3H), 6.09 (br s, 1H), 6.17 (dd, J = 3.6, 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 3.6, 1.6 Hz, 1H), 7.01 (br s, 1H), 7.11 (ddd, J = 8.4, 6.8, 0.8 Hz, 1H), 7.18 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.99 (br s, 1H), 9.48 (d, J = 1, 2 Hz, 1H) ppm; ^{13}C NMR δ = 28.6, 52.6, 60.5, 110.0, 110.3, 111.1, 118.3, 119.6, 122.1, 122.7, 125.7, 127.0, 130.8, 131.2, 135.9, 170.6, 179.5 ppm; IR ν = 3017, 2872, 1743, 1658, 1457, 1402, 1372, 1345, 1223, 1151, 1092, 1079, 1034, 997,

977, 912, 758, 733 703, 666, 651 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{17}N_2O_3$ 297.1239, found 297.1237.

General procedure for reductive amination of pyrralines 5 with benzylamine

2-Benzyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6a). The mixture of methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (**5a**) (120 mg, 0.72 mmol) and benzylamine (116 mg, 1.08 mmol) in MeOH (5 mL) was stirred at room temperature for 12 h, and then $NaBH_4$ (20 mg, 0.53 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 9 h, quenched with 10% $NaHCO_3$ solution, and extracted with EtOAc. The organic layer was washed with brine and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was treated with DBU (0.53 g, 3.48 mmol) in toluene (10 mL). The mixture was heated at 120 °C for 12 h and cooled to room temperature. The reaction mixture was concentrated under reduced pressure and purified by SiO_2 flash column chromatography to give **6a** (59 mg, 0.26 mmol) in 36% yield as light-yellow liquid.

*Data for **6a**.* ^{1}H-NMR $\delta = 4.43$ (s, 2H), 4.70 (s, 2H), 4.75 (s, 2H), 5.91 (dd, $J = 2.4$, 1.6 Hz, 1H), 6.21 (dd, $J = 3.6$, 2.4 Hz, 1H), 6.61 (dd, $J = 2.4$, 1.6 Hz, 1H), 7.26–7.37 (m, 5H) ppm; ^{13}C-NMR $\delta =$ 44.2, 48.4, 50.0, 103.2, 109.6, 118.0, 121.9, 127.9, 128.2, 128.8, 135.8, 164.6 ppm; IR (neat) $\nu = 3034$, 2926, 2848, 1715, 1651, 1543, 1491, 1450, 1424, 1323, 1256, 1204, 1182, 1073, 1025, 950, 902, 816, 742, 697, 608 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}N_2O$ + Na 249.0998, found 249.1001.

(*S*)-2-Benzyl-4-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6b). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (**5b**) (120 mg, 0.66 mmol) and benzylamine (106 mg, 0.99 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (20 mg, 0.53 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.50 g, 3.28 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6b** (105 mg, 0.44 mmol) in 66% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6b**.* ^{1}H-NMR $\delta = 1.68$ (d, $J = 7.2$ Hz, 3H), 4.36 (A of ABq, $J = 15.2$ Hz, 1H), 4.42 (B of ABq, $J = 15.2$ Hz, 1H), 4.72 (s, 2H), 4.74 (q, $J = 7.2$ Hz, 1H), 5.89 (m, 1H), 6.20 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.64 (dd, $J = 2.8$, 2.0 Hz, 1H), 7.24–7.36 (m, 5H) ppm; ^{13}C-NMR $\delta = 20.2$, 43.8, 50.2, 54.7, 103.1, 109.4, 117.0, 121.6, 127.7, 128.0, 128.7, 135.9, 168.1 ppm; IR (neat) $\nu = 3068$, 3030, 2974, 2926, 2848, 1711, 1651, 1543, 1483, 1450, 1319, 1256, 1204, 1144, 1073, 1029, 965, 932, 896, 738, 697, 611 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}N_2O$ + Na 263.1155, found 263.1158.

(*S*)-2-Benzyl-4-isopropyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6c). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (**5c**) (120 mg, 0.57 mmol) and benzylamine (87 mg, 0.81 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (16 mg, 0.43 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.41 g, 2.69 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6c** (112 mg, 0.42 mmol) in 73% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6c**.* ^{1}H-NMR $\delta = 0.84$ (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J =$ 7.2 Hz, 3H), 2.39 (m, 1H), 4.27 (A of ABq, $J = 15.6$ Hz, 1H), 4.39 (B of ABq, $J = 15.6$ Hz, 1H), 4.52 (d, $J = 4.4$ Hz, 1H), 4.59 (A of ABq, $J = 14.8$ Hz, 1H), 4.82 (B of ABq, $J = 14.8$ Hz, 1H), 5.89 (dd, J $= 3.6$, 1.6 Hz, 1H), 6.16 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.57 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.22–7.34 (m, 5H) ppm; ^{13}C-NMR $\delta = 17.6$, 19.9, 34.7, 44.2, 50.2, 65.2, 103.0, 108.6, 119.1, 122.5, 127.7, 128.2, 128.7, 136.0, 167.4 ppm; IR (neat) $\nu = 3094$, 3027, 2967, 2933, 2870, 1655, 1543, 1495, 1469, 1454, 1387, 1353, 1290, 1275, 1216, 1152, 1070, 991, 957, 891, 861, 790, 749, 716, 696, 662, 615 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_2O$ + Na 291.1468, found 291.1470.

(*S*)-2-Benzyl-4-((*S*)-*sec*-butyl)-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6d). The reaction of methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (**5e**) (0.12 g, 0.54 mmol) and benzylamine (87 mg, 0.81 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (16 mg, 0.43 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.41 g, 2.69 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6d** (131 mg, 0.46 mmol) in 86% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6d**.* ^{1}H-NMR $\delta = 0.90$ (t, $J = 7.2$ Hz, 3H), 1.00 (d, $J =$ 6.8 Hz, 3H), 1.05–1.17 (m, 1H), 1.49–1.60 (m, 1H), 2.05–2.16 (m, 1H), 4.30 (A of ABq, $J = 15.2$ Hz, 1H), 4.43 (B of ABq, $J = 15.2$ Hz, 1H), 4.62 (d, $J = 4.4$ Hz, 1H), 4.67 (A of ABq, $J = 14.8$ Hz, 1H), 4.78 (B of ABq, $J = 14.8$ Hz, 1H), 5.89 (dd, $J = 3.2$, 2.0 Hz, 1H), 6.18 (dd, $J = 3.2$, 2.8 Hz, 1H), 6.59 (dd, $J = 2.8$, 2.0 Hz, 1H), 7.26–7.36 (m, 5H) ppm; ^{13}C-NMR $\delta = 11.5$, 15.9, 24.9, 41.7, 44.3, 50.3, 64.3, 103.0, 108.9, 118.8, 122.6, 127.8, 128.3, 128.7, 136.1, 167.2 ppm; IR (neat) $\nu = 3019$, 2963, 2926, 2874, 1707, 1651, 1543, 1487, 1454, 1323, 1215, 1141, 1073, 1029, 950, 928, 898, 742, 697, 667, 634, 611 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}N_2O$ + Na 305.1624, found 305.1628.

(*S*)-2,4-Dibenzyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6e). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (**5f**) (120 mg, 0.47 mmol) and benzylamine (76 mg, 0.71 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (17 mg, 0.45 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.43 g, 2.82 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6e** (61 mg, 0.19 mmol) in 41% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6e**.* ^{1}H-NMR $\delta = 3.09$ (d, $J = 15.2$ Hz, 3H), 3.26 (d of A of ABq, $J_{AB} = 13.6$, $J_d = 4.4$ Hz, 1H), 3.41 (d of B of ABq, $J_{AB} =$ 13.6, $J_d = 4.4$ Hz, 1H), 3.93 (d, $J = 15.2$ Hz, 1H), 4.39 (A of ABq, $J_{AB} = 14.8$ Hz, 1H), 4.65 (B of ABq, $J_{AB} = 14.8$ Hz, 1H), 5.03 (t, $J =$ 4.4 Hz, 1H), 5.71 (dd, $J = 3.6$, 1.6 Hz, 1H), 6.22 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.62 (dd, $J = 2.8$, 1.6 Hz, 1H), 6.66–6.70 (m, 2H), 7.00–7.06 (m, 2H), 7.13–7.17 (m, 3H), 7.24–7.32 (m, 3H) ppm; ^{13}C-NMR $\delta = 41.5$, 43.6, 50.1, 60.0, 102.4, 109.8, 116.9, 122.8, 127.2, 127.7, 128.1, 128.5, 128.6, 129.6, 134.9, 135.6, 166.6 ppm; IR (neat) $\nu = 3068$, 3027, 2933, 2844, 1647, 1483, 1439, 1394, 1327, 1252, 1204, 1170, 1077, 1029, 965, 898, 861, 742, 693, 663, 630, 611 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}N_2O$ + Na 339.1468, found 339.1470.

(*S*)-2-Benzyl-4-phenethyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6f). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (**5g**) (120 mg, 0.44 mmol) and benzylamine (71 mg, 0.66 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (13 mg, 0.34 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.34 g, 2.23 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6f** in 64% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6f**.* ^{1}H-NMR $\delta = 2.25$–2.40 (m, 2H), 2.44–2.53 (m, 1H), 2.56–2.65 (m, 1H), 4.31 (A of ABq, $J_{AB} = 15.6$ Hz, 1H), 4.39 (B of ABq, $J_{AB} = 15.6$ Hz, 1H), 4.61 (A of ABq, $J_{AB} = 14.4$ Hz, 1H), 4.74 (B of ABq, $J_{AB} = 14.4$ Hz, 1H), 4.75 (dd, $J = 5.6$, 5.2 Hz, 1H), 5.89 (dd, $J = 3.6$, 1.6 Hz, 1H), 6.21 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.60 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.09–7.18 (m, 3H), 7.21–7.33 (m, 7H) ppm; ^{13}C-NMR δ = 30.6, 36.2, 43.9, 50.1, 58.7, 103.1, 109.4, 117.6, 121.9, 126.0, 127.7, 128.0, 128.2, 128.3, 128.6, 135.9, 140.2, 167.2 ppm; IR (neat) ν = 3067, 3027, 2922, 2856, 1652, 1485, 1452, 1328, 1256, 1078, 1026, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{22}N_2O$ + Na 353.1624, found 353.1626.

Methyl (*S*)-2-(2-benzyl-3-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-4-yl)acetate (6g). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (**5h**) (120 mg, 0.50 mmol) and benzylamine (80 mg, 0.75 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (15 mg, 0.40 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.38 g, 2.50 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6g** (125 mg, 0.42 mmol) in 84% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6g**.* ^{1}H-NMR $\delta = 3.14$ (d of A of ABq, $J_{AB} = 16{,}8$, $J_d =$ 4.8 Hz, 1H), 3.18 (d of B of ABq, $J_{AB} = 16{,}8$, $J_d = 5.2$ Hz, 1H), 3,62 (s, 3H), 4.37 (d of A of ABq, $J_{AB} = 15.2$, $J_d = 0.8$ Hz, 1H), 4.68 (B of ABq, $J_{AB} = 15.2$ Hz, 1H), 4.70 (A of ABq, $J_{AB} = 14.8$ Hz, 1H), 4.79 (B of ABq, $J_{AB} = 14.8$ Hz, 1H), 5.05 (dd, $J = 5.2$, 4,8 Hz, 1H), 5.88 (dd, $J = 3.6$, 1.6 Hz, 1H), 6.19 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.63 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.26–7.37 (m, 5H) ppm; ^{13}C-NMR δ = 38.3, 44.0, 50.4, 52.0, 55.0, 103.3, 109.7, 117.3, 122.2, 127.7, 128.1, 128.7, 135.7, 166.4, 170.2 ppm; IR (neat) ν = 3031, 2923, 2854, 1735, 1654, 1487, 1437, 1370, 1330, 1249, 1201, 1168, 1077, 1018, 987, 896, 744, 699 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_3$ + Na 321.1210, found 321.1214.

(*S*)-2-Benzyl-4-(2-(methylthio)ethyl)-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (6h). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate (**5j**) (120 mg, 0.50 mmol) and benzylamine (80 mg, 0.75 mmol) in MeOH (5 mL) at room temperature for 12 h, followed by $NaBH_4$ (15 mg, 0.40 mmol) reduction at 0 °C for 9 h, and then cyclization by DBU (0.38 g, 2.50 mmol) in toluene (10 mL) at 120 °C for 12 h produced **6h** (71 mg, 0.24 mmol) in 47% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **6h**.* ^{1}H-NMR $\delta = 2.06$ (s, 3H), 2.23–2.33 (m, 2H), 2.34–2.49 (m, 2H), 4.33 (A of ABq, $J = 15.6$ Hz, 1H), 4.41 (B of ABq, $J =$ 15.6 Hz, 1H), 4.67 (A of ABq, $J = 14.8$ Hz, 1H), 4.73 (B of ABq, $J =$ 14.8 Hz, 1H), 4.87 (t, $J = 5.6$ Hz, 1H), 5.89 (dd, $J = 2.8$, 1.6 Hz, 1H), 6.19 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.63 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.24–7.36 (m, 5H) ppm; ^{13}C-NMR $\delta = 15.2$, 29.2, 33.6, 44.0, 50.4, 58.0, 103.4, 109.6, 117.9, 122.1, 127.9, 128.2, 128.8, 136.0, 167.3 ppm; IR (neat) ν = 3008, 2915, 2837, 1647, 1483, 1431, 1331, 1286, 1252, 1159, 1073, 1025, 950, 898, 820, 742, 697, 626, 611 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_2OS$ + Na 323.1189, found 323.1192.

General procedure for cyclization of pyrralines 5 with ethane-1,2-diamine

1,2,3,10*b*-Tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7a). The mixture of methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (**5a**) (1.00 g, 5.98 mmol) and ethane-1,2-diamine (360 mg, 5.99 mmol) in MeOH (10 mL) was heated at 70 °C for 1 h and cooled to room temperature. The reaction mixture was concentrated under reduced pressure and purified by SiO_2 flash column chromatography to give **7a** (615 mg, 3.47 mmol) in 58% yield as white solid.

*Data for **7a**.* ^{1}H-NMR $\delta = 2.14$ (br s, 1H), 3.18–3.30 (m, 1H), 3.48–3.62 (m, 3H), 4.55 (A of ABq, $J = 16.8$ Hz, 1H), 4.60 (B of ABq, $J = 16.8$ Hz, 1H), 5.25 (br s, 1H), 6.22–6.26 (m, 2H), 6.66 (dd, $J = 2.0$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 43.9$, 45.0, 49.0, 70.4, 104.2, 109.5, 119.1, 124.8, 162.1 ppm; IR (KBr) ν = 3226, 3115, 3098, 2976, 2960, 2885, 2857, 1636, 1470, 1441, 1305, 1216, 1173, 1159, 1126, 1070, 1004, 968, 951, 932, 906, 856, 770, 756, 729, 681 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}N_3O$ + Na 200.0794, found 200.0797.

(6*S*)-6-Methyl-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7b). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (**5b**) (1.00 g, 5.52 mmol) and ethane-1,2-diamine (332 mg, 5.52 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7b** (918 mg, 4.80 mmol) in 87% yield (a 3 : 1 mixture of stereoisomers) as white solid after purification by SiO_2 column chromatography.

*Data for **7b**.* ^{1}H-NMR (major) $\delta = 1.61$ (d, $J = 7.2$ Hz, 3H), 2.14 (br s, 1H), 3.20–3.31 (m, 1H), 3.47–3.61 (m, 3H), 4.68 (q, $J =$ 7.2 Hz, 1H), 5.26 (br s, 1H), 6.22–6.28 (m, 2H), 6.68 (dd, $J = 2.4$, 2.0 Hz, 1H) ppm; ^{13}C-NMR (major) δ = 21.2, 43.8, 44.8, 55.8, 69.7, 103.8, 109.3, 117.9, 124.2, 165.7 ppm; (minor) δ = 14.6, 44.2, 44.8, 53.4, 69.7, 103.9, 108.7, 116.9, 125.9, 164.6 ppm; IR (KBr) ν = 3065, 3030, 2946, 2920, 2872, 2844, 1648, 1543, 1486, 1460, 1431, 1357, 1329, 1252, 1221, 1140, 1073, 1025, 962, 766, 739, 700 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}N_3O$ + Na 214.0951, found 214.0954.

(6*S*)-6-Isopropyl-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7c). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (**5c**) (1.00 g, 4.78 mmol) and ethane-1,2-diamine (287 mg, 4.78 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7c** (985 mg, 4.49 mmol) in 94% yield as white solid after purification by SiO_2 column chromatography.

*Data for **7c**.* ^{1}H-NMR $\delta = 0.93$ (d, $J = 6.4$ Hz, 3H), 1.08 (d, $J =$ 6.8 Hz, 3H), 2.10 (br s, 1H), 2.22–2.34 (m, 1H), 3.17–3.28 (m, 1H), 3.47–3.60 (m, 3H), 4.39 (d, $J = 5.2$ Hz, 1H), 5.25 (s, 1H), 6.22 (dd, $J = 3.6$, 2.0 Hz, 1H), 6.24 (dd, $J = 3.6$, 1.2 Hz, 1H), 6.64 (dd, $J =$ 2.0, 1.2 Hz, 1H) ppm; ^{13}C-NMR $\delta = 18.1$, 19.6, 34.3, 44.2, 45.0, 66.3, 70.4, 103.8, 108.7, 120.0, 125.6, 165.1 ppm; IR (KBr) ν = 3278, 2971, 2891, 1654, 1567, 1463, 1430, 1395, 1372, 1325,

1303, 1251, 1221, 1178, 1153, 1112, 1075, 950, 922, 903, 855, 750, 717, 667 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_3O$ + Na 242.1264, found 242.1265.

(6*S*)-6-((*S*)-*sec*-Butyl)-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7d). The reaction of methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (**5e**) (1.00 g, 4.48 mmol) and ethane-1,2-diamine (270 mg, 4.48 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7d** (951 mg, 4.08 mmol) in 91% yield as white solid after purification by SiO_2 column chromatography.

*Data for **7d**.* ^{1}H-NMR $\delta = 0.90$ (t, $J = 7.2$ Hz, 3H), 0.98 (d, $J = 7.2$ Hz, 3H), 1.05–1.17 (m, 1H), 1.49–1.61 (m, 1H), 1.92–2.04 (m, 1H), 2.25 (br s, 1H), 3.13–3.24 (m, 1H), 3.42–3.56 (m, 3H), 4.42 (d, $J = 5.6$ Hz, 1H), 5.21 (br s, 1H), 6.17–6.21 (m, 2H), 6.62 (dd, $J = 2.0$, 2.0 Hz, 1H) ppm; ^{13}C-NMR $\delta = 11.1$, 15.3, 24.7, 40.8, 44.0, 44.7, 65.0, 70.2, 103.5, 108.6, 119.3, 125.4, 164.6 ppm; IR (KBr) $\nu = 3292$, 3103, 2962, 2931, 2880, 2860, 1638, 1464, 1430, 1349, 1323, 1277, 1247, 1221, 1189, 1108, 1078, 1025, 958, 902, 877, 772, 710 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_3O$ + Na 256.1420, found 256.1421.

(6*S*)-6-Benzyl-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7e). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (**5f**) (1.00 g, 3.89 mmol) and ethane-1,2-diamine (234 mg, 3.89 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7e** (894 mg, 3.34 mmol) in 86% yield as white solid after purification by SiO_2 column chromatography.

*Data for **7e**.* ^{1}H-NMR $\delta = 1.94$ (br s, 1H), 2.90–2.99 (m, 1H), 3.24 (d of A of ABq, $J_{AB} = 13.6$, $J_d = 4.4$ Hz, 1H), 3.30 (d of B of ABq, $J_{AB} = 13.6$, $J_d = 4.8$ Hz, 1H), 3.25–3.39 (m, 2H), 3.43–3.52 (m, 1H), 3.79 (s, 1H), 4.90 (dd, $J = 4.8$, 4.4 Hz, 1H), 6.07 (dd, $J = 3.6$, 1.2 Hz, 1H), 6.23 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.59 (dd, $J = 2.8$, 1.2 Hz, 1H), 6.74–6.79 (m, 2H), 7.12–7.18 (m, 2H), 7.19–7.24 (m, 1H) ppm; ^{13}C-NMR $\delta = 41.4$, 43.6, 44.7, 61.3, 69.6, 103.5, 109.7, 118.2, 125.6, 127.5, 128.2, 129.5, 134.8, 164.0 ppm; IR (KBr) $\nu = 3276$, 3064, 3031, 2951, 2885, 2857, 1644, 1469, 1459, 1436, 1328, 1306, 1217, 1173, 1119, 1076, 942, 914, 773, 728, 696 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_3O$ $[M + 1]^+$ 268.1444, found 268.1448.

(6*S*)-6-Phenethyl-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7f). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (**5g**) (1.00 g, 3.69 mmol) and ethane-1,2-diamine (222 mg, 3.69 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7f** (914 mg, 3.25 mmol) in 88% yield as white solid after purification by SiO_2 column chromatography.

*Data for **7f**.* ^{1}H-NMR $\delta = 2.08$ (br s, 1H), 2.14–2.24 (m, 1H), 2.25–2.35 (m, 1H), 2.58–2.67 (m, 1H), 2.68–2.77 (m, 1H), 3.17–3.28 (m, 1H), 3.47–3.60 (m, 3H), 4.63 (dd, $J = 6.8$, 6.4 Hz, 1H), 5.24 (s, 1H), 6.23–6.27 (m, 2H), 6.66 (dd, $J = 2.4$, 1.6 Hz, 1H), 7.13–7.21 (m, 3H), 7.24–7.30 (m, 2H) ppm; ^{13}C-NMR $\delta = 31.3$, 36.7, 44.2, 45.0, 60.1, 70.2, 104.2, 109.4, 119.1, 125.1, 126.2, 128.3, 128.5, 140.0, 165.3 ppm; IR (KBr) $\nu = 3276$, 3028, 2950, 2885, 2859, 1652, 1458, 1429, 1334, 1305, 1221, 1158, 1118, 1073, 912, 771, 752, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_3O$ $[M + 1]^+$ 282.1601, found 282.1604.

Methyl 2-((6*S*)-5-oxo-1,2,3,5,6,10*b*-hexahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (7g). The reaction of dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (**5h**) (1.00 g, 4.18 mmol) and ethane-1,2-diamine (251 mg, 4.18 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7g** (750 mg, 3.01 mmol) in 72% yield (a 3 : 1 mixture of stereoisomers) as white solid after purification by SiO_2 column chromatography.

*Data for **7g**.* ^{1}H-NMR (major) $\delta = 2.31$ (br s, 1H), 2.91 (d of A of ABq, $J_{AB} = 16.8$, $J_d = 8.0$ Hz, 1H), 3.02 (d of B of ABq, $J_{AB} = 16.8$, $J_d = 4.4$ Hz, 1H), 3.17–3.48 (m, 1H), 3.45–3.59 (m, 3H), 3.66 (s, 3H), 4.99 (dd, $J = 8.0$, 4.4 Hz, 1H), 5.26 (s, 1H), 6.18–6.23 (m, 2H), 6.72 (br s, 1H) ppm; (minor) $\delta = 2.31$ (br s, 1H), 3.17–3.38 (m, 3H), 3.45–3.58 (m, 3H), 3.67 (s, 3H), 4.91 (dd, $J = 5.2$, 4.8 Hz, 1H), 5.23 (s, 1H), 6.22–6.27 (m, 2H), 6.62 (br s, 1H) ppm; ^{13}C-NMR (major) $\delta = 38.9$, 44.0, 44.8, 52.0, 56.1, 70.0, 104.1, 109.5, 119.1, 124.7, 163.7, 169.9 ppm; (minor) $\delta = 35.1$, 44.3, 44.8, 51.9, 54.5, 70.0, 104.7, 109.3, 116.8, 125.1, 163.7, 170.5 ppm; IR (KBr) $\nu = 3287$, 2999, 2941, 2878, 1734, 1653, 1461, 1438, 1376, 1330, 1307, 1214, 1173, 1118, 1072, 909, 750, 725 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}N_3O_3$ $[M + 1]^+$ 250.1186, found 250.1188.

(6*S*)-6-(2-(Methylthio)ethyl)-1,2,3,10*b*-tetrahydroimidazo[1,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (7h). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate (**5j**) (1.00 g, 4.18 mmol) and ethane-1,2-diamine (251 mg, 4.18 mmol) in MeOH (10 mL) at 70 °C for 1 h produced **7h** (914 mg, 3.64 mmol) in 87% yield as white solid after purification by SiO_2 column chromatography.

*Data for **7h**.* ^{1}H-NMR $\delta = 2.00$–2.11 (m, 1H), 2.07 (s, 3H), 2.15–2.25 (m, 1H), 2.38–2.46 (m, 1H), 2.50–2.58 (m, 1H), 3.14–3.24 (m, 1H), 3.42–3.52 (m, 3H), 4.71 (dd, $J = 8.0$, 5.2 Hz, 1H), 5.20 (s, 1H), 6.17–6.21 (m, 2H), 6.67 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 14.7$, 29.1, 33.6, 43.7, 44.6, 58.5, 69.7, 103.7, 108.9, 118.7, 124.6, 164.6 ppm; IR (KBr) $\nu = 3272$, 3108, 2959, 2922, 2885, 2851, 1643, 1454, 1412, 1335, 1298, 1220, 1159, 1156, 1073, 948, 923, 897, 761, 708 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{18}N_3OS$ $[M + 1]^+$ 252.1165, found 252.1168.

General procedure for cyclization of pyrralines 5 with (*S*)-2-aminopropan-1-ol

(3*S*)-3-Methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8a). The mixture of methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (**5a**) (1.12 g, 6.70 mmol) and (*S*)-2-aminopropan-1-ol (0.52 mL, 6.70 mmol) in toluene (5 mL) was stirred at room temperature for 2.5 h and then heated at 110 °C for 6 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by SiO_2 flash column chromatography to give **8a** (154 mg, 0.80 mmol) in 12% yield as light-yellow liquid.

*Data for **8a**.* ^{1}H-NMR $\delta = 1.41$ (d, $J = 6.0$ Hz, 3H), 3.63 (ddd, $J = 6.8$, 6.4, 1.2 Hz, 1H), 4.40 (dd, $J = 7.2$, 6.8 Hz, 1H), 4.44 (ddq, $J_d = 7.2$, 6.4, $J_q = 6.0$ Hz, 1H), 4.60 (A of ABq, $J_{AB} = 16.8$ Hz, 1H), 4.65 (d of B of ABq, $J_{AB} = 16.8$, $J_d = 0.8$ Hz, 1H), 5.88 (br s, 1H), 6.29 (dd, $J = 4.0$, 2.4 Hz, 1H), 6.33 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.64 (dd, $J = 2.4$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 18.0$, 48.5, 51.0, 72.2, 81.7, 106.2, 110.3, 119.1, 122.2, 162.7 ppm; IR (neat) $\nu = 2928$, 2870, 1712, 1660, 1542, 1463, 1428, 1345, 1310, 1229,

1168, 1075, 1046, 976, 747, 720 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}N_2O_2$ + Na, 215.0791, found 215.0791.

(3*S*,6*S*)-3,6-Dimethyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8b). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (**5b**) (1.12 g, 6.19 mmol) and (*S*)-2-aminopropan-1-ol (0.49 mL, 6.19 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8b** (523 mg, 2.53 mmol) in 41% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8b**.* ^{1}H-NMR $\delta = 1.39$ (d, $J = 6.8$ Hz, 3H), 1.63 (d, $J = 6.8$ Hz, 3H), 3.59–3.67 (m, 1H), 4.34–4.44 (m, 2H), 4.67 (q, $J = 6.8$ Hz, 1H), 5.79 (br s, 1H), 6.26–6.31 (m, 2H), 6.60 (dd, $J = 2.4$, 2.0 Hz, 1H) ppm; ^{13}C-NMR $\delta = 16.3$, 17.9, 51.4, 53.5, 72.1, 81.5, 106.3, 110.0, 117.7, 122.9, 165.7 ppm; IR (neat) $\nu = 3129$, 2989, 2931, 2872, 1714, 1655, 1539, 1460, 1422, 1367, 1302, 1206, 1176, 1142, 1018, 978, 920, 820, 746, 719 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}N_2O_2$ + Na, 229.0947, found 229.0952.

(3*S*,6*S*)-6-Isopropyl-3-methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8c). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (**5c**) (1.12 g, 5.36 mmol) and (*S*)-2-aminopropan-1-ol (0.42 mL, 5.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8c** (917 mg, 3.91 mmol) in 73% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8c**.* ^{1}H-NMR $\delta = 0.92$ (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.40 (d, $J = 6.0$ Hz, 3H), 2.27 (m, 1H), 3.60–3.68 (m, 1H), 4.33–4.43 (m, 3H), 5.80 (s, 1H), 6.26 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.30 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.62 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 17.8$, 18.0, 19.3, 34.9, 51.1, 65.8, 72.3, 82.1, 105.2, 109.4, 119.7, 123.8, 165.0 ppm; IR (neat) $\nu = 3116$, 2963, 2920, 2857, 1714, 1666, 1564, 1449, 1417, 1381, 1370, 1301, 1229, 1197, 1100, 1057, 973, 867, 814, 766, 703 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}N_2O_2$ + Na 257.1260, found 257.1262.

(3*S*,6*S*)-6-((*S*)-*sec*-Butyl)-3-methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8d). The reaction of methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (**5e**) (1.12 g, 5.02 mmol) and (*S*)-2-aminopropan-1-ol (0.39 mL, 5.02 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8d** (959 mg, 3.86 mmol) in 77% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8d**.* ^{1}H-NMR $\delta = 0.90$ (d, $J = 6.8$ Hz, 3H), 0.93 (t, $J = 7.6$ Hz, 3H), 1.08–1.20 (m, 1H), 1.38 (d, $J = 6.8$ Hz, 3H), 1.54–1.65 (m, 1H), 1.91–2.02 (m, 1H), 3.57–3.65 (m, 1H), 4.31–4.40 (m, 2H), 4.51 (d, $J = 4.8$ Hz, 1H), 5.79 (br s, 1H), 6.24 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.27 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.61 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 11.4$, 15.0, 17.6, 25.0, 41.7, 50.9, 64.3, 72.0, 81.9, 104.9, 109.4, 119.0, 123.6, 164.5 ppm; IR (neat) $\nu = 3099$, 2958, 2925, 2867, 1709, 1666, 1563, 1539, 1460, 1430, 1386, 1295, 1216, 1195, 1068, 1055, 978, 871, 817, 766, 708 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}N_2O_2$ + Na 271.1417, found 271.1419.

(3*S*,6*S*)-6-Benzyl-3-methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8e). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (**5f**) (1.12 g, 4.36 mmol) and (*S*)-2-aminopropan-1-ol (0.34 mL, 4.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8e** (639 mg, 2.26 mmol) in 52% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8e**.* ^{1}H-NMR $\delta = 1.21$ (d, $J = 6.0$ Hz, 3H), 3.23 (dd, $J = 13.6$, 4.4 Hz, 1H), 3.30–3.37 (m, 2H), 4.18–4.30 (m, 2H), 4.35 (s, 1H), 4.93 (t, $J = 4.4$ Hz, 1H), 6.10 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.31 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.66–6.72 (m, 3H), 7.11–7.16 (m, 2H), 7.20–7.25 (m, 1H) ppm; ^{13}C-NMR $\delta = 17.2$, 41.8, 50.6, 60.4, 72.1, 80.8, 104.7, 110.5, 117.6, 124.0, 127.5, 128.0, 129.8, 134.3, 163.8 ppm; IR (neat) $\nu = 3027$, 2962, 2923, 2861, 1704, 1659, 1561, 1456, 1437, 1404, 1361, 1311, 1234, 1165, 1077, 1041, 972, 822, 744, 695 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_2$ + Na 305.1260, found 305.1264.

(3*S*,6*S*)-3-Methyl-6-phenethyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8f). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (**5g**) (1.12 g, 4.13 mmol) and (*S*)-2-aminopropan-1-ol (0.32 mL, 4.13 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8f** (269 mg, 0.91 mmol) in 22% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8f**.* ^{1}H-NMR $\delta = 1.37$ (d, $J = 6.4$ Hz, 3H), 2.24–2.33 (m, 2H), 2.47–2.55 (m, 1H), 2.60–2.68 (m, 1H), 3.59–3.66 (m, 1H), 4.35–4.44 (m, 2H), 4.68 (t, $J = 6.0$ Hz, 1H), 5.78 (s, 1H), 6.30 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.32 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.66 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.12–7.16 (m, 2H), 7.16–7.22 (m, 1H), 7.24–7.30 (m, 2H) ppm; ^{13}C-NMR $\delta = 17.8$, 30.9, 37.4, 51.1, 59.5, 72.3, 81.7, 105.7, 110.2, 118.7, 122.9, 126.3, 128.3, 128.5, 140.0, 165.6 ppm; IR (neat) $\nu = 3016$, 2966, 2930, 2857, 1714, 1666, 1561, 1449, 1434, 1406, 1359, 1302, 1227, 1168, 1076, 1058, 977, 826, 766, 725, 693 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}N_2O_2$ + Na, 319.1417, found 319.1419.

Methyl 2-((3*S*,6*S*)-3-methyl-5-oxo-2,3,5,6-tetrahydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (8g). The reaction of dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (**5h**) (1.12 g, 4.68 mmol) and (*S*)-2-aminopropan-1-ol (0.36 mL, 4.68 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8g** (334 mg, 1.26 mmol) in 27% yield (a 1.05 : 1 mixture of stereoisomers) as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **8g**.* ^{1}H-NMR (major) $\delta = 1.42$ (d, $J = 6.4$ Hz, 3H), 2.97 (dd, $J = 16.4$, 6.8 Hz, 1H), 3.06 (dd, $J = 16.4$, 4.4 Hz, 1H), 3.60–3.70 (m, 1H), 3.65 (s, 3H), 4.35–4.46 (m, 2H), 4.99 (dd, $J = 6.7$, 4.4 Hz, 1H), 5.82 (br s, 1H), 6.26 (dd, $J = 3.6$, 1.6 Hz, 1H), 6.30 (dd, $J = 3.6$, 2.4 Hz, 1H), 6.70 (dd, $J = 2.4$, 1.6 Hz, 1H) ppm; (minor) $\delta = 1.40$ (d, $J = 6.4$ Hz, 3H), 3.21 (dd, $J = 17.2$, 5.6 Hz, 1H), 3.36 (dd, $J = 17.2$, 5.6 Hz, 1H), 3.60–3.70 (m, 1H), 3.71 (s, 3H), 4.35–4.48 (m, 2H), 5.00 (t, $J = 5.6$ Hz, 1H), 5.79 (br s, 1H), 6.27–6.36 (m, 2H), 6.64 (m, 1H) ppm; ^{13}C-NMR (major) $\delta = 17.9$, 39.5, 51.2, 52.2, 54.5, 72.4, 81.5, 106.8, 110.4, 118.8, 122.9, 164.1, 169.9 ppm; (minor) $\delta = 17.6$, 36.2, 51.7, 52.1, 55.8, 72.0, 81.3, 105.8, 110.5, 117.5, 122.7, 164.7, 170.6 ppm; IR (neat) $\nu = 2957$, 2926, 2856, 1737, 1671, 1563, 1461, 1442, 1379, 1336, 1310, 1272, 1220, 1203, 1172, 1077, 1055, 976, 914, 776, 733, 673 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}N_2O_4$ + Na 287.1002, found 287.1002.

(3*S*,6*S*)-3-Methyl-6-(2-(methylthio)ethyl)-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (8h). The reaction

of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio) butanoate (**5j**) (1.12 g, 4.68 mmol) and (*S*)-2-aminopropan-1-ol (0.36 mL, 4.68 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **8h** (299 mg, 1.12 mmol) in 24% yield as light-yellow liquid after purification by SiO_2 column chromatography.

Data for ***8h***. ^{1}H-NMR $\delta = 1.40$ (d, $J = 6.0$ Hz, 3H), 2.09 (s, 3H), 2.12–2.22 (m, 1H), 2.22–2.31 (m, 1H), 2.33–2.41 (m, 1H), 2.47–2.55 (m, 1H), 3.61–3.69 (m, 1H), 4.34–4.44 (m, 2H), 4.78 (dd, $J =$ 6.8, 5.6 Hz, 1H), 5.80 (s, 1H), 6.28 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.31 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.68 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 15.2$, 17.7, 29.2, 34.9, 51.1, 58.6, 72.3, 81.7, 105.8, 110.2, 118.8, 122.9, 165.4 ppm; IR (neat) $\nu = 2967$, 2910, 2862, 1645, 1556, 1465, 1412, 1398, 1354, 1307, 1228, 1168, 1041, 975, 830, 766, 719 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}N_2O_2S$ + Na, 289.0981, found 289.0985.

General procedure for cyclization of pyrralines 5 with (*S*)-2-amino-3-methylbutan-1-ol (L-valinol)

(3*S*)-3-Isopropyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9a). The mixture of methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (**5a**) (1.12 g, 6.70 mmol) and L-valinol (0.69 g, 6.70 mmol) in toluene (5 mL) was stirred at room temperature for 2.5 h and then heated at 110 °C for 6 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by SiO_2 flash column chromatography to give **9a** (59 mg, 0.27 mmol) in 4% yield as light-yellow liquid.

Data for ***9a***. ^{1}H-NMR $\delta = 0.98$ (d, $J = 6.8$ Hz, 3H), 1.01 (d, $J =$ 6.4 Hz, 3H), 2.14 (m, 1H), 3.83 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.21 (dd, $J = 8.8$, 8.0 Hz, 1H), 4.29 (ddd, $J = 8.0$, 7.2, 6.8 Hz, 1H), 4.63 (A of ABq, $J_{AB} = 17.2$ Hz, 1H), 4.72 (B of ABq, $J_{AB} = 17.2$ Hz, 1H), 5.74 (s, 1H), 6.30 (dd, $J = 3.6$, 2.4 Hz, 1H), 6.33 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.65 (dd, $J = 2.4$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta =$ 17.5, 19.2, 30.8, 48.4, 60.2, 67.7, 82.5, 106.5, 110.4, 119.1, 121.9, 163.9 ppm; IR (neat) $\nu = 2952$, 2929, 2872, 1666, 1561, 1460, 1429, 1367, 1322, 1268, 1227, 1189, 1081, 1048, 973, 870, 825, 761, 713 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}N_2O_2$ + Na, 243.1104, found 243.1107.

(3*S*,6*S*)-3-Isopropyl-6-methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9b). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (**5b**) (1.12 g, 6.19 mmol) and L-valinol (0.64 g, 6.19 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9b** (392 mg, 1.67 mmol) in 27% yield as light-yellow liquid after purification by SiO_2 column chromatography.

Data for ***9b***. ^{1}H-NMR $\delta = 0.97$ (d, $J = 7.2$ Hz, 3H), 1.01 (d, $J =$ 6.8 Hz, 3H), 1.79 (d, $J = 7.2$ Hz, 3H), 2.11 (m, 1H), 3.83 (dd, $J =$ 8.8, 6.8 Hz, 1H), 4.17 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.26 (ddd, $J = 8.0$, 7.6, 6.8 Hz, 1H), 4.68 (q, $J = 7.2$ Hz, 1H), 5.74 (s, 1H), 6.30 (dd, $J =$ 3.6, 2.8 Hz, 1H), 6.33 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.76 (dd, $J =$ 2.8, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 17.2$, 17.7, 19.3, 30.8, 53.4, 60.7, 67.6, 82.2, 106.6, 110.1, 117.9, 122.4, 167.1 ppm; IR (neat) $\nu = 2958$, 2942, 2872, 1703, 1661, 1562, 1544, 1460, 1422, 1365, 1301, 1216, 1111, 1085, 1058, 984, 950, 857, 825, 751, 708 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}N_2O_2$ + Na, 257.1260, found 257.1263.

(3*S*,6*S*)-3,6-Diisopropyl-2,3-dihydro-10b*H*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9c). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (**5c**) (1.12 g, 5.36 mmol) and L-valinol (0.55 g, 5.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9c** (858 mg, 3.27 mmol) in 61% yield as light-yellow liquid after purification by SiO_2 column chromatography.

Data for ***9c***. ^{1}H-NMR $\delta = 0.95$ (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J =$ 7.2 Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 2.17–2.33 (m, 2H), 3.86 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.17 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.28 (ddd, $J = 7.6$, 7.2, 6.8 Hz, 1H), 4.46 (d, $J =$ 5.2 Hz, 1H), 5.77 (s, 1H), 6.26 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.28 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.63 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 17.5$, 18.2, 19.2, 19.2, 30.3, 35.0, 60.1, 65.9, 67.2, 83.0, 105.2, 109.5, 119.4, 123.8, 165.9 ppm; IR (neat) $\nu = 3100$, 2958, 2857, 1702, 1661, 1561, 1455, 1429, 1396, 1375, 1306, 1227, 1189, 1105, 1058, 967, 867, 825, 765, 708 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}N_2O_2$ + Na, 285.1573, found 285.1575.

(3*S*,6*S*)-6-((*S*)-*sec*-Butyl)-3-isopropyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9d). The reaction of methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (**5e**) (1.12 g, 5.02 mmol) and L-valinol (0.52 g, 5.02 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9d** (694 mg, 2.51 mmol) in 50% yield as light-yellow liquid after purification by SiO_2 column chromatography.

Data for ***9d***. ^{1}H-NMR $\delta = 0.90$ (d, $J = 7.2$ Hz, 3H), 0.95 (t, $J =$ 7.6 Hz, 3H), 0.98 (d, $J = 6.0$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.08–2.22 (m, 1H), 1.57–1.68 (m, 1H), 1.93–2.03 (m, 1H), 2.14–2.26 (m, 1H), 3.85 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.17 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.28 (ddd, $J = 7.6$, 7.2, 6.8 Hz, 1H), 4.56 (d, $J = 5.2$ Hz, 1H), 5.77 (s, 1H), 6.26–6.28 (m, 2H), 6.63 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 11.6$, 15.2, 17.6, 19.2, 25.4, 30.4, 42.0, 60.2, 64.6, 67.3, 83.0, 105.2, 109.7, 119.0, 123.8, 165.6 ppm; IR (neat) $\nu = 2958$, 2939, 2878, 1709, 1655, 1568, 1544, 1460, 1431, 1381, 1295, 1232, 1200, 1077, 1058, 967, 879, 833, 766, 713 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}N_2O_2$ + Na, 299.1730, found 299.1734.

(3*S*,6*S*)-6-Benzyl-3-isopropyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9e). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (**5f**) (1.12 g, 4.36 mmol) and L-valinol (0.45 g, 4.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9e** (961 mg, 3.10 mmol) in 71% yield as light-yellow liquid after purification by SiO_2 column chromatography.

Data for ***9e***. ^{1}H-NMR $\delta = 0.76$ (d, $J = 7.2$ Hz, 3H), 0.88 (d, $J =$ 6.8 Hz, 3H), 2.09 (m, 1H), 3.29 (d of A of ABq, $J_{AB} = 13.6$, $J_d =$ 4.8 Hz, 1H), 3.34 (d of B of ABq, $J_{AB} = 13.6$, $J_d = 4.4$ Hz, 1H), 3.68 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.04 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.17 (ddd, $J = 7.6$, 7.2, 6.8 Hz, 1H), 4.86 (s, 1H), 4.96 (t, $J = 4.8$ Hz, 1H), 6.16 (ddd, $J = 3.6$, 1.6, 0.8 Hz, 1H), 6.31 (dd, $J = 3.6$, 2.8 Hz, 1H), 6.64 (dd, $J = 2.8$, 1.6 Hz, 1H), 6.66–6.70 (m, 2H), 7.12–7.23 (m, 3H) ppm; ^{13}C-NMR $\delta = 17.1$, 19.0, 30.0, 41.6, 60.2, 60.6, 66.6, 82.2, 105.1, 110.4, 117.7, 123.6, 127.2, 128.2, 129.4, 134.5, 165.3 ppm; IR (neat) $\nu = 3032$, 2962, 2926, 2872, 1708, 1661, 1556, 1455, 1430, 1403, 1350, 1306, 1297, 1237, 1175, 1113, 1079, 1041, 967, 853, 816, 729, 693 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}N_2O_2$ + Na, 333.1573, found 333.1575.

(3*S*,6*S*)-3-Isopropyl-6-phenethyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9f). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (**5g**) (1.12 g, 4.13 mmol) and L-valinol (0.43 g, 4.13 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9f** (683 mg, 2.11 mmol) in 51% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **9f**.* ^{1}H-NMR $\delta = 0.99$ (d, $J = 7.2$ Hz, 3H), 1.02 (d, $J = 7.2$ Hz, 3H), 2.19 (m, 1H), 2.25–2.32 (m, 2H), 2.41–2.50 (m, 1H), 2.63–2.72 (m, 1H), 3.86 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.20 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.30 (ddd, $J = 7.6$, 7.2, 6.8 Hz, 1H), 4.71 (t, $J = 5.6$ Hz, 1H), 5.79 (s, 1H), 6.29–6.33 (m, 2H), 6.63 (dd, $J = 2.4$, 1.6 Hz, 1H), 7.11–7.15 (m, 2H), 7.16–7.22 (m, 1H), 7.24–7.30 (m, 2H) ppm; ^{13}C-NMR $\delta = 17.5$, 19.2, 30.6, 31.0, 38.0, 59.6, 60.1, 67.6, 82.6, 105.9, 110.3, 118.6, 122.8, 126.3, 128.3, 128.5, 140.1, 166.6 ppm; IR (neat) $\nu = 3015$, 2963, 2925, 2878, 1709, 1666, 1549, 1455, 1422, 1403, 1343, 1302, 1232, 1158, 1058, 983, 876, 828, 713, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_2$ + Na, 347.1730, found 347.1732.

Methyl 2-((3*S*,6*S*)-3-isopropyl-5-oxo-2,3,5,6-tetrahydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (9g). The reaction of dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (**5h**) (1.12 g, 4.68 mmol) and L-valinol (0.48 g, 4.69 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9g** (137 mg, 0.47 mmol) in 10% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **9g**.* ^{1}H-NMR $\delta = 0.99$ (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 7.2$ Hz, 3H), 2.26 (m, 1H), 3.00 (d of A of ABq, $J_{AB} = 16.4$, $J_d = 6.8$ Hz, 1H), 3.08 (d of B of ABq, $J_{AB} = 16.4$, $J_d = 4.4$ Hz, 1H), 3.65 (s, 3H), 3.89 (dd, $J = 8.0$, 6.0 Hz, 1H), 4.21 (dd, $J = 8.0$, 7.6 Hz, 1H), 4.26 (ddd, $J = 7.6$, 6.8, 6.0 Hz, 1H), 5.01 (dd, $J = 6.4$, 4.4 Hz, 1H), 5.79 (s, 1H), 6.27 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.29 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.70 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 17.2$, 19.0, 30.4, 39.7, 52.1, 55.9, 60.3, 67.5, 82.5, 106.0, 110.5, 118.6, 122.8, 165.0, 169.8 ppm; IR (neat) $\nu = 2958$, 2931, 2862, 1740, 1655, 1570, 1449, 1439, 1399, 1371, 1317, 1237, 1191, 1168, 1063, 978, 862, 822, 772, 713 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}N_2O_4$ + Na, 315.1315, found 315.1316.

(3*S*,6*S*)-3-isopropyl-6-(2-(methylthio)ethyl)-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (9h). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio) butanoate (**5j**) (1.12 g, 4.68 mmol) and L-valinol (0.48 g, 4.65 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **9h** (331 mg, 1.12 mmol) in 24% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **9h**.* ^{1}H-NMR $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H), 2.06 (s, 3H), 2.13–2.36 (m, 4H), 2.46–2.55 (m, 1H), 3.84 (dd, $J = 8.8$, 6.8 Hz, 1H), 4.17 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.25 (ddd, $J = 7.6$, 7.2, 6.8 Hz, 1H), 4.78 (dd, $J = 6.4$, 5.6 Hz, 1H), 5.74 (s, 1H), 6.26 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.28 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.67 (dd, $J = 2.8$, 1.6 Hz, 1H) ppm; ^{13}C-NMR $\delta = 15.3$, 17.5, 19.2, 29.2, 30.5, 35.3, 58.7, 60.1, 67.5, 82.6, 106.0, 110.3, 118.7, 122.8, 166.4 ppm; IR (neat) $\nu = 2958$, 2910, 2872, 1703, 1661, 1550, 1544, 1449, 1422, 1406, 1345, 1307, 1237, 1163, 1114, 1053, 978, 870, 831, 777, 715 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}N_2O_2S$ + Na, 317.1294, found 317.1296.

General procedure for cyclization of pyrralines 5 with (*S*)-2-amino-2-phenylethan-1-ol (l-phenylalaninol)

(3*S*)-3-Benzyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10a). The mixture of methyl 2-(2-formyl-1*H*-pyrrol-1-yl)acetate (**5a**) (1.12 g, 6.70 mmol) and L-phenylalaninol (1.01 g, 6.70 mmol) in toluene (5 mL) was stirred at room temperature for 2.5 h and then heated at 110 °C for 6 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and purified by SiO_2 flash column chromatography to give **10a** (108 mg, 0.40 mmol) in 6% yield as light-yellow liquid.

*Data for **10a**.* ^{1}H-NMR $\delta = 2.98$ (dd, $J = 13.6$, 8.8 Hz, 3H), 3.29 (dd, $J = 13.6$, 4.0 Hz, 1H), 3.85 (dd, $J = 9.2$, 8.0 Hz, 1H), 4.21 (dd, $J = 9.2$, 7.6 Hz, 1H), 4.60–4.68 (m, 1H), 4.64 (A of ABq, $J_{AB} = 17.2$ Hz, 1H), 4.69 (B of ABq, $J_{AB} = 17.2$ Hz, 1H), 5.54 (s, 1H), 6.26–6.30 (m, 2H), 6.65 (dd, $J = 2.4$, 1.6 Hz, 1H), 7.22–7.28 (m, 3H), 7.29–7.36 (m, 2H) ppm; ^{13}C-NMR $\delta = 37.7$, 48.6, 55.7, 69.6, 82.5, 106.1, 110.3, 119.1, 122.3, 126.9, 128.7, 129.5, 136.2, 163.0 ppm; IR (neat) $\nu = 3026$, 2925, 2877, 1719, 1666, 1547, 1498, 1465, 1429, 1347, 1317, 1269, 1216, 1079, 1047, 973, 750, 693 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}N_2O_2$ + Na, 291.1104, found 291.1107.

(3*S*,6*S*)-3-Benzyl-6-methyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10b). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)propanoate (**5b**) (1.12 g, 6.19 mmol) and L-phenylalaninol (0.94 g, 6.19 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10b** (559 mg, 1.98 mmol) in 32% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10b**.* ^{1}H-NMR $\delta = 1.65$ (d, $J = 7.2$ Hz, 3H), 3.08 (dd, $J = 13.6$, 8.0 Hz, 3H), 3.18 (dd, $J = 13.6$, 4.0 Hz, 1H), 3.88 (dd, $J = 8.8$, 8.0 Hz, 1H), 4.24 (dd, $J = 8.8$, 8.0 Hz, 1H), 4.62 (dddd, $J = 8.0$, 8.0, 8.0, 4.0 Hz, 1H), 4.71 (q, $J = 7.2$ Hz, 1H), 5.41 (s, 1H), 6.22 (ddd, $J = 4.0$, 1.6, 0.8 Hz, 1H), 6.26 (dd, $J = 4.0$, 2.8 Hz, 1H), 6.65 (dd, $J = 2.8$, 1.6 Hz, 1H), 7.20–7.28 (m, 3H), 7.29–7.34 (m, 2H) ppm; ^{13}C-NMR $\delta = 22.4$, 37.2, 55.3, 55.7, 69.4, 82.3, 105.6, 110.3, 118.1, 122.1, 127.0, 128.6, 129.8, 136.1, 166.7 ppm; IR (neat) $\nu = 3027$, 2973, 2920, 2857, 1714, 1655, 1566, 1449, 1422, 1402, 1370, 1307, 1221, 1153, 1114, 1074, 1031, 973, 819, 751, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_2O_2$ + Na, 305.1260, found 305.1264.

(3*S*,6*S*)-3-Benzyl-6-isopropyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10c). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylbutanoate (**5c**) (1.12 g, 5.36 mmol) and L-phenylalaninol (0.81 g, 5.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10c** (682 mg, 2.20 mmol) in 41% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10c**.* ^{1}H-NMR $\delta = 0.89$ (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.4$ Hz, 3H), 2.25 (m, 1H), 2.92 (dd, $J = 13.2$, 9.2 Hz, 1H), 3.34 (dd, $J = 13.2$, 4.0 Hz, 1H), 3.85 (dd, $J = 8.8$, 7.2 Hz, 1H), 4.17 (dd, $J = 8.8$, 7.6 Hz, 1H), 4.44 (d, $J = 4.8$ Hz, 1H), 4.60 (dddd, $J = 9.2$, 7.6, 7.2, 4.0 Hz, 1H), 5.64 (s, 1H), 6.24 (dd, $J = 3.6$, 2.4 Hz, 1H),

6.26 (ddd, J = 3.6, 1.6, 0.8 Hz, 1H), 6.62 (dd, J = 2.4, 1.6 Hz, 1H), 7.22–7.28 (m, 3H), 7.29–7.34 (m, 2H) ppm; ^{13}C-NMR δ = 18.1, 19.3, 34.8, 37.7, 56.0, 65.9, 69.8, 82.7, 105.2, 109.4, 119.6, 123.8, 126.9, 128.6, 129.5, 136.4, 165.4 ppm; IR (neat) ν = 3032, 2958, 2925, 2878, 1666, 1560, 1465, 1425, 1399, 1361, 1302, 1227, 1194, 1158, 1063, 1058, 1030, 967, 861, 756, 703 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}N_2O_2$ + Na, 333.1573, found 333.1576.

(3*S*,6*S*)-3-Benzyl-6-((*S*)-*sec*-butyl)-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10d). The reaction of methyl (2*S*,3*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-methylpentanoate (**5e**) (1.12 g, 5.02 mmol) and L-phenylalaninol (0.76 g, 5.02 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10d** (505 mg, 1.56 mmol) in 31% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10d**.* ^{1}H-NMR δ = 0.91 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.00–1.14 (m, 1H), 1.50–1.62 (m, 1H), 1.92–2.04 (m, 1H), 2.93 (dd, J = 13.2, 8.8 Hz, 1H), 3.33 (dd, J = 13.2, 4.4 Hz, 1H), 3.85 (dd, J = 8.8, 7.6 Hz, 1H), 4.17 (dd, J = 8.8, 7.6 Hz, 1H), 4.55 (d, J = 5.2 Hz, 1H), 4.60 (dddd, J = 8.8, 7.6, 7.6, 4.4 Hz, 1H), 5.64 (s, 1H), 6.23–6.26 (m, 2H), 6.62 (dd, J = 2.8, 1.6 Hz, 1H), 7.22–7.28 (m, 3H), 7.29–7.35 (m, 2H) ppm; ^{13}C-NMR δ = 11.6, 15.4, 25.1, 37.8, 41.8, 56.1, 64.7, 69.8, 82.7, 105.1, 109.6, 119.2, 123.8, 126.9, 128.6, 129.5, 136.4, 165.2 ppm; IR (neat) ν = 3020, 2958, 2920, 2872, 1705, 1655, 1561, 1455, 1431, 1398, 1366, 1290, 1227, 1189, 1151, 1068, 1052, 1026, 978, 862, 735, 703 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_2$ + Na, 347.1730, found 347.1732.

(3*S*,6*S*)-3,6-Dibenzyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10e). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-3-phenylpropanoate (**5f**) (1.12 g, 4.36 mmol) and L-phenylalaninol (0.66 g, 4.36 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10e** (969 mg, 2.70 mmol) in 62% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10e**.* ^{1}H-NMR δ = 2.41 (dd, J = 13.2, 10.4 Hz, 1H), 3.28 (d of A of ABq, J_{AB} = 13.6, J_d = 4.8 Hz, 1H), 3.32 (d of B of ABq, J_{AB} = 13.6, J_d = 4.8 Hz, 1H), 3.44 (dd, J = 13.2, 4.4 Hz, 1H), 3.56 (dd, J = 9.2, 7.6 Hz, 1H), 3.99 (dd, J = 9.2, 7.6 Hz, 1H), 4.45 (dddd, J = 10.4, 7.6, 7.6, 4.4 Hz, 1H), 4.52 (s, 1H), 4.95 (t, J = 4.8 Hz, 1H), 6.12 (ddd, J = 4.0, 1.6, 0.8 Hz, 1H), 6.28 (dd, J = 4.0, 2.8 Hz, 1H), 6.63 (dd, J = 2.8, 1.6 Hz, 1H), 6.71–6.76 (m, 2H), 7.15–7.32 (m, 8H) ppm; ^{13}C-NMR δ = 37.6, 41.8, 55.7, 60.6, 70.1, 81.4, 104.9, 110.4, 117.9, 123.7, 126.8, 127.5, 128.2, 128.7, 129.1, 129.7, 134.5, 136.5, 164.2 ppm; IR (neat) ν = 3016, 2915, 2862, 1655, 1544, 1460, 1438, 1405, 1361, 1316, 1206, 1158, 1079, 1049, 1029, 975, 851, 740, 698 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_2$ + Na, 381.1573, found 381.1577.

(3*S*,6*S*)-3-Benzyl-6-phenethyl-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10f). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-phenylbutanoate (**5g**) (1.12 g, 4.13 mmol) and l-phenylalaninol (0.63 g, 4.13 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10f** (877 mg, 2.35 mmol) in 57% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10f**.* ^{1}H-NMR δ = 2.19–2.36 (m, 2H), 2.47–2.58 (m, 1H), 2.63–2.73 (m, 1H), 2.99 (dd, J = 13.6, 8.4 Hz, 1H), 3.21 (dd, J = 13.6, 4.0 Hz, 1H), 3.86 (dd, J = 8.8, 7.6 Hz, 1H), 4.21 (dd, J = 8.8, 7.6 Hz, 1H), 4.62 (dddd, J = 8.4, 7.6, 7.6, 4.0 Hz, 1H), 4.69 (t, J = 6.0 Hz, 1H), 5.51 (s, 1H), 6.26 (ddd, J = 3.6, 1.6, 0.8 Hz, 1H), 6.28 (dd, J = 3.6, 2.8 Hz, 1H), 6.65 (dd, J = 2.8, 1.6 Hz, 1H), 7.14–7.19 (m, 2H), 7.19–7.33 (m, 8H) ppm; ^{13}C-NMR δ = 31.0, 37.5, 37.5, 55.6, 59.5, 69.6, 82.4, 105.7, 110.2, 118.7, 122.9, 126.3, 127.0, 128.3, 128.6, 128.6, 129.6, 136.2, 140.0, 165.9 ppm; IR (neat) ν = 3025, 2964, 2920, 2862, 1709, 1666, 1544, 1443, 1431, 1338, 1325, 1211, 1074, 1026, 973, 772, 687 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{24}N_2O_2$ + Na, 395.1730, found 395.1733.

Methyl 2-((3*S*,6*S*)-3-benzyl-5-oxo-2,3,5,6-tetrahydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-6-yl)acetate (10g). The reaction of dimethyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)succinate (**5h**) (1.12 g, 4.68 mmol) and L-phenylalaninol (0.71 g, 4.69 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10g** (223 mg, 0.66 mmol) in 14% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10g**.* ^{1}H-NMR δ = 2.91 (dd, J = 16.4, 7.6 Hz, 1H), 3.02 (dd, J = 13.6, 8.8 Hz, 1H), 3.07 (dd, J = 16.4, 4.0 Hz, 1H), 3.29 (dd, J = 13.6, 4.0 Hz, 1H), 3.69 (s, 3H), 3.89 (dd, J = 9.2, 7.6 Hz, 1H), 4.22 (dd, J = 9.2, 7.6 Hz, 1H), 4.59 (dddd, J = 8.8, 7.6, 7.6, 4.0 Hz, 1H), 5.05 (dd, J = 7.6, 4.0 Hz, 1H), 5.54 (s, 1H), 6.22–6.27 (m, 2H), 6.70 (dd, J = 2.4, 1.6 Hz, 1H), 7.22–7.36 (m, 5H) ppm; ^{13}C-NMR δ = 37.2, 39.7, 52.2, 55.8, 55.9, 69.7, 82.3, 105.8, 110.4, 118.9, 122.8, 127.0, 128.7, 129.6, 136.2, 164.4, 169.9 ppm; IR (neat) ν = 3032, 2947, 2927, 2867, 1735, 1666, 1555, 1455, 1438, 1442, 1400, 1365, 1317, 1221, 1168, 1084, 1026, 1029, 973, 898, 858, 830, 766, 703 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_4$ + Na, 363.1315, found 363.1319.

(3*S*,6*S*)-3-Benzyl-6-(2-(methylthio)ethyl)-2,3-dihydro-10*bH*-oxazolo[3,2-*a*]pyrrolo[2,1-*c*]pyrazin-5(6*H*)-one (10h). The reaction of methyl (*S*)-2-(2-formyl-1*H*-pyrrol-1-yl)-4-(methylthio) butanoate (**5j**) (1.12 g, 4.68 mmol) and L-phenylalaninol (0.70 g, 4.65 mmol) in toluene (5 mL) at room temperature for 2.5 h and then at 110 °C for 6 h produced **10h** (353 mg, 1.03 mmol) in 22% yield as light-yellow liquid after purification by SiO_2 column chromatography.

*Data for **10h**.* ^{1}H-NMR δ = 2.07–2.17 (m, 1H), 2.11 (s, 3H), 2.20–2.31 (m, 1H), 2.32–2.40 (m, 1H), 2.48–2.57 (m, 1H), 3.04 (dd, J = 13.6, 8.4 Hz, 1H), 3.22 (dd, J = 13.6, 4.0 Hz, 1H), 3.88 (dd, J = 9.2, 7.6 Hz, 1H), 4.21 (dd, J = 9.2, 7.6 Hz, 1H), 4.61 (dddd, J = 8.4, 7.6, 7.6, 4.0 Hz, 1H), 4.79 (dd, J = 7.2, 5.6 Hz, 1H), 5.49 (s, 1H), 6.23–6.27 (m, 2H), 6.67 (dd, J = 2.4, 2.0 Hz, 1H), 7.20–7.35 (m, 5H) ppm; ^{13}C-NMR δ = 15.2, 29.3, 35.0, 37.3, 55.6, 58.6, 69.5, 82.4, 105.7, 110.1, 118.9, 122.9, 127.0, 128.6, 129.6, 136.2, 165.7 ppm; IR (neat) ν = 3015, 2915, 2846, 1709, 1655, 1570, 1539, 1478, 1455, 1426, 1347, 1323, 1302, 1211, 1200, 1147, 1075, 1032, 977, 854, 818, 739, 701 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}N_2O_2S$ + Na, 365.1294, found 365.1296.

Conclusions

We demonstrated a practically efficient transformation method of D-ribose as sustainable reducing sugar with various α-amino acids into pyrralines **5** as platform chemicals. Up to 300% yield increasement of pyrralines **5** (32–63% yield) were realized by one-pot pressurized conversion of D-ribose with various α-

amino esters at 2.5 atm and 80 °C. The pyrrole-based platform chemicals **5** containing formyl and ester groups as linchpin units were further cyclized to form the piperazin-2-one scaffold as the second pharmacophore. Reductive amination of the formyl group with benzylamine, followed by intramolecular amination with the ester group provided pyrrolo-piperazinones **6** in reasonable yields. 1,2-Ethanediamine reacted with the formyl group of pyrralines **5** by double amination, and the resulting secondary amine underwent subsequent amination with the ester group to produce pyrrolo-piperazinones **7** with an imidazolidine ring as the third structural unit in high yields. Likewise, 2-amino alcohols derived from natural α-amino acids, alanine, valine, and phenylalanine, respectively reacted with the formyl group of pyrralines **5** to give intermediate oxazolidines, which underwent further cyclization with the ester group to produce triply fused heterocycles **8–10** of pyrrole, piperazin-2-one, and oxazolidine in acceptable yields. Pyrrolo-piperazinones **8h** and **10g** with an oxazolidine motif exhibited significant anti-inflammation activities with high cell viability. The practical synthetic method of platform chemicals **5** from sustainable biomass would open a paved road to the discovery of new therapeutic agents and value-added functional materials.

Author contributions

S. Cho: synthesis (lead); L. Gu: synthesis (equal); I. J. In: synthesis (supporting); B. Wu: investigation (equal), synthesis (supporting); T. Lee: bioassays (lead); H. Kim: bioassay (equal), funding acquisition (equal); S. Koo: project administration (lead), funding acquisition (lead), investigation (lead), formal analysis (lead), data curation (lead), writing manuscript (lead).

Conflicts of interest

There are no conflicts to declare.

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