2,5-Diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylic acids: synthesis, resolution, absolute configuration and crystal structures of the racemic and (–)-enantiomeric forms

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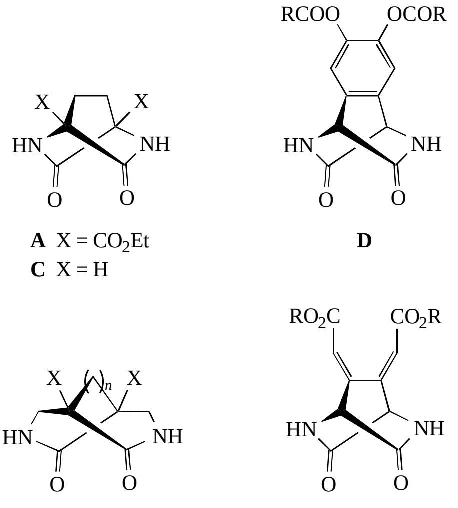
Title dilactam diacid **1** has been synthesised and resolved into enantiomers *via* diastereomeric salts **2** with a chiral amine; the absolute configuration of (1*R*,4*R*)-(–)-**1** was established by decarboxylation and transformation into the parent dilactam (1*R*,4*R*)-(–)-**C**; the molecular and crystal structures of (±)-**1** and (–)-**1** (space groups $P2_1/n$ and $P2_1$, respectively) were determined.

Bicyclic bislactams (BL) of the symmetry C_2 are perfect building blocks for supramolecular chemistry and the engineering of crystals on the basis of self-assembling due to H-bonding[1–7] (Scheme 1, other H-bonded systems see in refs. 7–11).

Chirally directed self-assembling of crystalline parent bislactam **C** into heterochiral infinite tapes of the linear zigzag type [for the (±)-form] and into intricate tetramers of a quite different type [for the (–)-form] were studied by the J.-M. Lehn's group.[2] In the latter case, the expected hexamers have not been realised despite a careful selection of well-matched guest molecules.[3] Functionalised derivatives **D** and **E** have been synthesised, and compound **D** (R = Pr) was resolved into enantiomers;[3] however, its deacylation with the aim of preparing optically active derivatives such as **E** was unsuccessful.



A X = CO_2Et
C X = H

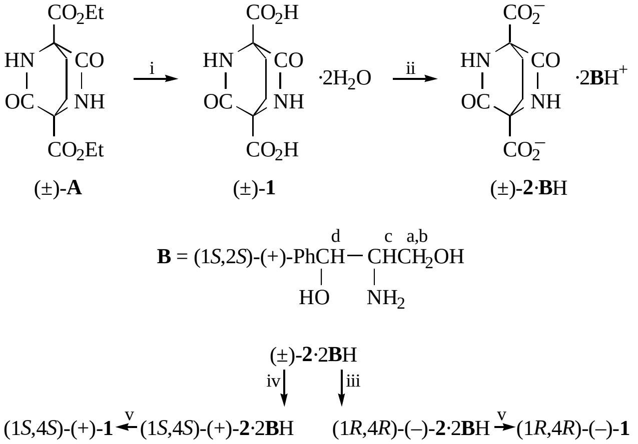
D

F X = H, *n* = 0
G X = H, *n* = 1
H X = CO_2Et, *n* = 0
I X = CO_2Et, *n* = 1

E

Scheme 1

We have developed simple methods for the synthesis of functionalised bislactam **A** from this series[4] as well as parent bislactams **F** and **G** and their functionalised derivatives **H** and **I**.[5,6] For crystalline bislactam **A**, heterochiral self-assembling of the linear zigzag type was observed[4] like the case of (±)-**C**.[2] For bislactams **F**[5] and **I**,[6] heterochiral self-assembling of a new type (diagonal zigzag) was found, whereas homochiral self-assembling into helical suprastructures (space group $P2_12_12_1$) takes place in the case of **G**[6] (Scheme 1).



Scheme 2 *Reagents and conditions*: i, KOH in EtOH–H_2O (3:2), 10 h at 20 °C, then CF_3CO_2H in H_2O at 20 °C and 5 days at 3–5 °C; ii, 2**B** in H_2O at 20 °C and evaporation; iii, triple crystallisation from EtOH–H_2O (10:1), evaporation of combined mother solutions and triple crystallisation of the residue from the same solvent. The residue after evaporation of the initial mother liquid was used in iv; iv, double crystallisation from the same solvent as in iii; v, CF_3CO_2H in H_2O at 20 °C and crystallisation.

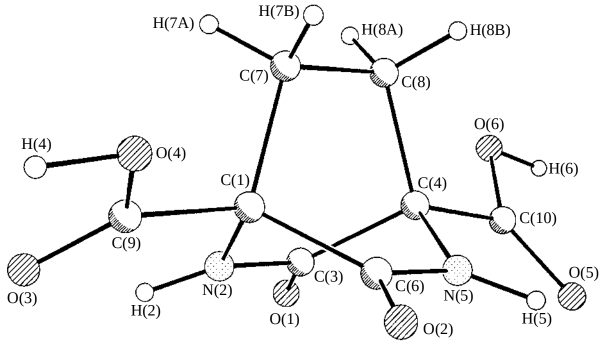


Figure 1 The general view of (±)-**1** and (1*R*,4*R*)-(–)-**1**. Selected bond lengths (Å) for (±)-**1** and (1*R*,4*R*)-(–)-**1** (in brackets): O(1)–C(3) 1.229(1) [1.224(3)], O(2)–C(6) 1.228(1) [1.220(3)], O(3)–C(9) 1.211(1) [1.207(3)], O(5)–C(10) 1.205(1) [1.193(3)], N(2)–C(3) 1.333(1) [1.337(3)], N(2)–C(1) 1.460(1) [1.455(3)], N(5)–C(6) 1.343(1) [1.340(3)], N(5)–C(4) 1.466(1) [1.467(3)]; selected bond angles (°) for (±)-**1** and (1*R*,4*R*)-(–)-**1** (in brackets): C(3)–N(2)–C(1) 117.74(8) [117.9(2)], C(6)–N(5)–C(4) 117.20(8) [117.2(2)], N(2)–C(1)–C(6) 107.84(8) [107.8(2)], N(2)–C(1)–C(7) 108.22(8) [108.3(2)], C(6)–C(1)–C(7) 105.51(8) [105.9(2)], O(1)–C(3)–N(2) 126.3(1) [126.7(2)], O(1)–C(3)–C(4) 124.91(9) [124.7(2)], N(2)–C(3)–C(4) 108.79(8) [108.5(2)], N(5)–C(4)–C(3) 107.55(8) [107.8(2)], N(5)–C(4)–C(8) 108.44(8) [107.8(2)], C(3)–C(4)–C(8) 105.86(8) [106.0(2)], O(2)–C(6)–N(5) 125.8(1) [126.4(2)], O(2)–C(6)–C(1) 125.38(9) [124.9(2)], N(5)–C(6)–C(1) 108.75(8) [108.8(2)], C(8)–C(7)–C(1) 108.28(8) [107.8(2)].

Table 1 The parameters of H-bonds in the crystal stuctures of (±)-**1** and (1*R*,4*R*)-(–)-**1**.

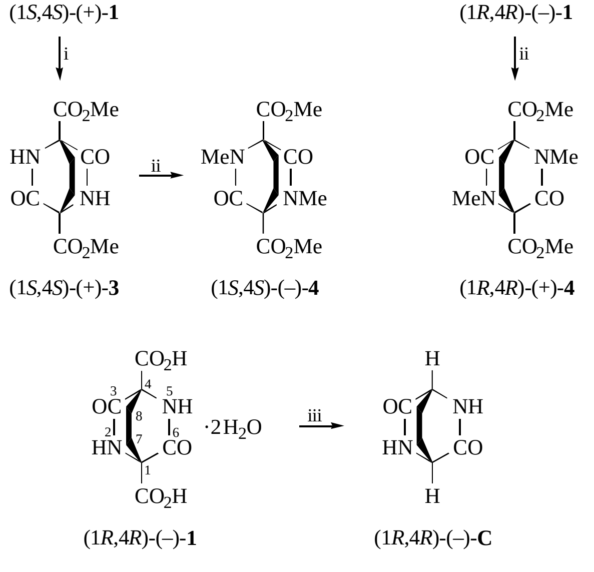
Entry	Parameter	(±)-**1**	(1*R*,4*R*)-(–)-**1**
1	N(2)–H(2)···O(5′)	1.96 Å	1.97 Å
	N(2)–H(2)–O(5′)	156°	161°
	N(2)···O(5′)	2.791(1) Å	2.780(2) Å
		(1/2 – *x*, –1/2 + *y*, 3/2 – *z*)[a]	(–*x*, 1/2 + *y*, –2 + *z*)
2	N(5)–H(5)···O(1′′)	2.33 Å	2.22 Å
	N(5)–H(5)–O(1′′)	166°	163°
	N(5)···O(1′′)	3.198(1) Å	3.086(3) Å
		(1/2 – *x*, –1/2 + *y*, 3/2 – *z*)	(–*x*, –1/2 + *y*, 2 – *z*)
3	O(4)–H(4)···O(1w)	1.545 Å	1.76 Å
	O(4)–H(4)–O(1w)	177°	176°
	O(4)···O(1w)	2.542(1) Å	2.559(3) Å
4	O(6)–H(6)···O(2w)	1.689 Å	1.675 Å
	O(6)–H(6)–O(2w)	176°	167°
	O(6)···O(2w)	2.600(1) Å	2.581(3) Å
5	O(1w)–H($1w_A$)···O(1)	2.074 Å	2.15 Å
	O(1w)–H($1w_A$)–O(1)	155°	146°
	O(1w)···O(1)	2.868(1) Å	2.848(3) Å
6	O(1w)–H($1w_B$)···O(2′)	2.04 Å	1.93 Å
	O(1w)–H($1w_B$)–O(2′)	176°	173°
	O(1w)···O(2′)	2.901(1) Å	2.848(3) Å
		(1/2 – *x*, –1/2 + *y*, 3/2 – *z*)	(–*x*, 1/2 + *y*, –3 + *z*)
7	O(2w)–H($2w_A$)···O(2)	2.39 Å	2.294 Å
	O(2w)–H($2w_A$)–O(2)	176.3°	149°
	O(2w)···O(2)	3.086(1) Å	2.977 Å
8	O(2w)–H($2w_A$)···O(4)	2.116 Å	2.38 Å
	O(2w)–H($2w_A$)–O(4)	141°	130°
	O(2w)···O(4)	2.843(1) Å	2.933(3) Å
9	O(2w)–H($2w_B$)···O(3′)	1.926 Å	2.022 Å
	O(2w)–H($2w_B$)–O(3′′)	177°	163°
	O(2w)···O(3′)	2.834(1) Å	2.832(3) Å
		(1/2 – *x*, 1/2 + *y*, 3/2 + *z*)	(1 – *x*, –1/2 + *y*, 3 – *z*)

[a]The symmetrical transformation was used to generate equivalent atoms.

In this work, bislactam diacid **1** has been synthesised from bislactam diester **A**[4] for the first time, and its complete resolution into enantiomers was carried out using aminodiol **B** stable to carbonization as a resolving reagent[12] (Scheme 2). The esterification, N-methylation and decarboxylation of enantiomers **1** were studied (Scheme 3).

All products were characterised by elemental analysis and spectroscopic data (*cf.* **A**[4]).[†] The optical purity (> 95%) of derivative (–)-**4** was determined by ^{1}H NMR spectroscopy using a chiral shift reagent. The absolute configuration of diacid (1*R*,4*R*)-(–)-**1** was found on the basis of its thermal decarboxylation into the bislactam of the known absolute configuration (1*R*,4*R*)-(–)-**C** [the synthesis of (1*S*,4*S*)-(+)-**C** based on (*S*)-homoserine was reported earlier[13]]. Under severe conditions of decarboxylation,[13] the optical purity of product **C** substantially decreases (ref. 2).

The X-ray diffraction study[‡] of dihydrates (±)-**1** and (–)-**1** (Figure 1) revealed an astonishing similarity between their crystal packing patterns (Figure 2). The molecules are assembled by H-bonding both of the lactamic CO with NH groups and the lactamic NH with CO of the group CO_2H (Table 1, entries 1 and 2, respectively). As a result, the homochiral helices are formed, which can be regarded as tapes of the double zigzag type with the zigzag width d_1 equal to 11.26 and 11.59 Å for (–)-**1** and (±)-**1**, respectively (Figure 2). These tapes are



Scheme 3 *Reagents and conditions*: i, 2 equivalents of CH_2N_2 in Et_2O/MeOH, 15 min at 20 °C; ii, excess of CH_2N_2 in Et_2O/MeOH, 24 h at 20 °C; iii, heating of the mixture with sand, 15–20 min at 250–280 °C *in vacuo* (10–20 Torr) accompanied with sublimation of the product.

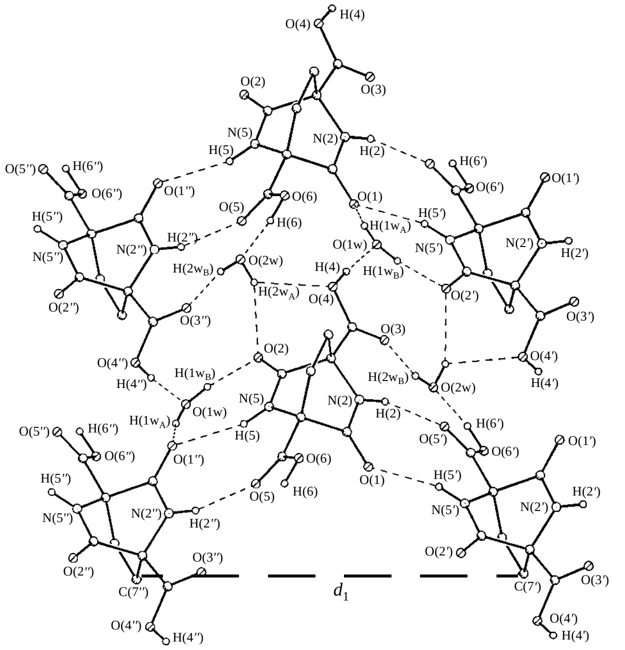


Figure 2 The embedding of the 'corrugated' layers in the crystal structures of (±)-**1** and (1*R*,4*R*)-(–)-**1**.

assembled by H_2O molecules into the corrugated homochiral layers (Figure 3, Table 1), and the layers are embedded to one another in a manner as the (–) layer into (–) layer in a homochiral crystal and the (–) layer into the (+) layer in a racemic one. The parameters of embedding d_2 are equal to 1.13 and 1.21 Å for (–)-**1** and (±)-**1**, respectively (Figure 3). Like (±)-**A**,[4] in the case of (±)-**1**, the C–H···O contacts (*ca.* 3.28 Å) were found between the bridge C(7)–C(8) hydrogen and O(2), O(5) oxygen atoms of the adjacent layer. It is noteworthy that the similarity of packings was not observed for the pair of (–)- and (±)-**C**.[2] In the latter, as well as in all other bislactams studied earlier such as (±)-**A**,[5] **F**, **H**,[5] and **G**, **I**,[6] the molecular self-assembling in crystals occurs solely by H-bonding of lactam groups.

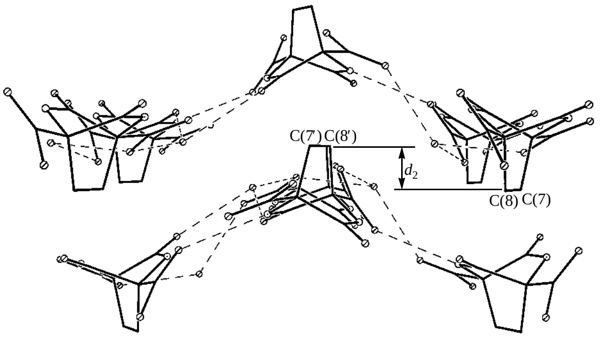


Figure 3 ‘Corrugated’ layers in the crystal structures of (±)-**1** and (1*R*,4*R*)-(–)-**1**.

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† *Characteristics and spectroscopic data.* The NMR spectra were measured on a Bruker WM-400 spectrometer (at 400.13 MHz for ^1H and 100.62 MHz for ^{13}C with reference to TMS). Optical rotation was measured on a Polamat A polarimeter. The CD spectra were taken on a JASCO J-500A instrument. Compound (±)-**A** was obtained by the method described previously.[4]

(±)-**1**: yield 80%, mp 284–286 °C (H_2O). ^1H NMR (CD_3OD) δ: 2.33 (m, 7,8-CH_2, AA′BB′ spectrum, $\Delta\nu$ 38.0 Hz, $^2J_{AB} = {}^2J_{A'B'} = -13.5$ Hz, $^3J_{AB'} = {}^3J_{A'B} = 10.9$ Hz, $^3J_{BB'}$ 4.8 Hz, $^3J_{AA'}$ 3.9 Hz). Found (%): C, 36.36; H, 4.56. Calc. for $C_8H_{12}N_2O_8$ (%): C 36.37; H 4.58.

dipotassium salt of (±)-1: mp > 360 °C. ^1H NMR (D_2O) δ: 2.28 (m, 7,8-CH_2, AA′BB′ spectrum, $\Delta\nu \approx 25$ Hz). ^{13}C NMR {^1H}(D_2O) δ: 30.38 (7,8-CH_2), 68.75 (1,4-C), 173.22 (3,6-CO), 174.60 (CO_2^-).

(1*S*,2*S*)-(+)-**B**: $[\alpha]_D^{20}$ +27.0° (*c* 1.0, MeOH). ^1H NMR (CD_3OD) δ: 2.90 (ddd, 1H, H_c, $^3J_{cd}$ 6.7 Hz, $^3J_{ac}$ 6.4 Hz, $^3J_{bc}$ 4.4 Hz), 3.38 (m, 2H, CH_2, ABX spectrum, $\Delta\nu$ 52 Hz, $^2J_{ab}$ –10.7 Hz, $^3J_{ac}$ 6.4 Hz, $^3J_{bc}$ 4.4 Hz), 4.55 (d, 1H, H_d, $^3J_{cd}$ 6.7 Hz), 7.26–7.35 (m, 5H, Ph).

(±)-**2**·2**B**H: yield ≈ 100%, mp 231–233 °C, $[\alpha]_D^{20}$ 20.3° (*c* 1.2, H_2O). ^1H NMR (CD_3OD) δ: 2.22 (m, 4H, 7,8-CH_2, AA′BB′ spectrum, $\Delta\nu$ 96 Hz), 3.27 (ddd, 2H, 2H_c, $^3J_{cd}$ 8.8 Hz, $^3J_{ac}$ 6.0 Hz, $^3J_{bc}$ 3.4 Hz), 3.46 (m, 4H, 2CH_2, ABX spectrum, $\Delta\nu$ 56 Hz, ^2J –11.7 Hz, $^3J_{ac}$ 6.0 Hz, $^3J_{dc}$ 3.4 Hz), 4.73 (d, 2H, 2H_d, $^3J_{cd}$ 8.8 Hz), 7.30–7.45 (m, 10H, 2Ph).

(1*R*,4*R*)-(–)-**2**·2**B**H: yield 46%, mp 238–239 °C, $[\alpha]_D^{20}$ +17.2° (*c* 0.7, H_2O).

(1*S*,4*S*)-(+)-**2**·2**B**H: yield 22.6%, mp 240–241 °C, $[\alpha]_D^{20}$ +23.5° (*c* 0.7, H_2O).

(1*S*,4*S*)-(+)-**1**: yield 50%, mp 273–275 °C, $[\alpha]_D^{20}$ +35.3° (*c* 0.7, MeOH); CD (MeOH): $\Delta\varepsilon$ +0.3 (246 nm), +0.25 (243 nm), +5.35 (225 nm), 0 (210 nm), –4.5 (201.5 nm).

(1*R*,4*R*)-(–)-**1**: yield 70%, mp 275 °C (decomp.), $[\alpha]_D^{20}$ –35.8° (*c* 0.6, MeOH); CD (MeOH): $\Delta\varepsilon$ –0.37 (246 nm), –0.28 (243 nm), –6.53 (225 nm), 0 (210 nm), –5.5 (201.5 nm).

(1*S*,4*S*)-(+)-**3**: yield 70.5%, mp 234 °C (MeOH), $[\alpha]_D^{20}$ +45.2° (*c* 0.6, MeOH). ^1H NMR ($CDCl_3$) δ: 2.40 (m, 4H, 7,8-CH_2, AA′BB′ spectrum, $\Delta\nu$ 84 Hz), 3.95 (s, 6H, 2MeO), 6.82 (br. s, 2H, 2,5-NH).

(1*S*,4*S*)-(–)-**4**: yield 50%, mp 160–162 °C (MeOH), $[\alpha]_D^{20}$ –12.2° (c 0.3, MeOH). ^1H NMR ($CDCl_3$) δ: 2.25 (br. s, 4H, 7,8-CH_2), 2.98 (s, 6H, 2,6-MeN), 3.94 (s, 6H, 2MeO).

(1*R*,4*R*)-(+)-**4**: yield 76.3%, mp 161–162 °C (MeOH), $[\alpha]_D^{20}$ +12.5° [*c* 1.7, in the presence of the chiral shift reagent Eu(tfc)$_3$, the signal of MeN was shifted from 2.98 to 3.27 ppm; when (+)-**4** was added, another signal ($\Delta\nu$ 4.4 Hz) appeared in this field; thus, the optical purity of (–)-**4** is higher than 95%].

(1*R*,4*R*)-(–)-**C**: yield 30–52%, mp 272–273 °C, $[\alpha]_D^{20}$ –7.0° (*c* 0.6, MeOH), optical purity ≈ 9%. ^1H NMR (CD_3OD) δ: 1.98 (m, 4H, 7,8-CH_2, AA′BB′ spectrum at {3.9 ppm}, $\Delta\nu$ 64 Hz), 3.90 (m, 2H, 1,4-CH, $^3J \approx 3.0$ Hz).

‡ *Crystallographic data for* (±)-**1** and (1*R*,4*R*)-(–)-**1** at 25 °C: crystals of $C_8H_{12}N_2O_8$ (±)-**1** are monoclinic, space group $P2_1/n$, $a = 8.900(4)$ Å, $b = 11.590(3)$ Å, $c = 10.401(2)$ Å, $\beta = 92.93(3)°$, $V = 1071.5(6)$ Å^3, $Z = 4$, $M = 264.20$, $d_{calc} = 1.638$ g cm^{-3}, μ(MoKα) = 1.40 cm^{-1}, $F(000) = 552$; crystals of $C_8H_{12}N_2O_8$ (1*R*,4*R*)-(–)-**1** are monoclinic, space group $P2_1$, $a = 6.871(3)$ Å, $b = 11.260(3)$ Å, $c = 7.162(2)$ Å, $\beta = 93.98(3)°$, $V = 552.8(3)$ Å^3, $Z = 2$, $M = 264.20$, $d_{calc} = 1.587$ g cm^{-3}, μ(MoKα) = = 1.44 cm-1, $F(000) = 276$. Intensities of 4101 reflections for (±)-**1** and 1373 reflections for (1*R*,4*R*)-(–)-**1** were measured on a Siemens P3 diffractometer at 25 °C (λ MoKα radiation, $\theta/2\theta$-scan technique, $2\theta_{max}$ 52° and 63°), 3894 for (±)-1 and 1272 for (1*R*,4*R*)-(–)-**1** independent reflections were used in further calculations and refinement. The structures were solved by the direct method and refined by a full-matrix least squares 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 $wR_2 = 0.1310$ and COF = 1.040 for all independent reflections [$R_1 = 0.0419$ is calculated against F for the 3314 observed reflections with $I > 2\sigma(I)$] for structure (±)-1 and to $wR_2 = 0.0955$ and COF = 1.063 for all independent reflections [$R_1 = 0.0319$ is calculated against F for the 1186 observed reflections with $I > 2\sigma(I)$] for structure (1*R*,4*R*)-(–)-**1**. All calculations were performed using the SHELXTL PLUS 5.0 program 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 should quote the full literature citation and the reference number 1135/45.