A New Family of C_3-Symmetrical Carbohydrate Receptors

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The formation of the new optically active C_3-symmetrical receptors (*S*,*S*,*S*)-**2**–**4** (*Fig. 1*), incorporating 1,3,5-triphenylbenzene and 1,3,5-tris(phenylethynyl)benzene platforms as 'floors' and 'ceilings', is described. The tris(phenylethynyl)benzene derivatives **9** and (*S*,*S*,*S*)-**10** (*Scheme 1*) for the three-fold peptide coupling to yield the macrocyclic skeletons (*Scheme 2*) were prepared starting from 1,3,5-triethynylbenzene by the *Sonogashira* cross-coupling reaction. The optical rotations of the three macrocycles (*S*,*S*,*S*)-**2**–**4**, two of which ((*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3**) are constitutional isomers, differ significantly, which is explained by differential twists induced into the macrocyclic skeletons by the leucine spacer in these bridges. 1:1 Host–guest complexes of (*S*,*S*,*S*)-**2**–**4** with octyl glucosides (*Fig. 3*) in $CDCl_3$ are of modest stability ($K_a \leq 270\ M^{-1}$ at 300 K). In these complexes, the monosaccharides are most probably nesting on one of the H-bonding faces of the receptor rather than being accommodated in the cavity.

1. Introduction. – In our program targeting the development of large cyclophanes for inclusion complexation of small biomolecules, we had reported the synthesis and recognition properties of the optically active, C_3-symmetrical receptor (*S*,*S*,*S*)-**1** [1]. Complexation studies in $(CDCl_2)_2$ showed that the macrobicyclic cavity accommodates derivatives of excitatory amino acids such as *N*-Cbz-Asp or *N*-Cbz-Glu (Cbz = benzyloxycarbonyl) with substantial enantioselectivity. Thus, the diastereoisomeric complexes formed by the enantiomers of *N*-Cbz-Glu differed in stability by $\Delta(\Delta G) = 1$ kcal mol^{-1} (300 K). On the other hand, the cavity of this macrobicyclic receptor was found too small to accommodate carbohydrate guests such as monosaccharides (for references to carbohydrate recognition by artificial receptors, see the preceding paper in this issue [2]). To widen the cavity for monosaccharide incorporation, we decided to extend the platforms, constituting 'floor' and 'ceiling' in (*S*,*S*,*S*)-**1** (*Fig. 1*), by introduction of acetylene spacers between the phenyl rings, while, at the same time, maintaining salient features such as the C_3-symmetry (for a classification of macrocyclic hosts according to symmetry properties, see [3]) and the three peptide bridges with the H-bonding centers. Here, we report synthesis and binding properties of the three novel macrobicyclic receptors (*S*,*S*,*S*)-**2**–**4** incorporating 1,3,5-tris(phenethynyl)benzene platforms. Computer modeling using the program package MacroModel V. 6.0 [4] with the OPLS* force field [5] and gas-phase energy minimizations by the conjugate gradient method and 4000-steps *pseudo*-Monte-Carlo multiple minimum (MCMM) conformational searches [6] suggested that these novel cyclophanes possess preorganized, open-cavity binding sites suitable for the incorporation of monosaccharides.

2. Results and Discussion. – 2.1. *Synthesis of Receptors* (S,S,S)-**2**–**4**. Detailed protocols for the preparation of the two 1,3,5-triphenylbenzene derivatives **5** and

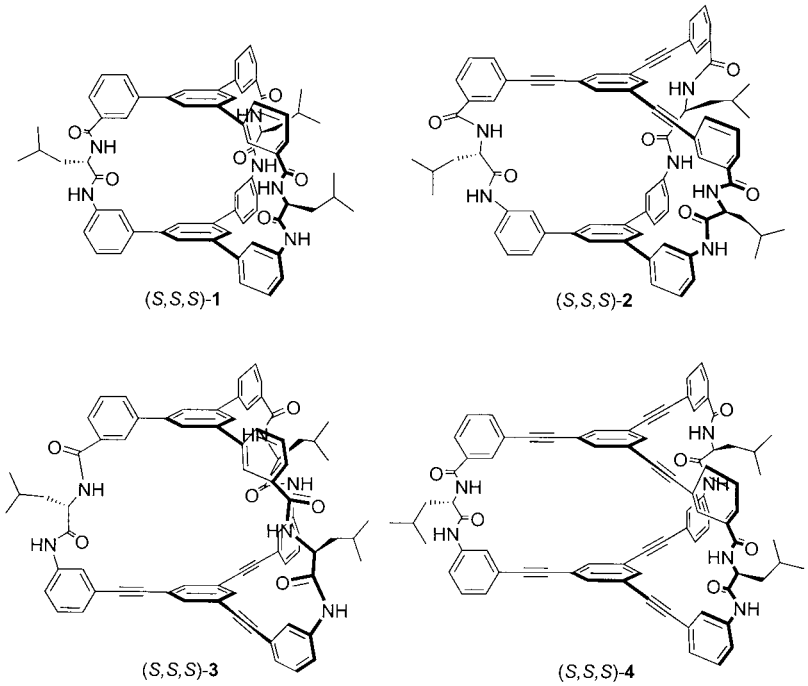
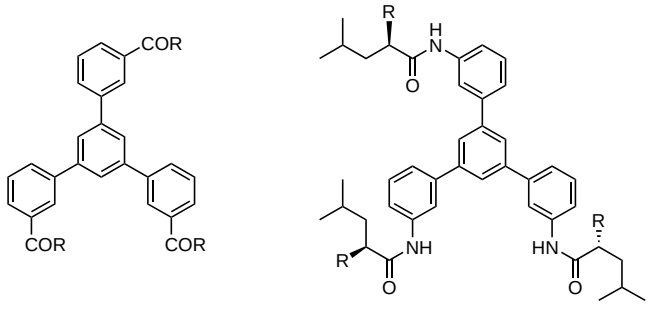


Fig. 1. *Extension of the 'floor'- and 'ceiling'-forming platforms in* (*S*,*S*,*S*)-**1** *by acetylene insertions providing the novel* C_3*-symmetrical receptors* (*S*,*S*,*S*)-**2**–**4**.

(*S*,*S*,*S*)-**6**, required for the macrocyclization to (*S*,*S*,*S*)-**2** and (*S*,*S*,*S*)-**3**, had been previously developed for the construction of (*S*,*S*,*S*)-**1** [1b]. Tris(acyl halide) **5** and tris(ammonium trifluoroacetate) (*S*,*S*,*S*)-**6** were conveniently prepared *in situ* from tris(carboxylic acid) **7** [7] and *N*-Boc-protected (*S*,*S*,*S*)-**8**, respectively, immediately before the macrolactamizations to yield the targeted receptors.

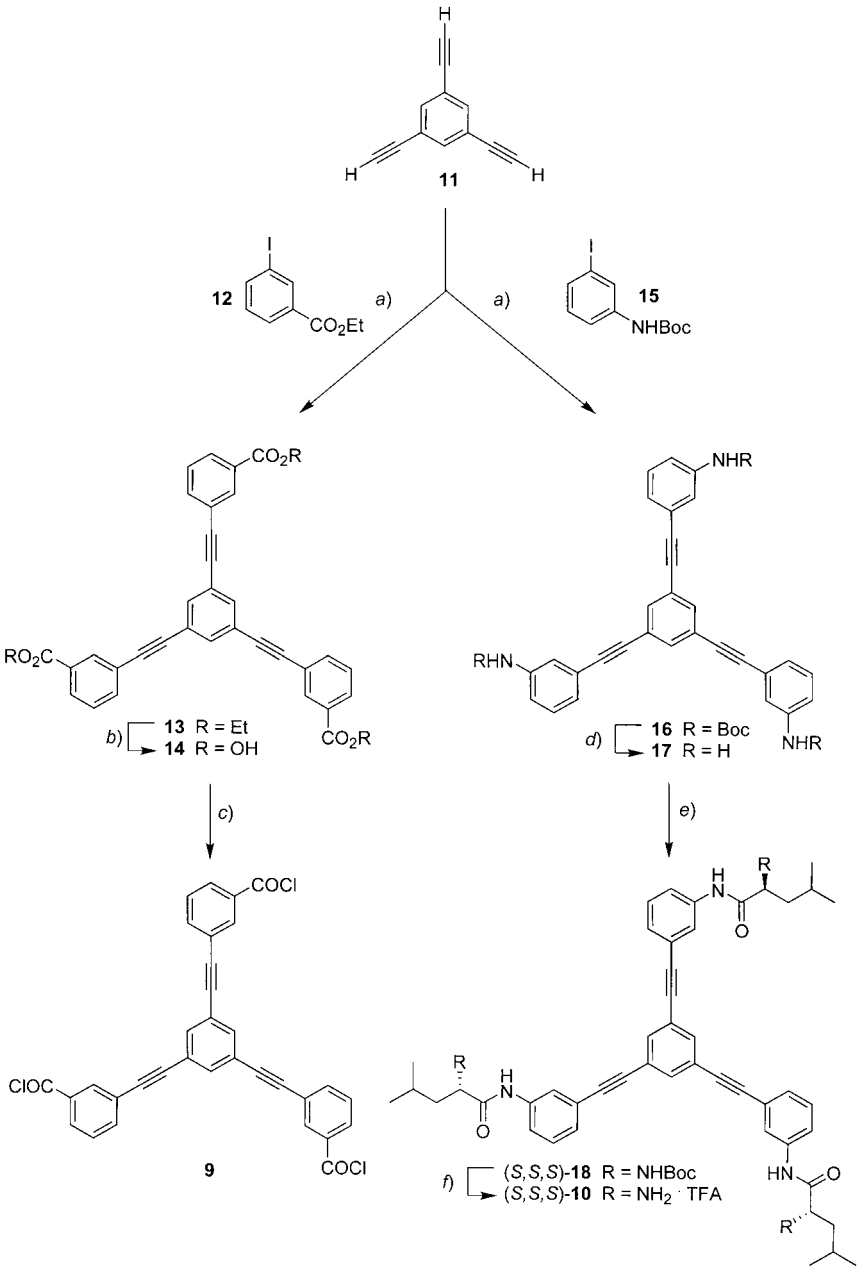


7 R = OH
5 R = Cl

(*S*,*S*,*S*)-**8** R = NHBoc
(*S*,*S*,*S*)-**6** R = $NH_2 \cdot$ TFA

The 1,3,5-tris(phenylethynyl)benzene derivatives **9** and (*S*,*S*,*S*)-**10** (*Scheme 1*) were obtained starting from 1,3,5-triethynylbenzene (**11**) [8] by *Sonogashira* cross-coupling

Scheme 1. *Synthesis of the Cyclization Components* **9** *and* (S,S,S)-**10**.



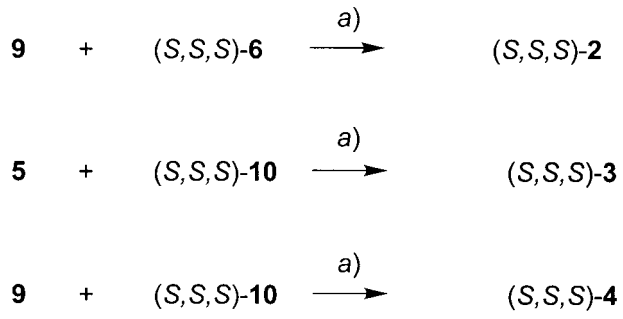
a) $[PdCl_2(PPh_3)_2]$, CuI, $HNEt_2$, Ar, r.t., 3 d; 79% (**13**), 74% (**16**). *b*) LiOH, THF, H_2O, 50°, 1 d; 60%. *c*) $SOCl_2$, Δ, 1 d. *d*) TFA, CH_2Cl_2, 0°, 1 h; 98%. *e*) *N*-Boc-L-Leu, EDC · HCl, DMAP, 0°, 2 d; 51%. *f*) TFA, CH_2Cl_2, r.t., 3 h. Boc = (*tert*-butoxy)carbonyl; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; DMAP = (4-dimethylamino)pyridine); TFA = trifluoroacetic acid.

protocols in the key C–C-bond forming steps [9]. Coupling of **11** with ethyl 3-iodobenzoate (**12**) afforded triester **13**, which was hydrolyzed to give the tris(carboxylic acid) **14**. As for **5**, tris(acyl halide) **9** was prepared *in situ* from **14** immediately before the macrocyclization.

Similarly, coupling of **11** with *N*-Boc-protected 3-iodoaniline **15** provided the tris-carbamate **16**, which was deprotected to give triamine **17**. Coupling of **17** with *N*-Boc-L-Leu in the presence of EDC·HCl and DMAP gave triamide (*S*,*S*,*S*)-**18**, which was deprotected immediately before macrocyclization to afford tris(ammonium trifluoroacetate) (*S*,*S*,*S*)-**10**.

The macrocyclizations to the C_3-symmetrical receptors (*S*,*S*,*S*)-**2**–**4** were all conducted in THF under high dilution in the presence of Et_3N to transform the tris(ammonium trifluoroacetates) *in situ* into the corresponding triamines and to trap the liberated HCl (*Scheme 2*). In each case, complex product mixtures were obtained that were extremely difficult to purify.

Scheme 2. *Macrocyclizations to* (S,S,S)-**2**–**4**



a) NEt_3, THF, r.t., 80 h; *ca.* 5–10%.

The progress of the macrocyclizations was monitored by analytical gel-permeation chromatography (GPC) on two sequential *Shodex GPC KF-803L* columns with THF as eluent. For purification, residual carboxylic acids were first removed by flash chromatography on SiO_2. Molecules of significantly different weight were subsequently separated by preparative GPC on *BioRad BioBeads S-X1* with THF as the eluent. Pure compounds for analytical characterization and complexation studies were finally obtained by multiple flash chromatography involving up to ten runs. HPLC on SiO_2 as well as on reversed-phase SiO_2 did not prove more efficient. By this tedious purification protocol, the macrobicyclic target compounds were obtained in *ca.* 5–10% yield, in quantities between 50 and 100 mg. Despite this purification effort, minor residual impurities remained in the samples of (*S*,*S*,*S*)-**4**.

The molecular formulae of the receptors were proven by high-resolution matrix-assisted laser-desorption-ionization mass spectrometry (HR-MALDI-MS) by the 'double-layer' protocol with 3,5-dihydroxybenzoic acid (DHB) as the matrix. In each spectrum, the Na complex of the molecular ion was observed as the base peak, with no fragment ions appearing above *m/z* 420 [(*S*,*S*,*S*)-**2**: 1169.493 and (*S*,*S*,*S*)-**3**: 1169.494 (100, $[M+Na]^+$, $C_{75}H_{66}N_6O_6Na^+$; calc. 1169.494); (*S*,*S*,*S*)-**4**: 1243.492 (100, $[M+Na]^+$, $C_{81}H_{66}N_6O_6Na^+$, calc. 1242.494)].

The ^{1}H- and ^{13}C-NMR spectra supported the proposed constitution of the three macrobicycles. As an example, the 500-MHz ^{1}H-NMR spectrum of (*S*,*S*,*S*)-**3** is depicted in *Fig. 2*, with an enlargement of the aromatic spectral region. All resonances in the

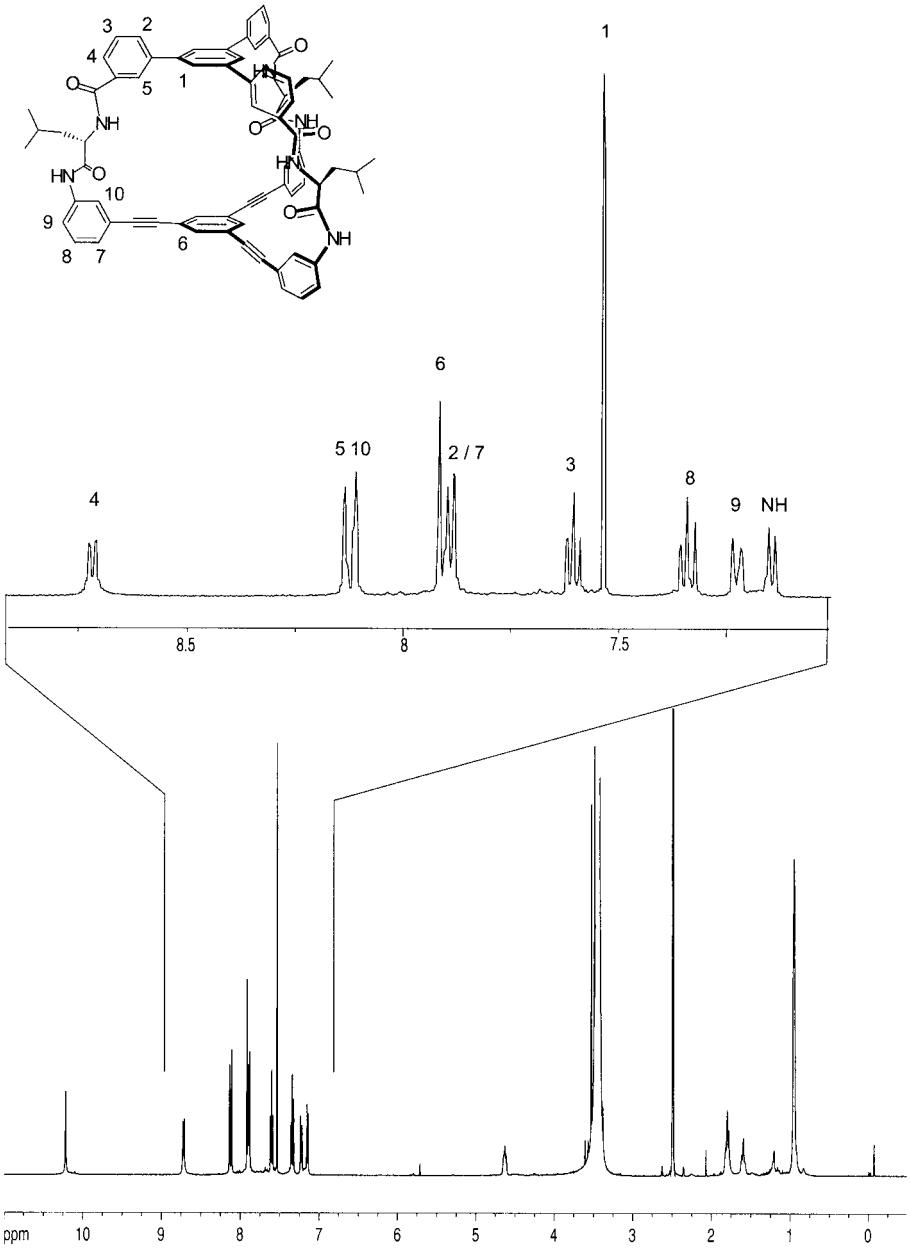


Fig. 2. *^{1}H-NMR Spectrum* (500 MHz, $(CD_3)_2SO$, 300 K) *of receptor (*S,S,S*)*-**3**. The aromatic region is expanded.

^{1}H-NMR spectra of the three receptors were resolved, thereby allowing complete assignment. With one exception (see below), the aromatic resonances in the spherical receptors appeared at chemical shifts similar to those measured for the corresponding signals in the free platforms **7**, (*S*,*S*,*S*)-**8**, **14**, and (*S*,*S*,*S*)-**18**, respectively. This finding provides experimental support for the preorganized, open cavities in the receptors, predicted by computer modeling (see *Sect. 1*). In case of collapsed structures, with the 'floor' and 'ceiling' platforms approaching each other, distinct upfield shifts of the aromatic resonances in the cyclophanes, compared with the free platforms, would have been observed. The only aromatic resonance in (*S*,*S*,*S*)-**3** encountering a major change in chemical shift corresponds to H–C(4) (arbitrary numbering; see *Fig. 2*). When compared to the corresponding resonance in triacid **7**, this signal moves downfield by 0.73 ppm, indicating conformational changes due to the macrocyclic bridging.

Although the three stereogenic centers are identical in all three optically active macrocycles, their optical rotations differ significantly. Thus, the optical rotation adopts an increasingly negative value when changing from (*S*,*S*,*S*)-**4** ($[\alpha]_D^{23} = -14$ ($c = 1$, $CHCl_3$), to (*S*,*S*,*S*)-**3** ($[\alpha]_D^{23} = -90$ ($c = 0.1$, THF), and to (*S*,*S*,*S*)-**2** ($[\alpha]_D^{23} = -153$ ($c = 0.1$, THF). This suggests an increasing twist of the macrobicycles, induced by the amino acid spacers. This twist transfers chirality, which at first glance seems to reside only in the periphery, to the interior of the cavity where the H-bonding centers become aligned in a helical orientation [1b].

2.2. *Complexation Studies.* ^{1}H-NMR Binding titrations with the octyl glucosides **19**–**21** (*Fig. 3*) were executed in $CDCl_3$ at 300 K and at constant receptor concentration, and the results are shown in the *Table*. In contrast to our expectations based on molecular modeling (*Sect. 1*) and the ^{1}H-NMR-spectroscopic evidence for non-collapsed, open-cavity binding sites, the affinities towards the monosaccharide guests are only modest, with all measured association constants K_a below 300 M^{-1} ($-\Delta G <$ 3.5 kcal mol^{-1}). Differences in the binding performance between the three receptors are substantial, with (*S*,*S*,*S*)-**2** exhibiting the highest affinity and diastereoselectivity and its constitutional isomer (*S*,*S*,*S*)-**3** being the weakest host.

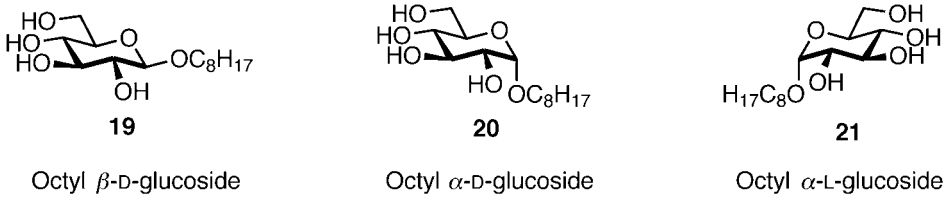


Fig. 3. *Monosaccharides investigated as guests in this study*

In view of the modest complex stabilities, cavity incorporation of the monosaccharides is highly questionable. The observed association strengths may in fact be better explained by a 'nesting' complexation of the monosaccharides outside the cavity (for similarly stable, 'nesting' association octyl glucosides on the face of a macrolactam lacking a suitably sized cavity, see [2]). In view of the observed modest binding

Table. *Association Constants* K_a [M^{-1}] *and Complexation Free Enthalpies* ΔG *Determined by* ^{1}*H-NMR Titrations for the Complexes of Receptor* (S,S,S)-**2** *with Monosaccharides* **19**–**21** *in* $CDCl_3$ (300 K)

Host[a])	Guest[a])	K_a [M^{-1}]	ΔG[b]) [kcal mol^{-1}]	$\Delta\delta_{sat}$[c]) [ppm]	Degree of saturation ($\Delta\delta_{max.\,obs}$ / $\Delta\delta_{sat}$)
(*S*,*S*,*S*)-**2**	**19**	270	−3.4	0.05	0.74
(*S*,*S*,*S*)-**2**	**20**	70	−2.5	0.15	0.53
(*S*,*S*,*S*)-**2**	**21**	110	−2.8	0.11	0.45
(*S*,*S*,*S*)-**3**	**19**[d])	*ca.* 60	*ca.* −2.4	0.02	0.36
(*S*,*S*,*S*)-**4**	**19**[d])	*ca.* 130	*ca.* −2.9	0.05	0.36

[a]) $[Host]_0 = 10^{-3}$ M; $[guest]_0$ varied between 1 and 20 mM. [b]) Uncertainty in ΔG: ±0.1 kcal mol^{-1}. [c]) The downfield shift of the anilide NH resonance in the receptor was monitored. Similar association constants were calculated from the shifts of other host resonances. $\Delta\delta_{sat}$ = shift at saturation binding; $\Delta\delta_{max.\,obs}$ = maximum shift reached in the titration. [d]) Binding of **20** and **21** by (*S*,*S*,*S*)-**3** and (*S*,*S*,*S*)-**4** too weak to be quantified. Uncertainties of the thermodynamic quantities are large in view of the small complexation-induced changes in chemical shift.

strength, we did not pursue further experiments to correct the measured 'apparent' association constants shown in the *Table* for competing self-association between the receptors. Evidence for strong self-association in $CDCl_3$ was provided by the concentration- and solvent-dependence of the NH resonances in the free receptors. Preliminary experiments with (*S*,*S*,*S*)-**2** in CD_3CN suggested that receptor self-association is less pronounced than in $CDCl_3$, and that monosaccharide complexation also occurs in this more competitive solvent. Complexation-induced downfield shifts of all amide resonances as well as differential up- and downfield shifts of the aromatic signals were observed upon addition of **19**–**21** to the receptor in CD_3CN; however, quantitative assessment of the association strength based on a 1:1 host–guest complexation model was not possible.

3. Conclusions. – Macrolactamization under high dilution provided the new family of optically active, C_3-symmetrical receptors (*S*,*S*,*S*)-**2**–**4**, which had been predicted by molecular modeling to form stable inclusion complexes with monosaccharides. The macrocyclization proceeded in low yield only, and purification from the abundantly formed side products proved to be extremely tedious, which we assign, among others, to the reduced nucleophilicity of the secondary amino groups in (*S*,*S*,*S*)-**6** and (*S*,*S*,*S*)-**10**, resulting from steric hindrance by the leucine side chain. Although the three stereogenic centers are identical in all three macrotricycles, their optical rotations differ significantly, which we explain by differential twists induced into the macrocyclic skeletons by the leucine spacers. In contrast to computational predictions and ^{1}H-NMR evidence for open-cavity binding sites, the cyclophanes complexed monosaccharides in $CDCl_3$ with modest affinity only. In view of the high association constants measured for true carbohydrate inclusion complexes of other spherical hosts [10], we assume that, in the weak complexes formed by (*S*,*S*,*S*)-**2**–**4**, the monosaccharides are nesting on one of the H-bonding faces of the receptor rather than being accommodated in the cavity. At present, we do not have a good explanation for why the experimental findings (weak 'nesting' complexation mode) differ so much from the computational predictions (strong cavity-inclusion complexation). As in previous ^{1}H-NMR investigations of

carbohydrate recognition by cyclophane receptors [11], self-association phenomena involving the receptors and their complexes prevented more extensive analysis of the recognition phenomena.

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Experimental Part

General. See [2]. Prep. GPC in open glass columns (125 × 4 cm) was performed at r.t. and ambient pressure on *BioBeads S-X1* from *BioRad* with THF as eluent; product elution was monitored at 290 nm with a *Knauer Variable-Wavelength Monitor* UV detector. Anal. GPC was performed on a *Merck-Hitachi LaChrom* system, consisting of a *Merck-Hitachi LaChrom L-7100* HPLC pump, a *LaChrom L-7360* column oven, a *LaChrom L-7400* UV detector, and a *LaChrom L-7490* RI detector. Two sequential *Shodex GPC KF-803L* columns were used with THF as eluent at a flow rate of 1 ml min^{-1} and an oven temp. of 40°; detection occurred at 290 nm.

^{1}H-NMR Binding Titrations. See [2].

Triethyl 3,3′,3″-(Benzene-1,3,5-triyl)tris(ethyne-1,2-diyl)tribenzoate (**13**). A soln. of **11** (1.121 g, 7.46 mmol) and **12** (8.231 g, 29.82 mmol) in $HNEt_2$ (140 ml) was flushed with Ar for 1 h in an ultrasonic bath. After addition of CuI (213 mg, 1.12 mmol) and $[PdCl_2(PPh_3)_2]$ (263 mg, 0.376 mmol), the mixture was stirred for 3 h at r.t. under Ar and exclusion of light. Evaporation *in vacuo* and precipitation of the crude product from CH_2Cl_2/MeOH, followed by drying at 10^{-2} Torr, provided **13** (3.503 g, 79%). Pale-yellow powder. M.p. 125°. IR (KBr): 3010*m*, 1716*s*, 1582*m*, 1477*w*, 1427*w*, 1297*s*, 1241*s*, 1104*m*, 1022*w*, 881*w*. ^{1}H-NMR (200 MHz, $CDCl_3$): 8.23 (*dd*, *J* = 1.6, 1.6, 3 H); 8.05 (*ddd*, *J* = 7.9, 1.6, 1.6, 3 H); 7.72 (*ddd*, *J* = 7.9, 1.6, 1.6, 3 H); 7.71 (*s*, 3 H); 7.48 (*dd*, *J* = 7.9, 7.9, 3 H); 4.42 (*q*, *J* = 7.1, 6 H); 1.43 (*t*, *J* = 7.1, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.16; 135.91; 134.62; 133.06; 131.19; 129.89; 128.81; 124.08; 123.36; 89.87; 88.61; 61.39; 14.33. HR-MALDI-MS: 594.2041 (100, M^+, $C_{29}H_{30}O_6^+$; calc. 594.2042). Anal. calc. for $C_{39}H_{30}O_6$: C 78.77, H 5.08; found: C 78.74, H 5.18.

3,3′,3″-(Benzene-1,3,5-triyl)tris(ethyne-1,2-diyl)tris(benzoic Acid) (**14**). To **13** (115 mg, 0.19 mmol) in THF (10 ml), LiOH (46 mg, 1.93 mmol) in H_2O (1 ml) was added, and the mixture was heated to 50° for 24 h. After cooling, 1M NaOH was added, and the mixture was washed with CH_2Cl_2. The aq. phase was acidified with conc. HCl to pH 1 and extracted with AcOEt (3 ×). The combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo* to provide, after drying, **14** (60 mg, 60%). Pale-yellow powder. M.p. >250° (dec.). IR (KBr): 3411*m*, 2917 (br.), 2644*w*, 2533*w*, 1699*s*, 1600*m*, 1583*m*, 1484*w*, 1443*m*, 1412*m*, 1306*m*, 984*w*, 910*w*, 873*w*, 753*m*, 678*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 12.80–13.40 (br. *s*, 3 H); 8.13 (*s*, 3 H); 8.00 (*d*, *J* = 7.8, 3 H); 7.86 (*s*, 3 H); 7.83 (*d*, *J* = 7.8, 3 H); 7.59 (*dd*, *J* = 7.8, 7.8, 3 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 166.38; 135.40; 134.17; 132.16; 131.39; 129.76; 129.23; 123.33; 122.05; 89.80; 88.01. ESI-MS: 509.1 (40, $[M-H]^-$).

*Tri-(*tert*-butyl)* N,N′,N″*-(Benzene-1,3,5-triyl)tris[ethyne-1,2-diyl(1,3-phenylene)]tricarbamate* (**16**). A soln. of **11** (1.121 g, 7.47 mmol) and **15** (9.54 g, 29.88 mmol) in $HNEt_2$ (160 ml) was flushed with Ar for 1 h in an ultrasonic bath. After addition of CuI (210 mg, 1.1 mmol) and $[PdCl_2(PPh_3)_2]$, the mixture was stirred for 3 d at r.t. under Ar and exclusion of light. After filtration, the filtrate was evaporated *in vacuo*, and the residue was purified by FC (SiO_2; CH_2Cl_2) to give **16** (4.010 mg, 74%). Amorphous colorless solid. M.p. 127°. IR (KBr): 3326 (br.), 2976*m*, 1705*s*, 1604*s*, 1595*s*, 1526*m*, 1488*m*, 1432*w*, 1401*w*, 1367*w*, 1234*m*, 1156*s*, 1053*w*, 994*w*, 877*w*, 795*w*, 694*m*, 531*m*. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 9.55 (*s*, 3 H); 7.77 (*s*, 3 H); 7.76 (*s*, 3 H); 7.46 (*d*, *J* = 7.8, 3 H); 7.33 (*dd*, *J* = 7.8, 7.8, 3 H); 7.19 (*d*, *J* = 7.8, 3 H); 1.49 (*s*, 27 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 152.88; 138.76; 134.39; 129.32; 126.65; 124.19; 123.76; 121.67; 119.67; 90.61; 88.01; 28.38. HR-MALDI-TOF: 723.352 (M^+, $C_{45}H_{45}N_3O_6^+$; calc. 723.331). Anal. calc. for $C_{45}H_{45}N_3O_6$: C 74.67, H 6.27, N 5.80; found: C 74.71, H 6.32, N 5.83.

3,3′,3″-(Benzene-1,3,5-triyl)tris(ethyne-1,2-diyl)trianiline (**17**). TFA (1 ml) was added at 0° to a soln. of **16** in CH_2Cl_2 (9 ml), and the mixture was stirred at 0° for 1 h. Evaporation *in vacuo* provided a residue, which was taken up in 1M HCl. The acidic aq. soln. was washed with AcOEt (3 ×) and subsequently made basic (pH 14) by addition of solid NaOH. The mixture was extracted with AcOEt (3 ×), and the combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo* to give **17** (57 mg, 98%). Pale-yellow solid. M.p. 152.5°. IR (KBr): 3411*s*, 3324*m*, 3211*w*, 3044*w*, 2744*w*, 2611*w*, 2355*w*, 2333*w*, 2215*m*, 1721*m*, 1599*s*, 1489*m*, 1466*m*, 1216*m*, 1165*m*, 994*m*, 860*s*, 732*s*. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 7.61 (*s*, 3 H); 7.05 (*dd*, *J* = 7.8, 7.8, 3 H); 6.58–6.76 (*m*, 9 H); 5.29

(br. *s*, 6 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 147.21; 131.75; 127.63; 122.29; 120.26; 117.44; 114.55; 113.37; 90.11; 84.39. HR-MALDI-MS: 423.172 (100, M^+, $C_{30}H_{21}N_3^+$; calc. 423.173).

*Tri-(*tert*-butyl)* N,N′,N″*-(Benzene-1,3,5-triyl)tris{(*S*)-[(ethyne-1,2-diyl)-(1,3-phenylene)iminocarbonyl](2-methylpropyl)methylene}tricarbamate* ((*S*,*S*,*S*)-**18**). A soln. of **17** (600 mg, 1.42 mmol), *N*-Boc-L-Leu (645 mg, 2.79 mmol), DMAP (30 mg, 0.24 mmol), and EDC · HCl (760 mg, 3.96 mmol) in dry DMF (50 ml) was stirred for 24 h at 0°. Additional *N*-Boc-L-Leu (645 mg, 2.79 mmol) and EDC · HCl (760 mg, 3.96 mmol) were added, and stirring was continued at 0° for 24 h. After repeating once more this addition and stirring for 24 h, the mixture was evaporated *in vacuo*, and the residue was taken up in CH_2Cl_2. The org. phase was washed with 1M HCl (3×), sat. aq. $NaHCO_3$ soln. (3×), and dried ($MgSO_4$). Evaporation *in vacuo* and FC (SiO_2; CH_2Cl_2/AcOEt 4:1) afforded (*S*,*S*,*S*)-**18** (772 mg, 51%). M.p. 176°. $[\alpha]_D^{23} = +71.8$ ($c = 1$, $CHCl_3$). IR (KBr): 3310 (br.), 2957*m*, 1669*s*, 1607*m*, 1584*m*, 1551*w*, 1367*m*, 1250*m*, 1166*s*, 1122*w*, 1047*w*, 876*m*, 788*m*, 683*m*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 10.08 (*s*, 3 H); 7.93 (*s*, 3 H); 7.77 (*s*, 3 H); 7.58 (*d*, $J = 7.8$, 3 H); 7.38 (*dd*, $J = 7.8$, 7.8, 3 H); 7.28 (*d*, $J = 7.8$, 3 H); 7.04 (*d*, $J = 7.7$, 3 H); 4.14–4.11 (*m*, 3 H); 1.66–1.33 (*m*, 3 H); 1.57–1.55 (*m*, 3 H); 1.48–1.42 (*m*, 3 H); 1.37 (*s*, 27 H); 0.89 (*t*, $J = 4.8$, 18 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 172.1; 155.4; 142.7; 139.2; 133.8; 129.3; 126.4; 124.3; 123.6; 121.9; 121.8; 120.1; 90.7; 87.1; 78.0; 53.6; 28.1; 24.3; 22.8; 21.5. HR-MALDI-MS: 1085.573 (100, $[M + Na]^+$, $C_{63}H_{78}N_6O_9Na^+$; calc. 1085.573). Anal. calc. for $C_{63}H_{78}N_6O_9$: C 71.16, H 7.39, N 7.09; found: C 71.24, H 7.53, N 7.73.

*(5*S*,17*S*,24*S*)-5,17,24-Triisobutyl-3,6,16,19,22,25-hexaaza-1,11(1,3,5),2,8,14,20,21,27(1,3)-octabenzenabicyclo[9.9.9]nonacosaphane-9,12,28-triyne-4,7,15,18,23,26-hexaone* ((*S*,*S*,*S*)-**2**). A soln. of (*S*,*S*,*S*)-**8** (1.486 mg, 1.51 mmol) in CH_2Cl_2/TFA 1:1 (10 ml) was stirred for 3 h under Ar. Evaporation *in vacuo* provided a residue, which was taken up in EtOH, and the soln. was again evaporated to give (*S*,*S*,*S*)-**6**, which was dried at 10^{-2} Torr. In parallel, **14** (0.760 g, 1.51 mmol) was suspended in $SOCl_2$, and the mixture was heated to reflux for 24 h. Excess $SOCl_2$ was removed by distillation, and crude **9** was dried at 10^{-2} Torr. A soln. of **9** in THF (20 ml) and a soln. of (*S*,*S*,*S*)-**6** in THF (20 ml) containing Et_3N (1.8 ml, 13.5 mmol) were added synchronously over 8 h *via* syringe pump to THF (1.5 l) containing Et_3N (1.8 ml, 13.5 mmol). The mixture was stirred for 3 d at r.t., and the solvent was evaporated *in vacuo*. FC (SiO_2; CH_2Cl_2/AcOEt 2:1), followed by prep. GPC and multiple FC (10 × SiO_2, CH_2Cl_2/AcOEt 4:1) yielded (*S*,*S*,*S*)-**2** (*ca.* 85 mg, 5%). Colorless powder. M.p. > 300°. R_f (SiO_2; CH_2Cl_2/AcOEt 4:1) 0.45. t_R (GPC): 17.86 min. $[\alpha]_D^{23} = -153$ ($c = 0.1$, THF). IR (KBr): 2410 (br.), 2955*m*, 2364*w*, 2336*w*, 1653*s*, 1531*m*, 1397*m*, 1300*w*, 1166*w*, 1090*w*, 877*w*, 787*w*, 696*w*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 10.17 (*s*, 3 H); 8.68 (*d*, $J = 8.5$, 3 H); 8.13 (*s*, 3 H); 7.82 (*s*, 3 H); 7.78 (*d*, $J = 7.8$, 3 H); 7.68 (*s*, 3 H); 7.65 (*d*, $J = 7.7$, 3 H); 7.57 (*s*, 3 H); 7.51 (*dd*, $J = 7.7$, 7.7, 3 H); 7.46 (*m*, 3 H); 7.41 (*m*, 6 H); 4.80 (*m*, 3 H); 1.72–1.58 (*m*, 9 H); 0.94 (*s*, 18 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 170.76; 166.12; 142.13; 141.18; 139.52; 135.50; 134.31; 132.85; 131.27; 129.36; 129.17; 128.53; 125.12; 123.35; 122.66; 121.46; 118.75; 118.33; 90.06; 87.79; 52.92; 24.57; 22.78; 22.01. HR-MALDI-MS; 1169.493 (100, $[M + Na]^+$, $C_{75}H_{66}N_6O_6Na^+$; calc. 1169.494).

*(5*S*,17*S*,24*S*)-5,17,24-Triisobutyl-4,7,15,18,23,26-hexaaza-1,11(1,3,5),2,8,14,20,21,27(1,3)-octabenzenabicyclo[9.9.9]nonacosaphane-9,12,28-triyne-3,6,16,19,22,25-hexaone* ((*S*,*S*,*S*)-**3**). A soln. of (*S*,*S*,*S*)-**18** (809 mg, 0.761 mmol) in CH_2Cl_2/TFA 1:1 (10 ml) was stirred for 3 h at r.t. under Ar. After evaporation *in vacuo*, EtOH was added, the solvent was evaporated again, and the resulting crude (*S*,*S*,*S*)-**10** was dried at 10^{-2} Torr. In parallel, **7** (0.332 g, 0.761 mmol) was suspended in $SOCl_2$ (10 ml), and the mixture was heated to reflux for 24 h. After evaporation of excess $SOCl_2$, crude **5** was dried at 10^{-2} Torr. A soln. of **5** in THF (20 ml) and a soln. of (*S*,*S*,*S*)-**10** in THF (20 ml) containing Et_3N (0.9 ml, 6.8 mmol) were added synchronously over 8 h *via* syringe pump to THF (750 ml) containing Et_3N (0.9 ml, 6.8 mmol). After stirring for 3 d at r.t., the mixture was filtered over *Celite* and evaporated *in vacuo*. FC (SiO_2; CH_2Cl_2/AcOEt 2:1), followed by GPC and multiple FC (5 × SiO_2; CH_2Cl_2/AcOEt 4:1), provided (*S*,*S*,*S*)-**3** (87 mg, 10%). Colorless powder. M.p. > 300°. R_f (SiO_2; CH_2Cl_2/AcOEt 4:1) 0.76. t_R (GPC) 17.64 min. $[\alpha]_D^{23} = -90$ ($c = 0.1$, THF). IR (KBr): 3312 (br.), 2955*m*, 2212*w*, 1675*s*, 1604*s*, 1581*s*, 1526*s*, 1432*w*, 1401*m*, 1303*w*, 1247*w*, 1169*w*, 1082*w*, 995*w*, 878*m*, 786*m*, 749*m*, 684*m*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 10.21 (*s*, 3 H); 8.87 (*d*, $J = 7.8$, 3 H); 8.14 (*s*, 3 H); 8.11 (*s*, 3 H); 7.91 (*s*, 3 H); 7.89 (*d*, $J = 7.6$, 6 H); 7.60 (*dd*, $J = 7.6$, 7.6, 3 H); 7.53 (*s*, 3 H); 7.34 (*dd*, $J = 7.8$, 7.8, 3 H); 7.22 (*d*, $J = 7.2$, 3 H); 7.14 (*d*, $J = 7.7$, 3 H); 4.62 (*m*, 3 H); 1.79 (*m*, 6 H); 1.59 (*m*, 3 H); 0.95 (*s*, 18 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 171.91; 167.37; 141.95; 140.73; 139.04; 135.09; 134.02; 130.63; 129.34; 129.11; 127.10; 126.40; 125.83; 124.81; 124.55; 123.65; 122.08; 120.16; 91.22; 87.42; 53.02; 24.71; 23.25; 21.29. HR-MALDI-MS: 1169.494 (100, $[M + Na]^+$, $C_{75}H_{66}H_6O_6Na^+$; calc. 1169.494.

*(7*S*,19*S*,30*S*)-7,19,30-Triisobutyl-5,8,18,21,28,31-hexaaza-1,13(1,3,5),4,10,16,22,27,33(1,3)-octabenzenabicyclo[11.11.11]pentatriacontaphane-2,11,14,23,25,34-hexayne-6,9,17,20,29,32-hexaone* ((*S*,*S*,*S*)-**4**). A soln. of (*S*,*S*,*S*)-**18** (700 mg, 0.658 mmol) in CH_2Cl_2/TFA 1:1 (10 ml) was stirred for 3 h at r.t. under Ar. After evaporation *in vacuo*, EtOH was added, the solvent was evaporated again, and the resulting crude (*S*,*S*,*S*)-**10** was

dried at 10^{-2} Torr. In parallel, **14** (335 mg, 0.658 mmol) was suspended in $SOCl_2$ (10 ml), and the mixture was heated to reflux for 24 h. After evaporation of excess $SOCl_2$, crude **9** was dried at 10^{-2} Torr. A soln. of **9** in THF (20 ml) and a soln. of (*S*,*S*,*S*)-**10** in THF (20 ml) containing Et_3N (0.8 ml, 5.9 mmol) were added synchronously over 8 h *via* syringe pump to THF (650 ml) containing Et_3N (0.8 ml, 5.9 mmol). After stirring for 3 d at r.t., the mixture was filtered over *Celite* and evaporated *in vacuo*. FC (SiO_2; CH_2Cl_2/AcOEt 2:1), followed by GPC and multiple FC ($10 \times SiO_2$; CH_2Cl_2/AcOEt 4:1) provided (*S*,*S*,*S*)-**3** (50 mg, 6%). Colorless powder. M.p. $> 260°$. R_f (SiO_2; CH_2Cl_2/AcOEt 4:1) 0.47. t_R (GPC) 17.44 min. $[\alpha]_D^{23} = -14$ ($c = 1$, $CHCl_3$). IR (KBr): 3301 (br.), 2955*m*, 2212*w*, 1645*s*, 1603*s*, 1582*m*, 1527*m*, 1401*m*, 1303*m*, 1166*w*, 1085*w*, 998*w*, 878*m*, 789*m*, 749*w*, 685*m*, 534*m*. ^{1}H-NMR (500 MHz, $(CD_3)_2SO$): 10.20 (*s*, 3 H); 8.73 (*d*, $J = 8.2$, 3 H); 8.14 (*s*, 3 H); 8.05 (*s*, 3 H); 7.82 (*d*, $J = 8.0$, 3 H); 7.75–7.72 (*m*, 6 H); 7.66 (*s*, 3 H); 7.53 (*dd*, $J = 7.8, 7.8$, 3 H); 7.37–7.34 (*m*, 6 H); 7.21 (*d*, $J = 12.0$, 3 H); 4.71 (*m*, 3 H); 1.72–1.58 (*m*, 9 H); 0.94 (*s*, 18 H). HR-MALDI-MS: 1242.493 (100, $[M + Na]^+$, $C_{81}H_{66}N_6O_6Na^+$; calc. 1242.494.

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