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Macrocyclic Cyclo[*n*]malonates – Synthetic Aspects and Observation of Columnar Arrangements by X-ray Crystallography

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A variety of achiral and chiral macrocyclic oligomalonates were synthesised in a one-step procedure through condensation of malonyl dichloride with α,ω-diols. We have investigated the applicability of this method by varying the length and type of the spacers in the diol. Product distribution analysis revealed that the preferential formation of monomeric, dimeric, or trimeric macrocyclic malonates can be controlled by choosing diols with specific spacers connecting the hydroxy groups. Of special interest are the macrocyclic bismalonates, as they show pronounced crystallisability and arrange into columnar motifs in the solid state. They feature distinctive dihedral angles: all ester moieties adopt *anti* conformations whereas the planes of the carboxy moieties of each malonate residue arrange in an approximately orthogonal fashion. The latter geometry is enforced by the macrocyclic structures, as revealed by a conformational search in the Cambridge Structural Database. The X-ray diffraction data show that C=O···H–C, and C–O···H–C hydrogen bonds stabilise the columnar arrangement of the dimeric rings with formation of tubular assemblies.

Introduction

Essential activities of a living organism depend on the relative concentrations of alkali metal cations inside and outside the cell.[1] Ionophores are molecular vehicles that transport ions across biological membranes, an important function at the cellular level. Several antibiotics can selectively induce ion transport across the cellular membrane.[2,3] Valinomycin, enniatin, nonactin, and enterobactin are examples of naturally occurring macrocyclic ionophores with structures controlled by repetitive amide and/or ester bonds.[4] Since the seminal discovery of the crown ethers by Pedersen,[5] a plethora of nonnatural macrocycles, mimicking the properties of the natural ionophores, have been prepared by a variety of synthetic approaches. A first comprehensive review covering the synthesis and the cation-binding properties of synthetic ionophores, including macrocyclic di- and tetralactones, was published by Bradshaw et al. in 1979.[6]

The synthesis of the first macrocyclic bislactone, compound **1** (Scheme 1), incorporating a malonate ester moiety, was reported in 1933 by Hill and Carothers;[7] the main interest in macrocyclic dilactones (and tetralactones) at that time involved their use in the perfume industry. The preparation of a series of cyclic monomalonate esters (**2**) with oligoether chains was described by Bradshaw and coworkers,[8] and their ability to complex ions such as Na^+, K^+, or Ba^{2+} was investigated. "Dimeric" macrolactones incorporating two malonate moieties have been prepared either by condensation of malonyl dichloride with ethyleneglycol at low temperatures under high-dilution conditions[9] or by treatment of dipotassium malonate with *o*-bis(bromomethyl)benzene at ordinary dilution, as reported by Drewes and Riphagen for the synthesis of **3**[10] (Scheme 1). Furthermore, a metal-ion-templated synthesis involving the transesterification of dimethyl malonate with ethylene- or diethyleneglycol (Scheme 1) has been introduced by Thulin and Vögtle,[11] yielding the bis- and trismalonate macrocycles **4**, **5**, and **6**.[12]

We have recently reported[13] a simple synthesis of new macrocyclic malonates, such as **7** (Scheme 1), by the condensation of malonyl dichloride with a variety of α,ω-alkanediols. The reactions were performed in dichloromethane under high-dilution conditions, with pyridine as a base, providing facile access to a variety of cyclo[*n*]alkylmalonates with varying lengths of the bridging alkyl chains and ring sizes. Purification was accomplished by flash column chromatography on silica gel, and the newly synthesised macrocycles were studied for the regioselective remote functionalisation of [60]fullerene through multiple Bingel ad-

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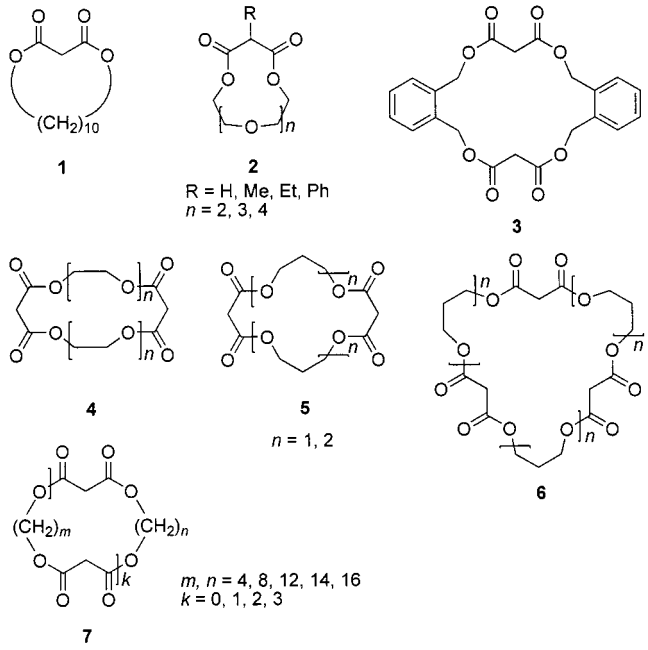


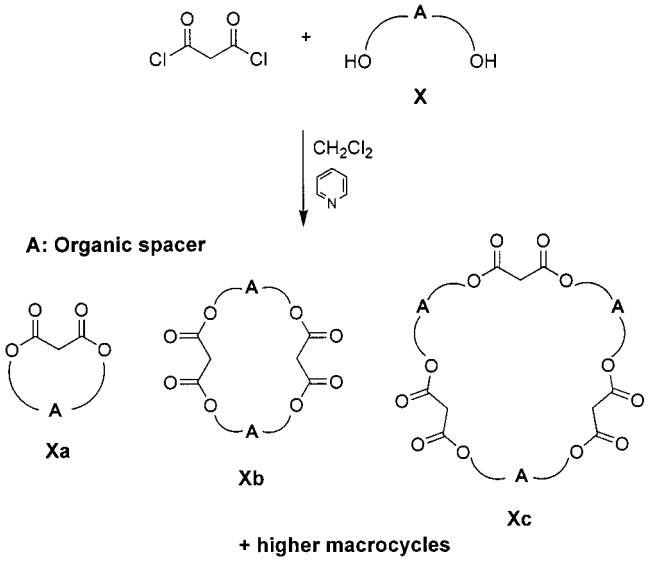
Scheme 1. Cyclic oligomalonate esters reported in the literature.

ditions.[13,14] Here we report a detailed study on the synthesis of macrocyclic malonates from malonyl dichloride and appropriate α,ω-diols. We focus our interest on the effect of the natures and chain lengths of the alkyl spacers connecting the hydroxy groups of the diol and on how these properties affect the product distribution between monomeric, dimeric, and trimeric cyclomalonates formed in the condensation reaction. Exclusively cyclo[*n*]malonates such as **7**, containing one type of spacer only (*m* = *n*), are considered in this study. Furthermore, we report the preparation of a series of chiral, nonracemic mono-, bis-, and trismalonate macrocycles through the use of enantiomerically pure diols of different chain lengths. A remarkable observation involving the bismalonate macrocycles is their pronounced ability to crystallise on slow diffusion of pentane into their dichloromethane solutions. X-ray crystallography revealed that the cyclobismalonates arrange in columnar structures with formation of a channel (pore) in the middle of each column. The dimensions of the channels can be tuned by variation of the chain length, thereby giving facile access to supramolecular tubular assemblies with formation of porous crystals.

Results and Discussion

General Procedure for the Synthesis of Macrocyclic Oligomalonates

Macrocyclic malonates were synthesised as shown in Scheme 2. A solution of malonyl dichloride (2 equiv.) in CH_2Cl_2 was added very slowly to a solution of the diol **X** (1 equiv.) and pyridine (2 equiv.) in CH_2Cl_2, at a maximum diol concentration of about 30 mmol·L^{-1}. FAB MS analysis of the crude mixture revealed the formation of macrocycles incorporating up to nine diol repeat units in most cases. The cyclomalonates can be obtained in pure form by flash column chromatography on silica gel (eluent: EtOAc/CH_2Cl_2), the elution sequence following the size of the macrocycles, with the smaller rings eluting first. In this



Scheme 2. Synthesis of macrocyclic oligomalonates by condensation of malonyl dichloride with diols.

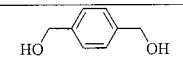
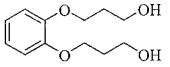
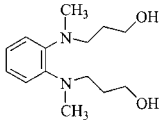
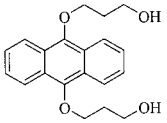
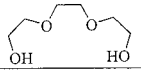
Table 1. Distributions and physical properties of the oligomalonate macrocycles obtained from condensation reactions betwee malonyl dichloride and alkanediols.

Entry (**X**)	Diol	Monomer (**Xa**)		Dimer (**Xb**)		Trimer (**Xc**)	
		Yield[a] (%)	State	Yield[a] (%)	State	Yield[a] (%)	State
8	HO–$(CH_2)_3$–OH	not formed	–	17	white solid	11	colourless oil
9	HO–$(CH_2)_5$–OH	traces	yellowish oil	16	white solid	8	yellowish oil
10	HO–$(CH_2)_8$–OH	traces	yellowish oil	16	white solid	9	yellowish oil
11	HO–$(CH_2)_{11}$–OH	traces	yellowish oil	12	white solid	not isolated	–
12	HO–$(CH_2)_{12}$–OH	traces	yellowish oil	8	white solid	not isolated	–
13	HO–$(CH_2)_{13}$–OH	4	colourless oil	14	white solid	not isolated	–
14	HO–$(CH_2)_{14}$–OH	6	colourless oil	14	waxy solid	7	waxy solid
15	HO–$(CH_2)_{15}$–OH	9	colourless oil	10	waxy solid	not isolated	–
16	HO–$(CH_2)_{16}$–OH	11	white solid	10	waxy solid	5	waxy solid
17	HO–$(CH_2)_{20}$–OH	16	white solid	5	waxy solid	3	waxy solid

[a] Isolated yield. Some of the yields are reported with an accuracy of 1% for the sake of uniformity.

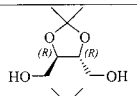
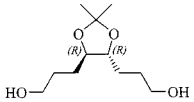
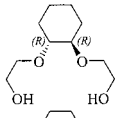
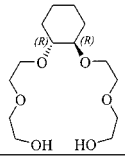
study we have isolated the monomeric (**Xa**), dimeric (**Xb**), and trimeric (**Xc**) malonate macrocycles (Tables 1, 2, and 3).

Table 2. Distributions and physical properties of the oligomalonate macrocycles derived from condensation reactions between malonyl dichloride and aromatic diols and diols containing heteroatoms in the spacer.

Entry (X)	Diol	Monomer (Xa) Yield[a] (%)	State	Dimer (Xb) Yield[a] (%)	State	Trimer (Xc) Yield[a] (%)	State
18[b]		not formed	–	6	white solid	1	yellowish oil
19[16]		5	colorless oil	12	white solid	not isolated	–
20[16]		10	colorless oil	16	colorless oil	3	yellowish oil
21[16]		10	yellow solid	13	yellow solid	traces	–
22		38	yellowish oil	13	yellowish oil	not formed	–

[a] Isolated yield. Some of the yields are reported with an accuracy of 1% for the sake of uniformity. [b] The reaction was performed at a diol concentration of 0.166 mol·L^{-1}. The macrocycles were separated by GPC with tetrahydrofuran as eluent.

Table 3. Distributions and physical properties of the oligomalonate macrocycles obtained from condensations between malonyl dichloride and optically active diols.

Entry (X)	Diol	Monomer (Xa) Yield[a] (%)	State	Dimer (Xb) Yield[a] (%)	State	Trimer (Xc) Yield[a] (%)	State
(–)-**23**		not formed	–	17	white solid	4	colorless oil
(+)-**24**		7	yellowish oil	7	white solid	2	colorless oil
(–)-**26**		28	white solid	2	yellowish oil	< 0.5 impure	yellowish oil
(–)-**28**		33	yellowish oil	2	yellowish oil	not isolated	–

[a] Isolated yield. Some of the yields are reported with an accuracy of 1% for the sake of uniformity.

The relative yields of the macrocycles can be easily obtained from the FAB mass spectra of the crude reaction mixture, as the peak intensities correlate exactly with the relative isolated yields of the corresponding compounds. This was demonstrated for the cyclo[*n*]octylmalonates by comparison of the relative intensities of the molecular ion peaks with the relative isolated (molar) yields of the purified products, as determined by gravimetric methods. This provides an ideal tool for the optimisation of the product distribution, since the relative molar yield of the cyclo[*n*]-octylmalonates plotted against *n* can be perfectly fitted to a Lorentzian function (Figure 1). It was found that the product distribution is virtually independent of the diol concentration over a range of 15–35 mmol·L^{-1}. The only effect is a decrease in the total yield with increasing concentration. The main factor governing the product distribution seems to be the duration of the malonyl dichloride addition.

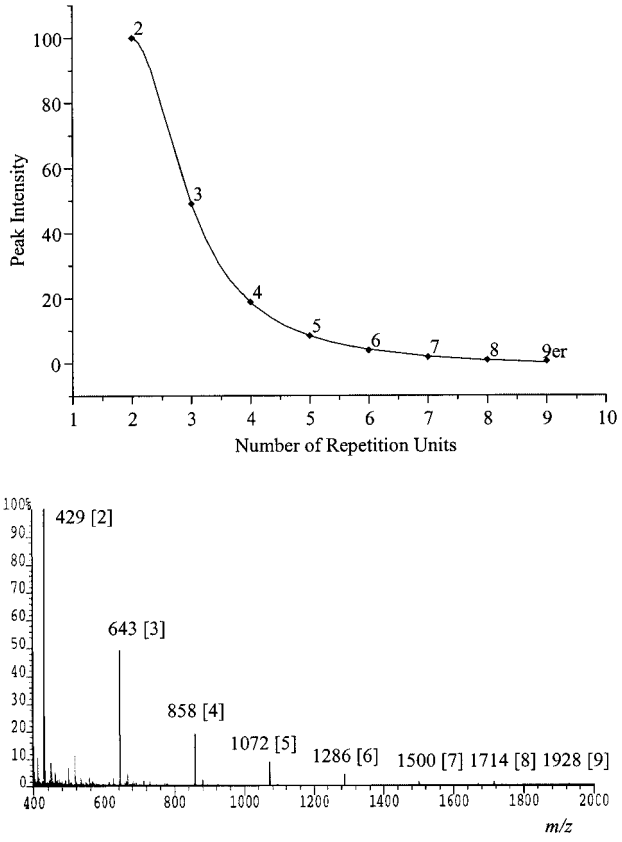


Figure 1. Lorentz fit of the relative molar yields for the cyclo[*n*] octylmalonates determined from FAB mass spectrometry.

It should be noted here that the isolated yields of the macrocyclic malonates are not high, ranging from 2 to 17% in the case of the bismalonates (Tables 1, 2, and 3). In principle, the yields could be improved by use of multi-step methods involving tedious protecting-group chemistry, ultimately allowing a single final intramolecular ring closure. However, our original goal was to find a quick route to the oligomalonate macrocycles in order to test them for regioselectivity in Bingel macrocyclisations with C_{60}.

Condensation of Malonyl Dichloride with α,ω-Alkanediols

The distribution of the different (mono-, bis-, and tris-) cyclomalonates formed in a cyclisation reaction between malonyl dichloride and a diol would be expected to depend on both the length and the nature of the chain connecting

the hydroxy groups. In order to investigate the effect of the chain length, we subjected a series of alkanediols (**8**–**17**), differing in carbon chain length, to cyclisation with malonyl dichloride; the results are summarised in Table 1. The following conclusions can be drawn from the reported data:
a) The monomalonate macrocycles **Xa** were formed only in traces when diols containing three to twelve methylene units were utilised, whereas the formation of the monomeric rings was favoured when long-chain alkanediols were used (**16**–**17**).
b) The yields of the cyclic dimers **Xb** and trimers **Xc** tended to decrease with increasing chain length of the diol, while at the same time the formation of polymeric products became pronounced.
c) The monomeric malonates **Xa** with up to C_{15} alkyl spacers exist as highly viscous oils while monomers with larger ring sizes are isolated as solids.
d) The bismalonates **Xb** with up to C_{13} alkyl spacers are all crystalline solids, whereas diols containing more than 14 methylene units afford dimers that are isolated as waxy materials.
e) The trimeric malonates **Xc** have a morphological appearance similar to that of the monomeric counterparts. Thus, trimeric macrocycles with short spacers exist as highly viscous oils while the long-alkyl-chain derivatives are isolated as waxy solids.

An interesting observation concerns the melting points of the cyclobismalonates: the macrocycles containing C_{11}–C_{16} alkyl chains with even numbers of carbon atoms have slightly higher melting points than their neighbouring homologues with odd numbers of carbon atoms, thus showing a behaviour similar to that of linear alkanes (Figure 2).[15] This behaviour – along with their X-ray structures – is evidence of the highly ordered structures of such macrocycles in the solid state.

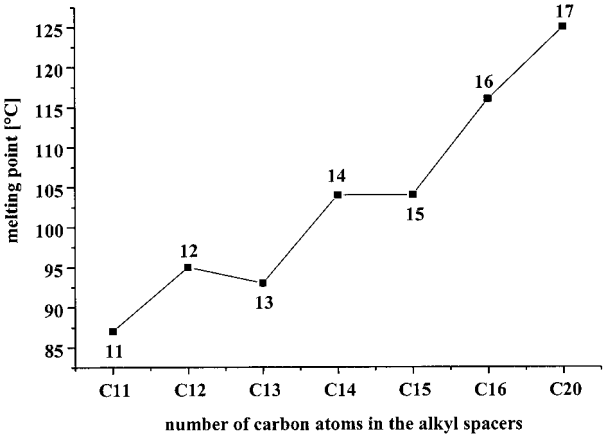


Figure 2. Diagram of the melting points of the cyclo[2]alkylmalonates vs. the number of carbon atoms in the alkyl spacers.

Condensation of Malonyl Dichloride with Aromatic Diols and Diols Containing Heteroatoms in the Spacers

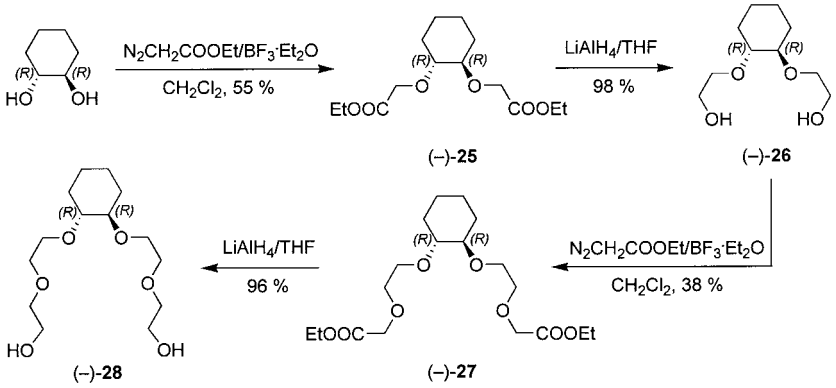
To investigate the influence of the nature of the organic chains in the diols on the distributions of the cyclic malonates formed during cyclisations with malonyl dichloride, the diols **18**–**22** shown in Table 2 were examined. The behaviour of benzene-1,4-dimethanol (**18**) was found to correspond to that of short-chain alkanediols. Macrocycles up to nonamers were formed and separated by GPC, whereas the cyclic monomalonate **18a** was not detected in the crude reaction mixture. In diols **19**, **20** and **21** the rigid core was retained but oxygen or nitrogen heteroatoms were introduced into the side chains.[16] In this case, the formation of monomeric **19a**, **20a**, **21a** and dimeric **19b**, **20b** and **21b** is favoured, and they were isolated in yields ranging from 5 to 16%. The trimeric malonates **19c**, **20c** and **21c** are only minor products of these transformations. This trend is most pronounced when triethyleneglycol **22** is used as diol. The monomeric **22a** is formed as the major product in 38% yield, while the formation of the trimeric **22c** is completely suppressed.

The different macrocyclisation behaviour of triethyleneglycol (**22**) and the corresponding octane-1,4-diol (**10**) can be readily explained in terms of different conformational preferences. Whereas all-alkyl chains clearly prefer all-*anti* torsion angles, triethyleneglycol prefers *gauche* conformations of its O–C–C–O fragments (*gauche* effect).[17] The "folding" induced by the *gauche* dihedral angles presumably preorganises **22** for the formation of the monomeric macrocycle. The condensation between malonyl dichloride and triethyleneglycol under solid–liquid phase-transfer catalysis conditions with KF as a base and template, benzyltriethylammonium chloride as catalyst and dichloromethane as solvent has been reported.[18] In this case, macrocycles with more than three malonate units were also obtained, possibly as a result of cation templating effects.

Chiral Cyclomalonates

In a next step we targeted the preparation of chiral, nonracemic macrocycles. For this purpose, diols (–)-**23**, (+)-**24**, (–)-**26** and (–)-**28** (Table 3) were subjected to cyclisation with malonyl dichloride under the experimental conditions reported above. (4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-dimethanol [(–)-**23**] is commercially available, while (–)-**26** and (–)-**28** were synthesised as shown in Scheme 3. The synthesis of (+)-**24** has been reported previously.[19]

Diol (–)-**23** (Table 3) showed a behaviour similar to that of short-chain alkanediols, resulting in the formation of optically active macrocycles with up to nine repeat units, as confirmed by FAB MS of the crude reaction mixture. Monomeric *ent*-**23a** was not detected, and the cyclisation with malonyl dichloride afforded dimeric (+)-**23b** as the major product. In the case of diol (+)-**24**, with two longer C_4 chains emanating from the five-membered ring, the monomeric and dimeric rings were formed in equal yields, while the yield of the trimeric ring was significantly lower, as was also observed with longer-chain alkanediols (Table 1). Dimeric (+)-**23b** and (+)-**24b** are readily crystallisable solids, whereas the corresponding trimeric rings exist as highly viscous oils. The enantiomerically pure diols (–)-**26** and (–)-**28**,



Scheme 3. Synthesis of the optically active diols (–)-**26** and (–)-**28**.

bearing glycolic chains, gave results similar to those obtained with triethyleneglycol, with monomeric (–)-**26a** and (–)-**28a** being formed as the major products in 28 and 33% yields, respectively. The corresponding bis- and trismalonates were formed as minor products, and their separation by column chromatography proved to be tedious, due to their high polarities and low yields. Trimeric *ent*-**26c** was isolated in impure form, while the column chromatographic separation of *ent*-**28c** on SiO_2 could not be accomplished. Finally, in contrast to the crystalline states of the dimeric rings obtained from diols (–)-**23** and (+)-**24**, the bismalonates *ent*-**26b** and *ent*-**28b** exist as highly viscous oils.

X-ray Crystallographic Study of the Macrocyclic Bismalonates

A common characteristic of the bismalonates synthesised in this study (Tables 1, 2, and 3) is their ability to form colourless, X-ray quality crystals when pentane slowly diffuses into their dichloromethane solutions. This crystallisation method was applied to all bismalonates except for **18b**, which afforded crystals suitable for X-ray analysis on slow concentration of its chloroform solution. Only the bismalonates containing glycol chains or long alkyl chains could not be crystallised but rather yielded highly viscous oils.

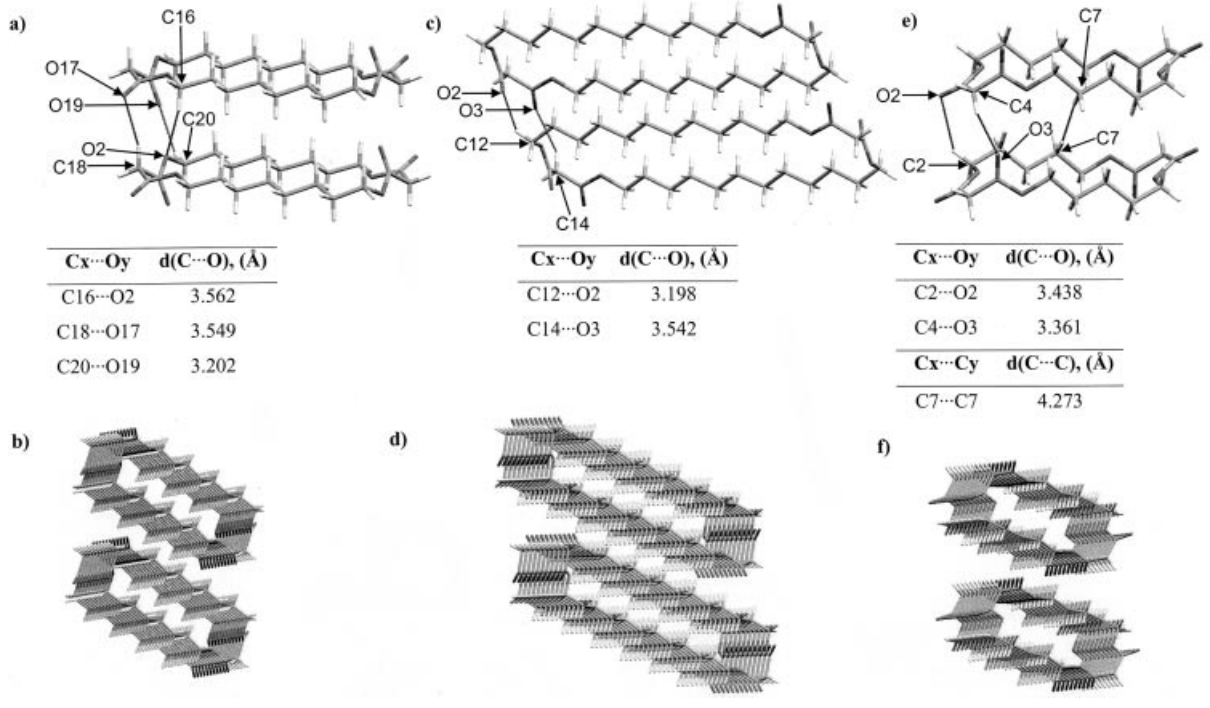
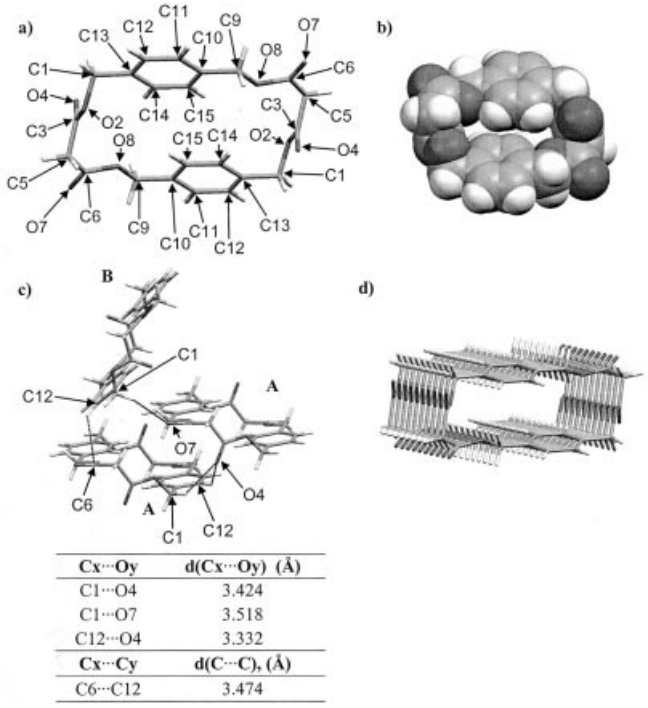


Figure 3. Columnar arrangement of **10b** (left),[13] **12b** (center),[13] and **9b** (right) in single crystals: a) Intermolecular C–H···O hydrogen bonds between neighbouring molecules of **10b** in the stacks and measured C*x*···O*y* distances. b) Columnar structure of **10b**. c) Intermolecular C–H···O hydrogen bonds between neighboring molecules of **12b** and measured C*x*···O*y* distances. d) Columnar structure of **12b**. e) Intermolecular C–H···O hydrogen bonds and C–H···H–C interactions between neighbouring molecules of **9b** and measured C*x*···O*y* and C*x*···C*y* distances. f) Columnar structure of **9b**.

Tubular structures[20] are versatile functional modules in nanoconstruction and the supramolecular approach[21] has been used extensively to produce well-defined organic nanotubes. Among the different molecule-based synthetic strategies, the self-assembly or stacking of macrocycles offers the potential to create hollow tubular structures in the solid state. Cyclic peptides,[22] cyclic oligosaccharides, phenylene macrocycles, coil-ring-coil block copolymers and cyclodextrins have been successfully used as molecular building blocks, and their self-assembly to form tubular structures has been examined.[23] Recently, we reported[13] the crystal structures of bismalonates **10b** and **12b**. These macrocycles crystallise in perfectly rectangular shapes, with the molecules arranging into columnar structures (Figure 3) forming very narrow inner channels with dimensions depending on the lengths of the alkyl chains in the macrocycle. Distinct dihedral-angle preferences are apparent: the alkyl chains, as would be expected, prefer the all-*anti* conformation, whereas the two carboxy planes in each malonate moiety are nearly orthogonal to one another [torsion angles between the planes through C–O–C(O)–C and C′–C′(O′)–O′–C average 77°]. Space-filling-model representations show that the inner space in each macrocycle is nearly filled with hydrogen atoms engaged in favourable intramolecular van der Waals interactions. The columnar assemblies are also stabilised by intermolecular CH···CH van der Waals interactions. In addition, several intermolecular C–H···O hydrogen bonds[24] presumably make important contributions to the stabilities of the columnar stacks. Such intermolecular contacts [*d*(C···O) distances between 3.198 and 3.562 Å] are seen between the C=O groups and the methylene groups of the malonates (C18 in **10b**, C14 in **12b**) and the terminal methylene groups of the diols (C20 in **10b**, C12 in **12b**). As a result of the inductive effect of the neighbouring oxygen atoms, these CH_2 moieties are particularly favourably polarised to participate in C–H···O interactions.

Like the bismalonates **10b** and **12b**, macrocycle **9b** (Figure 3) crystallises in a rectangular shape with a nearly filled internal macrocyclic void. Again the tubular structures are held together by intermolecular C–H···O hydrogen bonds [*d*(C···O) = 3.361–3.438 Å] between the C=O residues of the malonates and the methylene groups of the malonate (C4) and terminal methylene groups of the diol (C2). Additional short C–H···O contacts are seen between neighbouring molecules in different stacks [*d*(C···O) = 3.440–3.571 Å].

Whereas the inner pores in the columnar stacks of **9b**, **10b** and **12b** are nearly completely filled by C–H residues engaged in through-space van der Waals interactions, the bridging of the two malonate residues by *p*-xylylene moieties in [7.7]paracyclophane **18b** opens up a void space. The molecule crystallises in a rectangular shape, and the two benzene rings adopt a coplanar parallel-shifted orientation (Figure 4). The normal distance between the two parallel benzene planes amounts to 5.867 Å (centroid–centroid distance) and the centres of the rings are parallel shifted by 5.550 Å. The unit cell contains two differently oriented molecules A and B. The dihedral angle between the planes of the benzene rings in molecules A and B is 38.91°, whereas benzene rings of the same kind of molecules (A or B) adopt a parallel alignment and sit atop each other. Molecules of the same kind pack in columnar stacks that are stabilised by several intermolecular C–H···O hydrogen bonds [*d*(C···O) = 3.332 and 3.425 Å] between malonate C=O groups and aliphatic and aromatic C–H residues. Interestingly, there are also close C–H···O contacts between malonate carbonyl groups and benzene C–H units as well as with the favourably polarised, acidic malonate CH_2 groups.



Cx···Oy	d(Cx···Oy) (Å)
C1···O4	3.424
C1···O7	3.518
C12···O4	3.332
Cx···Cy	**d(C···C), (Å)**
C6···C12	3.474

Figure 4. Molecular structure and columnar arrangement of **18b**. a) X-ray crystal structure of **18b** with numbering of atoms. b) Space-filling representation of the molecular structure. c) Alignment of the two molecules A and B with different structures found in the unit cell, intermolecular C–H···O hydrogen bonds and C–H···C=O interaction between molecules of the same kind in a columnar alignment and between molecules of a different kind, and measured C···O and C···C distances. d) Columnar structure formed by molecule A.

The asymmetric unit cell of a single crystal of optically active bismalonate (+)-**23b** showed a rectangularly shaped macrocycle with a nearly closed internal cavity (Figure 5). As in the previously discussed structures, the molecules organise into columnar stacks held together by van der Waals interactions and C–H···O=C hydrogen bonding, with *d*(C···O) = 3.414 Å. A variety of intermolecular C–H···O hydrogen bonds, involving not only the carbonyl oxygen atoms but also the ether oxygen atoms of the malonate ester residues, are also seen between macrocycles in neighbouring stacks. Similar structural features are observed for (+)-**24b** (Figure 5); these include: a) a nearly closed macrocyclic cavity, b) assembly of the macrocycles into columnar stacks promoted by intermolecular C–H···O hydrogen bonds, and c) stabilisation of the crystal lattice by additional C–H···O hydrogen bonds between molecules in neighbouring stacks.

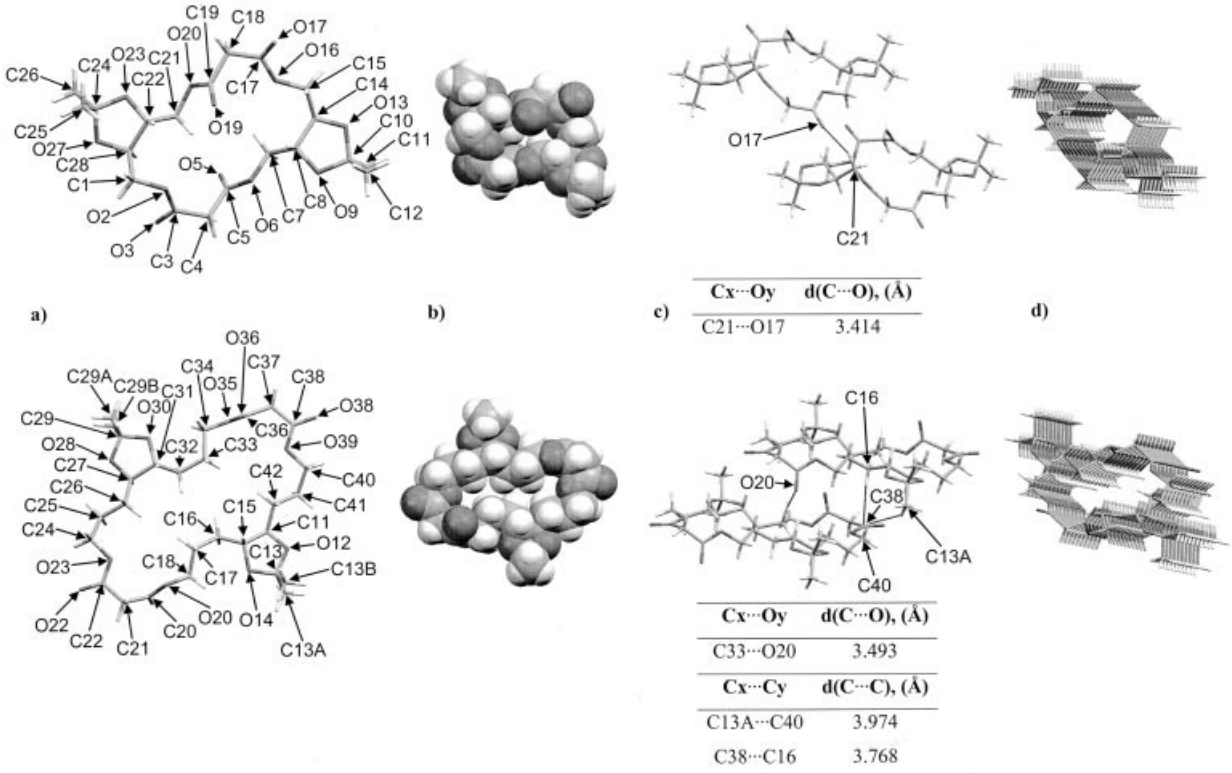


Figure 5. Molecular structure and columnar arrangement of (+)-**23b** (top) and (+)-**24b** (bottom). a) X-ray crystal structures with numbering of atoms. b) Space-filling representation of the molecular structures. c) C–H···O hydrogen bonds and C–H···H–C interactions between molecules in a columnar alignment and their measured distances. d) Columnar structures showing the channels formed in the crystal.

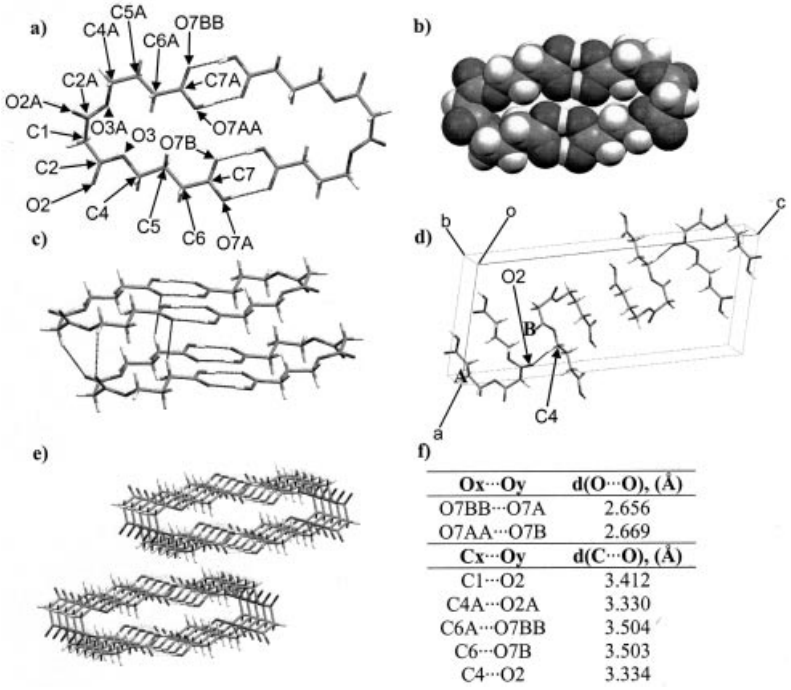
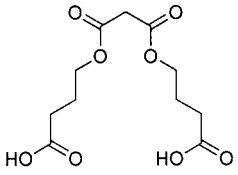


Figure 6. Molecular structure and columnar arrangement of **29** in the crystal. a) X-ray crystal structure of **29** and numbering of atoms. b) Space-filling representation of the supramolecular dimer. c) Intermolecular C–H···O hydrogen bonds between dimers of the same stack. d) Unit cell representation with the C–H···O hydrogen bond between molecules A and B. e) Columnar structure formed by the dimers. f) Measured distances for hydrogen bonds O–H···O and C–H···O.

Hydrogen Bond-Assisted Formation and Columnar Stacking of Supramolecular Cyclobismalonates

The synthesis of cyclobismalonates through condensations between malonyl dichloride and appropriate diols proved to be an easy method to access this family of macrocycles, the only disadvantage being the low product yields. The ability of these molecules to crystallise in columnar structures forming an inner channel prompted us to adopt a simpler approach for the formation of the dimeric rings and to investigate the possibility of their tubular stacking. We therefore investigated a supramolecular approach by forming a bismalonate macrocycle with intermolecular hydrogen bonding between two identical subunits. For this purpose, 4,4′-malonylbis(butanoic acid) (**29**) was synthesised as described before[25] and allowed to crystallise by slow concentration of its chloroform solution, yielding crystals suitable for X-ray analysis.



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The crystal structure (Figure 6) shows that two molecules are held together by intermolecular linear hydrogen bonds [*d*(C···O) = 2.656 and 2.669 Å] between the carboxylic groups, resulting in the formation of a supramolecular cyclobismalonate in the solid state. The unit cell contains two pairs of different molecules **29** (A and B), oriented nearly perpendicularly to one another. A C–H···O=C hydrogen bond with *d*(C···O) = 3.334 Å is observed between A and B. The supramolecular bismalonate dimers behave similarly to the covalent analogues and form columnar structures with an inner channel (Figure 6). Again, the columnar stacks are stabilised by short C–H···O contacts, which clearly represent the prominent directional intermolecular interactions in the assemblies of both the covalent and the supramolecular dimers.

Conformational Analysis of Malonates

Malonates bearing two COOMe ester groups have proven preferentially to adopt *anti* ester orientations [Figure 7a; *anti* is defined for the orientation of the bonds R^1–O and C(O)–C(R^2,R^3)].[26] The rotational barrier around the ester bond leading to the higher-energy *syn* conformer has been shown to be as large as 30 kJ·mol^{-1}.[27,28] The preference for the *anti* conformation originates from both steric and stereoelectronic (n→σ*) factors. A Cambridge Structural Database (CSD version 5.26) search of 526 crystal structures containing a total of 683 malonate moieties of the general type R^1OOC–CR^2R^3–$COOR^4$ (with R^1, R^4 being carbon-terminated residues and R^2, R^3 being hydrogen or any other carbon residue) clearly supports the previous results. The scatterplots (Θ_1 vs. Θ_4, Figure 7b) show distinct clustering at dihedral angles Θ_1 [R^1–O–C(O)–C] = Θ_4 [R^4–O–C(O)–C] = 0°. A total of 584 (86%) of the investigated structures lie within a range of ±10°. The few exceptions to this preference are observed in malonates with either one or two ester groups incorporated in small-ring lactone structures adopting the energetically unfavourable *syn* conformation.

With respect to the dihedral angles Θ_2 and Θ_3 (O=C–C–C), the results of the search are not as homogeneous. Recent publications applying low-temperature matrix-isolation infrared spectroscopy and quantum mechanical calculations at the DFT(B3LYP)/6-311++G** and MP2/6-31++G** levels of theory to dimethyl malonate predict two types of low-energy conformers.[27] One is characterised by C_2 symmetry, with both torsion angles being around 120°. The second shows C_1 symmetry and a "*gauche*" conformation. The energies of these minima were calculated to be very similar, separated only by barriers of 1.5 kJ·mol^{-1} for the conversion of the two possible C_2 conformers to the "*gauche*" conformers and of 1.8 kJ·mol^{-1} for the interconversion of the four "*gauche*" conformers. Our CSD search reflects these preferences although the clustering is not as pronounced as in the earlier case. Out of 683 malonate moieties found, 318 (47%) adopt a C_2 conformation showing a O=C–C–C torsion angle of 100° < Θ_2 < 150° or –150°

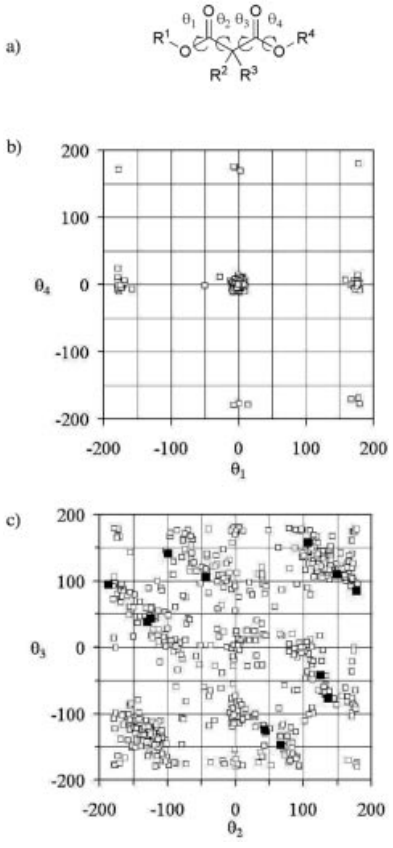

Figure 7. a) General graphical representation of the geometrical parameters used for the CSD search. b) Scatterplot correlating the pair of torsion angles (θ_1, θ_4). c) Scatterplot correlating the pair of torsion angles (θ_2, θ_3) (filled squares represent parameters for molecules described in this article).

$< \Theta_3 < -100°$, respectively (Figure 7c). Since the potential energy surface is calculated to be rather flat, the structures with "*gauche*" conformations only show a widespread agglomeration in the scatter diagram. In the case of one torsion angle being close to 0°, a tendency for the second torsion angle to lie in the range of 80–110° can be observed. In cases in which either steric repulsion or cyclic structures induce other than the expected conformations, the deviation from these predictions is greater.

The structures presented in this article clearly reflect the latter case. The preferred torsion angles are induced by the macrocyclic structure rather than by preferential geometries of the malonate moieties, leading to three "C_2-like" conformations and nine "*gauche*-like" conformations, all of them lying out of the boundaries discussed above (Figure 7c).

Conclusions

The synthesis of macrocyclic malonates through condensations between malonyl dichloride and chiral or achiral diols is a versatile one-step method providing cyclomalonates with a variety of organic spacers connecting the malonate ester moieties. The selectivity towards the preferential formation of monomeric, dimeric, or trimeric ring structures was tuned by varying the natures and lengths of the spacers in the diols, as demonstrated by the results obtained with alkanediols or diols bearing more rigid aromatic spacers or spacers with heteroatoms. The majority of the bismalonates synthesised showed pronounced crystallisability. The X-ray crystal structures of these macrocycles – both achiral and chiral – feature a large number of common characteristics:
(i) The dihedral angle between the planes of the two carboxy groups in a malonate tends to adopt values around 90 ± 30°. A conformational search in the CSD suggests that these conformational preferences are largely enforced by the macrocyclic structure. In all cases, *anti* ester conformations are observed.
(ii) The macrocycles assemble into columnar stacks, forming narrow channels and pores extending through the entire single crystals. Filling of the pores is favoured by intramolecular van der Waals interactions between methylene units in the dimers.
(iii) The most noticeable directional intermolecular interactions between neighbouring molecules in the columnar structures are C–H···O hydrogen bonds between the oxygen atoms of the malonate residues – with a preference for the participation of the C=O units – and polarised aromatic C–H and aliphatic CH_2 moieties. The distances of these C–H···O contacts vary between d(C···O) = 3.198 and 3.571 Å and are therefore in the range of those reported in the literature.[24] Such intermolecular C–H···O interactions are also observed between molecules of neighbouring columns. Remarkably, a similar tubular stacking was also observed for supramolecular bismalonate macrocycles formed by carboxylic acid dimerisation between two identical malonates with terminal carboxylates.

The supramolecular and covalent construction of macrocyclic bis- and trismalonates with more preorganised cavities enforced by more extended, rigid spacers will be pursued in future work. This study indeed raises expectations that such systems should have the potential to form columnar assemblies featuring pores for molecular recognition and transport.

Experimental Section

General: All starting materials were purchased from commercial sources or were prepared by known literature procedures. The solvents were dried by standard techniques. Reactions were monitored by thin layer chromatography on silica gel $60F_{254}$ (Merck) aluminium plates. Products were isolated by flash column chromatography (FC) (silica gel 60, particle size 0.04–0.0063 nm, Merck) and GPC (BioBeads S-X1 from Bio-Rad). ^{1}H NMR and ^{13}C NMR spectra were recorded with JEOL JNM EX 400, JEOL JNM GX 400, JEOL A 500 MHz and Bruker Avance 300 MHz spectrometers. The chemical shifts are given in ppm relative to the appropriate solvent peak as standard reference. The resonance multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), or combinations of these. Broad resonances are designated with br. Mass spectra were measured with a Micromas Zab (FAB) Finnigan MAT 900 spectrometer with 3-nitrobenzyl alcohol as the matrix. MALDI mass spectra were recorded with an IonSpec Fourier Transform (FT) instrument with 2,5-dihydrobenzoic acid (DHB) as a matrix. IR spectra were recorded with a Bruker FT-IR IFS 88. The spectra were measured as KBr pellets or as films on NaCl plates. Optical rotations were measured with a Perkin–Elmer Model 341 polarimeter. Elemental analyses were carried out with an EA 1110 CHNS machine from CE Instruments. X-ray crystallographic analysis was performed with an Enraf–Nonius MACH 3 diffractometer. Calculations were carried out with SHELX software; the graphics were generated with the Mercury 1.3 program. The purities of the achiral and chiral macrocyclic oligomalonates isolated in this study were higher than 98% as confirmed by TLC analysis and ^{1}H NMR spectroscopy. Compounds **10b**, **10c**, **12b**, **16a**, **16b** and **16c**,[13] **20a**, **20b**, **20c**, **21a** and **21b**,[16] (+)-**24a**, (+)-**24b** and (+)-**24c**[19] and **29**[25] were synthesised and characterised previously.

Synthesis of Diols (–)-26 and (–)-28

(1*R*,2*R*)-*trans*-1,2-Bis[2-ethoxycarbonyl-1-oxaethyl]cyclohexane [(–)-25]: Boron trifluoride–diethyl ether (0.1 mL) was added slowly under N_2 and with magnetic stirring to an ice-cooled solution of ethyl diazoacetate (90% in CH_2Cl_2, 1.98 mL, 19.12 mmol) and (1*R*,2*R*)-*trans*-cyclohexane-1,2-diol (1 g, 8.62 mmol) in dry CH_2Cl_2 (15 mL). After the addition was complete, stirring was continued at room temperature for 1 h, and then at 45 °C for 1 h. The solution was neutralised by addition of $NaHCO_3$ and filtered, and the solvent was evaporated under reduced pressure. The diester product was purified by flash column chromatography on SiO_2 with a mixture of hexane/EtOAc (1:1) as eluent. Yellow oil, yield 1.375 g (55%). $[a]_D^{22} = -38$ (c = 0.00239, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.29 (d, ^2J = 16.4 Hz, 2 H), 4.21 (d, ^2J = 16.4 Hz, 2 H), 4.16 (q, ^3J = 7.1 Hz, 4 H), 3.27 (m, 2 H), 2.02, (m, 2 H), 1.64 (m, 2 H), 1.24 (t, ^3J = 7.1 Hz, 6 H), 1.22 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.41, 83.54, 68.41, 61.05, 30.83, 24.07, 14.57 ppm. IR (CH_2Cl_2) $\tilde{\nu}_{max}$ = 3675, 3600, 3293, 3055, 2943, 2866, 1755, 1606, 1452, 1353, 1332, 1263, 1214, 1150, 1119, 1029, 1008, 986, 911, 848, 760, 746, 725, 712 cm^{-1}. MS (FAB, NBA): m/z = 289 $[M + H]^+$.

(1*R*,2*R*)-*trans*-1,2-Bis[2-hydroxyethoxy]cyclohexane [(–)-26]: Diester (–)-**25** (1.37 g, 4.75 mmol) was reduced with $LiAlH_4$ in dry THF in

the usual manner. Diol (–)-**26** was obtained as a yellowish oil. Yield 0.95 g (98%). $[\alpha]_D^{22}$ = –54.5 (*c* = 0.00332, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (m, 2 H), 3.69 (m, 4 H), 3.55 (m, 2 H), 3.26 (s, 2 H, –OH), 3.20 (m, 2 H), 2.04 (m, 2 H), 1.66 (m, 2 H), 1.17 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.96, 71.26, 62.58, 31.11, 24.36 ppm. IR (CH_2Cl_2) $\tilde{\nu}_{max}$ = 3675, 3443, 3054, 2940, 2864, 1725, 1606, 1452, 1366, 1277, 1257, 1210, 1118, 1093, 1057, 1005, 937, 885, 827, 760, 747, 731, 708 cm^{-1}. MS (FAB, NBA): *m*/*z* = 205 $[M + H]^+$.

(1*R*,2*R*)-*trans*-1,2-Bis[5-ethoxycarbonyl-1,4-dioxapentyl]cyclohexane [(–)-27]: Boron trifluoride–diethyl ether (0.2 mL) was added slowly under N_2, with magnetic stirring over a period of 0.5 h, to an ice-cooled solution of (–)-**26** (2.19 g, 10.7 mmol) and ethyl diazoacetate (90% in CH_2Cl_2, 2.61 mL, 25.20 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 2 h and was then neutralised by the addition of $NaHCO_3$ and filtered. The solvent was evaporated under reduced pressure and the product was purified by flash column chromatography on SiO_2 with a mixture of hexane/EtOAc (1:1) as eluent. Yellow oil, yield 1.5 g (37.3%). $[\alpha]_D^{23}$ = –27 (*c* = 0.00212, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.17 (q, ^3J = 7.1 Hz, 4 H), 4.12 (s, 4 H), 3.74 (m, 4 H), 3.66 (m, 4 H), 3.16 (m, 2 H), 1.95 (m, 2 H), 1.61 (m, 2 H), 1.24 (t, ^3J = 7.1 Hz, 6 H), 1.16 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.96, 82.43, 71.69, 69.80, 69.09, 61.12, 30.60, 24.00, 14.60 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3447, 2926, 2858, 2363, 1730, 1654, 1648, 1636, 1570, 1559, 1540, 1534, 1522, 1517, 1507, 1453, 1420, 1384, 1353, 1314, 1273, 1245, 1220, 1168, 1122, 1069, 1046, 933, 896, 850, 842, 815, 781, 688, 608, 578, 520, 464, 414 cm^{-1}. MS (FAB, NBA): *m*/*z* = 377 $[M + H]^+$.

(1*R*,2*R*)-*trans*-1,2-Bis[2-(2-hydroxyethoxy)ethoxy]cyclohexane [(–)-28]: Diester (–)-**27** (1.3 g, 3.45 mmol) was reduced with $LiAlH_4$ in dry THF in the usual manner. Diol (–)-**28** was isolated as a colourless oil. Yield 0.97 g (96%). $[\alpha]_D^{23}$ = –29 (*c* = 0.00286, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.67 (m, 16 H), 3.31 (m, 2 H), 3.31 (s, 2 H, –OH), 3.23 (m, 2 H), 2.03 (m, 2 H), 1.66 (m, 2 H), 1.17 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.70, 73.09, 71.37, 69.39, 62.11, 30.90, 24.31 ppm. IR (CH_2Cl_2) $\tilde{\nu}_{max}$ = 3682, 3584, 3451, 3053, 2938, 2865, 2304, 1737, 1605, 1547, 1452, 1353, 1261, 1099, 1004, 895, 760, 746, 724, 697 cm^{-1}. MS (FAB, NBA): *m*/*z* = 293 $[M + H]^+$.

General Procedure for the Synthesis of the Cyclomalonates: The diol (15 mmol, 1.0 equiv.) was dissolved under argon in dry CH_2Cl_2 (1 L) in a dry 2-L round-bottomed flask fitted with a gas inlet, a dropping funnel (500 mL), and a magnetic stirrer, followed by the addition of pyridine (2.0 equiv.). Subsequently, a solution of malonyl dichloride (2.0 equiv.) in dry CH_2Cl_2 (500 mL) was added dropwise over a period of 8 h. After stirring at room temperature for 2 d, the mixture was concentrated with a rotary evaporator and filtered through a silica gel plug (6×6 cm) with CH_2Cl_2/EtOAc (50:50) as eluent to remove polymeric material and pyridine salts. The solution was concentrated and the crude product was separated by flash column chromatography on silica gel with a mixture of CH_2Cl_2/EtOAc as eluent. The order of elution was monomalonate, bismalonate, trismalonate macrocycles.

Synthesis of Macrocycles 8b and 8c: The synthesis was performed according to the General Procedure, with propanediol (1.14 g, 15 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **8b** and **8c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (70:30) as eluent.

Cyclo[2]propylenemalonate 8b: White solid, yield 356.5 mg (16.5%, based on propanediol). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.18 (t, ^3J = 5.7 Hz, 8 H), 3.34 (s, 4 H), 1.96 (quint, ^3J = 5.7 Hz, 4 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 165.91, 60.80, 42.10, 26.67 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3015, 2972, 2929, 2909, 1754, 1735, 1470, 1429, 1415, 1385, 1362, 1282, 1229, 1154, 1118, 1086, 1060, 1008, 977, 897, 758, 682, 615, 561 cm^{-1}. MS (FAB, NBA): *m*/*z* = 289 $[M + H]^+$. $C_{12}H_{16}O_8$ (288.25): calcd. C 50.00, H 5.59; found C 49.90, H 5.65.

Cyclo[3]propylenemalonate 8c: Colourless, highly viscous oil, yield 241 mg (11.2%, based on propanediol). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.21 (t, ^3J = 6.2 Hz, 12 H), 3.36 (s, 6 H), 1.99 (quint, ^3J = 6.2 Hz, 6 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.22, 61.89, 41.55, 27.51 ppm. IR (film): $\tilde{\nu}_{max}$ = 2968, 2906, 1734, 1460, 1414, 1335, 1152, 1044, 893, 765, 666 cm^{-1}. MS (FAB, NBA): *m*/*z* = 433 $[M + H]^+$.

Synthesis of Macrocycles 9b and 9c: The synthesis was performed according to the General Procedure, with pentanediol (6.89 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **9b** and **9c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (95:5) as eluent.

Cyclo[2]pentylenemalonate 9b: White solid, yield 551 mg (16%, based on pentanediol), m.p. 71 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13 (t, ^3J = 5.6 Hz, 8 H), 3.35 (s, 4 H), 1.65 (m, 8 H), 1.43 (m, 4 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.34, 65.30, 42.00, 27.90, 22.92 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2987, 2958, 2899, 2876, 1742, 1721, 1477, 1418, 1372, 1320, 1277, 1241, 1166, 1134, 1061, 1029, 1004, 976, 938, 912, 866, 804, 769, 739, 696, 598, 577, 519, 456, 420 cm^{-1}. MS (FAB, NBA): *m*/*z* = 345 $[M]^+$. $C_{16}H_{24}O_8$ (344.36): calcd. C 55.81, H 7.02; found C 55.91, H 7.29.

Cyclo[3]pentylenemalonate 9c: Yellowish, highly viscous oil, yield 275 mg (8%, based on pentanediol). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.11 (t, ^3J = 5.4 Hz, 12 H), 3.33 (s, 6 H), 1.60 (m, 12 H), 1.41 (m, 6 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.21, 65.15, 41.93, 27.75, 22.81 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2961, 2920, 2853, 1744, 1477, 1332, 1263, 1217, 1138, 1099, 1022, 975, 910, 892, 852, 802, 720. 676, 616, 584, 470 cm^{-1}. MS (FAB, NBA): *m*/*z* = 516 $[M]^+$.

Synthesis of Macrocycles 11a, 11b and 11c: The synthesis was performed according to the General Procedure, with undecane-1,11-diol (3.76 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **11a**, **11b** and **11c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (90:10) as eluent.

Cyclo[2]undecylenemalonate 11b: White solid, yield 614 mg (12%), m.p. 87 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.14 (t, ^3J = 6.4 Hz, 8 H), 3.35 (s, 4 H), 1,61 (m, 8 H), 1.27 (m, 16 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.54, 65.58, 42.09, 29.52, 29.50, 29.25, 25.90 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2929, 2856, 2687, 2362, 2344, 1737, 1461, 1411, 1385, 1277, 1152, 1034, 892, 803, 723, 691, 581, 502, 409 cm^{-1}. MS (FAB, NBA): *m*/*z* = 513 $[M]^+$.

Synthesis of Macrocycles 13a, 13b and 13c: The synthesis was performed according to the General Procedure, with tridecane-1,13-diol (4.32 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **13a**, **13b** and **13c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (90:10) as eluent.

Cyclo[2]tridecylenemalonate 13b: White solid, yield 796 mg (14%), m.p. 93 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.11 (t, ^3J = 6.4 Hz, 8 H), 3.33 (s, 4 H), 1.61 (m, 8 H), 1.24 (m, 36 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.54, 65.59, 42.07, 29.61, 29.55, 29.27, 28.49, 25.88 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2961, 2920, 2853, 1744, 1477,

1332, 1263, 1217, 1138, 1099, 1022, 975, 910, 892, 852, 802, 676, 616, 584, 470 cm^{-1}. MS (FAB, NBA): *m*/*z* = 569 $[M]^+$.

Synthesis of Macrocycles 14a, 14b and 14c: The synthesis was performed according to the General Procedure, with tetradecane-1,14-diol (4.60 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **14a**, **14b** and **14c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (98:2) as eluent.

Cyclo[1]tetradecylenemalonate 14a: Colourless oil, yield 356 mg (6%). MS (FAB, NBA): *m*/*z* = 298 $[M]^+$.

Cyclo[2]tetradecylenemalonate 14b: Waxy solid, yield 835 mg (14%), m.p. 104 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.12 (t, ^3J = 6.4 Hz, 8 H), 3.33 (s, 4 H), 1.61 (m, 8 H), 1.24 (m, 44 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.54, 65.61, 42.07, 29.70, 29.65, 29.59, 29.28, 28.51, 25.87 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2980, 2931, 2860, 1745, 1479, 1335, 1260, 1220, 1115, 1095, 1020, 971, 900, 860, 832, 802, 655, 610, 585, 466 cm^{-1}. MS (FAB, NBA): *m*/*z* = 596 $[M]^+$. $C_{34}H_{60}O_8$ (596.84): calcd. C 68.42, H 10.13; found C 67.99, H 10.08.

Cyclo[3]tetradecylenemalonate 14c: Waxy solid, yield 418 mg (7%). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.10 (t, *J* = 6.2 Hz, 12 H), 3.31 (s, 6 H), 1.60 (m, 12 H), 1.23 (m, 66 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.50, 65.60, 42.06, 29.68, 29.65, 29.57, 29.27, 28.50, 25.85. MS (FAB, NBA): *m*/*z* = 895 $[M]^+$.

Synthesis of Macrocycles 15a, 15b and 15c: The synthesis was performed according to the General Procedure, with pentadecane-1,15-diol 4.88 g (20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **15a**, **15b** and **15c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (95:5) as eluent.

Cyclo[2]pentadecylenemalonate 15b: Waxy solid, yield 625 mg (10%), m.p. 104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.12 (t, ^3J = 6.6 Hz, 8 H), 3.35 (s, 4 H), 1.62 (m, 8 H), 1.24 (m, 44 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.64, 65.62, 41.75, 29.59, 29.53, 29.47, 29.18, 28.42, 25.77 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2961, 2920, 2853, 1744, 1477, 1332, 1263, 1217, 1138, 1099, 1022, 975, 910, 892, 852, 802, 720. 676, 616, 584, 470 cm^{-1}. MS (FAB, NBA): *m*/*z* = 624 $[M]^+$.

Synthesis of Macrocycles 17a, 17b and 17c: The synthesis was performed by the General Procedure, with eicosane-1,20-diol (6.29 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **17a**, **17b** and **17c** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (98:2) as eluent.

Cyclo[2]eicosylenemalonate 17b: Waxy solid, yield 362 mg (5%), m.p. 125 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.10 (t, ^3J = 6.6 Hz, 8 H), 3.30 (s, 4 H), 1.61 (m, 8 H), 1.26 (m, 64 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.29, 65.40, 41.81, 28.85, 28.80, 28.70, 28.38, 28.06, 27.97, 27.70, 25.64 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2928, 2854, 2361, 2343, 1736, 1467, 1385, 1321, 1270, 1240, 1218, 1183, 1150, 1019, 727, 691, 585, 478 cm^{-1}. MS (FAB, NBA): *m*/*z* = 765 $[M]^+$.

Synthesis of Macrocycles 18b and 18c: A solution of malonyl dichloride (0.96 mL, 10 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise under N_2 over a period of 1 h to a mixture of benzene-1,4-dimethanol (1.38 g, 10 mmol) and pyridine (1.6 mL, 20 mmol) in dry CH_2Cl_2 (50 mL). After stirring at room temperature for 12 h, the mixture was concentrated and chromatographed on SiO_2 with a mixture of EtOAc/hexane (3:1) as eluent. A white solid (500 mg) was isolated as a single fraction. The separation of the cyclo[*n*]benzene-1,4-dimethylenemalonates was achieved by GPC chromatography with THF as eluent.

Cyclo[2]benzene-1,4-dimethylenemalonate (18b): White solid, yield 270 mg (6.5%, based on benzene-1,4-dimethanol), m.p. 122.8 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (s, 8 H), 5.15 (s, 8 H), 3.51 (s, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.34, 135.65, 128.37, 67.10, 42.59 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3453, 2994, 2971, 2947, 1735, 1654, 1648, 1559, 1518, 1463, 1449, 1423, 1376, 1324, 1271, 1238, 1202, 1137, 1032, 1022, 986, 942, 919, 888, 844, 820, 791, 753, 677, 639, 615, 557, 508, 456, 435 cm^{-1}. MALDI-FT-MS (DHB): *m*/*z* = 435 $[M + Na]^+$. $C_{22}H_{20}O_8$ (412.39): calcd. C 64.07, H 4.89; found C 63.73, H 5.13.

Cyclo[3]benzene-1,4-dimethylenemalonate (18c): Yellowish, highly viscous oil, yield 90 mg (1.5%, based on benzene-1,4-dimethanol). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (s, 12 H), 5.11 (s, 12 H), 3.44 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.83, 136.06 128.88, 66.93, 41.57 ppm. MALDI-FT-MS (DHB): *m*/*z* = 641 $[M + Na]^+$.

Synthesis of Macrocycles 19a, 19b and 19c: The synthesis was performed according to the General Procedure, with 3,3′-[1,2-phenylenebis(oxy)]bis(propan-1-ol) (4.53 g, 20 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **19a** and **19b** were isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (80:20) as eluent.

Cyclo[2]-[*O*,*O*′-bis(3-oxypropoxy)phenyl]malonate 19b: White solid, yield 688 mg, (12%), m.p. 67 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (m, 8 H), 4.35 (t, ^3J = 6.1 Hz, 8 H), 4.12 (t, ^3J = 5.9 Hz, 8 H), 3.40 (s, 4 H), 2.14 (m, 8 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.35, 149.97, 122.92, 118.46, 67.27, 62.40, 42.27, 28.58 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2950, 2887, 2361, 1763, 1752, 1728, 1654, 1648, 1451, 1283, 1226, 1157, 1046, 995, 951, 770, 749, 610, 565, 420 cm^{-1}. MS (FAB, NBA): *m*/*z* = 588 $[M]^+$. $C_{30}H_{36}O_{12}$ (588.60): calcd. C 61.22, H 6.16; found C 60.81, H 6.12.

Synthesis of Macrocycles 22a and 22b: The synthesis was performed according to the General Procedure, with triethyleneglycol (2 g, 13.3 mmol) being subjected to the condensation reaction with malonyl dichloride. Compounds **22a** and **22b** were isolated by flash column chromatography on SiO_2 with EtOAc as eluent.

Cyclo[1]triethyleneglycolmalonate 22a: Yellowish, highly viscous oil, yield 1119.2 mg (38.5%, based on triethyleneglycol). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.30 (t, ^3J = 4.3 Hz, 4 H), 3.71 (t, ^3J = 4.3 Hz, 4 H), 3.60 (s, 4 H), 3.39 (s, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.10, 69.35, 68.41, 64.26, 42.37 ppm. IR (film): $\tilde{\nu}_{max}$ = 2955, 2910, 2867, 1733, 1451, 1415, 1387, 1354, 1306, 1214, 1149, 1086, 1048, 946, 924, 848, 666 cm^{-1}. MS (FAB, NBA): *m*/*z* = 219 $[M + H]^+$.

Cyclo[2]triethyleneglycolmalonate 22b: Yellowish, highly viscous oil, yield 367.5 mg (12.6%, based on triethyleneglycol). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.28 (t, ^3J = 4.7 Hz, 8 H), 3.69 (t, ^3J = 4.7 Hz, 8 H), 3.62 (s, 8 H), 3.43 (s, 4 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 166.38, 70.67, 68.84, 64.67, 41.42 ppm. IR (film): $\tilde{\nu}_{max}$ = 2953, 2875, 1734, 1452, 1413, 1370, 1355, 1331, 1273, 1140, 1045, 964, 856, 734, 666 cm^{-1}. MS (FAB, NBA): *m*/*z* = 437 $[M + H]^+$.

Synthesis of Macrocycles (+)-23b and *ent*-23c: The synthesis was performed according to the General Procedure, with (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol [(–)-**23**, 1 g, 6.17 mmol] being subjected to the condensation reaction with malonyl dichloride. Compounds (+)-**23b** and *ent*-**23c** were isolated by flash column chromatography on SiO_2 with mixtures of CH_2Cl_2/EtOAc (80:20 and 70:30, respectively).

Cyclo[2]-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethyl]malonate (+)-23b: White solid, yield 485 mg (17%, based on the diol), m.p. 157.4 °C. $[\alpha]_D^{22}$ = +3.4 (*c* = 0.00537, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.27 (m, 8 H), 4.04 (m, 4 H), 3.46 (s, 4 H), 1.40 (s, 12 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.50, 108.52, 73.63, 63.09, 39.38, 24.74 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3439, 2991, 2941, 2359, 1746, 1727, 1701, 1696, 1684, 1653, 1647, 1636, 1559, 1521, 1507, 1473, 1458, 1420, 1378, 1329, 1263, 1221, 1166, 1152, 1127, 1089, 1059, 1018, 1005, 913, 893, 843, 668, 626, 587, 536, 512, 491, 458, 419 cm^{-1}. MS (FAB, NBA): *m*/*z* = 461 $[M + H]^+$. $C_{20}H_{28}O_{12}$ (460.43): calcd. C 52.17, H 6.13; found C 52.09, H 5.97.

Cyclo[3]-[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethyl]malonate *ent*-23c: Colourless, highly viscous oil, yield: 185 mg (4.3%, based on the diol). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.26 (m, 12 H), 4.02 (m, 6 H), 3.46 (s, 6 H), 1.38 (s, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.77, 108.32, 73.64, 62.93, 38.89, 24.72. MS (FAB, NBA): *m*/*z* = 691 $[M + H]^+$.

Synthesis of Macrocycles (–)-26a and *ent*-26b: Diol (–)-**26** (0.90 g, 4.4 mmol) was treated with malonyl dichloride according to the General Procedure, with (–)-**26a** and *ent*-**26b** being isolated by flash column chromatography on SiO_2 with a mixture of CH_2Cl_2/EtOAc (70:30 and 60:40, respectively).

Cyclo[1]-[(1*R*,2*R*)-*trans*-1,2-bis(2-hydroxyethoxy)cyclohexyl]-malonate (–)-26a: White solid, yield 340 mg (28.4%, based on the diol), m.p. 43 °C. $[\alpha]_D^{22}$ = –2.5 (*c* = 0.00497, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.41 (ddd, ^2J = 11.9 Hz, ^3J = 3.3 Hz, ^3J = 1.8 Hz, 2 H), 4.06 (ddd, ^2J = 11.9 Hz, ^3J = 9.3 Hz, ^3J = 2.4 Hz, 2 H), 3.66 (m, 4 H), 3.31 (s, 2 H), 3.02 (m, 2 H), 1.93 (m, 2 H), 1.60 (m, 2 H), 1.09 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.49, 82.30, 68.24, 64.87, 42.79, 30.98, 24.50 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3456, 2838, 2867, 1737, 1653, 1636, 1559, 1452, 1270, 1134, 1042, 952, 891, 850, 685, 584, 473 cm^{-1}. MS (FAB, NBA): *m*/*z* = 273 $[M + H]^+$. $C_{13}H_{20}O_6$ (272.29): calcd. C 57.34, H 7.40; found C 57.03, H 7.68.

Cyclo[2]-[(1*R*,2*R*)-*trans*-1,2-bis(2-hydroxyethoxy)cyclohexyl]-malonate *ent*-26b: Yellowish, highly viscous oil, yield 50 mg (2%, based on the diol). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.23 (m, 8 H), 3.76 (m, 8 H), 3.40 (s, 4 H), 3.12 (m, 4 H), 1.95 (m, 4 H), 1.63 (m, 4 H), 1.15 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.94, 83.09, 67.98, 65.63, 41.69, 31.07, 24.26 ppm. MS (FAB, NBA): *m*/*z* = 545 $[M + H]^+$.

Synthesis of Macrocycles (–)-28a and *ent*-28b: Diol (–)-**28** (0.85 g, 2.91 mmol) was treated with malonyl dichloride according to the General Procedure, with (–)-**28a** and *ent*-**28b** being isolated by flash column chromatography on SiO_2 with EtOAc as eluent.

Cyclo[1]-[(1*R*,2*R*)-*trans*-1,2-bis[2-(2-hydroxyethoxy)ethoxy]cyclohexyl]malonate (–)-28a: Yellowish, highly viscous oil, yield 350 mg (33.4%, based on the diol). $[\alpha]_D^{24}$ = –14.7 (*c* = 0.00335, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.24 (m, 4 H), 3.85–3.53 (m, 12 H), 3.37 (s, 2 H), 3.11 (m, 2 H), 1.94 (m, 2 H), 1.60 (m, 2 H), 1.13 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.61, 83.23, 71.74, 70.22, 69.16, 65.78, 42.39, 31.38, 24.53 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3442, 2937, 2865, 2359, 1844, 1830, 1734, 1701, 1696, 1684, 1676, 1670, 1663, 1653, 1647, 1636, 1628, 1617, 1576, 1570, 1559, 1540, 1534, 1522, 1517, 1507, 1499, 1490, 1473, 1458, 1419, 1384, 1262, 1110, 1038, 801, 668, 458, 419 cm^{-1}. MS (FAB, NBA): *m*/*z* = 361 $[M + H]^+$. $C_{17}H_{28}O_8$ (360.40): calcd. C 56.66, H 7.83; found C 56.28, H 7.65.

Cyclo[2]-[(1*R*,2*R*)-*trans*-1,2-bis[2-(2-hydroxyethoxy)ethoxy]cyclohexyl]malonate *ent*-28b: Yellowish, highly viscous oil, yield 40 mg (1.9%, based on the diol). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.27 (m, 8 H), 3.76–3.57 (m, 24 H), 3.42 (s, 4 H), 3.16 (m, 4 H), 1.96 (m, 4 H), 1.63 (m, 4 H), 1.17 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.93, 82.76, 71.43, 69.78, 69.13, 65.13, 41.66, 30.97, 24.23 ppm. MS (FAB, NBA): *m*/*z* = 721 $[M + H]^+$.

X-ray Analysis: The structures were solved by direct methods (SIR97)[29] and refined by full-matrix least-squares analysis (SHELXL-97),[30] with use of an isotropic extinction correction. All heavy atoms were refined anisotropically, hydrogen atoms isotropically, with hydrogen positions being based on stereochemical considerations. CCDC-288520 (**9b**), -290106 (**18b**), -288517 (**23b**), -288518 (**24b**) and CCDC-288519 (**29**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

X-ray Crystal Structure of 9b: Crystal data at 173(2) K for $C_{16}H_{24}O_8$ (344.35). Monoclinic, space group $P2_1/c$, D_c = 1.323 g cm^{-3}, *Z* = 2, *a* = 4.68710(10), *b* = 22.9169(11), *c* = 8.24710(10) Å, β = 102.567(2)°, *V* = 864.63(5) $Å^3$. Bruker–Nonius Kappa-CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.106 mm^{-1}. A colourless crystal of **9b** (linear dimensions ca. 0.30 × 0.30 × 0.15 mm) was obtained by slow diffusion of pentane into a CH_2Cl_2 solution. Number of measured and unique reflections are 2699 and 1480, respectively (R_{int} = 0.0443). Final *R*(*F*) = 0.0394, *wR*(F^2) = 0.0820 for 109 parameters and 987 reflections with $I > 2\sigma(I)$ and 2.68° < θ < 25.02° (corresponding *R* values based on all 1480 reflections are 0.0762 and 0.0930, respectively).

X-ray Crystal Structure of 18b: Crystal data at 193(2) K for $C_{22}H_{20}O_8$ (412.38). Monoclinic, space group $P2_1/c$ (no. 14), D_c = 1.457 g cm^{-3}, *Z* = 2, *a* = 11.7989(4), *b* = 5.8463(2), *c* = 14.1202(5) Å, β = 105.132(2)°, *V* = 940.24(6) $Å^3$. Bruker–Nonius Kappa-CCD diffractometer, Mo-K_α radiation, λ = 0.7107 Å, μ = 0.112 mm^{-1}. A colourless crystal of **18b** (linear dimensions 0.25 × 0.23 × 0.15 mm) was obtained by slow concentration of a $CHCl_3$ solution. Numbers of measured and unique reflections are 3720 and 2151, respectively (R_{int} = 0.033). Final *R*(*F*) = 0.041, *wR*(F^2) = 0.105 for 147 parameters and 1680 reflections with $I > 2\sigma(I)$ and 1.79° < θ < 27.49° (corresponding *R* values based on all 2151 reflections are 0.056 and 0.119, respectively).

X-ray Crystal Structure of (+)-23b: Crystal data at 173(2) K for $C_{20}H_{28}O_{12}$ (460.42). Orthorhombic, space group $P2_12_12_1$, D_c = 1.408 g cm^{-3}, *Z* = 4, *a* = 8.7037(3), *b* = 15.5372(2), *c* = 16.0611(4) Å, *V* = 2171.96(10) $Å^3$. Bruker–Nonius Kappa-CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.117 mm^{-1}. A colourless crystal of (+)-**23b** (linear dimensions 0.25 × 0.25 × 0.25 mm) was obtained by slow diffusion of pentane into a CH_2Cl_2 solution. Numbers of measured and unique reflections are 4953 and 4953, respectively (R_{int} = 0.000). Final *R*(*F*) = 0.0349, *wR*(F^2) = 0.0820 for 289 parameters and 4323 reflections with $I > 2\sigma(I)$ and 2.54° < θ < 27.48° (corresponding *R* values based on all 4953 reflections are 0.0437 and 0.0864, respectively).

X-ray Crystal Structure of (+)-24b: Crystal data at 173(2) K for $C_{28}H_{44}O_{12}$ (572.63). Triclinic, space group *P*1, D_c = 1.309 g cm^{-3}, *Z* = 1, *a* = 7.8292(16), *b* = 8.1741(16), *c* = 11.902(2) Å, *a* = 87.96(3)°, β = 75.89(3)°, γ = 79.54(3)°, *V* = 726.4(3) $Å^3$. Bruker–Nonius Kappa-CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.102 mm^{-1}. A colourless crystal of (+)-**24b** (linear dimensions 0.25 × 0.20 × 0.10 mm) was obtained by slow diffusion of pentane into a CH_2Cl_2 solution. Numbers of measured and unique reflections are 6507 and 6507, respectively (R_{int} = 0.000). Final *R*(*F*) = 0.0415, *wR*(F^2) = 0.0993 for 361 parameters and 5593 reflections with $I > 2\sigma(I)$ and 2.73° < θ < 27.47° (corresponding

R values based on all 6507 reflections are 0.0522 and 0.1060, respectively).

X-ray Crystal Structure of 29: Crystal data at 173(2) K for $C_{11}H_{16}O_8$ (276.24). Monoclinic, space group $P2_1/n$, D_c = 1.454 g cm^{-3}, Z = 4, a = 10.7635(3), b = 4.6693(1), c = 25.6082(6) Å, β = 101.426(2)°, V = 1261.51(5) Å^3. Bruker–Nonius Kappa-CCD diffractometer, Mo-K_α radiation, λ = 0.71073 Å, μ = 0.126 mm^{-1}. A colourless crystal of **29** (linear dimensions ca. 0.35 × 0.20 × 0.20 mm) was obtained by slow concentration of a $CHCl_3$ solution. Number of measured and unique reflections are 4058 and 2211, respectively (R_{int} = 0.0147). Final $R(F)$ = 0.0323, $wR(F^2)$ = 0.0848 for 180 parameters and 1885 reflections with $I > 2\sigma(I)$ and 1.62° < θ < 25.01° (corresponding *R* values based on all 2211 reflections are 0.0394 and 0.0904, respectively).

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