JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

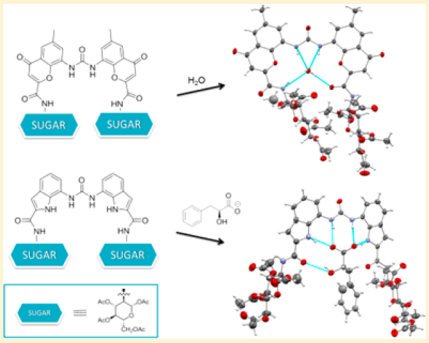
Exploring the Chiral Recognition of Carboxylates by C_2-Symmetric Receptors Bearing Glucosamine Pendant Arms

Dawid Lichosyt, Sylwia Wasiłek, and Janusz Jurczak*

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Supporting Information

ABSTRACT: Two urea-based receptors containing a glucosamine derivative were synthesized and investigated in terms of their ability to recognize chiral and achiral anions. Both receptors demonstrated a high affinity toward carboxylates in very competitive DMSO/water mixtures. The chiral recognition properties of these compounds were studied using structurally differentiated guests derived from mandelic acid and α-amino acids. We found that receptor **1** exhibits significantly higher enantioselectivities than compound **2** for all anions investigated, with a K_S/K_R ratio of up to 2. This low enantiodiscrimination in the case of receptor **2** is attributed to a lack of interactions between its sugar moieties and the side chain of chiral anions, due to their inadequate spatial arrangement.



INTRODUCTION

Chiral recognition, the phenomenon whereby a chiral receptor differentiates between enantiomers of a guest, is based on subtle differences in both the enthalpy and entropy of the binding of the opposite isomers.[1] These differences are driven by minute effects, such as distinct conformations of a guest or host in the case of alternative host−guest complexes, different numbers of repulsive and attractive interactions in the case of diastereoisomeric complexes, etc. Consequently, chiral recognition is one of the least understood processes in supramolecular chemistry. Given the importance of chirality and chiral recognition in Nature, there is a great need for in-depth studies elucidating the rules governing this process and clarifying the correlation between a putative receptor's structure and its ability for efficient chiral differentiation. Despite the immense progress that has been made in the field of supramolecular recognition,[2] it nevertheless remains nearly impossible to design receptors with desired properties or even to predict how known receptors will interact with new guest molecules. Hence, one of the most common approaches to developing receptors amenable to chiral recognition is based on the combinatorial evaluation of series of receptors with a wide range of guests.[3]

Whereas biological systems are able to effectively differentiate between stereoisomers of guests in water (recognition of thalidomide enantiomers in the human body being a representative example[4]), designing artificial receptors capable of recognizing chiral guests still remains a very challenging area of research. As many chiral host−guest systems important for living organisms involve anionic species, much recent attention has therefore been devoted to the development of synthetic systems for the chiral recognition of anions.[5] Although numerous reports have been published, the enantioselectivities of the reported synthetic receptors—defined as the ratio of stability constants for the enantiomers—are low and rarely exceed 2. Notably, the previously reported high enantioselectivities for synthetic chiral receptors,[6] which set the *gold standard* for the field, have recently been found to be experimental artifacts.[3]

The most common strategy followed in constructing chiral receptors involves the functionalization of a known (achiral) anion binding platform with chiral moieties. This approach, simple in principle, requires the connection of a binding pocket ensuring strong binding of a negatively charged (usually carboxylic) group with precisely selected moieties, providing effective enantiodiscrimination. Immense progress in understanding the supramolecular chemistry of achiral anions[7] has led to the design and synthesis of many efficient receptors capable of selectively binding structurally different anions even in very polar solvents.[8] However, when their geometry is considered, many of them prove to be unsuitable for effective chiral recognition of carboxylates. Therefore, we decided to focus our research on two promising urea-containing platforms, based on chromenone[9] and indole[10] moieties (Figure 1). These structures offer different numbers of hydrogen bond donors and geometry, providing an opportunity to evaluate the influence of the binding platform on the complexation of chiral anions and their enantioselectivities.

Among the natural sources of chirality, sugars are attractive to use in constructing artificial receptors for chiral recognition. In the cyclic form, they adopt relatively rigid, well-defined conformations and introduce additional heteroatoms into the structure that can be involved in chiral guest complexation and differentiation.[11] Herein we report the synthesis and the chiral anion binding properties of C_2-symmetrical receptors **1** and **2**, constructed on the chromenone− and indole−urea platforms,

Received: April 7, 2016
Published: July 27, 2016

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

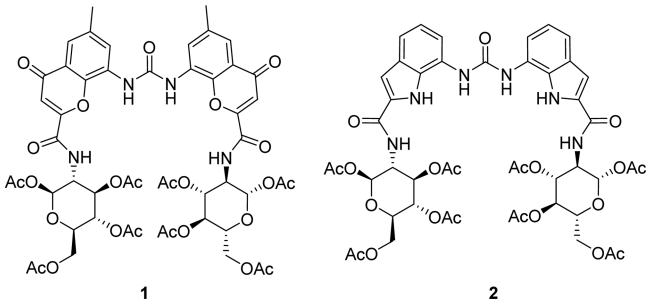


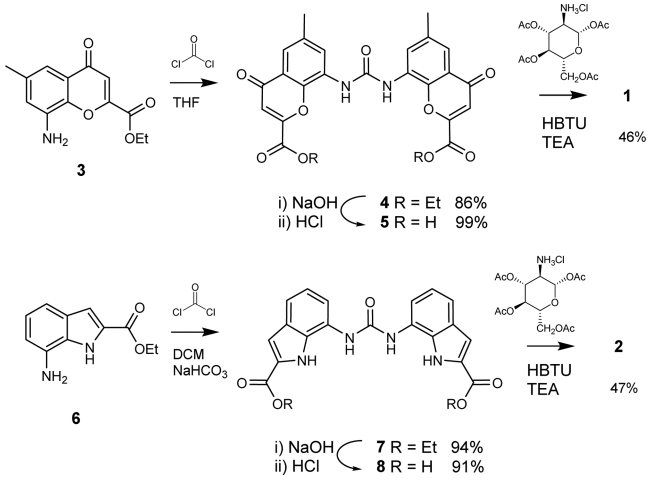
Figure 1. Structures of the chromenone (**1**)- and indole-based (**2**) receptors investigated in this work.

which are functionalized with easily accessible 1,3,4,6-tetra-*O*-acetyl-D-glucosamine (Figure 1).

RESULTS AND DISCUSSION

Receptors **1** and **2** were synthesized in three straightforward steps (Scheme 1), starting from amines **3**[12] and **6**,[13]

Scheme 1. Synthesis of Receptors 1 and 2



respectively, obtained according to the literature procedures. Their condensation with phosgene afforded ureas **4** and **7**, which after hydrolysis of ester groups yielded carboxylic acids **5** and **8**. The acid compounds so obtained were then condensed with D-glucosamine derivative[14] to afford the desired products **1** and **2** in 46% and 47% yields, respectively.

First, we evaluated the binding properties of receptors **1** and **2** with respect to model achiral anions, such as chloride, dihydrogen phosphate, acetate, benzoate, and diphenylacetate. In all cases we observed that the receptors formed complexes with 1:1 anion:receptor stoichiometry, with high association constants even in DMSO/0.5% H_2O (Table 1).

In contrast to what may be expected, receptor **1**, equipped with four H-bond donors, forms more stable complexes than does receptor **2**, equipped with six H-bond donors. This demonstrates that the binding site of **1** is well tailored for interactions with anions, as is also shown by the remarkable binding constants in DMSO with 0.5% of water (Table 1). In most cases, carboxylates form complexes with stability constants above the limit of the ^{1}H NMR titration technique (10^4 M^{-1}). Therefore, we next performed binding constant measurements in a more competitive solvent, namely DMSO with a 5% content of water (Table 1). The experiments in this

Table 1. Binding Constants for the Formation of 1:1 Complexes of Receptors 1 and 2 with Various Anions in [D_6]DMSO/H_2O Mixtures[a]

		stability constant (M^{-1})			
receptor	water (%)	Cl^-	$MeCO_2^-$	$PhCO_2^-$	$Ph_2CHCO_2^-$
1	0.5	9600	*b*	$>10^4$	3500
2	0.5	16	$>10^4$	$>10^4$	2600
1	5	1500	$>10^4$	2600	2100
2	5	*c*	2000	1700	770

[a]Values determined by ^{1}H NMR titration experiments at T = 298 K, with estimated errors <10%. Tetrabutylamonium (TBA) salts were used as source of anions. Stability constants of complexes with $H_2PO_4^-$ could not be determined due to slow exchange on the NMR time scale; for details see the Supporting Information. [b]Slow exchange on the NMR time scale. [c]Not determined.

medium showed that the stability constants decreased to optimal values in almost all cases, with the exception of acetate, for which receptor **1** still demonstrates remarkable affinity.

Subsequently, we evaluated the influence of the size of the anion on the strength of the interactions with receptors **1** and **2**. We found that both receptors bind the small acetate anion significantly more strongly than the more sterically demanding benzoate and diphenylacetate. From the relative stability constants standardized to K_{AcO} as depicted in Figure 2, the

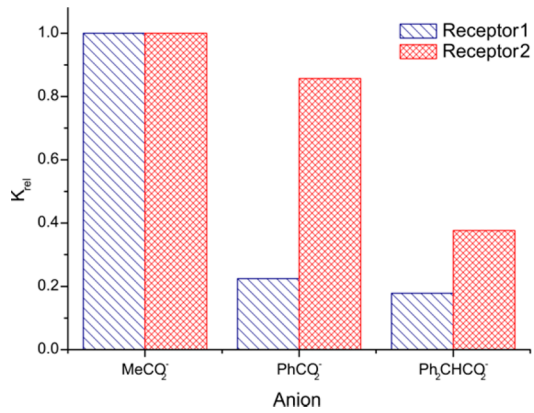


Figure 2. Plot of relative stability constants of carboxylate anions standardized to the binding constant with acetate (K_{rel} = K_{anion}/$K_{MeCO_2^-}$).

ratio of stability constants of complexes of **2** with benzoate and acetate (K_{PhCOO}/K_{AcO}) is higher in comparison to that of receptor **1**. This suggests that the receptors differ significantly in terms of steric hindrance, which is manifested during the binding event.

Next, to estimate the potential of receptors **1** and **2** for chiral recognition, we evaluated their binding properties with respect to anions derived from chiral acids possessing a stereogenic center in an α position—a common structural motif in natural compounds and synthetic drugs (Figure 3). To investigate the relation between anion structure and affinity toward receptors **1** and **2** in chiral recognition, we selected structurally diverse guests. We used the TBA salts of a series of *N*-acetyl-D/L-amino acids and (*R*/*S*)-mandelate with its analogues, as shown in Figure 3. Given the observed strong affinity of **1** and **2** toward acetate, we performed all the titration experiments in a mixture of DMSO with 5% water.

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

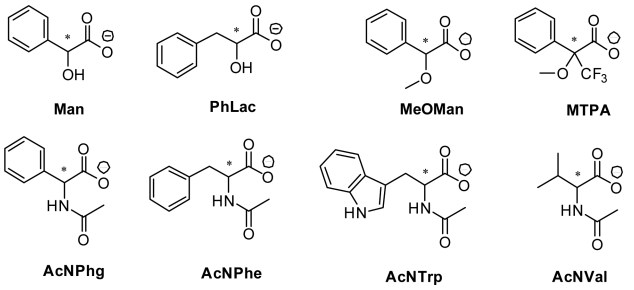


Figure 3. Structures of the anionic guests investigated in this study, used as TBA salts.

By analogy to simple achiral carboxylates, we observed that the chiral anions formed complexes with **1** and **2** with the same 1:1 anion:receptor stoichiometry, with stability constants shown in Tables 2 and 3. In most cases, the values of K_S and K_R lie in the optimal range for the ^{1}H NMR technique. To clarify further discussion, in Figure 4 we also show a logarithmic plot of the stability constants standardized to acetate ($\log K_{rel} = \log(K_{anion}/K_{AcO})$).

Table 2. Binding Constants for the Formation of 1:1 Complexes of Receptors 1 and 2 with Various Anions in a [D_6]DMSO/5% H_2O Mixture[a]

entry	receptor	anion	stability constant (M^{-1})	K_S/K_R
1	**1**	(*R*)-Man	210	1.8
2	**1**	(*S*)-Man	380	
3	**1**	(*R*)-PhLac	510	1.2
4	**1**	(*S*)-PhLac	630	
5	**1**	(*R*)-MeOMan	3900	2.0
6	**1**	(*S*)-MeOMan	7800	
7	**1**	(*R*)-MTPA	61	1.6
8	**1**	(*S*)-MTPA	95	
9	**2**	(*R*)-Man	300	1.0
10	**2**	(*S*)-Man	310	
11	**2**	(*R*)-PhLac	660	1.1
12	**2**	(*S*)-PhLac	700	
13	**2**	(*R*)-MeOMan	500	1.0
14	**2**	(*S*)-MeOMan	520	
15	**2**	(*R*)-MTPA	21	1.1
16	**2**	(*S*)-MTPA	23	

[a]Values determined by ^{1}H NMR titration experiments at T = 298 K, with estimated errors <10%. TBA salts used as source of anions.

Investigation of these stability constants reveals that receptor **1** binds *S* enantiomers of anions more strongly than *R* enantiomers in all cases, with enantioselectivities in the range of 1.2−2.0. A similar trend but with weaker preference for binding *S* enantiomers is observed for receptor **2** in most of the cases investigated. Nevertheless, according to the estimated errors for stability constants (<10%), K_S/K_R ratios in the range of 0.9−1.1 obtained from direct, noncompetitive[15] titrations do not allow us to elucidate the influence of the anion structure on enantiodiscrimination for compound **2**.

The highest levels of chiral recognition, in terms of selective binding toward one enantiomer over another, were observed for receptor **1** with mandalate anions (Table 2, entries 1 and 2) and their O-methylated analogues (Table 2, entries 5 and 6) with K_S/K_R ratios up to 2.0. Interestingly, we observed a considerable difference in the stabilities of the complexes formed by those anions with receptor **1** (Figure 5a vs 5b). The

Table 3. Binding Constants for the Formation of 1:1 Complexes of Receptors 1 and 2 with Various Anions in a [D_6]DMSO/5% H_2O Mixture[a]

entry	receptor	anion	stability constant (M^{-1})	K_S/K_R
1	**1**	D-AcNPhg	170	1.5
2	**1**	L-AcNPhg	250	
3	**1**	D-AcNPhe	*b*	*b*
4	**1**	L-AcNPhe	*b*	
5	**1**	D-AcNTrp	340	1.2
6	**1**	L-AcNTrp	420	
7	**1**	D-AcNVal	410	1.2
8	**1**	L-AcNVal	510	
9	**2**	D-AcNPhg	1800	0.9
10	**2**	L-AcNPhg	1700	
11	**2**	D-AcNPhe	2600	1.1
12	**2**	L-AcNPhe	2900	
13	**2**	D-AcNTrp	2600	1.0
14	**2**	L-AcNTrp	2700	
15	**2**	D-AcNVal	3700	1.1
16	**2**	L-AcNVal	3900	

[a]Values determined by ^{1}H NMR titration experiments at T = 298 K, with estimated errors <10%. TBA salts used as source of anions. [b]Data cannot be fitted to a simple 1:1 model.

binding constants (Table 2, entries 1 vs 5 and 2 vs 6) differ by nearly 20-fold, which could be rationalized as an effect of these anions having different solvation—due to the presence or absence of a free hydroxyl group, which interacts with the solvent not only as a hydrogen bond acceptor but also as a donor.

A similar difference in binding of mandalate anions and of their *O*-Me analogues was observed in our previous study, which showed that the presence of a hydroxyl group in the structure of this guest is crucial for its chiral recognition.[16] In contrast, the results for receptor **1** reported above show that the presence of a hydrogen bond donor is not critical for distinguishing the enantiomers of these anions. This suggests that receptor **1** recognizes chiral guests by steric interaction with sugar moieties. This hypothesis is supported by observations concerning relative stability constants (Figure 4) as well as K_S/K_R values in the mandalate anion series: reducing the steric hindrance on the α carbon in the anion by substituting Ph with $PhCH_2$ (Table 2, entries 1, 2 and 3, 4) results in increased stability constants and decreased K_S/K_R, whereas enhancing this steric hindrance by replacing the hydrogen atom with a CF_3 group (Table 2, entries 7, 8 and 5, 6) results in significantly decreased stability constants and decreased K_S/K_R in reference to mandalate anion.

Interestingly, no difference in stability constants similar to that found for receptor **1** with mandalate and its *O*-Me analogue was seen for receptor **2** (Table 2, entries 9 vs 13 and 10 vs 14; Figure 5c vs 5d). This suggests additional possible interactions of the hydroxyl group of mandalate with receptor **2**, compensating for the difference in solvation between mandalate and its O-methylated analogue, as depicted in Scheme 2.

Comparison of the stability constants for receptors **1** and **2** with amino acid derivatives shows that the latter forms stronger complexes in all cases. Moreover, compound **2** binds amino acids more strongly than it binds mandalate anion and its analogues (Table 2 vs 3). Significant differences in stability constants for receptors **1** and **2** suggest that the side chain of

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

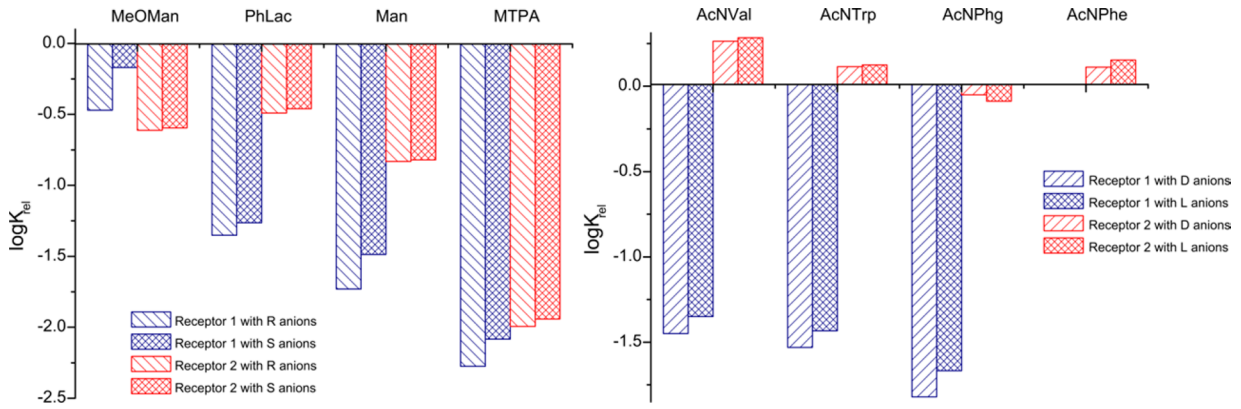


Figure 4. Logarithmic plot of relative stability constants of carboxylate anions standardized to acetate ($K_{rel} = K_{anion}/K_{MeCO_2^-}$).

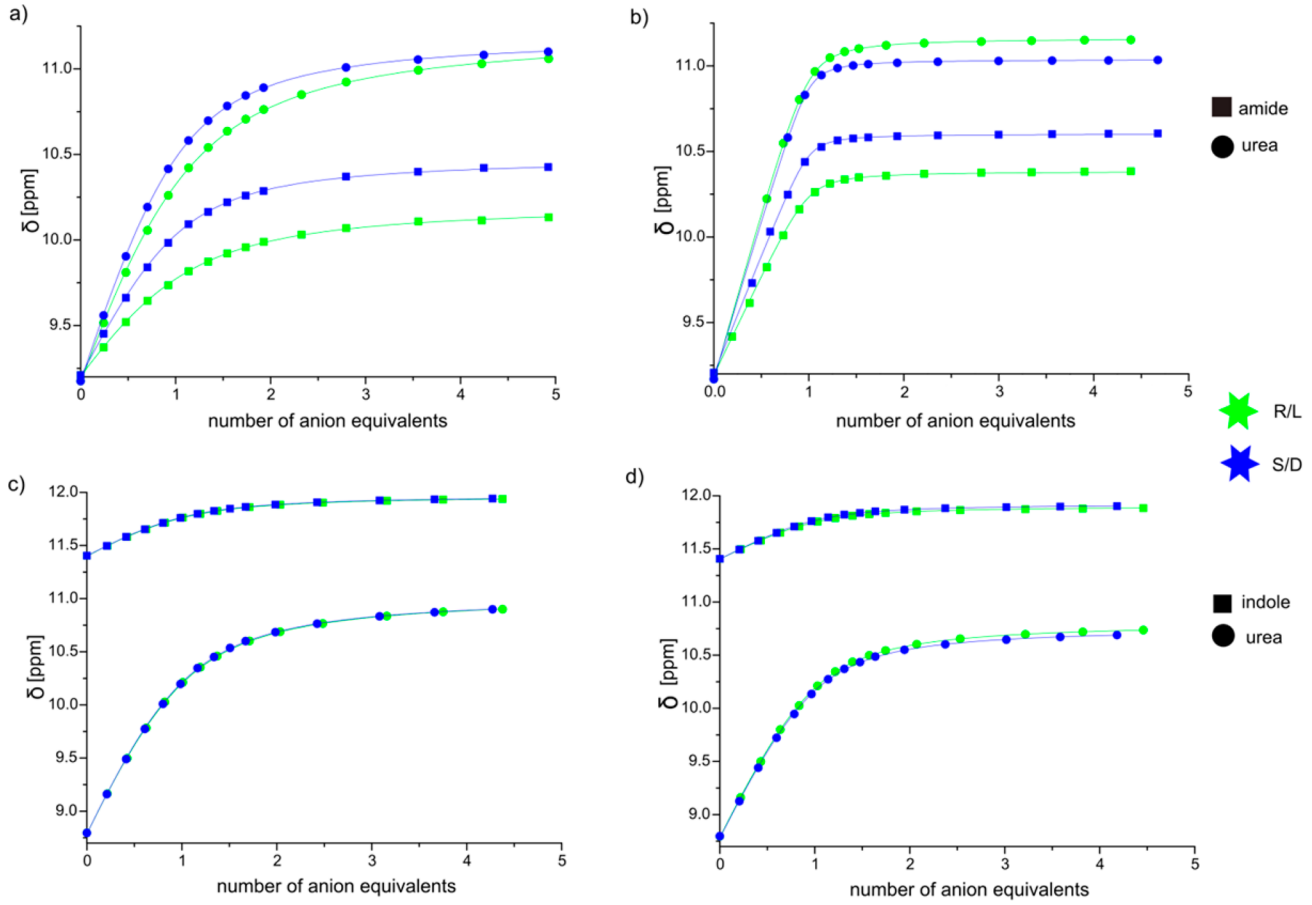
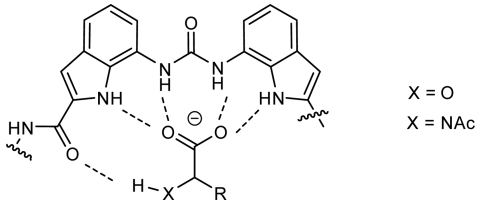


Figure 5. Titration curves of receptors **1** (a, b) and **2** (c, d) with Man (a, c) and MeOMan (b, d).

Scheme 2. Plausible Binding Model for Receptor 2



the anion may be involved in binding to the receptor, through a hydrogen bond between **2** and amino acid derivatives, with the model shown in Scheme 2. Indeed, further experiments showed that the amide NH proton of *N*-acetylphenylglycine shifts upon binding to receptor **1**, whereas analogous perturbation of this proton does not occur in the case of receptor **2** (Figure 6).

Finally, adding anions to a solution of receptor **2** does not trigger noticeable changes in the chemical shifts of protons belonging to sugar moieties, as found to occur for receptor **1** (see the Supporting Information). This may suggest that in the case of receptor **2** the sugar parts do not interact with the side chain of anions during complexation, which may explain the weak enantiodiscrimination. A similar observation was made in our previous work.[5g] Moreover, amide NH signals in receptor **2** are not significantly perturbed during titration, suggesting that they are not involved in the formation of interactions with anion as hydrogen bond donors. These observations support

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

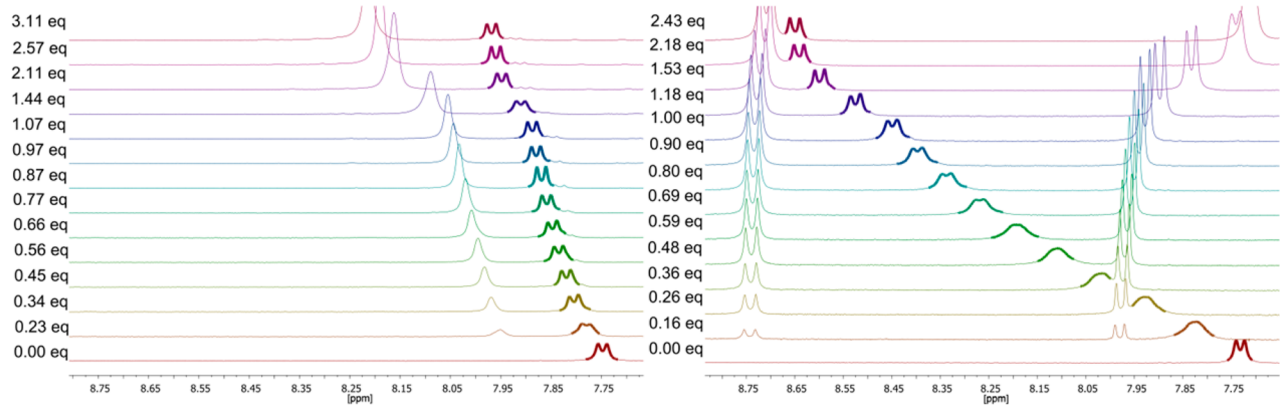


Figure 6. Fragments of stacked spectra from ^{1}H NMR titration of the TBA salt of *N*-acetylphenylglycine with receptors **1** (left) and **2** (right). The amide N*H* signal is presented as the boldface part of the spectra.

the conclusion that receptor **2** adopts a conformation with syn-anti or anti-anti arranged amide hydrogen bond donors. In such conformations, the sugar arms are oriented outside of the binding pocket, excluding their interactions with the side chain of the chiral guest.

To expand our research, we decided to perform a structural analysis of receptors **1** and **2** and their anion complexes in the solid state. We obtained two diffraction-grade crystals of **1**·H_2O and **2**·(*R*)-PhLac, for which X-ray crystallographic analysis was performed. Receptor **1** crystallizes from DMSO solution as a solvate containing disordered DMSO and water molecules. The unit cell of the investigated sample contains two disordered molecules of **1** slightly differentiated in conformation. One of them is presented in Figure 7, showing that the receptor adopts

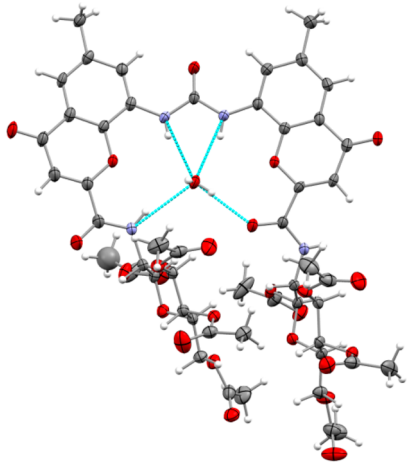


Figure 7. Crystal structure of **1**·H_2O. Thermal ellipsoids are drawn at the 50% probability level.

a conformation with three convergent NH bond donors. These NH groups are involved in strong interactions (2.98, 2.96, 3.02, 2.85 Å) with a water molecule located inside the binding pocket. This molecule of water also forms interactions as a donor, with the oxygen atom belonging to the anti-arranged amide group and with the neighboring molecule of DMSO, which stabilizes crystal packing. The sugar rings are almost perpendicular and are arranged relatively closely due to the geometry of the binding platform—distances between the anomeric carbon atoms equal 5.61 and 5.70 Å for both molecules in the independent part. The occurrence of a syn-anti conformation in the solid state may be rationalized as being due to a stabilizing interaction with solvent molecules as well as the effect of hydrogen bonding between receptor molecules, which stabilizes the crystal.

Slow evaporation of DMSO solution of receptor **2** in the presence of (*R*)-PhLac anion resulted in diffraction grade crystals, for which X-ray analysis results are presented in Figure 8. The independent part of the structure contains two slightly

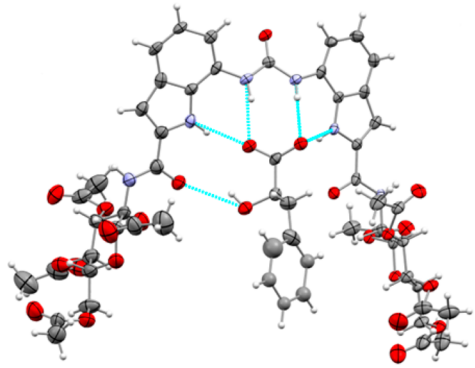


Figure 8. Crystal structure of **2**·(*R*)-PhLac. Thermal ellipsoids are drawn at the 50% probability level.

differentiated complexes. The carboxylic group of the anion is bound by four strong hydrogen bonds (2.73, 2.83, 2.93, 2.86 Å) formed by urea and indole groups. Both amide groups are oriented outside the binding pocket. One of them is involved in a hydrogen bond (3.01 Å) with the hydroxyl group of the anion. The other amide group forms an interaction as a hydrogen bond donor with the urea group of another molecule of the receptor, which stabilizes crystal packing.

Importantly, the organization of sugar moieties outside the binding pocket excludes interactions with the side chain of the anion, which can ensure enantiodiscrimination of guests—distances between anomeric carbon atom are equal to 13.47 and 13.69 Å for both molecules in the independent part. These distances are significantly higher than in the structure of **1**·H_2O. Importantly, the structure shows that the binding mode for receptor **2** in the solid state is the same as that proposed in solution (Scheme 2).

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

CONCLUSION

In conclusion, we have presented the synthesis and anion binding properties of two anion receptors containing sugar moieties. Compounds **1** and **2** show remarkable affinity toward both achiral and chiral carboxylate anions even in such competitive media as DMSO with 5% H_2O. Receptor **1**, which possesses a smaller number of potential H-bond donors than receptor **2**, is better tailored to all the achiral carboxylates investigated. However, receptor **2** was found to be more effective at binding amino acid derivatives due to an additional hydrogen bond with the side chain of anions. We also found differences between the receptors investigated in terms of their steric hindrance, which is manifested during complexation (Figure 2). Compound **1** exhibits significantly higher enantioselectivities than compound **2** for all anions investigated. We found that the receptors differ in terms of the interaction of their sugar moieties with chiral anions, which correlates with their chiral recognition abilities. The nonconvergently arranged amide groups in compound **2** affect the spatial arrangement of the sugar moieties, excluding interactions with the side chain of anions. This shows that the proper geometry and favored conformation of binding platforms play an important role in effective enantiodiscrimination of chiral anions by sugar-containing receptors.

EXPERIMENTAL SECTION

All precursors for synthesis were obtained from commercial suppliers and were used without further purification. All solvents were of reagent grade quality and were dried under standard conditions. Flash chromatography was carried out by using silica gel 60 (63−100 mesh); typically, a 40-fold mass excess of gel was used. TLC analysis was carried out on precoated silica gel plates (60 F_{254}). NMR spectra were recorded with 400 and 600 MHz NMR instruments. HRMS measurements were performed with a ESI and TOF analyzer. Optical rotations (OR) were measured in 10 cm cuvettes, and $[\alpha]_D^{20}$ values are given in deg cm^3 dm^{-1} g^{-1}.

Diethyl 8,8′-(Carbonylbis(azanediyl))bis(6-methyl-4-oxo-4*H*-chromene-2-carboxylate) (4). As this procedure involves the very toxic compound phosgene, the reaction should be carried out with caution under a well-ventilated hood, and the rotary evaporator should be equipped with a water jet pump to absorb the gaseous phosgene. The reaction was carried out under argon. Amine **3** (2.4 g, 9.71 mmol), obtained according to the literature procedure,[12] was dissolved in dry tetrahydrofuran (40 mL). Then, 20 mL of this solution was added dropwise to 20% phosgene solution in toluene (63.5 mL, 97 mmol) and the reaction mixture was refluxed for 15 min. After cooling, solvents were removed on a rotary evaporator. To the dry residue was added the remaining solution of amine **3** in tetrahydrofuran (20 mL), and the mixture was refluxed overnight. After cooling, the precipitate was filtered off and dried in vacuo, yielding **4** as a yellow powder (2.16 g, 86%). Mp: 283−287 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.24 (s, 2H), 8.69 (d, J = 1.8 Hz, 2H), 7.59 (dd, J = 2.1, 0.9 Hz, 2H), 7.14 (s, 2H), 4.53 (q, J = 7.1 Hz, 4H), 2.47 (s, 6H), 1.47 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2, 162.0, 152.3, 150.1, 143.8, 136.8, 129.2, 124.7, 123.9, 117.4, 115.3, 63.9, 21.6, 14.0. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{27}H_{24}N_2O_9Na$, 543.1375; found, 543.1380. Anal. Calcd for $C_{27}H_{24}N_2O_9{\cdot}2H_2O$: C, 58.27; H, 5.07; N, 5.03. Found: C, 58.03; H, 4.96; N, 5.09.

8,8′-(Carbonylbis(azanediyl))bis(6-methyl-4-oxo-4*H*-chromene-2-carboxylic acid) (5). Diester **4** (1 g, 1.92 mmol) was suspended in a 0.1 M solution of NaOH in 98% ethanol (46 mL) and stirred overnight. Then the reaction mixture was acidified with concentrated HCl and filtered off. The precipitate was washed with water (3 × 30 mL) and dichloromethane (3 × 30 mL) and dried in vacuo, yielding **5** as a yellow powder (0.88 g, 99%). Mp: 289−290 °C. ^{1}H NMR (400 MHz, DMSO): δ 9.42 (s, 2H), 8.22 (d, J = 2.0 Hz, 2H), 7.52 (d, J = 1.1 Hz, 2H), 6.92 (s, 2H), 2.41 (s, 6H). ^{13}C NMR (101 MHz, DMSO): δ 177.4, 161.5, 152.9, 152.5, 145.1, 135.3, 128.6, 127.3, 123.9, 117.8, 113.4, 20.9. HRMS (ESI-TOF): m/z $[M^{2-} + Na^+]^-$ calcd for $C_{23}H_{14}N_2O_9Na$, 485.0603; found, 485.0597. Anal. Calcd for $C_{23}H_{16}N_2O_9$: C, 59.49; H, 3.47; N, 6.03. Found: C, 59.25; H, 3.49, N, 5.87.

Diethyl 7,7′-(Carbonylbis(azanediyl))bis(1*H*-indole-2-carboxylate) (7). As this procedure involves the very toxic compound phosgene, the reaction should be carried out with caution under a well-ventilated hood. Amine **6** (0.9 g, 4.4 mmol), obtained according to the literature procedure,[13] was dissolved in dichloromethane (200 mL), and this solution was added to a saturated aqueous solution of $NaHCO_3$. Afterward, phosgene solution in toluene (1.3 g, 2.64 mmol) was added to the organic phase in two portions and the mixture was vigorously stirred overnight. Then, the organic phase was separated, dried over $MgSO_4$, and evaporated, yielding **7** as a white solid (0.9 g, 94%). Mp: 273−277 °C. ^{1}H NMR: δ 11.70 (s, 2H), 9.07 (s, 2H), 7.62 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.18 (s, 2H), 7.06 (t, J = 7.8 Hz, 2H), 4.33 (q, J = 13.8, 6.8 Hz, 4H), 1.34 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, DMSO): δ 161.2, 153.1, 129.2, 128.2, 127.2, 125.2, 120.7, 116.5, 114.9, 108.2, 60.5, 14.2. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{23}H_{22}N_4O_5Na$, 457.1488; found, 457.1488. Anal. Calcd for $C_{23}H_{22}N_4O_5{\cdot}H_2O$: C, 61.05; H, 5.35; N, 12.38. Found: C, 61.20; H, 5.23; N, 12.32.

7,7′-(Carbonylbis(azanediyl))bis(1*H*-indole-2-carboxylic acid) (8). Diester **7** (1.05 g, 2.42 mmol) was suspended in a 0.1 M solution of NaOH in 98% ethanol (266 mL) and refluxed for 2 h. After cooling, the mixture was concentrated on a rotary evaporator to one-third of the starting volume, acidified with concentrated HCl, filtered off, washed with water (3 × 30 mL) and ethanol (3 × 30 mL), and dried in vacuo, yielding **8** as a gray powder (0.83 g, 91%). Mp: 277−281 °C. ^{1}H NMR (400 MHz, DMSO): δ 11.55 (s, 2H), 8.90 (s, 2H), 7.56 (d, J = 7.4 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 2.0 Hz, 2H), 7.05 (t, J = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO): δ 162.7, 153.1, 129.1, 128.4, 128.2, 125.0, 120.5, 116.5, 114.8, 107.9. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{19}H_{14}N_4O_5Na$. 401.0851; found, 401.0862. Anal. Calcd for $C_{19}H_{14}N_4O_5{\cdot}H_2O$: C, 57.58; H, 4.07; N, 14.14. Found: C, 57.74; H, 4.00; N, 14.14.

Receptor 1. The reaction was carried out under argon. To a suspension of diacid **5** (232 mg, 0.5 mmol) in anhydrous dimethylformamide (10 mL) was added triethylamine (0.28 mL, 2 mmol), yielding a dark brown solution. Then HBTU (0.46 g, 1.2 mmol) was added and, after 5 min of stirring, per-OAc-glucosamine hydrochloride (1.2 mmol, 0.46 g), obtained according to the literature procedure,[14] was added and the reaction mixture was stirred overnight. Afterward, the solvent was evaporated under reduced pressure and water (20 mL) was added. The mixture was vigorously stirred for 1/2 h to disperse the precipitate. Then the residue was filtered off, washed with water, and air-dried. The precipitate was washed with dichloromethane/methanol (50 mL, 95/5 v/v), and fractions containing the soluble product were collected and evaporated to dryness. The crude product was purified by column chromatography on silica gel, with a dichloromethane/methanol (98.5/1.5 v/v) mixture as eluent. The product was crystallized from dichloromethane/hexane (1/3 v/v) mixture, yielding **1** as a yellow solid (0.26 g, 46%), Mp: 177−180 °C. $[\alpha]_D^{20}$ = −36.59 (c 1.1, DMSO). ^{1}H NMR (600 MHz, DMSO): δ 9.18 (s, 2H), 9.13 (d, J = 9.1 Hz, 2H), 8.32 (s, 2H), 7.50 (s, 2H), 6.79 (s, 2H), 5.92 (d, J = 8.7 Hz, 2H), 5.37 (t, J = 9.9 Hz, 2H), 5.01 (t, J = 9.7 Hz, 2H), 4.26−4.19 (m, 4H), 4.11−4.07 (m, 2H), 4.05−4.01 (m, 2H), 2.43 (s, 6H), 2.04 (s, 6H), 2.01 (s, 6H), 1.99 (s, 6H), 1.90 (s, 6H). ^{13}C NMR (151 MHz, DMSO): δ 177.0, 170.0, 169.2, 168.9, 159.9, 154.4, 152.1, 144.2, 135.4, 128.5, 126.0, 123.7, 117.6, 111.1, 91.5, 72.0, 71.7, 67.8, 61.4, 53.0, 21.0, 20.6, 20.5, 20.4, 20.3. HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{51}H_{54}N_4O_{25}Na$, 1145.2942; found, 1145.2975. Anal. Calcd for $C_{51}H_{54}N_4O_{25}{\cdot}2H_2O$: C, 52.85; H, 5.04; N, 4.83. Found: C, 52.98; H, 5.11; N, 4.79.

Receptor 2. The reaction was carried out under argon. To a suspension of diacid **8** (680 mg, 1.46 mmol) in anhydrous dimethyl sulfoxide (10 mL) was added triethylamine (5.86 mmol, 0.82 mL) under an inert atmosphere, yielding a gray solution. Then HBTU (3.5

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342−7348

mmol, 1.33 g) was added and, after 5 min of stirring, per-OAc-glucosamine hydrochloride (3.5 mmol, 1.22 g), obtained according to the literature procedure,[14] was added and the reaction mixture was stirred overnight. Afterward, water (10 mL) was added and the residue was filtered off, washed with water, and air-dried. The precipitate was washed with dichloromethane/methanol (50 mL, 95/5 v/v), and fractions containing soluble product were collected and evaporated to dryness. The crude product was purified by column chromatography on silica gel, with dichloromethane/methanol (99/1 v/v) mixture as eluent. The product was crystallized from a dichloromethane/hexane (1/3 v/v) mixture, yielding **2** as a white solid (0.65 g, 47%). Mp: 174–177 °C. $[\alpha]_D^{20}$ = −54.20 (*c* 1.0, DMSO). ^{1}H NMR (600 MHz, DMSO): δ 11.49 (s, 2H), 8.82 (s, 2H), 8.67 (d, *J* = 9.2 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 2.0 Hz, 2H), 7.03 (t, *J* = 7.8 Hz, 2H), 5.93 (d, *J* = 8.8 Hz, 2H), 5.39 (t, *J* = 9.9 Hz, 2H), 5.01 (t, *J* = 9.6 Hz, 2H), 4.29–4.20 (m, 4H), 4.08–3.99 (m, 4H), 2.04 (s, 6H), 2.02 (s, 6H), 2.00 (s, 6H), 1.87 (s, 6H). ^{13}C NMR (151 MHz, DMSO): δ 170.0, 169.5, 169.3, 168.8, 161.1, 153.1, 130.6, 128.4, 128.3, 124.9, 120.4, 116.2, 114.3, 103.4, 91.8, 72.3, 71.7, 68.1, 61.5, 52.3, 20.5, 20.5, 20.4, 20.3. HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{47}H_{52}N_6O_{21}Na$, 1059.3080; found, 1059.3083. Anal. Calcd for $C_{47}H_{52}N_6O_{21}\cdot 2H_2O$: C, 52.61; H, 5.26; N, 7.83. Found: C, 52.72; H, 5.28; N, 7.70.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00763.

Crystallographic data (CIF)
Crystallographic data (CIF)
Details concerning the determination of binding constants, TBA salt preparation, titration curves, and changes in ^{1}H NMR spectra, ^{1}H and ^{13}C COSY NMR spectra, and X-ray structure elucidation (including CCDC numbers) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*J.J.: e-mail, jurczak_group@icho.edu.pl; fax, +48 22 632 66 81; tel, +48 22 343 23 30.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financed by a Polish National Science Centre grant (Opus UMO-2014/15/B/ST5/05038). We acknowledge Dr. Ł. Dobrzycki for the crystallographic measurements, Dr. O. Staszewska-Krajewska for assistance with the NMR experiments, and P. Dydio, F. Ulatowski, J. Granda, and K. Dąbrowa for fruitful discussions.

■ REFERENCES

(1) (a) Berthod, A. *Chiral Recognition in Separation Methods: Mechanisms and Applications*; Springer: Berlin, Heidelberg, 2010. (b) Hembury, G. A.; Borovkov, V. V.; Inoue, Y. *Chem. Rev.* **2008**, *108*, 1.

(2) (a) Ariga, K.; Kunitake, T. *Supramolecular Chemistry-Fundamentals and Applications: Advanced Textbook;* Springer: Berlin, Heidelberg, 2006. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: Hoboken, NJ, 2009.

(3) Ulatowski, F.; Jurczak, J. *J. Org. Chem.* **2015**, *80*, 4235.

(4) Ito, T.; Ando, H.; Suzuki, T.; Ogura, T.; Hotta, K.; Imamura, Y.; Yamaguchi, Y.; Handa, H. *Science* **2010**, *327*, 1345.

(5) (a) Ulatowski, F.; Jurczak, J. *Asian J. Org. Chem.* **2016**, *5*, 715. (b) Qing, G.-y.; He, Y.-b.; Zhao, Y.; Hu, C.-g.; Liu, S.-y.; Yang, X. *Eur. J. Org. Chem.* **2006**, *2006*, 1574. (c) Willener, Y.; Joly, K. M.; Moody, C. J.; Tucker, J. H. R. *J. Org. Chem.* **2008**, *73*, 1225. (d) Bartoli, S.; Mahmood, T.; Malik, A.; Dixon, S.; Kilburn, J. D. *Org. Biomol. Chem.* **2008**, *6*, 2340. (e) Qing, G.-y.; Sun, T.-l.; Wang, F.; He, Y.-b.; Yang, X. *Eur. J. Org. Chem.* **2009**, *2009*, 841. (f) Granda, J. M.; Jurczak, J. *Org. Lett.* **2013**, *15*, 4730. (g) Hamankiewicz, P.; Granda, J. M.; Jurczak, J. *Tetrahedron Lett.* **2013**, *54*, 5608.

(6) Kim, Y. K.; Lee, H. N.; Singh, N. J.; Choi, H. J.; Xue, J. Y.; Kim, K. S.; Yoon, J.; Hyun, M. H. *J. Org. Chem.* **2008**, *73*, 301.

(7) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: London, 2006.

(8) (a) Kubik, S. *Chem. Soc. Rev.* **2010**, *39*, 3648. (b) Jurczak, J.; Chmielewski, M. J.; Dydio, P.; Lichosyt, D.; Ulatowski, F.; Zieliński, T. *Pure Appl. Chem.* **2011**, *83*, 1543. (c) Dydio, P.; Lichosyt, D.; Zieliński, T.; Jurczak, J. *Chem. - Eur. J.* **2012**, *18*, 13686. (d) Sommer, F.; Kubik, S. *Org. Biomol. Chem.* **2014**, *12*, 8851.

(9) (a) Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1995**, *36*, 3255. (b) de la Torre, M. F.; Campos, E. G.; González, S.; Morán, J. R.; Caballero, M. C. *Tetrahedron* **2001**, *57*, 3945. (c) Raposo, C.; Martin, M.; Mussons, M. L.; Crego, M.; Anaya, J.; Caballero, M.; Moran, J. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, *1*, 2113. (d) Raposo, C.; Almaraz, M.; Pérez, N.; Martín, M.; Weinrich, V.; Grande, M.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1996**, *37*, 1485. (e) Hernández, J. V.; Oliva, A. I.; Simón, L.; Muñiz, F. M.; Mateos, A. A.; Morán, J. R. *J. Org. Chem.* **2003**, *68*, 7513. (f) Raposo, C.; Crego, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R. *Tetrahedron Lett.* **1994**, *35*, 3409. (g) de la Torre, M. F.; González, S.; Campos, E. G.; Mussons, M. L.; Morán, J. R.; Caballero, M. C. *Tetrahedron Lett.* **1997**, *38*, 8591.

(10) (a) Caltagirone, C.; Gale, P. A.; Hiscock, J. R.; Brooks, S. J.; Hursthouse, M. B.; Light, M. E. *Chem. Commun. (Cambridge, U. K.)* **2008**, 3007. (b) Sambrook, M. R.; Hiscock, J. R.; Cook, A.; Green, A. C.; Holden, I.; Vincent, J. C.; Gale, P. A. *Chem. Commun. (Cambridge, U. K.)* **2012**, *48*, 5605. (c) Makuc, D.; Lenarcic, M.; Bates, G. W.; Gale, P. A.; Plavec, J. *Org. Biomol. Chem.* **2009**, *7*, 3505.

(11) Granda, J. M.; Jurczak, J. Sugar decorated receptors for chiral anions. In *Carbohydrate Chemistry*; Rauter, A. P., Lindhorst, T., Queneau, Y., Eds.; Royal Society of Chemistry: London, 2014; Vol. *40*, p 445.

(12) Anderluh, M.; Marc, G.; Dolenc, M. S. *Synth. Commun.* **2005**, *35*, 1461.

(13) Rether, C.; Sicking, W.; Boese, R.; Schmuck, C. *Beilstein J. Org. Chem.* **2010**, *6*, 3.

(14) Krishnamurthy, V. R.; Dougherty, A.; Kamat, M.; Song, X.; Cummings, R. D.; Chaikof, E. L. *Carbohydr. Res.* **2010**, *345*, 1541.

(15) Ulatowski, F.; Jurczak, J. *Tetrahedron: Asymmetry* **2014**, *25*, 962.

(16) Granda, J. M.; Jurczak, J. *Chem. - Eur. J.* **2015**, *21*, 16585.

DOI: 10.1021/acs.joc.6b00763
J. Org. Chem. 2016, 81, 7342–7348