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Enantiomerically pure piperazines via $NaBH_4/I_2$ reduction of cyclic amides

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ABSTRACT

Enantiomerically pure (3*S*,7*R*,8a*S*)-3-phenyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol, (3*S*,7*R*,8a*S*)-3-methyl octahydropyrrolo[1,2-*a*]pyrazine-7-ol, (3*S*,7*R*,8a*S*)-3-isopropyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol and (3*S*,7*R*,8a*S*)-3-isobutyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol **16d** were synthesized via preparation of the corresponding cyclic amides from enantiomerically pure L-proline and hydroxyproline derivatives followed by reduction using sodium borohydride-iodine.

1. Introduction

The chiral piperazine moiety is present in several biologically active compounds.[1] Some of these chiral piperazine derivatives are also useful as chiral auxiliaries and ligands in asymmetric synthesis.[2] Over recent years, several convenient methods have been reported from this laboratory to access chiral diols, amino alcohols, diamines, and piperazines.[3] For example, resolution methods were reported to access enantiomerically pure chiral piperazines by the Ti(III) promoted diastereoselective cyclization of diimines prepared using ethylene diamine and aryl aldehydes.[4] However, the development of a method to readily access piperazine derivatives from readily accessible starting materials would be desirable. Therefore, we turned our attention towards the synthesis of chiral amines via the reduction of chiral diamides prepared using naturally occurring amino acids. L-Proline derived diketopiperazine derivatives have been prepared by condensation followed by lithium aluminum hydride (LAH) reduction to access the corresponding piperazine.[5a] Methods for the reduction of diketopiperazines were previously reported using $NaBH_4/F_3B{:}OEt_2$[5b,c] and $NaBH_4$-$TiCl_4$ reagent systems.[5d] Some tyrosine based piperazines have also been prepared by the reduction of the corresponding diketopiperazine derivatives using diborane in THF.[6] Previously, a simple protocol for the reduction of various substrates using a sodium borohydride-iodine reagent system was reported.[7] Herein, we report convenient, general methods for the preparation of chiral piperazines based on enantiomerically pure chiral proline derivatives.

2. Results and discussion

We have observed that the reduction of the readily accessible chiral (5a*R*,10a*S*)-octahydrodipyrrolo[1,2-a:1′,2′-*d*]pyrazine-5,10-dione[8] **3** gave enantiomerically pure (5a*R*,10a*S*)-decahydrodipyrrolo[1,2-a:1′,2′-*d*]pyrazine **4** in 73% yield using an $NaBH_4/I_2$ reagent system (Scheme 1).

We have also observed that the diketopiperazine derivatives **8** prepared following a previously reported reaction sequence (Scheme 2)[9] upon reduction using $NaBH_4/I_2$ in anhydrous THF gave the corresponding piperazine derivatives **9** in good yields. Thus, enantiomerically pure piperazine derivatives (*S*)-1-benzyl-3-methylpiperazine **9a** and (*S*)-1,3-dibenzylpiperazine **9b** were obtained in 69% and 77% yields, respectively (Scheme 2).

The L-proline based diketo derivatives **13** were readily obtained in 71–78% yields following a slightly modified synthetic protocol.[5a,10] We observed that these compounds could also be converted into the corresponding enantiomerically pure piperazine derivatives **14** in 68–74% yields by the $NaBH_4/I_2$ reduction (Scheme 3).

This synthetic sequence is also useful for the synthesis of enantiomerically pure piperazine derivatives **16** by the reduction of the corresponding 4-hydroxyproline based diketopiperazines **15** prepared using the enantiomerically pure hydroxyproline **17** (Table 1) (Fig. 1).

The (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate **18** was prepared from 4-hyrdroxyproline **17** using $SOCl_2$ in methanol (Table 1). The resulting (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate **18** was reacted with *N*-boc protected amino acid derivatives **11** and 3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine hydrochloride (EDC·HCl) as a coupling agent in DCM as the solvent in the presence of NEt_3 to prepare compounds

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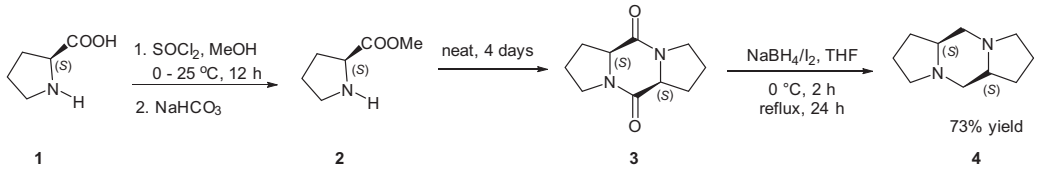
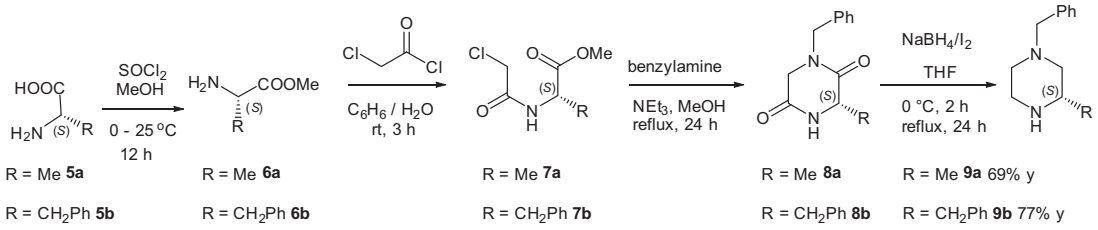
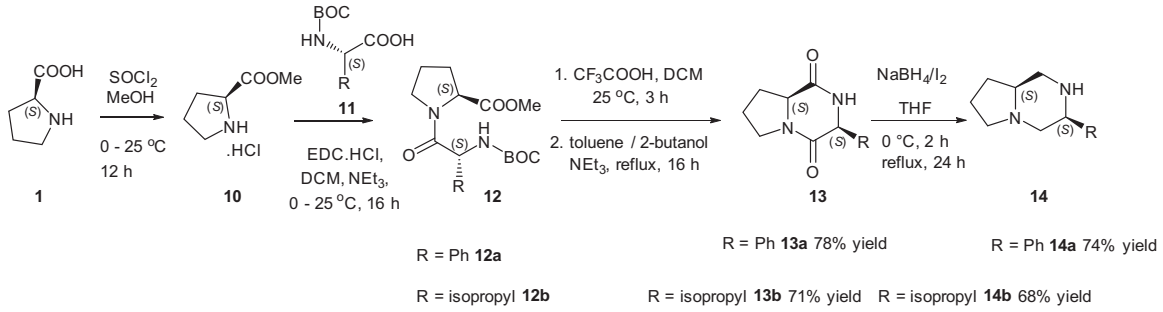


Scheme 1.



Scheme 2.



Scheme 3.

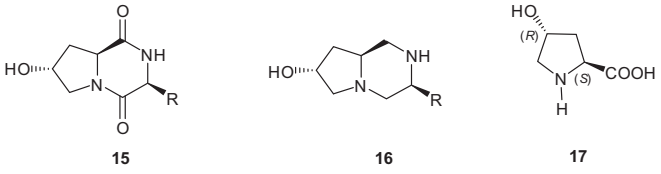


Figure 1. Diketopiperazines **15** and piperazines **16** prepared using hydroxyproline **17**.

19, which after CF_3COOH treatment and cyclization afforded diketopiperazine derivatives **15**. The results are summarized in Table 1.

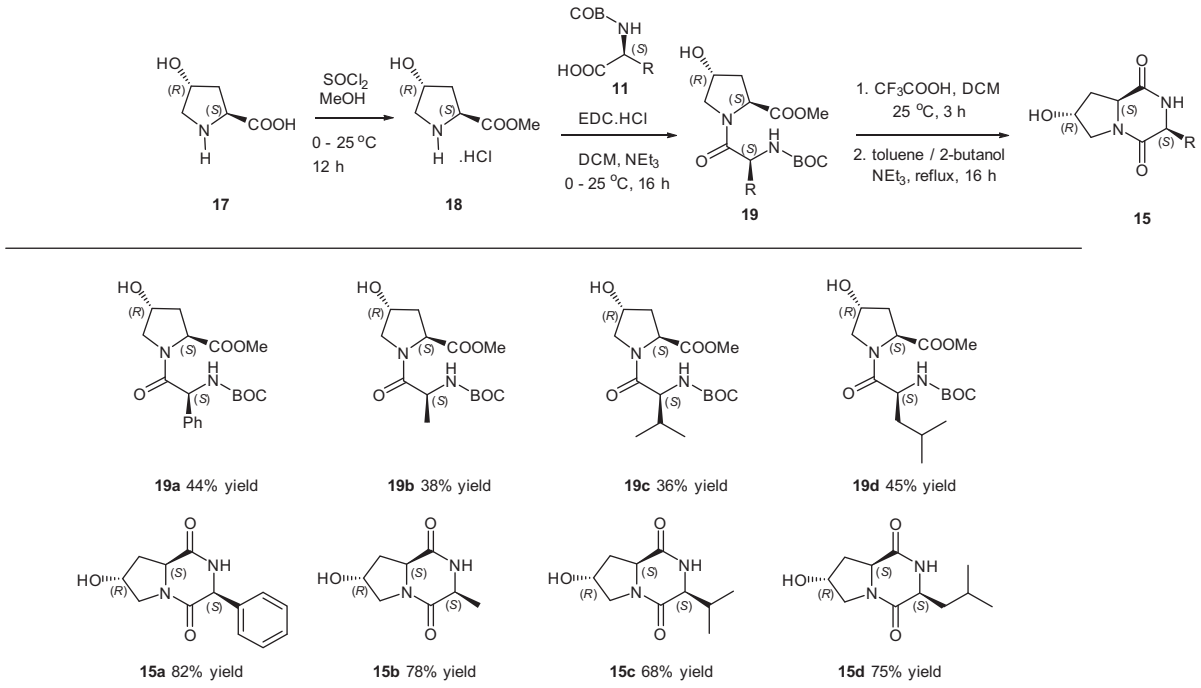
(2′*S*,4′*R*)-Methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino)-2-phenylacetyl)-4′-hydroxypyrrolidine-2′-carboxylate **19a** in 44% yield, while (2′*S*,4′*R*)-methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino) propanoyl)-4′-hydroxypyrrolidine-2′-carboxylate **19b** was obtained in 38% yield following this method. The *N*-boc valine **11c** and *N*-boc leucine **11d** derived products **19c** and **19d** were obtained in 36%, and 45% yield, respectively. These *N*-boc amide derivatives **19a–d** were converted into the corresponding diketo derivatives **15a–d** by deprotection using trifluoroacetic acid followed by cyclization in presence of triethylamine in refluxing toluene/2-butanol in 82%, 78%, 68% and 75% yields, respectively. The structure of **15c** was further confirmed by X-ray crystal structure analysis.[11] The ORTEP diagram is shown in Figure 2.

The hydroxy proline based chiral diketopiperazine derivatives **15** were readily reduced to enantiomerically pure piperazine derivatives **16** using an easy to handle sodium borohydride-iodine reagent system in anhydrous tetrahydrofuran solvent (Table 2). Enantiomerically pure (3*S*,7*R*,8a*S*)-3-phenyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol **16a** was obtained in 79% yield, while derivatives **16b**, **16c** and **16d** were obtained in 73%, 66% and 70% yields, respectively (Table 2).

3. Conclusion

We have developed a convenient method for the synthesis of enantiomerically pure diketopiperazine derivatives. The method described for the reduction of diketopiperazine derivatives involves a simple, inexpensive and easy to handle $NaBH_4/I_2$ reagent system in THF as the solvent and compares favourably with reported methods using lithium aluminum hydride (LAH),[5a] $NaBH_4/F_3B{:}OEt_2$[5b,c] and $NaBH_4$-$TiCl_4$ reagent systems.[5d] The LAH is hazardous and flammable upon exposure to air during synthetic operations, while the $F_3B{:}OEt_2$ and $TiCl_4$ systems are highly hygroscopic in nature and hence are not suitable for larger scale processes. The methods reported herein using the $NaBH_4/I_2$ reagent system give comparable results when the reductions were carried out on a 50–100 mmol scale. Hence, the methods described herein are useful for the preparation of enantiomerically pure piperazine derivatives for application in asymmetric organic synthesis. Recently, some pyrrolidine derivatives derived from 4-hydroxyproline were reported to exhibit potent inhibitory activity against influenza A neuraminidase.[12] Therefore, the methods described also have potential for further exploitation in medicinal chemistry.

Table 1
Synthesis of diketopiperazine derivatives using two aminoacid derivatives **17** and **11**



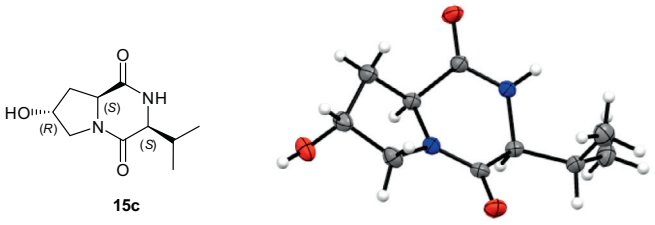


Figure 2. ORTEP representation of the crystal structure of diketopiperazine **15c** (thermal ellipsoids are drawn at 50% probability).

4. Experimental

4.1. General

Sodium borohydride ($NaBH_4$) was purchased from SRL and used as received. Iodine purchased from E-Merck (India) was used as received. Amino acids were purchased from SRL and were used as received. The melting points reported are uncorrected and were determined using a superfit capillary point apparatus. IR spectra were recorded on a FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz and 500 MHz Spectrometer with chloroform-d, Methanol-d and dimethylsulfoxide as solvents and TMS as reference. Optical rotations were measured in an AUTOPOL-IV digital polarimeter (readability ±0.001°).

4.2. General procedure for the preparation of amide derivatives

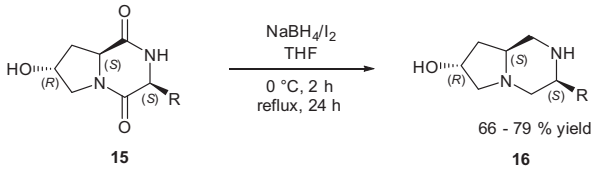
4.2.1. Preparation of diketopiperazine 3

We prepared **3** following the reported procedure.[8] To a suspension of L-proline (10 mmol) in methanol (50 mL) was added thionyl chloride (15 mmol) dropwise at ice cold bath. This solution was allowed to return to rt and stirred for 12 h. The solvent was evaporated under reduced pressure to give the HCl salt of L-proline methyl ester. The HCl salt was dissolved in CH_2Cl_2 (100 mL), and then neutralized with sodium hydrogen carbonate. The residue was removed by filtration and the solvent was evaporated under reduced pressure. The neat was stirred at rt for 4 days. The filtrate was dissolved in CH_2Cl_2 and washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by recrystallization from ethyl acetate provided the diketopiperazine as colorless needles.

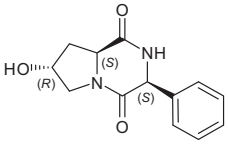
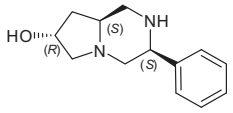
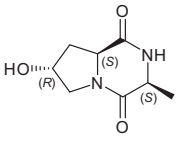
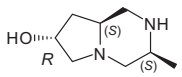
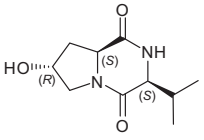
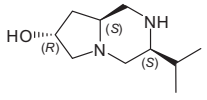
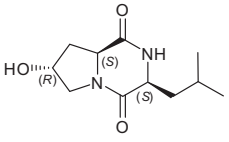
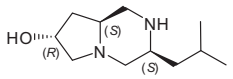
4.2.2. General procedure for the preparation of diketopiperazines 8

We prepared compound **8** following the reported procedure.[9] To a suspension of L-amino acid (10 mmol) in CH_3OH (50 mL) cooled in an ice-salt bath, $SOCl_2$ (40 mmol) was added dropwise. The resulting mixture was stirred for an additional 6 h at room temperature. The solution was concentrated to dryness, and without any further purification. The residue was dissolved in water (4 mL) and cooled in ice-salt bath. To the solution, $NaHCO_3$ (20 mmol) was added in one portion, after which a solution of chloroacetyl chloride (10 mmol) in benzene (15 mL) was added dropwise. The reaction mixture was stirred for an additional 3 h at rt. The aqueous layer was extracted twice with ethyl acetate (30 mL), and the combined organic phases were dried over anhydrous Na_2SO_4. After evaporation of the solvents, the crude product was purified using column chromatography. Next, a solution of benzylamine (10 mmol) in CH_3OH (10 mL) was added dropwise over 1.5 h to a solution of compound **7** and TEA (10 mmol) in CH_3OH (10 mL) and refluxed for 20 h. The pale yellow solution was then cooled to rt and concentrated, and the residue was dissolved in 30 mL of CH_2Cl_2. The organic phase was washed with 20 mL of 5% aqueous citric acid, 20 mL of saturated aqueous $NaHCO_3$, and 20 mL of brine, and dried over Na_2SO_4.

Table 2
Reduction of diketopiperazine to piperazine[a,b,c]



15 16

S. No	Substrate	Product	Yield[b]
1	 15a	 16a	79
2	 15b	 16b	73
3	 15c	 16c	66
4	 15d	 16d	70

[a] All reactions were carried out with DKP **15** (3 mmol), $NaBH_4$ (15 mmol), I_2 (7 mmol) and THF (15 mL) for 24 h at 0 °C to reflux.
[b] Isolated yields of **16**.
[c] The products were characterized by spectroscopic data (IR, ^1H NMR, ^{13}C NMR and HRMS).

4.2.3. General procedure for preparation of diketopiperazines 13

Diketo piperazine derivatives **13** were prepared using a slightly modified reported procedure.[5a,10] (see general procedure **3** and **4**).

Preparation of L-proline methyl ester. To a suspension of L-proline **1** (10 mmol) in methanol (50 mL) was added thionyl chloride (15 mmol) dropwise at ice cold bath. This solution was allowed to warm to rt and stirred for 12 h. The solvent was evaporated under reduced pressure, to give HCl salt of L-proline methyl ester.

4.3. General procedure for reduction using sodium borohydride-iodine reagent system

An oven dried three necked reaction flask was cooled under a nitrogen atmosphere with a stirring bar. Diketopiperazine (3 mmol) was dissolved in freshly distilled THF (10 mL) and $NaBH_4$ (15 mmol) was added at 0 °C. A solution of iodine (7 mmol) in freshly distilled THF (5 mL) was added dropwise over 30 min via the side neck of the reaction flask and allowed to stir for 2 h and refluxed for 24 h. The reaction was brought to room temperature and quenched with methanol (the residue was carefully poured into the methanol containing ice cold beaker slowly) after which the solvents were evaporated. The residue obtained after evaporation, was refluxed with 5 M KOH (10 mL) for 6 h and the resultant mono protected piperazine was extracted with DCM (2 × 30 mL) and dried over anhydrous Na_2SO_4. The combined organic extract was evaporated and chromatographed on basic Al_2O_3 column using 50:50 hexane and ethyl acetate as the eluent.

4.3.1. (5a*S*,10a*S*)-Decahydrodipyrrolo[1,2-a:1′,2′-*d*]pyrazine 4

Yield: 0.363 g (73%); pale yellow liquid; $[\alpha]_D^{25}$ = +8.2 (*c* 0.27, $CHCl_3$), [lit. $[\alpha]_D^{25}$ = +12.6 (*c* 2.6, $CHCl_3$)];[8] IR (neat): 2772, 1463, 1345, 1267, 1035, 937, 880 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 2.91–2.85 (m, 2H), 2.65–2.63 (m, 4H), 2.52–2.46 (m, 4H), 1.91–1.60 (m, 8H). ^{13}C NMR (100 MHz, ppm, $CDCl_3$):61.1, 54.3, 53.1, 26.6, 21.7.

4.3.2. (*S*)-1-Benzyl-3-methylpiperazine 9a

Yield: 0.393 g (69%); pale yellow liquid; $[\alpha]_D^{25}$ = −7.3 (*c* 0.15, $CHCl_3$), [lit. $[\alpha]_D^{25}$ = −5.4 (*c* 0.51, $CHCl_3$)];[9] IR (neat): 2925, 2806, 1435, 1138, 1055, 802, 735, 699 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 7.34–7.29 (m, 5H), 3.51 (s, 2H), 2.96–2.88 (m, 2H), 2.80–2.77 (m, 2H), 2.05–1.99 (m, 2H), 1.68 (t, *J* = 10.4, 2H) 1.03 (d, *J* = 6.3, 3H). ^{13}C NMR (125 MHz, ppm,$CDCl_3$): 138.0, 129.2, 128.2, 127.0, 63.4, 61.3, 53.6, 50.5, 45.9, 20.0.

4.3.3. (*S*)-1,3-Dibenzylpiperazine 9b

Yield: 0.582 g (77%); pale yellow liquid; $[\alpha]_D^{25}$ = −1.5 (*c* 0.49, $CHCl_3$); IR (neat): 2930, 2812, 1479, 1443, 1314, 1117, 1055 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 7.35 (d, *J* = 4.3, 4H), 7.33–7.28 (m, 3H), 7.24–7.21 (m, 3H), 3.60–3.56 (m, 2H), 3.03–3.01 (m, 1H), 2.93–2.81 (m, 3H), 2.79–2.72 (m, 2H), 2.60–2.54 (m, 1H), 2.15–2.10 (m, 1H), 1.93 (t, *J* = 10.2, 1H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 138.6, 138.1, 129.2, 129.2, 128.5, 128.2, 127.0, 126.4, 63.4, 59.8, 56.3, 53.5, 45.8, 40.9.

4.3.4. (3*S*,8a*S*)-3-Phenyloctahydropyrrolo[1,2-*a*]pyrazine 14a

Yield: 0.448 g (74%); light brown liquid; $[\alpha]_D^{25}$ = +48.6 (*c* 0.14, $CHCl_3$), [lit. $[\alpha]_D^{25}$ = +50.4 (*c* 0.5, $CHCl_3$)];[5a] IR (neat): 2951, 2786, 1598, 1438, 1030, 761, 689 cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$):7.50 (d, *J* = 7.3, 2H), 7.33–7.30 (m, 2H), 7.26–7.23 (m, 1H), 3.98–3.96 (dd, *J* = 3.4, *J* = 6.4, 1H), 3.19–3.16 (dd, *J* = 3.4, *J* = 12.0, 1H), 2.94–2.88 (m, 3H), 2.70–2.68 (dd, *J* = 3.5, *J* = 11.1, 1H), 2.62–2.58 (m, 2H), 1.93–1.72 (m, 4H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 142.8, 128.2, 127.4, 127.0, 60.9, 57.1, 55.4, 54.3, 45.9, 25.5, 25.2.

4.3.5. (3*S*,8a*S*)-3-Isopropyloctahydropyrrolo[1,2-*a*]pyrazine 14b

Yield: 0.342 g (68%); light brown liquid; $[\alpha]_D^{25}$ = +6.4 (*c* 0.22, $CHCl_3$), [lit. $[\alpha]_D^{25}$ = +7.9 (*c* 1.0, $CHCl_3$)];[5a] IR (neat): 2956, 2781, 1458, 1288, 1066, 761 cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$): 2.94–2.91 (m, 1H), 2.89–2.86 (m, 1H), 2.82–2.79 (dd, *J* = 4.1, *J* = 11.0, 1H), 2.70–2.69 (dd, *J* = 7.7, *J* = 11.8, 1H), 2.33–2.29 (m, 2H), 2.27–2.22 (m, 2H), 2.14–2.09 (m, 1H), 2.05–2.01 (m, 1H), 1.82–1.77 (m, 1H), 1.71–1.60 (m, 2H), 1.49–1.43 (m, 1H), 0.91 (d, *J* = 6.7, 3H), 0.87 (d, *J* = 6.6, 3H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 62.6, 59.4, 54.5, 53.4, 45.9, 27.4, 26.5, 20.9, 20.3, 19.6.

4.4. General procedure for the preparation of amide derivatives

(*S*)-*N*-Boc amino acid **11** (20 mmol) was dissolved in CH_2Cl_2 (50 mL) at 0 °C, after which (*S*)-amino ester **18** (20 mmol) and Et_3N (20 mmol) were added, followed by 3-(ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine hydrochloride (EDC·HCl) (20 mmol). The reaction mixture was stirred for 16 h at 0 °C to room temperature then washed with 1 M citric acid (25 mL) 2 N. $NaHCO_3$ (25 mL) dried with Na_2SO_4 filtered and evaporated to dryness to give gummy type compound. The crude product was further purified by column chromatography on silica gel (100–200 mesh) using 50:50 hexane and ethyl acetate.

4.4.1. (2′*S*,4′*R*)-Methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino)-2-phenylacetyl)-4′-hydroxypyrrolidine-2′-carboxylate 19a

Yield: 2.401 g (44%); colorless liquid; $[\alpha]_D^{25}$ = +52.6 (*c* 0.16, EtOH); IR (neat): 3416, 2977, 1753, 1711, 1644, 1438, 1365, 1169, 709 cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$): 7.43–7.34 (m, 5H), 5.86 (d, *J* = 7.7, 1H), 5.42 (d, *J* = 7.6, 1H), 4.67 (t, *J* = 8.1, 1H), 4.40 (s, 1H), 3.73 (s, 3H), 3.64–3.62 (m, 1H), 3.17–3.13 (m, 1H), 2.32–2.27 (m, 1H), 1.95–1.89 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): 172.3, 169.1, 155.4, 136.4, 128.9, 128.4, 128.3, 80.0, 70.2, 58.1, 56.6, 55.1, 52.2, 37.4, 28.3.

4.4.2. (2′*S*,4′*R*)-Methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino) propanoyl)-4′-hydroxypyrrolidine-2′-carboxylate 19b

Yield: 2.476 g (38%); colorless liquid; $[\alpha]_D^{25}$ = −84.2 (*c* 0.28, EtOH); IR (neat): 3369, 2977, 2930, 1742, 1686, 1634, 1531, 1458, 1371, 1159 cm^{-1}; ^1H NMR (500 MHz, ppm, $CDCl_3$): 5.53–5.49 (m, 1H), 4.59–4.55 (m, 1H), 4.48 (s, 1H), 4.39–4.36 (m, 1H), 4.13–4.12 (m, 1H), 3.75–3.72 (m, 1H), 3.67 (s, 3H), 3.64–3.60 (m, 1H), 2.30–2.25 (m, 1H), 1.99 (s, 1H), 1.36 (s, 9H), 1.27 (d, *J* = 6.8, 3H). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): 172.5, 172.0, 155.4, 79.8, 70.0, 57.7, 54.9, 52.2, 47.8, 37.3, 28.9, 17.8.

4.4.3. (2′*S*,4′*R*)-Methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino)-3-methylbutanoyl)-4′-hydroxypyrrolidine-2′-carboxylate 19c

Yield: 2.470 g (36%); colorless liquid; $[\alpha]_D^{25}$ = −79.5 (*c* 0.28, EtOH); IR (neat): 3390, 2961, 1737, 1691, 1629, 1520, 1443, 1365, 1169, 1004, 875 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 5.37 (d, *J* = 8.7, 1H), 4.61 (t, *J* = 8.3, 1H), 4.48 (s, 1H), 4.19–4.15 (m, 1H), 3.93–3.86 (m, 2H), 3.68 (s, 3H), 2.33–2.27 (m, 3H), 2.00–1.95 (m, 2H), 1.38 (s, 9H), 1.24–1.22 (m, 1H), 0.98 (d, *J* = 6.7, 3H), 0.89 (d, *J* = 6.7, 3H). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): 172.6, 171.5, 156.2, 79.8, 69.9, 57.7, 57.0, 55.4, 52.1, 37.4, 30.9, 28.3, 19.2, 17.3.

4.4.4. (2′*S*,4′*R*)-Methyl 1′-((*S*)-2-*tert*-butoxycarbonyl)amino)-4-methylpentanoyl)-4′-hydroxypyrrolidine-2′-carboxylate 19d

Yield: 3.22 g (45%); colorless liquid; $[\alpha]_D^{25}$ = −58.3 (*c* 0.27, EtOH); IR (neat): 3344, 2961, 2868, 1753, 1701, 1649, 1520, 1427, 1365, 1179, 1092 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 5.17 (d, *J* = 8.4, 1H), 4.72–4.68 (m, 1H), 4.56 (s, 1H), 4.45–4.39 (m, 1H), 4.09 (d, *J* = 11.2, 1H), 3.75 (s, 3H), 3.69–3.67 (m, 1H), 3.07 (s, 1H), 2.41–2.36 (m, 1H), 2.05–1.98 (m, 1H), 1.812 (s, 3H), 1.43 (s, 9H), 1.00–0.96 (m, 6H). ^{13}C NMR (100 MHz, ppm, $CDCl_3$): 172.6, 172.1, 156.0, 79.8, 70.1, 57.6, 54.9, 52.2, 50.4, 41.5, 37.4, 28.3, 24.5, 23.2, 21.9.

4.5. General procedure for the preparation of diketopiperazine derivatives

A solution of amide **19** (5 mmol) in dry CH_2Cl_2 (20 mL) was treated with trifluoroacetic acid (0.4 mL) at rt for 3 h. The solvent was then evaporated and the reaction mixture was dissolved in 2-butanol:toluene (1:2 mL) followed by addition of triethylamine (5 mmol). The mixture was allowed to reflux for 16 h. After evaporation of the solvent, diketopiperazine **15** precipitated as a white solid, which was further purified by column chromatography on silica gel (100–200 mesh) using 90:10 ethyl acetate and methanol.

4.5.1. (3*S*,7*R*,8a*S*)-7-Hydroxy-3-phenylhexahydropyrrolo[1,2-*a*] pyrazine-1,4-dione 15a

Yield: 1.00 g (82%); White solid, mp 228–230 °C; $[\alpha]_D^{25}$ = −57.9 (*c* 0.1, EtOH); IR (KBr): 3321, 3240, 2925, 1665, 1634, 1433, 973, 720 cm^{-1}; ^1H NMR (500 MHz, ppm, DMSO-d_6): 8.41 (s, 1H), 7.37–7.32 (m, 2H), 7.25 (d, *J* = 7.2, 2H), 5.24 (s, 1H), 5.15 (s, 1H), 4.51–4.47 (m, 1H), 4.33 (s, 1H), 3.59–3.56 (m, 1H), 3.23 (d, *J* = 12.5, 1H), 2.50–2.49 (m, 1H), 2.14–2.10 (m, 1H), 2.02–1.97 (m, 1H). ^{13}C NMR (100 MHz, ppm, DMSO-d_6):170.2, 165.4, 137.2, 129.3, 128.4, 128.3, 67.3, 60.2, 57.6, 54.6, 37.8.; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{13}H_{14}N_2O_3$: 247.1082; found 247.1083.

4.5.2. (3*S*,7*R*,8a*S*)-7-Hydroxy-3-methylhexahydropyrrolo[1,2-*a*] pyrazine-1,4-dione 15b

Yield: 0.717 g (78%); White solid; mp 198–201 °C; $[\alpha]_D^{25}$ = −130.2 (*c* 0.09, EtOH); IR (KBr): 3380, 3235, 1675, 1639, 1422, 1283, 1097, 957, 756 cm^{-1}; ^1H NMR (400 MHz, ppm, MeOH-d_4): 4.56–4.48 (m, 1H), 4.27–4.25 (m, 1H), 3.70–3.68 (m, 1H), 3.47–3.44 (m, 1H), 3.33 (s, 1H), 2.32–2.28 (m, 1H) 2.13–2.07 (m, 1H), 1.41 (d, *J* = 6, 3H). ^{13}C NMR (125 MHz, ppm, MeOH-d_4): 171.4, 167.7, 67.7, 57.5, 53.8, 50.6, 36.8, 14.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_8H_{12}N_2O_3$: 185.0926; found 185.0925.

4.5.3. (3*S*,7*R*,8a*S*)-7-Hydroxy-3-isopropylhexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione 15c

Yield: 0.669 g (75%); White solid, mp 196–198 °C; $[\alpha]_D^{25}$ = −136.7 (*c* 0.08, EtOH); IR (KBr): 3369, 3271, 2967, 2879, 1675, 1644, 1422, 1092, 740, 601 cm^{-1}; ^1H NMR (400 MHz, ppm, MeOH-d_4): 4.52–4.48 (m, 2H), 4.10 (s, 1H), 3.76–3.72 (dd, *J* = 4.5, *J* = 12.9, 1H), 3.44 (d, *J* = 13, 1H), 2.53–2.50 (m, 1H), 2.33–2.28 (dd, *J* = 6.1, *J* = 13.1, 1H) 2.10–2.02 (m, 1H), 1.12 (d, *J* = 7.2, 3H), 0.96 (d, *J* = 6.9, 3H). ^{13}C NMR (125 MHz, ppm, MeOH-d_4):171.5, 166.2, 67.5, 60.0, 56.9, 53.8, 37.2, 28.3, 17.5, 15.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{10}H_{16}N_2O_3$: 213.1239; found 213.1237.

4.5.4. (3*S*,7*R*,8a*S*)-7-Hydroxy-3-isobutylhexahydropyrrolo[1,2-*a*] pyrazine-1,4-dione 15d

Yield: 0.847 g (91%); White solid, mp 176–178 °C; $[\alpha]_D^{25}$ = −141.8 (*c* 0.07, EtOH); IR (KBr): 3447, 3276, 2941, 1686, 1670, 1618, 1433, 1097 cm^{-1}; ^1H NMR (400 MHz, ppm, MeOH-d_4): 4.56–4.48 (m, 2H), 4.19–4.18 (m, 1H), 3.70–3.66 (m, 1H), 3.47–3.44 (m, 1H), 3.33 (s, 1H), 2.32–2.27 (m, 1H) 2.14–2.07 (m, 1H), 1.95–1.92 (m, 2H), 1.55–1.51 (m, 1H), 0.99–0.98 (m, 6H). ^{13}C NMR (125 MHz, ppm, MeOH-d_4): 171.6, 167.6, 67.7, 57.3, 53.7, 53.2, 37.9, 36.7, 24.4, 21.9, 20.8; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{18}N_2O_3$: 227.1395; found 227.1395.

4.6. General procedure for the reduction of diketopiperazine derivatives

An oven dried three necked reaction flask was cooled under nitrogen atmosphere with a stirring bar. Diketopiperazine **15** (3 mmol) was dissolved in freshly distilled THF (10 mL) and $NaBH_4$ (15 mmol) added at 0 °C. A solution of iodine (7 mmol) in freshly distilled THF (5 mL) was added dropwise over 30 min via the side neck of the reaction flask and allowed to stir for 2 h and then refluxed for 24 h. The reaction was brought to room temperature and quenched with methanol (the residue was carefully poured into the methanol containing ice cold beaker slowly) and the solvents were evaporated. The residue obtained after evaporation, was refluxed with 5 M KOH (10 mL) for 6 h and the resultant chiral piperazine **16** was extracted with DCM (2 × 30 mL) dried over anhydrous Na_2SO_4. The combined organic extract was evaporated and chromatographed on basic Al_2O_3 column using 50:50 hexane and ethyl acetate as the eluent.

4.6.1. (3*S*,7*R*,8a*S*)-3-Phenyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol 16a

Yield: 0.516 g (79%); light brown liquid,; $[\alpha]_D^{25}$ = +6.9 (*c* 0.19, EtOH); IR (neat): 3282, 2925, 2843, 1453, 1309, 1092 cm^{-1}; ^1H NMR (400 MHz, ppm, $CDCl_3$): 7.50 (d, *J* = 7.36, 2H), 7.36–7.27 (m, 3H), 4.57–4.53 (m, 1H), 4.02–3.99 (m, 1H), 3.65 (s, 1H), 3.33–3.29 (dd, *J* = 6.6, *J* = 11.2, 1H), 3.19–3.15 (dd, *J* = 3.3, *J* = 12.0, 1H), 3.06–3.02 (m, 1H), 2.93–2.88 (m, 2H), 2.84–2.80 (m, 1H), 2.63–

2.59 (dd, J = 4.6, J = 11.2, 1H), 2.17–2.13 (m, 1H), 2.03 (s, 1H), 1.76–1.71 (dd, J = 6.0, J = 13.4, 1H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 142.5, 128.3, 127.5, 127.1, 69.7, 64.1, 59.2, 56.8, 55.9, 45.6, 37.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{18}N_2O$: 219.1497; found 219.1498.

4.6.2. (3*S*,7*R*,8a*S*)-3-Methyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol 16b

Yield: 0.341 g (73%); light brown liquid; $[\alpha]_D^{25}$ = −6.6 (c 0.26, EtOH); IR (neat): 3375, 2930, 2858, 1551, 1463, 1102, 802, 673 cm^{-1}; ^{1}H NMR (400 MHz, ppm, $CDCl_3$): 4.46–4.41 (m, 1H), 3.33–3.28 (s, 3H), 3.09–3.06 (m, 1H), 2.97–2.93 (dd, J = 3.1, J = 12.3, 1H), 2.78–2.72 (m, 1H), 2.58–2.54 (dd, J = 3.5, J = 10.9, 1H), 2.46–2.39 (m, 2H), 2.21–2.17 (dd, J = 5.3, J = 10.2, 1H), 1.87–1.79 (m, 1H), 1.64–1.59 (dd, J = 5.8, J = 13.0, 1H), 1.20 (d, J = 6.7, 3H).^{13}C NMR (125 MHz, ppm, $CDCl_3$): 68.8, 64.1, 60.6, 57.3, 47.8, 44.8, 38.3, 18.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_8H_{16}N_2O$: 157.1341; found 157.1346.

4.6.3. (3*S*,7*R*,8a*S*)-3-Isopropyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol 16c

Yield: 0.364 g (66%); light brown liquid; $[\alpha]_D^{25}$ = −22.1 (c 0.10, EtOH); IR (neat): 3395, 2920, 1567, 1097, 802, 673 cm^{-1}; ^{1}H NMR (400 MHz, ppm, $CDCl_3$): 4.40–4.34 (m, 1H), 3.47 (s, 1H), 3.21–3.17 (m, 1H), 2.89–2.84 (m, 1H), 2.67–2.58 (m, 2H), 2.55–2.51 (m, 1H), 2.34–2.18 (m, 3H), 1.97–1.87 (m, 2H), 1.83–1.75 (m, 1H), 1.56–1.51 (dd, J = 5.9, J = 13.0, 1H), 0.85–0.79 (m, 6H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 68.8, 64.1, 60.0, 59.2, 53.1, 45.4, 37.9, 27.3, 20.0, 19.4; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{20}N_2O$: 185.1654; found 185.1654.

4.6.4. (3*S*,7*R*,8a*S*)-3-Isobutyloctahydropyrrolo[1,2-*a*]pyrazine-7-ol 16d

Yield: 0.415 g (70%); light brown liquid; $[\alpha]_D^{25}$ = −20.9 (c 0.11, EtOH); IR (neat): 3364, 2956, 2925, 1562, 1402, 1102, 870 cm^{-1}; ^{1}H NMR (400 MHz, ppm, $CDCl_3$): 4.41–4.36 (m, 1H), 3.49 (s, 1H), 3.27–3.22 (m, 1H), 2.92–2.88 (m, 2H), 2.67–2.62 (m, 1H), 2.57–2.53 (m, 1H), 2.46–2.37 (m, 1H), 2.19–2.15 (m, 1H), 1.98 (s, 1H), 1.82–1.73 (m, 1H), 1.61–1.48 (m, 3H), 1.33–1.28 (m, 1H), 0.86–0.83 (m, 6H). ^{13}C NMR (125 MHz, ppm, $CDCl_3$): 68.6, 64.0, 60.4, 55.8, 50.2, 44.9, 40.4, 38.3, 24.8, 22.8, 22.3; HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{22}N_2O$: 199.1810; found 199.1812.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.12.002.

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11. Diketopiperazine **15c** was characterized by X-ray crystallography. Crystal data for **15c**, was collected on a Bruker SMART APEX CCD area detector system using graphite monochromated Mo Kα radiation (l = 0.71073 Å). Data reduction was carried out with SAINTPLUS, and the structures were solved and refined with SHELXL-2014/7. All non-hydrogen atoms were refined anisotropically. Molecular formula: $C_{10}H_{16}N_2O_3$, MW = 212.25, orthorhombic, space group: $P212121$, a = 9.3814(7) Å, b = 10.2308(7) Å, c = 11.2657(8) Å, α = 90°, β = 90°, γ = 90°, v = 1081.27(13) Å^3, Z = 4, ρ_c = 1.304 Mg/m^3 μ = 0.097 mm^{81}, T = 298(2) k. Of the 10981 reflections collected, 2167 reflections were unique (R(int) = 0.0305). Refinement on all data converged at R_1 = 0.0454, wR_2 = 0.1038 (CCDC Deposition Number: CCDC 1500569).
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