3,7-Dimethyl-3,7-diazabicyclo[3.3.1]nonane-2,6-dione-1,5-dicarboxylic acid derivatives: synthesis, structure and resolution

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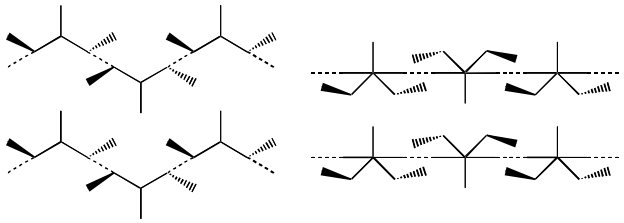
Diamide monohydrate **6** was found to form a conglomerate (space group $P2_1$), and it was spontaneously resolved by crystallization; esters **1** and **2** were optically enriched by classical methods; the above compounds were structurally characterised by NMR spectroscopy and X-ray analysis.

As we have found recently,[1] the crystalline parent dilactam 3,7-diazabicyclo[3.3.1]nonane-2,6-dione forms expected[2] homochiral H-bonded helical suprastructures, whereas its 1,5-diethoxycarbonyl derivative[1] and the other parent dilactam 3,7-diazabicyclo[3.3.0]octane-2,6-dione[3] are self-assembled in heterochiral H-bonded tapes of the diagonal zigzag type. Each link of this zigzag is cloned in infinite columns, which are alternated in the direction of the skeleton packing (Scheme 1).



Heterochiral zigzag, lactamic H-bonding

Homochiral packing, H-bonding with the skeleton substituents

Scheme 1

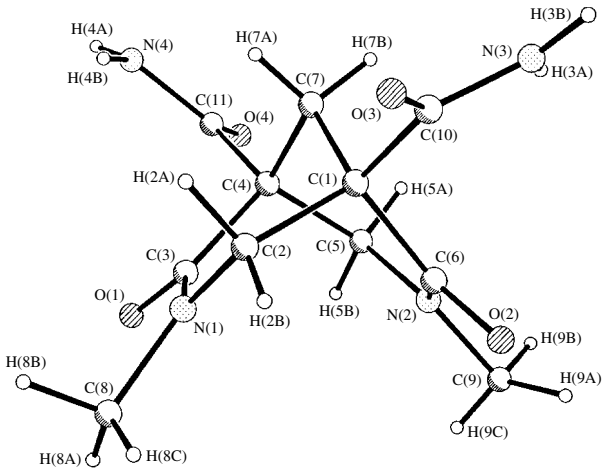
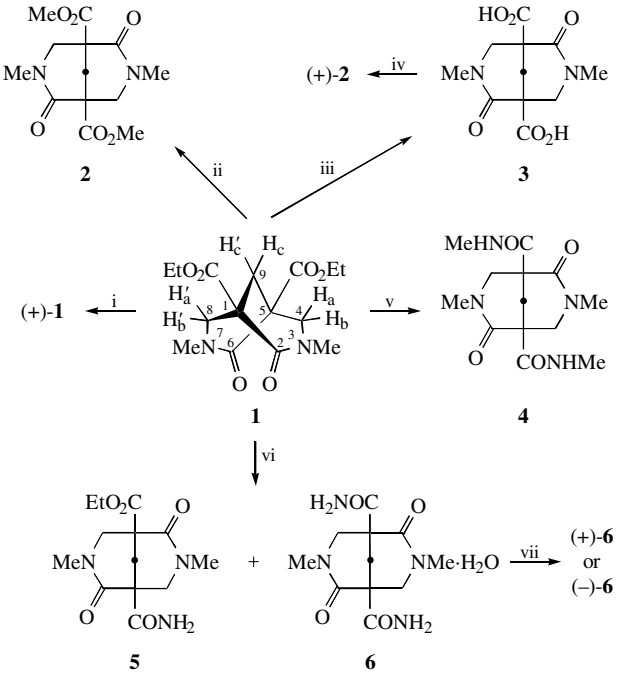


Figure 1 The general view of **6**. Selected bond lengths (Å): O(1)–C(3) 1.232(2), O(2)–C(6) 1.237(2), O(3)-C(10) 1.227(2), O(4)-C (11) 1.228(2), N(1)–C(3) 1.341(2), N(1)–C(2) 1.461(3), N(2)–C(6) 1.330(2), N(2)–C(5) 1.466(2), N(3)-C(10) 1.328(3), N(4)–C(11) 1.337(3); selected bond angles (°): C(3)-N(1)-C (2) 124.5(2), C(3)–N(1)-C(8) 117.8(2), C(2)-N (1)–C(8) 117.6(2), C(6)-N(2)-C (9) 120.0(2), C(6)-N(2)-C(5) 124.6(2), C(9)–N(2)–C(5) 115.4(2), C(6)–C(1)-C (7) 113.0(1), C(6)-C (1)–C(2) 106.9(2), C(7)–C(1)-C (2) 107.3(1), C(6)-C(1)-C(10) 107.5(1), C(7)-C(1)-C(10) 112.1(2), C(2)-C (1)–C(10) 110.0(1), O(1)-C (3)-N(1) 122.4(2), O(1)-C (3)–C(4) 119.2(2), N(1)-C (3)-C(4) 118.2(2), C(5)-C (4)–C(7) 107.1(1), C(5)-C (4)–C(3) 107.1(2), C(7)–C(4)-C (3) 114.2(2), C(5)-C(4)-C (11) 109.1(1), C(7)–C(4)-C(11) 112.8(2), C(3)-C(4)-C(11) 106.3(1), O(2)–C(6)-N (2) 122.5(2), O(2)–C(6)-C (1) 117.8(2), N(2)-C(6)–C(1) 119.7(2), C(1)-C(7)–C(4) 106.3(2).

It was suggested that homochiral self-assembling can be accomplished through H-bonding of the columns by modified 1,5-substituents with the elimination of the lactamic H-bonding by N-methylation (Scheme 1). In this study, we performed a search for conglomerates in the series of 3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane-2,6-dione-1,5-dicarboxylic acid derivatives[1,4,5] (Scheme 2).

Dilactam **1** was prepared by the known method;[4] it was partially enriched with dextrorotatory enantiomer (+)-**1** (ee ≈ 9%) using chromatography on a chiral phase. It was shown that **1** readily undergoes transesterification into **2** and saponification into diacid **3**.[5] The salt of **3** and (*S*)-(–)- -phenylethylamine was partially resolved by crystallization and converted into diester (+)-**2** (ee ≈ 2.5%). Dilactam **1** also readily undergoes amidation with the retention of lactam groups to form bismethylamide **4** under the action of $MeNH_2$ or monoamide **5** and diamide monohydrate **6** on treatment with NH_3. The structures of the products were confirmed by spectroscopic data† and, in



Scheme 2 *Reagents and conditions*: i, chromatography on microcrystalline cellulose triacetate (Fluka), eluent: *n*-hexane-Pr ^{i}OH (95:5); ii, MeOH, cat. MeONa, 18 h at 20 °C; iii, KOH in EtOH, boiling for 0.5 h, 12 h at 20 °C, then HCl in an H_2O-Et $_2O$ mixture, evaporation and extraction with MeCN; iv, (*S*)-(–)- -phenylethylamine in EtOH, crystallization from MeCN and treatment with CH_2N_2 in an Et_2O-M eOH mixture; v, $MeNH_2$ in EtOH, 72 h at 20 °C; vi, an excess of NH_3 in EtOH, cat. EtONa, 6 days at 20 °C; vii, crystallization from H_2O.

the case of **6**, X-ray diffraction analysis‡ (Figure 1). Parameters of the NMR spectra are in a good agreement with those described for dilactams of this series.[1,4,5] The C_2 symmetry of the molecules was confirmed by equivalency of H and C in pairs in the groups 1,5; 2,6; 3,7; 4,8 and 9-CH_2. The chirality of molecules was confirmed by non-equivalency of CH_2O protons in **1**, **5** and by doubling of the signals of **1** in the presence of a chiral shift reagent. The assignment of the spin–spin coupling constants $^3J_{CNCH_b}$ = 2.2 Hz, observed for **1**, **2**, **4** and **6**, is based on the average dihedral angles $MeNCH_b$ and $MeNCH_a$ in **6**, which are equal to 38 and 83°, respectively. For **6**, the found average dihedral angles between carbon in the 9-position and protons H_b, H'_b and between carbon atoms in the 4,8-positions and protons H'_c, H_c are almost equal (173°). However, the spin–spin coupling constants $^3J_{9C\text{-}H_b}$ = 5.8–7.0 Hz observed for **1**, **2**, **4** and **6** are considerably higher than $^3J_{4C\text{-}H'_c}$ = 4.0–4.4 Hz because of the virtual nature of the latter.[5,6] Characteristic virtual long-range spin–spin coupling constants $^4J_{HH}$ of 9-CH_2 protons with H_b, H'_b were observed for compounds **1**–**4**, **6** (*cf.* refs. 1

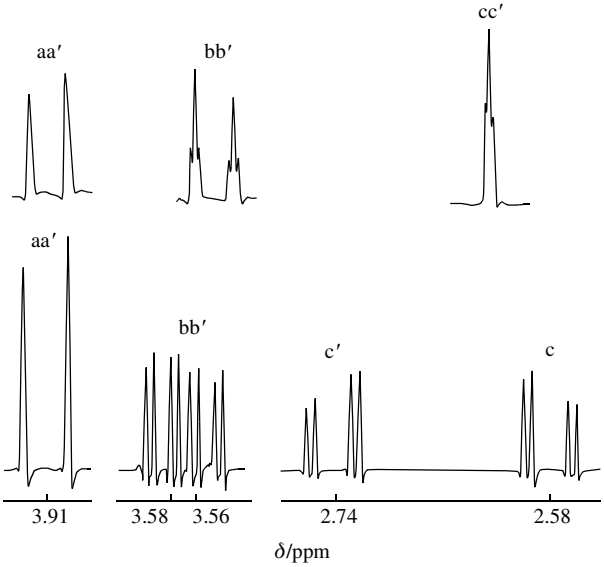


Figure 2 ^{1}H NMR spectra (in CD_3OD) of the ring protons: **5**, $^4J_{bc'}$ = = $^4J_{b'c}$ = 2.7 Hz (below) and **6**, $^4J_{obs}$ 1.3 Hz (above).

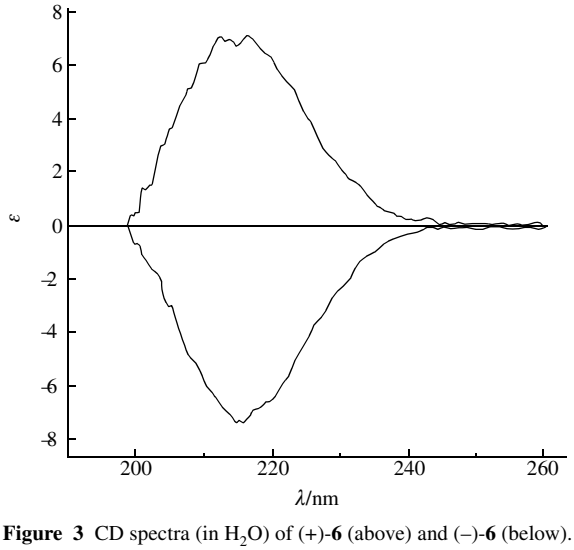


Figure 3 CD spectra (in H_2O) of (+)-**6** (above) and (–)-**6** (below).

† *Characteristics and spectroscopic data.* NMR spectra were measured on a Bruker WM-400 spectrometer (at 400.13 MHz for ^{1}H and at 100.62 MHz for ^{13}C; TMS was an internal standard). Optical rotation was measured on a Polamat A polarimeter, and CD spectra were taken on a JASCO J-500A instrument with a DP-500N data processor.

1 was prepared by the known method,[4] yield 75%, mp 103–104 °C. ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 6H, 2$MeCH_2$, ^3J 7.3 Hz), 2.66 (t, 2H, 9-CH_2, $^4J_{HH_b\ obs}$ 1.2 Hz), 3.00 (s, 6H, 2,7-NMe), 3.67 (dt, 2H, 4,8-CH_b, ^2J –12.7 Hz, $^4J_{H\text{-}9\text{-}C\ H_2\ obs}$ 1.2 Hz), 3.87 (d, 2H, 4,8-CH_a, ^2J –12.7 Hz), 4.25 (m, 4H, 2CH_2Me, ABX_3 spectrum, ν 20.0, ^2J –12.2 Hz, ^3J 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.62 (qt, *Me*CH_2, ^1J 127.3 Hz, ^2J 2.5 Hz), 33.12 (tt, 9-CH_2, ^1J 137.3 Hz, $^3J_{C\text{–}H_b}$ 6.7 Hz), 34.48 (qd, 3,7-NMe, ^1J 139.5 Hz, $^3J_{CNCH_b}$ 2.2 Hz), 49.36 (quint, 1,5-C, ^2J 3.7 Hz), 54.76 (ttq, 4,8-CH_2, ^1J 145.7 Hz, $^3J_{C\text{-}9\text{-}C\ H_2}$ = $^3J_{CNMe}$ = 4.4 Hz), 61.68 (tq, CH_2O, ^1J 148.2 Hz, ^2J 4.4 Hz), 166.0 (sh. s, 2,6-CO), 168.4 (sh. s, 1,5-CCO).

(+)-**1**: yield 36%, $[\alpha]^{20}_{578}$ = +4.6°; $[\alpha]^{20}_{546}$ = +5.1° (*c* 2.3, MeOH); the positive Cotton effect was observed in the CD spectra (MeOH) at 216 nm. In the ^{1}H NMR spectrum of (+)-**1** ($CDCl_3$) in the presence of Eu(tfc)$_3$ the signals from *Me*CH_2, 9-CH_2, and MeN groups are split and shifted to the low field; the δ (ν) values are 12 (1.8), 520 (5.2) and 24 (5.2) Hz, respectively. In the latter case, the ratio between the integral intensity of the enantiomer signals is ~ 1.2, and hence ee ≈ 9%.

2: yield 84%, mp 200–202 °C. ^{1}H NMR ($CDCl_3$) δ: 2.67 (t, 2H, 9-CH_2, $^4J_{HH_b\ vis}$ 1.2 Hz), 3.0 (s, 6H, 3,7-NMe), 3.68 (dt, 2H, 4,8-CH_b, ^2J –12.8 Hz, $^4J_{H\text{-}9\text{-}CH_2\ vis}$ 1.2 Hz), 3.78 (s, 6H, 2MeO), 3.87 (d, 2H, 4,8-CH_a, ^2J –12.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 33.0 (tt, 9-CH_2, ^1J 137.0 Hz, $^3J_{CH_b}$ 7.0 Hz), 34.6 (qd, 3,7-NMe, ^1J 139.5 Hz, $^3J_{CH_b}$ 2.2 Hz), 49.35 (quint, 1,5-C, ^2J 3.6 Hz), 52.66 (q, MeO, ^1J 148.2 Hz), 54.68 (ttq, 4,8-CH_2, ^1J 146.0 Hz, $^3J_{C\text{-}9\text{-}\ CH_2}$ = $^3J_{CNMe}$ = 4.4 Hz), 165.9 (sh. s, 2,6-CO), 168.85 (sh. s, 1,5-C*C*O).

(+)-**2**: yield 68.7%, mp 202–205 °C (MeOH), $[\alpha]^{20}_{D}$ = +0.78°, $[\alpha]^{20}_{546}$ = +1.3° (*c* 1.1, MeOH). According to ^{1}H NMR ($CDCl_3$) in the presence of Eu(tfc)$_3$ [like the case of (+)-**1**], ee ≈ 2.5%.

3: yield 80%, mp 184–185 °C. ^{1}H NMR (CD_3OD) δ: 2.72 (t, 2H, 9-CH_2, $^4J_{HH_b\ vis}$ 1.2 Hz), 2.97 (s, 6H, 3,7-NMe), 3.58 (dt, 2H, 4,8-CH_b, ^2J –12.8 Hz, $^4J_{H\text{-}9\text{-}C\ H_2\ vis}$ 1.2 Hz), 3.94 (d, 2H, 4,8-CH_a, ^2J –12.8 Hz).

4: yield 22%, after sublimation at 230 °C (10 Torr), mp 262–264 °C. ^{1}H NMR ($CDCl_3$) δ: 2.71 (t, 2H, 9-CH_2, $^4J_{HH_b\ vis}$ 1.2 Hz), 2.81 (d, 6H, 2*Me*NH, $^3J_{HCNH}$ 4.9 Hz), 2.96 (s, 6H, 3,7-NMe), 3.50 (dt, 2H, 4,8-H_b, ^2J –12.2 Hz, $^4J_{H\text{–}9\text{–}CH_2\ vis}$ 1.2 Hz), 3.76 (d, 2H, 4,8-H_a, ^2J –12.2 Hz), 8.31 (sh. s, 2H, HN). ^{13}C NMR ($CDCl_3$) δ: 26.44 (qd, MeNH, ^1J 138.1 Hz, ^2J 2.9 Hz), 33.11 (tt, 9-CH_2, ^1J 138.0 Hz, $^3J_{CH_b}$ 6.0 Hz), 35.03 (qd, 3,7-NMe, ^1J 139.5 Hz, $^3J_{CNCH_b}$ 2.2 Hz), 47.86 (quint., 1,5-C, ^2J 3.5 Hz), 58.58 (tm, 4,8-CH_2, ^1J 146.0 Hz), 168.6 (d, CONH, ^2J 7.0 Hz), 169.55 (sh. s, 2,6-CO).

5: yield 25%, mp 158–162 °C (EtOH–Et_2O, 1:2). ^{1}H NMR (CD_3OD) δ: 1.26 (t, 3H, *Me*CH_2, ^3J 7.0 Hz), 2.66 (ddd, 2H, 9-CH_2, ABXY spectrum, ν 64.0, ^2J –13.1 Hz, $^4J_{bc'}$ = $^4J_{b'c}$ = 2.7 Hz), 2.96 (s, 3H, 7-NMe), 2.97 (s, 3H, 3-NMe), 3.56 (dd, 1H, H′$_b$, ^2J –12.7 Hz, $^4J_{b'c}$ 2.7 Hz), 3.58 (dd, 1H, H_b, ^2J –12.7 Hz, $^4J_{bc'}$ 2.7 Hz), 3.91 (d, 2H, $H_aH'_a$, ^2J –12.7 Hz), 4.21 (m, 2H, CH_2O, ABX_3 spectrum, $\nu \approx 3.5$, ^2J –10.7 Hz, ^3J 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 13.6 (qt, ^1J 127.0 Hz, ^2J 2.5 Hz), 32.72 (tt, 9-CH_2, ^1J 137.0 Hz, $^3J_{CH_b}$ = $^3J_{CH'_b}$ = 6.3 Hz), 34.46 (qd, 3-NMe, ^1J 139.3 Hz, $^3J_{CNCH'_b}$ 2.2 Hz), 34.95 (qd, 7-NMe, ^1J 139.0 Hz, $^3J_{CNCH'_b}$ 2.1 Hz), 47.9 (s, 5-C), 49.35 (quint., 1-C, ^2J 3.7 Hz), 55.06 (tm, 8-CH_2, ^1J 146.0 Hz), 57.74 (tm, 4-CH_2, ^1J 147.0 Hz), 61.74 (tq, CH_2O, ^1J 148.0 Hz, ^2J 4.0 Hz), 166.14, 168.61, 168.80 and 170.60 (s, CO).

6: yield 62%, mp 320–325 °C (MeCN). ^{1}H NMR (CD_3OD) δ: 2.63 (t, 2H, 9-CH_2, $^4J_{HH_b\ vis}$ 1.3 Hz), 2.96 (s, 6H, 3,7-NMe), 3.53 (dt, 2H, 4,8-CH_b, ^2J –12.5 Hz, $^4J_{H\text{-}9\text{-}C\ H_2\ vis}$ 1.3 Hz), 3.90 (d, 2H, 4,8-CH_a, ^2J –12.5 Hz). ^{13}C NMR (CD_3OD) δ: 29.17 (tt, 9-CH_2, ^1J 136.6 Hz, $^3J_{CH_b}$ 5.8 Hz), 30.47 (qd, 3,7-NMe, ^1J 141.0 Hz, $^3J_{CNCH_b}$ 2.2 Hz), 44.90 (quint, 1,5-C, ^2J 3.0 Hz), 51.2 (ttq, 4,8-CH_2, ^1J 146.8 Hz, $^3J_{C\text{-}9\ \text{-}CH_2}$ = $^3J_{CNMe}$ = 4.0 Hz), 164.1 (m, 2,6-CO), 168.12 (s, 1,5-C*C*O).

(+)-**6**: yield 11%, $[\alpha]^{18}_{D}$ = +108.5° (*c* 0.14, H_2O), ε +7.25 (λ_{max} 215 nm).

(–)-**6**: yield 3%, $[\alpha]^{18}_{D}$ = –107.3° (*c* 0.12, H_2O), ε –7.25 (λ_{max} 215 nm).

‡ *Crystallographic data for* **6**: $C_{11}H_{18}N_4O_5$, M = 289.29, monoclinic crystals, space group $P2_1$, at –120 °C, a = 7.343(2) Å, b = 9.018(2) Å, c = 9.989 Å, β = 97.26°, V = 656.2(3) Å^3, Z = 2, d_{calc} = 1.449 g cm^{-3}, μ(MoK) = 1.15 cm^{-1}, F(000) = 304. Intensities of 2564 reflections were measured on a Siemens P3 diffractometer at –120 °C (λ MoK radiation, $\theta/2\theta$ scan technique, $2\theta < 64°$) and 2408 independent reflections were used in further calculations and refinement. The structure was solved by the direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the difference Fourier synthesis and refined in the isotropic approximation. The refinement converged to wR_2 = 0.1206 and COF = 1.028 for all independent reflections [R_1 = 0.0406 is calculated against F for 1957 observed reflections with $I > 2\sigma(I)$]. The number of the refined parameters is 253. All calculations were performed using SHELXTL PLUS 5.0 on an IBM PC/AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1999, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/48.

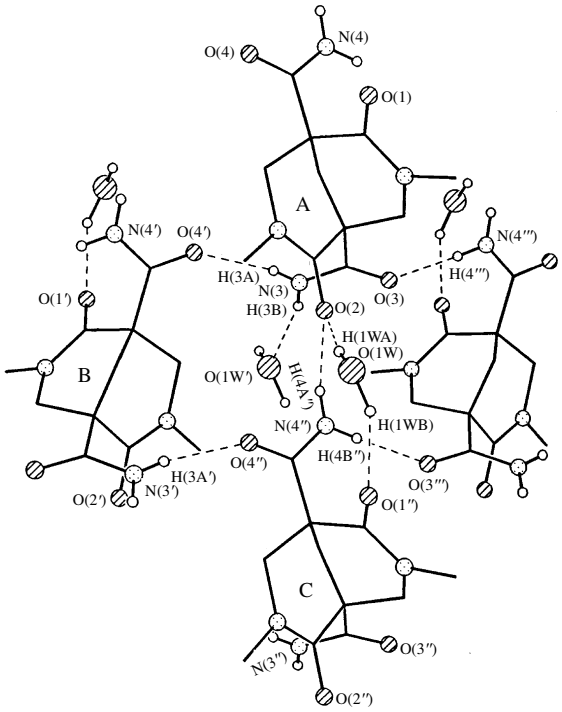


Figure 4 Formation of the H-bonded 'corrugated' layers in the crystal structure of **6**.

and 5). In the desymmetrised system of **5**, they disappear and transform into two sets of usual spin–spin coupling constants, which are approximately two times higher in the absolute value than the virtual constants (Figure 2).

According to the X-ray diffraction data, diamide monohydrate **6** forms a crystalline conglomerate (space group $P2_1$).‡ This fact made it possible to spontaneously resolve **6** by simple crystallization. Racemate (±)-**6** (40 mg) was dissolved in H_2O (1.5 ml) at 60 °C and kept for 24 h at 20 °C; 13.2 mg (33%) of a precipitate was obtained, and four crystals (1.4–1.5 mg each) were selected. Three of these crystals were found to be dextrorotating with $[\alpha]_D^{18}$ = +108.5° (*c* 0.14, H_2O), and one was laevorotating with $[\alpha]_D^{18}$ = –107.3° (*c* 0.12, H_2O); the CD spectra are shown in Figure 3. The mother liquor exhibited no optical activity.

The bond lengths and bond angles in the crystal structure of **6** (Figure 1) are very similar to those of the previously investigated derivatives of a dilactam from the bicyclo[3.3.1]nonane series.[1] The molecule is characterised by almost ideal C_2 local symmetry with small deviations from it for only $CONH_2$ groups. The angle between this C_2 local axis and the crystallographic 2_1 axis is approximately 70°. The bicyclic molecule of **6** is characterised by the double half-chair–half-boat conformation with the deviation of the C(7) atom by 0.7 Å from the planes of the corresponding atoms of the six-membered rings. The rings are twisted with the pseudotorsion angles C(3)–C(4)–C(1)–C(2) and C(5)–C(4)–C(1)–C(6) equal to 17.5 and 17.8°, respectively. The angle between the six-membered rings is 100°.

The angles between the C(1)–C(4)–C(7) plane and the planes of the amido groups are 73.8 and 79.4° for C(10)–O(3)–N(3) and C(11)–O(4)–N(4), respectively. All nitrogen atoms have a planar configuration, the maximum deviation (0.13 Å) was found for the N(4) atom; this is probably caused by the formation of H-bonds.

In the crystal structure, molecules of **6** are assembled into homochiral H-bonded layers (Figure 4), which are in turn connected by H-bonds with solvate water molecules to form a three-dimensional framework. The corrugated layer (parallel with the crystallographic plane *bc*) consists of H-bonded helixes (molecules A···B···C). The C(10)–N(3)–O(3) group takes part in the formation of helixes by the H-bond N(3)–H(3A)···O(4′) (–1 – *x*, 1/2 + *y*, 2 – *z*) [N(3)···O(4′) 3.000(2) Å, N(3)–H(3)–O(4′) 170°] and forms the H-bond with an H_2O molecule of another layer: N(3)–H(3B)···O(1W) (–1 + *x*, *y*, *z*) [N(3)···O(1W) 2.887(2) Å, N(3)–H(3B)–O(1W) 159°] (Figure 5), whereas the C(11)–N(4)–O(4) group interlinks the molecules (A···C) into helixes by the H-bond N(4)–H(4A)···O(2″) (*x*, –1 + *y*, *z*) [N(4)···O(2″) 2.893(2) Å, N(4)–H(4A)–O(2″) 162°] and associates these helixes into layers by the H-bond N(4)–H(4B)···O(3″) (–1 – *x*, –1/2 + *y*, –1 – *z*) [N(4)···O(3″) 2.988(2) Å, N(4)–H(4B)–O(3″) 170°]. Solvate H_2O molecules not only interlink the layers into a three-dimensional framework (Figure 5), but also frame the H-layers by additionally linking molecules (A···C) (Figure 4) by H-bonds with C=O groups of the bicyclic molecule of **6**: O(1W)–H(1WB)···O(1′) (*x*, 1 + *y*, *z*) [O(1W)···O(1′) 2.923(2) Å, O(1W)–H(1WA)–O(1′) 155°] and O(1W)–H(1WA)···O(2) [O(1W)···O(1) 2.792(2) Å, O(1W)–H(1WA)–O(2) 171°].

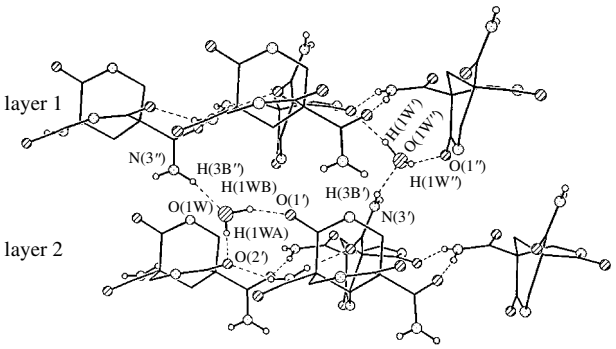


Figure 5 Formation of the three-dimensional H-bonded framework in the crystal structure of **6**. Methyl groups are omitted for clarity.

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