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New Supramolecular Host Systems. 5. Diacetals and Macro-*m*-Cyclophanes of Aldaric Esters: Synthesis, Stereochemistry and Conformational Analysis[1]

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Abstract: A general scheme of carbohydrate diacetal systems (Scheme 2) of the 1,3,5,7-tetraoxadecalin (TOD) type is presented. A sequence of reactions starting with dimethyl D-glucarate (**4**) (Scheme 3) lead to 2,6-diaryl-4,8-di (methoxycarbonyl)-cis-TOD podands (**5** and **6**) and to the novel dicarbamate macrocycles (**8a,b**), which constitute the first m-cyclophanes in the carbohydrate (*D*-gluco) series. The *D*-gluco - *L*-ido interconversion by equilibration of the methoxycarbonyl groups in **5**, **6** and **9**, was examined in the light of a conformational analysis of the methoxycarbonyl group and its *anomeric effect* in heterocyclic systems, using molecular mechanics techniques (MM3-GE, i.e., MM3 reparametrized for treatment of the *gauche effect*) and comparing with experimental data.

INTRODUCTION

We have recently put forward a new type of host systems based on 1,3,5,7-tetraoxadecalin (1,3,5,7-TOD) "core" units[1,2]. The 1,3,5,7-TOD system[3] is basically a diacetal existing in two chair-chair forms, of *trans* (**1**) or *cis* (**2**) configuration. While there is only one, conformationally fixed, *trans* form, the *cis*-1,3,5,7-TOD system can exist in two possible diastereoisomeric chair-chair forms, O_{inside} (**2**) and $O_{outside}$ (**3**)[2-6]. The latter two may interconvert by conformational ring inversion (**2** $\rightleftarrows$ **3**) or by chemical isomerization (*vide infra*). The formation of these, *trans* or *cis* diacetals involves usually the condensation of a 1,2,3,4-tetraol with an aldehyde under acid catalysis, as in the prototypical case of the unsubstituted parent compounds (Scheme 1)[4,5], derived from the reaction of formaldehyde with erythritol or threitol, respectively.

In our studies, we aim at introducing reactive functionalized substituents in the 2,6 positions of *cis*-1,3,5,7-TOD in its O_{inside} (**2**) form[1,2], for obtaining novel podands and corresponding macrocycles. The underlying idea is that the concave geometry of the *cis*-TOD system with its built-in cavity containing *gauche* O-C-C-O moieties and high electron lone pair concentration should constitute an excellent "core" of new host systems with ion and neutral molecules inclusion ability. In this framework, the *cis*-TOD system was first analysed in structural and computational studies[2], and the first, threitol based macrocyles in this series were then prepared[1,2c].

This type of diacetal systems is long known in carbohydrate chemistry as e.g., 2,4:3,5-di-O-methylene or -benzylidene derivatives[3] and a number of reviews on or including the carbohydrate diacetal derivatives have been published in the past[7]. The review of Mills[7b], Fraser-Stoddart[7c] and the articles of the latter's[4] and the Schroll[6] groups deserve special mention for the insight they provide.

In carbohydrates as well, the 1,3,5,7-TOD derivatives exist in the *trans* or *cis* configurations,

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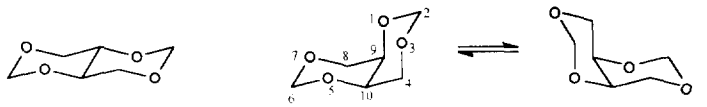
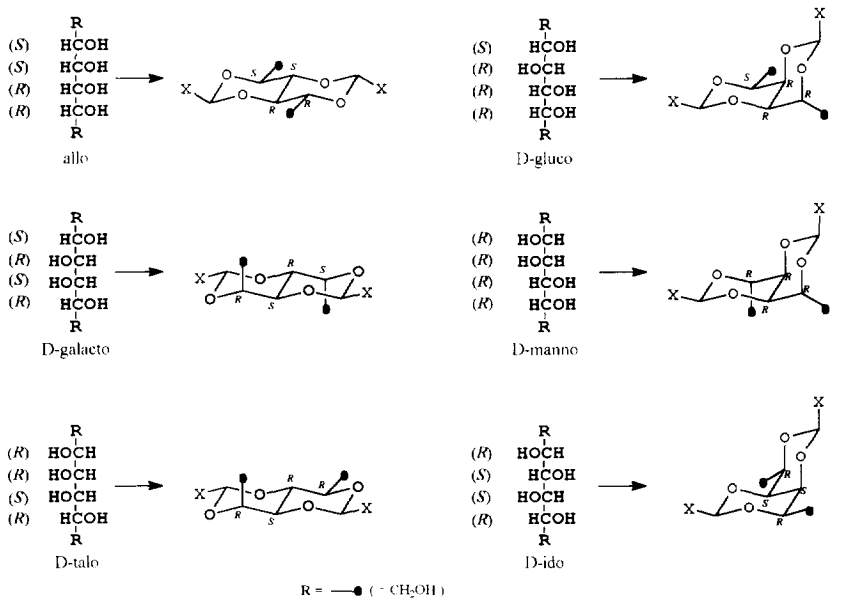


Scheme 1. The parent 1,3,5,7-tetraoxadecalin (TOD) diastereoisomers.



Scheme 2. 2,6-X-substituted-1,3,5,7-tetraoxadecalins (2,4:3,5-di-O-(X-methylene) diacetals), derived from hexose systems bearing identical termini, *e. g.*, R=COOMe in dimethyl glucarate (**4**).

depending on whether they provene from *erythro*- or *threo*-tetrahydroxy moieties of the carbohydrate backbone, respectively. This can be seen in Scheme 2, where, to illustrate the paradigm, we present a systematic list of 2,4:3,5-di-O-(X-methylene) diacetals of the hexose derived tetraols with two similar terminal substituents, *e.g.*, the alditols - R=CH_2OH or the aldaric acids - R=COOH, etc. (only the generally preferred O_{inside} isomers are shown, with the understanding that an $O_{outside}$ isomer could be formed if rendered thermodynamically more stable by suitable substitution[6a]). In addition to the mentioned stereospecificity criterion (the 3,4-*erythro* species on the left give *trans*-TOD, while the 3,4-*threo* on the right give *cis*-TOD products) one should pay attention to the relationship between the orientation of the terminal substituents in the starting tetraols and their orientation in the TOD products. Thus (Scheme 2), if the two central carbons are *R,S* (or *S,R*), the acetalization product will be a *trans*-TOD, preserving the central S_2 (*erythro*, *i*) symmetry in the TOD frame; analogously, an *R,R* (or *S,S*) arrangement in the center of the (*threo*) tetraol, is bound to yield a *cis*-TOD, preserving the C_2 symmetry in the TOD frame. Furthermore (Scheme 2), if an R group such as CH_2OH at the terminus of a tetraol backbone is attached to an *R,R* (or *S,S*) sequence, it will wind up equatorial in a *trans*-TOD and axial in a *cis*-TOD system and *vice versa* for an *R,S* (or *S,R*) arrangement; naturally, all above configurational assignments are to be reversed if the terminal R's (such as R = COOMe) have second and not last CIP (fiducial) priority (as for R = CH_2OH).

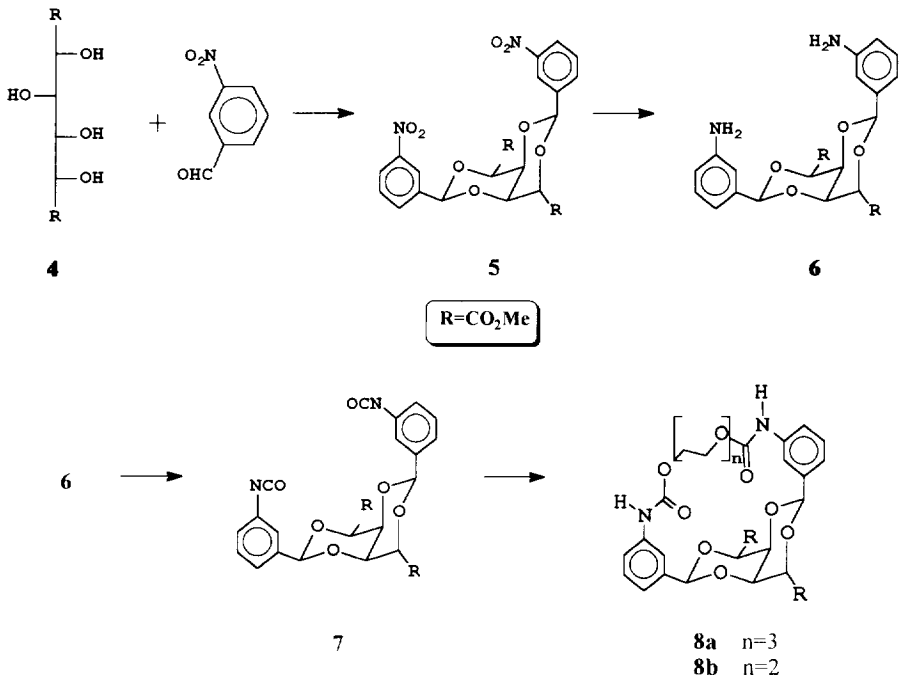
Various other aspects of these (TOD) diacetals have been discussed in the past, including stereochemical[6], structural (crystallographic[8]) and some applied[9] ones. 2,4:3,5-Diacetals of several alditol derivatives have been prepared and studied[10-18], *e.g.*, in the gluco[10-12,18,19], galacto[13], manno[8c,10,13,17], allo[14] and ido[15,16] series, using, *i.al.*, early NMR[10,15], MS[11] and kinetic[16] techniques. Some interesting exploratory studies of the condensation or co-condensation of suitably substituted TOD compounds in polyesters or polyamides are also worthy of mention[20], as is a recent paper on the aggregation ability of a 2,4:3,5-O-dimethylene-gluconamide-Cu^{2+} complex[20d].

RESULTS AND DISCUSSION

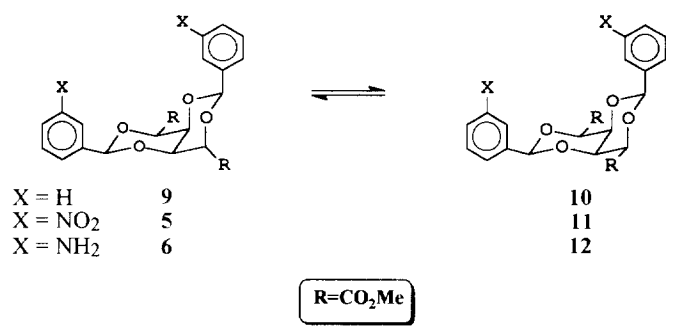
We present now the first results of implementing our above described approach to such functionalized carbohydrate *cis*-1,3,5,7-TOD compounds and to assess their propensity for macrocyclization. Besides the ubiquity of the starting materials (*e.g.*, D-glucose is the most abundant available organic compound), the additional reactive substituents in the 4 and 8 positions were thought to be a constitutional asset for these systems, for attachment of desired (*e.g.*, lipophilic) groups to the molecule or for intersystem linking, to form *poly-supramolecules*.

Straightforward as it may seem, the acetalization reaction is not so simple, depending on the intimate structural features of the reactants and products, the reaction conditions, the establishment of kinetic or thermodynamic control, etc.. In earlier procedures, a variety of acid catalysts have been used (often in non-catalytic quantities), such as zinc chloride[10-16], concentrated hydrochloric or sulfuric acid[4], calcium chloride (complexed with the tetraol)[21a] and p-toluenesulfonic acid[5a].

Following a recently developed reaction sequence[2c], we sought reactions between nitrobenzaldehydes and suitable, terminally protected *D-gluco* derivatives. After realizing that 1,6-di-O-benzoylglucitol exhibited great sensitivity and low yields in a variety of such acid catalysed condensations, we settled on the readily obtainable[21c] dimethyl-D-glucarate (**4**), as follows (Scheme 3). The condensation



Scheme 3. The sequence of reactions leading from dimethyl glucarate (**4**) to the *m*-cyclophanes (**8**).



Scheme 4. Base catalysed epimerization of the 4-methoxycarbonyl group in various 2,6-diaryl-TOD systems: a *D-gluco* - *L-ido* type isomerization

of **4** with *m*-nitrobenzaldehydes was carried out with zinc chloride catalysis or, even better, using concentrated sulfuric acid[4] as both condensation medium and catalyst. The drastic conditions imposed careful workup, to isolate (2R,4S,6R,8R,9S;9,10-*M*)-2,6-di(*m*-nitrophenyl)-4,8-di(methoxycarbonyl)-*cis*-1,3,5,7-tetraoxadecalin (**5**) as the desired and only product.

The reduction of the nitro groups in **5** could be carried out catalytically (on Pd/C) using either hydrogen or, not less conveniently, ammonium formate (in catalytic H-transfer)[22a], to the corresponding di(*m*-aminophenyl) derivative (**6**). A number of acylation attempts, as part of cyclization procedures, were unsuccessful. To understand this, one should take in consideration competitive trends, brought about by the fact that, f. ex. C_2-H or C_8-H acidities are higher or comparable, respectively, to those of aromatic amines (*vide infra*)[23]. Eventually, on treatment of **6** with phosgene in toluene[22b], the diisocyanate (**7**) was obtained and reacted without purification with tri- or diethyleneglycol, to give the respective dicarbamate *m*-cyclophanes (**8a,b**). These are, to the best of our knowledge, the first macrocyclic (*m*-cyclophane) compounds in the carbohydrate series. The complexation of these macrocycles and their podand precursors, with ammonium and transition metal ions, holds our interest presently, along with molecular and chiral recognition aspects of these and further TOD carbohydrate macrocycles. In this quest we seek support from computational methodologies, as illustrated in Figure 1, which presents the symmetrical conformational minimum of **8a**, as modeled using Insight II.

Of much interest in this study was the investigation of the possibility of stereoisomerization in the 4 and/or 8 positions and this, of course, justifies the choice of ester substituents in these positions. In the present case, this means entering the L-ido *via* the D-gluco series, by epimerising the axial methoxycarbonyl group in the 4 position of **5** or **6** to an equatorial one. Such a (barium hydroxide catalysed) isomerization had been performed earlier with the unsubstituted O-dimethylene derivative[21b], in poor yield and without paying attention to a possible equilibrium. We started the probe (Scheme 4) with the known[21a] diphenyl derivative (**9**) and, on treatment with NaOMe in absolute methanol, got a mixture of starting material (**9**) and only ca. 57% (by NMR) of the diequatorial (L-ido) isomer (**10**). On similar treatment of the di(m-nitrophenyl) derivative **5**, the isomerization to **11** was accompanied by extensive deterioration before equilibrium was reached. This could be understood, considering the relative high acidity of the nitrobenzylic (C_2) positions[23], which make the latter prone to electrophilic attack. The di(*m*-aminophenyl) compound (**6**), however, isomerized in the same conditions to a clean equilibrium mixture, containing again only 60% of the L-ido product, (2R,4R,6R,8R,9S;9,10-P)-2,6-di(*m*-aminophenyl)-4,8-di(methoxycarbonyl)-*cis*-1,3,5,7-tetraoxadecalin (**12**). An analogous partial isomerization was recently observed[20c] during the electrochemical oxidation of D-gluconic to a (8:1) mixture of 2,4:3,5-di-O-methylene-D-glucaric and -L-idaric acids. In this case, however, the product mixture had a non-equilibrium composition, presumably biased by the electrode process, thus precluding generalization. We felt compelled to understand the origin and extent of this behaviour and we proceeded to probe the problem computationally, using molecular mechanics.

We had previously parametrized MM2 for the *anomeric effect* (MM2-AE) in X-C-Y systems (X,Y = O, N, Hal)[24] and MM3[25] has been similarly parametrized for the O-C-O case[25b]. We then recently[2b] reparametrized MM3(92) for the *gauche effect* (hence, MM3-GE) in O-C-C-O containing systems. Therefore, the calculations in this study were performed using the MM3 force field[25], which takes care of the O-C-O moieties in 1,3-dioxanes or the MM3-GE version[26] for the TOD systems, which contain both O-C-O and O-C-C-O units. The conformational space covering all possible combinations of dihedral angles

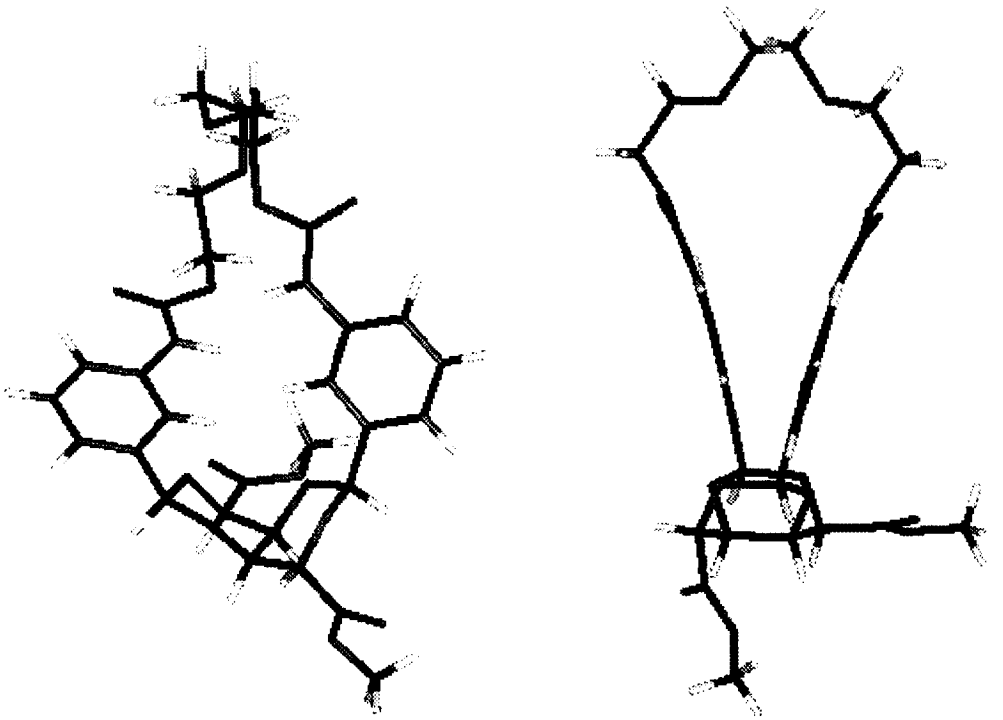


Figure 1. Two wiews of the m-cyclophane **8a** in its lowest *pseudo*symmetrical conformation, as modeled using BIOSYM/Molecular Simulations' Insight II (preoptimized with CVFF in the BUILDER module and then optimized with DISCOVER).

X			X	Y		
O	**13**	**13'**	CH_2	CH_2	**15**	**15'**
CH_2	**14**	**14'**	CH_2	O	**16**	**16'**
			O	O	**17**	**17'**

R=CO_2Me

Scheme 5. Isomerization of disubstituted decalin (**14**, X=CH_2) and tetraoxadecalin (**13**, X=O) compounds *vs.* that of corresponding cyclohexane (**15**, X,Y=CH_2), 2-tetrahydropyran (**16**, X=CH_2, Y=O) and 1,3-dioxan-4 (**17**, X,Y=O) monosubstituted derivatives.

around the C4-$COOCH_3$, C8-$COOCH_3$, as well as around the C2-Phenyl and C6-Phenyl bonds, was explored in each case, using the dihedral angle driver of MM3, in systematic conformational search procedures. The Newton-Raphson method was employed for energy minimization in driver calculations and that of full matrix minimization for calculating the molecular minimum energies and geometries, making sure that all vibrational frequencies were real in the calculated frequency list. The global minima were thus obtained.

The energy differences between the D-gluco and L-ido forms of 2,6-di(*m*-aminophenyl)-4,8-di(methoxycarbonyl)-*cis*-1,3,5,7-tetraoxadecalin (**6/12**) are shown in Table 1, along with those in the simple TOD (**13/13'**) and decalin (**14/14'**) diastereomeric pairs (Scheme 5); the dihedral angles, showing the orientation of the methoxycarbonyl groups, are also given. For comparison, we also included (Table 1 and Scheme 5) the methoxycarbonyl substituted diastereoconformeric pairs of cyclohexane (**15/15'**), 2-tetrahydropyran (**16/16'**) and 4-1,3-dioxane (**17/17'**).

First, the similar equilibrium compositions of **6**$\vec{\leftarrow}$**12** and **9**$\vec{\leftarrow}$**10** and then the similar steric energy differences of **6**$\vec{\leftarrow}$**12** and **13**$\vec{\leftarrow}$**13'** pairs indicate that the 2,6 substitution has only marginal influence on the relative stabilities and this is supported by the small experimental equilibrium constant found for **9**$\vec{\leftarrow}$**10**. The gap between the experimental energy differences and the calculated values for, say, **6**$\vec{\leftarrow}$**12**, amounts to ca. 0.5 kcal/mol (0.3 - -0.2) and can easily be taken as a medium effect in stabilizing the diequatorial form.

The fact remains, though, that the calculation shows a (albeit, small) preference for the methoxycarbonyl 4-axially substituted isomers **6** and **13** , while in the experimental equilibrium their contribution is around 40%. In contrast, the carbocyclic, decalin analogous pair (**14**$\vec{\leftarrow}$**14'**) was

Table 1. Conformational energy differences (in kcal/mol) in the ax/eq pairs: 4,8-di(methoxycarbonyl)-2,6-di(3-aminophenyl)-*cis*-1,3,5,7-tetraoxadecalin (**6/12**), 4,8-di(methoxycarbonyl)-*cis*-1,3,5,7-tetraoxadecalin (**13/13'**), 4,8-di(methoxycarbonyl)-*cis*-decalin (**14/14'**), methoxycarbonylcyclohexane (**15/15'**), 2-methoxycarbonyltetrahydropyran (**16/16'**), and 4-methoxycarbonyl-1,3-dioxane (**17/17'**).

	6$\vec{\leftarrow}$**12** ax/eq$\vec{\leftarrow}$eq/eq	**13**$\vec{\leftarrow}$**13'** ax/eq$\vec{\leftarrow}$eq/eq	**14**$\vec{\leftarrow}$**14'** ax/eq$\vec{\leftarrow}$eq/eq	**15**$\vec{\leftarrow}$**15'** ax$\vec{\leftarrow}$eq	**16**$\vec{\leftarrow}$**16'** ax$\vec{\leftarrow}$eq	**17**$\vec{\leftarrow}$**17'** ax$\vec{\leftarrow}$eq
Experimental						
ΔG°(300 K)	-0.2			-1.2 -1.1	-0.3,-1.6,-1.4	
ΔH°				-1.2 -1.7		
refs.	this work			27a, 28	28, 29, 30	
Calculated (MM3-GE).						
ΔE_{st},	0.3	0.35	-1.1	-1.4	-1.3	-0.7
ΔG°	0.0	0.5	-0.8	-1.65	-1.8	-1.2
ΔH°	0.15	0.2	-1.2	-1.35	-1.45	-0.9
μ, (D).	4.5:4.5	4.9:4.8	1.9:2.4	1.6:1.6	2.6:2.6	2.9:3.4
Torsional angles (deg)						
O3-C4-CO-OMe	-131.7:135.4	-131.8:136.5	-175.3:-178.9	171.1:-179.6	134.4:123.0	-131.1:-123.1
O7-C8-CO-OMe	135.5:135.7	136.6:136.5	179.0:-178.9			
refs.	---------- this work ----------					

calculated to behave in accordance with the known[27b] methoxycarbonylcyclohexane (**15**⇄**15'**) equilibrium value of about 85:15 in favor of the equatorial forms. To complete the picture we calculated also the mono- and diheterocycles 2-methoxycarbonyltetrahydropyran (**16**⇄**16'**) and 4-methoxycarbonyl-1,3-dioxane (**17**⇄**17'**) pairs and looked for available experimental data to compare with (Table 1). Only for the former (**16**⇄**16'**) could axial ⇄ equatorial equilibrium data be found: Anderson et al.[29] reported ΔG°_{298} -1.6 kcal/mol (in methanol), Eliel et al.[30] gave a value of ΔG°_{180} -1.4 kcal/mol (in CH_2Cl_2), whereas in a more recent paper, Booth et al.[28] claim a free energy difference of -0.3 (at 300 K) but an enthalpy difference of -1.7 kcal/mol (in ether/toluene 3:1). If true, this high entropy contribution may be due in large part to a solvent effect, since it is not at all borne out in our empirical force field calculation of both **16**⇄**16'** and **17**⇄**17'** (Table 1). Indeed, while our calculated enthalpy difference for 2-methoxycarbonyl- tetrahydropyran (**16**⇄**16'**) agrees quite well with Booth's et al.[28] experimental value, this is not so with the free energy difference, where our calculated results match the higher values. This will need further clarification at a later date. It stands to reason, though, that the polar methoxycarbonyl group has an inherently low rotational barrier (with a periodicity of 6) and is conformationally strongly influenced by solvation effects, but one still has to account for the role of the *anomeric effect* in this behaviour.

The interpretation of the conformational behaviour of the carboxyester group in heterocycles has an interesting history. After having been labeled as a "reverse anomeric effect"[29], it was reappraised as a "weak anomeric effect"[30], but in a recent paper by Kleinpeter and coworkers[31], the small equatorial preference of the ethoxycarbonyl group in the 2-position of anancomeric 1,3-dioxane systems ΔG°_{330} 0.9 kcal/mol (in CCl_4), was said to reflect a relatively "strong anomeric effect".

The appreciable conformational entropy difference seems to be characteristic to the methoxycarbonyl group. This can be also deduced from the fact that analogous methyl substituted systems exhibit almost no entropy differences. This holds for the axial⇄equatorial equilibrium of e.g., methylcyclohexane (**15**⇄**15'** R=Me) ($\Delta G^{\circ}/\Delta H^{\circ}$ -1.74/-1.75)[27a,32] as well as for 4-methyl-1,3-dioxane (**17**⇄**17'** R=Me) ($\Delta G^{\circ}/\Delta H^{\circ}$-2.9/-2.8)[33,34] and also for the corresponding values of 4-methyl-*cis*-1,3,5,7-tetraoxadecalin (**13**⇄**13'** R_8=H, R_4=Me), which we computed using MM3-GE, *viz.*, ΔG°=-2.0 and ΔH°=-2.2 kcal/mol. The main purpose for calculating the latter was, in fact, to probe the conformational effect of the 4-methoxycarbonyl group in the TOD system, using Kleinpeter's approach[31], namely, by calculating the correlation factor $\alpha = \Delta G^{\circ}_{Me}(TOD)/\Delta G^{\circ}_{Me}(cyclohexane)$ = -2.0/-1.75 = 1.15 and using it in $\Delta\Delta G^{\circ} = \Delta G^{\circ}_{COOMe}(TOD) - \alpha_x \Delta G^{\circ}_{COOMe}(cyclohexane)$ = -0.2 - [1.15x(-1.3)] = 1.3. This is close to, and even exceeds the number (0.9) defined by Kleinpeter et al.[31] as the value of the anomeric effect of COOEt in β position to an oxygen atom in a six-membered ring.

While in all appearances phenomenologically well based, Kleinpeter's interpretation is neither compelling nor ultimate. The argument we would like to put forward now is based on the fact that the MM3 force field emulates this behaviour and even indicates a slight preference of the methoxycarbonyl group for the axial conformation in **12** and **13'**, even though MM3 has not been explicitly parametrized for exhibiting an anomeric effect[25d]. The compelling conclusion is that the observed behaviour is due to a combination of steric and electrostatic effects, as accounted for by MM3. To assess the role of polar factors in this picture, we extracted the values of the methoxycarbonyl geometry and of the dipole moments from the MM3 calculations (Table 1). It was somewhat surprising to realize that the dipole moments are very similar in each diastereomeric pair, and thus play a relatively minor role in

directing the equilibrium, even in more polar solvents. This entire issue is well worth pursuing and forms the subject of a separate study, to be reported in due course.

In conclusion, we have formulated a general scheme of hexose derived 2,4:3,5-diacetal systems of the 1,3,5,7-tetraoxadecalin (TOD) type, we applied it to D-dimethyl glucarate, for obtaining corresponding 2,6-diaryl-4,8-di(methoxycarbonyl)-**cis**-TOD podands, leading to the novel dicarbamate m-cyclophanes (**8a,b**), which constitute a first model system for bridging the *cis*-TOD cavity in the carbohydrate (D-gluco) series, aimed at inclusion and recognition behaviour. The D-gluco - L-ido interconversion *via* axial $\rightleftarrows$ equatorial equilibration of the methoxycarbonyl groups in **5**, **6** and **9**, was examined in the light of a conformational analysis of the methoxycarbonyl group in carbo- and heterocyclic systems, suggesting that its behaviour is rooted in steric and electrostatic interactions rather than being a manifestation of an anomeric effect. This issue is bound to be of considerable significance and use in the chemistry of aldaric and aldonic acid derivatives as well as in acetal chemistry.

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EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were measured on a Perkin-Elmer FT-IR spectrophotometer and UV spectra on a Cary 219 spectrophotometer. NMR spectra were taken on Bruker AC-200 Cryospec and AM-360-WB spectrometers: chemical shifts are given in ppm downfield from TMS and coupling constants in Hz; peak assignments (indexed H or C, primed in aromatic rings) are based on extensive decoupling and NOE experiments. Mass spectra were taken on DuPont-21-491-B and VG Autospec mass spectrometers. HPLC work was done on a Merck instrument using Merck 7734 prepacked columns. All products were carefully purified by chromatographic methods. Purified solvents were used: PE = petrol ether 60-80; EtAc = ethyl acetate. Column chromatography: silica gel (Merck 63-200). Flash chromatography: silica gel (Merck 40-63). Thin layer chromatography (TLC): foil plates, silica gel 60-F254 (Merck, layer thickness 0.2 mm); detection by quenching of fluorescence or by immersion into a solution of 20 g of $(NH_4)_6Mo_7O_{24}.4H_2O$ and 0.4 g of $(NH_4)_4Ce(SO_4)_4$ in 400 ml of 10% H_2SO_4 and subsequent treatment at 120 °C for 10 min. Polarimetry was performed using a Perkin-Elmer 241 instrument at 300 K. All products were fully purified and characterized by spectroscopic methods; elemental analysis of selected compounds in the series and on the final cyclophane products were carried out at the Analytical Laboratory of the Hebrew University, Jerusalem.

Dimethyl D-glucarate (**4**). The preparation of **4** followed a published procedure[21c], but using a newly charged column of the ion exchange resin and abs. methanol for rinsing it before use, increased the yield to 76%. The oil did only crystallise after weeks and thus was used as such. TLC: (Tol/EtOH 1:1) Rf=0.57. PMR (200 MHz, $CDCl_3$), δ: 4.39 (d, 1H), 4.37 (d, 1H), 4.11 (dd, 1H), 3.99 (dd, 1H), 3.843 & 3.838 (2_{xs}, $6H_{2xMe}$), 2.35 (bs, $4H_{4OH}$).

(2R,4S,6R,8R,9S;9,10-M)-2,6-diphenyl-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**9**). The known[21] diacetal was prepared in an improved yield, as follows. To 1.00 g (5.54 mmol) dimethylglucarate (**4**), disolved in 10 ml (100 mmol) freshly distilled benzaldehyde, 1.26 g (9.25 mmol) anhydrous zinc chloride were added and the mixture stirred (r. t.) for 5 d. The reddish mixture was poured on 30 ml sat. ammonium chloride solution. A yellow oil containing some crystals was obtained after extracting with dichloromethane (3 x 30 ml), drying ($MgSO_4$) and evaporation of the solvent. Purification by flash chromatography, (PE/EtAc 1:0 to 2:1) yielded 590 mg (26%) of white crystals, mp. 141 °C (lit.[20b] 135-140). TLC (PE/EtAc 1:1): Rf=0.56. PMR (200 MHz, $CDCl_3$), δ: 7.64-7.32 (m, 10 H, Ph), 5.93 (s, $1H_2$), 5.66 (s, $1H_6$), 4.86 (d, $J_{4,10}$=1.2, $1H_4$), 4.67 (d, $J_{8,9}$=2.0, $1H_8$), 4.41 (bt, J≅1.4, $1H_{10}$), 4.33 (bt, J≅1.6, $1H_9$), 3.89 & 3.79 ($2x_S$, $6H_{Me}$). CMR (50.3 MHz, $CDCl_3$), δ: 169.5 & 167.6 (CO), 137.1 & 136.7 ($C_{1',1''}$), 129.4 & 129.0 ($C_{4',4''}$), 128.3 & 128.1 ($C_{3(5)',3(5)''}$), 126.7 & 126.3 ($C_{2(6)',2(6)''}$), 100.9 & 97.6 ($C_{2,6}$), 77.1 & 76.2 ($C_{4,8}$), 70.2 & 68.6 ($C_{9,10}$), 52.7 & 52.5 (Me). EIMS (70 eV; 400 °C): m/z (%) 414 (1.8) [M^+], 355 (2.0) [M^+, COOMe], 308 (10) [M^+, PhCHO], 207 (12), 127 (10), 105 (100) [Ph-CO^+]. $C_{22}H_{22}O_8$ 414.42.

(2R,4R,6R,8R,9S;9,10-M)-2,6-diphenyl-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**10**). 150 mg (0.36 mmol) of **9** were stirred into a solution made of 10 ml abs. MeOH with 0.5 mg (0.022 mmol) sodium. TLC (PE/EtAc 1:1) shows a mixture including a new (Rf=0.35) increasing spot. After 3 d at 20°C and constant NMR spectrum, the reaction is worked up like the one leading to **9** to give 120.7 mg (80%) colourless crystals, by NMR a (4:3) mixture of **9** and **10**. Separation and isolation of **10** were achieved by flash chromatography, using (PE/EtAc 2:1 to 1:1), TLC (PE/EtAc 1:1), Rf=0.35. M.p. 252°C (d.) $[\alpha]_D$ = + 42.5, $[\alpha]_{436}$ = + 81.6 (c=0.79, $CDCl_3$). PMR (200 MHz, $CDCl_3$), δ: 7.58-7.51 (m, $4H_{Ph}$), 7.37-7.33 (m, $6H_{Ph}$), 5.67 (s, $2H_{2,6}$), 4.70 (d, $J_{8,9}$=1.4, $2H_{4,8}$), 4.36 (d, $2H_{9,10}$), 3.80 (s, $6H_{Me}$). CMR (50.3 MHz, $CDCl_3$), δ: 167.7 (CO), 136.6 ($C_{1'}$), 129.2 ($C_{4'}$), 128.2 ($C_{3(5)'}$), 126.6 ($C_{2(6)'}$), 100.5 ($C_{2,6}$), 77.3 ($C_{4,8}$), 70.4 ($C_{9,10}$), 52.7 ($2x_{Me}$). EIMS (70 eV; 400°C): m/z (%) 414 (11.6) [M^+], 355 (5.8) [M^+-COOMe], 308 (21) [M-PhCHO]$^+$, 207 (9.6), 127 (8.8), 105 (100) [Ph-CO^+]. $C_{22}H_{22}O_8$ 414.42.

(2R,4S,6R,8R,9S;9,10-M)-2,6-di(3-nitrophenyl)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**5**). 340 mg (1.4 mmol) of dry **4** and 1.54 g (10.2 mmol) of 3-nitrobenzaldehyde were molten together in vacuo and kept at 0.1 torr for 30 min. After cooling down, 0.5 ml of conc. H_2SO_4 were added, and the mixture was left at room temperature for 4 days, gently swirling from time to time. Then slowly, 10 ml of abs. methanol were added and the reaction was completed by refluxing for 2 h. By then, one phase was present. The reaction was worked up by adding 2 g anh. K_2CO_3 (or by slowly pouring the methanolic solution into a mixture of 2 g K_2CO_3 and 20 g of ice while stirring quickly) in order to destroy any dimethylsulfate that has formed; after stirring for another 15 min, the mixture was evaporated, taken up in chloroform, filtered and evaporated again. The product was purified by subjecting the resulting crude brownish oil (2.03 g) to flash chromatography on about 50 g of silica gel (PE/EtAc 1:1), to yield 414 mg (58%) of colourless foamy crystals, m.p. 153°C. TLC (PE/EtAc 1:3), Rf=0.67. $[\alpha]_D$ = + 4.2, $[\alpha]_{436}$ = + 1.2 (c=1, $CDCl_3$). PMR (200 MHz, $CDCl_3$), δ: 8.44 (t, J=1.8, $1H_{2'}$), 8.35 (t, J=1.8, $1H_{2''}$), 8.26 (ddd, J=8.2, J=2.3, J=1.1, $1H_{4'}$), 8.21 (ddd, J=8.2, J=2.3, J=1.1, $1H_{4''}$), 7.99 (dt, J=7.8, J=1.2, $1H_{6'}$), 7.87 (dt, J=7.8, J=1.2, $1H_{6''}$), 7.59 (t, J=8.0, $1H_{5'}$), 7.55 (t, J=8.0, $1H_{5''}$), 6.07 (s, $1H_2$), 5.83 (s, $1H_6$), 4.93 (d, $J_{4,10}$=0.6, $1H_4$), 4.75 (d, $J_{8,9}$=2.0, $1H_8$), 4.50 (t, J=1.3, $1H_{10}$), 4.42 (bt, J≅1.7, $1H_9$), 3.94 & 3.87 (2 s, $6H_{2xMe}$). CMR (50.3 MHz, $CDCl_3$), δ: 168.8 & 167.1 (CO), 148.0 ($C_{3',3''}$), 138.7 & 138.2 ($C_{1',1''}$), 132.7 & 132.4 ($C_{6',6''}$), 129.5 & 129.3 ($C_{5',5''}$), 124.4 & 124.1 ($C_{4',4''}$),121.9 & 121.7

($C_{2',2''}$), 99.0 & 96.0 ($C_{2,6}$), 77.0 & 76.0 ($C_{4,8}$), 70.2 & 68.5 ($C_{10,9}$),53,1 & 52.9 ($_{2xMe}$). EIMS (70 eV; 150°C): m/z (%) 368 (3.8, $[M-CH_2C_6H_4NO_2]^+$), 256 (11), 171 (100), 158 (85), 136 (32), 60 (59), 45 (60). Analysis: calc. for $C_{22}H_{20}N_2O_{12}$ (504.41) C 52.39, H 4.00, N 5.55; found C 52.41, H 4.05, N 5.38.

*(2R,4S,6R,8R,9S;9,10-M)-2,6-di(3-aminophenyl)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**6**).*

(a) 670 mg (1.33 mmol) of **5** were stirred with Pd/C (5%, 10 mg) in 25 ml CH_2Cl_2 under H_2 at atmospheric pressure, until the calculated H_2-uptake (198 ml at 30 °C) was registered (sometimes, more catalyst had to be added); 20 to 40 h were usually necessary for completion. The Pd/C was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated to give a white foam, which was taken up in 30 ml hot PE, filtered, dissolved in CH_2Cl_2, charcoaled and filtered. This afforded 533 mg (90%) of the pure product as colourless crystals, mp. 196°C.

(b) 1580 mg (3.13 mmol) of **5** in MeOH/THF 1:1 (12 ml), Pd/C (50 mg) and ammonium formate (1400 mg, 22.20 mmol) were stirred 30 min at r.t. Then a further portion of ammonium formate was added (300 mg, 4.76 mmol) and the mixture was stirred for an additional period of 60 min. Ether (500 ml) was then added, the precipitate was removed by filtration and washed with ether and the organic solution was evaporated to give **6** (1380 mg, 99%), which was purified as above.

TLC (PE/EtAc 1:3): Rf=0.21. $[\alpha]_D$ = + 9.46, $[\alpha]_{436}$ = + 16.45 (c=3.92 in dichloromethane). UV (MeCN): λ_{max} (nm, log ε) 297 (3.26), 284 (3.04, sh), 244 (3.85). PMR (360 MHz, $CDCl_3$), δ: 7.16 (t, J=7.8, $1H_{5'}$), 7.14 (t, J=7.7, $1H_{5''}$), 7.01 (bt, J=1.8, $1H_{2'}$), 6.94 (bd, J=7.7, $1H_{6'}$), 6.92 (t, J=2.0, $1H_{2''}$), 6.89 (d, J=7.8, $1H_{6''}$), 6.69 (ddd, J=8.0, J=2.4, J=0.9, $1H_{4'}$), 6.67 (ddd, J=8.2, J=2.3, J=0.8, $1H_{4''}$), 5.83 (s, $1H_2$), 5.62 (s, $1H_6$), 4.84 (d, $J_{4,10}$=0.8, $1H_4$), 4.65 (d, $J_{8,9}$=2.0, $1H_8$), 4.38 (bt, J≅1.3, $1H_{10}$), 4.30 (bt, J≅1.7, $1H_9$), 3.87 & 3.78 ($_{2xS}$, $6H_{2xCH3}$), 3.64 (bs, $4H_{2xNH2}$). CMR (50.3 MHz, $CDCl_3$), δ: 169.5 & 167.7 ($_{2x}$CO), 146.6 & 146.4 ($C_{3',3''}$), 138.1 & 137.7 ($C_{1',1''}$), 129.1 & 129.0 ($C_{5',5''}$), 116.8, 116.6, 116.2 & 115.8 ($C_{4',4'',6',6''}$), 113.2 & 112.9 ($C_{2',2''}$), 100.9 & 97.7 ($C_{2,6}$), 77.2 & 76.2 ($C_{4,8}$), 70.2 & 68.6 ($C_{10,9}$), 52.7 & 52.5 ($_{2xMe}$). EIMS (7 eV; 400°C): m/z (%)=444 (100) [M^+], 121 (36), 43 (23). Analysis: calc. for $C_{22}H_{24}N_2O_8$ (444.45) C 59.45, H 5.44, N 6.30; found C 59.80, H 5.66, N 6.22.

*(2R,4R,6R,8R,9S;9,10-M)-2,6-di(3-aminophenyl)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**12**).*

171 mg (0.385 mmol) **6** were stirred in 80 ml of newly prepared abs. methanol + 1 ml of a methanolic soln. of NaOMe (0.43 M) for 8 d, to constant composition (see below). Working up like described for the preparation of **10** yielded 160.5 mg (94%) of white-to-yellow crystals poorly soluble in common solvents, except DMF and DMSO. The crude ^{1}H-NMR shows **12**/**6** = 3:2. For analytic purposes, 25.6 mg of this mixture were separated by flash chromatography on 9 ml of silica gel and CH_2Cl_2:EtAc (2:1 to 1:2) as the eluent. After evaporation, the residue was washed with chloroform and dried, to give 6.7 mg of colourless crystals, mp. 228-232 °C (d.). TLC (CH_2Cl_2:EtAc 1:1): Rf=0.20. $[\alpha]_D$ = + 19.3, $[\alpha]_{436}$ = + 27.2 (c=0.72 in DMSO). PMR (200 MHz, DMSO-d_6), δ: 7.06 (t, J=7.7, $2H_{5'}$), 6.74 (t, J=1.6, $2H_{2'}$), 6.65 (d, J=8.5, $2H_{4'\text{ or }6'}$), 6.64 (d, J=7.8, $2H_{6'\text{ or }4'}$), 5.60 (s, $2H_{2,6}$), 4.94 (bs, $2H_{4,8}$), 4.37 (bs, J=1.2, $2H_{9,10}$), 3.66 (s, $6H_{2xMe}$). [PMR (200 MHz, $CDCl_3$) (derived from equilibrium mixture) δ: 5.58 (s, $2H_{2,6}$), 4.67 (d, J=2.0, $2H_{4,8}$), 4.32 (d, $2H_{9,10}$), 3.80 (s, $6H_{2xMe}$)]. CMR (50.3 MHz, DMSO=39.5 ppm!), δ: 168.0 ($_{2x}$CO), 146.6 ($C_{3',3''}$), 138.3 ($C_{1',1''}$), 128.8 ($C_{5',5''}$), 115.8 & 115.6 ($C_{(4,6)',(4,6)''}$), 113.0 ($C_{2',2''}$), 99.5 ($C_{2,6}$), 76.2 ($C_{4,8}$), 70.1 ($C_{9,10}$), 52.2 ($_{2x}$Me).

(2R,4S,6R,8R,9S;9,10-M)-2,6-di(3-isocyanatophenyl)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin (**7**). A mixture of 301.6 mg (0.68 mmol) of **6** and 298.0 mg (3.527 mmol) $NaHCO_3$ was dried in vacuo,

suspended in 50 ml abs. CH_2Cl_2 and cooled to 0°C. A solution of 0.88 ml of 1.93 M phosgene in toluene (1.70 mmol) was added slowly and the mixture was stirred at r. t. for 5 days. Filtering, washing with chloroform and evaporation of the organic solution, gave a crude yield of 330.0 mg of a solid, which, according to NMR is about 80% pure (hence, ca. 78% yield). This was used as such for further reactions, since purification attempts caused extensive deterioration. PMR (200 MHz, $CDCl_3$), δ: 7.42 [dt, J=7.6, J=1.4, $1H_{6'}$) 7.45-7.16 (m, $5H_{2',2'',5',5'',6''}$), 7.12-7.05 (m, $2H_{4',4''}$), 5.91 (s, $1H_2$), 5.68 (s, $1H_6$), 4.86 (d, J=0.9, $1H_4$), 4.67 (d, J=2.0, $1H_8$), 4.41 (t, J=1.3, $1H_{10}$), 4.33 (t, J=1.6, $1H_9$), 3.91 & 3.83 (2 s, 2 Me). CMR (50.3 MHz, $CDCl_3$), δ: 169.2 & 167.4 (CO), 138.6 & 138.2 ($C_{1',1''}$), 133.5 & 133.4 ($C_{3',3''}$), 129.6 & 129.4 ($C_{5',5''}$), 125.6 & 125.3 ($C_{4',4''}$), 124.0 & 123.7 ($C_{6',6''}$), 123.0 & 122.8 ($C_{2',2''}$, N=C=O), 99.8 & 96.7 ($C_{2,6}$), 77.1 & 76.1 ($C_{4,8}$), 70.2 & 68.5 ($C_{9,10}$), 52.9 & 52.7 (Me).

*(2R,4S,6R,8R,9S;9,10-M)-2,6-(3,6-dioxaoctylidene-1,8-diyl-di-*m*-phenylurethane)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin* (**8a**). A solution of **7** (67 mg, 0.173 mmol) in 10 ml abs. dichloromethane was added slowly at 20°C and with stirring, to a solution of ca. 0.18 mmol of triethylene glycol containing ca. 55 mg (8 mmol; 4.3 mol-%) of lithium (prepared by heating a ca. 500-fold amount of these reagents at 60°C until the metal has dissolved and taking an aliquot of this solution) in 20 ml of freshly distilled dry diethyl ether. After 15 min., the reaction mixture was concentrated and taken up in 20 ml of abs. dichloromethane (occasionally 1 ml DMSO was added) and held at reflux for 4 hrs.. The unreacted triethyleneglycol (and DMSO) are removed by washing with (2x10 ml) water and the organic phase was dried ($MgSO_4$) and the solvents evaporated. Repeated filtration over 1 ml of SiO_2 in a Pasteur pipette, while rinsing with CH_2Cl_2/ethyl acetate afforded the pure product (**8a**) as an amorphous solid (20 mg. 18%). IR (KBr) ν_{max} (cm^{-1}) 3334, 3093, 1729, 1618, 1555. PMR (200 MHz, $CDCl_3$), δ: 7.99, 7.89 (bs, bs, $2H_{2',2''}$), 7.72, 7.68 (bs, bs, 2xNH) 7.61, 7.57 (bd, bd, J=7.4, $2H_{4',4''}$), 7.28 (t, J=7.4, $2H_{5',5''}$), 7.03 (bd, J=7.4, $2H_{6',6''}$), 5.94, 5.67 (s, s, $2H_{2,6}$), 4.76 (d, J=1.0, $1H_8$), 4.58 (d, J=1.0, $1H_4$), 4.4-4.2 (m, $6H_{9,10}$ & $COOCH_2$), 3.89, 3.72 (s, s, $6H_{OMe}$), 3.9-3.6 (m, $8H_{OCH2}$). CMR (50.3 MHz, $CDCl_3$), δ: 169.4, 167.7 (2xCOO), 153.8 (2xCON), 139.1, 138.7, 138.3, 137.8 ($C_{1',1'',3',3''}$), 128.6, 128.4 ($C_{5',5''}$), 122.4 ($C_{4',4''}$), 120.3 ($C_{6',6''}$), 117.0 ($C_{2',2''}$), 101.2 (C_2), 97.7 (C_6), 77.2, 75.9 ($C_{4,8}$), 71.7 (2xNCOOC), 69.7, 67.8 ($C_{9,10}$), 69.9, 65.2 (COC), 52.7 (C_{Me}). EIMS (7 eV; 300°C): m/z (%): 646 (8) [M^+]. Elemental analysis: calc. for $C_{30}H_{34}N_2O_{14}$ (646.61) C 55.73, H 5.30, N 4.33; found C 55.90, H 5.49, N 4.14.

*(2R,4S,6R,8R,9S;9,10-M)-2,6-(3-oxapentylidene-1,5-diyl-di-*m*-phenylurethane)-4,8-di(methoxycarbonyl)-cis-1,3,5,7-tetraoxadecalin* (**8b**). A similar procedure to that for **8a**, using diethylene glycol, led to **8b**, in 19% yield. PMR (200 MHz, $CDCl_3$), δ: 7.84, 7.74 (bs, bs, $2H_{2',2''}$), 7.67 (bd, J=7.7, $2H_{4',4''}$) 7.50 (bs, 2xNH), 7.27 (dt, J=7.7, J=3.4, $2H_{5',5''}$), 7.00 (bd, J=7.7, $2H_{6',6''}$), 5.96, 5.67 (s, s, $2H_{2,6}$), 4.74 (d, J=0.9, $1H_4$), 4.57 (d, ^{3}J=1.3, $1H_8$), 4.4-4.2 (m, $4H_{COOCH2}$), 3.9-3.7 (m, $2H_{9,10}$ & $4H_{OCH2}$), 3.88, 3.77 (s, s, $6H_{OMe}$). CMR (50.3 MHz, $CDCl_3$), δ: 169.3, 167.8 (2xCOO), 153.0 (2xCON), 138.8, 138.6, 138.3, 137.8 ($C_{1',1'',3',3''}$), 128.7 ($C_{5',5''}$), 122.1 ($C_{4',4''}$), 119.8, 119.5 ($C_{6',6''}$), 116.6, 116.4 ($C_{2',2''}$), 100.8 (C_2), 97.4 (C_6), 77, 75.6($C_{4,8}$), 69.9 (2xNCOOC), 69.5, 67.6 ($C_{9,10}$), 67.6, (COC), 52.8 (C_{Me}). EIMS (7 eV; 300°C): m/z (%): 602 (11) [M^+]. $C_{28}H_{30}N_2O_{13}$ 602.56.

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3. For the sake of clarity and consistency with all our studies, we use here the *cis*-1,3,5,7-tetraoxadecalin nomenclature (*cf.* **2** for atom numbering) and not the carbohydrate names, *e.g.*, 1,3:2,4-di-O-methylene-D-threitol or (as in Chemical Abstracts), (4aR)-(4a*r*,8a*c*)-tetrahydro[1,3]dioxino [5,4-*d*]-1,3-dioxin. In the same context, due to a minor but basic omission of the CIP rules, one cannot assign configurations to chiral *cis*-decalin (and similar) systems, other than by 9,10-helicity specification. Thus, the diastereoconformers **2** (O_{inside}) and **3** ($O_{outside}$) are, in fact, (9R;9,10-M)-and (9R;9,10-P)-*cis*-1,3,5,7-tetraoxadecalin, respectively.
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