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Tetrahedron: *Asymmetry* 15 (2004) 3477–3481

Highly efficient synthesis of (*R*)- and (*S*)-piperazic acids using proline-catalyzed asymmetric α-hydrazination

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Received 16 September 2004; accepted 30 September 2004

Abstract—The highly efficient synthesis of (*R*)- and (*S*)-piperazic acids, components of naturally occurring antibiotic cyclodepsipeptides, was achieved in 80% overall yield by the use of a proline-catalyzed asymmetric α-hydrazination as the key step.

1. Introduction

Piperazic acids (*R*)- and (*S*)-**1**, cyclic α-hydrazino acids, are not only components of several naturally occurring cyclodepsipeptides[1,2] with remarkable biological activities, but also useful synthetic intermediates in the preparation of medicinally important compounds, such as enzyme inhibitors.[3] To construct polyoxypeptins and GE3,[4] cyclodepsipeptides containing piperazic acids, in the quantities required for biological evaluation, we needed to produce multigram amounts of (*R*)- and (*S*)-piperazic acids. Several approaches have been reported so far,[5] although these methods require multi steps and/or expensive chiral auxiliaries, none of which are practical for large-scale production. Recent reports on proline-catalyzed asymmetric synthesis have disclosed that the selectivities of >90% ee are obtained in numerous aldol reactions, Mannich reactions, and α-oxidations.[6,7] In particular, we were quite interested in List's method,[8] which can be used for enantioselective α-hydrazination of aldehydes in high enantiomeric excess and yield. Herein we report a highly efficient synthesis of (*R*)- and (*S*)-piperazic acids using the proline-catalyzed asymmetric α-hydrazination as a key step (Fig. 1).

(*R*)-Piperazic acid **(*R*)-1** (*S*)-Piperazic acid **(*S*)-1**

Figure 1.

2. Results and discussion

The synthesis was commenced with optimization of the proline-catalyzed asymmetric α-hydrazination as shown in Table 1. The required bromoaldehyde **2** was prepared from commercially available pentane-1,5-diol in two steps according to the literature.[9] First, the reaction was carried out by the use of **2** and dibenzyl azodicarboxylate **3** in the presence of a catalytic amount of (*S*)-proline in acetonitrile at 0–23 °C for 8 h (entries 1 and 2). Since the resulting product was configurationally unstable, the enantiomeric excess was determined after reduction of the aldehyde with sodium borohydride in ethanol by the chiral HPLC analysis of the resulting alcohol. The enantiomeric excess was 85–87% but was still unsatisfactory. This problem was solved by maintaining the temperature at 0 °C. Finally, the reaction using a slight excess of aldehyde at 0 °C for 15 h was found to proceed in 92% yield and >99% enantiomeric excess. The absolute stereochemistry of the resulting **4a** was established to be of an (*R*)-configuration by its conversion to the final

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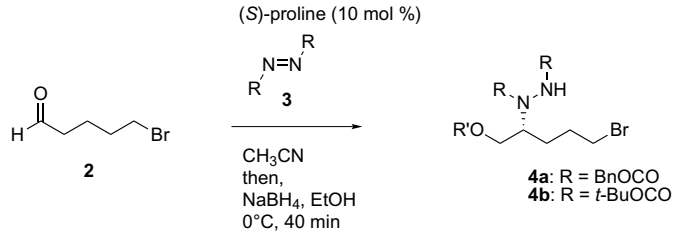
doi:10.1016/j.tetasy.2004.09.025

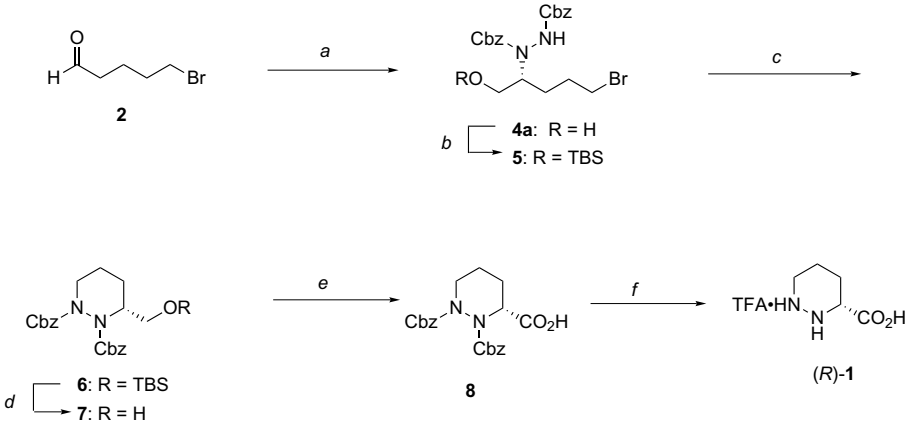
Table 1. Asymmetric α-hydrazination using (*S*)-proline



Entry	Aldehyde (equiv)	Azocarboxylate (R)	Conditions	Yield (%)[a]	% Ee[b]
1	1	BnOCO	0–23 °C, 8 h	43	87
2	1.48	BnOCO	0–23 °C, 8 h	83	85
3	1.51	BnOCO	0 °C, 15 h	92	>99
4[c]	1.50	BnOCO	0 °C, 15 h	91	>99
5	1.50	*t*-BuOCO	0 °C, 28 h	53	80[d]

[a] Isolated yields.
[b] Determined by HPLC analysis using CHIRALCEL OD-H.
[c] Large scale experiment (55.6 mmol scale).
[d] Determined as the *O*-benzoyl derivative.

piperazic acid trifluoroacetate and comparisons of the spectral and physical values with the literature values. For a demonstration of the reaction in large-scale synthesis, the reaction in a 55.6 mmol (16.1 g) of dibenzyl azodicarboxylate was performed with almost the same result as in the case of entry 3 being obtained (entry 4). In the case of di-*tert*-butyl azodicarboxylate, the efficiency of the reaction was found to decrease to 53% yield and 80% ee. With a generous amount of the key hydrazino alcohol **4a** in hand, we carried out the synthesis of (*R*)- and (*S*)-piperazic acids as summarized in Scheme 1. Alcohol (*R*)-**4a** was first protected with *tert*-butylchlorodimethylsilane (TBSCl) and imidazole because of failing the direct cyclization of (*R*)-**4a** with sodium hydride. Treatment of silyl protected (*R*)-**5** with sodium hydride in dimethylformamide at 0 °C for 40 min, however, produced tetrahydropyridazine (*R*)-**6** in 97% yield (two steps). Deprotection of (*R*)-**6** with tetra-*n*-butylammonium fluoride (TBAF) and oxidation of the resulting alcohol with sodium hypochlorite–sodium chlorite in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[10] in acetonitrile–phosphate buffer (pH 6.8) afforded di-Cbz-piperazic acid (*R*)-**8** in 90% yield (two steps). Careful examination about a loss of the stereointegrity during the oxidation revealed that the reaction proceeded with little to no racemization.[11] Final deprotection of (*R*)-**8** in the presence of trifluoroacetic acid in methylene chloride furnished piperazic acid trifluoroacetate (*R*)-**1** in quantitative yield. Interestingly, the use of methanol, a common solvent in hydrogenolysis, instead of methylene chloride in the hydrogenolysis unexpectedly yielded the aromatized product. The stereointegrity of (*R*)-**1** was unambiguously confirmed after its conversion to the DNP derivative by chiral HPLC analysis.[12] (*S*)-Piperazic acid (*S*)-**1** was also obtained by use of (*R*)- instead of (*S*)-proline in similar efficiency through the same reaction sequence.



Scheme 1. Synthesis of (*R*)-piperazic acid. Reagents and conditions: (a) dibenzyl azodicarboxylate **3** (1.51 equiv), 5-bromopentanal **2**, (*S*)-proline (10 mol%), acetonitrile, 0 °C, 15 h, then sodium borohydride, ethanol, 0 °C, 40 min, 91% yield (two steps in one-pot reaction), >99% ee; (b) TBSCl, imidazole, DMF, 23 °C, 3.5 h, 100% yield; (c) sodium hydride, DMF, 0 °C, 40 min, 97% yield; (d) TBAF, THF, 0 °C, 40 min, 100% yield; (e) TEMPO, $NaClO$–$NaClO_2$, acetonitrile, phosphate buffer (pH 6.8), 23 °C, 4 h, 90% yield; (f) hydrogen, 5% Pd–C, trifluoroacetic acid, methylene chloride, 23 °C, 12 h, 100% yield.

3. Conclusion

We have succeeded in the development of a highly efficient method for the synthesis of (*R*)- and (*S*)-piperazic acids from readily available bromoaldehyde **2** in 80% overall yield and six steps using the proline-catalyzed asymmetric α-hydrazination as a key step. The described method is noteworthy because most of the synthetic steps proceed in greater than 90% yield and will promote the use of piperazic acids to medicinal chemistry due to its simplicity and cost-effectiveness.

4. Experimental

4.1. General

Melting points were measured with a SHIBATA NEL-270 melting point apparatus. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical resolutions were determined on a JASCO DIP-140 and JASCO P-1020 polarimeter. Column chromatography was carried out with silica gel BW-820MH (Fuji silysia). Analytical thin layer chromatography was performed on Merck Kieselgel 60F254 0.25 mm thickness plates.

4.2. (*R*)-5-Bromo-2-*N*,*N*′-dibenzyloxycarbonyhydrazino-1-pentanol (*R*)-4a

To a stirred solution of 5-bromopentanal (13.8 g, 83.3 mmol) and dibenzyl azodicarboxylate (16.1 g, 55.6 mmol) in CH_3CN (400 mL) at 0 °C was added (*S*)-proline (638 mg, 5.54 mmol, 10 mol%). After stirring the mixture at 0 °C for 15 h, ethanol (160 mL) and $NaBH_4$ (1.70 g, 45.0 mmol) was added, and the mixture was stirred at 0 °C for 40 min. The reaction was quenched by slow addition of 10% aqueous citric acid and the whole solution concentrated in vacuo. This residue was diluted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo to give the title compound as colorless solids (>99% ee[†] judged by the chiral HPLC analysis). The crude material was purified by recrystallization from ethyl acetate/hexane to give pure **4a** (23.5 g, 50.4 mmol, 91%) as colorless solids: mp 94.0–95.5 °C; $[\alpha]_D^{22} = -10.7$ (*c* 1.04, $CHCl_3$); IR 3244, 3037, 1720, 1682, 1543, 1431 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 1.41–1.45 (m, 1H), 1.54 (br s, 1H), 1.82 (br s, 1H), 1.97 (br s, 1H), 3.29–3.34 (m, 2H), 3.41–3.46 (m, 2H), 4.09 (br s, 1H), 5.10 (br s, 4H), 7.32 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{26}BrN_2O_5$: 465.1025 ($M+H^+$). Found: 465.0979. Anal. Calcd for $C_{21}H_{25}BrN_2O_5$: C, 54.20; H, 5.42; N, 6.02. Found: C, 54.27; H, 5.45; N, 5.95.

4.3. (*S*)-5-Bromo-2-*N*,*N*′-dibenzyloxycarbonyhydrazino-1-pentanol (*S*)-4a

Prepared according to the procedure described above for (*R*)-**4a** in 100% yield: mp 95.0–96.0 °C (ethyl acetate/hexane); $[\alpha]_D^{22} = +12.4$ (*c* 1.03, $CHCl_3$); IR (neat) 3265, 3032, 2952, 1712, 1408, 1332, 1266, 1216, 1057, 743 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 1.40–1.49 (m, 1H), 1.56 (br s, 1H), 1.78–1.87 (m, 1H), 1.98 (br s, 1H), 3.31–3.51 (br s, 4H), 4.11 (br s, 1H), 4.72 (br s, 1H), 5.11 (br s, 4H), 7,33 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{26}BrN_2O_5$: 465.1025 ($M+H^+$). Found: 465.1015.

4.4. (*R*)-5-Bromo-2-*N*,*N*′-di-*tert*-butylcarbonyhydrazino-1-pentanol (*R*)-4b

A solution of 5-bromopentanal (840 mg, 5.09 mmol), di-*tert*-butyl azodicarboxylate (781 mg, 3.39 mmol), and (*S*)-proline (39.0 mg, 0.339 mmol) in CH_3CN (35 mL) was stirred at 0 °C for 28 h. Ethanol (35 mL) and $NaBH_4$ (135 mg, 3.55 mmol) were added at 0 °C and the mixture stirred at the same temperature. After 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was extracted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 2:l) to give **4b**, (715 mg, 53%, 80% ee, $[\alpha]_D^{23} = -8.0$ (*c* 1.00, $CHCl_3$)) as white solids. The enantiomeric excess was determined by chiral HPLC analysis of the benzoyl derivative of **4b** (Daicel Chiralcel OD-H, flow rate 1.0 mL/min, hexane/*i*-PrOH = 99:1, retention time: major 12.9 min, minor 9.9 min). The analytic sample of **4b** was obtained by recrystallization from ethyl acetate/hexane as colorless needles: mp 106–108 °C; $[\alpha]_D^{24} = -8.1$ (*c* 1.00, $CHCl_3$); IR (KBr) 3320, 3161, 2979, 1685, 1542, 1458, 1397, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 328 K) δ 1.30–1.90 (m, 4H), 1.40–1.60 (m, 18H), 3.35–3.57 (m, 3H), 4.25 (m, 1H), 6.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 328 K) δ 26.7, 28.1, 28.2, 29.4, 62.4, 81.4, 155.7. HRMS (FAB, NBA) calcd for $C_{15}H_{30}BrN_2O_5$: 397.1338 ($M+H^+$). Found: 397.1313.

4.5. (*R*)-2-(*N*,*N*′-Dibenzyloxycarbonylhydrazino)-5-bromo-1-(*tert*-butyldimethylsiloxy)pentane (*R*)-5

To a stirred solution of alcohol (*R*)-**4a** (121 mg, 0.260 mmol) and imidazole (91.1 mg, 1.34 mmol) in DMF (3 mL) at 23 °C was added TBSCl (45.2 mg, 0.300 mmol) and the mixture stirred for 3.5 h. The reaction mixture was diluted with hexane/ethyl acetate, washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 10:1) to give protected alcohol (*R*)-**5** (150 mg, 0.259 mmol, 100%) as colorless solids: mp 87 °C; $[\alpha]_D^{22} = +12.3$ (*c* 0.95, MeOH); IR (neat) 3291,

[†] Enantiomeric excess was determined by HPLC using CHIRALCEL OD-H (hexane/*i*-PrOH = 90/10 contained 0.1% TFA, flow rate 0.6 mL/min), retention time: 39.9 min for (*R*) and 34.8 min for (*S*).

3033, 2953, 2927, 2856, 1758, 1716, 1455, 1408, 1256, 1217, 1109, 836, 776 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 0.00 (s, 6H), 0.84 (s, 9H), 1.47–1.52 (m, 1H), 1.71 (br s, 2H), 1.89 (br s, 1H), 3.41–3.53 (m, 3H), 3.68 (dd, 1H, J = 5.6, 10.0 Hz), 4.03 (br s, 1H), 5.07 (s, 2H), 5.08 (s, 2H), 7.26–7.34 (m, 10H). HRMS (FAB, NBA) calcd for $C_{27}H_{40}BrN_2O_5Si$: 579.1890 ($M+H^+$). Found: 579.1873. Anal. Calcd for $C_{27}H_{38}N_2O_5Si$: C, 65.03; H, 7.68; N, 5.62. Found: C, 64.73; H, 7.63; N, 5.59.

4.6. (*S*)-2-(*N*,*N*′-Dibenzyloxycarbonylhydrazino)-5-bromo-1-(*tert*-butyldimethylsiloxy)pentane (*S*)-5

Prepared according to the procedure described above for (*R*)-**5** in 82% yield: mp 86 °C (ethyl acetate/hexane); $[\alpha]_D^{23} = -12.2$ (*c* 1.13, MeOH); IR (neat) 3288, 2953, 2927, 2883, 2856, 1720, 1497, 1454, 1255, 1218, 1110, 837, 777 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 0.02 (s, 6H), 0.86 (s, 9H), 1.50–1.57 (m, 1H), 1.73–2.49 (br s, 3H), 3.41–3.55 (br s, 3H), 3.69–3.73 (dd, 1H, J = 5.6, 10.0 Hz), 4.07 (br s, 1H), 5.09 (br s, 4H), 7.30–7.35 (m, 10H). HRMS (FAB, NBA) calcd for $C_{27}H_{40}BrN_2O_5Si$: 579.1890 ($M+H^+$). Found: 579.1873. Anal. Calcd for $C_{27}H_{38}N_2O_5Si$: C, 65.03; H, 7.68; N, 5.62. Found: C, 64.77; H, 7.58; N, 5.58.

4.7. (*R*)-1,2-Dibenzyloxycarbonyl-3-(*tert*-butyldimethylsiloxymethyl)tetrahydropyridazine (*R*)-6

To a stirred solution of (*R*)-**5** (12.0 g, 20.7 mmol) in DMF (100 mL) at 0 °C was added a suspension of sodium hydride (60%, 1.78 g, 37.0 mmol) in DMF (30 mL). After stirring the mixture at 0 °C for 40 min, the reaction mixture was quenched with 10% citric acid, and extracted with hexane/ethyl acetate. The combined extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 10:1) to give (*R*)-**6** (10.0 g, 20.1 mmol, 97%) as a colorless oil: $[\alpha]_D^{23} = +17.5$ (*c* 1.10, $CHCl_3$); IR (neat) 2952, 2928, 2883, 2856, 1709, 1456, 1413, 1299, 1256, 1085, 837 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ −0.02 (s, 6H), 0.83 (s, 9H), 1.44–1.48 (m, 1H), 1.62–1,77 (m, 3H), 3.04 (br s, 1H), 3.54 (dd, 1H, J = 8.4, 10.0 Hz), 3.67–3.71 (m, 1H), 3.93–3.98 (m, 1H), 4.18–4.21 (m, 1H), 5.04–5.15 (m, 4H), 7.30 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{27}H_{39}N_2O_5Si$: 499.2628 ($M+H^+$). Found: 499.2617.

4.8. (*S*)-1,2-Dibenzyloxycarbonyl-3-(*tert*-butyldimethylsiloxymethyl)tetrahydropyridazine (*S*)-6

Prepared according to the procedure described above for (*R*)-**6** in 90% yield: $[\alpha]_D^{23} = -16.7$ (*c* 1.16 $CHCl_3$); IR (neat) 2953, 2928, 2883, 2856, 1709, 1455, 1414, 1360, 1299, 1255, 1196, 1085, 837, 777, 752, 696 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ −0.01 (s, 6H), 0.84 (s, 9H), 1.45–1.49 (m, 1H), 1.63–1.77 (m, 3H), 3.06 (br s, 1H), 3.56 (dd, 1H, J = 8.4, 10.0 Hz), 3.68–3.72 (m, 1H), 3.95–3.99 (m, 1H), 4.21 (br s, 1H), 5.05–5.17 (m, 4H), 7.31 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{27}H_{39}N_2O_5Si$: 499.2628 ($M+H^+$). Found: 499.2658.

4.9. (*R*)-1,2-Dibenzyloxycarbonyl-3-hydroxymethyltetrahydropyridazine (*R*)-7

To a stirred solution of (*R*)-**6** (1.65 g, 3.30 mmol) in THF (20.0 mL) at 0 °C was added 0.5 M TBAF (8.0 mL, 4.00 mmol). After stirring the mixture at 0 °C for 40 min, the reaction was quenched with saturated brine, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 2:1 to 1:1) to give alcohol (*R*)-**7** (1.27 g, 100%) as a colorless oil: $[\alpha]_D^{23} = -11.0$ (*c* 1.48, $CHCl_3$); IR (neat) 3481, 2948, 2874, 1708, 1455, 1414, 1261, 1070, 753 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 1.41–1.46 (m, 1H), 1.66–1.76 (br s, 2 + 1H), 3.04 (br s, 1H), 3.37–3.43 (m, 1H), 3.51–3.56 (m, 1H), 3.95 (br s, 1H), 4.20 (br s, 1H), 5.12 (br s, 4H), 7.30 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{25}N_2O_5$: 385.1763. Found: 385.1748.

4.10. (*S*)-1,2-Dibenzyloxycarbonyl-3-hydroxymethyltetrahydropyridazine (*S*)-7

Prepared according to the procedure described above for (*R*)-**7** in 97% yield: $[\alpha]_D^{22} = +12.6$ (*c* 1.03 $CHCl_3$); IR (neat) 3471, 2948, 2975, 1708, 1453, 1413, 1359, 1321, 1262, 1217, 1145, 1071, 1029, 753 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO, 373 K) δ 1.42–1.47 (m, 1H), 1.65–1.78 (br s, 3H), 3.02 (br s, 1H), 3.41–3.45 (m, 1H), 3.53–3.59 (m, 1H), 3.96–4.00 (m, 1H), 4.22 (br s, 1H), 5.14 (br s, 4H), 7.32 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{25}N_2O_5$: 385.1763 ($M+H^+$). Found: 385.1737.

4.11. (*R*)-1,2-Dibenzyloxycarbonylpiperazic acid (*R*)-8

To a stirred solution of alcohol (*R*)-**7** (1.53 g, 3.99 mmol), TEMPO (97.7 mg, 0.63 mmol), and $NaClO_2$ (726 mg, 8.02 mmol) in CH_3CN (20 mL) and phosphate buffer (pH 6.8, 20 mL) at 23 °C was added 1.6 M NaClO (500 μL). After stirring the mixture at room temperature for 4 h, 1 M NaOH (10 mL) was added, and the mixture added to 1 M aqueous sodium sulfite (30 mL). The mixture was acidified with 1 M aqueous potassium hydrogen sulfate and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–ethyl acetate = 1:1) to give (*R*)-**8** (1.43 g, 3.59 mmol, 90%) as a colorless oil: $[\alpha]_D^{23} = +20.0$ (*c* 0.975, $CHCl_3$); IR (neat) 3178, 3033, 2955, 1716, 1456, 1418, 1360, 1254, 1192, 1130, 1088, 1052, 959, 913, 752, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 328 K) δ 1.59 (br s, 1H), 1.59–1.90 (br s, 2H), 2.17 (br s, 1H), 2.98–3.16 (br s, 1H), 4.02–4.16 (br s, 1H), 5.00 (br s, 1H), 5.21 (br s, 4H), 7.32 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{23}N_2O_6$: 399.1556 ($M+H^+$). Found: 399.1523.

4.12. (*S*)-1,2-Dibenzyloxycarbonylpiperazic acid (*S*)-8

Prepared according to the procedure described above for (*R*)-**8** in 91% yield: $[\alpha]_D^{23} = -19.6$ (*c* 1.04 $CHCl_3$); IR (neat) 3160, 3033, 2954, 1711, 1421, 1358, 1305, 1253, 1191, 1129, 1088, 1051, 752, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 328 K) δ 1.59 (br s, 1H), 1.71–2.02 (br s, 3H), 2.20 (br s, 1H), 2.98–3.16 (br s, 1H), 3.99–4.14 (br s, 1H), 4.99 (br s, 1H), 5.11–5.28 (br s, 4H), 7.33 (br s, 10H). HRMS (FAB, NBA) calcd for $C_{21}H_{23}N_2O_6$: 399.1556 ($M+H^+$). Found: 399.1531.

4.13. (*R*)-Piperazic acid trifluoroacetic acid salt (*R*)-1

A suspension of (*R*)-**8** (3.70 g, 9.29 mmol), trifluoroacetic acid (7.0 mL, 90.9 mmol), and 5% Pd–C (346.5 mg) in methylene chloride (50 mL) was stirred under hydrogen atmosphere at 23 °C for 12 h. Methanol (50 mL) was added and the mixture filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue purified by recrystallization from ethyl acetate/ethanol to give trifluoroacetic acid salt (*R*)-**1** (2.26 g, 100%) as colorless solids: mp 149–151 °C (lit.[11] mp 147–149 °C); $[\alpha]_D^{22} = -10.5$ (*c* 0.96, MeOH); IR (KBr) 3292, 3080, 2967, 2922, 2835, 2760, 1720, 1664, 1589, 1518, 1421, 1232, 1198, 1130, 1104, 1083, 916, 842, 801, 725 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.78–1.97 (m, 3H), 2.15–2.20 (m, 1H), 3.17–3.23 (m, 1H), 3.29–3.34 (m, 1H), 3.91–3.94 (m, IH); ^{13}C NMR (100 MHz, d_6-DMSO) δ 20.24, 24.92, 43.99, 55.88, 117.12 (q, $J = 297.8$ Hz), 158.49 (q, $J = 31.3$ Hz), 171.52. Anal. Calcd for $C_7H_{11}F_3N_2O_4$: C, 34.43; H, 4.54; N, 11.47. Found: C, 34.38; H, 4.57; N, 11.42.

4.14. (*S*)-Piperazic acid trifluoroacetic acid salt (*S*)-1

Prepared according to the procedure described above for (*R*)-**1** in 99% yield: mp 149–151 ° (ethyl acetate/ethanol); $[\alpha]_D^{22} = +11.1$ (*c* 0.98 MeOH); IR (KBr) 3292, 3080, 2967, 2922, 2836, 2760, 1720, 1664, 1589, 1509, 1421, 1232, 1198, 1183, 1130, 1082, 916, 842, 801, 725 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.85–1.95 (m, 3H), 2.13–2.18 (m, 1H), 3.14–3.21 (m, 1H), 3.27 (m, 1H), 3.89 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 20.22, 24.91, 43.99, 55.86, 117.12 (q, $J = 297.8$ Hz), 158.47 (q, $J = 31.3$ Hz), 171.52. Anal. Calcd for $C_7H_{11}F_3N_2O_4$: C, 34.43; H, 4.54; N, 11.47. Found : C, 34.32; H, 4.46; N, 11.38.

Acknowledgements

This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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