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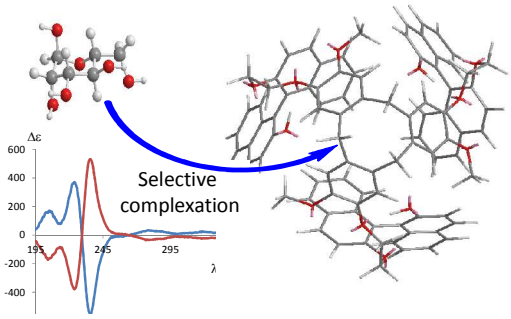
Cyclotriveratrylene-BINOL based host compounds: synthesis, absolute configuration assignment and recognition properties

Sara Lefevre[‡], Alexandre Héloin[‡], Delphine Pitrat[‡], Jean-Christophe Mulatier[‡], Nicolas Vanthuyne[†], Marion Jean[†], Jean-Pierre Dutasta*[,‡], Laure Guy*[,‡] and Alexandre Martinez*[,†]

[†] Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313
13397, Marseille, France
E-mail: alexandre.martinez@centrale-marseille.fr

[‡] Laboratoire de Chimie
École Normale Supérieure de Lyon, CNRS, UCBL
46, Allée d'Italie, F-69364 Lyon, France
Laure.guy@ens-lyon.fr, jean-pierre.dutasta@ens-lyon.fr



Abstract. New host compounds combining a cyclotriveratrylene (CTV) unit and three binaphthol moieties have been synthesized enantiomerically and diastereomerically pure. The use of a chemical correlation allows for the assignment of their absolute configuration. The energy barrier of epimerization was measured, suggesting that no intramolecular hydrogen bonding occurs between the hydroxyl groups of the binaphthols. These open-shell host compounds were then tested in the recognition of carbohydrates; a preferential binding of mannose toward glucose was observed and good diastereoselectivities were reached (up to 1:10). This recognition of sugar derivatives by open-shell CTV-based host compounds is unprecedented and opens up the way for a wider use of this easy accessible class of molecules as chiral sensors.

Introduction

The design of chiral molecular hosts is very attractive, since they can be used for the stereoselective recognition of chiral guest molecules or in asymmetric catalysis.[1-22] Two main approaches have been chosen to obtain chiral receptors: (i) the introduction of chiral units or (ii) the inherent chirality of the host due to its bowl shape scaffold. Among the cage compounds presenting inherent chirality, those based on the cyclotriveratrylene (CTV) unit have recently received a growing interest.[23,24] They are composed of two main classes: the cryptophanes and the hemicryptophanes. Cryptophanes containing two CTV units have found applications in the chiral discrimination of racemic mixtures of small molecules like epoxides or the small halogenoalkane CHFClBr.[25-30] The related hemicryptophanes combine a CTV moiety with another C_3 symmetrical unit and display chiral recognition properties towards molecules of biological interest like neurotransmitters and carbohydrates.[31-36] Although the efficiency and selectivity of these two classes of cage compounds were demonstrated, their quite complex and low yield syntheses raise the question about the potential applications of such sophisticated structures.[34-39] Thus, we decided to investigate the chiral recognition properties of "open-shell" enantiopure CTV units: their synthesis avoids the macrocyclization step, and therefore should be easier and shorter. However, such hosts are expected to be more flexible and less pre-organized than their cage counterparts and thus supposed to be less efficient and selective. Indeed open-shell CTV based host compound have been reported to complex ionic molecules such as choline, but with low binding constant and moderate selectivity; furthermore, the complexation of neutral molecules in solution has been rarely described with this kind of molecules.[40-41] Thus, in order to maintain both a good affinity and selectivity in the recognition processes we decided to balance this lack of rigidity and pre-organization by combining in a unique molecule the axial chirality of a binaphthol unit with the helicity of the CTV. We anticipate that the unprecedented association of these two chiral units will compensate the lower efficiency and selectivity expected from an open structure, when compared to the closed one. Here, we report on the synthesis of open-shell host molecules containing both a CTV unit and three binaphthol moieties. These compounds were obtained enantiomerically and

diastereomerically pure and their absolute configurations were assigned thanks to a chemical correlation. The new host molecules exhibit selective recognition toward carbohydrates.

Results and discussion

Synthesis

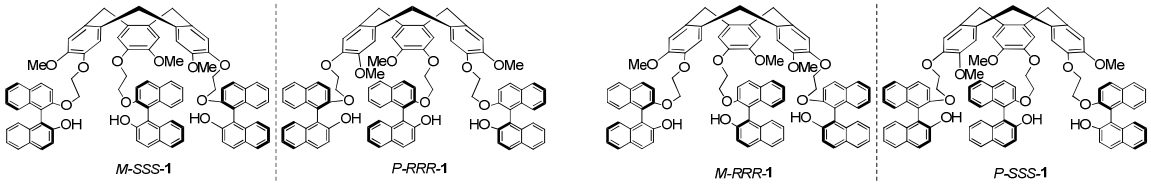
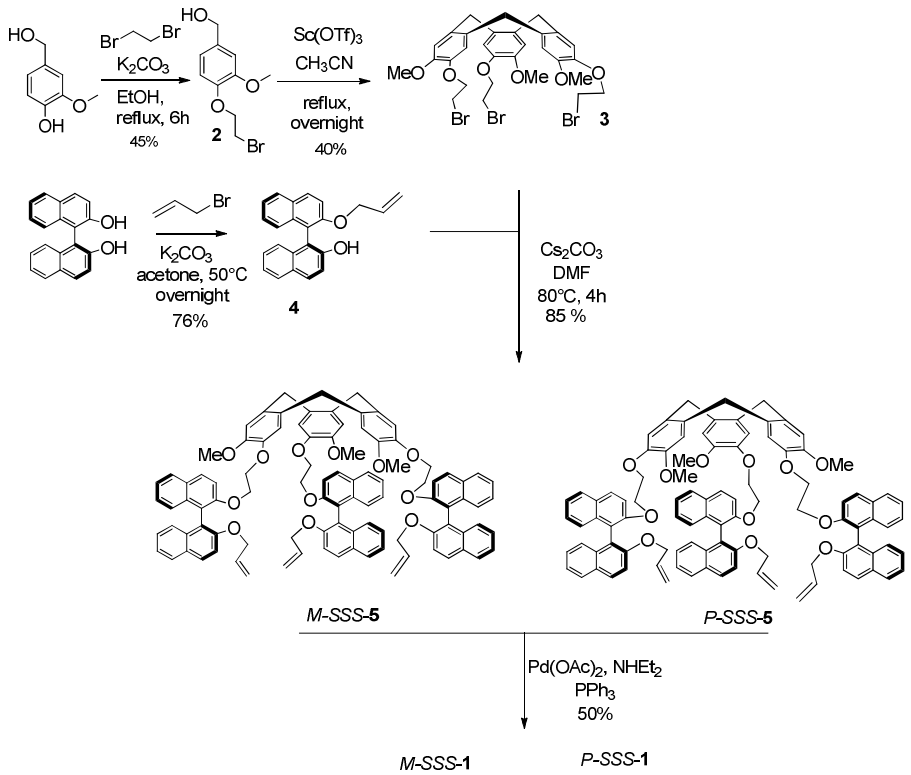


Figure 1. Structure of hemicryptophanes *M*-*SSS*-**1**, *P*-*RRR*-**1**, *M*-*RRR*-**1** and *P*-*SSS*-**1**

The strategy used to synthesize compounds *M*-*SSS*-**1**, *P*-*RRR*-**1**, *M*-*RRR*-**1** and *P*-*SSS*-**1** presented in Figure 1 is based on the CTV precursor **3** (Scheme 1). Compound **3** was prepared according to a previously reported two steps procedure: reaction between vanillic alcohol and dibromoethane affords compound **2** and the subsequent cyclization with scandium triflate in CH_3CN gives CTV *rac*-**3** in 18 % overall yield.[42] Mono-protection of the enantiopure *S*-binaphthol by an allyl group provides compound *S*-**4**, which then reacts with CTV *rac*-**3** to give a mixture of the two diastereomers *M*-*SSS*-**5** and *P*-*SSS*-**5** (the two stereoisomers *M*-*RRR*-**5**, *P*-*RRR*-**5**, were similarly obtained starting from *R*-binaphthol). Their separation reveals difficult and we were not able to isolate stereoisomerically pure compounds. Thus we decided to first deprotect the allyl group using triphenylphosphine and palladium acetate, and then to separate the resulting diastereomers *M*-*SSS*-**1** and *P*-*SSS*-**1** (Scheme 1). This strategy turned out to be successful, leading to an easier separation of the two diastereomers by column chromatography on silica gel (ΔR_f = 0.2) and providing hundreds of milligrams of each diastereomers. Similarly, the *M*-*RRR*-**5** and *P*-*RRR*-**5** isomers were deprotected and subsequent separation by column chromatography afforded the two other diasteromers *M*-*RRR*-**1** and *P*-*RRR*-**1**. The four isomers were thus obtained in five steps, starting from the commercially available vanillyl alcohol with an overall yield of 3% each.



Scheme 1. Synthesis of enantiopure hosts *M*-*SSS*-**1** and *P*-*SSS*-**1**.

The ^{1}H NMR spectra of *M*-*RRR*-**1** and *P*-*RRR*-**1** in $CHCl_3$ indicate that these molecules are on average of C_3 symmetry. They display the expected signals for the CTV unit (Figure 2): two singlets for the aromatic protons, and the characteristic AB system for the $ArCH_2$ bridges. The aromatic protons of the binaphthol units appear as a complex pattern and the OH protons give a singlet between 5.5 and 6.0 ppm.

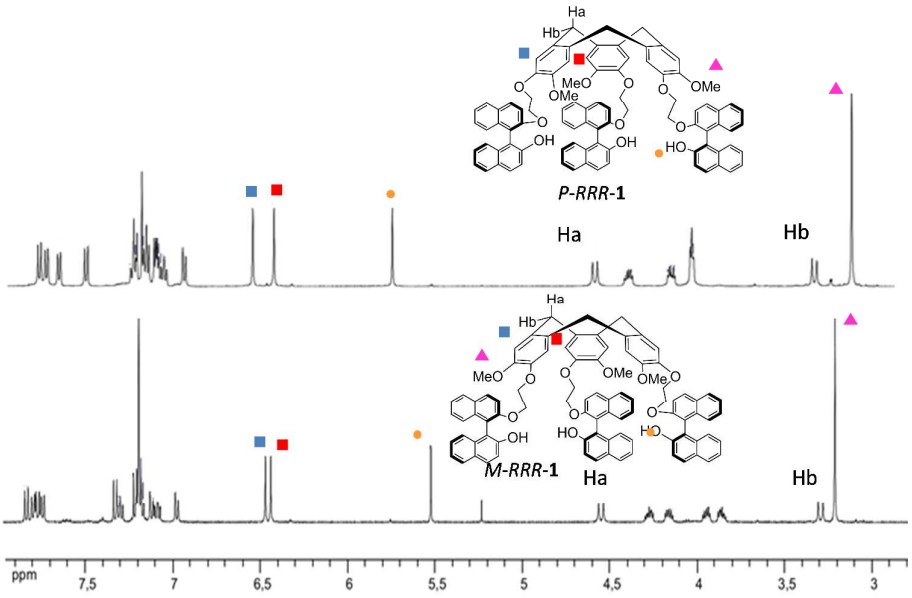


Figure 2. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of *P-RRR*-**1** and *M-RRR*-**1**.

Assignment of the absolute configuration

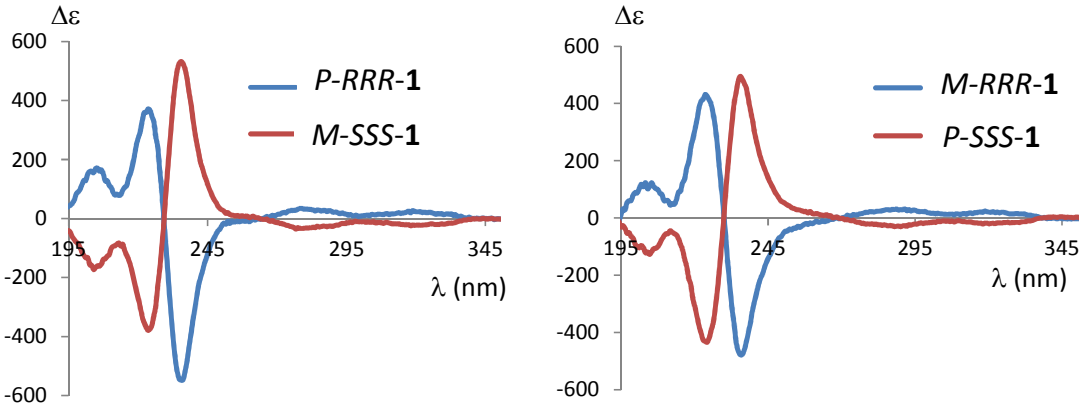
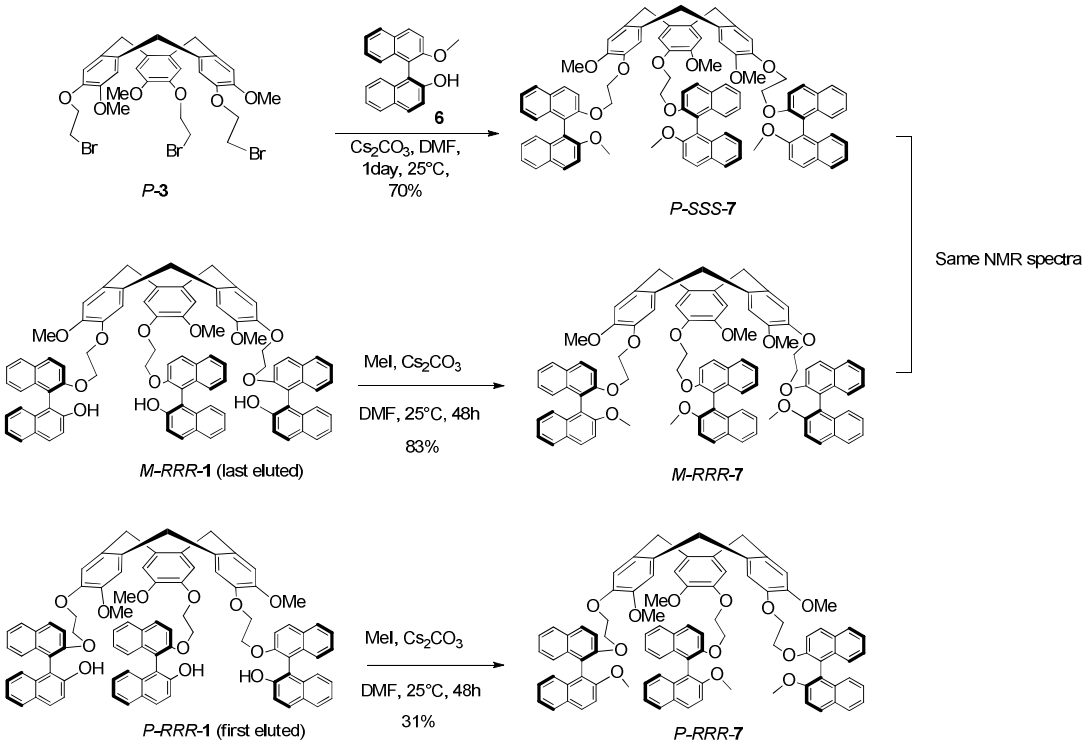


Figure 3. Experimental ECD spectra (CH_3CN, 298 K, c = 2.10^{-6} mol.L^{-1}) of the stereoisomers of **1** (left: first eluted compounds; right: second eluted compounds.

Electronic circular dichroism (ECD) spectra of the four enantiopure receptors were recorded in CH_3CN at 298 K (Figure 3). Each spectrum presents a similar behaviour that consists of one main exciton pattern centred on 230 nm. The absolute configurations of hemicryptophanes are usually determined by comparing the sign of the bands of the experimental ECD spectrum around the $^{1}L_A$

transition (240 nm) with those of the calculated ECD spectrum.[43] However, in compound **1** the signal of the CTV unit is fully hidden by that related to the three binaphthol units. Indeed, *M*-*SSS*-**1** and *P*-*SSS*-**1** diastereomers exhibit almost the same ECD spectrum. The overlap of the signals of these two units and the much stronger intensity of the signal induced by the binaphthol moieties, prompted us to investigate another method for the assignment of the absolute configuration. We decided to focus on the use of chemical correlation to determine unambiguously the absolute configuration of these new compounds. Thus, CTV *rac*-**3** was resolved using chiral HPLC, according to our previous published procedure.[44] The ECD spectra of the two enantiomers were recorded in CH_3CN at 293 K allowing the assignment of the absolute configuration of *P*-**3** (first eluted) and *M*-**3** (last eluted). Then each following steps of the synthesis of the open cages has to be performed at low temperature with reaction time no longer than two days. Indeed, the energy barrier for racemization of **3** is around 114-115 $kJ.mol^{-1}$, which corresponds to a half-life time of 6 months at 293 K. Therefore, the deprotection step of the allyl groups of *M*-*SSS*-**5** and *P*-*SSS*-**5**, which required heating at high temperature (80°C) for one night should be avoided, and a new procedure to access to the isomers of **1** has been developed (Scheme 2). Enantiopure *M*-**3** or *P*-**3** was first reacted with compound *S*-**6** at room temperature for two days, providing enantiomerically and diastereomerically pure *M*-*SSS*-**7** or *P*-*SSS*-**7.** In each case, the NMR spectrum of the crude product shows only one set of signals, demonstrating that the inversion of the stereochemistry of the CTV unit, which should lead to the diastereomer *P*-*SSS*-**7** (respectively *M*-*SSS*-**7**), can be neglected during this step. In parallel, reaction between *M*-*SSS*-**1** or *P*-*SSS*-**1** (Scheme 1) and iodomethane was performed in DMF at room temperature, affording enantiomerically and diastereomerically pure *M*-*SSS*-**7** or *P*-*SSS*-**7**, respectively. Again, no isomerization of the CTV was observed. Thus, compounds *M*-*SSS*-**7** and *P*-*SSS*-**7** were obtained by two different pathways, allowing the assignment of the absolute configuration of *M*-*SSS*-**1** (first eluted) or *P*-*SSS*-**1** (last eluted) by a simple comparison of the NMR spectra. This unique chemical correlation also allows the direct determination of the absolute configuration of *M*-*RRR*-**1** (last eluted) and *P*-*RRR*-**1** (first eluted).



Scheme 2. Synthetic pathway allowing the determination of the absolute configuration of the stereoisomers of **1**.

Energy barrier

We then wondered if the OH groups of the binaphthol units in host **1** are connected together by intramolecular hydrogen bonding - therefore closing the cavity thanks to these interactions - or if this host presents an open concave cavity. To address this issue, we decided to compare the energy barriers of racemization of *M-SSS*-**1** or *P-SSS*-**1** with those of *M-SSS*-**7** or *P-SSS*-**7**, which bear methoxy groups instead of OH groups, in two different solvents (Table 1). If intramolecular hydrogen bonding is occurring in *M-SSS*-**1** or *P-SSS*-**1**, hence (i) a much higher energy barrier of racemization are expected for *M-SSS*-**1** or *P-SSS*-**1** than for *M-SSS*-**7** or *P-SSS*-**7** and (ii) the effect should be less pronounced in a polar solvent (DMSO), which should be able to break such hydrogen bonding, than in an apolar

solvent (toluene). The energy barriers for stereoconversion were determined from ^{1}H NMR experiments: diastereomerically pure samples of **1** or **7** were dissolved in DMSO-d_6 or toluene-d_8, and equilibration was monitored by ^{1}H NMR spectroscopy: the changes in concentrations of the two diastereomers with time, allowed the measurement of the rate constants of epimerization which then gave access to the energy barriers (more details can be found in the supporting information). Similar values, also comparable to the energy barrier measured for compound **3**, were obtained for both compounds and no solvent effect was evidenced, suggesting that no intramolecular hydrogen bonding between the OH groups takes place in solution (Table 1). Interestingly, it appears that the diastereomers *M*-*SSS*-**1** and *P*-*SSS*-**1** are slightly more stable than their epimer counterparts, with a K (353K) of 1.4 and 1.6 in DMSO-d_6 and toluene-d_8 respectively.

Table 1. Energy barriers at 80°C for the epimerization process of **1** and **7**.

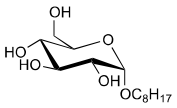
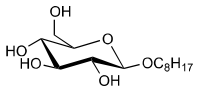
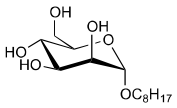
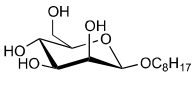
	Energy barrier (kJ.mol^{-1})	
	DMSO	Toluene
M-*SSS*-**1**/*P*-*RRR*-**1**	114.7	112.0
M-*RRR*-**1**/*P*-*SSS*-**1**	113.7	110.7
M-*SSS*-**7**/*P*-*RRR*-**7**	115.1	110.8
M-*RRR*-**7**/*P*-*SSS*-**7**	114.7	110.2

Recognition properties

The free OH groups of the binaphthol units may be of prime importance for the recognition of guest molecules capable of interacting through H-bond. Herein, we investigate the ability of these hosts to discriminate closely related carbohydrate guests.[45-46] The two *n*-octylpyranoside anomers of glucose (OctαGlc and OctβGlc) and mannose (OctαMan and OctβMan) were chosen as guest molecules (Table 2). Measurement of the binding constants was performed thanks to ^{1}H NMR titration experiments in $CDCl_3$ at 298 K. In all cases only one set of signals was observed for the complex and for the free

receptor, showing that host-guest exchange is fast on the NMR time scale. Since a Job's plot experiment performed with *M-RRR*-**1** and OctαMan evidences a 1:1 stoichiometry, the same stoichiometry is then assumed for all the other complexes (Figure S-1 in the SI). Complexation induced shifts of the OH groups of the host were plotted as a function of the guest/host ratio and these curves were fitted with the HypNMR2008 software[47] using a 1:1 model (see Figure S-2 in the SI), and allowing the determination of the binding constants (Table 2). Interestingly, the aromatic protons of the binaphthol units also display significant shift during the titration experiment suggesting that these units play an important role in the recognition process.

Table 2. Binding constants *K*a (M^{-1}) for the 1:1 complexes formed between the different isomers of host **1** and the carbohydrate guests.[a]

Guest	 OctαGlc	 OctβGlc	 OctαMan	 OctβMan
P-RRR-**1**	177	359	616	204
M-RRR-**1**	122	457	1174	375
M-SSS-**1**	161	403	393	288
P-SSS-**1**	98	334	749	197

[a] *K*a determined by fitting ^{1}H NMR titration curves ($CDCl_3$, 500 MHz, 298 K) on OH protons with HypNMR2008;[47] estimated error 10%.

These open shell hosts display interesting features when compared to hemicryptophane cage complexes. Firstly they show binding constants in the same range of magnitude as hemicryptophane cage complexes (up to 10^3 M^{-1}, Table 2). Secondly, for a given carbohydrate guest molecule, some previously reported hemicryptophanes showed almost identical binding constants whatever its stereochemistry, while host **1** exhibits association constants that depend on the configuration of its different components.[36] For instance, with OctαMan, *M-RRR*-**1** displays higher binding constants than all its stereoisomer counterparts. Furthermore, another trend slightly differs from that observed with

parent hemicryptophanes: the selectivity towards the different guests follows this order: OctαMan > OctβGlc > OctβMan > OctαGlc. This order is partially consistent with the ability of these carbohydrates to be involved in intermolecular hydrogen bonds emphasizing the crucial role played by this interaction in the recognition process.[48,49] It can also be noticed that self-association of alkyl-glycosides in solution might occurs at the end of the titration experiment, slightly affecting the accuracy of the binding constants.[50a] Further insight into the key role of hydrogen bonding was also provided thanks to the direct comparison of the recognition properties of hosts **1** and **7**. Indeed, no binding between OctαMan and host **7** was observed, demonstrating that once the acidic protons of the host **1** are removed, the association constant dramatically drops. Secondly, depending on the chirality of the CTV, different level of selectivity can be reached. In particular hosts with a *M*-CTV unit, discriminate more efficiently OctαMan from OctαGlc when compared to their *P* counterparts (a 1:10 and 1:3 diastereoselectivity can be obtained with host *M*-*RRR*-**1** and *P*-*RRR*-**1** respectively). Thus these hosts belong to the very limited class of artificial receptors able to recognize selectively mannose and its derivatives versus other glucoses.[50-56]

Conclusion

In conclusion, we have described the synthesis of new enantiopure host compounds based on the combination of CTV and binaphthol units. The assignment of their absolute configuration was realized by chemical correlation. The determination of the energy barrier for the interconversion process in **1** and **7** indicates that this epimerization is slow when compared to the time of a titration experiment. The lack of intramolecular hydrogen bonds between binaphthol moieties, closing the cavity, is in accord with these results and was further evidenced by recognition experiments with carbohydrate guests. Binding constants, similar to that obtained with covalently closed hemicryptophanes were measured, and interesting selectivities were reached. This recognition of sugar molecules by open-shell CTV-based host compounds is unprecedented, paving the way for a new and wider use of such structures as easy accessible and highly selective hosts for chiral recognition.

Experimental section

Methods and Materials.

All reactions were carried out under argon by means of an inert gas/vacuum double manifold and standard Schlenk techniques. Dichloromethane was dried and degassed on a solvent station by passage through an activated alumina column followed by an argon flush. Other solvents were dried prior to use over molecular sieves. ^{1}H and ^{13}C spectra were recorded at 500.1 MHz and 125.7 MHz respectively, and are reported relative to the residual protonated solvent signal (^{1}H, ^{13}C). The HRMS-ESI mass spectra were recorded in positive-ion mode (or negative) on a hybrid quadrupole time-of-flight mass spectrometer with an Electrospray Ionization (ESI) ion source.

Synthesis of *R*-4 and *S*-4.

A solution of *P* (or *M*) binaphthol (20.9 mmol, 1 eq) and K_2CO_3 (27 mmol, 1.3 eq) in 50 mL of acetone was stirred during 1h. Then allyl bromide (23 mmol, 1.1 eq) was added and the mixture was stirred at 50°C overnight. The mixture was filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel using a 30:70 mixture of CH_2Cl_2 and petroleum ether and then a 60:40 mixture of the same solvents as eluent to give a monoprotected binaphthol *P*-**4** (or *M*-**4**) with 76% yield (15.9 mmol). ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz) δ 7.94 (d, 1H, *J* = 8.8 Hz); 7.81-7.83 (m, 2H); 7.78 (d, 1H, *J* = 8.1 Hz); 7.36 (d, 1H, *J* = 8.8 Hz); 7.26-7.31 (m, 2H); 7.19-7.24 (m, 2H); 7.11-7.15 (m, 2H); 7.98 (d, 1H, *J* = 8.1 Hz); 5.64-5.72 (m, 1H); 4.99 (dd, 1H, *J* = 7.5 Hz and 1.4 Hz); 4.85 (s, 1H); 4.44-4.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 298 K, 125.7 MHz) δ 154.9; 151.24; 134.0; 133.8; 133.1; 130.8; 128.8; 129.6; 129.1; 128.2; 128.1; 127.3; 126.3; 125.0; 124.9; 124.3; 123.2; 117.5; 117.2; 116.5; 115.8; 115.1; 70.0. ESI-MS *m/z*: 327.1375 $[M+H]^+$ (calculated 327.1380 for $C_{23}H_{19}O_2$). *R*-**4**: $[\propto]_D^{25}$ = -12.4 (c = 0.109; CH_2Cl_2); S-**4**: $[\propto]_D^{25}$ = +15.3 (c = 0.100; CH_2Cl_2)

Synthesis of *RRR-5* or *SSS*-5.

A solution of *S* (or *R*-**4**) (2.11 mmol, 3 eq), CTV *rac*-**3** (0.705 mmol, 1 eq) and Cs_2CO_3 (803.9 mmol, 3.5 eq) in 10 mL of DMF was stirred overnight at 40°C under argon atmosphere. Then 75 mL of

AcOEt and 100 mL of 10% aqueous NaOH10% was added. The organic layer was separated and the aqueous phase was extracted with AcOEt (2×50 mL). The combined organic layers were washed with aqueous NaOH 10% (2x50 mL), dried over Na_2SO_4 and the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with CH_2Cl_2 then a 95:5 mixture of CH_2Cl_2 and AcOEt solvents as eluent to give *SSS*-**5** (or *RRR*-**5**) as a mixture of two diastereomers *PSSS*-**5** and *MSSS*-**5** with 85% yield (0.602 mmol). ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz), mixtures of the two diastereomers, δ 7.84-7.98 (m, 12H); 7.52 (dd, 3H, J = 9 Hz and 1.5 Hz); 7.36-7.41 (m, 6H); 7.24-7.30 (m, 6H); 7.15-7.19 (m, 9H); 6.50-6.57 (m, 6H); 5.69-5.74 (m, 3H); 4.94-5.02 (m, 6H); 4.59-4.64 (m, 3H); 4.48-4.51 (m, 6H); 4.27-4.34 (m, 6H); 3.88-4.00 (m, 6H); 3.46 and 3.38 (s and s, 9H), 3.29-3.37 (m, 3H). ^{13}C NMR ($CDCl_3$, 298 K, 125.7 MHz), mixtures of the two diastereomers, δ 154.2; 154.1; 154.1; 154.0; 148.3; 148.2; 146.7; 146.6; 134.1; 134.0; 134.0; 133.7; 133.6; 132.6; 132.2; 131.7; 129.6; 129.4; 129.4; 129.3; 129.3; 129.2; 129.1; 127.9; 127.8; 126.3; 126.3; 126.2; 125.6; 125.5; 125.4; 125.3; 123.8; 123.7; 123.6; 121.0; 120.9; 120.3; 120.1; 116.5; 116.5; 116.4; 116.4; 116.3; 116.1; 115.8; 115.7; 113.9; 133.7; 70.0; 68.2; 68.1; 67.8; 60.4; 56.1; 55.9; 53.1; 44.3; 36.2; 36.2. ESI-MS *m/z*: 1465.6015 $[M+H]^+$ (calculated 1465.6036 for $C_{99}H_{85}O_{12}$). *RRR*-**5**: $[\propto]_D^{25}$ = +26.4 (c = 0.074; CH_2Cl_2); *SSS*-**5**: $[\propto]_D^{25}$ = -29.1 (c = 0.079; CH_2Cl_2).

Synthesis of *P-RRR*-1, *M-SSS*-1, *P-SSS*-1 and *M-RRR*-1

R-**5** (or *S*-**5**) (0.546 mmol, 1 eq), $Pd(OAc)_2$ (0.033 mmol, 0.06 eq), PPh_3 (0.11 mmol, 0.2 eq) and $NHEt_2$ (25.1 mmol, 46 eq) 2 mL of H_2O and 8 mL of THF was stirred at 80°C under argon atmosphere during 4h. Then the mixture was cooled at room temperature and solvents was removed under vacuum. 10 mL of AcOEt was added and removed under vacuum, twice. 10 mL of AcOEt and 10 mL of H_2O was added. The organic layer was separated and the aqueous phase was extracted with AcOEt (2×10 mL). The combined organic layers were dried over Na_2SO_4 and the organic solvent was removed under vacuum. The solid was washed with Et_2O. The 2 diastereomers was separated by column chromatography on silica gel with a 95:5 mixture of CH_2Cl_2/EtOAc solvents as eluent to give *P-RRR*-**1** (or *P-SSS*-**1**) with 25% yield (0.137 mmol) and *M-RRR*-**1** (or *M-SSS*-**1**) with 24% (0.133 mmol) yield.

P-RRR-**1** / *M-SSS*-**1:** ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz) δ 7.77 (d, 3H, *J* = 8.9 Hz); 7.73 (d, 3H, *J* = 8.1 Hz); 7.66 (d, 3H, *J* = 8.3 Hz); 7.50 (d, 3H, *J* = 9.1 Hz); 7.21-7.24 (m, 6H); 7.14-7.17 (m, 6H); 7.08-7.11 (m, 6H); 7.04-7.07 (m, 3H); 6.94 (d, 3H, *J* = 8.3 Hz); 6.54 (s, 3H); 6.42 (s, 3H); 5.74 (s, 3H); 4.57 (d, 3H, *J* = 13.7 Hz); 4.35-4.40 (m, 3H); 4.11-4.15 (m, 3H); 4.00-4.02 (m, 6H); 3.30 (d, 3H, J = 13.7 Hz); 3.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 298 K, 125.7 MHz) δ 155.2; 151.6; 148.0; 145.8; 134.0; 133.9; 132.9; 131.9; 130.4; 129.9; 129.6; 129.0; 128.1; 128.0; 127.0; 126.3; 125.2; 124.8; 124.3; 123.1; 118.1; 117.8; 116.7; 115.7; 115.4; 113.4; 68.3; 67.4; 55.4; 36.3. ESI-MS *m/z*: 1345.5073 $[M+H]^+$ (calculated 1345.5097 for $C_{90}H_{73}O_{12}$). *P-RRR*-**1**: $[\propto]_D^{25}$ = +109.4 (c = 0.103; CH_2Cl_2); *M-SSS*-**1**: $[\propto]_D^{25}$ = -104.8 (c = 0.111; CH_2Cl_2)

P-SSS-**1** / *M-RRR*-**1:** ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz) δ 7.83 (d, 3H, *J* = 9.1 Hz); 7.79 (d, 3H, *J* = 8.1 Hz); 7.76 (d, 3H, *J* = 8.9 Hz); 7.74 (d, 3H, *J* = 8.1 Hz); 7.32 (d, 3H, *J* = 9.1 Hz); 7.27-7.29 (m, 3H); 7.21 (d, 3H, *J* = 8.9 Hz); 7.15-7.17 (m, 3H); 7.11 (d, 3H, *J* = 8.3 Hz); 7.06-7.09 (m, 3H); 6.97 (d, 3H, *J* = 8.1 Hz); 6.46 (s, 3H); 6.43 (s, 3H); 5.51 (s, 3H); 4.54 (d, 3H, *J* = 13.7 Hz); 4.24-4.29 (m, 3H); 4.13-4.17 (m, 3H); 3.92-3.96 (m, 3H); 3.83-3.87 (m, 3H); 3.29 (d, 3H, *J* = 13.7 Hz); 3.20 (s, 9H). ^{13}C NMR (CDCl3, 298 K, 125.7 MHz) δ 155.3; 151.6; 148.2; 146.1; 134.0; 133.8; 132.7; 131.7; 130.6; 129.9; 129.7; 129.0; 128.1; 128.0; 127.0; 126.3; 125.2; 124.9; 124.4; 123.1; 117.9; 117.7; 116.7; 115.8; 115.3; 113.6; 68.2; 68.0; 55.7; 36.3. ESI-MS *m/z*: 1345.5073 $[M+H]^+$ (calculated 1345.5097 for $C_{90}H_{73}O_{12}$). *P-SSS*-**1**: $[\propto]_D^{25}$ = -121.7 (c = 0.105; CH_2Cl_2); *M-RRR*-**1**: $[\propto]_D^{25}$ = +121.0 (c = 0.099; CH_2Cl_2)

Synthesis of *P-RRR*-7, *M-SSS*-7, *P-SSS*-7 and *M-RRR*-7

A solution of *P-RRR*-**1** (37.2 μmol, 1 eq), MeI (743 μmol, 60 eq) and Cs_2CO_3 (148 μmol, 4 eq) in 4 mL of DMF was stirred 2 days at 25°C under argon atmosphere. Then 15 mL of AcOEt and 15 mL of H_2O was added. The organic layer was separated and the aqueous phase was extracted with AcOEt (2×10 mL). The combined organic layers were washed with H_2O (2x10 mL), dried over Na_2SO_4 and the organic solvent was removed under vacuum. The crude product was purified by column

chromatography on silica gel with a 98:2 mixture of CH_2Cl_2 and Et_2O solvents as eluent to give *P-PPR*-**7** with 83% yield (31 μmol).

P-RRR-**7** / *M-SSS*-**7**: ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz) δ 7.96 (t, 6H); 7.91 (d, 3H, *J* =8.1 Hz); 7.86 (d, 3H, *J* =8.1 Hz); 7.52 (d, 3H, *J* = 9.1 Hz); 7.40 (d, 3H, *J* = 9.1 Hz); 7.37 (d, 3H, *J* = 7.8 Hz); 7.24-7.30 (m, 6H); 7.12-7.19 (m, 9H); 6.55 (s, 3H); 6.47 (s, 3H); 4.61 (d, 3H, *J* = 13.5 Hz); 4.25-4.34 (m, 6H); 3.90-3.99 (m, 6H); 3.70 (s, 9H); 3.35 (s, 9H); 3.30 (d, 3H, *J* = 13.5 Hz). ^{13}C NMR ($CDCl_3$, 298 K, 125.7 MHz) δ 154.9; 154.1; 148.4; 146.5; 134.1; 134.0; 132.7; 131.6; 129.7; 129.4; 129.3; 129.0; 128.0; 127.9; 126.4; 126.3; 125.5; 125.2; 123.9; 123.4; 121.1; 119.2; 116.6; 116.4; 113.8; 113.5; 68.3; 68.2; 56.5; 55.8; 36.1. ESI-MS *m/z*: 1387.5544 $[M+H]^+$ (calculated 1387.5566 for $C_{93}H_{79}O_{12}$)

P-SSS-**7** / *M-RRR*-**7**: ^{1}H NMR ($CDCl_3$, 298 K, 500.1 MHz) δ 7.86 (d, 3H, *J* = 5.4 Hz); 7.85 (d, 3H, *J* = 5.4 Hz); 7.78 (d, 3H, *J* =8.1 Hz); 7.74 (d, 3H, *J* = 8.1 Hz); 7.40 (d, 3H, *J* = 9.1 Hz); 7.31 (d, 3H, *J* = 9.1 Hz); 7.24-7.27 (m, 3H); 7.11-7.17 (m, 6H); 7.00-7.07 (m, 9H); 6.44 (d, 6H, *J* = 5.1 Hz); 4.52 (d, 3H, *J* = 13.8 Hz); 4.19 (t, 6H); 3.74-3.84 (m, 6H); 3.61 (s, 9H); 3.33 (s, 9H); 3.23 (d, 3H, *J* = 13.8 Hz). ^{13}C NMR ($CDCl_3$, 298 K, 125.7 MHz) δ 154.9; 154.1; 148.3; 146.7; 134.1; 134.0; 132.6; 131.8; 129.7; 129.5; 129.4; 129.1; 128.0; 127.9; 127.8; 126.3; 125.4; 125.3; 123.9; 123.5; 121.1; 119.4; 116.7; 116.0; 114.1; 114.0; 68.4; 68.0; 56.7; 54.1; 36.2. ESI-MS *m/z*: 1387.5544 $[M+H]^+$ (calculated 1387.5566 for $C_{93}H_{79}O_{12}$). *M-RRR*-**7**: $[\alpha]_D^{25}$ = +116 (c = 0.0965; CH_2Cl_2); *P-SSS*-**7**: $[\alpha]_D^{25}$ = -122 (c = 0.105; CH_2Cl_2)

Synthesis of *P-SSS*-7 (second method)

A solution of *P*-**3** (0.14 mmol, 1 eq), *S*-**6** (0.41 mmol, 3 eq) and Cs_2CO_3 (0.48 mmol, 3.5 eq) in 2 mL of DMF was stirred 1 day at 25°C under argon atmosphere. Then 10 mL of AcOEt and 10 mL of aqueous NaOH10% was added. The organic layer was separated and the aqueous phase was extracted with AcOEt (2×10 mL). The combined organic layers were washed with aqueous NaOH 10% (2x10 mL), dried over Na_2SO_4 and the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with a 98:2 mixture of CH_2Cl_2 and Et_2O solvents as

eluent to give *P-SSS*-**7** with 70% yield (0.098 mmol). The characterizations are identical to those obtained with the first method described above.

Complexation of octyl-D-gluco-, and manno-pyranosides by hemicryptophanes 1.

Solutions of hosts (1.0 mM in $CDCl_3$, 500 μL) were titrated in NMR tubes with small aliquots of solutions of guests (20 mM in $CDCl_3$). Complexation induced shifts $\Delta\delta$ of the aromatic protons or the OCH_3 protons of the host were measured after each addition and plotted as a function of the guest/host ratio. The resulting curves were fitted with HypNMR 2008 software, providing the reported binding constants.

Kinetic of epimerization of 1 and 7

Compounds **1** or **7** were heated in toluene or DMSO at 80°C. The evolution of the ratio of the two diastereoisomers was followed by ^{1}H NMMR, allowing the determination of the energy barrier.

AUTHOR INFORMATION

Corresponding Author

E-mail: alexandre.martinez@ens-lyon.fr

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ASSOCIATED CONTENTS

Supporting Information

^{1}H, ^{13}C NMR spectra, CD and mass spectra of compounds **1**, **4**, **5**, **7**; Job plot and titration experiments; kinetic of epimerization.

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