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PAPER

Concise synthesis of an enantiopure bicyclic pyrazinone as constrained peptidomimetic building block†

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A concise synthetic route has been developed for the preparation of a constrained peptidomimetic pyrazinone building block. From hydroxy-L-lysine, the desired pyrazinone is obtained in 43% overall yield (6 steps) *via* an efficient deprotection–double cyclization sequence.

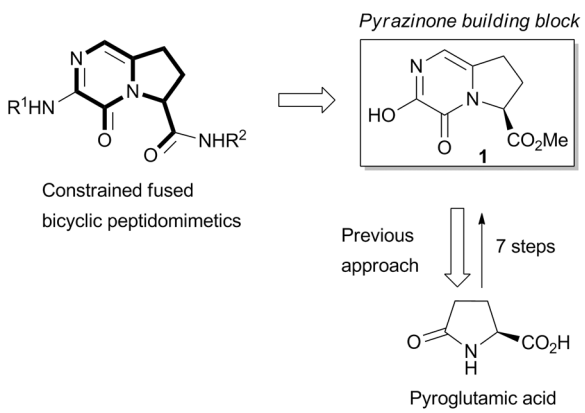
Introduction

Molecules containing a pyrazinone core structure have been widely recognized as biologically useful systems. In particular, they are known to be valuable serine protease inhibitors, a peptidase which plays a crucial role in many physiological functions (digestion, blood clotting, immune system…).[1] Among the broad range of peptidomimetics investigated in medicinal chemistry, bicyclic pyrazinones have been used as conformationally constrained peptide-like building blocks[2] and employed as key scaffolds for the development of thrombin,[2e] prolyl oligopeptidase[2f] or HCV NS3 protease inhibitors.[2g] In the course of a recent program aiming at exploring new routes to pharmaceutical intermediates, we became interested in the stereoselective preparation of the bicyclic pyrazinone **1** (Scheme 1). Although many pharmaceutical companies have used this enantiopure building block for the development of new potential drugs, only one route has been described to date.[2] Actually, the enantiopure bicyclic pyrazinone **1** was obtained in seven steps from pyroglutamic acid in a modest overall yield of 22%.[2d,e] However, this approach is severely limited by 1) the use of sodium cyanide reagent with acute toxicity; 2) some steps proceeded at very low temperature; 3) and the difficulty to scale-up the whole synthesis.[3]

Herein, we report a straightforward high yielding multigram scale synthesis of enantiopure pyrazinone **1** from commercially (5*R*)-hydroxyl-L-lysine (Scheme 2).

The retrosynthetic approach toward the desired bicyclic hydroxypyrazinone **1** is illustrated in Scheme 2. The desired fused bicyclic scaffold was envisioned to be the result of a dehydration of the fused bicycle **2**. As a key step, we hypothesized that the expected bicycle **2** would be generated from **3** under basic conditions by a one-pot domino sequence involving Fmoc-deprotection, and condensation cascade events involving the N^{α} amino-group with the ketone and the N^{ε} amino-group with the oxalate moiety. The intermediate **3** could be formed from the commercially available L-hydroxylysine[4] *via* a well orchestrated four step sequence requiring the protection of the N^{ε} amino-group, an esterification step, followed by a condensation of the N^{α} amino-group with methyl oxalyl chloride and oxidation of the alcohol at the C-5 position.

Firstly, L-hydroxylysine was involved in a regioselective protection of the N^{ε} amino-group using the method described by Kihlberg and co-workers (Scheme 3).[5] This approach makes use of a copper chelate of an α-amino acid moiety as a transient protective strategy. The resulting copper complex was then treated with Fmoc-*O*-succinimide followed by treatment with an aqueous solution of EDTA to liberate the mono-protected amino



Scheme 1 Previous synthesis.

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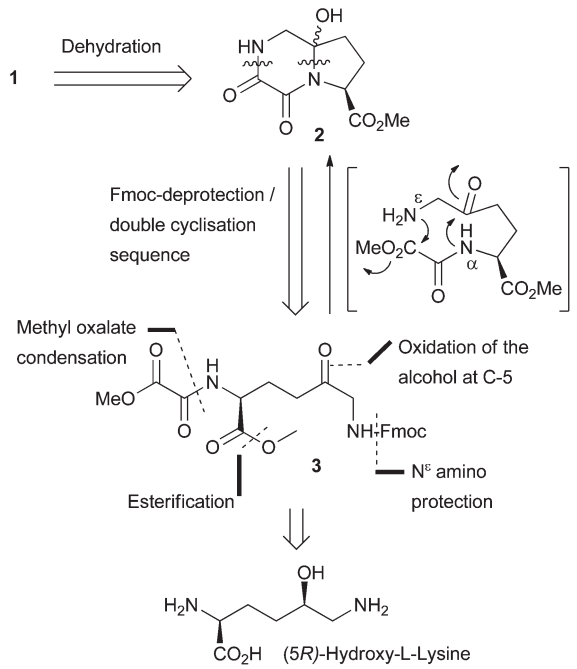
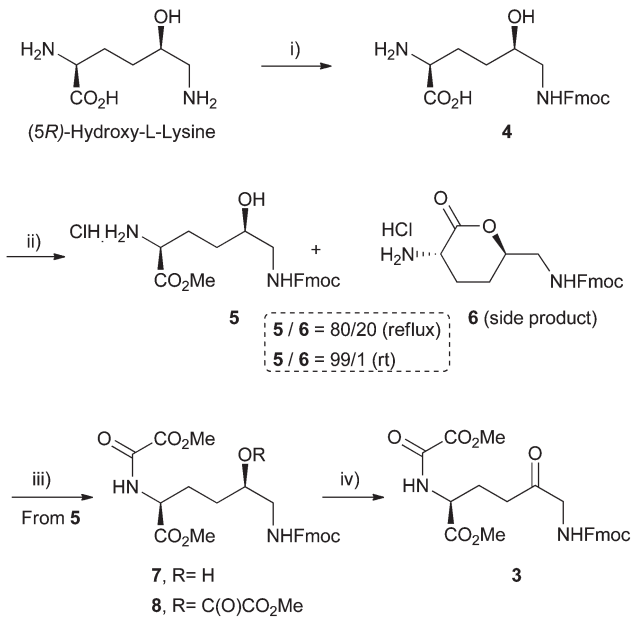
†Electronic supplementary information (ESI) available: Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **4**, **5** and **7**. See DOI: 10.1039/c2ob06762e



Scheme 2 Alternative approach to pyrazinone **1**.

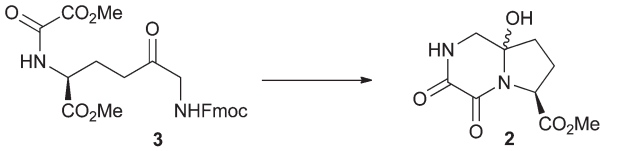


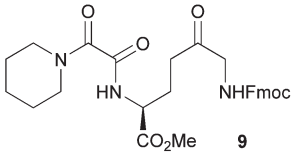
Scheme 3 *Reagents and conditions:* i) $CuSO_4.5H_2O$ (0.5 equiv), NaOH 0.5 N (1 equiv) then K_2CO_3 (1 equiv), Fmoc-OSu (1 equiv), H_2O–dioxane, and EDTA.2Na, H_2O, 95 °C, 83%; ii) thionyl chloride (2.2 equiv), MeOH, rt, 24 hours, 100%; iii) methyl oxalyl chloride (1 equiv), NEt_3, CH_2Cl_2, 0 °C, 81%; iv) Dess–Martin periodinane, CH_2Cl_2, 0 °C to rt, 80%.

acid **4** isolated in a good 83% yield after a simple filtration. This product was used in the next step without further purification.

Initially, we envisaged the esterification of **4** with thionyl chloride in methanol. When the reaction was conducted at reflux, the formation of the desired ester **5** was observed along with lactone **6** (10–20%) arising from the lactonization reaction

Table 1 Screening study of the Fmoc-deprotection–double cyclisation sequence



Entry	Base/solvent/*T*	Results
		
1	Piperidine[a]/DMF/25 °C	14%[c]
2	Piperidine[a]/DCM/25 °C	**9**, 15%[c]
3	DIEA[b]/DCM/25 °C	—[d]
4	DIEA[b]/AcOEt/reflux	—[d]
5	DIEA[b]/DMF/25 °C	—[e]
6	NEt_3[b]/MeOH/25 °C	—[d]
7	NEt_3[b]/MeOH/reflux	**2**, 90%[c,f]
8	NEt_3[b]/MeOH/reflux	**2**, 86%[c,g]

[a] 0.2 equiv. [b] 1 equiv. [c] Isolated yield. [d] Starting material was recovered. [e] No product was isolated. [f] 0.44 mmol scale. [g] 13.4 mmol scale (6.46 g).

between the hydroxyl group and the carboxylic acid moiety.[6] Unfortunately, we were not able to separate products **5** and **6** by flash column chromatography. Nevertheless, the formation of the lactone **6** was circumvented by conducting the reaction at room temperature for 24 hours. Under these reaction conditions, ester **5** was isolated quantitatively after simple evaporation of volatiles. Then, in the presence of methyl oxalyl chloride and triethylamine, compound **7** was obtained with a good yield of 81%. At this stage, it is crucial to maintain the reaction temperature at 0 °C to minimize the formation of the by-product **8** (6% yield) resulting from the condensation of methyl oxalyl chloride with alcohol at C-5. After further optimizations, we were pleased to find that alcohol **7** was smoothly oxidized by Dess–Martin periodinane to give the ketone **3** in good yield.

We next investigated the key cyclisation step of our strategy, *i.e.* the deprotection–double condensation sequence. In our initial experiment to obtain the desired bicycle **2**, we tested standard basic conditions commonly employed for the deprotection of the Fmoc group (Table 1).

When ketone **3** was placed in the presence of piperidine in DMF or DCM, only the addition of piperidine to the oxalate moiety was observed to afford compound **9** (entries 1, 2). Nevertheless, this result revealed the ability of the oxalate moiety to react with a nucleophilic amine. Thus, we investigated several basic conditions using less nucleophilic amine bases such as Hünig's base or triethylamine in various solvents (DMF, DCM, EtOAc) at different temperatures. Unfortunately, no transformation was observed in moderately polar solvent such as DCM or EtOAc (entries 3, 4), while compound **3** reacted in DMF but no identified product could be isolated (entry 5). Although no reaction occurred in MeOH at room temperature (entry 6), we were pleased to observe the formation of the bicyclic hemiaminal **2**, as a mixture of diastereomers, by refluxing ketone **3** in methanol

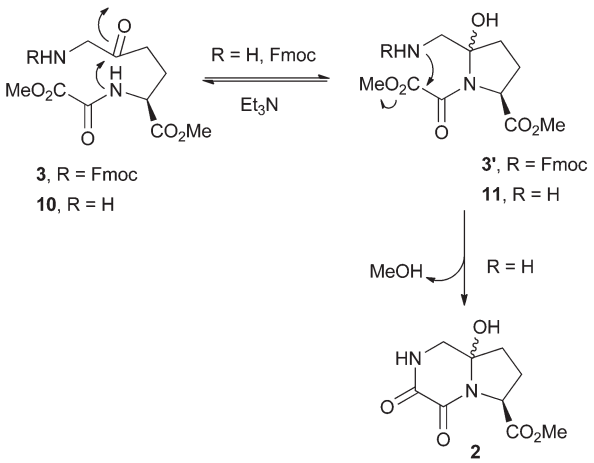
in the presence of triethylamine (entry 7). Pleasingly, this reaction could be efficiently performed on a multigram scale with a similar result (entry 8).

In order to explain this facile cyclisation cascade, we propose the following mechanism. Under these conditions, one can assume that N-Fmoc protected **3** (R = Fmoc) and/or deprotected **10** (R = H) are in equilibrium with the corresponding cyclic hemiaminal *via* the favourable five membered ring formation (Scheme 4). Condensation with the oxalate moiety is then facilitated (6 membered ring formation) from the primary amine **11** to afford the expected fused bicycle **2**. However, we cannot rule out that **2** results from an intramolecular macrolactamization followed by a condensation, although the 9-membered ring formation would suffer from severe trans-annular constraints.

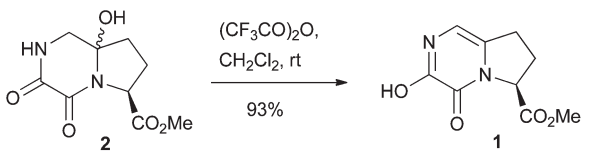
Finally, the facile dehydration of the tertiary alcohol **2** into hydroxyl pyrazinone **1** was accomplished by treatment with trifluoroacetic anhydride in dichloromethane at room temperature (Scheme 5). The desired product was isolated with a good yield (93%) without racemisation (ee > 95%) as determined by chiral HPLC analysis.

Conclusions

In summary, we have developed a straightforward and multigram scale synthesis of an enantiopure fused bicyclic pyrazinone **1** in six steps and a good overall yield of 43%. The whole process required only two purifications on column chromatography. This route, starting from L-hydroxylysine, features original domino-reactions involving a Fmoc-deprotection and successive cyclisation events providing an valuable alternative construction of this constrained peptidomimetic precursor.



Scheme 4 Hypothesized reaction pathway.



Scheme 5

Experimental

General

Chromatographic purification of compounds was achieved with 60 silica gel (40–63 μm). Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVANCE 300. Data appear in the following order: chemical shifts in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz, number of protons. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. The hydrogen multiplicity was obtained by DEPT135 or Attached Proton Test (APT) using JMOD pulse program. IR spectra were recorded on a Perkin Elmer IRTF 1650 spectrometer with solid dispersed on KBr pastille. Mp's stand uncorrected.

(2*S*,5*R*)-6-(((9*H*-Fluoren-9-yl)methoxy)carbonylamino)-2-amino-5-hydroxyhexanoic acid 4

To a flask filled with air equipped with a mechanical stirrer was added 5*R*-hydroxy-L-lysine (6.33 g, 25 mmol) and 0.5 N NaOH (100 mL, 50 mmol). To the resultant clear, colourless solution was added $CuSO_4.5H_2O$ (3.43 g, 13.75 mmol). After stirring for 15 min, K_2CO_3 (3.45 g, 25 mmol) was added followed by a mixture of H_2O–dioxane (80 mL/160 mL) and FmocOSu (8.43 g, 25 mmol) in one portion. After stirring for 3 hours, the blue precipitate was collected and rinsed with MeOH. The blue solid was added to a solution of EDTA.2Na (4.62 g, 13.75 mmol) in water (200 mL). The resultant slurry was heated to 95 °C with vigorous stirring for 2 hours and then cooled to room temperature. The white precipitate was collected and rinsed with H_2O. After drying under vacuum, 7.96 g (20.7 mmol, 83%) of a white solid **4**was obtained and used without any further purification. Mp = 168 °C. IR (KBr) *ν* max/cm^{-1} 3361, 2933, 1697, 1644, 1542, 1487, 1450, 1353, 1315, 1268, 1142. ^{1}H NMR (THF-d_8, as a TFA salt, 25 °C, 300 MHz): δ 8.31 (br s, 2 H), 7.80 (d, J = 7.2 Hz, 2 H), 7.67 (d, J = 7.3 Hz, 2 H), 7.40–7.27 (m, 4 H), 6.75 (br s, 1 H), 4.36 (d, J = 6.9 Hz, 2 H), 4.23–4.18 (m, 2 H), 3.72–3.63 (m, 1 H), 3.25–3.04 (m, 2 H), 2.26–2.01 (m, 2 H), 1.80–1.49 (m, 2 H) ppm. ^{13}C NMR (THF-d_8, as a TFA salt, The signal of TFA was not included, 25 °C, 75 MHz): δ 171.9 (C), 158.6 (C), 145.6 (C), 142.7 (C), 128.8 (CH), 128.2 (CH), 126.3 (CH), 121.0 (CH), 71.5 (CH), 67.9 (CH_2), 54.2 (CH), 48.7 (CH), 48.2 (CH_2), 30.7 (CH_2), 28.3 (CH_2) ppm. Elemental analysis for $C_{21}H_{24}N_2O_5$ (384.42): Calcd C 65.61, H 6.29, N 7.29; found C 65.59, H 6.32, N 7.28.

(2*S*,5*R*)-Methyl 6-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-2-amino-5-hydroxyhexanoate hydrochloride 5

A reaction flask charged with methanol (150 ml) was cooled in an ice–salt bath with stirring and thionyl chloride (3.0 mL, 42 mmol) was added dropwise. After the completion of addition, **4** (7.96 g, 20.7 mmol) was added in portions to the reaction mixture at 0 °C. The reaction mixture was then stirred for 24 hours at room temperature. The solution was evaporated to

dryness under reduced pressure to give ester **5** (9.0 g, 100%) which was used without any further purification. Mp < 50 °C. IR (KBr) ν max/cm^{-1} 3348, 2936, 1692, 1524, 1447, 1241, 1151, 1089. ^{1}H NMR (CD_3OD, 25 °C, 300 MHz): δ 7.80 (d, J = 7.2 Hz, 2 H), 7.67 (d, J = 7.3 Hz, 2 H), 7.40–7.27 (m, 4 H), 5.49 (s, 1 H), 4.37 (d, J = 6.9 Hz, 2 H), 4.21 (t, J = 6.6 Hz, 1 H), 4.07 (t, J = 6.6 Hz, 1 H), 3.81 (s, 3 H), 3.69–3.59 (m, 1 H), 3.19–3.06 (m, 2 H), 2.19–1.83 (m, 2 H), 1.67–1.37 (m, 2 H) ppm. ^{13}C NMR (CD_3OD, 25 °C, 75 MHz): δ 170.9 (C), 159.1 (C), 145.3 (C), 142.6 (C), 128.8 (CH), 128.2 (CH), 126.2 (CH), 121.2 (CH), 70.8 (CH), 67.8 (CH_2), 53.9 (CH), 53.7 (CH_3), 48.4 (CH), 47.7 (CH_2), 30.5 (CH_2), 28.0 (CH_2) ppm. HRMS (ESI+): Calcd for $C_{22}H_{27}N_2O_5$ $[M + H]^+$: 399.1920; Found: 399.1913.

(2*S*,5*R*)-Methyl 6-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-5-hydroxy-2-(2-methoxy-2-oxoacetamido)hexanoate 7

To a stirred solution of **5** (9.0 g, 20.7 mmol) and Et_3N (5.75 mL, 41.4 mmol) in CH_2Cl_2 (100 mL) at 0 °C, methyloxalyl chloride (1.9 mL, 20.7 mmol) was added dropwise. The reaction mixture was stirred for 2 hours at 0 °C then treated with H_2O, followed by extraction with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give the alcohol **7** (8.11 g, 81%) which was used without any further purification. R_f 0.32 (EtOAc). Mp < 50 °C. IR (KBr) ν max/cm^{-1}: 3347, 2951, 1742, 1693, 1531, 1449, 1251. ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ 7.88 (d, J = 7.3 Hz, 1 H), 7.77 (d, J = 7.4 Hz, 2 H), 7.59 (d, J = 7.7 Hz, 2 H), 7.40 (t, J = 7.0 Hz, 2 H), 7.31 (td, J = 7.4, 1.1 Hz, 2 H), 5.19–5.12 (m, 1 H), 4.70–4.63 (m, 1 H), 4.43 (d, J = 6.7 Hz, 2 H), 4.21 (t, J = 6.6 Hz, 1 H), 3.90 (s, 3 H), 3.77 (s, 3 H), 3.39–3.29 (m, 1 H), 3.13–3.02 (m, 1 H), 2.76 (*br* s, 1 H), 2.16–2.03 (m, 1 H), 1.93–1.81 (m, 1 H), 1.56–1.43 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C, 75 MHz): δ 171.4 (C), 160.3 (C), 157.2 (C), 156.3 (C), 143.8 (C), 143.7 (C), 141.2 (C), 127.6 (CH), 126.9 (CH), 124.9 (CH), 119.9 (CH), 70.5 (CH), 66.7 (CH_2), 53.6 (CH), 52.6 (CH_3), 52.5 (CH_3), 47.0 (CH), 46.7 (CH_2), 29.9 (CH_2), 28.2 (CH_2) ppm. HRMS (ESI+): Calcd for $C_{25}H_{32}N_3O_8$ $[M + NH_4]^+$: 502.2189; Found: 502.2173.

(*S*)-Methyl6-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-2-(2-methoxy-2-oxoacetamido)-5-oxohexanoate 3

To a solution of alcohol **7** (8.11 g, 16.76 mmol) in CH_2Cl_2 (75 mL) was added Dess–Martin periodinane (10.66 g, 25.14 mmol) in one portion at 0 °C. The reaction mixture was stirred at room temperature for 5 hours, then quenched with saturated aqueous $Na_2S_2O_3$ and the resulting mixture was stirred vigorously until it became clear. The mixture was then poured into CH_2Cl_2 and the organic phase was washed twice with 10% aq. $Na_2S_2O_3$–aq. $NaHCO_3$ (1 : 1 mixture) and brine. After drying ($MgSO_4$), removal of the solvent *in vacuo* afforded a brownish residue which was purified by flash chromatography (EtOAc–petroleum ether) to give ketone **3** (6.46 g, 80%) as a white solid. R_f 0.45 (EtOAc). Mp < 50 °C. IR (KBr) ν max/cm^{-1}: 3462, 2924, 1699, 1539, 1451, 1263.^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ 7.76 (d, J = 7.5 Hz, 2 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.59 (d, J = 7.5 Hz, 2 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.31 (td, J = 7.5, 1.2 Hz, 2 H), 5.47–5.45 (m, 1 H), 4.66–4.55 (m, 1 H), 4.39 (d, J = 7.2 Hz, 2 H), 4.22 (t, J = 6.6 Hz, 1 H), 4.08 (d, J = 5.1 Hz, 2 H), 3.91 (s, 3 H), 3.77 (s, 3 H), 2.69–2.43 (m, 2 H), 2.40–2.26 (m, 1 H), 2.08–1.92 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C, 75 MHz): δ 204.4 (C), 171.1 (C), 160.3 (C), 156.3 (C), 156.2 (C), 143.8 (C), 141.3 (C), 127.7 (CH), 127.1 (CH), 125.1 (CH), 120.0 (CH), 67.1 (CH_2), 53.8 (CH), 52.9 (CH_3), 51.9 (CH_3), 50.5 (CH_2), 47.1 (CH), 35.5 (CH_2), 25.8 (CH_2) ppm. HRMS (ESI+): Calcd for $C_{25}H_{30}N_3O_8$ $[M + NH_4]^+$: 500.2033; Found: 500.2046.

(*S*)-Methyl 8a-hydroxy-3,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate 2

To a solution of **3** (6.46 g, 13.4 mmol) in methanol (140 mL) was added Et_3N (3.72 mL, 26.8 mmol) at room temperature. Then, the mixture was refluxed for 5 hours. After cooling at room temperature, evaporation of the solvent gave a residue which was rinsed with pentane to afford **2** (2.63 g, 86%) as a brown–yellow solid. Mp < 50 °C. IR (KBr) ν max/cm^{-1}: 3476, 3258, 1736, 1659, 1626, 1455, 1438, 1370, 1294, 1177. ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ 8.33/8.24 (2 br s, 1 H), 6.43 (br s, 1 H), 4.63–4.60 (m, 1 H), 3.80–3.57 (m, 4 H), 3.18–1.86 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C, 75 MHz): δ 172.0/171.3 (C), 159.2/159.1 (C), 156.1/155.8 (C), 88.6/88.1 (C), 58.7/58.3 (CH), 53.1/52.7 (CH_3), 50.2/45.8 (CH_2), 37.4/36.4 (CH_2), 29.8/27.3 (CH_2) ppm. HRMS (ESI+): Calcd for $C_9H_{13}N_2O_5$ $[M + H]^+$: 229.0824; Found: 229.0817.

(*S*)-Methyl 3-hydroxy-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate 1

To a stirred solution of **2** (2.63 g, 11.52 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic anhydride (1.61 mL, 11.6 mmol) at 0 °C. The mixture was stirred for 2 hours at room temperature. Then, evaporation and purification by flash chromatography (EtOAc–MeOH 9 : 1) gave **1** (2.25 g, 93%) as a white solid in 95% ee. Chiral HPLC analysis was performed using chiralpack AS-H column with a mixture of isopropyl alcohol–heptane–methanol (47.5/47.5/5) and 0.1% of triethylamine as eluent (1.0 mL min^{-1}; 235 nm; retention time: 20.2 min (major enantiomer) and 36.1 min (minor enantiomer)). IR (KBr) ν max/cm^{-1}: 3521, 3182, 3087, 2916, 1746, 1636, 1477, 1372, 1200, 1159. R_f 0.05 (EtOAc–MeOH 9 : 1). Mp = 132 °C. ^{1}H NMR ($CDCl_3$, 25 °C, 300 MHz): δ 11.40 (s, 1 H), 6.33 (s, 1 H), 5.00 (dd, J = 9.0, 2.6 Hz, 1 H), 3.75 (s, 3 H), 2.98–2.78 (m, 2 H), 2.53–2.23 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C, 75 MHz): δ 169.6 (C), 157.8 (C), 155.0 (C), 126.4 (C), 104.1 (CH), 60.8 (CH), 53.1 (CH_3), 28.0 (CH_2), 26.7 (CH_2) ppm. MS (EI): m/z (%) = 210 (30) $[M]^{+\cdot}$, 185 (20), 150 (20), 123 (31), 101 (35), 86 (100). Elemental analysis for $C_9H_{10}N_2O_4$ (210.19): Calcd C 51.43, H 4.80, N 13.33; found C 51.31, H 4.74, N 13.29.

Acknowledgements

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Notes and references

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