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# Cyclotriveratrylene-BINOL-Based Host Compounds: Synthesis, Absolute Configuration Assignment, and Recognition Properties

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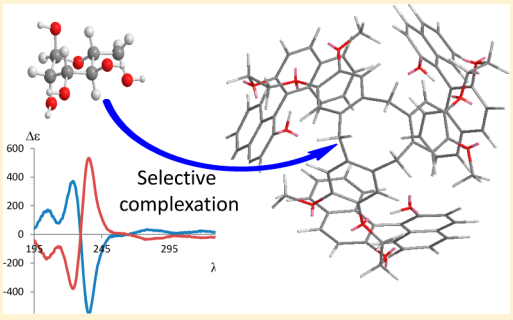
Supporting Information

**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 easily accessible class of molecules as chiral sensors.




## INTRODUCTION

The design of chiral molecular hosts is very attractive because 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-shaped 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 such as 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 toward molecules of biological interest, such as 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 preorganized than their cage counterparts and thus supposed to be less efficient and selective. Indeed open-shell CTV-based host compounds have been reported to complex ionic molecules such as choline but with a low binding constant and moderate selectivity; furthermore, the complexation of neutral molecules in solution has been rarely described with this kind of molecule.[40,41] Thus, in order to maintain both a good affinity and a good selectivity in the recognition processes, we decided to balance this lack of rigidity and preorganization 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 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 due to a chemical correlation. The new host molecules exhibit selective recognition toward carbohydrates.

## RESULTS AND DISCUSSION

**Synthesis.** 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-step 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] Monoprotection 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*-

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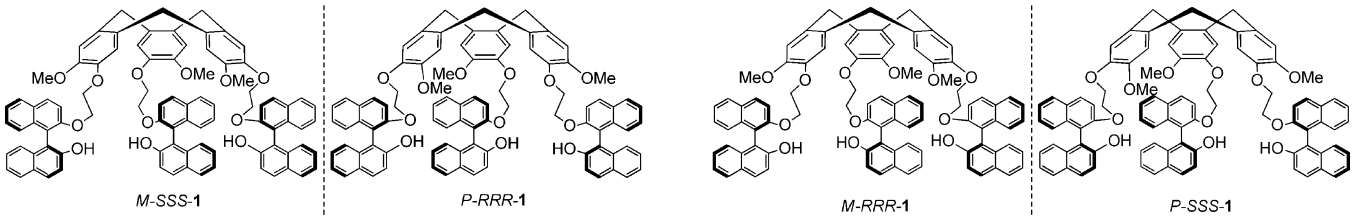
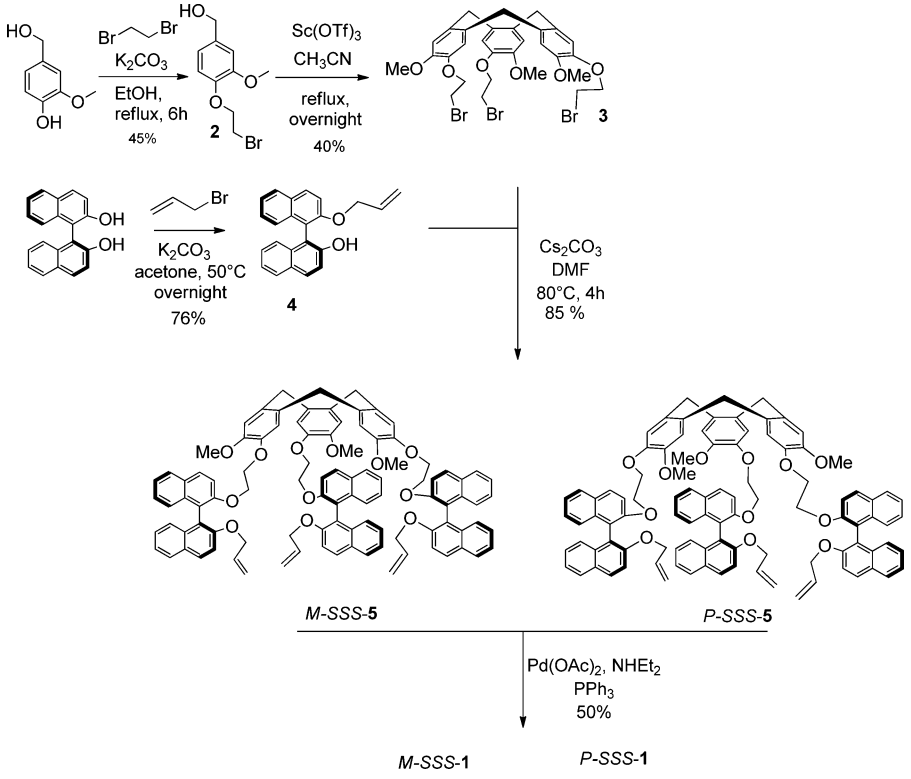



**Figure 1.** Structure of hemicryptophanes *M-SSS*-**1**, *P-RRR*-**1**, *M-RRR*-**1**, and *P-SSS*-**1**.

**Scheme 1. Synthesis of Enantiopure Hosts *M-SSS*-1 and *P-SSS*-1**



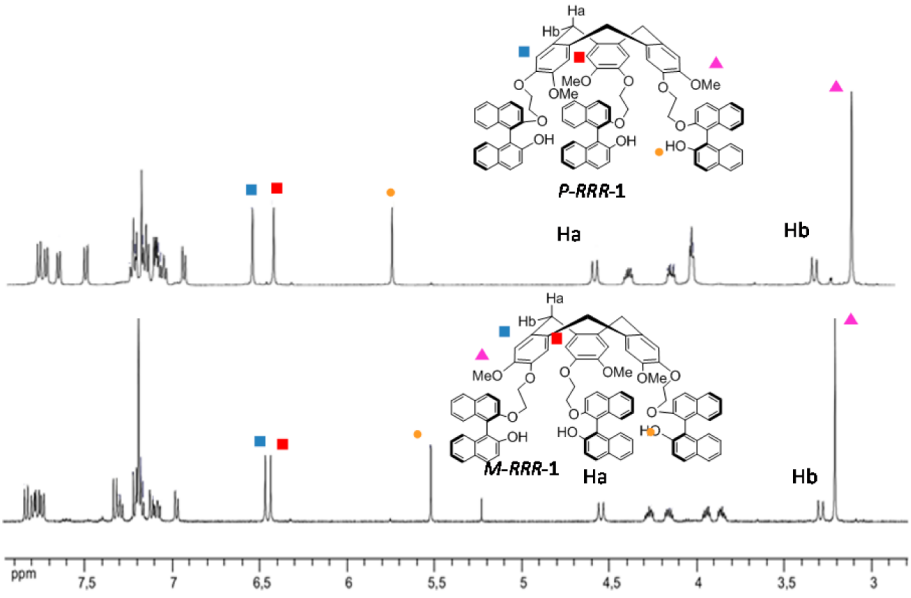




**Figure 2.** $^1$H NMR spectra (500 MHz, $CDCl_3$) of *P-RRR*-**1** and *M-RRR*-**1**.



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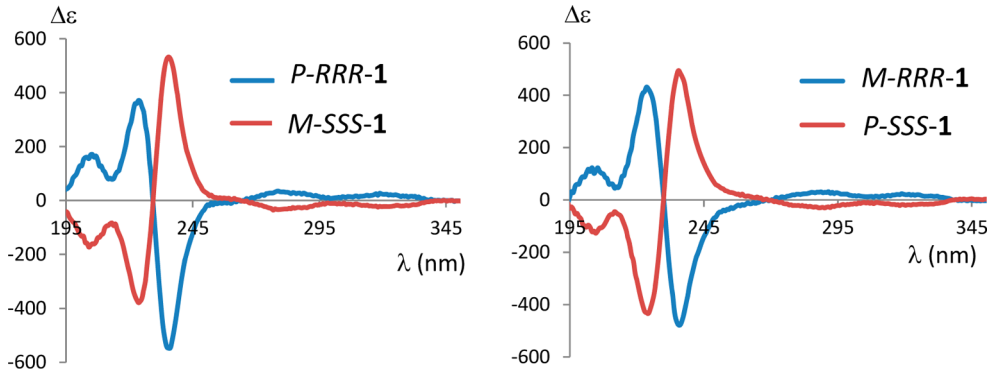
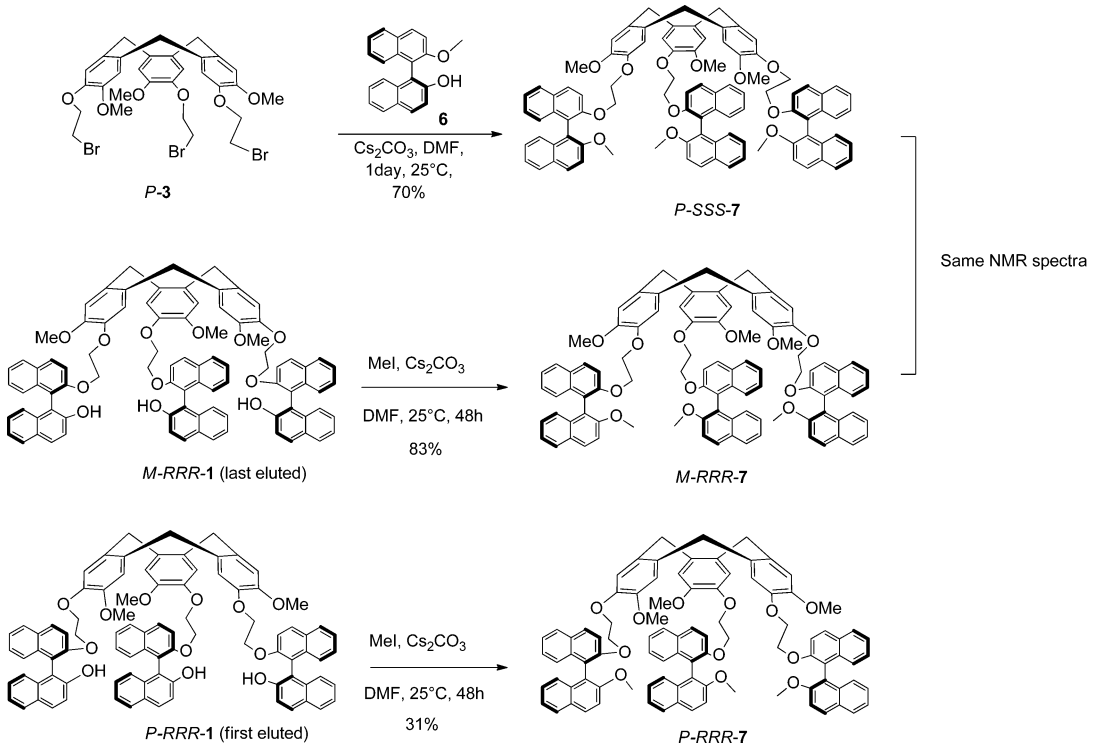



**Figure 3.** Experimental ECD spectra ($CH_3CN$, 298 K, $c = 2 \times 10^{-6}$ mol $L^{-1}$) of the stereoisomers of **1** (left, first eluted compounds; right, second eluted compounds).

**Scheme 2. Synthetic Pathway Allowing the Determination of the Absolute Configuration of the Stereoisomers of 1**




*RRR*-**5** and *P-RRR*-**5** were similarly obtained starting from *R*-binaphthol). Their separation was 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 to then 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 ($\Delta R_f$ = 0.2) and providing hundreds of milligrams of each diastereomer. Similarly, the *M-RRR*-**5** and *P-RRR*-**5** isomers were deprotected, and subsequent separation by column chromatography afforded the two other diastereomers *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.

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.

**Assignment of the Absolute Configuration.** 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 behavior that consists of one main exciton pattern centered at 230 nm. The absolute configurations of hemicryptophanes are usually determined by comparing the sign of the bands of the experimental ECD spectrum around the $^1L_A$ 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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chemical correlation to determine unambiguously the absolute configuration of these new compounds. Thus, CTV *rac*-**3** was resolved using chiral HPLC, according to our previously 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 step of the synthesis of the open cages has to be performed at low temperature, with reaction time no longer than 2 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 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 2 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).

**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 due 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**, (i) a much higher energy barrier of racemization is 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* (353 K) 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 a hydrogen bond. Herein, we investigate the ability of these hosts to discriminate closely related carbohydrate guests.[45,46] The two *n*-octylpyranoside anomers of glucose (Oct*α*Glc and Oct*β*Glc) and mannose (Oct*α*Man and Oct*β*Man) were chosen as guest molecules (Table 2). Measurement of the binding constants was determined by $^1$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 plot experiment performed with *M*-*RRR*-**1** and Oct*α*Man shows a 1:1 stoichiometry, the same stoichiometry is then assumed for all other complexes (Figure S-1 in the Supporting Information). 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 Supporting Information), allowing the determination of the binding constants (Table 2). Interestingly, the aromatic protons of the binaphthol units also display a significant shift during the titration experiment, suggesting that these units play an important role in the recognition process.

These open-shell hosts display interesting features compared to hemicryptophane cage complexes. First, they show binding constants in the same range of magnitude as hemicryptophane cage complexes (up to $10^3$ $M^{-1}$, Table 2). Second, 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 Oct*α*Man, *M*-*RRR*-**1** displays binding constants higher than those of all its stereoisomer counterparts. Furthermore, another trend slightly differs from that observed with parent hemicryptophanes: the selectivity toward the different guests follows the order Oct*α*Man > Oct*β*Glc > Oct*β*Man > Oct*α*Glc. 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 by the direct comparison of the recognition properties of hosts **1** and **7**. Indeed, no binding between Oct*α*Man and host **7** was observed, demonstrating that, once the acidic protons of the host **1** are removed, the association constant dramatically drops. Second, depending on the chirality of the CTV, a different level of selectivity can be reached. In particular, hosts with a *M*-CTV unit discriminate more


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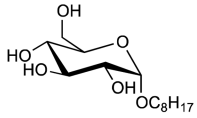
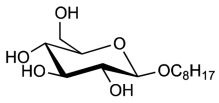
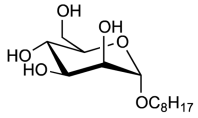
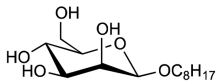
Table 2. Binding Constants $K_a$ ($M^{-1}$) for the 1:1 Complexes Formed between the Different Isomers of Host 1 and the Carbohydrate Guests[a]

| 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 is 10%.

efficiently Oct*α*Man from Oct*α*Glc 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 selectively recognize mannose and its derivatives versus other glucoses.[50−58]

## 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 easily 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 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 equiv) and $K_2CO_3$ (27 mmol, 1.3 equiv) in 50 mL of acetone was stirred for 1 h. Next, allyl bromide (23 mmol, 1.1 equiv) 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) $\delta$ 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 and 1.4 Hz), 4.85 (s, 1H), 4.44−4.51 (m, 2H); $^{13}$C NMR ($CDCl_3$, 298 K, 125.7 MHz) $\delta$ 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 $[M + H]^+$ (calcd 327.1380 for $C_{23}H_{19}O_2$); *R*-**4**, $[\alpha]_D^{25}$ = −12.4 ($c$ = 0.109, $CH_2Cl_2$); *S*-**4** $[\alpha]_D^{25}$ = +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 equiv), CTV *rac*-**3** (0.705 mmol, 1 equiv), and $Cs_2CO_3$ (803.9 mmol, 3.5 equiv) in 10 mL of DMF was stirred overnight at 40 °C under an argon atmosphere. Then, 75 mL of AcOEt and 100 mL of 10% aqueous NaOH were added. The organic layer was separated, and the aqueous phase was extracted with AcOEt (2 × 50 mL). The combined organic layers were washed with 10% aqueous NaOH (2 × 50 mL) and 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 $CH_2Cl_2$ and 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, $\delta$ 7.84−7.98 (m, 12H), 7.52 (dd, 3H, $J$ = 9 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, $\delta$ 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 $[M + H]^+$ (calcd 1465.6036 for $C_{99}H_{85}O_{12}$); *RRR*-**5**, $[\alpha]_D^{25}$ = +26.4 ($c$ = 0.074, $CH_2Cl_2$); *SSS*-**5**, $[\alpha]_D^{25}$ = −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 equiv), $Pd(OAc)_2$ (0.033 mmol, 0.06 equiv), $PPh_3$ (0.11 mmol, 0.2 equiv), $NHEt_2$ (25.1 mmol, 46 equiv), 2 mL of $H_2O$, and 8 mL of THF were stirred at 80 °C under an argon atmosphere for 4 h. Next, the mixture was cooled at room temperature, and solvents were removed under vacuum. Ten milliliters of AcOEt was added and removed under vacuum twice. Ten milliliters of AcOEt and 10 mL of $H_2O$ were added. The organic layer was



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J. Org. Chem. 2016, 81, 3199−3205

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 two diastereomers were 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) $\delta$ 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) $\delta$ 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 $[M + H]^+$ (calcd 1345.5097 for $C_{90}H_{73}O_{12}$); *P-RRR*-**1**, $[\alpha]_D^{25}$ = +109.4 ($c$ = 0.103, $CH_2Cl_2$); *M-SSS*-**1**, $[\alpha]_D^{25}$ = −104.8 ($c$ = 0.111, $CH_2Cl_2$).

*P-SSS-1/M-RRR-1:* $^1$H NMR ($CDCl_3$, 298 K, 500.1 MHz) $\delta$ 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 ($CDCl_3$, 298 K, 125.7 MHz) $\delta$ 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 $[M + H]^+$ (calcd 1345.5097 for $C_{90}H_{73}O_{12}$); *P-SSS*-**1**, $[\alpha]_D^{25}$ = −121.7 ($c$ = 0.105, $CH_2Cl_2$); *M-RRR*-**1**, $[\alpha]_D^{25}$ = +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 $\mu$mol, 1 equiv), MeI (743 $\mu$mol, 60 equiv), and $Cs_2CO_3$ (148 $\mu$mol, 4 equiv) in 4 mL of DMF was stirred for 2 days at 25 °C under an argon atmosphere. Next, 15 mL of AcOEt and 15 mL of $H_2O$ were added. The organic layer was separated, and the aqueous phase was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with $H_2O$ (2 × 10 mL) and 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 $\mu$mol).

*P-RRR-7/M-SSS-7:* $^1$H NMR ($CDCl_3$, 298 K, 500.1 MHz) $\delta$ 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) $\delta$ 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 $[M + H]^+$ (calcd 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) $\delta$ 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) $\delta$ 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 $[M + H]^+$ (calcd 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 equiv), *S*-**6** (0.41 mmol, 3 equiv), and $Cs_2CO_3$ (0.48 mmol, 3.5 equiv) in 2 mL of DMF was stirred for 1 day at 25 °C under an argon atmosphere. Next, 10 mL of AcOEt and 10 mL of 10% aqueous NaOH were added. The organic layer was separated, and the aqueous phase was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with 10% aqueous NaOH (2 × 10 mL) and 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 Mannopyranosides by Hemicryptophanes 1.** Solutions of hosts (1.0 mM in $CDCl_3$, 500 $\mu$L) 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 HypNMR2008 software, providing the reported binding constants.

**Kinetics of Epimerization of 1 and 7.** Compound **1** or **7** was heated in toluene or DMSO at 80 °C. The evolution of the ratio of the two diastereoisomers was followed by $^1$H NMR, allowing the determination of the energy barrier.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00159.

$^1$H and $^{13}$C NMR spectra, CD and mass spectra of compounds **1**, **4**, **5**, and **7**; Job plot and titration experiments; kinetics of epimerization (PDF)

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### Notes

The authors declare no competing financial interest.

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