Chirality-directed co-crystallization of different configurationally opposite dialkyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates

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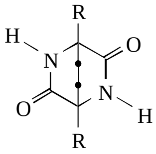
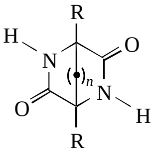
The title procedure gives quasi-racemic optically active (CD) co-crystals of **4** (space group $P2_1$) and **5** of the 1:1 composition; in [CD(–)230]-**4**, molecules of (–)-**1** and (+)-**2** are joined by amide H-bonds into infinite linear zigzag tapes packed as infinite columns.

In racemic bislactams of the C_2 symmetry, the chirality-directed stereospecific self-assembling of molecules in the crystal by H-bonding into infinite linear zigzag tapes for **A**,[1,2] (±)-**1**,[3] diagonal zigzags for **C**,[4] **D**[5] and double zigzags (helices) for **B**[4] with the formation of centrosymmetric crystals was observed.



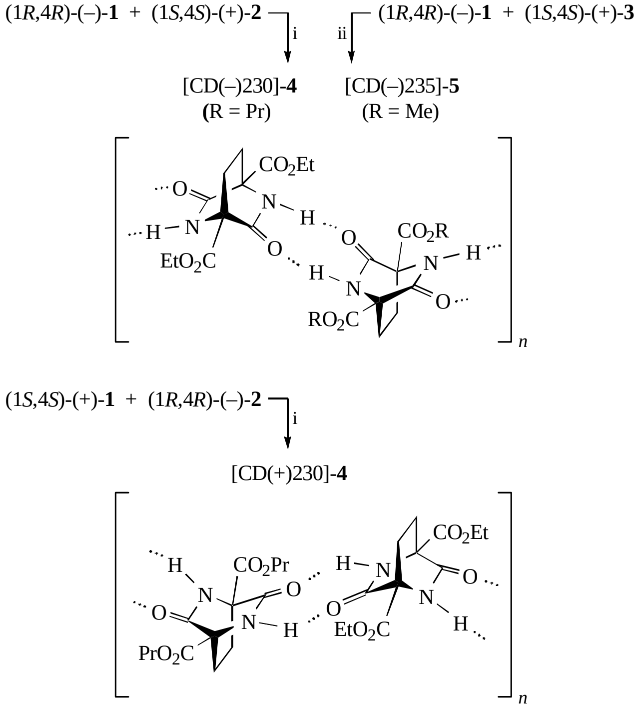
A R = H
B R = CO_2H
(±)-**1** R = CO_2Et



C R = H, *n* = 0
D R = CO_2Et, *n* = 1

Thus, in the case of bislactam diesters **1** and **D**, it was reasonable to expect the chirality-directed co-crystallization of two different diesters of opposite configurations to form a non-centrosymmetric quasi-racemic co-crystal. This possibility was implemented in this study.

Indeed, typical plate-like co-crystals of **4** and **5**, respectively, were formed in the co-crystallization of an enantiomerically pure diethyl ester with a dipropyl or dimethyl ester of the bislactam diacid of opposite configuration (Scheme 1). Their composition (1:1) was supported by NMR† and X-ray diffraction studies,‡ and optical activity was detected by the CD method.†



Scheme 1 *Reagents and conditions*: i, equimolar quantities of bislactams in MeCN (0.5 h at 20 °C), and separation of crystals; ii, the same, in MeOH.

Table 1 Distances between the centres of C(7)–C(8) bonds in adjacent molecules in a column (d_1), a zigzag (d_2) and adjacent zigzags (d_3).

Compound	d_1/Å	d_2/Å	d_3/Å
4	5.597	10.198	11.866
(±)-**1**[3]	5.568	10.189	11.626

According to X-ray diffraction data‡ (Figure 1), a co-crystal of [CD(–)230]-**4** is noncentrosymmetric. Molecules of (–)-**1** and (+)-**2** in this crystal are strictly alternating and joined by amide H-bonds into infinite linear zigzag tapes [Figure 1(B)]. Each of the esters is packed to form its own infinite columns [Figure 1(A)]. The unit-cell, structure and packing parameters of **4** are similar to those observed for (±)-**1**[3] (Table 1).

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† *Characteristics and spectroscopic data*. ^{1}H NMR spectra were measured on a Bruker WM-400 spectrometer at 400.13 MHz with TMS as an internal standard. Optical rotation and CD spectra were measured on a Polamat A polarimeter and a JASCO J-500 A instrument, respectively.

(1*S*,4*S*)-(+)-**1**: yield 45%, mp 233–234 °C, the ^{1}H NMR spectrum ($CDCl_3$) is identical to that described earlier,[3] in the presence of $Eu(tfc)_3$ the only signal of HN at 6.96 ppm was observed in the spectrum of (+)-**1**, whereas the signals of HN of enantiomers at 6.94 and 6.97 ppm ($\Delta\nu$ = 12 Hz) were observed for (±)-**1**; $[\alpha]_D^{20}$ = 38.6° (*c* 1.9, MeOH); CD spectrum, cell 0.5 mm, $\Delta\varepsilon$ (λ_{max}/nm): in H_2O (*c* 7.8×10^{-3} M): +0.1 (249), –0.7 (237), +6.9 (220), –4.2 (200); in MeOH (*c* 10^{-2} M): +0.7 (248), +15.5 (224), –8.6 (205); in MeCN (*c* 6.1×10^{-3} M): +6.0 (227), –5.5 (200).

(1*R*,4*R*)-(–)-**1**: yield 27%, mp 230–233 °C, $[\alpha]_D^{20}$ = –35.7° (*c* 1.3, MeOH); CD spectrum in MeOH (*c* 10^{-2} M), $\Delta\varepsilon$ (λ_{max}/nm): –0.6 (248), –14.3 (224), +8.0 (205).

(1*S*,4*S*)-(+)-**2**: yield 60%, mp 180 °C, $[\alpha]_D^{20}$ = 28.6° (*c* 0.5, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 6H, 2Me, ^3J 7.3 Hz), 1.76 (qt, 4H, $2CH_2$Me, ^3J 7.3 Hz), 2.40 [m, 4H, $(CH_2)_2$, AA′BB′ spectrum, $\Delta\nu \approx$ 88 Hz], 4.31 (m, 4H, $2CH_2O$, ABX_2 spectrum, $\Delta\nu$ = 15.0 Hz, ^2J –10.7 Hz, ^3J 7.3 Hz), 6.78 (br. s, 2H, 2HN).

(1*R*,4*R*)-(–)-**2**: yield 54%, mp 181 °C, $[\alpha]_D^{20}$ = –28.8° (*c* 0.7, MeOH).

(1*S*,4*S*)-(+)-**3**: yield 75%, mp 233–234 °C, $[\alpha]_D^{20}$ = 44.8° (*c* 0.2, MeOH).

(1*R*,4*R*)-(–)-**3**: yield 80%, mp 234 °C, $[\alpha]_D^{20}$ = –45° (*c* 0.2, MeOH). ^{1}H NMR spectra of (+)-**3** and (–)-**3** are identical to those described earlier.[4]

[CD(–)230]-**4**: yield ~100%, mp 219–220 °C, $[\alpha]_D^{20} \approx$ 0° (*c* 0.3, MeOH); CD spectrum in MeOH, cell 2 mm (*c* 4.5×10^{-3} M), $\Delta\varepsilon$ (λ_{max}/nm): –0.34 (230). ^{1}H NMR ($CDCl_3$) δ: 0.99 (t, 6H, 2*Me*CH_2, ^3J 7.2 Hz), 1.37 (t, 6H, 2*Me*CH_2O, ^3J 7.4 Hz), 1.75 (qt, 4H, $2CH_2$Me, ^3J 7.2 Hz), 2.40 [m, 8H, $(CH_2)_2$, AA′BB′ spectrum, $\Delta\nu \approx$ 88 Hz], 4.30 (m, 4H, CH_2CH_2O, ABX_2 spectrum), 4.40 (m, 4H, $2MeCH_2O$, ABX_3 spectrum, $\Delta\nu$ = 13.0 Hz, ^2J –12.0 Hz, ^3J 7.4 Hz), 6.81 (br. s, 2H, 2HN), 6.83 (br. s, 2H, 2HN).

[CD(+)230]-**4**, yield ~100%, mp 223 °C, $[\alpha]_D^{20} \approx$ 0° (*c* 0.3, MeOH); CD spectrum in MeOH (*c* 4×10^{-3} M), $\Delta\varepsilon$ (λ_{max}/nm): 0.36 (230).

[CD(–)235]-**5**: yield 15%, mp 228–229 °C, $[\alpha]_D^{20} \approx$ 0° (*c* 0.3, MeOH); CD spectrum in MeOH, cell 2 mm (*c* 1.2×10^{-3} M), $\Delta\varepsilon$ (λ_{max}/nm): –0.45 (235), +0.25 (220); ^{1}H NMR, δ: 1.40 (t, 6H, 2*Me*CH_2O, ^3J 7.1 Hz), 2.40 [m, 8H, $2(CH_2)_2$, AA′BB′ spectrum, $\Delta\nu \approx$ 82 Hz], 3.96 (s, 6H, 2MeO), 4.40 (m, 4H, $2CH_2O$, ABX_3 spectrum, $\Delta\nu$ = 13.0 Hz, ^2J –12.0 Hz, ^3J 7.1 Hz), 6.82 (br. s, 2H, 2HN), 6.85 (br. s, 2H, 2HN).

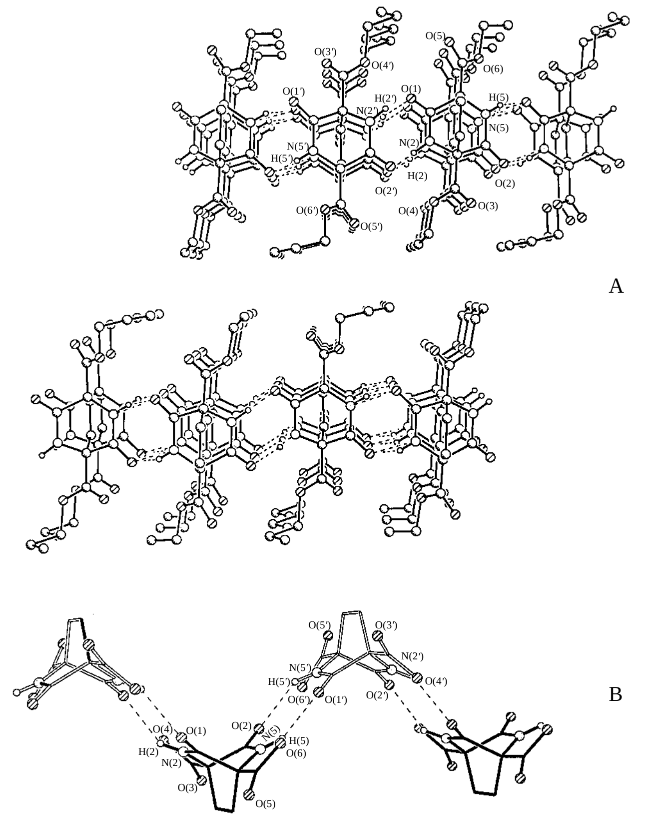


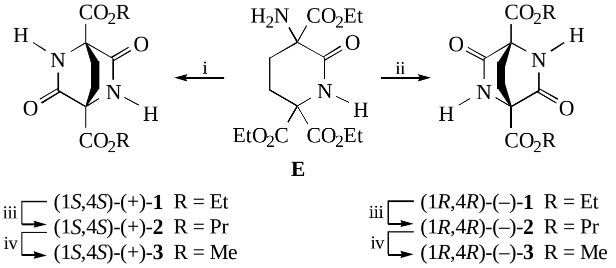
Figure 1 The zigzag tapes in the crystal structure of [CD(–)230]-**4** directed along the crystallographic axis *a* (in projections A and B) and columns directed along the axis *b* (projection A). In the projection B, the Et and Pr groups are omitted for clarity. The parameters of the H-bonds are: N(2)–H(2)···O(2′) (–1 + *x*, *y*, *z*) [H(2)···O(2′) 2.13 Å, N(2)–H(2)–O(2′) 146°, N(2)···O(2′) 2.901(7) Å]; N(5)–H(5)···O(1′) [H(5)···O(1′) 2.09 Å, N(5)–H(5)–O(1′) 152°, N(5)···O(1′) 2.893(7) Å]; N(2′)–H(2′)···O(1) (1 +*x*, *y*, *z*) [H(2′)···O(1) 2.15 Å, N(2′)–H(2′)–O(1) 148°, N(2′)···O(1) 2.930(7) Å]; N(5′)–H(5′)···O(2) [H(5′)···O(2) 2.15 Å, N(5′)–H(5′)–O(2) 149°, N(5′)···O(2) 2.940(7) Å].

Enantiomeric bislactam diesters **1**–**3** were prepared according to Scheme 2. Their structure was supported by spectral data† and X-ray diffraction data‡ for (–)-**1** (Figure 2).

Final enantiomeric purification of (+)- and (–)-**1** was performed by crystallization from MeCN. In this case, the racemate was initially precipitated. The optical purity of (+)-**1** was determined by ^{1}H NMR using a chiral shift reagent.† The optical purity of (+)-**3** was monitored by the value of $[\alpha]_D$ (*cf.* ref. 4). The absolute configuration of the diesters follows from the fact that the consecutive transesterification (+)-**1** → (+)-**2** → (+)-**3** gives (1*S*,4*S*)-(+)-**3**, the configuration of which was found by chemical correlation.[4] Moreover, the opposite configuration of diesters (–)-**1** and (+)-**2** (Figure 1) follows from the results of X-ray diffraction analysis of [CD(–)230]-**4**. The absolute configurations of (1*S*,4*S*)-(+)- and (1*R*,4*R*)-(–)-**1** were independently supported by the CD data.† The Cotton effect at 220–270 nm was attributed to the *n*–π* transition of the diketopiperazine chromophore on the basis of a typical long-wave shift with decreasing polarity of the solvent.† According to refs. 7–9, the sign of this Cotton effect is associated with the chirality of a fixed conformation of the bislactam.

Like the case of (–)-**A**,[2] expected cyclohexamerization[2] does not occur in the crystal structure of (–)-**1**, although similar H-bonded aggregation of molecules was observed previously (trimerization in solution[10] and hexamerization in crystals of trimesic acid, isophthalic acid derivatives[11] and tetralactams, which form molecular tectones[12]). Similarly to (–)-**B** and (±)-**B**,[4] molecules in a crystal of (–)-**1** are joined by H-bonds with the participation of CONH and CO_2 groups into helical suprastructures which can be considered as infinite double zigzag tapes (Figure 2). In this case, the molecules are packed in infinite columns as well as in crystals of **4**, (–)-**A**[2] and (±)-**1**[3] with similar values of the parameter d_1 = 5.534 Å (*cf.* Table 1). Note that the formation of columns was not observed in (±)-**A**.[2] In the case of (–)-**1** and (–)-**B**,[4] the C–H···O contacts[13] between hydrogen atoms of the C(7)–C(8) bridge and oxygen atoms of the lactam groups, which are typical of the majority of the bislactams examined [**4**, (±)-**A** and (–)-**A**,[2] (±)-**1**[3] and (±)-**B**[4]], are absent.

The results obtained are interesting from two standpoints. First of them is the problem of quasi-racemates,[14] the study of which dates back to Pasteur.[15] Examples of the use of quasi-racemates for separating enantiomers are well known.[14] In this respect, we attempt to choose CO_2R groups of bislactam diesters, which are appropriate for the formation of a hydrophobic zipper[16] in the co-crystallised substance. We anticipate to separate the racemate of one ester by co-crystallization with a half-molar amount of an enantiomer of another ester. Another procedure can consist in the preparation of a conglomerate like **4** by co-crystallization of racemates of two diesters (Scheme 1). The second aspect is intensely developed crystal engineering by co-crystallization.[1,13,17–23] Chirality-directed co-crystallization of different bislactams[5,6] and bisureas[24] is examined from this standpoint.



Scheme 2 *Reagents and conditions*: i, an equimolar amount of (–)-dibenzoyl-L-tartaric acid in MeCN at 20 °C, evaporation to dryness, single crystallization from a MeCN–C_6H_6 (1:15) mixture and separation from the mother liquor (for using in ii); next, treatment with Et_3N in Et_2O, separation of the precipitate, evaporation of the solution to dryness, and holding the residue in MeCN with a catalytic amount of DBU (1 week at 20 °C); the removal of the racemate precipitate and separation of DBU by chromatography on silica gel (40/100) with an AcOEt–EtOH (10:1) eluent; ii, evaporation of the mother liquor separated in i and further treatment according to i; iii, PrOH and a catalytic amount of DBU (1.5 months at 20 °C), evaporation and chromatography on silica gel according to i; iv, boiling in MeOH in the presence of DBU (12 h), cooling (10 h at 4 °C) and separation of the precipitate.

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‡ *Crystallographic data for* (1*R*,4*R*)-(–)-**1** and [CD(–)230]-**4** at –120 °C: crystals of $C_{12}H_{16}N_2O_6$ (–)-**1** are orthorhombic, space group $P2_12_12_1$, a = 5.534(3) Å, b = 9.908(4) Å, c = 25.773(10) Å, V = 1413(1) Å^3, Z = 4, M = 284.27, d_{calc} = 1.336 g cm^{-3}, μ(MoKα) = 1.08 cm^{-1}, F(000) = 600; crystals of $C_{26}H_{36}N_4O_{12}$ **4** are monoclinic, space group $P2_1$, a = = 10.199(7) Å, b = 5.597(3) Å, c = 25.11(2) Å, β = 95.96(5)°, V = = 1425(2) Å^3, Z = 2, M = 596.59, d_{calc} = 1.390 g cm^{-3}, μ(MoKα) = = 1.11 cm^{-1}, F(000) = 632. Intensities of 1922 independent reflections for (–)-**1** and of 3616 reflections for **4** were measured on a Siemens P3 diffractometer at –120 °C (λ MoKα radiation, $\theta/2\theta$-scan technique, $2\theta_{max}$ < 55°) and were used in further calculations and refinement. The structures were solved by a direct method and refined by a full-matrix least squares against F^2 in the anisotropic–isotropic approximation. The difference Fourier synthesis for (–)-**1** revealed additional peaks which were interpreted as the disorder of the ethyl group by two positions with equal occupancies. The hydrogen atoms were located from the difference Fourier synthesis with the exception of the hydrogens of the ethyl groups, the positions of which were calculated from the geometrical point of view. The refinement converged to wR_2 = 0.1814 and COF = = 1.168 for all independent reflections [R_1 = 0.0615 was calculated against F for the 1712 observed reflections with $I > 2\sigma(I)$] for the structure of (–)-**1** and to wR_2 = 0.2848 and COF = 0.918 for all independent reflections [R_1 = 0.0761 was calculated against F for the 1973 observed reflections with $I > 2\sigma(I)$] for the structure of **4**. All calculations were performed on an IBM PC/AT using the SHELXTL PLUS 5.0 program. 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.*, Issue 1, 1999. Any request to the CCDC should quote the full literature citation and the reference number 1135/53.

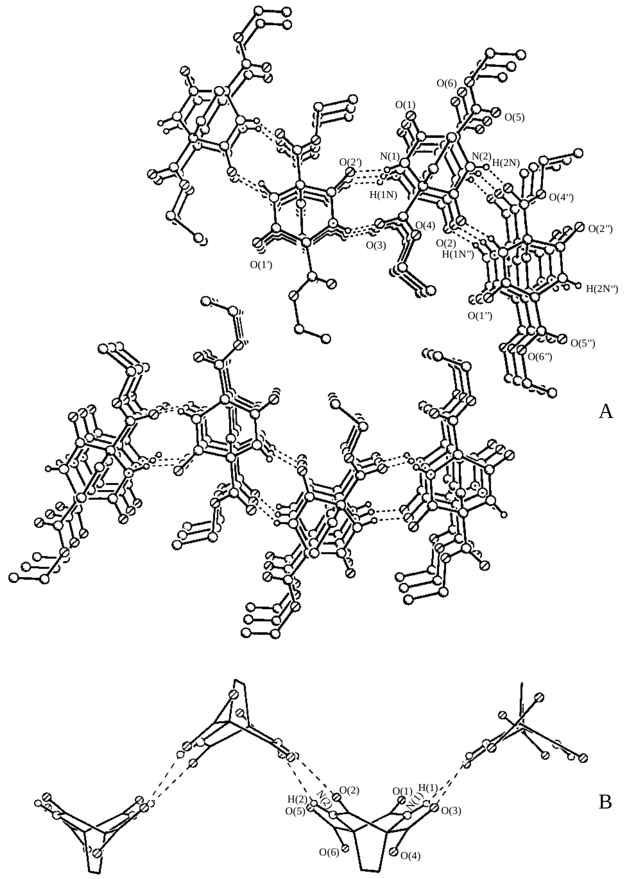

Figure 2 The homochiral helices in the crystal structure of (1*R*,4*R*)-(–)-**1** directed along the crystallographic axis *b* (in projections A and B) and columns directed along the axis *a* (projection A). In the projection B, the Et groups are omitted for clarity. The parameters of the H-bonds are: N(1)–H(1N)···O(2) ($1 - x$, $1/2 + y$, $-3/2 - z$) [H(1N)···O(2) 2.08 Å, N(1)–H(1N)–O(2) 156°, N(1)···O(2) 2.883(5) Å]; N(2)–H(2N)···O(3) ($1 - x$, $-1/2 + y$, $1/2 - z$) [H(2N)···O(3) 2.20 Å, N(2)–H(2N)–O(3) 147°, N(2)···O(3) 2.947(5) Å].

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