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USE OF DIKETOPIPERAZINES FOR DETERMINING ABSOLUTE CONFIGURATIONS OF α-SUBSTITUTED SERINES BY ^{1}H-NMR SPECTROSCOPY

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Abstract – A chiral α-substituted serine of interest was transformed into both of the corresponding diastereomers of diketopiperazines utilizing L- and D-phenylalanine methyl ester hydrochloride. The absolute configuration of the original chiral α-substituted serine was determined by ^{1}H-NMR analyses of the resulting diastereomers.

INTRODUCTION

Since non-proteinogenic α-substituted serine moieties were identified as key structures in various biologically active compounds, such as myriocin (ISP-I, thermozymocidin),[1] sphingofungin E,[2] (+)-conagenin,[3] and (+)-lactacystin,[4] interest in developing novel synthetic methods for α-substituted serines has intensified (Figure 1). Within this area, we developed several non-enzymatic and enzymatic asymmetric syntheses of α-substituted serines.[5] However, the absolute configurations of some of these α-substituted serines could not be determined because of the difficulty of chemically converting them into known compounds. Accordingly, we examined the ^{1}H-NMR spectroscopic behavior of both diastereomers of diketopiperazines obtained by the condensation of a chiral α-substituted *N*-Cbz-serine with L- and D-phenylalanine methyl ester hydrochloride. In this paper, we determine the absolute configurations of α-substituted serines utilizing ^{1}H-NMR spectra of the structurally correlated chiral diketopiperazines.

† Dedicated to the memory of the late Professor John W. Daly.

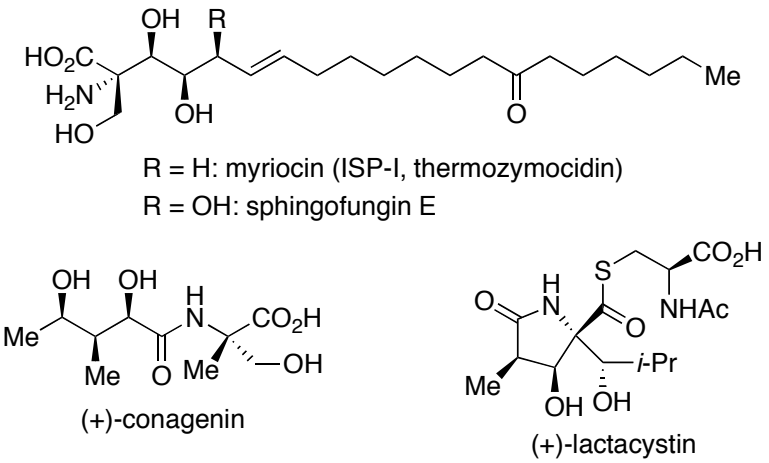
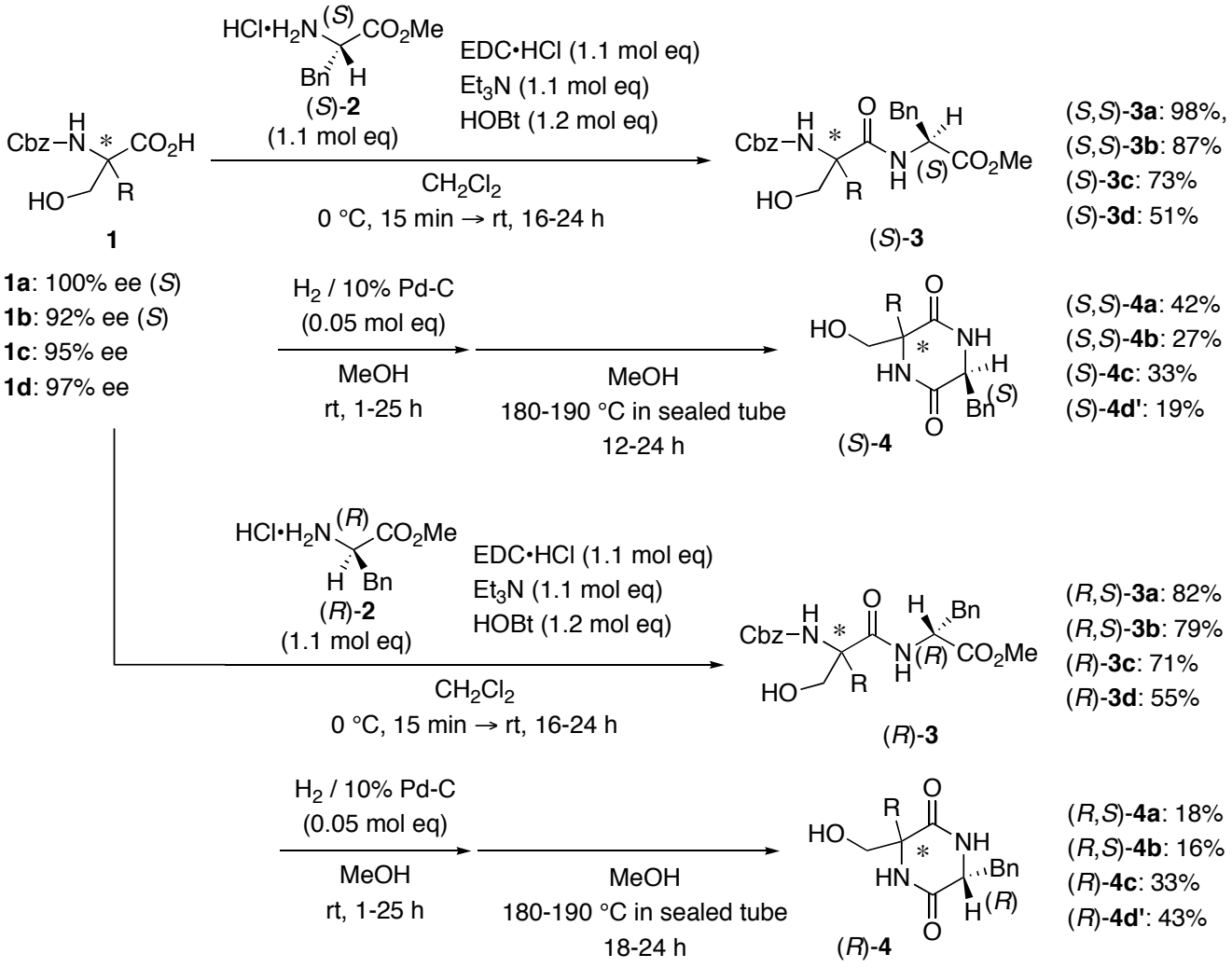


Figure 1. Bioactive natural products including an α-substituted serine moiety



a: R = Bn, **b**: R = Me, **c**: R = *n*-hexyl, **d**: R = allyl, **d'**: *n*-Pr

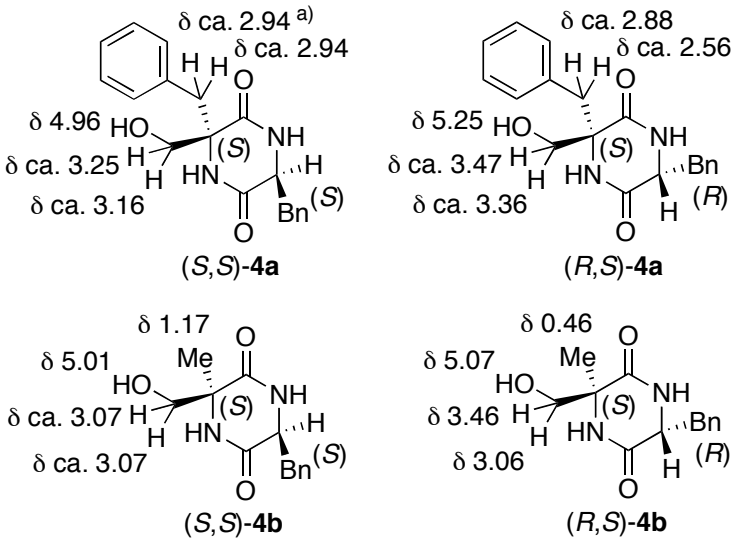
Scheme 1. Synthesis of the optically active diketopiperazines from α-substituted *N*-Cbz-serines **1a**-**d**

RESULTS AND DISCUSSION

Condensation of the optically active α-substituted *N*-Cbz-serines **1a**-**d** with L- and D-phenylalanine methyl ester hydrochloride [(*S*)- and (*R*)-**2**] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl)—1-hydroxybenzotriazole (HOBt) as coupling reagents afforded the diastereomers of dipeptides **3a**-**d** in 51-98% yields. Subsequent catalytic hydrogenolysis of **3a**-**d** with Pd-C under hydrogen at rt, followed by heating in a sealed tube at 180-190 °C, furnished both diastereomers of diketopiperazines **4a**-**c**,**d'** in 16-43% yields without any isomerization (Scheme 1). The descriptors (*S*,*S*)- or (*R*,*S*)- were employed for **3a**,**b** and **4a**,**b**, since the absolute configuration of **1a**,**b** was already determined to be *S* by their structural correlation to the known chiral compounds.[5]

Figure 2 shows selected data on the chemical shifts in the ^{1}H-NMR (400 MHz, DMSO-d_6) spectra of diketopiperazines (*S*,*S*)- and (*R*,*S*)-**4a**,**b** derived from (*S*)-α-substituted *N*-Cbz-serines (*S*)-**1a**,**b**. In the case of (*S*,*S*)-**4a**,**b**, the CH_2 and OH protons of the hydroxymethyl group appeared at a higher magnetic field than the corresponding protons of (*R*,*S*)-**4a**,**b** due to the shielding effect of the benzyl group originated from L-phenylalanine. That is to say, the benzyl group and the hydroxy group of (*S*,*S*)-**4a**,**b** are in a *cis* relationship to the plane of the diketopiperazine ring. As a result, the chemical shift difference in ppm ($\Delta\delta^{SR}$) of the **4a**,**b** hydroxy group showed large negative values. On the other hand, the CH_2 protons of the benzyl group (originated from the α-benzylserine moiety) of (*R*,*S*)-**4a** and the CH_3 protons of the methyl group of (*R*,*S*)-**4b** were observed at a higher magnetic field than that of (*S*,*S*)-**4a**,**b**, for the same reason. Based on the unambiguous spectroscopic results described above, we propose a plausible method (the DKP method) for determining the absolute configuration of α-substituted serines. Thus, an upfield shift of the CH_2 and OH protons of the hydroxymethyl group of a diketopiperazine furnished from chiral α-substituted serine and L-phenylalanine methyl ester hydrochloride [(*S*)-2] suggests that the absolute configuration of the α-substituted serine is *S*. Whereas, an upfield shift of the protons (CH_3, CH_2, or CH) of the R group should be observed in the diketopiperazine obtained from the (*S*)-α-substituted serine with D-phenylalanine methyl ester hydrochloride [(*R*)-2].

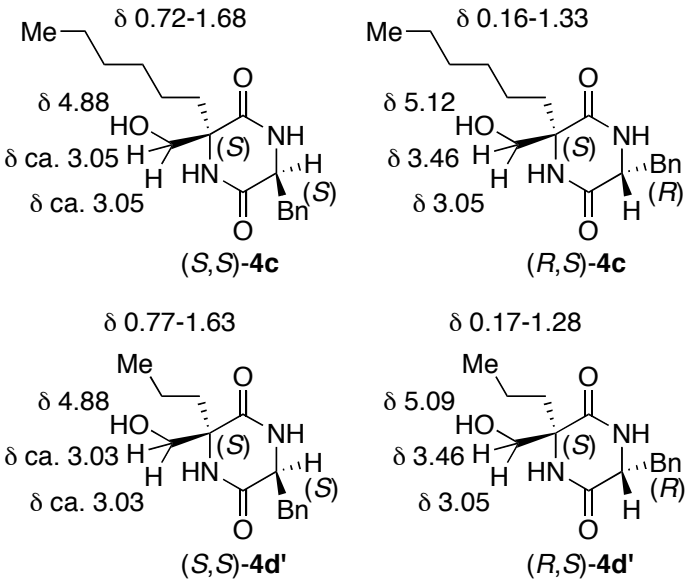
Next, we attempted to determine the absolute configuration of *N*-Cbz-α-*n*-hexylserine **1c** and *N*-Cbz-α-allylserine **1d** by the DKP method. Chemical shifts in the ^{1}H-NMR spectra of diketopiperazine **4c**,**d'** derived from **1c**,**d** are shown in Figure 3. The CH_2 and OH protons of the hydroxymethyl group of (*S*)-**4c**,**d'** were distinctly apparent at a higher magnetic field. An upfield shift of the protons (CH_3 or CH_2) of the R group were also observed in the ^{1}H-NMR spectra of diketopiperazine (*R*)-**4c**,**d'**. As a result, the absolute configuration of diketopiperazines **4c**,**d'** was found to be *S*,*S* or *R*,*S*, similar to those of **4a**,**b**. Consequently, the absolute configuration of **1c**,**d** was determined to be *S* based on the DKP method.



	$\Delta\delta^{SR}$ b)
4a	ca. –0.22 (CH_2OH) ca. –0.20 (CH_2OH) –0.29 (CH_2OH) ca. +0.06 (CH_2Ph) ca. +0.29 (CH_2Ph)
4b	ca. –0.39 (CH_2OH) ca. +0.01 (CH_2OH) –0.06 (CH_2OH) +0.71 (Me)

a) In the case where a signal's chemical shift was difficult to measure exactly due to overlap with other signals, the middle point was used as the chemical shift.
b) The $\Delta\delta^{SR}$ values are defined as $\delta(S) - \delta(R)$, where $\delta(S)$ and $\delta(R)$ are the chemical shifts of the corresponding protons in the L- and D-phenylalanine derivatives, respectively.

Figure 2. ^{1}H-NMR (400 MHz, DMSO-d_6) analysis of the diketopiperazines **4a**,**b**



	$\Delta\delta^{SR}$ b)
4c	ca. –0.41 (CH_2OH) 0 (CH_2OH) –0.23 (CH_2OH) +0.02 ($CH_2CH_2CH_2CH_2CH_2Me$)
4d'	ca. –0.43 (CH_2OH) ca. –0.02 (CH_2OH) –0.21 (CH_2OH) +0.34 (CH_2CH_2Me)

a) In the case where a signal's chemical shift was difficult to measure exactly due to overlap with other signals, the middle point was used as the chemical shift.
b) The $\Delta\delta^{SR}$ values are defined as $\delta(S) - \delta(R)$, where $\delta(S)$ and $\delta(R)$ are the chemical shifts of the corresponding protons in the L- and D-phenylalanine derivatives, respectively.

Figure 3. ^{1}H-NMR (400 MHz, DMSO-d_6) analysis of the diketopiperazines **4c**,**d'**

Compared to the conventional methods for determining the absolute configurations of chiral compounds by ^{1}H-NMR spectroscopy, such as the modified Mosher's method,[6] extremely large differences in chemical shifts ($\Delta\delta^{SR}$ values) were observed with the DKP method, as shown in Figures 2 and 3. For the most part, $\Delta\delta^{SR}$ values of more than 0.2 ppm were obtained in diketopiperazines **4a**-**c**,**d'** derived form chiral α-substituted *N*-Cbz-serines **1a**-**d**. In particular, the largest $\Delta\delta^{SR}$ value (0.71 ppm) was obtained in the case of α-methyl serine derivative **4b**. These results are attributed to the strong shielding effect of the benzyl group came from L- and D-phenylalanine methyl ester hydrochloride [(*S*)- and (*R*)-**2**]. The diketopiperazine probably adopts a folded conformation, as shown in Figure 4.[7] Needless to say, opposite signs of $\Delta\delta^{SR}$ values were obtained by the distinct differentiation of side chains of diketopiperazines, depending on the locations of their protons relative to the ring plane. The novel DKP method is expected to be further applicable for determining the absolute configurations of various α-amino acid derivatives.

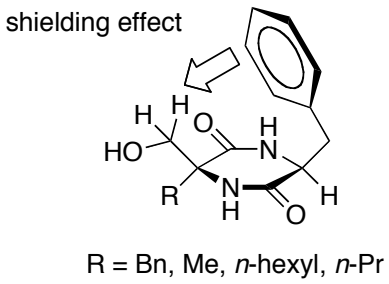


Figure 4. Folded conformation of diketopiperazines with benzyl group

In conclusion, the absolute configurations of the optically active α-substituted *N*-Cbz-serines **1a**-**d** have been successfully determined by ^{1}H-NMR analyses of both of the corresponding diastereomers of diketopiperazines **4a**-**c**,**d'** derived from L- and D-phenylalanine methyl ester hydrochloride [(*S*)- and (*R*)-**2**]. Further studies are under way to evaluate the practicality, efficacy, and accuracy of this novel DKP method for determining the absolute configuration of various α-amino acids.

EXPERIMENTAL

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-420 IR Fourier transform spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 or 75 MHz) spectra were recorded on JEOL JNM-AL400 and JEOL JNM-AL300 spectrometers, respectively. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization mass spectra (ESIMS) were

recorded on a Waters LCT Premier spectrometer. All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63-210 μm]. Anhydrous CH_2Cl_2 was commercially obtained from Kanto Chemical. Triethylamine was distilled prior to use. All other reagents were used as purchased.

Typical Procedure for Preparation of Dipeptides 3

To a solution of **1a** (36 mg, 0.109 mmol), triethylamine (17 μL, 0.120 mmol), and (*S*)-**2** (26 mg, 0.120 mmol) in anhydrous CH_2Cl_2 (3 mL) were added HOBt (18 mg, 0.131 mmol) and EDC•HCl (23 mg, 0.120 mmol) at 0 °C under argon. After being stirred at 0 °C for 15 min, the reaction mixture was allowed to warm to rt and then was stirred for 16 h. The reaction mixture was treated with 1 N HCl (2 mL) and then extracted with $CHCl_3$ (5 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography [*n*-hexane—AcOEt (1:1)] to afford (*S*,*S*)-**3a** (53 mg, 98%) as a white solid.

Typical Procedure for Preparation of Diketopiperazine 4

The mixture of (*S*,*S*)-**3a** (36 mg, 0.0734 mmol) and 10% Pd–C (3.9 mg, 0.00367 mmol) in MeOH (2 mL) was stirred at rt for 7 h under hydrogen. The reaction mixture was filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (2 mL) and heated at 190 °C in a sealed tube for 24 h. After cooling to rt, the reaction mixture was concentrated *in vacuo* and washed with MeOH to furnish (*S*,*S*)-**4a** (10 mg, 42%) as a white solid.

(3*S*,6*S*)-3,6-Dibenzyl-3-(hydroxymethyl)piperazine-2,5-dione [(*S*,*S*)-4a] White solid; mp >245 °C (dec); $[\alpha]_D^{28}$ –30.3° (*c* 0.05, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.59-2.68 (m, 1H), 2.74-2.82 (m, 1H), 2.87-2.98 (m, 2H), 3.12-3.30 (m, 3H), 4.93-5.01 (m, 1H), 7.32-7.04 (m, 10H), 7.82 (s, 1H), 7.91 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 54.5, 64.7, 67.0, 126.2, 126.5, 127.7, 127.8, 129.7, 130.3, 135.8, 136.4, 166.5, 167.4; IR (KBr) 2358, 1675, 1454 cm^{-1}; ESIMS calcd for $C_{19}H_{20}N_2NaO_3$ MW 347.1372, found *m*/*z* 347.1378 (M^+ + Na).

(3*S*,6*S*)-6-Benzyl-3-(hydroxymethyl)-3-methylpiperazine-2,5-dione [(*S*,*S*)-4b] White solid; mp >240 °C (dec); $[\alpha]_D^{27}$ –50.5° (*c* 0.06, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.17 (s, 3H), 3.00-3.14 (m, 4H), 4.04-4.12 (m, 1H), 4.98-5.04 (m, 1H), 7.15-7.32 (m, 5H), 7.79 (s, 1H), 7.86 (s, 1H); ^{13}C-NMR

(75 MHz, DMSO-d_6) δ 22.6, 40.1, 55.7, 59.7, 67.3, 126.3, 128.0, 129.7, 136.9, 166.6, 167.0; IR (KBr) 2360, 1664, 1454 cm^{-1}; ESIMS calcd for $C_{13}H_{16}N_2NaO_3$ MW 271.1059, found *m*/*z* 271.1046 (M^+ + Na).

(3*S*,6*S*)-6-Benzyl-3-hexyl-3-(hydroxymethyl)piperazine-2,5-dione [(*S*,*S*)-4c] White solid; mp 213-216 °C; $[\alpha]_D^{28}$ –32.7° (*c* 0.81, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.72-0.93 (m, 3H), 0.95-1.41 (m, 9H), 1.52-1.68 (m, 1H), 2.95-3.14 (m, 4H), 4.02-4.12 (m, 1H), 4.85-4.93 (m, 1H), 7.08-7.37 (m, 5H), 7.75 (s, 1H), 7.85 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 13.8, 21.9, 22.8, 28.5, 31.0, 34.5, 55.5, 63.5, 67.3, 126.3, 128.0, 129.7, 136.7, 166.9, 168.0; IR (KBr) 2358, 1671, 1455 cm^{-1}; ESIMS calcd for $C_{18}H_{26}N_2NaO_3$ MW 341.1841, found *m*/*z* 341.1824 (M^+ + Na).

(3*S*,6*S*)-6-Benzyl-3-(hydroxymethyl)-3-propylpiperazine-2,5-dione [(*S*,*S*)-4d'] White solid; mp >251 °C (dec); $[\alpha]_D^{27}$ –43.1° (*c* 0.04, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.77-0.86 (m, 3H), 1.02-1.14 (m, 1H), 1.20-1.38 (m, 2H), 1.51-1.63 (m, 1H), 2.98-3.12 (m, 4H), 4.04-4.10 (m, 1H), 4.85-4.91 (m, 1H), 7.16-7.33 (m, 5H), 7.74 (s, 1H), 7.85 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 13.8, 16.3, 36.7, 55.5, 63.5, 67.2, 126.3, 128.0, 129.7, 136.7, 166.9, 168.0; IR (KBr) 1673, 1454 cm^{-1}; ESIMS calcd for $C_{15}H_{20}N_2NaO_3$ MW 299.1372, found *m*/*z* 299.1373 (M^+ + Na).

(3*S*,6*R*)-3,6-Dibenzyl-3-(hydroxymethyl)piperazine-2,5-dione [(*R*,*S*)-4a] White solid; mp >263 °C (dec); $[\alpha]_D^{28}$ +67.4° (*c* 0.05, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.03 (m, 1H), 2.41-2.59 (m, 2H), 2.80-2.96 (m, 1H), 3.32-3.39 (m, 1H), 3.70-3.80 (m, 1H), 3.89-3.97 (m, 1H), 5.22-5.30 (m, 1H), 6.85-6.96 (m, 2H), 7.04-7.34 (m, 8H), 7.69 (s, 1H), 7.94 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 55.1, 65.2, 68.5, 126.1, 126.5, 127.97, 128.01, 129.4, 130.4, 135.9, 136.8, 167.4, 167.9; IR (KBr) 1666, 1444 cm^{-1}; ESIMS calcd for $C_{19}H_{20}N_2NaO_3$ MW 347.1372, found *m*/*z* 347.1376 (M^+ + Na).

(3*S*,6*R*)-6-Benzyl-3-(hydroxymethyl)-3-methylpiperazine-2,5-dione [(*R*,*S*)-4b] White solid; mp >272 °C (dec); $[\alpha]_D^{27}$ –7.6° (*c* 0.09, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.46 (s, 3H), 2.86 (dd, *J* = 4.9, 13.4 Hz, 1H), 3.06 (dd, *J* = 4.4, 10.1 Hz, 1H), 3.15 (dd, *J* = 4.9, 13.9 Hz, 1H), 3.46 (dd, *J* = 5.4, 10.0 Hz, 1H), 4.14-4.20 (m, 1H), 5.03-5.10 (m, 1H), 7.14-7.30 (m, 5H), 7.80 (s, 1H), 8.03 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 21.7, 37.9, 55.3, 59.9, 67.9, 126.4, 127.8, 130.2, 136.1, 166.4, 168.9; IR (KBr) 1673, 1463 cm^{-1}; ESIMS calcd for $C_{13}H_{16}N_2NaO_3$ MW 271.1059, found *m*/*z* 271.1046 (M^+ + Na).

(3*S*,6*R*)-6-Benzyl-3-hexyl-3-(hydroxymethyl)piperazine-2,5-dione [(*R*,*S*)-4c] White solid; mp 274-276 °C; $[\alpha]_D^{27}$ +19.5° (*c* 0.04, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.16-0.45 (m, 2H),

0.74-1.04 (m, 8H), 1.06-1.19 (m, 2H), 1.22-1.33 (m, 1H), 2.81 (dd, *J* = 4.6, 13.2 Hz, 1H), 3.05 (dd, *J* = 4.9, 10.0 Hz, 1H), 3.21 (dd, *J* = 2.2, 13.4 Hz, 1H), 3.46 (dd, *J* = 5.6, 10.0 Hz, 1H), 4.12-4.21 (m, 1H), 5.08-5.17 (m, 1H), 7.12-7.28 (m, 5H), 7.69 (s, 1H), 8.08 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 13.8, 21.4, 21.8, 28.5, 30.9, 33.0, 36.9, 54.9, 64.1, 68.3, 126.3, 127.5, 130.3, 136.0, 167.1, 168.4; IR (KBr) 1668, 1455 cm^{-1}; ESIMS calcd for $C_{18}H_{26}N_2NaO_3$ MW 341.1841, found *m*/*z* 341.1824 (M^+ + Na).

(3*S*,6*R*)-6-Benzyl-3-(hydroxymethyl)-3-propylpiperazine-2,5-dione [(*R*,*S*)-4d'] White solid; mp >280 °C (dec); $[\alpha]_D^{27}$ +17.0° (*c* 0.11, DMSO); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.17-0.43 (m, 2H), 0.45-0.54 (m, 3H), 0.81-0.93 (m, 1H), 1.19-1.28 (m, 1H), 2.82 (dd, *J* = 4.6, 13.2 Hz, 1H), 3.05 (dd, *J* = 4.9, 10.3 Hz, 1H), 3.21 (dd, *J* = 2.9, 13.2 Hz, 1H), 3.46 (dd, *J* = 5.6, 10.3 Hz, 1H), 4.14-4.20 (m, 1H), 5.07-5.13 (m, 1H), 7.12-7.32 (m, 5H), 7.62 (s, 1H), 8.08 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 13.8, 14.9, 35.2, 37.1, 55.0, 64.1, 68.2, 126.2, 127.6, 130.4, 136.1, 167.0, 168.2; IR (KBr) 1670, 1455 cm^{-1}; ESIMS calcd for $C_{15}H_{20}N_2NaO_3$ MW 299.1372, found *m*/*z* 299.1368 (M^+ + Na).

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