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Self-assembly of cage structures. Paper 12: The synthesis and crystal structures of 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylic acids and their diesters☆

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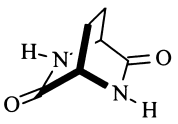
Abstract—Synthesis of racemic and enantiomeric 2,5-diazabicyclo[2.2.2]octane-3,6-dione-dicarboxylic acids and their diesters, as functionalized building blocks for supramolecular chemistry, is described. It is shown that heterochiral H-bonded zigzag tape with $R_2^2(8)$ graph and molecular 'brick wall' with a non-polar coating are persistent and stable motifs in the crystal structures of the racemic dialkyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates (**1**, **5**, **11**). This stability was confirmed by quasi-racemate [CD(−)230]-**1**·**4** formation and crystal structure determination. Packing of the diacids (±)-**2** and (−)-**2** dihydrates differed from that of esters, with H_2O molecules linking homochiral spirals, into corrugated homochiral layers, observed in both structures. The crystal structure of enantiomeric diester (−)-**1** contained spirals similar to those observed in diacids with participation of the ester carbonyl groups in H-bonding.

1. Introduction

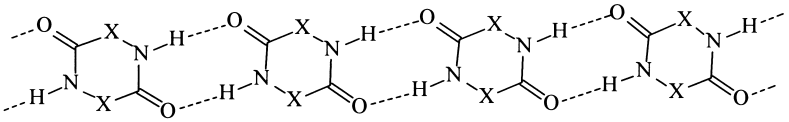
A lot of work has been performed to shed light on the relationship between molecular and solid state structure in organic crystals.[1] Despite several successful attempts,[2] in general, computational methods have not yet reached a satisfactory level of prediction. In order to meet modern challenges in solid state design, we have to use the methods and principles of supramolecular chemistry. A number of research groups have made considerable progress in using non-covalent interactions to build desirable superstructures in crystalline solids. The most common, and most natural non-covalent interaction used is the hydrogen bond, due to its strength and sensitivity to contact geometry.[3]

In our own studies of H-bond-based crystal engineering with bicyclic bis-lactams[4–6] and bis-ureas[7] we utilized the well-known ability of analogous monocyclic molecules -2,5-diketopiperazines[8] and other C_2-symmetric bis-lactams[9] to form H-bonded tapes of $R_2^2(8)$ pattern[3a] using complementary *cis*-amidic groups (Scheme 1). The resulting 1D tapes form a basis for further 2D layers[8d] and 3D crystal engineering.



DBO

From the series of molecules capable of such supramolecular organization we drew particular attention to the chiral C_2-symmetric bicyclic bis-lactam 2,5-diazabicyclo[2.2.2]octane-3,6-dione (DBO). The rigidity and simplicity of the molecular structure of DBO make it a reliable synthon for generation of H-bonded supramolecular assemblies. This was recognized for the first time by Lehn



Scheme 1. H-bonded tapes of $R_2^2(8)$ pattern formed by C_2-symmetric bis-lactams. X is any bivalent group.

☆ For previous communication, see ref. 24.

Keywords: bicyclic bis-lactams; diketopiperazines; X-ray crystal structures; self-assembly; chirality; quasi-racemates.
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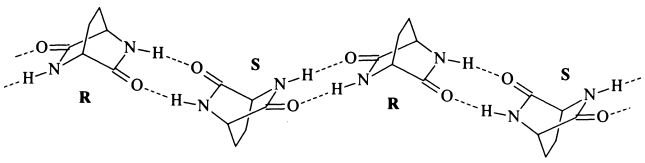


Scheme 2. Zigzag tapes formed by (±)-DBO.

and co-workers,[10] who studied crystal structures of parent DBO both in racemic and enantiomeric forms.[10a] The racemate consisted of the predicted heterochiral[10a] $R_2^2(8)$ tapes of zigzag shape (Scheme 2). Enantiomeric DBO was arranged in corrugated layers with mutually orthogonal infinite spirals of molecules with each molecule H-bonded to the four others. Surprisingly [10a] the tetrameric fragments were isolated from the whole structure, which clearly could not give enough information on the packing arrangement. Thus, (−)-DBO did not form the awaited hexameric bracelets[10] in the crystal, although the dihedral angle between the amidic groups planes is close to 120°.

Functionalized derivatives of DBO provide an easy way of introducing various substituents, thus allowing extra control of the self-assembly. Lehn's group performed multistep synthesis in order to obtain such derivatives,[10b] but there are existing ways to solve this problem.[11] Independently, using synthetic self-assembly of cage structures, in our group, we developed original and easy methods for the synthesis of DBO-1,4-dicarboxylates.[4,5c] In this paper, we summarize our studies on their synthesis, resolution and supramolecular self-assembly in crystal structures.

2. Results

As was briefly reported previously,[4a] we synthesized the target bis-lactam diethyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate **1** in a sequence starting from ethylene bismalonate (Scheme 3). By azide transfer reaction from tosylazide to ethylene bismalonate[13a] ethylene bisazidomalonate **1a**[13b] was obtained which was converted to ethylene bisaminomalonate **1b** by $SnCl_2$ reduction. Self-lactamisation of **1b**, a previously unknown unnatural bis-aminoacid derivative,[12a] led to monolactam **1c** and under strongly basic conditions to dilactam **1**[4a] (cf. synthesis of analogous bicyclic bis-lactone).[12b]

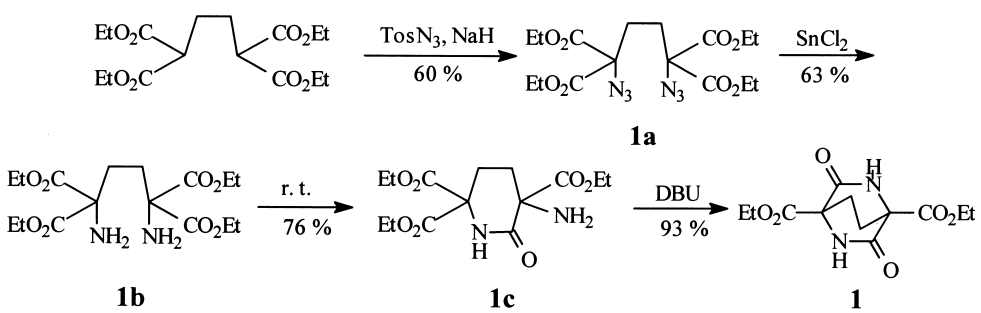
Enantiomers of **1** were obtained by partial optical resolution of its chiral precursor **1c** through diastereomeric salts with dibenzoyl L-tartaric acid and further cyclisation with optical refinement based on the large difference in solubility between racemic and enantiomeric **1**.[4b] The absolute configuration of (+)-**1** was determined by its conversion to diacid (+)-**2**, decarboxylation of which (Scheme 4) led to partially enriched (1*S*,4*S*)-(+)-DBO with known absolute configuration,[10a] probably because of the ring-opening racemisation during the process.[4c] Correlation of the fixed stereochemistry of DBO and **1** ((*R*,*R*)-DBO corresponds (*R*,*R*)-**1**) provides grounds to consider (+)-**1** (1*S*,4*S*), and (−)-**1** -(1*R*,4*R*)-enantiomer. CD spectra of (+)-**1** (Fig. 1) were recorded for the purpose of confirming chemical correlation (see Section 3).

Transformations of 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates are depicted in Scheme 4. By full saponification of diester **1** and acidification diacids (±)-**2**, (1*S*,4*S*)-(+)-**2** and (1*R*,4*R*)-(−)-**2** were prepared. Re-esterification of enantiomeric **1** by simple alcohols led to methyl and propyl esters (1*S*,4*S*)-(+)-**3** and (1*R*,4*R*)-(−)-**4**. Decarboxylation of the diacid (1*S*,4*S*)-(+)-**2** led to (1*S*,4*S*)-(+)-DBO. Cocrystallisation of (1*S*,4*S*)-(+)-**3** and (1*R*,4*R*)-(−)-**1** gave optically active quasi-racemate [CD(−)235]-**1**·**3**, of (1*S*,4*S*)-(+)-**1** and (1*R*,4*R*)-(−)-**4**—respectively quasi-racemate [CD(−)230]-**1**·**4**. Racemic or enantiomeric **2** was converted to esters either by general reaction of its DBU salt with alkyl (*n*-hexyl, *n*-hexadecyl, benzyl, 3,5-dimethylbenzyl, 9-anthrylmethyl, (*S*)-(+)-2-methylbutyl) bromides in acetonitrile or by direct esterification with diazopropane in the case of diisopropyl ester **11**. Bis[(2*S*)-2-methylbutyl]-ester (+)-**10**, prepared from racemate, was a cocrystalline mixture of 2 diastereomers in 1:1 ratio, inseparable by crystallization from common solvents. For the compounds (−)-**1**, (±)-**1**, (±)-**2**, (−)-**2**, (±)-**5**, (±)-**11** and [CD(−)230]-**1**·**4**, single crystals were prepared and X-ray diffraction studies were carried out (Table 1).

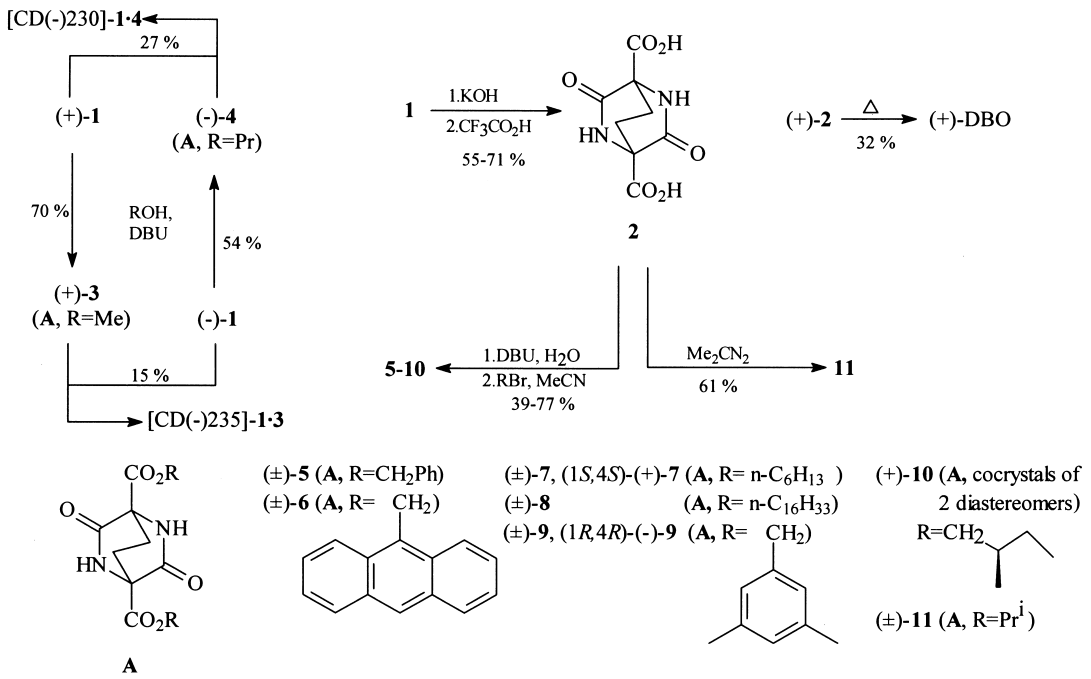
3. Discussion

3.1. Stereochemistry

The absolute configuration of 2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylates, deduced by chemical correlation, was confirmed by their CD spectra, as discussed for the (+)-**1** example. Recent high-level calculations of the electronic spectra of DBO[14] allowed us to make easy assignment of main bands in the CD spectrum of (1*S*,4*S*)-(+)-**1** (Fig. 1). A weak band with (−)-CE, λ_{min} at 237 nm (H_2O) and 240 (MeOH) nm, not observed in MeCN,



Scheme 3. Synthesis of diethyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate.



Scheme 4. Transformations of 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates.

corresponds to the $n-\pi^*(2^1A)$-transition of the amide chromophore, as in (1*S*,4*S*)-(+)-DBO.[14] An intense band with (+)-CE at λ_{max} 220 (H_2O), 224 (MeOH) and 227 (MeCN) nm together with the opposite sign band at 200 nm corresponds the exciton-coupled pair of $\pi-\pi^*$ transitions of the amide chromophore. As for DBO, long-wavelength shift of the two low-energy bands on decreasing the solvent polarity is observed. The presence of ester groups in the molecule is not evident from the spectra, probably because of many possible conformations and averaged rotational strength.

3.2. Chemical crystallography

The functionalization of DBO did not lead to the significant distortions of the molecular geometry (Fig. 2). The dihedral angles between the amide planes vary in the narrow range of 119.7–123.1° with the maximum value in **2**. The analysis of the bicyclic conformation have unambiguously shown that in contrast to similar dilactones the synchro-(+,+,+)twist conformation is not the only one observed[15] (Table 2). In addition, the type of conformation is determined not only by the substituent but also by crystal packing. For example the

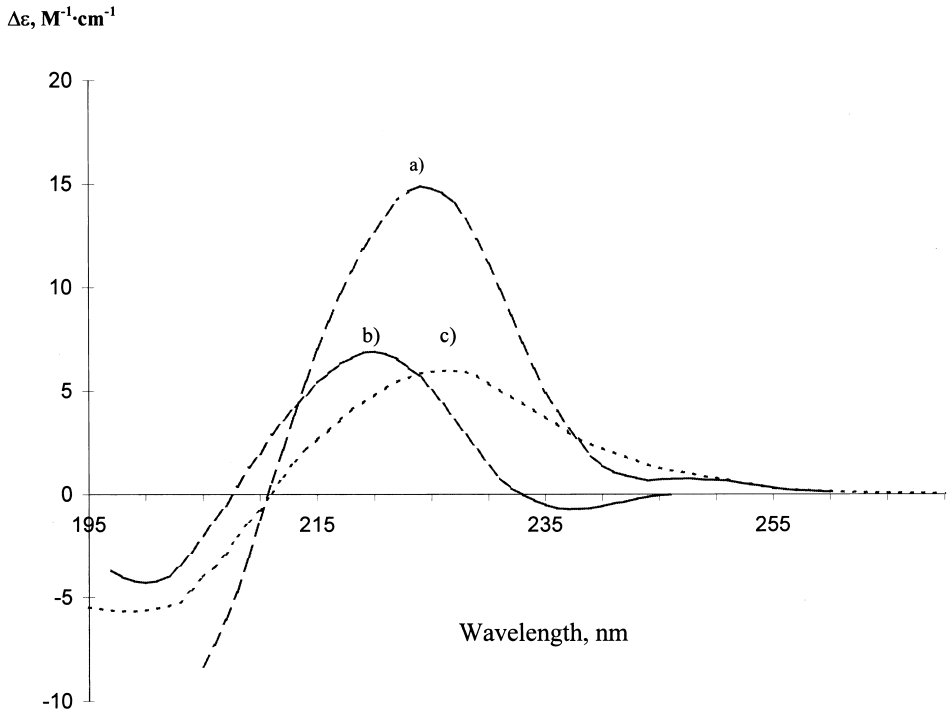


Figure 1. Circular dichroism spectra of (+)-**1**: (a) in MeOH; (b) in H_2O; (c) in MeCN.

Table 1. Crystallographic data and parameters of the refinement for 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates

Compound	(±)-**1**	(−)-**1**	(±)-**2**	(−)-**2**	(+)-**1**·(−)-**4**	(±)-**5**	(±)-**11**
Refcode[a]	DAJJED	DOGQFV	DOGQUL	DOGQJZ	DOGSIB		
Crystallization solvent	MeCN	H_2O	H_2O	H_2O	MeCN	MeCN	*i*-PrOH–Me_2CO
T (K)	293	153	298	298	153	298	298
Space group	$P2_1/n$	$P2_12_12_1$	$P2_1/n$	$P2_1$	$P2_1$	$P\bar{1}$	$P\bar{1}$
a (Å)	10.189(2)	5.534(3)	8.900(4)	6.871(3)	10.199(7)	5.583(4)	5.931(3)
b (Å)	5.568(1)	9.908(4)	11.590(3)	11.260(3)	5.597(3)	9.765(7)	10.381(6)
c (Å)	24.114(5)	25.77(1)	10.401(2)	7.162(2)	25.11(2)	17.76(1)	13.596(8)
α (deg)						93.45(5)	73.43(4)
β (deg)	95.39(2)		92.93(3)	93.98(3)	95.96(5)	92.14(5)	77.89(4)
γ (deg)						90.18(5)	89.45(5)
V (Å^3)	1361.9(5)	1413(1)	1071.5(6)	552.8(3)	1425(2)	965(1)	783.3(8)
Z	4	4	4	2	2	2	2
d_{calc} (g cm^{-3})	1.386	1.336	1.638	1.587	1.390	1.404	1.324
R_1 (%)	5.93	6.15	4.19	3.19	7.61	6.91	7.36
wR_2 (%)	18.23	18.14	13.10	9.55	28.48	17.64	23.90

[a] For crystal structures which have been previously published in short communications the corresponding refcodes in CCSD are reported.

conformation of the diethyl ester derivative in the racemic (±)-**1** and quasi-racemic [CD(−)230]-**1**·**4** crystals varies from synchro-(−,−,−) to asynchro-(−,+,−). Thus, probably the exchange of the oxa- by the N–H groups diminishes the contribution of the dipole–dipole interaction of the carbonyl groups to the stabilization of synchro-(+,+,+) conformation.[15]

While in parent DBO molecules the C_2-symmetry of the bicyclic ring in the crystal is preserved, in the case of the diesters studied the site-symmetry is always C_1. In general, the main distortions of C_2-symmetry are assigned to the orientation of the CO_2R moiety with respect to the bicyclic skeleton. Analysis of crystal structures **1**–**11** has revealed two different type of conformations, with approximately staggered orientation of C═O or C–OR bond in respect to the C(quarternary)–N bond. The range of the corresponding torsion angles for C–OR and C═O bonds are 12.4–27.0° and 0.5–24.4°, respectively. In both cases, such an orientation leads to a shortening of the intramolecular distance between the corresponding oxygen atom of the CO_2R group and the nitrogen of the amide group. The ranges of this O···N separation (2.533(3)–2.608(4) Å for proximal C–OR and 2.634(2)–2.748(5) Å for C═O groups) are within the sum of van der Waals radii suggesting that the stabilization of such orientation is due to an attractive intramolecular NH···O interaction.

Let us now consider the supramolecular organization in the crystal of the molecules under the investigation. While the

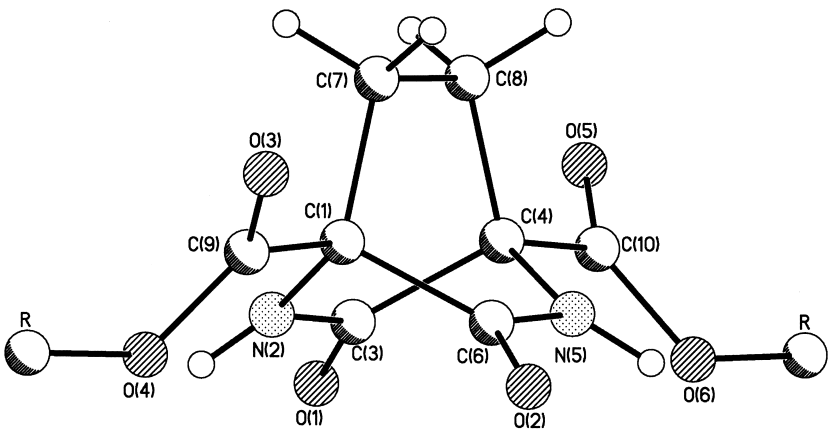


Figure 2. General view of the molecules of 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates.

Table 2. Torsion angles (deg) in the bis-lactam molecules studied

Compound		C(1)C(7)C(8)C(4)	C(4)N(5)C(6)C(1)	C(4)C(3)N(2)C(1)
(±)-**1**		−4.8	−3.1	−3.3
(±)-**5**		−7.9	−5.6	−2.8
(±)-**11**		4.2	2.7	3.1
(+)-**1**·(−)-**4**	(+)-**1**	−2.8	1.3	−4.2
	(−)-**4**	5.8	6.1	1.3
(−)-**2**		−1.4	5.0	4.7
(±)-**2**		−2.9	4.8	4.2
(−)-**1**		−5.4	−2.5	−3.6

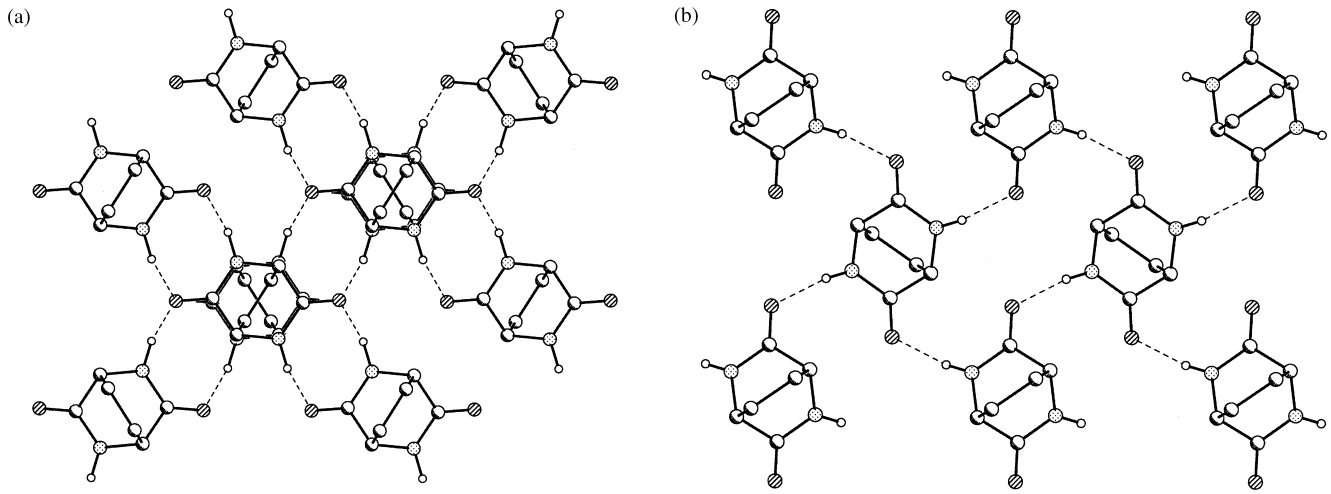


Figure 3. Projections of crystal packing of (±)-DBO (a) (space group *Pccn*, *Z*=4) and (−)-DBO (b) (space group $P2_12_12$, *Z*=2), according to published crystallographic data.[10a] In the case of (±)-DBO the superposition of H-bonded tapes is shown.

above-mentioned zigzag tapes of (±)-DBO appear to be the most likely type of supramolecular organization for racemic bis-lactams, the presence of the substituents could uncover other possibilities. Also important was to discover types of homochiral organization of bicyclic molecules, taking into account the fact that it seemed impossible for (−)-**1** or (−)-**2** to have the corrugated layer structure found for (−)-DBO (Fig. 3) because of the steric interference of the substituents. As a possible alternative, in the structure of enantiomerically pure bicyclic diketopiperazine cyclo-L-cystine[9e] molecules assemble into translation-formed homochiral tapes.

For racemic bis-lactam diesters it seemed logical to investigate the influence of the 1,4-substituents on packing. Such an investigation was carried out for different alkyl groups (ethyl, isopropyl and benzyl). The analysis of the packing of the racemic esters **1**, **5** and **11** revealed that as in the parent (±)-DBO (Fig. 3a) the molecules in the crystal are assembled in infinite zigzag tapes of the alternating (*R*,*R*) and (*S*,*S*) enantiomers directed along the crystallographic axis *a* through intermolecular H-bonds of moderate strength (Fig. 4) (structure of **5** is shown in Fig. 4, structures of **1** and **11** are analogous). The corresponding N···O distances vary in the narrow range 2.891(3)–2.939(2) Å being the shortest in the case of the Pr^i ester.

The major peculiarity of the crystal structures of **1**, **5** and **11**, which determined the direction of further studies is not only the formation of H-bonded zigzag tapes of $R_2^2(8)$ graph, but also the specific mutual orientation of the tapes. Indeed, in the parent (±)-DBO the zigzag tapes are skewed (Fig. 3), however, in all studied ester structures they are parallel to each other. As a result, the tapes stack and form columns of the molecules of the same chirality in the second dimension. Such combination of heterochiral H-bonded tapes and

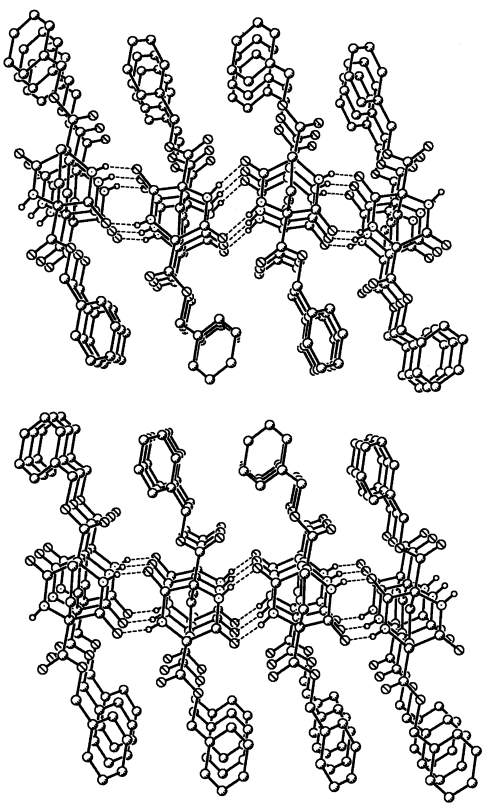


Figure 4. Projections of crystalline packing in *ab* plane, illustrating the packing of the tapes in **5**.

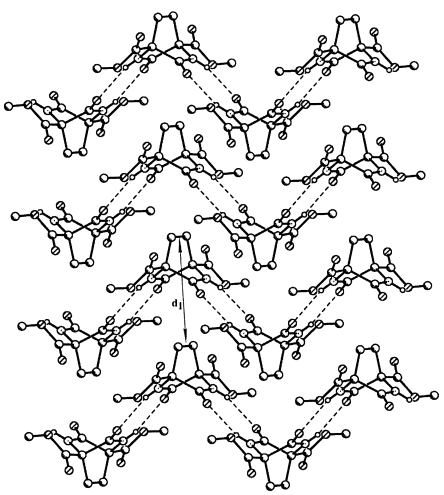


Figure 5. Scheme, illustrating formation of walls in the structures of diesters **1**, **5**, **11**.

homochiral columns leads to the formation of molecular 'brick walls' with non-polar alkyl or aryl coating (Figs. 4 and 5). The stabilization of such walls is certainly achieved by electrostatic dipole–dipole interactions between amidic groups in neighboring tapes and also by the additional C–H···O contacts formed by lactamic C═O groups and C(7)–C(8) ethylene bridge in **1**, **5** and by ester C═O and *i*-Pr groups in **11**. While all C–H···O contacts between adjacent tapes are weak (C···O ca. 3.5 Å), according to Desiraju's classification they can play a significant role in the formation of crystal structures. The distance (Fig. 5), characterizing embedding of the molecules (d_1), depends on the substituent shape. In diethyl **1** and dibenzyl **5** diesters d_1 is practically the same (5.58 Å), whereas in diisopropyl diester **11** with a slightly different system of C–H···O contacts, it reaches 5.93 Å. For comparison, the same value for racemic and enantiomeric DBO is equal to 5.56 Å. While in (±)-DBO the hydrogen atoms attached to C(1) and C(4) take part in the C–H···O contacts between the adjacent tapes, in **1**, **5** and **11** due to hydrophobic groups the corresponding distances are within the sum of van der Waals radii. Thus, the crystal packing is practically invariant to the substituents nature making such a system very attractive for the crystal engineering.

First of all, we can use the stable supramolecular 'wall' motif to realize the 'interwall' interactions. In order to accomplish directed self-assembly of bis-lactams in the dimension, orthogonal to the planes of molecular walls to engineer 3D crystals by H-bonding, carboxylic groups were used instead of the alkoxycarbonyl substituents. However, the racemic diacid (±)-**2**, crystallized from water, contained two solvate H_2O molecules (all attempts to obtain anhydrous X-ray quality crystals of **2** were unsuccessful) and possessed different structure from that of the diesters. Instead of heterochiral zigzag tapes, molecules in **2** were assembled in homochiral spiral tapes of $R_2^2(9)$ type both by amidic and acid carbonyl H-bond acceptors. In the crystal of (±)-**2**, water molecules served to link adjacent tapes of the same chirality into corrugated homochiral layers (Fig. 6). The whole crystal structure consisted of embedded layers of different chirality.

As mentioned above, it was important to investigate the structure of (−)-**2**, remembering that homochiral layers were already present in the racemic diacid. This crystal structure was also a dihydrate and appeared astonishingly similar to that of (±)-**2** with identical homochiral layers. The only difference was that the crystal structure consisted of layers of the same chirality.[4c] The observed homochiral suprastructure in racemic crystals gives an example that the self-assembly of chiral molecules into helices or any other chiral entities does not mean that the entire crystal should be enantiomerically pure.

Taking into account this surprising similarity of the (±)-**2** and (−)-**2** suprastructures, we analyzed the crystal structure of the chiral diester (−)-**1**. The suprastructure of (−)-**1**, like **2** and unlike DBO, in some features is similar to that of the racemate (Fig. 7).[4a,b] In one direction the molecules are incorporated into tapes (although of different $R_2^2(9)$ graph), and the columns described above orthogonal to the tapes, remain practically unchanged, as does the distance d_1 (5.568

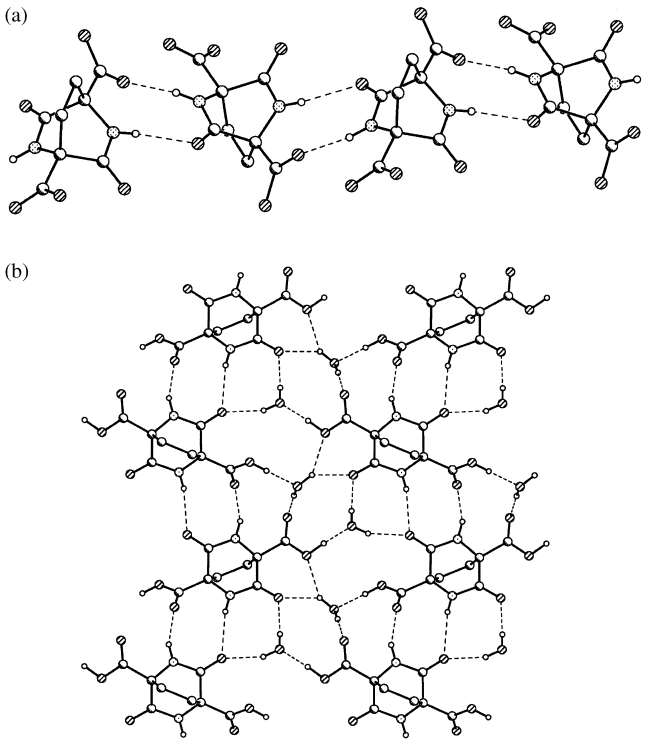


Figure 6. Projections of the crystal structure of (±)-**2**: (a) H-bonded homochiral tapes; (b) formation of homochiral layers.

in (±)-**1** and 5.534 in (−)-**1**)). In spite of this similarity, the difference is quite obvious. The symmetrical transformations, connecting molecules in the tapes, as well as H-bond type and its graph differ in (±)-**1** and (−)-**1**. Tapes in the racemate are centrosymmetric, whereas in the enantiomer

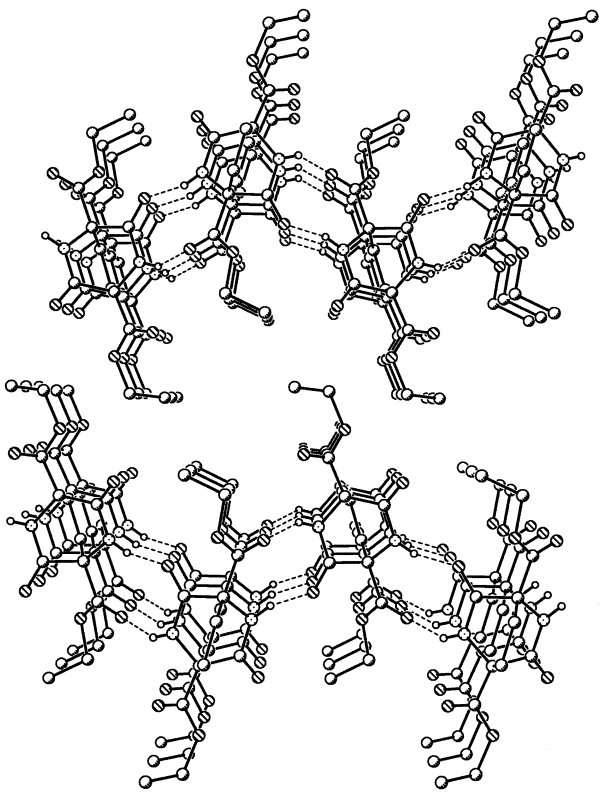
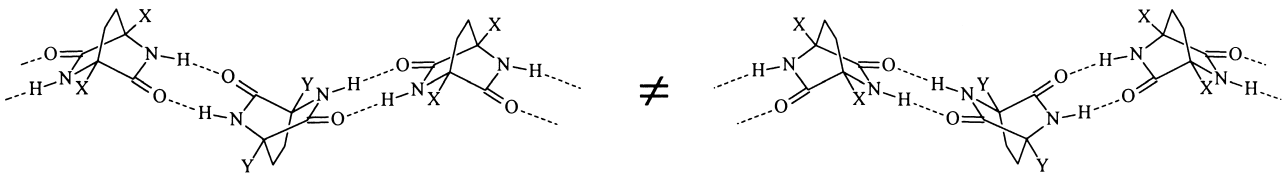


Figure 7. Projection of the H-bonded tapes in (−)-**1**.



Scheme 5. Chiral zigzag tapes in pseudoracemates of bicyclic bis-lactams.

they are formed by screw axe 2_1. In (±)-**1**, tapes with $R_2^2(8)$ graph are formed solely by amide groups while in the case of (−)-**1**, as in the diacids (Fig. 6a) in the $R_2^2(9)$ cycle the first carbonyl acceptor is amidic, while the second is carboxylic. As a result, one of the amidic carbonyls of the dilactam molecule does not participate in any specific contacts including C–H···O interactions. Thus the supramolecular structure of (−)-**1** can be described as 'corrugated brick walls'. Such a shape of the walls is probably the main reason for the lower calculated density of (−)-**1** (1.336) compared to (±)-**1** (1.386). Other characteristics which also witness lower thermodynamic stability (ΔH) of the enantiomeric crystals are the lower melting point (233°C in enantiomer against 271°C in racemate) and higher solubility in organic solvents. So the homochiral crystal of diester is unfavorable both from the H-bonding and crystal density point of view, making this class of compounds undesirable for engineering non-centrosymmetric and chiral crystals.[5d]

Despite the fact that the tape, depicted in Scheme 2 is centrosymmetric and achiral, making use of the substituents to asymmetrize it was challenging (Scheme 5). Taking into account the lower thermodynamic stability of homochiral $R_2^2(9)$ motif compared to heterochiral $R_2^2(8)$, repeated in the structures of (±)-**1**, **5** and **11**, we were eager to realize a chiral structure for the zigzag tapes and molecular walls. Thus, simple cocrystallization of dimethyl (+)-**3** and dipropyl (−)-**4** esters with enantiomeric **1** (Scheme 4) of the respective opposite configuration (Scheme 5) yielded characteristic plate-like crystals of optically active (CD in solution) quasi-racemates (quasi-racemate is a chiral crystalline complex of two molecules, close to mutual mirror symmetry, but not real enantiomers)[16] [CD(−)235]-**1**·**3** and [CD(−)230]-**1**·**4** containing both constituents, according to NMR, in a 1:1 ratio. For **1**·**4**, the crystal structure has been studied. It possessed all the elements, enumerated in the description of the crystal structures of (±)-**1**, **5** and **11**. The principal parameters of the suprastructures are practically identical. Thus, distance d_1 in the quasi-racemate equals 5.597 Å, and the NH···O bond length is in a range of 2.893–2.940 Å (compared with (±)-**1**, see above). Besides, molecules of **1** and **4** alternated strictly in the crystal and each formed its own homochiral column (Fig. 8). As anticipated, the space group of the quasi-racemate **1**·**4** was chiral ($P2_1$).[4b]

The cocrystallization of enantiomeric diesters proves the high stability of molecular walls, found in racemic analogs. The supramolecular methodology is based on strict recognition and self-sorting of pseudo-antipodes. This methodology is close to that used by Lehn et al. in his study of the melamine-barbiturate system.[17] If we take chiral X=Y=R* groups on Scheme 5, we may then find that quasi-racemate formed is a complex of two diastereomers. We obtained such a complex **10**, which crystallizes from common solvents in a 1:1 ratio, using (2*S*)-2-methylbutyl substituents, analogously to bis[2-methylbutyl] 3,7-diazabicyclo[3.3.1]octane-2,6-dione-1,5-dicarboxylate.[5c] Such cocrystallization is quite interesting, taking into account that the usual method of resolution of racemates (used also in this study for **1c**) is partial crystallization of corresponding diastereomers. Cocrystallization of diastereomers is to our knowledge a rare and uncontrolled event.[18] The system described above is also interesting from the point of view of creation of functional motifs on the basis of self-assembly of photo-, electro- or ionoactive components. Sorting molecules in the quasi-racemate crystal could lead to specific macroscopic properties of the material. For example, ordered location of photoactive or ionoactive fragments, may lead to directed transmission of energy or endow the structure with the properties of an ionic channel.[10b] Another possible way of application of the phenomenon could be spontaneous resolution to enantiomeric crystals of a mixture of two racemic esters because of the formation of highly stable quasi-racemate, e.g.

$$(\pm)\text{-}\mathbf{X} + (\pm)\text{-}\mathbf{Y} = (+)\text{-}\mathbf{Y}\cdot(-)\text{-}\mathbf{X}\downarrow + (+)\text{-}\mathbf{X}\cdot(-)\text{-}\mathbf{Y}\downarrow$$

The stability of crystal packing of the esters could also lead to their use as the base for liquid crystalline phases.[5b]Indeed, we have found evidence for strong self-assembly of the alkyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylates in non-crystalline phases. First, we revealed that

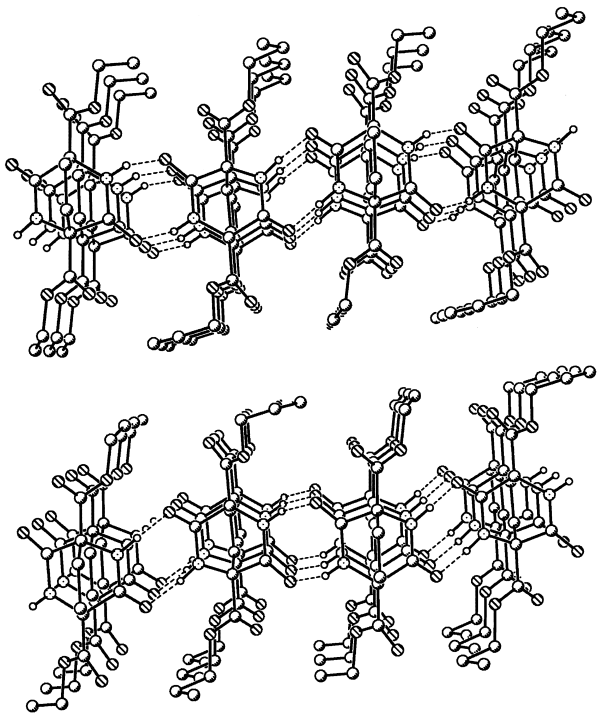


Figure 8. Crystal structure of [CD(−)230]-**1**·**4**.

dissolution of non-equal quantities of enantiomers of di(3,5-dimethylbenzyl) diester **9** in $CDCl_3$ (room temperature) gives rise to splitting of the NH proton signal in ^1H NMR spectrum, in a ratio equal to the ratio of the enantiomers in the mixture. This phenomenon is known in the literature as statistically controlled associate-diastereomery (SCAD)[19] and is ascribed to a difference between the chemical shifts of homo- and heterochiral dimeric aggregates. Another interesting example of self-assembly of dilactams was found by studying enantiomerically pure dihexyl diester (+)-**7**. This compound, dissolved in hot cyclohexane, on cooling (25°C) gives an opaque gel. This phenomenon has been described for 2,5-diketopiperazines with branched substituents[20a] and is connected with formation of extended aggregates.[20b] Remarkably, racemate of **7** simply crystallizes from cyclohexane.

4. Conclusion

We have shown that new dialkyl 1,4-dicarboxylate functionalized racemic derivatives of 2,5-diazabicyclo-[2.2.2]octane-3,6-dione DBO utilize their H-bonded polymerization capabilities in the solid state by forming heterochiral zigzag tapes of $R_2^2(8)$ graph with lactamic H-bonding, where molecules of different chirality alternate, in close similarity to crystal structure of (±)-DBO itself. In the case of all the investigated crystals of the racemic diesters **1**, **5** and **11**, a new motif appears, by stacking of the tapes, translated orthogonal to the tape propagation axis. We call this motif 'molecular brick wall with non-polar coating'. The stability of both motifs, tapes and walls, is illustrated by self-assembly of two optically active esters with opposite backbone chirality (+)-**1** and (−)-**4** into an optically active (CD) quasi-racemate and in the crystal structure the tapes consist of strictly alternating molecules of **1** and **4**. An attempt to predict crystal structures of diacids (±)-**2** and (−)-**2**, where walls could have been directly linked by the dimerisation of carboxylic acid moieties, failed. The structures instead contained solvate water molecules, linking homochiral spirals of $R_2^2(9)$ graph into corrugated homochiral layers. The crystal structure of enantiomeric diester (−)-**1** contained spirals similar to those observed in diacids with participation of the ester carbonyl groups in hydrogen bonding. The packing features of (−)-**1** were similar to those of racemate—both zigzag tapes (although with different H-bonding graph) and corrugated brick walls were preserved. As anticipated, enantiomeric 1,4-derivatives of DBO could not form homochiral layers with one molecule H-bonded to the four others by lactamic functional groups, a type of H-bonded polymerisation found in enantiomeric DBO crystals. We found evidence for strong aggregation of enantiomeric and racemic diesters in solutions, for example (+)-**7**, which formed a gel in cyclohexane, and **9**, which showed SCAD in $CDCl_3$ solution.

5. Experimental

5.1. Crystallography

The crystallographic data for (−)-**1**, (±)-**1**, (±)-**2**, (−)-**2**, (±)-**5**, (±)-**11** and [CD(−)230]-**1**·**4** is represented in Table 1. Experimental details for crystallographic studies of (−)-**1**,[4b] (±)-**1**,[4a] (±)-**2**,[4c] (−)-**2**,[4c] and [CD(−)230]-**1**·**4**[4b] were already published. The data collection for **5** and **11** was carried out on Siemens P3/PC diffractometer (Mo Kα (λ=0.71072 Å), $\theta/2\theta$ scan technique, θ_{max}=50°). Both structures were solved by direct method and refined by full-matrix least squares against F^2 in the anisotropic (H-atoms isotropic) approximation using SHELXTL-97 package. All hydrogen atoms in **5** and **11** were located from the electron density difference synthesis and were included in the refinement in isotropic approximation and riding model (ester substituents).

Crystallographic data (excluding structure factors) for **5** and **11** reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary nos. CCDC-179307 (**5**) and 179306 (**11**). All other structures were deposited earlier (for ref codes, see Table 1). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: (internat.) +44-1223/336-033; e-mail: deposit @ccdc.cam.ac.uk.

5.2. General

CD spectra were recorded on a Jasco J-500A spectrometer, NMR ^1H and ^{13}C spectra were recorded on a Bruker WM-400 spectrometer at 400.13 MHz for ^1H and 100.61 MHz for ^{13}C, using TMS or residual ^1H signal of solvents as an internal reference in proton spectra and solvent C signal in carbon spectra. Mass spectra were recorded on a VG 7070E instrument. IR spectra were recorded on a UR 20 spectrometer. Optical rotations were measured on a Polamat A instrument (cell length 0.1 m). Elemental analyses were performed in the Microanalyses laboratory of the Institute of organic chemistry of RAS. Melting points are corrected. Dioxane, 1,2-dimethoxyethane, Et_2O, MeCN were distilled from CaH_2, MeOH and EtOH—from corresponding magnesium alcoholates, and stored over 3A molecular sieves. Analytical thin-layer chromatography was performed on Merck polymer-backed pre-coated plates (0.2 mm), spots visualized in iodine vapors. Column chromatography was performed using Merck silica gel 32–60 μm. 9-(Bromomethyl)antracene was synthesized in two steps according to literature procedures starting from 9-anthrylcarbaldehyde.[21] 2-Diazopropane was synthesized according to usual procedure.[22] 1-Bromo-2-(*S*)-methylbutane was prepared according to published procedure[23] from optically active 2-(*S*)-methylbutanol-1 (Acros). 1-*n*-Bromohexadecane (Fluka), 1,8-diazabicyclo[5.4.0]undec-8-ene (DBU, Aldrich) were used without purification. 1,1,4,4-Butanetetracarboxylate was synthesized as described previously.[15a]

5.3. Synthesis

5.3.1. Tetraethyl 1,4-diazido-1,1,4,4-butanetetracarboxylate 1a. To a suspension of NaH (3.22 g, 0.134 mol) in dioxane (130 ml) in N_2 atmosphere at 20°C was added tetraethyl 1,1,4,4-butanetetracarboxylate (22.9 g, 66.1 mmol) in portions with constant stirring. Gas evolution was observed, and the internal temperature rose to 50°C. The mixture was kept at this temperature for 3 h, then a

solution of tosylazide (26.4 g, 0.133 mmol) in 1,2-dimethoxyethane (130 ml) was added in portions and the mixture refluxed with stirring. After 25 h, the yellow–brown mixture containing very fine precipitate, was cooled to room temperature, diluted with 300 ml of wet ether and after 20 min filtered. The filtrate was concentrated, inhomogeneous residue was diluted with 200 ml of Et_2O, filtered once more and concentrated to give a light-brown oil. Flash chromatography (ether/*n*-hexane 0–17%) afforded 17 g (60%) of colorless oil, which solidified on standing, mp 44–46°C. IR (thin layer) ν, cm^{-1} 2130 (N_3), 1755 (CO). ^1H NMR ($CDCl_3$, δ, ppm, *J*, Hz) 1.34 (t, 12H, Me, ^3J=7.0) 1.90 (s, 4H, $(CH_2)_2$) 4.31 (q, 8H, $4CH_2O$, ^3J=7.0) ^{13}C NMR ($CDCl_3$, δ, ppm, *J*, Hz) 13.7 (q, Me, ^1J=128.1) 27.9 (t, $(CH_2)_2$, ^1J=135.2) 62.6 (t, CH_2O, ^1J=144.1) 70.6 (s, CN_3) 166.5 (s, CO). Anal. calcd for $C_{16}H_{24}N_6O_8$ (%) C 44.9, H 5.7, N 19.6, found (%) C 50.2, H 5.7, N 19.7.

5.3.2. Tetraethyl 1,4-diamino-1,1,4,4-butanetetracarboxylate 1b. To the mixture of **1a** (5.75 g, 13.4 mmol) and anhydrous EtOH (10 ml) at −5°C was added cooled solution of anhydrous $SnCl_2$ (10.2 g, 53.8 mmol) in EtOH (15 ml). After several minutes intensive gas evolution started and temperature of the mixture rose to 40–50°C. The mixture was kept for 12 h at 20°C and evaporated to dryness. The residual odorous paste was suspended in H_2O (200 ml), $NaHCO_3$ (2 g) was added and the mixture was stirred until gas evolution stopped. Then Et_2O (150 ml) was added and $NaHCO_3$ (30 g) was added in small portions with constant stirring. After 2.5 h the 3-phase mixture was filtered, the precipitate was washed with ethyl acetate (3×100 ml) and the water phase was extracted by EtOAc (3×200 ml). Combined organic phases were concentrated. Flash chromatography of the residue (1:1 EtOAc–petroleum ether–100% EtOAc) afforded 3.2 g (63%) of the product as an oily liquid. The tetraester **1b** partially lactamizes in the conditions of silica gel chromatography and during storage (after 12 h at 20°C conversion is 85–90%), and always contains some **1c** (see further).^1H NMR ($CDCl_3$, δ, ppm, *J*, Hz) 1.27 (t, 12H, 4Me, ^3J=7.0), 1.93 (br s, 4H, $2NH_2$), 1.96 [s, 4H, $(CH_2)_2$], 4.21 (q, 8H, $4CH_2O$, ^3J=7.0). ^{13}C NMR ($CDCl_3$, δ, ppm, *J*, Hz) 13.06 (qt, Me, ^1J=126.4, ^2J=2.9), 28.82 (tt, $(CH_2)_2$, ^1J=132.2, ^2J=5.8), 60.75 (tq, CH_2O, ^1J=148.2, ^2J=4.4), 64.35 (s, CN), 170.33 (br s, CO). MS (EI, 70 eV) *m/z*: 377 [M+1] (1.0), 303 [M−CO_2Et] (3.0), 286 [M−CO_2Et−NH_3] (100), 257 [M−CO_2Et−NH_3−Et] (98).

1b, dihydrochloride precipitated on treatment of **1b** (1.0 g) by excess of dry HCl in Et_2O and the precipitate was recrystallized from Et_2O–MeCN: white feathery crystals, yield 1.0 g (84%), mp 173–174°C (decomp.). ^1H NMR (CD_3OD, δ, ppm, *J*, Hz) 1.34 (t, 12H, 4Me, ^3J=7.0), 2.36 (s, 4H, $(CH_2)_2$), 4.39 (m, 8H, $4CH_2O$). Anal. calcd for $C_{16}H_{30}N_2O_8Cl_2$ (%) C 42.5, H 6.7, N 6.1, found (%): C 42.8, H 6.7, N 6.2.

5.3.3. Aminolactam (±)-1c. A solution of **1b** (0.3 g, 0.8 mmol) in EtOAc (1.5 ml) was applied on silica gel. After 2.5 days of standing at 20°C chromatography (Et_2O) afforded 0.2 g (76%) of the white crystals of monolactam, mp 74–76°C (Et_2O). ^1H NMR ([$^2H_8$]toluene, δ, ppm, *J*, Hz) 0.81, 0.83 and 0.91 (t, 3×3H, 3Me, ^3J=7.0), 1.59 (ddd, 1H, H_a, $^2J_{ab}$=−14.0, ^3J=7.0, ^3J=4.6), 2.0 (br s, 2H, H_2N), 2.21 (ddd, 1H, H_b, $^2J_{ab}$=−14.0, $^3J_{bc}$=8.9, ^3J=4.6), 2.45 (m, 1H, H_c), 2.48 (m, 1H, H_d), 3.77, 3.80 and 3.88 (m, 3×2H, $3CH_2O$), 6.9 (br s, NH). ^{13}C NMR ([$^2H_6$]benzene, δ, ppm, *J*, Hz) 13.8 (qt, 5,5-(*Me*CH_2O_2C), ^1J=127.0, ^2J=2.7), 14.0 (qt, 2-*Me*CH_2O_2C, ^1J=127.0, ^2J=2.7), 24.9 (ttd, 5-CH_2, ^1J=134.4, ^2J=3.6, ^3J=3.6), 30.3 (tt, 4-CH_2, ^1J=131.5, ^2J=3.6), 61.8 (m, 2-C), 61.75 (tq, 2-Me*C*H_2O_2C, ^1J=148.5, ^2J=4.3), 62.44 and 62.7 (tq, 5,5-(Me*C*H_2O_2C), ^1J=149.0, ^2J=4.3), 66.7 (m, 5-C), 168.18 (m, CO), 168.37 (m, CO), 170.1 (br s, CON), 173.6 (m, CO). MS (EI, 70 eV) *m/z*: 258 [M−C_2H_4−CO_2] (100), 243 (28), 183 (28), 155 (17), 137 (10), 128 (10), 116 (12), 111 (30), 100 (12), 42 (22), 29 (35), 28 (61). Anal. calcd for $C_{11}H_{22}N_2O_7$ (%) C 50.9, H 6.7, N 8.5, found (%) C 50.8, H 6.7, N 8.5.

5.3.4. Diethyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate (±)-1. Monolactam (±)-**1c** (2 g, 6.1 mmol) was dissolved in MeCN (2 ml) and DBU (50 mg) was added. After 7 days at 20°C the white crystalline product was filtered off, washed with cold MeCN and dried to yield 1.6 g (93%) of (±)-**1**, mp 271°C (MeCN). (Tetraester **1b** could be used in this procedure as well, without monolactam isolation.) ^1H NMR (CD_3OD, δ, ppm, *J*, Hz) 1.3 (t, 6H, 2Me, ^3J=7.0), 2.25–2.35 (4H, $(CH_2)_2$, AA′BB′ spectrum, $^2J_{AB}$=−13.4, $^2J_{A'B'}$=−13.4, $^3J_{AB'}$=10.8, $^3J_{A'B}$=10.8, $^3J_{BB'}$=4.5, $^3J_{AA}$=4.2), 4.3 (4H, $2CH_2O$, ABX_3 spectrum, $^2J_{AB}$=−11.1). ^1H NMR ($CDCl_3$, δ, ppm, *J*, Hz) 1.39 (t, 6H, 2Me, ^3J=7.0), 2.29–2.49 (4H, $2CH_2$, AA′BB′ spectrum), 4.40 (4H, $2CH_2O$, ABX_3 spectrum, $^2J_{AB}$=−12.0), 6.85 (br s, 2H, HN). ^{13}C NMR ([$^2H_6$]DMSO, δ, ppm, *J*, Hz) 14.12 (qt, Me, ^1J=126.4, ^2J=2.9), 27.7 (t, $(CH_2)_2$, ^1J=138.1), 62.0 (tq, CH_2O, ^1J=148.2, ^2J=4.4), 65.31 (s, CCO_2Et), 165.85 (CO_2). MS (EI, 70 eV, M^+ found: 284.1008, calcd for $C_{12}H_{16}N_2O_6$: 284.100836) *m/z*: 284 [M^+] (48), 238 (38), 213 (20), 182 (12), 167 (25), 165 (57), 154 (13), 136 (12), 58 (46), 43 (100).

5.3.5. Optical resolution of aminolactam 1c. Dilactam (1*R*,4*R*)-(−)-1. Solutions of (±)-**1c** (1.5 g, 4.5 mmol) and O,O-dibenzoyl-L-tartaric acid (1.71 g, 4.5 mmol) in minimal amounts of MeCN were mixed and the mixture was evaporated to dryness in vacuo, then the oily residue was crystallized from acetonitrile–benzene 1:15 mixture (~50 ml). The precipitate of the partially resolved acid salt (1.32 g, 1.92 mmol, yield 41%) was filtered off the mother liquor, washed with cold solvent mixture and dried in vacuo. ^1H NMR (CD_3OD, δ, ppm, *J*, Hz) 1.28 (m, 9H, 3M), 2.12, 2.4, 2.52 (m, $(CH_2)_2$), 4.28 (m, $3OCH_2$), 5.91 (s, 2CH), 7.49 (t, ^3J=8, 1H(4)) 7.62 (t, ^3J=8, 2H(3)) 8.12 (d, ^3J=8, 2H(2)), $[\alpha]_D^{20}$=−66.2 (*c* 4, EtOH). The isolated salt was dissolved in minimal amount of dioxane (≈3 ml) and triethylamine was added (0.8 ml, 5.8 mmol). After 5 h the crystalline precipitate of triethylammonium dibenzoyl-tartrate was filtered off and washed with cold dioxane. Filtrate was diluted with ether (~50 ml), after 1 h mixture was once again filtered and the solution was evaporated to dryness. The oily residue of partially resolved **1c** (0.63 g, ~100%) (^1H NMR ($CDCl_3$) close to that of racemate) was dissolved in MeCN (5 ml), DBU was added (50 mg) and the solution was left at 20°C. After 7 days, massive crystals of

(±)-**1** were separated, the solution evaporated to ~3 ml volume, left at 0°C and after 2 h filtered for final racemate removal. The filtrate was evaporated and for DBU removal was chromatographed on silica gel with EtOAc–EtOH 10:1 eluent. The eluate was evaporated to dryness and the residue recrystallized from *i*-PrOH to give white crystals of (−)-**1** (360 mg, 1.3 mmol, 66%), mp 230–233°C, $[\alpha]_D^{20}=-35.7$ (*c* 1.3, EtOH), ^{1}H NMR ($CDCl_3$) was close to that of racemate. CD spectrum (7.7×10^{-3} M, MeOH, 0.5 mm cell, $\Delta\varepsilon$, λ_{max}): −0.6, 248 nm, −14.3, 224 nm, 8.0, 205 nm (without maximum). Anal. calcd for $C_{12}H_{16}N_2O_6$ (%) C 50.7, H 5.7, N 9.85, found (%) C 50.5, H 5.7, N 9.95.

5.3.6. Dilactam (1*S*,4*S*)-(+)-1. The mother liquor after the crystallization of diastereomeric salts was evaporated, and the oily residue (1.9 g, 2.7 mmol) of salt was subjected to above procedures. Yield of (+)-**1** was 350 mg (45%, 1.2 mmol), mp 233–234°C, $[\alpha]_D^{20}=+38.6$ (*c* 1.9, MeOH), ^{1}H NMR ($CDCl_3$) is close to racemate spectrum, CD (7.8×10^{-3} M, H_2O, 0.5 mm cell, $\Delta\varepsilon$, λ_{max}) −0.7, 237 nm, +6.9, 220 nm, −4.2, 200 nm; (10^{-2} M, MeOH, 0.5 mm cell, $\Delta\varepsilon$, λ_{max}) +0.7, 248 nm, +15.5, 224 nm, −8.6, 205 nm (without maximum); (6.1×10^{-3} M, MeCN, 0.5 mm cell, $\Delta\varepsilon$, λ_{max}) +6.0, 227 nm, −5.5, 200 nm. The optical purity of (+)-**1** (>95%) was determined in $CDCl_3$ in the presence of Eu(tfc)$_3$, where only one NH signal was present, while the racemate NH signal was split in two with 0.05 ppm separation. Anal. calcd for $C_{12}H_{16}N_2O_6$ (%) C 50.7, H 5.7, N 9.85, found (%) C 50.9, H 5.8, N 9.85.

5.3.7. 2,5-Diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylic acid dihydrate (±)-2. To a suspension of (±)-**1** (150 mg, 0.53 mmol) in EtOH–H_2O mixture (1:1, 1 ml) was added 90% KOH (100 mg, 1.6 mmol), followed by internal heating, accompanied by full dissolution of the dilactam. After 12 h at 0°C the crystalline precipitate of disalt is filtered off, subsequently washed with EtOH and Et_2O and dried in open air. Yield 126 mg, mp >360°C. ^{1}H NMR (D_2O, δ, ppm): 2.25–2.31 ($(CH_2)_2$, AA′BB′ spectrum). The salt was dissolved in a minimal amount of H_2O (60°C) and to the solution was added CF_3COOH (0.5 ml). After 8 h at 0°C the fine crystalline precipitate of (±)-**2** was filtered off, washed with cold H_2O and dried in air, yield 99 mg (71% for two steps), mp 285°C, ^{1}H NMR (CD_3OD, δ, ppm, *J*, Hz): 2.28–2.38 ($(CH_2)_2$, AA′BB′ spectrum, $^2J_{AB}=^2J_{A'B'}=-13.5$, $^3J_{AB'}=^3J_{A'B}=10.9$, $^3J_{BB'}=4.8$, $^3J_{AA'}=3.9$). Anal. calcd for $C_8H_{12}N_2O_8$ (%): C 36.4, H 4.6, N 10.6, found (%) C 36.4, H 4.6, N 10.9.

5.3.8. 2,5-Diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylic acid dihydrate (1*R*,4*R*)-(−)-2. Similar procedure as for racemic diacid starting from 100 mg of (1*R*,4*R*)-(−)-**1** gives 51 mg (55%) of white crystals of (1*R*,4*R*)-(−)-**2**. Mp 273–275°C, $[\alpha]_D^{20}=-35.8$ (*c* 0.6, MeOH), CD (6×10^{-3} M, MeOH, 0.5 mm cell, $\Delta\varepsilon$, λ_{max}) −0.37, 246 nm, −0.28, 243 nm, −6.53, 225, 0, 210 nm, 5.5, 202 nm. Anal. calcd for $C_8H_{12}N_2O_8$ (%): C 36.4, H 4.58, found(%) C 36.2, H 4.55.

5.3.9. Decarboxylation of (−)-2. (1*R*,4*R*)-(−)-DBO. (−)-**2** (30 mg, 0.11 mmol) was mixed with 5 g of quartz sand in a sublimator and the mixture was heated on the oil bath (250–280°C) for 15 min. The product sublimated in vacuo to yield 5 mg (32%) of partially enriched (−)-DBO. Mp 272–273°C, $[\alpha]_D^{20}=-7$ (*c* 0.5, MeOH), optical purity 9%.[10a] ^{1}H NMR (CD_3OD, δ, ppm): 1.98 (m, 4H, $(CH_2)_2$), 3.90 (m, 2H, 1,4-CH).

5.3.10. Dimethyl (1*S*,4*S*)-(+)-2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylate 3. (+)-**1** (15 mg, 0.053 mmol) was dissolved in methanol (10 ml), DBU (50 mg) was added and the solution was refluxed for 8 h. Chromatography (MeOH–EtOAc 1:10) afforded 9.5 mg (70%) of the product (white powder), mp 234°C, $[\alpha]_D^{20}=+45.2$ (*c* 0.6. MeOH). ^{1}H NMR ($CDCl_3$, δ, ppm): 2.30–2.50 (4H, $(CH_2)_2$, AA′BB′ spectrum), 3.95 (s, 2Me, 6H), 6.82 (NH, br s, 2H). Anal. calcd for $C_{10}H_{12}N_2O_6$ (%): C 46.9, H 4.7, N 10.9, found (%) C 46.5, H 4.8, N 11.1.

5.3.11. Dipropyl (1*R*,4*R*)-(−)-2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylate 4. Prepared from (−)-**1** analogously to (+)-**3**. Yield 54% (white crystals), mp 180–181°C, $[\alpha]_D^{20}=-28.8$ (*c* 0.7, MeOH), ^{1}H NMR ($CDCl_3$, δ, ppm, *J*, Hz): 0.99 (2Me, t, 6H, ^3J=7.3), 1.76 (2C*H*$_2$Me, sext, 4H, ^3J=7.3), 2.30–2.50 (4H, m, $(CH_2)_2$, AA′BB′ spectrum), 4.31 (2OCH$_2$, ABX$_2$-spectrum, 4H, $^2J_{AB}=-10.7$, ^3J=7.3), 6.78 (NH, br s, 2H). Anal. calcd for $C_{14}H_{20}N_2O_6$ (%): C 53.8, H 6.5, N 9.0, found (%) C 53.8, H 6.7, N 9.0.

5.3.12. Quasi-racemates (−)-4·(+)-1 and (+)-3·(−)-1. Prepared by joint crystallization of the constituents. ^{1}H NMR indicates the presence of the constituents in equal molar concentrations. (−)-**4**·(+)-**1**: colourless plates, yield 27%, mp 219–220°C (MeCN), $[\alpha]_D^{20}=0$ (*c* 1, MeOH), CD (4.5×10^{-3} M, MeOH, cell 2 mm, $\Delta\varepsilon$, λ_{max}): −0.34, 230 nm (no maximum). Anal. calcd for $C_{14}H_{20}N_2O_6\cdot C_{12}H_{16}N_2O_6$ (%): C 52.3, H 6.1, N 9.4, found (%) C 52.3, H 6.1, N 9.3.

5.3.13. (+)-3·(−)-1. Colourless plates, yield 15%, mp 235°C (MeOH), $[\alpha]_D^{20}=0$ (*c* 0.3, MeOH), CD (1.2×10^{-3} M, MeOH, cell 2 mm, $\Delta\varepsilon$, λ_{max}): −0.45, 235 nm, +0.25, 220 nm (no maximum). Anal. calcd for $C_{10}H_{12}N_2O_6\cdot C_{12}H_{16}N_2O_6$ (%): C 48.9, H 5.2, N 10.4, found (%) C 48.5, H 5.2, N 10.4.

5.4. General method for synthesis of the esters of diacids (±)-2, (1*S*,4*S*)-(+)-2 and (1*R*,4*R*)-(−)-2

To a suspension of 100 mg (0.38 mmol) of dihydrate of **2** in 1 ml of MeCN was added DBU (116 mg, 0.76 mmol) and the mixture was refluxed until the precipitate disappeared. The resulting solution was concentrated (50 mm Hg), and to remove traces of water the oily residue was twice dissolved in MeCN (3 ml) and evaporated to dryness. The residue was dissolved in MeCN (1 ml) and was added to the solution of appropriate alkyl halide (0.76 mmol) in acetonitrile (1 ml) and the mixture was refluxed for 12 h, reaction progress being controlled by TLC. Sparingly soluble esters ((±)-**5**, (±)-**6**, (±)-**8**) were filtered off, washed with MeCN, dried and recrystallized from a suitable solvent. Mother liquor, or the mixture itself, in the case of high solubility of the product ((±)-**7**, (±)-**9**, (+)-**10**, (1*S*,4*S*)-(+)-**7**, (1*R*,4*R*)-(−)-**9**), was then filtered through 5 g of silica gel (afterwards washed with MeCN) for removal of salts, evaporated and the residue recrystallized.

5.4.1. Dibenzyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate (±)-5. Yield 77% (colourless plates) (MeCN), mp 240–241°C, ^{1}H NMR (DMSO-d$_6$, δ, ppm, J, Hz) 2.22 ((CH$_2$)$_2$, AA′BB′ spectrum, 4H), 5.20–5.30 (2OCH$_2$, AB-spectrum, ^2J=−12, 4H), 7.40 (2Ph, m, 10H), 9.30 (2NH, br s, 2H). Anal. calcd for $C_{22}H_{20}N_2O_6$ (%): C 64.7, H 4.9, N 6.9, found (%) C 65.0, H 5.0, N 7.0.

5.4.2. Bis(9-anthrylmethyl) 2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylate (±)-6. Yield 67% (yellow powder) (DMSO), mp 235–237°C, ^{1}H NMR (DMSO-d$_6$, δ, ppm, J, Hz) 2.02 ((CH$_2$)$_2$, m, 4H), 6.10 (2H$_A$ in OCH$_2$, d, ^2J=−12.5, 2H), 6.29 (2H$_B$ in OCH$_2$, d, ^2J=−12.5, 2H), 7.55 (Ar, m, 8H), 8.11 (Ar, d, ^3J=8, 4H), 8.36 (Ar, d, ^3J=8.7, 4H), 8.69 (Ar, s, 2H), 9.21 (2NH, s, 2H). ^{13}C NMR (DMSO-d$_6$, δ, ppm) 27.39, 60.32, 65.31, 124.16, 125.30, 126.77, 128.87, 129.19, 130.60, 130.84, 165.89, 169.09. Anal. calcd for $C_{38}H_{28}N_2O_6$ (%): C 75.0, H 4.6, N 4.6, found (%) C 74.6, H 4.6, N 4.7.

5.4.3. Dihexyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate (±)-7. Yield 50% (white leaflets) (EtOH), mp 179–180°C, ^{1}H NMR (CDCl$_3$, δ, ppm, J, Hz) 0.90 (2CH$_3$, t, ^3J=7, 6H), 1.31 (4CH$_2$, m, 8H), 1.37 (2CH$_2$, quin., ^3J=7, 4H), 1.72 (2CH$_2$, quin., ^3J=7, 4H), 2.27, 2.50 ((CH$_2$)$_2$, m, 4H), 4.33 (2OCH$_2$, m, 4H), 6.73 (2NH, br s, 2H). Anal. calcd for $C_{20}H_{32}N_2O_6$ (%): C 60.6, H 8.1, N 7.1, found (%) C 60.5, H 8.3, N 7.1.

5.4.4. Dihexyl (1*S*,4*S*)-(+)-2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate 7. Purified by column chromatography (EtOAc–hexane). Yield 72%, opaque elastic film. $[\alpha]^{20}_{578}$=36.4, $[\alpha]^{20}_{546}$=42.3, $[\alpha]^{20}_{436}$=87.6, $[\alpha]^{20}_{406}$=113, $[\alpha]^{20}_{366}$=173 (*c* 1.2, benzene). ^{1}H NMR close to that of racemate. Anal. calcd for $C_{20}H_{32}N_2O_6$ (%): C 60.6, H 8.1, N 7.1, found (%) C 60.2, H 8.1, N 6.9.

Transparent solution of (+)-**7** in hot cyclohexane (1.6×10^{-2} M) on cooling to room temperature forms opaque gel, in which gradually (1–2 days) small crystals are formed. Lower limit of concentration necessary for the formation of gel is $\sim3\times10^{-3}$ M.

5.4.5. Dihexadecyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate (±)-8. Yield 68% (white leaflets) (MeCN), mp 148–149°C, ^{1}H NMR (CDCl$_3$, δ, ppm, J, Hz) 0.87 (2Me, t, ^3J=7.2, 6H), 1.25 (26CH$_2$, m, 52H), 1.71 (2CH$_2$, quint., ^3J=7.2, 4H), 2.27, 2.48 ((CH$_2$)$_2$, m, 4H), 4.32 (2CH$_2$, ABX$_2$-spectrum, $^2J_{AB}$=−11.5, $^3J_{AX}$=7, 4H), 6.84 (2NH, br s, 2H). ^{13}C NMR (CDCl$_3$, δ, ppm) 22.66, 25.66, 28.08, 28.39, 29.13, 29.32, 29.44, 29.54, 29.65 (br), 31.90, 64.73, 67.31, 165.61, 167.07. Anal. calcd for $C_{40}H_{72}N_2O_6$ (%): C 71.0, H 10.7, N 4.1, found (%) C 71.3, H 10.8, N 4.1.

5.4.6. Bis(3,5-dimethylbenzyl) 2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylate (±)-9. Yield 48% (white crystals) (MeOH). Mp 170–174°C. ^{1}H NMR (CDCl$_3$, δ, ppm, J, Hz) 2.33 (4Me, s, 12H), 2.25, 2.50 ((CH$_2$)$_2$, m, 4H), 5.24–5.30 (2OCH$_2$, AB-spectrum, ^2J=−12, 4H), 6.99 (2CH(4), s, 2H), 7.01 (4CH(2), s, 4H), 7.13 (2NH, br s, 2H). ^{13}C NMR (CDCl$_3$, δ, ppm, J, Hz) 21.08 (Me, q, ^1J=124.7), 28.00 (CH$_2$CH$_2$, t, ^1J=135.1), 64.84 (1,4-C, s), 68.72 (CH$_2$O, t, ^1J=148.3), 126.11 (CH(Ar), d, ^1J=158.9), 130.27 (CH(Ar), d, ^1J=155.7), 134.21 (C(Ar), s), 138.18 (C(Ar), s), 165.42 (CO, s), 167.11 (CO, s). Anal. calcd for $C_{26}H_{28}N_2O_6$ (%): C 67.2, H 6.1, N 6.0, found (%) C 67.2, H 6.1, N 6.0.

5.4.7. Bis(3,5-dimethylbenzyl) (1*R*,4*R*)-(−)-2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate 9. Yield 42% (white crystals) (MeOH). Mp 154–157°C. $[\alpha]^{20}_{578}$=−38, $[\alpha]^{20}_{546}$=−42, $[\alpha]^{20}_{436}$=−84, $[\alpha]^{20}_{406}$=105, $[\alpha]^{20}_{366}$=−141 (*c* 1.1, MeOH). ^{1}H and ^{13}C NMR close to that of racemate. Anal. calcd for $C_{26}H_{28}N_2O_6$ (%): C 67.2, H 6.1, N 6.0, found (%) C 67.3, H 6.1, N 6.0.

SCAD experiment. (±)-**9** (107 mg) and (−)-**9** (99 mg) were dissolved in CDCl$_3$ (0.8 ml). In the NH region of spectrum (7.3 ppm) were seen two separate br s with 1:3 integral ratio (25°C). On cooling below room temperature $\Delta\nu$ increased. On heating to 60°C, coalescence of signals was observed (at 6.9 ppm).

5.4.8. Bis[(2*S*)-2-methylbutyl] 2,5-diazabicyclo[2.2.2]-octane-3,6-dione-1,4-dicarboxylate (+)-10 (diastereomeric mixture). Yield 39% (white needles) (MeOH), mp 195–197°C, $[\alpha]^{20}_{578}$=4.1, $[\alpha]^{20}_{546}$=4.7, $[\alpha]^{20}_{436}$=8.8, $[\alpha]^{20}_{406}$ 10.0 (*c* 0.9 MeCN). ^{1}H NMR (C$_6$D$_6$, δ, ppm, J, Hz) 0.75 and 0.77 (t, 6H, 2*Me*CH$_2$, ^3J=7.5, diastereomers **a** and **b**), 0.79 and 0.81 (d, 6H, *Me*CH, ^3J=6.7, diastereomers **a** and **b**), 0.88, 1.00, and 1.27 (m, 4H, 2*CH*$_2$Me), 1.55 (m, 2H, HC), 1.50 and 1.96 (m, 4H, (CH$_2$)$_2$, AA′BB′), 3.80–4.15 (m, 2H, CH$_2$O, ABX, $^2J_{AB}$=−10.4, $^3J_{AX}$=6.8, $^3J_{BX}$=5.6, diastereomer **a**), 3.96–3.98 (m, 2H, CH$_2$O, AB, $^2J_{AB}$=−10.5, $^3J_{AX}$=$^3J_{BX}$=0), 6.72 (s, 2H, HN). ^{1}H NMR (CDCl$_3$, δ, ppm, J, Hz) 0.90 (t, 6H, 2*Me*CH$_2$, ^3J=7.4), 0.94 (d, 6H, 2MeCH, ^3J=6.7), 1.21 and 1.44 (m, 4H, 2CH$_2$Me), 1.79 (m, 2H, 2HC), 2.27 and 2.46 (m, 4H, (CH$_2$)$_2$, AA′BB′), 4.10–4.20 (m, 2H, CH$_2$O, ABX, $^2J_{AB}$=−10.6, $^3J_{AX}$=8.0, $^3J_{BX}$=6.0, diastereomer **a**), 4.12–4.17 (m, 2H, CH$_2$O, ABX, $^2J_{AB}$=−10.5, $^3J_{AX}$=6.8, $^3J_{BX}$=6.0, diastereomer **b**), 6.96 (br s, 2H, HN). ^{13}C NMR (CDCl$_3$, δ, ppm, J, Hz) 10.60 (q, *Me*CH$_2$, ^1J=124.7), 16.16 (q, *Me*CH, ^1J=126.0), 25.76 (t, *CH*$_2$Me, ^1J=127.5), 27.99 (t, (CH$_2$)$_2$, ^1J=134.3), 33.91 (d, CH, ^1J=129.3), 64.74 (s, 4,7-C), 71.35 (t, CH$_2$O, ^1J=141.6), 165.60 (s) and 167.20 (t) (O=*C*OCH$_2$, ^3J=6.6). Anal. calcd for $C_{18}H_{28}N_2O_6$ (%): C 58.7, H 7.7, N 7.6, found (%) C 58.4, H 7.5, N 7.6.

5.4.9. Diisopropyl 2,5-diazabicyclo[2.2.2]octane-3,6-dione-1,4-dicarboxylate (±)-11. Synthesis was performed before general method development. To a cooled (≈−10°C) solution of (±)-**2** (60 mg, 0.23 mmol) in MeOH (3 ml) was added an excess of a solution of 2-diazopropane in Et$_2$O (~2 M, 1 ml, 2 mmol) (−70°C) (CAUTION: toxic) and the mixture was quickly evaporated (20 mm Hg). The residue was taken up in hot CHCl$_3$ (3×5 ml), combined solutions were filtered and evaporated to dryness. The residue was recrystallized from acetone to give 44 mg (61%) of colourless blocks of the product, mp 251–252°C. ^{1}H NMR (CDCl$_3$, δ, ppm, J, Hz): 1.33 (Me$_a$, d, 6H, ^3J=6.4), 1.37 (Me$_b$, d, 6H, ^3J=6.4), 2.24, 2.45 (4H, m, (CH$_2$)$_2$), 5.23, (OCH, sept, 2H, ^3J=6.4), 6.73, (NH, br s, 2H). Anal. calcd for $C_{14}H_{20}N_2O_6$ (%): C 53.8, H 6.5, N 9.0, found (%) C 53.9, H 6.3, N 9.0.

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