Synthesis of a Novel Class of Carbohydrate-Containing Calix[4]resorcinarene Adopting an Asymmetrical Diamond Structure

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Dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 65th birthday

A novel type of calixsugars, containing sugar moieties at the methine bridges of the calixarene is introduced. These calixsugars were prepared *via* a nonconvergent stepwise fragment condensation. Four new stereogenic centers were formed simultaneously, and only one diastereoisomer **5** was isolated. The condensation procedure is remarkably mild allowing for a large diversity of labile groups to be used. The solution structure of calixarene **5** with two D-glucose and two hexyl moieties was determined by NMR spectroscopy by means of NOEs and coupling constants for molecular dynamics (MD). Chemical shifts were used to validate the conformation with the least NOE and *J* violations. The structure of calixsugar **5** has the configuration rctc referring to one sugar residue (*r* = reference, *c* = cis, *t* = trans) and adopts a diamond conformation for the macrocyclic backbone with the two sugar moieties axial on opposite sides of the macrocyclic ring and the two hexyl groups on the same side.

Introduction. – Resorcenarenes [1–3] are macrocyclic compounds that are easily obtained by condensation reactions of resorcinol (= benzene-1,3-diol) or resorcinol ethers with a variety of aliphatic as well as aromatic aldehydes under catalysis with mineral acids, carried out in a one-pot reaction. Resorcenarenes exhibit an extensive host–guest chemistry, a property which makes them of potential interest for development of molecular vehicles. The acid-catalyzed condensation reaction generally affords the most favored all-*cis* (rccc) isomer [4][5] (*r* = reference, *c* = cis). One of the key steps in the syntheses of this type of macrocyclic compound is the right choice of the employed catalyst, which could be shown to predominantly determine the yield and progress of the condensation reaction. According to a large body of publications, both types of catalysts relying either on aqueous mineral acids or non-aqueous *Lewis* acids have been successfully used. Recently, the influence of the applied *Lewis* acid catalysts on the formation of different types of calix[4]resorcinarene conformers [6], when working in a H_2O-free system has been studied. The most broadly used conditions for the synthesis of symmetric resorcarenes remains the aqueous mineral-acid-induced one-pot reaction [7], which is generally considered to be the favored and accepted way for the synthesis of calix[4]resorcinarenes. However, the catalysis by aqueous mineral acids requiring often high temperatures for efficiency constitutes a rather drastic condition that is not compatible with acid-sensitive residues or complex natural products attached to the calix[4]arenes. Therefore, the use of acid-hemilabile protecting groups when introducing complex natural-product building blocks into the framework of resorcarenes has lost some of its attraction.

In a pioneering study, *Dondoni*, *Ungaro*, and co-workers [8–10] have developed methods for the attachment of carbohydrates to the upper and lower rim of

calix[4]arene to form a variety of (*O*-glycosyl)- and also (*C*-glycosyl)-calix[4]arenes [11][12], so-called 'calixsugars'. This approach has been expanded since then. The strategies summarized in the following are mainly based on chemical modifications of an already condensed calix[*n*]arene backbone by attaching natural products onto the upper and lower rim of the calixarene. Lower-rim products have been obtained, for example, by amide-bond formation. The 1,3-bis(aminoethoxy)calix[4]arene with the two amino groups located at the lower rim was condensed with 2,3,4,5,6-penta-*O*-acetyl-D-gluconyl chloride to yield a lower-rim calix[4]arene-carbohydrate [13]. The same 1,3-bis(aminoethoxy)calix[4]arene has been employed in a coupling reaction with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanates to yield, after deprotection, a bisglycosyl-thiourea-calix[4]arene scaffold [14].

Upper-rim calix[4]arenes modified with carbohydrates have been obtained, for example, by a *Suzuki*-type reaction of 4-bromophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside with calix[4]arene boronic acid that was located at the upper rim of the scaffold resulting in a bis-glycosylated product with an enlarged cavity size [15]. (*C*-Glycosyl)-calix[4]arene architectures have been constructed from 6-deoxy-1,2:3,4-di-*O*-isopropylidene-6-(triphenylphosphino)-α-D-galactopyranose iodide salt with 5,11,17,23-tetraformyl-25,26,27,28-tetrapropoxycalix[4]arene by using BuLi as a strong base, constituting a *Wittig*-type olefination reaction, leading to a C–C linkage of the sugar with the macrocylce at the upper rim [16].

Further upper-rim-connected (*O*-glycosyl)-calix[4]arenes have been prepared *via* a $Cu(OTf)_2$-catalyzed *O*-glycosylation of hydroxymethyl substituents at the upper rim of calix[4]arene with methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside and *via Mitsunobu* reaction of the 1-OH group of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose with the phenolic OH groups of 5,11,17,23-tetrakis(hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene.

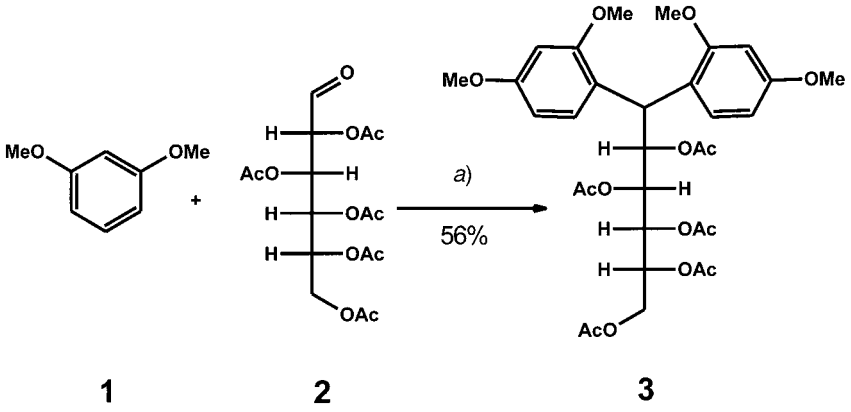
However, to our knowlege, no attempt has been undertaken so far to incorporate open-chain aldehydic carbohydrates (=aldoses) into the skeleton of calix[4]resorcinarenes. Although, these aldoses do not represent the most common constitution of sugars found in nature, they make accessible a large diversity of highly functionalized resorcarenes through the natural chiral pool.

In this work, we take advantage of sugar aldehydes (=aldoses) to establish the first example of a new type of carbohydrate-containing calix[4]resorcinarenes, substituted at their methine bridges with 1,2,3,4,5-*O*-acetylated arabitol-1-yl residues. In the present work, the surprising stability of open-chain *O*-acetyl-protected aldose **2** towards harsh non-aqueous acidic conditions was exploited to insert this building block into the calixresorcarenes.

Results and Discussion. – *Synthesis.* Recently, *White* and co-workers [17] described the $BF_3 \cdot Et_2O$-catalyzed condensation reaction between an equimolar ratio of 1-*O*-methylresorcinol and different types of aldehydes in dry CH_2Cl_2. The smooth and efficient reaction conditions presented there encouraged us to apply similar reaction conditions to the desired condensation reaction of aldoses with 1,3-dimethoxybenzene (**1**) (*Scheme 1*). When we were using an equimolar ratio of **1** and 2,3,4,5,6-penta-*O*-acetyl-D-glucose (**2**) with the above mentioned catalyst in dry CH_2Cl_2, a non-uniform product distribution was observed, whereas taking a four-fold excess of **1** led to the

exclusive formation of **3** (*Scheme 1*), which could be isolated as a colorless foam in a yield of 56% after column chromatography (NMR parameters in *Table 1*). Unfortunately, all trials to obtain the all-sugar substituted calix[4]resorcinarene from **3** and the protected aldose **2** failed despite variation of the reaction conditions (temperature, time, stoichiometry). *In situ* TLC control indicated that, after the first condensation step, the condensation reaction became so slow that the reaction simply stopped. Still, a small amount of a new product could be isolated after column chromatography. The identity of the compound was established by ESI-MS (*m/z* 1181.5 ($C_{56}H_{70}O_{26}^{+}$, $[M+Na]^{+}$)) and NMR-spectroscopy (to be published elsewhere) to consist of a linear resorcinol ether 'trimer' **4** (*Fig. 1*) containing two alditol-1-yl residues. The ^{1}H-NMR spectra of compound **4** confirm unambiguously the acyclic nature of the trimer. Its ^{1}H-NMR spectrum exhibits 6 different MeO signals and in addition 8 nonequivalent aromatic protons. Thus, the configuration of the anomeric positions is determined to be (*R*,*S*) (*Fig.* 1).

Scheme 1. *Preparation of the Precursor Derivative* **3** *from 2,3,4,5,6-Penta-*O*-acetyl-*D*-glucose*



a) $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t., 1.5 h.

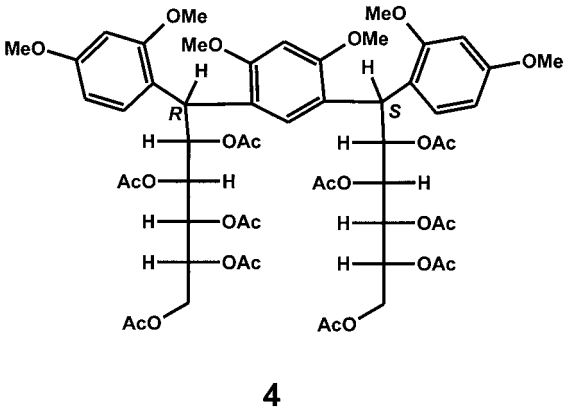


Fig. 1. *Molecular structure of the linear 'trimer' product* **4**

The structure of **3** was found to be 2,3,4,5,6-penta-*O*-acetyl-1-deoxy-1,1-bis(2,4-dimethoxyphenyl)-D-glucitol according to ^{1}H-NMR spectroscopy (*Fig. 2* and *Table 1*). This 'dimer' is the basis for the further condensation reactions with aldehydes to prepare different ring sizes and types of calixsugars.

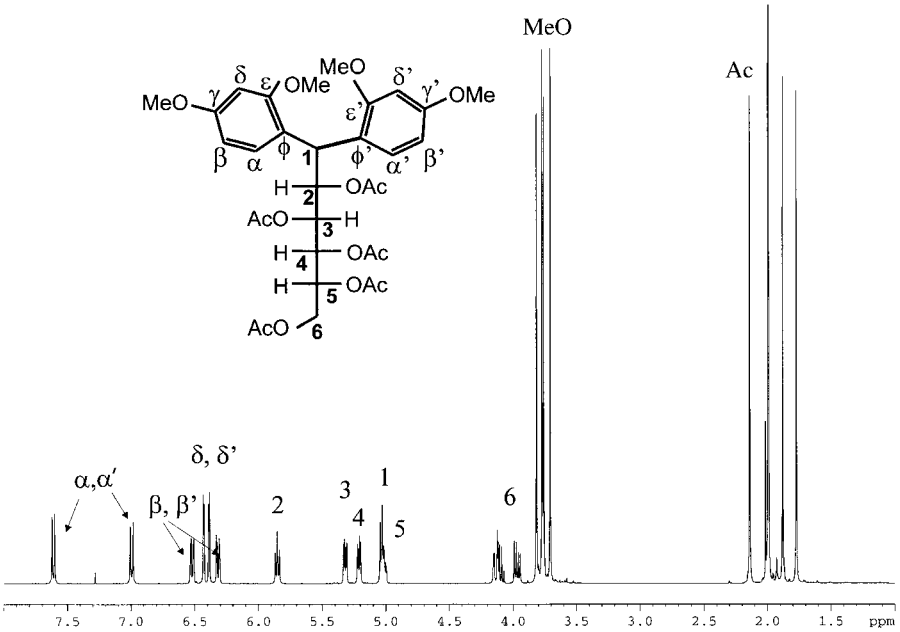


Fig. 2. *400.13-MHz-^{1}H-NMR Spectrum* ($CDCl_3$) *and signal assignments of compound* **3** *at 303 K*

Table 1. *^{1}H- and ^{13}C-NMR Data* (303 K) *for compound* **3**. δ in ppm, ^3J(H,H) in Hz.

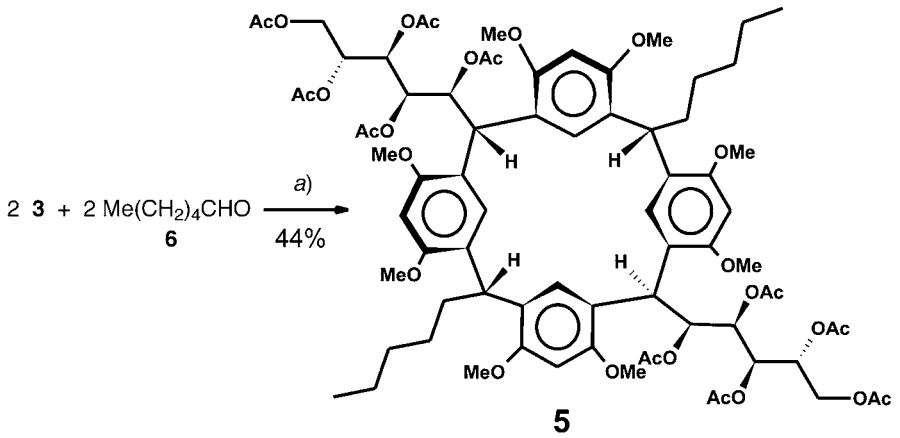
	^{1}H-NMR			^{13}C-NMR
	δ	multiplicity	^3J(H,H)	δ
H–C(α), H–C(α')	7.61, 7.00	*d*	8.6	133.6, 132.8
H–C(β), H–C(β')	6.52, 6.32	*d*	8.6	106.7, 106.9
H–C(δ), H–C(δ')	6.43, 6.39	*s*		101.5, 101.4
H–C(1)	5.04	*d*	6.6	41.1
H–C(2)	5.85	*dd*	6.6, 7.2	74.9
H–C(3)	5.32	*dd*	7.2, 3.3	73.1
H–C(4)	5.21	*dd*	3.3, 7.2	71.4
H–C(5)	5.02	*m*	–	71.5
H–C(6)	4.14, 3.98	*m*	–	63.4
MeO	3.81, 3.77, 3.76, 3.71	*s*		58.4, 57.9, 58.3,57.8
*Me*COO	2.14, 2.00, 1.99, 1.88, 1.77	*s*		23.2–23.3
Me*C*OO				173.1, 172.4, 172.3, 172.3, 172.1
quat. C				133.7, 133.5, 132.8, 132.8, 123.2, 123.2, 122.4, 122.4

Phenyl-substituted glucitols such as compound **3** have already been synthesized and described in the literature in numerous publications. However, in the majority of these cases, they could only be obtained by the application of relatively harsh reaction conditions to suitable aldehydes and aromatic compounds, such as methylbenzene, ethylbenzene [18], and methoxybenzene [19] in HF solution [20], or by treatment with concentrated HCl solution at high temperature [21], or alternatively by adding several batches of $AlCl_3$ as catalyst during the reaction [22].

As mentioned above, we aimed to obtain a calixsugar with four sugar residues attached to it at the methine bridges. An extensive screening of reaction conditions varying reaction time, temperature, and catalysts both for the reaction of 'dimer' **3** as well as 'trimer' **4** with additional **2** failed, due to decomposition and instability of the reactants under the prevailing acidic conditions. We assume that the desired product is sterically not feasible due to the space-requiring acetyl groups at the sugar residues. If this assumption was true, then we should expect successful condensation reactions with sterically less demanding unbranched alkanals leading to bis-glycosyl-substituted resorcarenes.

Such a concept of obtaining resorcarenes with mixed substituents at the methine bridges has already been introduced by *Paulus*, *Böhmer*, and co-workers [23]. They developed a two-step strategy to obtain calix[4]resorcinarenes with alternating alkyl and aryl substituents by a condensation reaction in aqueous acidic media such as HCl. Relying on this concept, the glucitol derivative **3** was subjected to a one-pot condensation reaction (*Scheme 2*) with hexanal (**6**) to obtain a macrocyclic ring. Using this ring closure approach, we were successful in the synthesis of the chiral calix[4]resorcinarene **5** with alternating pentyl and arabinitol-1-substituents at the methine bridges. Compound **5** could be isolated in 44% yield as a colorless solid after column chromatography.

Scheme 2. *Preparation of Calix[4]sugar* **5** via Lewis *Acid Induced Ring-Closure Reaction of* **3** *with Hexanal* (**6**)



a) $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t., 1.5 h.

Configuration. The NMR spectrum of **5** agrees with the formation of a single stereoisomer (*Fig. 3* and *Table 2*), indicating the selective formation of four new stereogenic centers. Of course, the configuration of these newly formed stereogenic centers is not known *a priori*, and they have to be determined together with the structure calculation, namely those at the methine atoms C(ε_1), C(ϕ_1), C(λ_1), and C(ω_1). Due to the fact that the NMR spectrum indicates only chemically inequivalent resonances, **5** is asymmetric. In the constitutionally symmetric molecule, there are 6 possible stereoisomers due to these four stereogenic centers. However, there is an additional multitude of conformational stereoisomers due to the fact that the aromatic rings do not lie in the plane of the macrocycle but are twisted out of this plane allowing them to be either up or down with respect to the plane of the macrocycle. As a consequence, 68 stereoisomers originate. They are schematically represented in *Fig. 4,a*. Out of these stereoisomers, 8 have C_2 symmetry thus leaving 60 conformations that are compatible with the asymmetry of the NMR spectrum. Since initial calculations showed that conformations with one aromatic ring in a different conformation than the others have high conformational and restraint energy, 16 of these stereoisomers (boxed in *Fig. 4,a*) were not calculated. The remaining 44 conformations and the symmetric ones amounting to 52 were then used as starting conformations for structure calculations. The symmetric ones were calculated to check whether they would provide high conformational and restraint energies as well.

For each of the 52 starting stereoisomers, we used two assignments that are interconverted by rotation about the constitutional symmetry axis perpendicular to the macrocyclic ring by 180° (*Fig. 4,b*, left top and bottom). In principle, there is another pair of assignments that is generated from the two described ones by inverting the sense

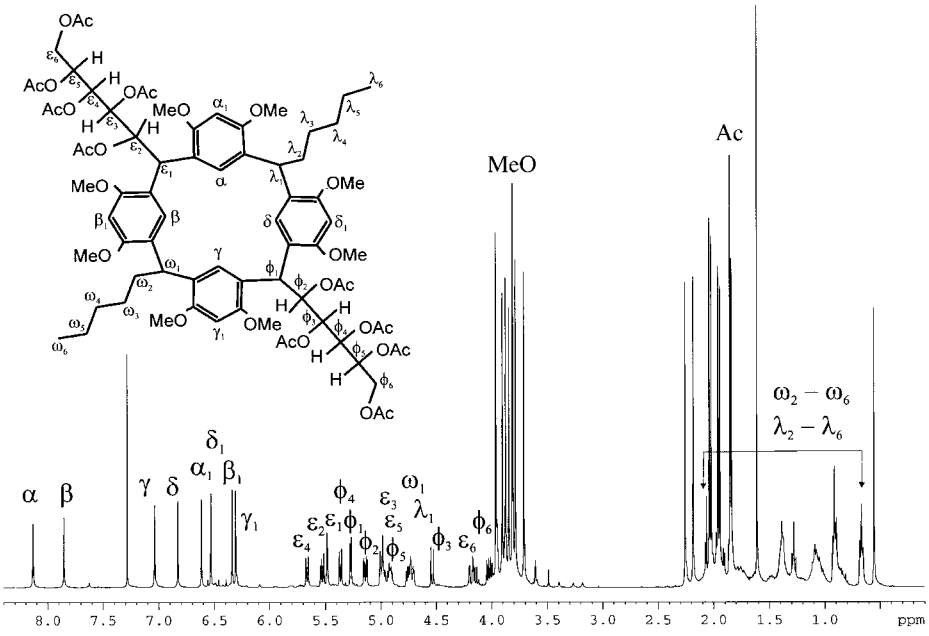


Fig. 3. *400.13-MHz-^{1}H-NMR Spectrum* ($CDCl_3$) *and signal assignments of compound* **5** *at 303 K*

Table 2. *^{1}H- and ^{13}C-NMR Data* (303 K) *for compound* **5**. δ in ppm, ^3J(H,H) in Hz.

	^{1}H-NMR			^{13}C-NMR
	δ	multiplicity	^3J(H,H)	δ
H–C(α)	8.13	*s*		133.2
H–C(α_1)	6.61	*s*		98.2
H–C(β)	7.85	*s*		130.3
H–C(β_1)	6.34	*s*		99.5
H–C(γ)	7.04	*s*		131.2
H–C(γ_1)	6.30	*s*		98.6
H–C(δ)	6.83	*s*		132.2
H–C(δ_1)	6.53	*s*		98.1
H–C(ε_1)	5.48	*d*	3.7	34.0
H–C(ε_2)	5.53	*dd*	3.7, 9.1	76.8
H–C(ε_3)	5.00	*dd*	9.1, 1.2	73.5
H–C(ε_4)	5.66	*dd*	1.2, 7.8	71.2
H–C(ε_5)	4.98	*m*	–	71.5
CH$_2$(ε_6)	4.19	*m*	–	65.1
H–C(ϕ_1)	5.27	*d*	3.7	34.1
H–C(ϕ_2)	5.14	*dd*	3.7, 9.5	75.5
H–C(ϕ_3)	4.53	*dd*	9.5, <1	73.7
H–C(ϕ_4)	5.36	*dd*	<1, 7.8	70.6
H–C(ϕ_5)	4.92	*m*	–	71.5
CH$_2$(ϕ_6)	4.02	*m*	–	65.1
H–C(ω_1)	4.75	*dd*	5.6, 10.0	34.4
H–C(λ_1)	4.71	*dd*	3.5, 10.0	39.1
CH$_2$(ω_2)–CH$_2$(ω_5), Me(ω_6), CH$_2$(λ_2)–CH$_2$(λ_5), Me(λ_6)	2.08, 2.00, 1.78, 1.72, 1.64, 1.49, 1.44, 1.39, 1.37, 1.35, 1.10,1.10, 1.06, 1.06, 0.91, 0.89, 0.67	*m*	–	39.5, 36.2, 35.0, 34.4, 33.3, 32.6, 28.1, 27.6, 19.9, 19.5
MeO	3.96, 3.90, 3.88, 3.85, 3.82, 3.81, 3.73, 3.71	*s*		58.2, 57.7, 58.7, 57.9, 58.7, 58.8, 59.2, 58.6
*Me*COO	2.26, 2.19, 2.04, 2.02, 1.96, 1.95, 1.86, 1.86, 1.84, 1.61	*s*		23.1–23.6
Me*C*OO				173.1, 173.0, 172.7, 172.3, 172.2, 172.0, 172.0, 171.6, 171.2
quat. C				138.5, 138.4, 133.7, 133.7, 133.5, 133.5, 133.4, 133.4, 133.3, 131.9, 130.2, 128.2, 124.6, 122.8, 122.6, 120.5, 119.1

of rotation (right top and bottom). However, these assignments were not taken into account since there are only two NOEs including the sugar stereogenic centers, namely proton H–C(ε_3), and H–C(ϕ_3) (*vide infra*). Since these NOEs were never violated, it cannot be expected that the sense of rotation in the assignment is relevant for the structure of the macrocycle.

NMR Spectroscopy. The NOEs were quantitatively extracted by integration and were calibrated by the H–C(ε_1)/H–C(ε_2) and the H–C(ϕ_1)/H–C(ϕ_2) NOEs (*Fig. 5*). The corresponding distances are known since the coupling constants ^3J between these two vicinal proton pairs is 3.7 Hz indicating the predominance of the *gauche*

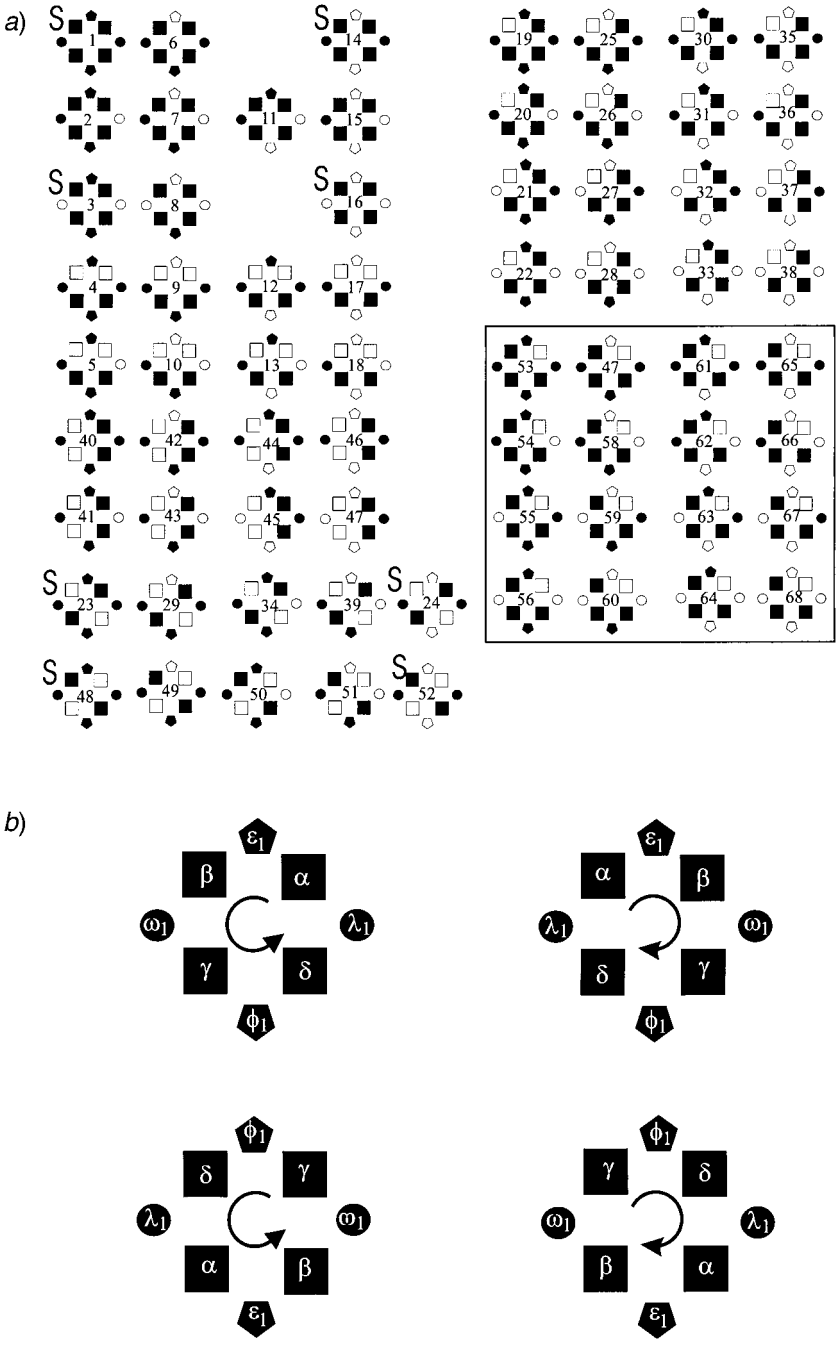


Fig. 4. a) *Schematic representation of all 68 possible stereoisomers of the calixsugar* **5** (black and white mean positions above and below of the sheet plane, resp.; square = resorcinol-derived ring, circle = hexyl chain, pentagon = sugar moiety; all stereoisomers, except for the 16 boxed ones, are used as starting points for molecular dynamics). b) *Left upper and lower parts represent the two possible assignments for each of the 52 stereoisomers that were used for the structure calculations* (the right upper and lower parts represent assignments that are obtained from the two left ones by inverting the sense of rotation).

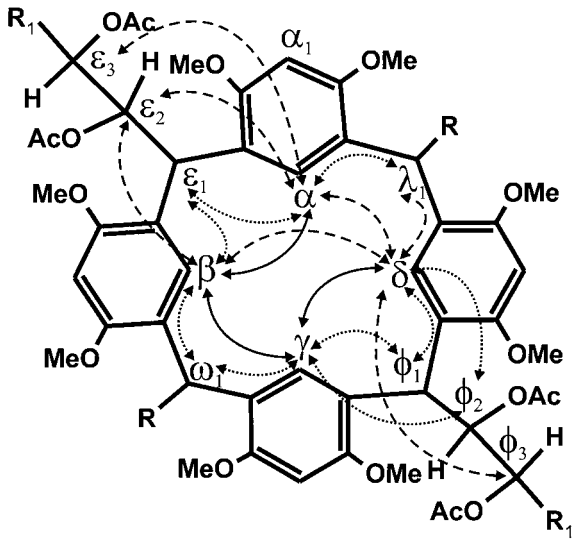


Fig. 5. *NOE Relationships of compound* **5**. Solid arrow = strong NOE ($2 \leq d < 3$ Å), hatched arrow = medium NOE ($3 \leq d < 4$ Å), dotted arrow = small NOE ($4 \leq d \leq 5$ Å). The assignment depicted in *Fig. 5* can be directly transferred to the formula in *Scheme 2*. The second assignment mentioned in the text is obtained by rotation of the assignments about the axis through the two sugar methine bridges.

conformation. The four cross-peak integrals match within 87% and can, therefore, be used for the calibration.

Structure Calculation. By means of molecular-dynamics protocols, we generated 5200 structures using 52 different starting conformations with the two assignments for each of the conformations according to *Fig. 4*,*a* and *b*. These starting conformations differed in the relative orientation of the aromatic rings with respect to each other.

The potential energy E_p and the distance-restraint-forcing potential varied from a minimum of 269.0 and 1.3 to a maximum of 328.5 and 17.4 kcal mol^{-1}, respectively. From each 'assignment pair', we selected the structure based on the NOE-restraint energy. The restraint energies of 52 stereoisomers are shown in *Fig. 6*. We selected the best 9 structures that correspond to lowest distance-restraint-violation energies ($E_{NOE} \leq 5$ kcal mol^{-1}) (*Fig. 6*). As an indication for a well-adapted force field and good NOE-distance calibration, the generated structure **S12** with the lowest violation energy ($E_{NOE} = 1.3$ kcal mol^{-1}) has also the lowest total energy ($E_{total} = 269.0$ kcal mol^{-1}). This 'best' conformation **S12** has a 'diamond' macrocyclic scaffold, is in the rctc configuration referring to C(ε_1)(r), and has the hexyl and sugar chains all in axial positions (*Fig. 7*,*b*). The 8 other low-violation-energy structures correspond to different ring-core conformations: **S5** ($E_{total} = 292.2$ kcal mol^{-1} and $E_{NOE} = 4.8$ kcal mol^{-1}), **S18** ($E_{total} = 284.82$ kcal mol^{-1} and $E_{NOE} = 1.8$ kcal mol^{-1}), and **S28** ($E_{total} = 284.7$ kcal mol^{-1} and $E_{NOE} = 3.8$ kcal mol^{-1}) adopt a 'chair' conformation; **S8** ($E_{total} = 279.2$ kcal mol^{-1} and $E_{NOE} = 4.9$ kcal mol^{-1}), **S15** ($E_{total} = 272.6$ kcal mol^{-1} and $E_{NOE} = 4.5$ kcal mol^{-1}), and **S16** ($E_{total} = 276.5$ kcal mol^{-1} and $E_{NOE} = 2.5$ kcal mol^{-1}) exhibit a 'crown' conformation; **S43** ($E_{total} = 272.3$ kcal mol^{-1} and $E_{NOE} = 4.5$ kcal mol^{-1}) and **S46**

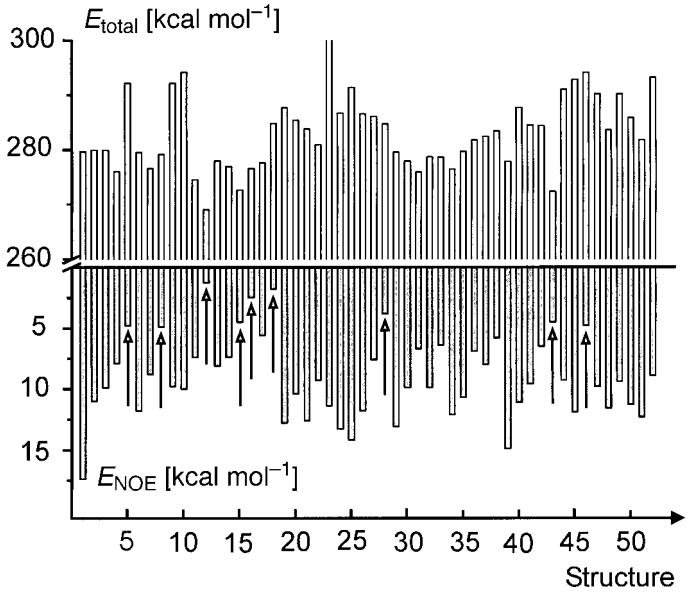


Fig. 6. *Energy profile of the 'best' structures generated by MD.* Numbering of the structures corresponds to the starting conformations shown in *Fig. 4,a*. The upper part displays the total conformational energy (E_{total}) and the lower part the distance-violation energy (E_{NOE}), with a scale factor of 10 for E_{NOE}. Arrows indicate the conformations with the least violations ($E_{NOE} \leq 5$ kcal mol^{-1}). To exhibit the energy differences better, the highest energy (**S23** $E_{total} = 328.5$ kcal mol^{-1}) was cut off.

($E_{total} = 294.1$ kcal mol^{-1} and $E_{NOE} = 4.8$ kcal mol^{-1}) have also a 'diamond' structure, however, with much higher conformational and NOE-violation energies, which differ from the **S12** conformation by the relative position of ring pairs. Although structure **S12** has the lowest energy and the least distance-restraints violations, we sought for an independent proof that **S12** is the correct structure of **5** by excluding the other 8 structures that differ from **S12** with respect to conformational and restraint energy.

Two major structural differences have to be taken into account, first the relative configurations of the sugar and hexyl 'anomeric' (methine-bridge) protons, second the macrocyclic conformation. To differentiate the configurations of the 'anomeric' protons H–C(ε_1), H–C(ω_1), H–C(ϕ_1), and H–C(λ_1) relatively to the rings, we used some characteristic NOEs. The NOE cross-peaks between the ring protons H–C(α), H–C(β), H–C(γ), or H–C(δ) and the 'anomeric' protons have a weak intensity (or medium to weak in the case of H–C(δ)/H–C(λ_1)), which define a preferred axial position of the methine substituents (*Fig. 5*). Eight of the above mentioned 9 'best' conformations generated by distance-restraint molecular dynamics show large violations of these NOEs: **S5** (H–C(δ)/H–C(ϕ_1) 2.6 Å, H–C(γ)/H–C(λ_1) 2.1 Å), **S8** (H–C(α)/H–C(ε_1) 2.1 Å, H–C(β)/H–C(ε_1) 2.4 Å), **S15** (H–C(β)/H–C(ω_1) 2.4 Å, H–C(γ)/H–C(ω_1) 2.3 Å), **S18** (H–C(δ)/H–C(λ_1) 2.2 Å), **S43** (H–C(α)/H–C(ε_1) 2.2 Å), and **S46** (H–C(α)/H–C(λ_1) 2.4 Å). These NOE violations corroborate the 'diamond' structure **S12**. However, the 'crown' conformation **S16** cannot be excluded based on this argument.

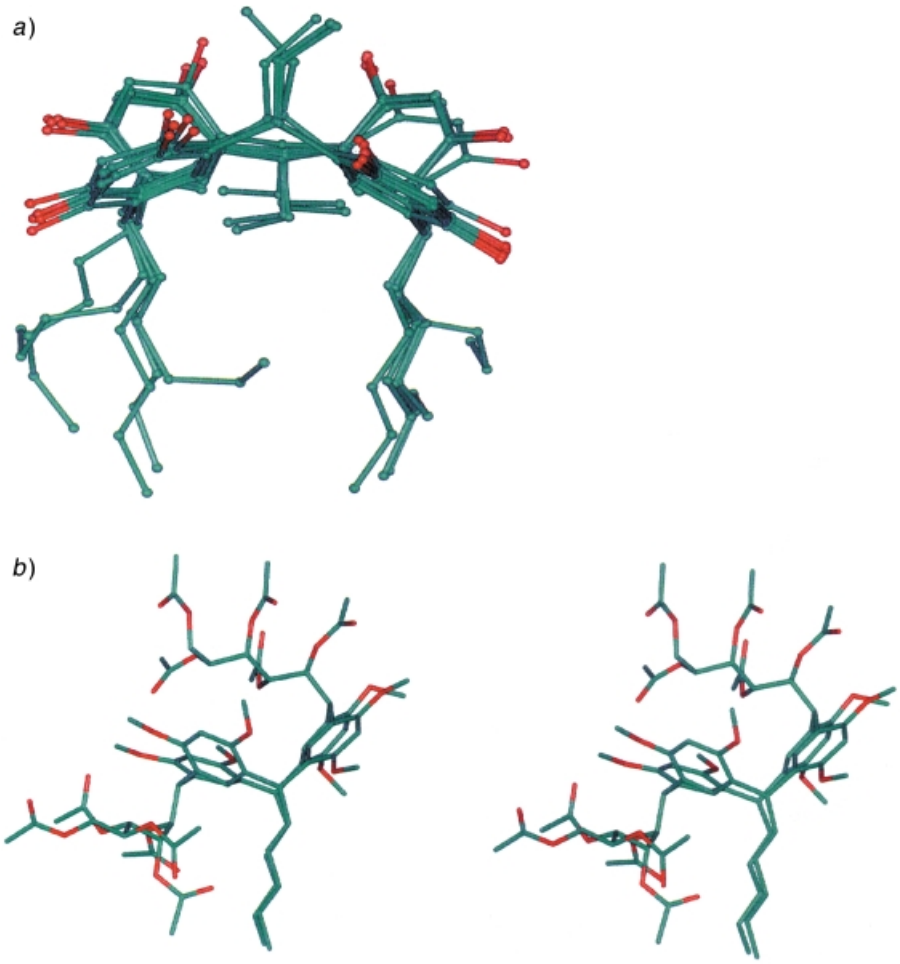


Fig. 7. *'Best' structures obtained by MD with distances restraints for the stereoisomer* **S12**. *a*) *Superimposition of lowest-energy 'diamond-like' structures showing some flexibility of the sugar and pentyl chains* (for clarity, Me groups are not displayed and the sugar chain is truncated). *b*) *Stereoview of the lowest energy* (E_{total} and E_{NOE}) *conformation of* **S12** *showing a 'diamond like' macrocyclic ring scaffold.*

A second selection criterion for the 9 'best' conformations was based on the fact that they adopt different macrocyclic conformations, namely 'crown', 'diamond', and 'chair'. Since the aromatic rings in the calixsugar have strong anisotropic magnetic susceptibilities, a differentiation of the macrocyclic-ring conformations should be possible. Indeed, in the experimental ^{1}H-NMR spectrum, the constitutionally equivalent proton signals show large differences: H–C(α) and H–C(β) resonate at low field (δ 8.13 and 7.85) and H–C(γ) and H–C(δ) at high field (δ 7.04 and 6.83). We quantitatively calculated the chemical shifts induced by the proximal resorcinol-derived rings for the aromatic-ring protons H–C(α), H–C(β), H–C(γ), and H–C(δ) by means of the *Haigh* and *Mallion* [24] formula for the ring-core conformations of the

9 'best' structures, thereby ignoring any other influence on their chemical shift. This is justified since the acetyl groups are well away from these protons or mobile enough according to the lack of NOEs. For simplicity, we assumed that the anisotropies of each proximal resorcinol-derived ring was identical. We calculated the r.m.s. (root-mean-square) deviation of the experimental *vs.* the calculated chemical shifts: $\text{r.m.s.d.}(\Delta\delta) = \sqrt{\sum_{x,y}\left(\Delta\delta_x^{\text{exp}} - \Delta\delta_y^{\text{exp}} - \Delta\delta_x^{\text{HM}} + \Delta\delta_y^{\text{HM}}\right)^2}$ where the *x*,*y* pair runs over the following six pairs of ring protons: H−C(α),H−C(β), H−C(α),H−C(γ), H−C(α),H−C(δ), H−C(β),H−C(γ), H−C(β),H−C(δ), and H−C(γ),H−C(δ). We obtained for **S5**, **S8**, **S12**, **S15**, **S16**, **S18**, **S28**, **S43**, and **S46** the r.m.s.d($\Delta\delta$) values 2.45, 2.16, 0.90, 2.25, 2.35, 2.96, 2.97, 2.72, and 2.95 ppm, respectively. Also by this selection criterion, the 'diamond' structure **S12** is found.

Thus, chemical shifts independently corroborate the 'diamond' conformation **S12** (*Fig. 7*) and exclude the 'chair' or 'crown' conformation. Chemical shifts thus constitute a qualitative method to differentiate conformations of the macrocyclic ring of asymmetric calixarenes.

There is an additional complication that stems from the inability to differentiate between the two assignments, which differ by the sense of rotation in the macrocycle (*Fig. 4*,*b*). This stems from the fact that we do not have unique spectroscopic information to infer the configuration of the stereogenic centers at atoms C(ε_1) and C(ϕ_1) from the sugar stereogenic centers. However, this additional complication will not change the rctc macrocyclic backbone, since it will conserve the relative position of rings and 'anomeric' protons with respect to each other. Only the detailed conformation of the sugar chains with respect to the macrocycle could be affected.

Thus, we have the remarkable situation that the configuration and the conformation of **5** can be unambiguously determined while we obtain two possible assignments for the compound that differ in the sense of rotation. The same is also found for compound **4** whose configuration is unambiguously defined from the spectra but not its assignment.

Conclusions. – We have introduced a new class of calixsugars in which two different types of aldehydes, *i.e.*, two aldose and two sterically less demanding hexanal molecules are condensed in a stepwise reaction with 1,3-dimethoxybenzene. The condensation reaction generates the rctc configuration referring to one sugar methine moiety (*r*), and the macrocyclic ring adopts a diamond conformation. We have also shown that the chemical shifts of the aromatic protons are well suited for a quick distinction between the different possibilities of macrocyclic ring conformations. Currently, we are investigating the preparation of further analogous compounds, using different types of aldoses in various combinations and protecting groups as well as using different *Lewis* acid catalysts. We, thus, explore their effect on the resulting ring size of the macrocycle as well as its conformations. We also plan to study the properties of deprotected calixsugars, which should be H_2O-soluble and be able to host various amphiphilic guest molecules.

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Experimental Part

General. Starting materials were commercially available unless noted otherwise. D-Glucose diethyl dithioacetal [25], 2,3,4,5,6-penta-*O*-acetyl-D-glucose diethyl dithioacetal [26] and 2,3,4,5,6-penta-*O*-acetyl-D-glucose (**2**) were prepared according to literature procedures. $BF_3 \cdot Et_2O$ was purchased in the highest purity available from *Sigma-Aldrich Chemie GmbH*, Germany. All moisture-sensitive reactions were performed under Ar in oven-dried glassware. All solvents were dried with standard drying agents [27] and freshly distilled prior to use. TLC: *Macherey-Nagel* silica gel *Polygram-SIL-G/UV$_{254}$* plates; detection by UV and/or by charring with 20% aq. H_2SO_4 soln. followed by heating at 150°. Flash column chromatography (FC): silica gel *60* (0.015 – 0.040 mm). M.p.s: *Stuart-Scientific* (*BIBBY*, UK) capillary apparatus; uncorrected. Electrospray ionization (ESI) MS: *Finnigan LCQ* (ion-trapp) mass spectrometer; positive mode. Elemental analyses were performed by the microanalytical laboratory of the Institut für Organische Chemie, Universität Göttingen, Germany.

NMR Spectra. 400-MHz *Bruker Avance* spectrometer (*Bruker AG*, Rheinstetten, Germany) equipped with a TXI HCN z-grad probe, at 303 K; processing with XWINNMR 3.1 (*Bruker AG*, Karlsruhe, Germany); chemical shifts δ referenced to DSS (2,2-dimethyl-2-silapentane-5-sulfonic acid). For measurements in $CDCl_3$, compounds **3** and **5** were lyophilized from a solvent mixture MeCN/H_2O 1:1 and dissolved in $CDCl_3$. The following experiments were used for resonance assignments: 2D-^{1}H,^{1}H-DQF-COSY (10240 × 406 complex points, t_{1max} 89 ms, t_{2max} 620 ms, NS 8) [28]; 2D-^{1}H,^{1}H-ROESY (4096 × 1024 complex points, t_{1max} 213 ms, t_{2max} 320 ms, mixing time 300 ms, NS 8) [29–32]; 2D-^{1}H,^{1}H-NOESY (4096 × 1024 complex points, t_{mix} 300 ms, t_{1max} 213 ms, t_{2max} 320 ms, NS 16) [33]; 2D-^{13}C,^{1}H-HSQC (2048 × 512 complex points, t_{1max} 51 ms, t_{2max} 128 ms, NS 32) [34–37] at natural isotope abundance; 2D-^{13}C,^{1}H-HMBC (8192 × 503 complex points, t_{1max} 50 ms, t_{2max} 511 ms, NS 32, defocusing delay 50 ms) [38].

Molecular Modelling. The calculations were run on a *Silicon-Graphics* computer using the *Accelrys* software 'INSIGHT II' and 'DISCOVER 2.98' with the CVFF force field [39]. The 52 stereoisomers of *Fig. 4* were built in 'INSIGHT II'. To take solvent into account for these *in vacuo* calculations, a dielectric constant of $\varepsilon = 5$ was used for the *Coulomb* interaction. NOE-Derived distances (strong 2–3 Å, medium 3–4 Å, and weak 4–5 Å) were used as input restraints for the 'Discover' program. For each structure, we performed 5000 energy-minimization steps. After an equilibration period of 6 ps, a 1-ps MD run was performed at 300 K followed by 7 ps of slow temperature jump to 550 K and then cooling to 300 K, in 50 K steps. The trajectory was sampled after the last 300 K dynamics step, and then the protocol was repeated with different initial trajectories. The final conformers were further minimized to a gradient of less than 0.01 kcal/mol to obtain their energy with a higher accuracy. Thus, we obtained 50 structures per run. During MD runs, we used an NOE-restraint constant force of 500 kcal mol^{-1} Å^{-2} and reduced it to 50 kcal mol^{-1} Å^{-2} for the final minimization to allow more flexibility. Ring-current shifts for the resorcinol-derived protons H–C(α), H–C(β), H–C(γ), and H–C(δ) were calculated from a given conformation with a program based on the source code of the *Williamson*'s 'total' software with the default-ring-intensity factor of benzene [40]. The general form expected for ring-current contributions is $\sigma_{rc} = iBG(r)$ where r is the vector from the observed proton to the aromatic ring, $G(r)$ is a geometric factor and i and B are constants. $B = 5.455 \cdot 10^{-6}$ Å relative to benzene, and i (the ring-intensity factor, 1.00 in our case) represents the ratio between the intensity expected for the ring and that of a benzene ring. For the model given by *Haigh* and *Mallion*, the geometric factor is $G(r) = \sum S_{ij} \left\{ \left(r_i^3\right)^{-1} + \left(r_j^3\right)^{-1} \right\}$ where r_i and r_j are the distances from ring atoms i and j to the proton and S_{ij} is the area of the triangle formed by atoms i and j and the proton projected onto the plane of the aromatic ring. Also, the relative position of the proton to the normal vector of the ring plane is used to define the sign of the chemical shift.

*2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1,1′-bis(2,4-dimethoxyphenyl)-*D*-glucitol* (**3**). $BF_3 \cdot Et_2O$ (1.50 g, 10.56 mmol) was added to a stirred soln. of 1,3-dimethoxybenzene (**1**; 1.45 g, 10.52 mmol) and 2,3,4,5,6-penta-*O*-acetyl-D-glucose (**2**; 1.03 g, 2.63 mmol) in anh. CH_2Cl_2 (20 ml), and stirring was continued at r.t. for 1.5 h. The mixture was then diluted with H_2O (20 ml). The org. phase was washed with brine, dried ($MgSO_4$), and evaporated, and the red oily residue purified by FC (silica gel; AcOEt/heptane 2:1, R_f 0.6): **3** (0.95 mg, 56%). Colorless foam. M.p. 60°. ESI-MS: 671.4 ([M + Na]$^+$), 1318.7 ([2 M + Na]$^+$). Anal. calc. for $C_{32}H_{40}O_{14}$ (648.65): C 59.29, H 6.22; found: C 59.54 H 6.49.

4,6,10,12,16,18,22,24-Octamethoxy-8,20-bis[(1S,2R,3R,4R)-1,2,3,4,5-penta(acetyloxy)pentyl]-2,14-dipentylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (**5**). The procedure for the preparation of **3** was repeated with **3** (200 mg, 0.31 mmol), hexanal (**6**; 30.88 mg, 0.31 mmol), and $BF_3 \cdot Et_2O$ (175 mg, 1.23 mmol) in anh. CH_2Cl_2 (8 ml) to afford, after normal workup, an oily residue. The crude product was submitted to FC (silica gel; acetone/hexane 2:3, R_f 0.17): **5** (100 mg, 44%). Colorless amorphous crystal. M.p. 97–98°. ESI-MS: 1484.1 ($[M+Na]^+$). Anal. calc. for $C_{76}H_{100}O_{28}$ (1461.59): C 62.45, H 6.90; found: C 62.70 H 6.61.

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