ChemPubSoc Europe

DOI: 10.1002/chem.201504110

CHEMISTRY
A European Journal
Communication

Click Chemistry

Biologically Active Heteroglycoclusters Constructed on a Pillar[5]arene-Containing [2]Rotaxane Scaffold

Stéphane P. Vincent,*[a] Kevin Buffet,[a] Iwona Nierengarten,[b] Anne Imberty,*[c] and Jean-François Nierengarten*[b]

Abstract: A synthetic approach combining recent concepts for the preparation of multifunctional nanomolecules (click chemistry on multifunctional scaffolds) with supramolecular chemistry (self-assembly to prepare rotaxanes) gave easy access to a large variety of sophisticated [2]rotaxane heteroglycoclusters. Specifically, compounds combining galactose and fucose have been prepared to target the two bacterial lectins (LecA and LecB) from the opportunistic pathogen *Pseudomonas aeruginosa*.

The synthesis of complex multifunctional molecules exhibiting specific properties for applications in materials science or biology is at the forefront of modern synthetic chemistry. The availability of these compounds is, however, a critical aspect for their applicability. For the synthetic chemist, the challenge is often to increase the complexity of the molecular structures without being limited by the synthetic route. In this respect, the use of pre-constructed nanoscaffolds allowing the successive grafting of different molecular entities through the use of efficient orthogonal synthetic strategies is very attractive.[1] Functionalizable scaffolds have been particularly useful for the efficient preparation of new materials for various applications, including liquid–crystalline materials[2] or photo- and electroactive molecular devices.[3] As part of this research, we became interested in the use of pillar[5]arene cores as scaffolds for the preparation of nanomaterials.[4,5] The existing pillar[5]arenes prepared so far have, however, some limitations. Actually, whereas building blocks with 10 identical peripheral groups are conveniently prepared, pillar[5]arenes combining different monomeric moieties are only accessible under statistical conditions.[6] A controlled synthesis appears difficult as cleavage of the Ar–CH_2 bonds occurs under the Friedel–Crafts conditions used for their preparation and scrambling cannot be avoided.[7] In order to overcome this problem, we now propose to take profit of the capability of pillar[5]arenes to form host–guest complexes with alkyl chains to build [2]rotaxane scaffolds.[8] The macrocyclic pilar[5]arene component can carry ten copies of a first functional group and the molecular axis can be substituted with additional functional subunits. The structure of the [2]rotaxane scaffold provides a perfect control of the spatial organization of the different functional subunits as the ten peripheral groups attached on the macrocyclic core generate an equatorial belt, whereas the two stoppers are located at the opposite poles of the ring. As a proof of concept, we have applied this strategy for the construction of heteroglycoclusters.

In order to mimic the multivalent presentation of carbohydrates on glycoprotein or cell surfaces, multivalent glycoconjugates have been built using a large variety of scaffolds.[9] Heteromultivalent glycosystems presenting two or more carbohydrates have also been prepared.[10] Multivalent glycoconjugates can be used as high avidity competitors for blocking the binding of bacterial receptors to glycoconjugates on the cell surface. Among others, major targets of synthetic glycoclusters are the two soluble lectins of the opportunistic pathogen *Pseudomonas aeruginosa*, LecA and LecB,[9a,c,h,10a,b] that are virulent factors responsible for cell adhesion, internalization, and biofilm formation.[11] As part of this research, we report herein [2]rotaxanes[12] combining two different sugar residues, namely galactose and fucose, in order to target simultaneously the two bacterial lectins from *P. aeruginosa* with a single supermolecule.

In order to show that sugar moieties are suitable stoppers for the construction of pillar[5]arene-containing [2]rotaxanes, the preparation of model compound **7** was attempted first (Scheme 1).

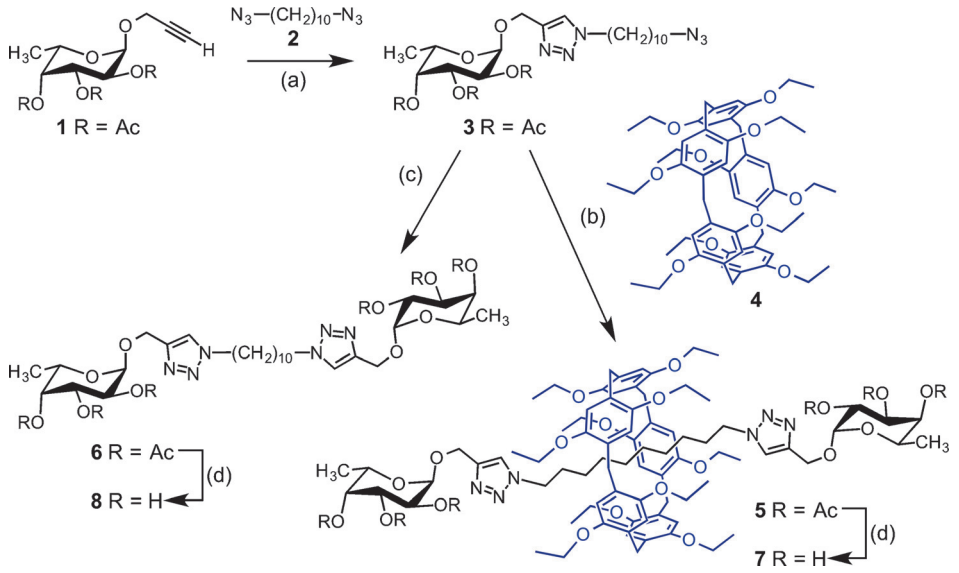
Treatment of bis-azide **2** with alkyne **1** under copper-catalyzed alkyne azide cycloaddition (CuAAC) conditions provided **3** in 75% yield. [2]Rotaxane **5** was then prepared from **1**, **3**, and **4**. The reaction was carried out in $CHCl_3$, a solvent unable to form an inclusion complex with pillar[5]arene **4** thus pre-

[a] *Prof. S. P. Vincent, Dr. K. Buffet*
University of Namur (UNamur), Académie Louvain
Département de Chimie, Laboratoire de Chimie Bio-Organique
rue de Bruxelles 61, 5000 Namur (Belgium)
E-mail: stephane.vincent@unamur.be

[b] *Dr. I. Nierengarten, Dr. J.-F. Nierengarten*
Laboratoire de Chimie des Matériaux Moléculaires
Université de Strasbourg et CNRS (UMR 7509)
Ecole Européenne de Chimie, Polymères et Matériaux (ECPM)
25 rue Becquerel, 67087 Strasbourg Cedex 2 (France)
E-mail: nierengarten@unistra.fr

[c] *Dr. A. Imberty*
CERMAV (UPR5301), CNRS and Université Grenoble Alpes
BP 53, 38041, Grenoble (France)
E-mail: anne.imberty@cermav.cnrs.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201504110.



Scheme 1. a) CuBr·SMe_2, $CHCl_3$, RT (75%); b) **1**, **4** (4 equiv), CuBr·SMe_2, $CHCl_3$, −20 °C to RT (75%); c) **1**, CuBr·SMe_2, $CHCl_3$, RT (62%); d) MeOH, MeONa (from **5**: **7** (85%); from **6**: **8** (84%)).

venting any competition for the binding of reagent **3**. To further favor the threading of reagent **3** and, therefore, the formation of [2]rotaxane **5**, the reaction was carried out at low temperature (−20 °C) and at the highest possible concentration. Moreover, the macrocyclic reagent was used in large excess (4 equiv). Under these conditions, the threading/stoppering process using the CuAAC reaction was efficient. Effectively, the targeted [2]rotaxane (**5**) was thus obtained in 75% yield. Owing to the D_5-symmetry of the pillar[5]arene ring, it is worth noting that compound **5** was obtained as an inseparable 1:1 mixture of two diastereomers differing by the absolute configuration of the macrocyclic component. For comparison purposes, axle **6** was also prepared by reaction of **1** with **3** in the presence of CuBr·SMe_2. Inspection of the ^{1}H NMR spectra of compounds **5** and **6** revealed a dramatic shielding for all the signals arising from the $-(CH_2)_{10}-$ chain of [2]rotaxane **5** when compared to axle **6** (Figure S1, Supporting Information). This effect results from the ring current effect of the pillar[5]arene aromatic moieties on the methylene groups of the axle in **5** and is a diagnostic signature for a [2]rotaxane structure.[8] Finally, deacetylation of **5** and **6** under Zemplén conditions (MeOH/MeONa) afforded **7** and **8**, respectively. Importantly, the chemical shifts of the signals corresponding to the methylene groups of the axle moiety in **7** are typical of a [2]rotaxane structure (Figure S2, Supporting Information). Moreover, no evolution of the ^{1}H NMR spectrum of **7** is observed even after several days in solution thus showing that both components of **7**, namely the pillar[5]arene macrocycle and the fucosylated molecular axle, remain associated through mechanical bonding. In other words, the deprotected carbohydrate residues of **7** are large enough to prevent the dissociation of the [2]rotaxane.

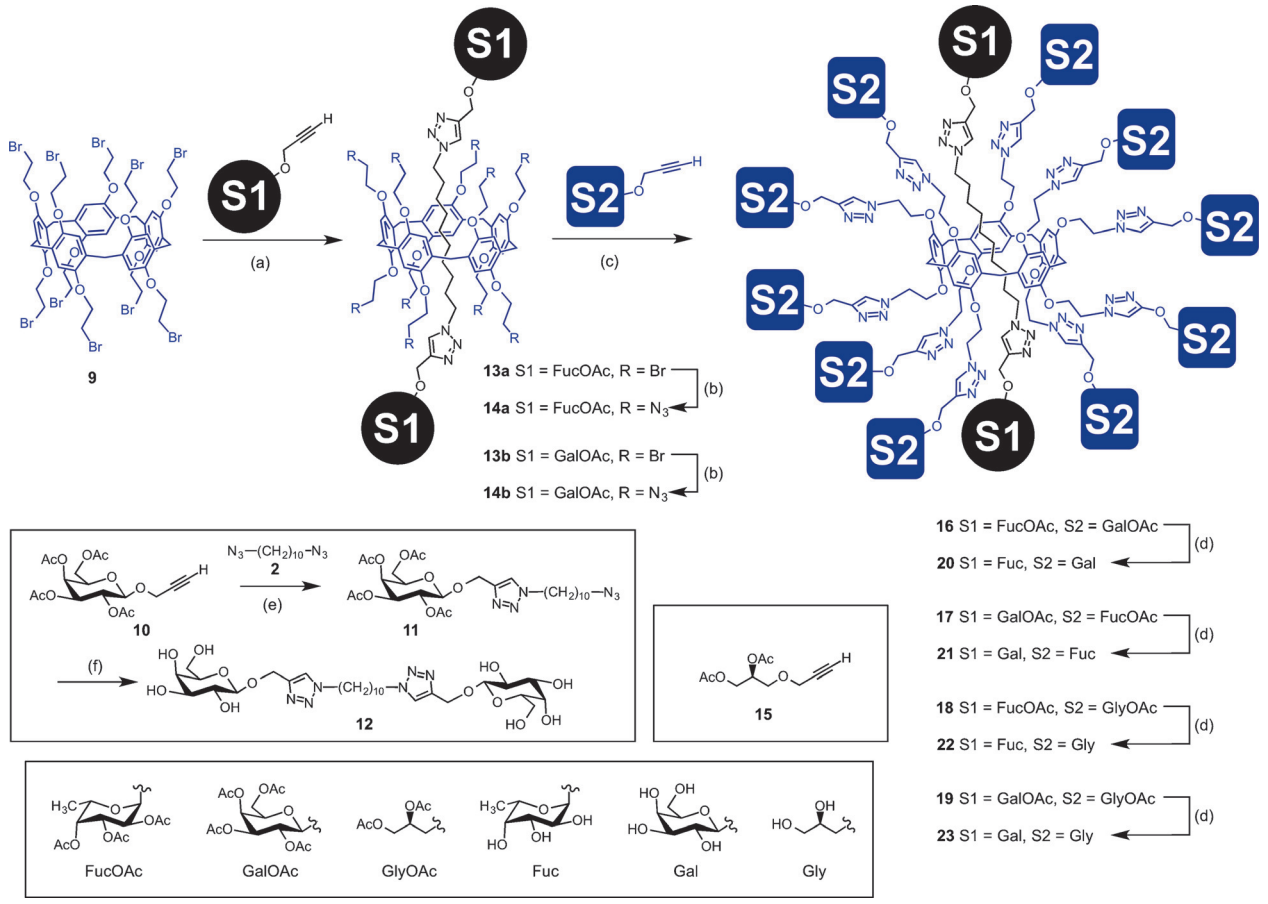
In order to prepare [2]rotaxane derivatives incorporating additional sugar residues on their pillar[5]arene subunit, pillar[5]arene **9** bearing 10 brominated alkyl chains was used as the starting material (Scheme 2). [2]Rotaxane **13a** incorporating acetylated fucose residues was obtained from **1**, **3**, and **9** under the conditions developed for the preparation of **5**. The yield in [2]rotaxane was, however, lower, most probably due to negative steric effects resulting from the presence of the bromides on the macrocycle.[13]

The corresponding [2]rotaxane derivative with acetylated galactosyl stoppers (**13b**) was prepared by following a similar synthetic approach. Treatment of **2** with alkyne **10** and subsequent reaction of the resulting azide (**11**) with **10** in the presence of **9** afforded [2]rotaxane **13b**. For comparison purposes, compound **12** was also prepared from **11**. Treatment of **13a** and **13b** with NaN_3 in DMF afforded polyazides **14a** and **14b**, respectively. Post-functionalization of the macrocyclic component of [2]rotaxanes **14a**–**b** was then efficiently achieved under CuAAC conditions. In both cases, the complementary sugar subunits were introduced onto the [2]rotaxane scaffolds to generate the corresponding heteroglycoclusters (**16** and **17**). In the aromatic region of the ^{1}H NMR spectra of **16** and **17**, a diagnostic signal is observed at $\delta =$ 7.76–7.95 ppm for the 10 1,2,3-triazole rings generated in the last step. The signals arising from the 1,2,3-triazole rings of the stoppers are also observed in the spectra ($\delta = 7.35$–7.68 ppm) as well as the typical resonances of the pillar[5]arene aromatic protons ($\delta = 6.56$–6.70 ppm). The structure of **16** and **17** was further confirmed by their mass spectra showing the expected molecular ion peak at *m/z*: 6045.4 (**16**; calcd for $C_{265}H_{340}N_{36}O_{126}$: 6045.71) and 5581.3 (**17**; calcd for $C_{249}H_{324}N_{36}O_{110}$: 5581.42).

Model [2]rotaxanes **18** and **19** were prepared by introducing acetylated glycerol moieties onto the macrocyclic moiety. Finally, treatment of compounds **16**–**19** with MeOH/MeONa gave the corresponding unprotected [2]rotaxanes **20**–**23** in good yields.

The [2]rotaxane heteroglycoclusters (**20** and **21**) were tested by isothermal titration calorimetry (ITC) as ligands of the two bacterial lectins from *Pseudomonas aeruginosa*, namely galactolectin LecA and fucolectin LecB. These compounds were compared to [2]rotaxanes **22** and **23** displaying only carbohydrate stoppers and to monovalent references β-GalOMe (methyl-β-D-galactopyranoside)[14] and α-FucOMe (methyl-α-L-fucopyranoside).[15] The ITC data are summarized in Table 1.

The stoichiometry derived for the binding of LecA and LecB to rotaxanes with Gal (**21** and **23**) and Fuc (**20** and **22**) stoppers, respectively, is close to 0.5 (0.43 to 0.66) and similar to the binding of the axle alone (**8** and **12**). This is in agreement with the binding of one divalent molecule to two lectin mono-



Scheme 2. a) **1** and **3** or **10** and **11**, CuBr·SMe_2, $CHCl_3$, −20 °C to RT (from **1** and **3**: **13a** (32%); from **10** and **11**: **13b** (26%)); b) NaN_3, DMF, RT (from **13a**: **14a** (85%); from **13b**: **14b** (84%)); c) **1**, **10**, or **15**, $CuSO_4$·5 H_2O, sodium ascorbate, CH_2Cl_2/H_2O, RT (from **13a** and **10**: **16** (85%); from **13b** and **1**: **17** (82%); from **13a** and **15**: **18** (65%); from **13b** and **15**: **19** (79%)); d) MeOH, MeONa, RT (from **16**: **20** (86%); from **17**: **21** (91%), from **18**: **22** (89%); from **19**: **23** (88%)); e) CuBr·SMe_2, $CHCl_3$, RT (62%); f) **10**, CuBr·SMe_2, $CHCl_3$, RT then MeOH, MeONa, RT (62%).

Table 1. ITC data for the binding of lectins LecA and LecB to [2]rotaxanes **20**–**23** and to reference compounds β-GalOMe, α-FucOMe, **8** and **12**. Standard deviations on data are less than 10%.

Ligand	Lectin	*n*	K_D nM	$-\Delta G$ [kJ mol^{-1}]	$-\Delta H$ [kJ mol^{-1}]	$-T\Delta S$ [kJ mol^{-1}]
β-GalOMe[a]	LecA		70000	24.0	39.0	15.0
α-FucOMe[b]	LecB		430	36.4	41.3	4.9
8 $(Fuc)_2$	LecB	0.55	112	39.7	77.2	37.5
12 $(Gal)_2$	LecA	0.58	158	38.9	78.2	39.3
20 $(Gal)_{10}(Fuc)_2$	LecA	0.15	261	37.6	153.8	116.2
	LecB	0.43	279	37.4	91.1	53.7
21 $(Fuc)_{10}(Gal)_2$	LecA	0.66	5360	30.1	64.7	34.6
	LecB	0.28	625[c]	35.4	79.4	44.0
22 $(Gly)_{10}(Fuc)_2$	LecB	0.54	212	38.1	77.0	38.9
23 $(Gly)_{10}(Gal)_2$	LecA	0.6	5160	30.2	70.4	40.2

[a] From Ref. [14]. [b] From Ref. [15]. [c] Only one experiment available.

mers thus indicating an effective binding of both stoppers onto the target in all the cases. Concerning the peripheral sugar residues grafted onto the pillar[5]arene moiety, the stoichiometry towards the targeted lectin varies from 0.15 (**20**) to 0.28 (**21**) indicating that 3 (**21**) to 6 (**20**) out of the 10 monosaccharides reach a binding site. Altogether, the stoichiometry values obtained for **20** and **21** towards LecA and LecB indicate that these compounds are able to bind simultaneously to the two lectins.

Comparison of **20** with the corresponding model compound bearing the same stoppers (**22**) reveals similar dissociation constants for LecB. Similar K_D values are also observed for the binding of **21** and **23** to LecA. In both cases, the nature of the substituents of the pillar[5]arene unit has no

significant influence on the binding of the stoppers to LecA and LecB.

Fucolectin LecB has a unique mode of binding involving two bridging calcium ions and thus a high affinity for monovalent fucose derivatives such as α-FucOMe.[14a] The tetrameric structure presents the binding sites in opposite orientation in space[14b] and therefore this particular lectin is also not very sensitive to multivalent effects.[16] In the particular case of **21**, a significant decrease in affinity is even observed when compared to monovalent ligand α-FucOMe thus suggesting that negative steric effects are certainly playing a role for the binding of fucose moieties of decavalent compound **21** to LecB. Conversely, comparison of the K_D values of the Fuc-stoppered rotaxanes (**20** and **22**) with the corresponding divalent model compound (**8**) reveals only limited steric effects resulting from the presence of the macrocyclic component in **20** and **22** (Figure S3, Supporting Information).

Owing to the close presentation of two neighboring galactose binding sites in LecA, this lectin is very sensitive to multivalent effects.[17] The K_D value is already increased by more than two orders of magnitude when going from the monovalent model compound (β-GalOMe) to divalent model compound **12**. As schematically represented in Figure 1A, the two Gal residues of **12** are most probably bound to the same LecA. In contrast, the lower affinity of divalent Gal derivatives **21** and **23** suggests that their macrocyclic subunit prevents the folding of the axel and thus the simultaneous binding of their two Gal residues onto the same lectin (Figure 1B and Figure S4, Supporting Information). For [2]rotaxane **20** bearing ten Gal residues, the affinity for LecA is further increased. A 268-fold increase is effectively observed when going from β-GalOMe to **20**. Importantly, the combination of ten Gal residues with two Fuc stoppers in [2]rotaxane **20** is perfectly suited to achieve high affinities for both LecA and LecB. Compound **20** appears to be more efficient than the only known heteroglycocompound directed against *P.aeruginosa* lectins: an octoglycodendrimer presenting galactose and fucose that could precipitate LecB but with weak activity for LecA.[10b] As schematically shown in Figure 1C, the high affinity of **20** results from the clustering of LecA and the aggregation of LecB.

In conclusion, we have developed a synthetic approach combining recent concepts for the preparation of multifunctional nanomolecules (click chemistry on multifunctional scaffolds) with supramolecular chemistry (self-assembly to prepare rotaxanes) allowing the synthesis of sophisticated supramolecular heteroglycoclusters for biological applications. As the CuAAC reaction conditions used for the functionalization of the rotaxane scaffold are tolerant to a large variety of functional units, this synthetic approach will allow for the easy preparation of unprecedented multifunctional materials for various applications.

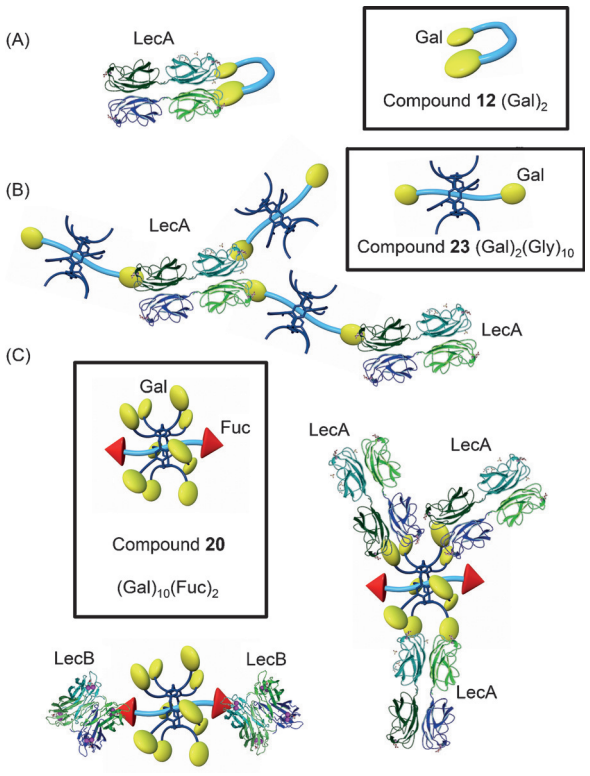


Figure 1. Schematic representations showing possible binding modes of divalent ligands **12** (A) and **23** (B) to LecA (ligands and proteins are not represented at real scale). In the case of heteroglycorotaxane **20** (C), clustering of LecA to the decavalent macrocyclic component and aggregation of LecB to the divalent axle moiety provide high affinity for both lectins.

Acknowledgements

We gratefully acknowledge financial support from the University of Strasbourg, the CNRS, the International Center for Frontier Research in Chemistry (icFRC) and the LabEx Chimie des Systèmes Complexes. A. I. acknowledges support from GDR Pseudomonas and Labex ARCANE (ANR-11-LABX-003). S. V. acknowledges support from FNRS. A. I. and S. V. acknowledge COST Action CM-1102 MultiGlycoNano. The technical expertise of Emilie Gillon (CERMAV-Grenoble) for ITC experiments was much appreciated. We further thank Dr. M. Holler for helpful discussions.

Keywords: click chemistry · glycoclusters · lectin · pillar[5]arenes · rotaxane

[1] I. Nierengarten, J.-F. Nierengarten, *Chem. Rec.* **2015**, *15*, 31 – 51.
[2] a) S. Guerra, J. Iehl, M. Holler, M. Peterca, D. A. Wilson, B. E. Partridge, S. Zhang, R. Deschenaux, J.-F. Nierengarten, V. Percec, *Chem. Sci.* **2015**, *6*, 3393 – 3401; b) I. Nierengarten, S. Guerra, M. Holler, J.-F. Nierengarten, R. Deschenaux, *Chem. Commun.* **2012**, *48*, 8072 – 8074; c) S. Pan, M. Ni, B. Mu, Q. Li, X.-Y. Hu, C. Lin, D. Chen, L. Wang, *Adv. Funct. Mater.* **2015**, *25*, 3571 – 3580.
[3] a) K. Yoosaf, J. Iehl, I. Nierengarten, M. Hmadeh, A.-M. Albrecht-Gary, J.-F. Nierengarten, N. Armaroli, *Chem. Eur. J.* **2014**, *20*, 223 – 231; b) J. Iehl, J.-F. Nierengarten, A. Harriman, T. Bura, R. Ziessel, *J. Am. Chem. Soc.* **2012**, *134*, 988 – 998; c) J. Iehl, M. Frasconi, H.-P. Jacquot de Rouville, N. Renaud, S. M. Dyar, N. L. Strutt, R. Carmieli, M. R. Wasielewski, M. A. Ratner, J.-F. Nierengarten, J. F. Stoddart, *Chem. Sci.* **2013**, *4*, 1462 – 1469.
[4] For reviews on pillar[*n*]arenes, see: a) P. J. Cragg, K. Sharma, *Chem. Soc. Rev.* **2012**, *41*, 597 – 607; b) M. Xue, Y. Yang, X. Chi, Z. Zhang, F. Huang, *Acc. Chem. Res.* **2012**, *45*, 1294 – 1308; c) T. Ogoshi, *J. Inclusion Phenom. Macrocyclic Chem.* **2012**, *72*, 247 – 262; d) T. Ogoshi, T.-a. Yamagishi, *Eur.*

J. Org. Chem. **2013**, 2961 – 2975; e) D. Cao, H. Meier, *Asian J. Org. Chem.* **2014**, *3*, 244 – 262; f) T. Ogoshi, T. Yamagishi, *Chem. Commun.* **2014**, *50*, 4776 – 4787; g) N. L. Strutt, H. Zhang, S. T. Schneebeli, J. F. Stoddart, *Acc. Chem. Res.* **2014**, *47*, 2631 – 2642.

[5] a) I. Nierengarten, M. Nothisen, D. Sigwalt, T. Biellmann, M. Holler, J.-S. Remy, J.-F. Nierengarten, *Chem. Eur. J.* **2013**, *19*, 17552 – 17558; b) I. Nierengarten, S. Guerra, M. Holler, L. Karmazin-Brelot, J. Barbera, R. Deschenaux, J.-F. Nierengarten, *Eur. J. Org. Chem.* **2013**, 3675 – 3684; c) I. Nierengarten, K. Buffet, M. Holler, S. P. Vincent, J.-F. Nierengarten, *Tetrahedron Lett.* **2013**, *54*, 2398 – 2402.

[6] a) Z. Zhang, B. Xia, C. Han, Y. Yu, F. Huang, *Org. Lett.* **2010**, *12*, 3285 – 3287; b) L. Liu, D. Cao, Y. Jin, H. Tao, Y. Kou, H. Meier, *Org. Biomol. Chem.* **2011**, *9*, 7007 – 7010.

[7] M. Holler, N. Allenbach, J. Sonet, J.-F. Nierengarten, *Chem. Commun.* **2012**, *48*, 2576 – 2578.

[8] For examples of pillar[*n*]arene-containing rotaxane, see: a) N. L. Strutt, R. S. Forgan, J. M. Spruell, Y. Y. Botros, J. F. Stoddart, *J. Am. Chem. Soc.* **2011**, *133*, 5668 – 5671; b) T. Ogoshi, Y. Nishida, T.-a. Yamagishi, Y. Nakamoto, *Macromolecules* **2010**, *43*, 7068 – 7072; c) T. Ogoshi, D. Yamafuji, T. Aoki, T.-a. Yamagishi, *Chem. Commun.* **2012**, *48*, 6842 – 6844; d) T. Ogoshi, D. Yamafuji, T. Aoki, K. Kitajima, T.-a. Yamagishi, Y. Hayashi, S. Kawauchi, *Chem. Eur. J.* **2012**, *18*, 7493 – 7500; e) P. Wei, X. Yan, J. Li, Y. Ma, Y. Yao, F. Huang, *Tetrahedron* **2012**, *68*, 9179 – 9185; f) T. Ogoshi, T. Aoki, R. Shiga, R. Iizuka, S. Ueda, K. Demachi, D. Yamafuji, H. Kayama, T.-a. Yamagishi, *J. Am. Chem. Soc.* **2012**, *134*, 20322 – 20325; g) X.-Y. Hu, X. Wu, Q. Duan, T. Xiao, C. Lin, L. Wang, *Org. Lett.* **2012**, *14*, 4826 – 4829; h) T. Ogoshi, D. Yamafuji, T.-a. Yamagishi, A. M. Brouwer, *Chem. Commun.* **2013**, *49*, 5468 – 5470; i) C. Ke, N. L. Strutt, H. Li, X. Hou, K. J. Hartlieb, P. R. McGonigal, Z. Ma, J. Iehl, C. L. Stern, C. Cheng, Z. Zhu, N. A. Vermeulen, T. J. Meade, Y. Y. Botros, J. F. Stoddart, *J. Am. Chem. Soc.* **2013**, *135*, 17019 – 17030; j) X. Hou, C. Ke, C. Cheng, N. Song, A. K. Blackburn, A. A. Sarjeant, Y. Y. Botros, Y.-W. Yang, J. F. Stoddart, *Chem. Commun.* **2014**, *50*, 6196 – 6199; k) T. M. N. Trinh, I. Nierengarten, M. Holler, J.-L. Gallani, J.-F. Nierengarten, *Chem. Eur. J.* **2015**, *21*, 8019 – 8022.

[9] For selected reviews, see: a) V. Wittmann, R. Pieters, *Chem. Soc. Rev.* **2013**, *42*, 4492 – 44503; b) Y. M. Chabre, R. Roy, *Adv. Carbohydrate Chem. and Biochem.* **2010**, *63*, 165 – 393; c) M. Hartmann, T. K. Lindhorst, *Eur. J. Org. Chem.* **2011**, 3583 – 3609; d) S. Cecioni, A. Imberty, S. Vidal, *Chem. Rev.* **2015**, *115*, 525 – 561; e) Y. Chen, A. Star, S. Vidal, *Chem. Soc. Rev.* **2013**, *42*, 4532 – 4542; f) Y. M. Chabre, R. Roy, *Chem. Soc. Rev.* **2013**, *42*, 4657 – 4708; g) M. Gingras, Y. M. Charbre, M. Roy, R. Roy, *Chem. Soc. Rev.* **2013**, *42*, 4823 – 4841; h) A. Bernardi, J. Jiménez-Barbero, A. Casnati, C. De Castro, T. Darbre, F. Fieschi, J. Finne, H. Funken, K.-E. Jaeger, M. Lahmann, T. K. Lindhorst, M. Marradi, P. Messner, A. Molinaro, P. V. Murphy, C. Nativi, S. Oscarson, S. Penadés, F. Peri, R. J. Pieters, O. Renaudet, J.-L. Reymond, B. Richichi, J. Rojo, F. Sansone, C. Schäffer, W. B. Turnbull, T. Velasco-Torrijos, S. Vidal, S. P. Vincent, T. Wennekes, H. Zuilhof, A. Imberty, *Chem. Soc. Rev.* **2013**, *42*, 4709 – 4727; i) I. Nierengarten, J.-F. Nierengarten, *Chem. Asian J.* **2014**, *9*, 1436 – 1444.

[10] For a review on heteroglycodendrimers, see a) J. L. Jiménez Blanco, C. Ortiz Mellet, J. M. Garcia Fernandez, *Chem. Soc. Rev.* **2013**, *42*, 4518 – 4531. For examples see: b) I. Deguise, D. Lagnoux, R. Roy, *New J. Chem.* **2007**, *31*, 1321 – 1331; c) B. Gerland, A. Goudot, G. Pourceau, A. Meyer, S. Vidal, E. Souteyrand, J.-J. Vasseur, Y. Chevolot, F. Morvan, *J. Org. Chem.* **2012**, *77*, 7620 – 7626; d) D. Ponader, P. Maffre, J. Aretz, D. Pussak, N. M. Ninnermann, S. Schmidt, P. H. Seeberger, C. Rademacher, G. U. Nienhaus, L. Hartmann, *J. Am. Chem. Soc.* **2014**, *136*, 2008 – 2016; e) B. Thomas, M. Fiore, I. Bossu, P. Dumy, O. Renaudet, *Beilstein J. Org. Chem.* **2012**, *8*, 421 – 427.

[11] a) A. Imberty, M. Wimmerova, E. P. Mitchell, N. Gilboa-Garber, *Microbes Infect.* **2004**, *6*, 221 – 229; b) C. Chemani, A. Imberty, S. de Bentzman, P. Pierre, M. Wimmerová, B. P. Guery, K. Faure, *Infect. Immun.* **2009**, *77*, 2065 – 2075; c) T. Eierhoff, B. Bastian, R. Thuenauer, J. Madl, A. Audfray, S. Aigal, S. Juillot, G. E. Rydell, S. Müller, S. de Bentzmann, A. Imberty, C. Fleck, W. Römer, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 12895 – 12900.

[12] For examples of sugar-containing rotaxanes, see: a) P. R. Ashton, S. R. L. Everitt, M. Gomez-Lopez, N. Jayaraman, J. F. Stoddart, *Tetrahedron Lett.* **1997**, *38*, 5691 – 5694; b) A. Nelson, J. M. Belitsky, S. Vidal, C. S. Joiner, L. G. Baum, J. F. Stoddart, *J. Am. Chem. Soc.* **2004**, *126*, 11914 – 11922; c) F. Coutrot, E. Busseron, J.-L. Montero, *Org. Lett.* **2008**, *10*, 753 – 756; d) F. Coutrot, E. Busseron, *Chem. Eur. J.* **2008**, *14*, 4784 – 4787; e) F. Coutrot, E. Busseron, *Chem. Eur. J.* **2009**, *15*, 5186 – 5190; f) A. Fernandes, A. Viterisi, F. Coutrot, S. Potok, D. A. Leigh, V. Aucagne, S. Papot, *Angew. Chem. Int. Ed.* **2009**, *48*, 6443 – 6447; *Angew. Chem.* **2009**, *121*, 6565 – 6569; g) E. Busseron, C. Romuald, F. Coutrot, *Chem. Eur. J.* **2010**, *16*, 10062 – 10073; h) R. Barat, T. Legigan, I. Tranoy-Opalinski, B. Renoux, E. Péraudeau, J. Clarhaut, P. Poinot, A. E. Fernandes, V. Aucagne, D. A. Leigh, S. Papot, *Chem. Sci.* **2015**, *6*, 2608 – 2613.

[13] The yields of [2]rotaxane are influenced by the size of the peripheral substituents of the pillar[5]arene building block; for a systematic investigation, see: R. Milev, A. Lopez-Pacheco, I. Nierengarten, T. M. N. Trinh, M. Holler, R. Deschenaux, J.-F. Nierengarten, *Eur. J. Org. Chem.* **2015**, 479 – 485.

[14] S. Cecioni, J.-P. Praly, S. E. Matthews, M. Wimmerova, A. Imberty, S. Vidal, *Chem. Eur. J.* **2012**, *18*, 6250 – 6263.

[15] a) C. Sabin, E. P. Mitchell, M. Pokorna, C. Gautier, J.-P. Utille, M. Wimmerova, A. Imberty, *FEBS Lett.* **2006**, *580*, 982 – 987; b) E. Mitchell, C. Houles, D. Sudakevitz, M. Wimmerova, C. Gautier, S. Pérez, A. M. Wu, N. Gilboa-Garber, A. Imberty, *Nat. Struct. Biol.* **2002**, *9*, 918 – 921.

[16] K. Buffet, E. Guillon, M. Holler, J.-F. Nierengarten, A. Imberty, S. P. Vincent, *Org. Biomol. Chem.* **2015**, *13*, 6482 – 6492.

[17] a) S. Cecioni, V. Oerthel, J. Iehl, M. Holler, D. Goyard, J.-P. Praly, A. Imberty, J.-F. Nierengarten, S. Vidal, *Chem. Eur. J.* **2011**, *17*, 3252 – 3261; b) J.-L. Reymond, M. Bergmann, T. Darbre, *Chem. Soc. Rev.* **2013**, *42*, 4814 – 4822; c) A. Novoa, T. Eierhoff, J. Topin, A. Varrot, S. Barluenga, A. Imberty, W. Römer, N. Winssinger, *Angew. Chem. Int. Ed.* **2014**, *53*, 8885 – 8889; *Angew. Chem.* **2014**, *126*, 9031 – 9035; d) F. Pertici, D. J. de Mol, J. Kemmink, R. J. Pieters, *Chem. Eur. J.* **2013**, *19*, 16923 – 16927.

Received: October 13, 2015
Published online on November 3, 2015

