Title:

N4-Methylation Changes the Conformation of (3*S*,6*S*)-3-Alkyl-6-benzylpiperazine-2,5-diones from Folded to Extended

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Abstract:

N4-Methylation of (3*S*,6*S*)-3-alkyl-6-benzylpiperazine-2,5-diones (*S*,*S*)-**1a**–**c** was found to change their folded conformation to an extended conformation. Conformational aspects of N1- and/or N4-methylated (*S*,*S*)-**1a**–**c** were revealed by single crystal X-ray crystallography and ^{1}H NMR spectroscopy.

Keywords:

Piperazine-2,5-dione
N-methylation
Folded conformation
Extended conformation
CH/π interaction
X-ray crystal structure

1. Introduction

Piperazine-2,5-diones (2,5-DKPs) are an important class of heterocyclic compounds because of their wide range of biological activities [1–5]. In addition, 2,5-DKPs could be regarded as an attractive scaffold for functional molecules including pharmaceuticals due to the structural diversity achieved by introducing substituents on the 2,5-DKP ring [6–12]. Therefore, the regulation of their conformation by chemical modification has recently attracted much attention. In general, C3- or C6-mono-benzylated 2,5-DKPs are known to adopt a folded conformation, in which the benzyl moiety is folded over the 2,5-DKP ring [13–21]. Previously, we reported that 2,5-DKPs derived from L- or D-phenylalanine and α-substituted L-serine adopted a folded conformation based on their ^{1}H NMR spectra [22]. In addition, our recent study has demonstrated the importance of intramolecular CH/π interaction in the folded conformation of mono-benzylated 2,5-DKPs due to the electronic effects of *para*-substituents on the benzyl group in the ^{1}H NMR spectra [23]. Intriguingly, similar folded conformations were also observed in chiral 5-benzylimidazolidin-4-ones, which are known as effective organocatalysts [24–30]. As the next step in our ongoing research on the conformation of 2,5-DKPs, we herein investigated the possibility of using N1- and/or N4-methylation to change the conformation of (3*S*,6*S*)-3-alkyl-6-benzylpiperazine-2,5-diones (*S*,*S*)-**1a**–**c** from a folded to an extended one (Figure 1). In this context, we note that *N*-methylation of amide bonds is considered to be one of the important chemical modifications for control of the conformation and the biological function of peptides or proteins [31].

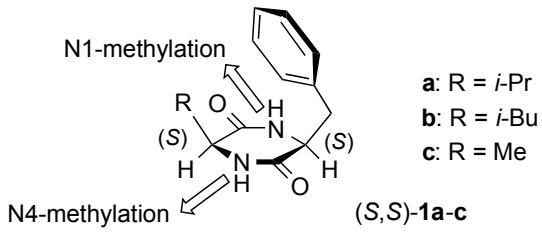


Fig. 1. N1- and N4-methylation of (3*S*,6*S*)-3-alkyl-6-benzylpiperazine-2,5-diones (*S*,*S*)-**1a**–**c**.

2. Experimental section

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 mm]. Anhydrous CH_2Cl_2 and DMF were used as purchased from Kanto Chemical. Triethylamine was distilled prior to use. All other reagents were used as purchased. All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AV500 spectrometer. 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. Elemental combustion analyses were performed using a Yanagimoto CHN CORDER MT-5 and a J-SCIENCE LAB JM10. The microwave-assisted was performed utilizing an automated single-mode microwave synthesizer (Initiator^{TM} 60; Biotage AB). Single crystal X-ray diffraction experiments were performed on a Rigaku RAXIS-RAPID diffractometer using graphite monochromated Mo-Kα (λ = 0.71075 Å, 50 kV, 40 mA) radiation. Data were corrected for Lorentz and polarization effects. The structure was solved by direct methods [32] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure [33] crystallographic software package.

2.1. General procedure for the preparation of dipeptides (*S*,*S*)-**4a**–**c** and (*S*,*S*)-**6a**–**c**

2.1.1. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,3-dimethylbutanamido]-3-phenylpropanoate [(*S*,*S*)-**4a**]

To a solution of (*S*)-**2a** (172 mg, 0.793 mmol) and (*S*)-**3d** (200 mg, 0.872 mmol) in anhydrous CH_2Cl_2 (3 mL) was added HOBt (118 □g, 0.872 mmol), EDC • HCl (228 □g, 1.19 mmol) and triethylamine (122 μL, 0.872 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was treated with 5% citric acid (5 mL) and then extracted with $CHCl_3$ (10 mL × 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N: *n*-hexane–AcOEt (3:1)] to afford (*S*,*S*)-**4a** (192.1 mg, 62%). White solid; mp 87.0–88.0 °C; $[\alpha]_D^{29}$ −69.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.36 (d, *J* = 6.7 Hz, 0.4H), 0.66 (d, *J* = 6.7 Hz, 0.4H), 0.89 (d, *J* = 6.8 Hz, 2.6H), 0.95 (d, *J* = 6.8 Hz, 2.6H), 1.41 (s, 9H), 1.87–1.98 (m, 1H), 2.92/2.94 (s × 2, 3H), 3.00 (dd, *J* = 10.1, 14.6 Hz, 1H), 3.39 (dd, *J* = 5.7, 14.6 Hz, 1H), 3.72/3.73 (s × 2, 3H), 4.00–4.05 (m, 0.2H), 4.34 (dd, *J* = 6.1, 9.4 Hz, 0.8H), 4.94 (d, *J* = 9.8 Hz, 0.2H), 4.99 (dd, *J* = 4.4, 10.3 Hz, 0.2H), 5.05 (d, *J* = 9.3 Hz, 0.8H), 5.34 (dd, *J* = 5.7, 10.1 Hz, 0.8H), 7.15–7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 17.20, 17.27, 18.9, 19.5, 28.29, 28.34, 29.7, 30.7, 31.2, 32.8, 34.5, 35.2, 52.3, 52.6, 54.9, 55.0, 58.4, 61.4, 79.3, 79.4, 126.8, 127.1, 128.5, 128.8, 128.9, 129.2, 136.75, 136.80, 155.4, 155.7, 170.5, 171.1, 172.9, 173.1; IR (KBr) 2971, 1734, 1710, 1642, 1516, 1364 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{21}H_{32}N_2NaO_5$ $[M+Na]^+$, 415.2209; found, 415.2206.

2.1.2. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,4-dimethylpentanamido]-3-phenylpropanoate [(*S*,*S*)-**4b**]

White solid, mp 127–129 °C; $[\alpha]_D^{29}$ −79.4 (*c* 1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.69/0.71 (d × 2, *J* = 6.6 Hz, 1H), 0.92/0.96 (d × 2, *J* = 6.7, 6.5 Hz, 5H), 1.30–1.45 (m, 2H), 1.40/1.41 (s × 2, 9H), 1.65–1.75 (m, 1H), 2.90/2.93 (s × 2, 3H), 3.05 (dd, *J* = 10.5, 14.5 Hz, 1H), 3.38 (dd, *J* = 5.3, 14.5 Hz, 1H), 3.73/3.75 (s × 2, 3H), 4.31 (dt, *J* = 3.8, 10.1 Hz, 0.2H), 4.53 (dt, *J* = 4.0, 9.6 Hz, 0.8H), 4.88 (d, *J* = 9.8 Hz, 0.2H), 4.96 (dd, *J* = 4.1, 10.8 Hz, 0.2H), 5.02 (d, *J* = 9.2 Hz, 0.8H), 5.20 (dd, *J* = 5.5, 10.4 Hz, 0.8H), 7.16–7.53 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 21.5, 21.8, 23.2, 23.3, 24.2, 24.6, 28.28, 28.33, 29.9, 32.9, 34.5, 35.2, 41.1, 42.4, 47.8, 48.8, 52.2, 52.6, 58.9, 61.3, 79.3, 79.4, 126.8, 127.1, 128.5, 128.8, 129.0, 129.1, 136.76, 136.84, 155.2, 155.5, 170.5, 171.0, 173.5, 173.7; IR (KBr) 3385, 2978, 1731, 1705, 1645, 1517, 1363 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{22}H_{34}N_2NaO_5$ $[M+Na]^+$, 429.2365; found, 429.2343.

2.1.3. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*-methylpropanamido]-3-phenylpropanoate [(*S*,*S*)-**4c**]

Colorless needles (CH_2Cl_2–*n*-hexane), mp 88–89 °C; $[\alpha]_D^{19}$ −64.9 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.72 (d, *J* = 6.6 Hz, 0.5H), 1.25 (d, *J* = 6.8 Hz, 2.5H), 1.40/1.42 (s × 2, 9H), 2.86 (s, 2.5H), 2.92 (s, 0.5H), 2.95–3.02 (m, 0.2H), 3.08 (dd, *J* = 10.6, 14.5 Hz, 0.8H), 3.38 (dd, *J* = 5.2, 14.5 Hz, 1H), 3.73/3.74 (s × 2, 3H), 4.26–4.33 (m, 0.2H), 4.50 (brquint, 0.8H), 4.94 (brdd, 0.2H), 5.05–5.15 (m, 1H), 5.26 (brd, 0.8H), 7.15-7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 18.5, 18.6, 28.3, 28.4, 29.9, 32.4, 33.4, 34.4, 34.7, 35.2, 45.2, 46.5, 52.3, 52.6, 58.1, 59.5, 61.4, 79.4, 79.5, 126.8, 126.9, 127.2, 128.5, 128.77, 128.83, 128.9, 129.1, 136.6, 136.9, 154.8, 155.0, 170.4, 170.9, 173.2, 173.6; IR (KBr) 3387, 2980, 2946, 1737, 1710, 1644, 1513, 1360 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{19}H_{28}N_2NaO_5$ $[M+Na]^+$, 387.1896; found, 387.1916.

2.1.4. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*-methyl-3-phenylpropanamido]-3-methylbutanoate [(*S*,*S*)-**6a**]

Colorless oil; $[\alpha]_D^{28}$ −68.9 (*c* 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.55 (d, *J* = 6.7 Hz, 0.3H), 0.80 (d, *J* = 6.7 Hz, 2.7H), 0.91 (d, *J* = 6.5 Hz, 0.3H), 0.95 (d, *J* = 6.5 Hz, 2.7H), 1.38/1.40 (s × 2, 9H), 2.07–2.18 (m, 1H), 2.72 (s, 2.7H), 2.86 (s, 0.3H), 2.93 (dd, *J* = 5.7, 13.1 Hz, 1H), 3.01 (dd, *J* = 8.6, 13.1 Hz, 1H), 3.66/3.69 (s × 2, 3H), 4.02 (d, *J* = 10.4 Hz, 0.1H), 4.79–4.86 (m, 0.9H), 4.91 (d, *J* = 10.7 Hz, 0.9H), 4.95–5.01 (m, 0.1H), 5.13 (brd, 0.1H), 5.28 (brd, 0.9H), 7.16–7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 18.5, 19.6, 27.2, 28.3, 30.7, 39.4, 51.70, 51.75, 61.3, 79.8, 126.79, 126.84, 128.40, 128.46, 129.5, 129.6, 136.2, 155.3, 170.9, 173.0; IR (neat) 3315, 3029, 2972, 2876, 1740, 1711, 1659, 1642, 1513, 1494, 1453, 1411, 1391, 1367, 1294, 1249, 1170 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{21}H_{32}N_2NaO_5$ $[M+Na]^+$, 415.2209; found, 415.2210.

2.1.5. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*-methyl-3-phenylpropanamido]-4-methylpentanoate [(*S*,*S*)-**6b**]

Colorless oil; $[\alpha]_D^{29}$ −21.8 (*c* 1.34, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.80/0.83 (d × 2, *J* = 6.4, 7.0 Hz, 0.5H), 0.89/0.91 (d × 2, *J* = 6.5, 6.7 Hz, 5.5H), 1.37/1.39 (s × 2, 9H), 1.42–1.49 (m, 1H), 1.60–1.74 (m, 2H), 2.79/2.81 (s × 2, 3H), 2.90 (dd, *J* = 6.2, 13.5 Hz, 1H), 3.08 (dd, *J* = 7.5, 13.5 Hz, 0.9H), 3.15 (dd, *J* = 7.7, 12.9 Hz, 0.1H), 3.67 (s, 3H), 4.55–4.60 (m, 0.1H), 4.84 (brq, 0.9H), 5.11 (brd, 0.1H), 5.26 (brd, 0.9H), 5.30 (dd, *J* = 5.2, 10.5 Hz, 1H), 7.17–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 21.4, 22.2, 22.7, 23.2, 24.66, 24.72, 28.1, 28.3, 31.0, 37.2, 38.2, 39.0, 39.7, 51.3, 51.7, 52.1, 52.3, 54.5, 57.8, 79.7, 126.7, 126.8, 128.37, 128.41, 129.5, 129.6, 136.3, 136.7, 155.2, 171.2, 171.9, 172.7; IR (neat) 3319, 3029, 2956, 2871, 1741, 1711, 1643, 1495, 1454, 1411, 1391, 1366, 1249, 1172 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{22}H_{34}N_2NaO_5$ $[M+Na]^+$, 429.2365; found, 429.2375.

2.1.6. Methyl (*S*)-2-[(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*-methyl-3-phenylpropanamido]propanoate [(*S*,*S*)-**6c**]

Colorless oil; $[\alpha]_D^{29}$ −19.1 (*c* 0.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of rotamers) δ 0.91 (d, *J* = 7.0 Hz, 0.5H), 1.36 (d, *J* = 7.3 Hz, 2.5H), 1.40/1.41 (s × 2, 9H), 2.73 (s, 0.5H), 2.81 (s, 2.5H), 2.91 (dd, *J* = 6.3, 13.6 Hz, 0.8H), 2.99 (d, *J* = 7.2 Hz, 0.4H), 3.06 (dd, *J* = 7.1, 13.6 Hz, 0.8H), 3.67 (s, 0.5H), 3.70 (s, 2.5H), 4.40 (q, *J* = 7.0 Hz, 0.2H), 4.80–4.88 (m, 1H), 5.14 (q, *J* = 7.3 Hz, 0.8H), 5.30 (brd, 0.8H), 5.37 (brd, 0.2H), 7.17–7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 14.2, 14.7, 28.3, 28.8, 31.4, 39.3, 40.5, 51.4, 51.6, 52.2, 52.5, 52.6, 54.9, 79.6, 126.8, 126.9, 128.4, 128.6, 129.4, 129.6, 136.2, 136.5, 154.9, 155.1, 171.2, 171.8, 172.0, 172.1; IR (neat) 3318, 2979, 1743, 1711, 1659, 1642, 1513, 1494, 1484, 1462, 1452, 1410, 1366, 1248, 1171 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{19}H_{28}N_2NaO_5$ $[M+Na]^+$, 387.1896; found, 387.1862.

2.2. General procedure for the preparation of piperazine-2,5-diones (*S*,*S*)-**5a**–**c** and (*S*,*S*)-**7a**–**c**

2.2.1. (3*S*,6*S*)-6-Benzyl-3-isopropyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**5a**]

A suspension of dipeptide (*S*,*S*)-**4a** (80 mg, 0.204 mmol) in a mixed solvent of H_2O (1.5 mL) with MeOH (0.5 mL) was irradiated at 170 °C for 10 min using an automated single-mode microwave synthesizer. The reaction mixture was treated with H_2O (2 mL) and then extracted with $CHCl_3$ (5 mL × 2). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (50:1)] to afford (*S*,*S*)-**5a** (47.3 mg, 89% yield). Colorless columns (CH_2Cl_2–AcOEt); mp 173–175 °C; $[\alpha]_D^{27}$ −53.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.49 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 1.35–1.46 (m, 1H), 2.96 (s, 3H), 3.26 (dd, *J* = 4.7, 14.2 Hz, 1H), 3.30 (dd, *J* = 5.0, 14.2 Hz, 1H), 3.60 (dd, *J* = 2.7, 5.9 Hz, 1H), 4.18 (brt, 1H),

6.34 (brs, 1H), 7.14–7.19 (m, 2H), 7.21–7.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 19.3, 32.5, 33.6, 38.1, 60.8, 63.5, 127.4, 128.8, 129.9, 135.7, 165.5, 167.3; IR (KBr) 3247, 2972, 1687, 1661, 1456, 1301 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{15}H_{20}N_2NaO_2$ $[M+Na]^+$, 283.1422; found, 283.1401. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.20; H, 7.88; N, 10.55%.

2.2.2. (3*S*,6*S*)-6-Benzyl-3-isobutyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**5b**]

Colorless columns (CH_2Cl_2–AcOEt); mp 170–172 °C; $[\alpha]_D^{26}$ −11.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.22 (ddd, *J* = 4.5, 11.0, 13.7 Hz, 1H), 0.70 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H), 1.03 (ddd, *J* = 3.9, 10.3, 13.7 Hz, 1H), 1.28–1.40 (m, 1H), 3.07 (s, 3H), 3.16 (dd, *J* = 4.6, 14.0 Hz, 1H), 3.33 (dd, *J* = 3.7, 14.0 Hz, 1H), 3.74 (brdt, 1H), 4.20 (brt, 1H), 6.27 (brs, 1H), 7.09–7.15 (m, 2H), 7.25–7.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 22.9, 23.8, 33.0, 36.6, 43.6, 53.3, 63.1, 127.7, 128.8, 130.2, 134.9, 166.7, 166.8; IR (KBr) 3609, 3520, 3328, 2956, 1681, 1649, 1468 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{16}H_{22}N_2NaO_2$ $[M+Na]^+$, 297.1579; found, 297.1552. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.97; H, 8.11; N, 10.24%.

2.2.3. (3*S*,6*S*)-6-Benzyl-1,3-dimethylpiperazine-2,5-dione [(*S*,*S*)-**5c**]

Colorless plates (CH_2Cl_2–AcOEt), mp 143.5–145.5 °C; $[\alpha]_D^{28}$ +30.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50 (d, *J* = 7.1 Hz, 3H), 3.08 (s, 3H), 3.18 (dd, *J* = 4.6, 14.1 Hz, 1H), 3.33 (dd, *J* = 3.7, 14.1 Hz, 1H), 3.87 (dq, *J* = 2.6, 7.1 Hz, 1H), 4.20 (brt, 1H), 6.27 (brs, 1H), 7.10–7.14 (m, 2H), 7.24–7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7, 33.0, 36.7, 51.1, 63.2, 127.6, 128.9, 130.2, 134.8, 166.5, 166.8; IR (KBr) 3181, 3137, 1681, 1632, 1477 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{13}H_{16}N_2NaO_2$ $[M+Na]^+$, 255.1109; found, 255.1099. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.21; H, 6.86; N, 11.88%.

2.2.4. (3*S*,6*S*)-3-Benzyl-6-isopropyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**7a**]

Colorless prisms (CH_2Cl_2–AcOEt); mp 133–134 °C; $[\alpha]_D^{29}$ −155.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 2.25 (dsept, *J* = 4.2, 7.0 Hz, 1H), 2.80 (dd, *J* = 11.4, 13.5 Hz, 1H), 3.03 (s, 3H), 3.54 (dd, *J* = 3.2, 13.5 Hz, 1H), 3.75 (brd, 1H), 4.17 (brt, 1H), 5.67 (brs, 1H), 7.19–7.24 (m, 2H), 7.26–7.31 (m, 1H), 7.32–7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.1, 19.7, 31.6, 34.6, 41.5, 57.0, 67.7, 127.4, 129.1, 129.4, 136.1, 165.6, 165.8; IR (KBr) 3207, 3133, 2984, 2972, 1690, 1636, 1456, 1412, 1336 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{15}H_{20}N_2NaO_2$ $[M+Na]^+$, 283.1422; found, 283.1438. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.05; H, 7.87; N, 10.71%.

2.2.5. (3*S*,6*S*)-3-Benzyl-6-isobutyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**7b**]

Colorless columns (CH_2Cl_2–AcOEt); mp 105–109 °C; $[\alpha]_D^{18}$ −82.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.15 (ddd, *J* = 5.2, 8.7, 14.1 Hz, 1H), 1.33 (ddd, *J* = 4.2, 8.8, 14.1 Hz, 1H), 1.77–1.88 (m, 1H), 2.95 (s, 3H), 2.99 (dd, *J* = 8.7, 13.6 Hz, 1H), 3.26 (dd, *J* = 3.7, 13.6 Hz, 1H), 3.73 (dd, *J* = 4.2, 8.7 Hz, 1H), 4.22 (brdt, 1H), 5.94 (brs, 1H), 7.20–7.22 (m, 2H), 7.26–7.30 (m, 1H), 7.31–7.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 23.1, 24.8, 33.0, 41.1, 42.4, 57.1, 60.2, 127.4, 128.9, 129.9, 135.8, 165.4, 168.0; IR (KBr) 3242, 2960, 1683, 1638, 1442, 1344 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{16}H_{22}N_2NaO_2$ $[M+Na]^+$, 297.1579; found, 297.1578. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.92; H, 8.12; N, 10.15%.

2.2.6. (3*S*,6*S*)-3-Benzyl-1,6-dimethylpiperazine-2,5-dione [(*S*,*S*)-**7c**]

Colorless needles (CH_2Cl_2–AcOEt), mp 126–129 °C; $[\alpha]_D^{27}$ −47.8 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 7.1 Hz, 3H), 2.92 (s, 3H), 3.09 (dd, *J* = 7.5, 13.7 Hz, 1H), 3.17 (dd, *J* = 3.9, 13.7 Hz, 1H), 3.78 (q, *J* = 7.1 Hz, 1H), 4.27 (brquint, 1H), 6.14 (brs, 1H), 7.18–7.23 (m, 2H), 7.25–7.30 (m, 1H), 7.31–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.0, 32.2, 41.1, 56.8, 57.5, 127.4, 128.8, 130.1, 135.5, 164.8, 168.6; IR (KBr) 3242, 1687, 1643, 1455, 1340, 1322 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{13}H_{16}N_2NaO_2$ $[M+Na]^+$, 255.1109; found, 255.1119.

2.3. General procedure for the preparation of piperazine-2,5-diones (*S*,*S*)-**8a**–**c**

2.3.1. (3*S*,6*S*)-3-Benzyl-6-isopropyl-1,4-dimethylpiperazine-2,5-dione [(*S*,*S*)-**8a**]

NaH (50-72%, 6.9 mg, 0.144 mmol) was added to a solution of (*S*,*S*)-**7a** (25 mg, 0.096 mmol) in anhydrous DMF (2 mL) and stirred at 0 °C for 15 min under argon. After adding MeI (8.96 μL, 0.144 mmol), the mixture was stirred at 0 °C for 30 min under argon. The reaction mixture was treated with 1N HCl (2 mL) and then extracted with AcOEt (5 mL × 3). The extract was washed with sat. $Na_2S_2O_3$ (5 mL) and H_2O (5 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (30:1)] to afford (*S*,*S*)-**8a** (24.1 mg, 91% yield). White solid; mp 77–80 °C; $[\alpha]_D^{30}$ −81.4 (*c* 0.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.61–1.73 (m, 1H), 2.67 (s, 3H), 3.01 (s, 3H), 3.09 (dd, *J* = 7.7, 14.1 Hz, 1H), 3.38 (dd, *J* = 4.4, 14.1 Hz, 1H), 3.55 (d, *J* = 7.1 Hz, 1H), 4.12 (dd, *J* = 4.4, 7.7 Hz, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 20.6, 33.5, 33.9, 35.8, 40.3, 65.1, 68.9, 127.3, 128.9, 129.5, 137.1, 165.8, 166.4; IR (KBr) 2934, 2874, 1662, 1477, 1456, 1402 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{16}H_{22}N_2NaO_2$ $[M+Na]^+$, 297.1579; found, 297.1578.

2.3.2. (3*S*,6*S*)-3-Benzyl-6-isobutyl-1,4-dimethylpiperazine-2,5-dione [(*S*,*S*)-**8b**]

White solid; mp 144.5–145.5 °C; $[\alpha]_D^{30}$ –5.5 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.28 (ddd, *J*

= 5.2, 9.2, 14.1 Hz, 1H), 0.66 (ddd, *J* = 4.2, 9.3, 14.1 Hz, 1H), 0.72 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 1.66–1.75 (m, 1H), 2.86 (s, 3H), 2.94 (s, 3H), 3.17 (dd, *J* = 4.6, 14.0 Hz, 1H), 3.29 (dd, *J* = 4.9, 14.0 Hz, 1H), 3.61 (dd, *J* = 4.2, 9.2 Hz, 1H), 4.18 (brt, 1H), 7.09–7.14 (m, 2H), 7.22–7.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.7, 25.1, 32.5, 32.8, 37.7, 42.4, 60.1, 64.0, 127.6, 128.9, 130.0, 135.7, 165.2, 166.6; IR (KBr) 2953, 2866, 1651, 1491, 1455, 1404 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{17}H_{24}N_2NaO_2$ $[M+Na]^+$, 311.1735; found, 311.1737.

2.3.3. (3*S*,6*S*)-3-Benzyl-1,4,6-trimethylpiperazine-2,5-dione [(*S*,*S*)-**8c**]

White solid, mp 123.5–127 °C; $[\alpha]_D^{30}$ −2.0 (*c* 0.74, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.48 (d, *J* = 7.1 Hz, 3H), 2.82 (s, 3H), 3.03 (s, 3H), 3.15 (dd, *J* = 4.4, 14.0 Hz, 1H), 3.32 (dd, *J* = 4.2, 14.0 Hz, 1H), 3.69 (q, *J* = 7.1 Hz, 1H), 4.21 (brt, 1H), 7.07–7.12 (m, 2H), 7.21–7.26 (m, 1H), 7.26–7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 31.7, 32.7, 37.3, 57.6, 63.5, 127.5, 128.9, 130.1, 135.3, 164.5, 166.8; IR (KBr) 3476, 3385, 2942, 1651, 1493, 1453, 1405, 1346 cm^{-1}; ESIMS *m*/*z*: calcd for $C_{14}H_{18}N_2NaO_2$ $[M+Na]^+$, 269.1266; found, 269.1288.

2.4. X-ray diffraction studies of (*S*,*S*)-**5a** and (*S*,*S*)-**7a**

2.4.1. (3*S*,6*S*)-6-Benzyl-3-isopropyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**5a**]

A colorless prism crystal of (*S*,*S*)-**5a** having approximate dimensions of 0.400 × 0.300 × 0.300 mm was mounted on a glass fiber. The data were collected at a temperature of −180 ± 1 °C to a maximum 2θ value of 54.8°. A total of 44 oscillation images were collected. A sweep of data was done using ω scans from 130.0 to 190.0° in 5.0° step, at χ = 45.0° and ϕ = 80.0°. The exposure rate was 130.0 [sec./°]. A second sweep was performed using ω scans from 0.0 to 160.0° in 5.0° step, at χ = 45.0° and ϕ = 260.0°. The exposure rate was 130.0 [sec./°]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. The absolute configuration was deduced from the synthetic pathway.

Deposition number: CCDC-1429971

Empirical formula: $C_{15}H_{20}N_2O_2$

Formula weight: 260.34

Crystal system, Space group: orthorhombic, *P* $2_12_12_1$ (No. 19)

Unit cell dimensions: a = 8.1071(3) Å, b = 12.3418(4) Å, c = 13.9765(5) Å

Volume: 1398.44(8) Å^3

Z, Calculated density: 4, 1.236 g/cm^3

Absorption coefficient μ(Mo-Kα): 0.826 cm^{-1}

Final R indices [I > 2.00σ(I)]: R1 = 0.0340, wR2 = 0.1042.

2.4.2. (3*S*,6*S*)-3-Benzyl-6-isopropyl-1-methylpiperazine-2,5-dione [(*S*,*S*)-**7a**]

A colorless block crystal of (*S*,*S*)-**7a** having approximate dimensions of 0.300 × 0.250 × 0.200 mm was mounted on a glass fiber. The data were collected at a temperature of −150 ± 1 °C to a maximum 2θ value of 54.8°. A total of 44 oscillation images were collected. A sweep of data was done using ω scans from 130.0 to 190.0° in 5.0° step, at χ = 45.0° and ϕ = 0.0°. The exposure rate was 130.0 [sec./°]. A second sweep was performed using ω scans from 0.0 to 160.0° in 5.0° step, at χ = 45.0° and ϕ = 180.0°. The exposure rate was 130.0 [sec./°]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode. The absolute configuration was deduced from the synthetic pathway.

Deposition number: CCDC-1429972

Empirical formula: $C_{15}H_{20}N_2O_2$

Formula weight: 260.34

Crystal system, Space group: orthorhombic, *P* $2_12_12_1$ (No. 19)

Unit cell dimensions: a = 8.4741(5) Å, b = 12.8041(7) Å, c = 12.7997(9) Å

Volume: 1388.8(2) $Å^3$

Z, Calculated density: 4, 1.245 g/cm^3

Absorption coefficient μ(Mo-Kα): 0.832 cm^{-1}

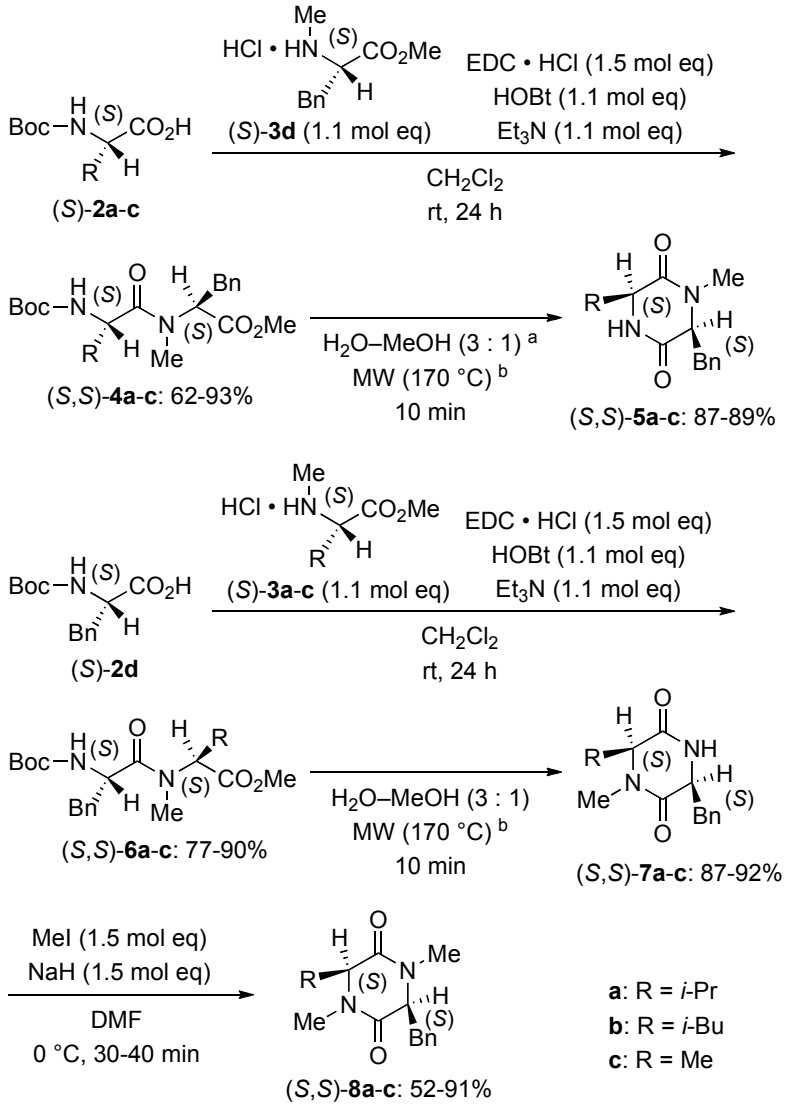
Final R indices [I > 2.00σ(I)]: R1 = 0.0326, wR2 = 0.0996.

3. Results and discussion

3.1. Synthesis of N-methylated and N,N'-dimethylated 2,5-DKPs

N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** were synthesized as shown in Scheme 1. Methyl, isopropyl, and isobutyl groups, which came from L-alanine, L-valine, and L-leucine, were chosen as 3-alkyl substituents of (*S*,*S*)-**1a**–**c**. Condensation of Boc-L-α-amino acids (*S*)-**2a**–**c** with *N*-methyl-L-phenylalanine methyl ester hydrochloride [(*S*)-**3d**] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) as a coupling reagent in the presence of 1-hydroxybenzotriazole (HOBt) and triethylamine afforded the dipeptides (*S*,*S*)-**4a**–**c**. Subsequently, microwave-assisted removal of the Boc group followed by intramolecular cyclization furnished the N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c** by a one-pot reaction [34].

N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c** were also synthesized in a similar way. Furthermore, *N*-methylation of (*S*,*S*)-**7a**–**c** afforded *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c**.



Scheme 1. Synthesis of N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c**.

[a] H_2O was used alone as the solvent in the reaction of (*S*,*S*)-**4a**.

[b] Initiator™ 60 (Biotage AB).

3.2. Crystallographic studies of N1- and N4-methylated 2,5-DKPs

Conformations of the 2,5-DKPs (*S*,*S*)-**5a** and (*S*,*S*)-**7a** in the solid state were examined by single crystal X-ray crystallography as shown in Figures 2 and 3. Unfortunately, the results showed that N1-methylated 2,5-DKP (*S*,*S*)-**5a** adopted a folded conformation, and the perpendicular distance (2.3778 Å) of the methine hydrogen atom [H(10)] of the isopropyl group from the plane of the benzene ring ($P_{benzene}$) was clearly shorter than the conventional van der Waals limit (2.9 Å: 1.2 Å for C-H plus 1.7 Å for a half

thickness of the aromatic molecule) (Figure 2) [35–38]. The C(12)–H(10)•••$C_{benzene}$ (the centroid of the benzene ring) angle of 173.74° was also observed. Therefore, the crystal structure of N1-methylated 2,5-DKP (*S*,*S*)-**5a** strongly suggested the existence of an intramolecular CH/π interaction [35–43] as a stabilizing factor for the folded conformation of (*S*,*S*)-**5a**. Intermolecular CH/π interactions of (*S*,*S*)-**5a** leading to a molecular packing were not observed. However, N4-methylation of (*S*,*S*)-**1a** successfully changed the folded conformation to the extended one. As shown in Figure 3, the crystal structure of N4-methylated 2,5-DKP (*S*,*S*)-**7a** was found to exist in an extended conformation in which the benzyl moiety was apart from the 2,5-DKP ring [44].

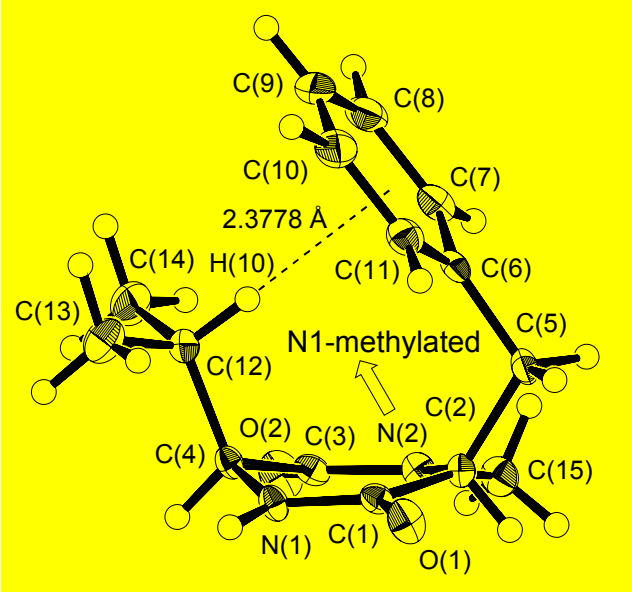


Fig. 2. ORTEP drawing of N1-methylated 2,5-DKP (*S*,*S*)-**5a** with 50% probability ellipsoids. Selected distances (Å) and angles (°) are: H(10)•••$P_{benzene}$ = 2.3778, C(12)•••$P_{benzene}$ = 3.3745(12), C(5)•••C(12) = 4.2910(15), C(12)–H(10)••• $C_{benzene}$ = 173.74, C(2)–C(5)–C(6) = 113.63(8), C(4)–C(12)–H(10) = 106.0.

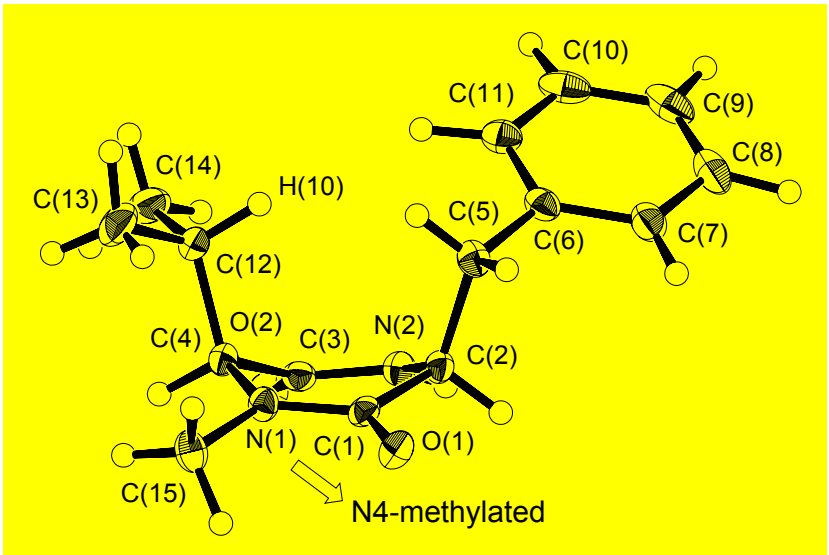


Fig. 3. ORTEP drawing of N4-methylated 2,5-DKP (*S*,*S*)-**7a** with 50% probability ellipsoids. Selected distances (Å) and angles (°) are: C(5)•••C(12) = 3.7541(16) , C(2)–C(5)–C(6) = 112.48(9), C(4)–C(12)–H(10) = 107.2.

3.3. ^{1}H NMR analysis of N-methylated and N,N'-dimethylated 2,5-DKPs

Next, we investigated the conformational aspects of N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** in solution by ^{1}H NMR spectroscopy. Selected chemical shifts of (*S*,*S*)-**5a**–**c**, (*S*,*S*)-**7a**–**c**, and (*S*,*S*)-**8a**–**c** in ^{1}H NMR spectra (500 MHz, $CDCl_3$) are given in Figure 4. Protons of the *cis*-substituent (on the same side of the 2,5-DKP ring as the benzyl moiety) of (*S*,*S*)-**5a**–**c** were found to appear at higher magnetic fields than those of (*S*,*S*)-**7a**–**c**. In particular, the isopropyl protons (H_A and Me_A) of (*S*,*S*)-**5a**, isobutyl protons (H_C and H_D) of (*S*,*S*)-**5b**, and methyl protons (Me_E) of (*S*,*S*)-**5c** exhibited remarkable upfield chemical shifts. The *trans*-protons H_B (on the opposite side of the 2,5-DKP ring with the benzyl moiety) of (*S*,*S*)-**5a**–**c** and (*S*,*S*)-**7a**–**c** did not show large differences in chemical shifts. The upfield chemical shifts of protons of the *cis*-substituent of (*S*,*S*)-**5a**–**c** could be attributed to the strong shielding effect of the benzene ring of the benzyl moiety. Therefore, it was suggested that N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c** adopted a folded conformation and the protons of the *cis*-substituent were close to the benzene ring in solution. On the other hand, N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c** seemed to prefer an extended conformation because the signals of protons of the *cis*-substituent were not observed in higher magnetic fields such as that of (*S*,*S*)-**5a**–**c**. However, *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** showed upfield chemical shifts of protons of the *cis*-substituent compared to those of (*S*,*S*)-**7a**–**c**, which suggests the predominance of the folded conformation in (*S*,*S*)-**8a**–**c** relative to (*S*,*S*)-**7a**–**c**.

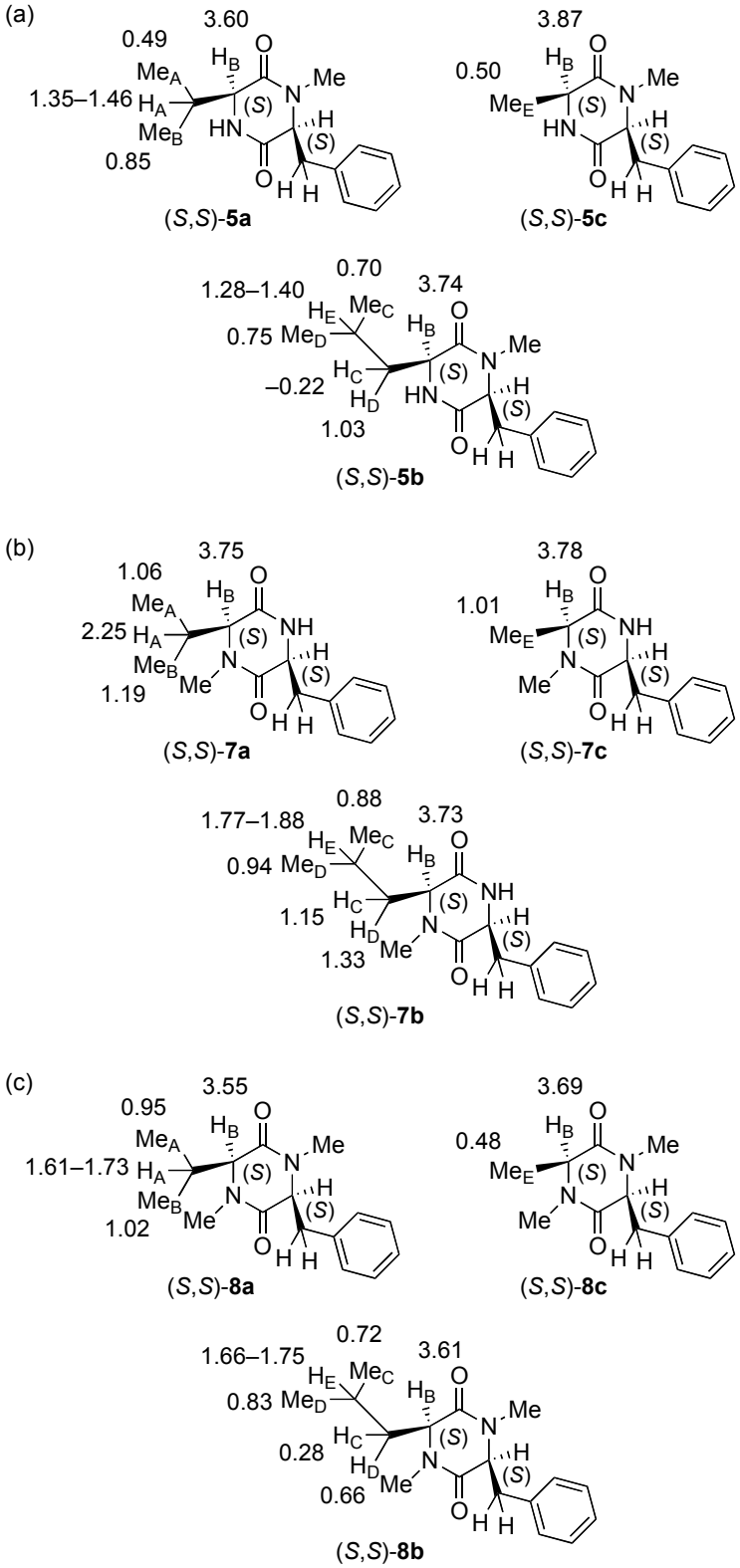


Fig. 4. Selected chemical shifts of (a) N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, (b) N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and (c) *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** in ^{1}H NMR (500 MHz, $CDCl_3$) analysis.

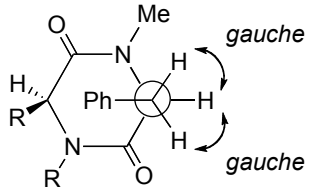
The vicinal coupling constants (J_1 and J_2) between the benzylic protons and the adjacent methine proton of N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** are listed in Table 1. The results showed that similar values of the vicinal coupling

constants (J_1 = 3.7–4.7 Hz, J_2 = 4.6–5.0 Hz) were observed for (*S*,*S*)-**5a**–**c**. Therefore, a *gauche* relationship was presumed to exist in the $CDCl_3$ solution between the two benzylic hydrogens and the adjacent methine hydrogen, indicating that the N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c** adopted the folded conformation [14]. On the other hand, it was found that J_1 and J_2 were quite different (J_1 = 3.2–3.9 Hz, J_2 = 7.5–11.4 Hz) in N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**. The large difference in the vicinal coupling constants suggested that one of the two benzylic hydrogens and the adjacent methine hydrogen could be in a *gauche* relationship, while the other benzylic hydrogen and adjacent methine hydrogen were in an *anti*-relationship [14]. Therefore, it was strongly suggested that the extended conformation of (*S*,*S*)-**7a**–**c** was predominant in $CDCl_3$ solution. The values of the vicinal coupling constants for *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** were similar to those for (*S*,*S*)-**5a**–**c**, and the preference for the folded conformation of (*S*,*S*)-**8a**–**c** was estimated. It is remarkable that differences of the vicinal coupling constants between (*S*,*S*)-**5a**–**c** and (*S*,*S*)-**7a**–**c** were correlated to the bulkiness of 3-alkyl substituents (methyl, isopropyl, and isobutyl groups) of the corresponding 2,5-DKPs. In the case of (*S*,*S*)-**5a** and (*S*,*S*)-**7a**, a methine carbon is directly connected to the 3-position of the 2,5-DKP ring and a larger difference of vicinal coupling constants (J_1 = 3.2 Hz, J_2 = 11.4 Hz) is observed. Thus, the ^{1}H NMR spectra of (*S*,*S*)-**5a** and (*S*,*S*)-**7a** showed a good agreement with the conformations in the solid state established by X-ray crystallography, as depicted in Figures 2 and 3.

Table 1

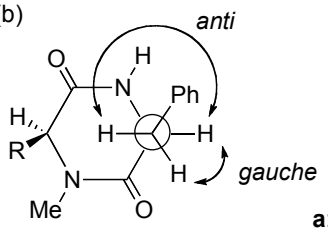
Vicinal coupling constants (J_1 and J_2) between the benzylic protons and the adjacent methine proton (a) N1-methylated 2,5-DKPs (*S*,*S*)-**5a**–**c**, (b) N4-methylated 2,5-DKPs (*S*,*S*)-**7a**–**c**, and (c) *N*,*N'*-dimethylated 2,5-DKPs (*S*,*S*)-**8a**–**c** in ^{1}H NMR (500 MHz, $CDCl_3$) analysis.

(a), (c)



(*S*,*S*)-**5a**-**c**: R = H
(*S*,*S*)-**8a**-**c**: R = Me

(b)



(*S*,*S*)-**7a**-**c**

a: R = *i*-Pr
b: R = *i*-Bu
c: R = Me

Compounds	R	J_1	J_2
(*S*,*S*)-**5a**	*i*-Pr	4.7	5.0
(*S*,*S*)-**5b**	*i*-Bu	3.7	4.6
(*S*,*S*)-**5c**	Me	3.7	4.6
(*S*,*S*)-**7a**	*i*-Pr	3.2	11.4
(*S*,*S*)-**7b**	*i*-Bu	3.7	8.7
(*S*,*S*)-**7c**	Me	3.9	7.5
(*S*,*S*)-**8a**	*i*-Pr	4.4	7.7
(*S*,*S*)-**8b**	*i*-Bu	4.6	4.9
(*S*,*S*)-**8c**	Me	4.2	4.4

4. Conclusions

A series of novel N1- and/or N4-methylated 2,5-DKPs [(*S*,*S*)-**5a**–**c**, (*S*,*S*)-**7a**–**c**, and (*S*,*S*)-**8a**–**c**] have been prepared and fully characterized. Their conformational aspects have been confirmed by ^{1}H NMR spectroscopy in solution. Single crystal X-ray structural analysis of (*S*,*S*)-**5a** and (*S*,*S*)-**7a** has also been performed. In conclusion, N1-methylation and N1,N4-dimethylation have no influence on the folded conformation of (*S*,*S*)-**1a**–**c**. However, we have succeeded in changing the folded conformation of (*S*,*S*)-**1a**–**c** to the extended conformation by N4-methylation of the 2,5-DKP ring. This simple chemical modification could be applied to access novel functional molecules such as organocatalysts and pharmaceuticals based on the 2,5-DKP ring.

Acknowledgements

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Appendix A. Supplementary data

Deposition number CCDC-1429971 for compound (*S*,*S*)-**5a** and CCDC-1429972 for compound (*S*,*S*)-**7a** contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Highlights

- A series of novel N-methylated and N,N'-dimethylated 2,5-DKPs were prepared.
- Conformational analysis of prepared N-methylated and N,N'-dimethylated 2,5-DKPs based on ^{1}H NMR spectroscopy were performed.
- Single crystal X-ray structural analysis of prepared N1-methylated and N4-methylated 2,5-DKPs were performed.
- N4-methylation of mono-benzylated 2,5-DKPs, which overcome the intramolecular CH/π interaction, was found to change their conformation from folded to extended.