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6,6′-Bis-substituted BINOL boronic acids as enantioselective and chemoselective fluorescent chemosensors for D-sorbitol

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Abstract

A new chiral fluorescent BINOL boronic acid **1** has been synthesized. The chiral recognition properties of **1** are drastically different from BINOL boronic acid **c**. Sensor **1** shows improved enantioselectivity as well as chemoselectivity toward sugar alcohols, such as D-sorbitol and D-mannitol.The enantioselectivity of sensor **1** toward D-sorbitol (K_R/K_S) is 1:35 (pH 9.0), and the chemoselectivity for D-sorbitol/D-mannitol is 20:1.

Keywords: BINOL boronic acid; Chiral recognition; Enantioselective sensors; Sugar alcohols

1. Introduction

As the chemistry of saccharides and related compounds plays a significant role in the metabolic pathways of living organisms, detecting the presence and concentration of biologically important sugars (glucose, fructose, galactose, etc.) and other chiral molecules in aqueous solution is necessary in a variety of medicinal and industrial contexts.[1–8] The recognition ability of many synthesized receptors is based on hydrogen bonding or complexation interactions.[9–12] The efficiency of such interactions has been well demonstrated in nonaqueous systems, but in aqueous media, hydrogen bonding between the solvent and analytes will compete with hydrogen bonding between the sensor and analytes. However, a boronic acid readily forms covalent bonds with saccharides in aqueous media, and this unique recognition mechanism represents an important alternative binding force for the recognition of saccharides and related molecular species in aqueous media. Recently, much attention has been paid to boron-containing sensors,[13–32] including simple boronic acids. Yoon and Czarnik have shown that 2- and 9-anthryboronic acid could be used to detect saccharides,[15] however, with simple boronic acids, saccharide binding requires a high pH of the solution. To overcome this disadvantage, molecular fluorescent sensors that contain a boronic acid group and an amine group have been developed.[16,17] With these systems binding is strong even at neutral pH. Thereafter many boronic sensors based on this structure motif have been employed to recognize saccharides.[13–34]

Sugar alcohols, such as D-sorbitol and D-mannitol, are bioactive metabolic intermediates and have been used as medicines. Therefore, it is necessary to develop fluorescent sensors for these chiral polyhydroxyl compounds. To our surprise, very few fluorescent sensors for these important sugar alcohols have been reported to date. The diboronic acid with a small binding pocket was synthesized and was shown to be selective for small saccharides such as D-sorbitol (Scheme 1, **a**).[18] However, the binding constants are small. An achiral boronic acid sensor for sorbitol was reported (Scheme 1, **b**).[27c] To the best of our knowledge, only compounds **c** and **d** have been reported as chiral fluorescent chemosensors for sugar alcohols (Scheme 1).[31–33] The BINOL diboronic acid **c** is not selective for D-sorbitol.[32] In order to develop improved fluorescent chiral discriminating systems for sugar alcohols,

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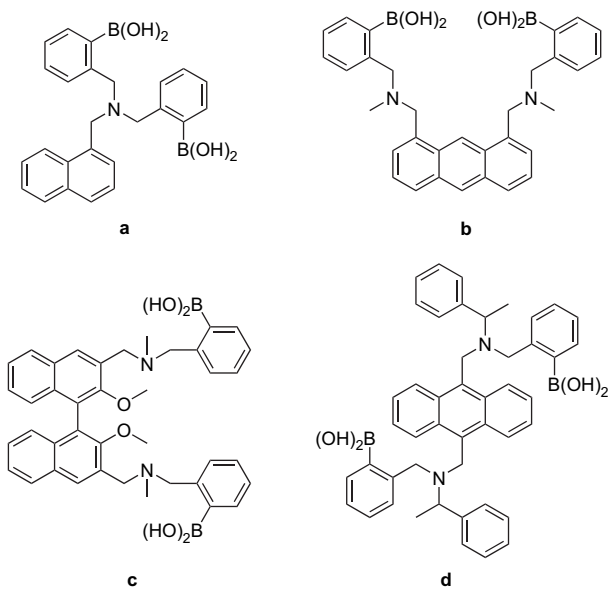
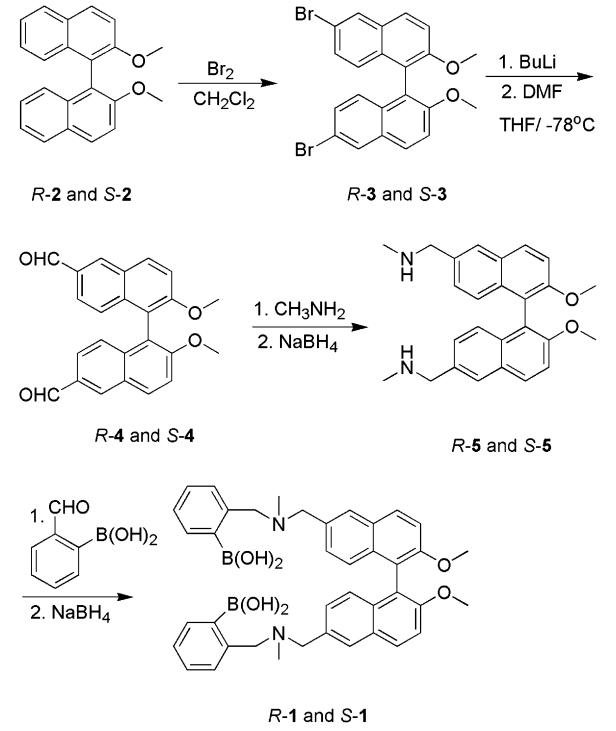


Scheme 1. Fluorescent chemosensors for sugar alcohols.

we synthesized sensor **1** (*R* and *S*) and the interaction of the two enantiomers with saccharides was investigated. It is found that sensor **1** shows a drastically different binding profile from its regioisomer (Scheme 1, **c**),[32] and is sensitive, highly enantioselective, and chemoselective for sugar alcohols, such as D-sorbitol and D-mannitol.

2. Results and discussion

The synthesis of sensor **1** is summarized in Scheme 2. Treatment of *R*-**2** with bromine at room temperature gave **3**



Scheme 2. Synthesis of the fluorescent sensors *R*-**1** and *S*-**1**.

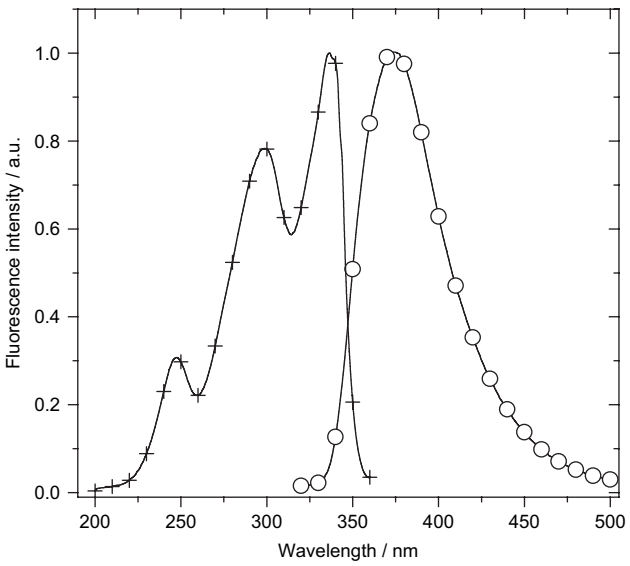


Figure 1. Normalized excitation (cross) and emission spectrum (circles) of chiral boronic acid sensor *R*-**1**. 9.26×10^{-6} mol dm^{-3} of sensor in 5×10^{-2} mol dm^{-3} NaCl ionic buffer (52.1% methanol in water). pH=1.99, λ_{ex} at 305 nm, λ_{em} at 374 nm.

in 74% yield. Compound **3** was formylated with *n*-BuLi and DMF in dry THF and **4** was obtained in 66.2% yield. Reductive amination with methylamine and $NaBH_4$ led to **5** in 79.6% yield. Reaction of *R*-**5** with 2-formylphenylboronic acid, followed by $NaBH_4$ reduction, gave the fluorescent sensor *R*-**1** in 54.5% yield. *S*-**1** was prepared with similar methods.

The excitation and emission fluorescence spectrum of sensor *R*-**1** is shown in Figure 1. An emission maxima at 374 nm (λ_{ex} at 305 nm) was observed. The excitation wavelength and emission wavelength of sensor *R*-**1** are red-shifted compared to that of the reported boronic acid (Scheme 1, **c**) (λ_{ex} at 289 nm, λ_{em} at 358 nm), which is a regioisomer of sensor **1**.[32,35]

It is known that the fluorescence response of the boronic acid chemosensors as well as the binding of the boronic acid with polyhydroxyl or hydroxyl acid is pH-dependent therefore, the fluorescence–pH profile of sensor **1** in the presence of various analytes was investigated since this would allow a rapid preview of the optimal pH region of the boronic acid sensors. As an example, the results observed for sensors *R*-**1** and *S*-**1** with D-sorbitol and xylitol are shown in Figure 2. In the presence of D-sorbitol, sensors *R*-**1** and *S*-**1** display different fluorescence responses (Fig. 2). The apparent pK_a value of *R*-**1** is 5.32±0.08 and this value shifts to 7.66±0.14 in the presence of D-sorbitol. Large fluorescence changes were observed in the pH range of 6–10. In this range, the fluorescence enhancement is high and the enantioselective recognition by the boronic acid sensors for D-sorbitol is significant.

In the presence of xylitol, which is an achiral sugar alcohol, no enantioselectivity was observed. The apparent pK_a value of *R*-**1** is 5.32±0.08 and in the presence of xylitol this value shifts to 9.94±0.03. Similarly, the pK_a of *S*-**1** is 5.31±0.14 and in the presence of xylitol this value shifts to 9.90±0.03. This result gives a negative control for the chiral recognition of the D-sorbitol by *R*- and *S*-**1**.

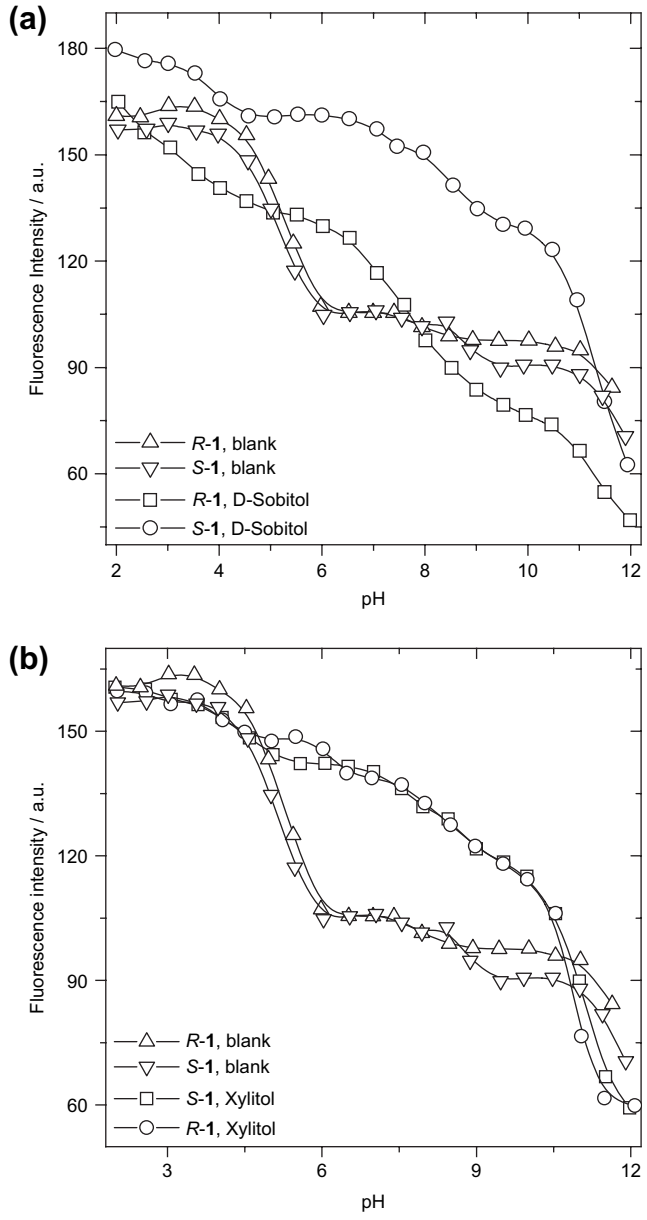


Figure 2. Fluorescence intensity–pH profile of sensors *R*-**1** and *S*-**1** versus D-sorbitol (a) and xylitol (b). λ_{ex} at 305 nm, λ_{em} at 374 nm, 9.26×10^{-6} mol dm^{-3} of sensors in 5.0×10^{-2} mol dm^{-3} NaCl ionic buffer (52.1% methanol in water), [D-sorbitol] and [xylitol]$=5.0\times10^{-2}$ mol dm^{-3}.

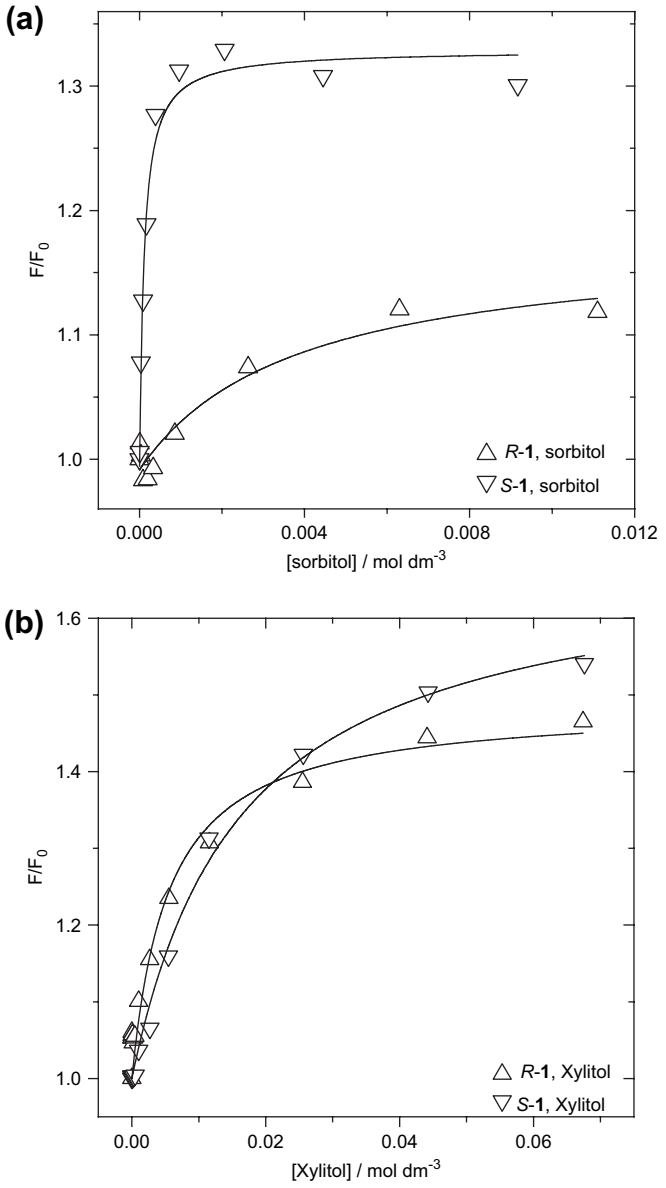


Figure 3. Relative fluorescence intensity of sensors *R*-**1** and *S*-**1** versus concentration of D-sorbitol (a) and xylitol (b). λ_{ex} at 305 nm, λ_{em} at 374 nm, pH=9.0, 9.26×10^{-6} mol dm^{-3} of sensors in 0.05 mol dm^{-3} NaCl ionic buffer (52.1% methanol in water).

Titrations of the sensors with D-sorbitol were carried out at pH 6.0, 8.0, and 9.0 to determine the binding constants. At pH 9.0, a significant fluorescence enhancement was observed with *S*-**1** in the presence of D-sorbitol, whereas with *R*-**1**, smaller fluorescence enhancement was observed (Fig. 3). The binding constants of the sensors with the D-sorbitol are also significantly different. The binding constant of *S*-**1** with D-sorbitol is $(9.30\pm1.75)\times10^3$ M^{-1}, while the binding constant of *R*-**1** with D-sorbitol is only $(2.63\pm1.55)\times10^2$ M^{-1}, thus the enantioselectivity is K_R/K_S=1:35. Based on the fluorescence enhancement, the response selectivity was calculated as $F_R/F_S=(K_R\times F_R)/(K_S\times F_S)$=1:42. As a control experiment, no enantioselectivity was observed when using achiral xylitol (Fig. 3b).

Titrations with D-glucose were also carried out (pH 6.0 and 8.0). No enantioselective recognition by the boronic acid sensors **1** for D-glucose was observed at pH 8.0. At pH 6.0, the enantioselectivity of the boronic acid sensors *R*-**1** and *S*-**1** for D-glucose is K_R/K_S=1.4:1 (Table 1). These values are similar to those reported for the regioisomers (Scheme 1, **c**).[32] The fluorescence enhancement of *R*-**1** was similar to *S*-**1** in the presence of D-glucose at pH 8.0. The binding constant of *R*-**1** sensor with the D-glucose is $(2.42\pm0.69)\times10^2$ M^{-1}, while the binding constant of *S*-**1** with the D-glucose is $(2.32\pm0.40)\times10^2$ M^{-1}, the enantioselectivity is weak (Table 1).

The recognition of sugar acids with sensor **1** was also studied. Titrations of the sensor with sodium D-gluconate were carried out at pH 3.0 and 6.0. At pH 3.0, the fluorescence intensity of sensor *R*-**1** and *S*-**1** decreased in the presence of sodium

Table 1
Fluorescence enhancement F on binding and enantioselectivity (K_R/K_S) of sensors *R*-**1** and *S*-**1**[a]

Analytes	pH	*R*-**1**		*S*-**1**		Response selectivity[b]	
		K	F/F_0	K	F/F_0	K_R/K_S	R/S
D-Tartaric acid	6.0	$(1.72\pm0.41)\times10^5$	1.49	$(8.43\pm2.70)\times10^4$	1.67	2.04:1	1.82:1
L-Tartaric acid	6.0	$(6.54\pm1.73)\times10^4$	1.50	$(1.26\pm0.45)\times10^5$	1.48	1:1.93	1:1.90
D-Gluconate	3.0	$(5.99\pm1.30)\times10^3$	0.88	$(3.02\pm1.66)\times10^3$	0.90	1.98:1	1.94:1
	6.0	$(1.50\pm0.19)\times10^4$	1.38	$(4.52\pm0.56)\times10^4$	1.30	1:3.01	1:2.84
D-Sorbitol	6.0	$(1.09\pm0.15)\times10^3$	1.30	$(5.88\pm0.94)\times10^3$	1.31	1:5.39	1:5.43
	8.0	$(1.13\pm0.36)\times10^3$	1.21	$(1.13\pm0.25)\times10^4$	1.32	1:10.0	1:10.9
	9.0	$(2.63\pm1.55)\times10^2$	1.12	$(9.30\pm1.75)\times10^3$	1.33	1:35.4	1:42.0
D-Mannitol	6.0	$(5.16\pm0.49)\times10^2$	1.37	$(2.82\pm0.19)\times10^2$	1.50	1.83:1	1.67:1
	7.0	$(3.24\pm0.29)\times10^2$	1.52	$(1.35\pm0.67)\times10^3$	1.41	1:4.17	1:3.87
	8.5	$(2.45\pm0.40)\times10^2$	1.30	$(3.02\pm0.52)\times10^2$	1.38	1:1.23	1:1.31
Xylitol	9.0	$(1.16\pm0.16)\times10^2$	1.46	$(0.65\pm0.07)\times10^2$	1.54	1.78:1	1.69:1
D-Glucose	6.0	$(2.01\pm0.33)\times10^2$	1.36	$(1.46\pm0.15)\times10^2$	1.32	1.38:1	1.42:1
	8.0	$(2.42\pm0.69)\times10^2$	1.24	$(2.32\pm0.40)\times10^2$	1.26	1.04:1	1.02:1

[a] 9.26×10^{-6} mol dm^{-3} *R*-**1** or *S*-**1** in 0.05 mol dm^{-3} NaCl ionic buffer (52.1% methanol in water), λ_{ex} at 305 nm, λ_{em} at 374 nm. Constants determined by fitting a 1:1 binding model to I/I_0. r^2=0.99 in most cases. F values agree well with the experimental results.
[b] Response selectivity=$(K_R\times F_R)/(K_S\times F_S)$.

D-gluconate. A significant fluorescence reduction was observed with *R*-**1** in the presence of sodium D-gluconate compared to that of *S*-**1**. The binding constant of *R*-**1** with sodium D-gluconate is $(5.99\pm1.30)\times10^3$ M^{-1}, whilst the binding constant of *S*-**1** with sodium D-gluconate is $(3.02\pm1.66)\times10^3$ M^{-1}, the enantioselectivity is K_R/K_S=1.98:1 (Table 1).

The regioisomer of sensor **1**, compound **c** (Scheme 1), was reported to be highly enantioselective for tartaric acid, and a novel fluorescence response profile was found that either an increased or diminished fluorescence response was observed in the presence of the enantiomers of tartaric acids.[32] For sensor **1**, however, only minor enantioselectivity was found for tartaric acid (Fig. 4 and Table 1). The apparent pK_a of the sensor **1** is 5.23±0.05. With tartaric acid, this value changed to 8.36±0.13 (for D-tartaric acid) and 9.08±0.02 (for L-tartaric acid). The fluorescence enhancement of the D- and L-tartaric acid is nearly the same. Therefore, there is no significant enantioselectivity for tartaric acid. The binding constant study proved this (Fig. 4b). The binding constants of *R*-**1** with D- and L-tartaric acid at pH 6.0 are $(1.72\pm0.41)\times10^5$ M^{-1} and $(6.54\pm1.73)\times10^4$ M^{-1}, respectively.

The binding of the sensor **1** with other sugar alcohols, such as D-mannitol was also investigated and the binding constants, fluorescent enhancement, and enantioselectivities (K_R/K_S) are listed in Table 1.

The data in Table 1 indicate that this system is highly enantioselective and sensitive for D-sorbitol, compared to a reported BINOL boronic acid, which shows no enantioselectivity for D-sorbitol (Scheme 1, **c**).[32] Sensor **1** shows an enantioselectivity of 1:35 with D-sorbitol versus 1:1 for the previously reported chiral sensor (Scheme 1, **c**).[32] An improved chemoselectivity of 20:1 with sorbitol/mannitol was also observed, compared to a chemoselectivity of 10:1 for the previously reported sensor (Scheme 1, **c**).[32]

Binding with sugar alcohols is pH-dependent. Sensor **1** is more selective for D-sorbitol over D-mannitol, compared to the reported chiral sensor (Scheme 1, **d**) and the binding of the present sensor for D-sorbitol is 5–10 fold higher than that of compound **a** (Scheme 1), which is an achiral sensor.[18,33]

We have demonstrated that the chirality of the sensors can be used to improve the enantioselectivity as well as the chemoselectivity.[33] Similar results are also found for sensor **1**, with *R*-**1**, the selectivity for sorbitol over mannitol is 2:1 (at pH 6). With *S*-**1**, however, the chemoselectivity increases to 20:1. Similar results are also found for other analytes. For example, the selectivity for sorbitol over glucose at pH 8.0 is 5:1. With *S*-**1**, the chemoselectivity is improved to nearly 50:1.

Fluorescence lifetimes of the sensors with and without the analytes were studied and the preliminary results are listed in Table 2. Longer fluorescence lifetimes were observed for the sensor in the presence of D-sorbitol. This is consistent with the fluorescence enhancement as well as the photo-induced electron transfer (PET) mechanism of the sensor. Furthermore, a longer lifetime was found for *S*-**1** compared to *R*-**1**, which is consistent with the fact that *S*-**1** gives a tighter binding with D-sorbitol. For D-gluconate, no significant changes were observed for the fluorescence lifetimes. The variation of the fluorescence lifetimes of the chemosensor in the presence of analytes is interesting. In principle, especially for those with longer emission lifetimes, this kind of response can be used for the technique of fluorescence lifetime imaging microscopy (FLIM), which is intrinsically superior to intensity-based analysis.

3. Conclusions

In summary, new BINOL fluorescent chiral chemosensors **1** were synthesized and a different recognition profile to that of the regioisomeric chemosensor (Scheme 1, **c**) was observed. The new chiral sensor gives higher binding constants for sugar alcohols. An improved response selectivity was observed for D-sorbitol/D-mannitol. The chemoselectivity between D-sorbitol/D-glucose is also improved compared to the achiral

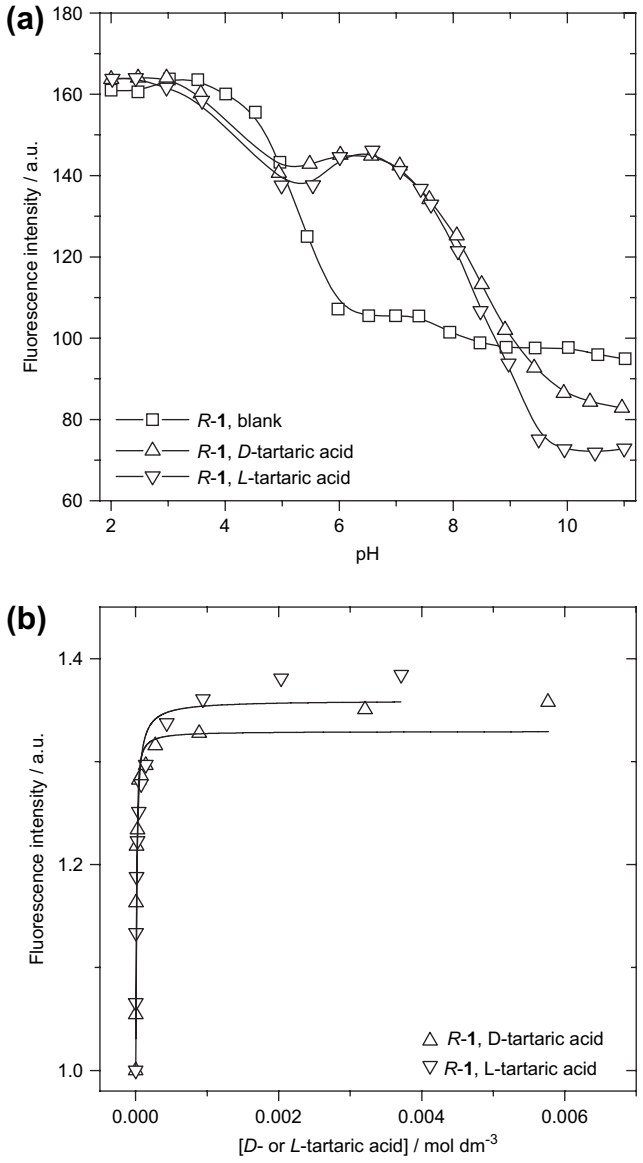


Figure 4. Fluorescence intensity–pH profile of *R*-**1** sensor versus D- or L-tartaric acid (a) and the titration curve of *R*-**1** with L- and D-tartaric acid at pH 6.0 (b). λ_{ex} at 295 nm, λ_{em} at 372 nm, 9.26×10^{-6} mol dm^{-3} of sensor in 2.5×10^{-2} mol dm^{-3} NaCl ionic buffer (52.1% methanol in water), [L- and D-tartaric acid]=5.0×10^{-2} mol dm^{-3}.

sensors. Our future aim will be to design chiral sensors, which are specific for other biologically interesting sugar alcohols.

Table 2
Fluorescence lifetimes of sensor *R*-**1** and *S*-**1** in the presence of D-sorbitol and sodium D-gluconate

Sensor/analytes	*R*-**1** τ (ns)	*S*-**1** τ (ns)
Blank sensor[a]	4.52±0.01	4.81±0.01
D-Sorbitol[a]	5.08±0.01	5.74±0.01
Blank sensor[b]	5.82±0.02	5.71±0.02
D-Gluconate[b]	5.86±0.02	5.71±0.02

[a] 2.23×10^{-5} mol dm^{-3} *R*-**1** and *S*-**1** in 0.05 mol dm^{-3} NaCl ionic buffer (52.1% methanol in water), at pH 7.5, [D-sorbitol]=9.15×10^{-3} mol dm^{-3}.
[b] 8.38×10^{-6} mol dm^{-3} *R*-**1** and *S*-**1** in 0.05 mol dm^{-3} NaCl ionic buffer (52.1% methanol in water), at pH 2.5, [D-gluconate]=6.88×10^{-3} mol dm^{-3}.

4. Experimental

4.1. General

Fluorescence spectra were measured on a F4500 fluorospectrometer (Hitachi) and CRT 970 fluorescence spectrometer. A 0.05 M NaCl (52.1% methanol in water, w/w) ionic buffer was used in the experiment. The final concentration of the sensors was fixed at 9.26×10^{-6} mol dm^{-3} (by dilution of a stock solution of the sensor into the buffer by more than 500 times). All pH measurements were recorded on a Delta 320 Microprocessor pH meter (Mettler Toledo), which was routinely calibrated using standard buffer solutions. The fluorescence emission spectra of the sensors, with or without the analytes, were recorded as the pH was changed from pH 2 to 12 in approximate intervals of 0.5 pH units. The pH was controlled using minimum volumes of sodium hydroxide and hydrochloric acid solutions. The fluorescence spectra of the sensors in the presence of the analytes were recorded as increasing amounts of the analyte were added to the solution. For all titrations the final pH was controlled to within less than 0.03 units of the desired pH. The fluorescence lifetime was measured with frequency-domain instrument of Chronos 95145 Fluorescence Lifetime Spectrometer (ISS, Inc., Champaign, IL, USA) with 9 KHz–1.2 GHz signal generator. The phase angle and the modulation ratio were recorded with scanning of the modulation frequency. The regression of the experimental curves was carried out with the software VINCI Analysis (BETA 1.6). Titration curves were generated using the Origin 5.0 (Microcal software). The binding constants were calculated using custom-written nonlinear least-square curve-fitting programs implemented within SigmaPlot 2000 (SPSS Inc.).

4.2. (*R*)- and (*S*)-6,6′-Dibromo-2,2′-dimethoxy-1,1′-binaphthalene (**3**)

(*R*)-2,2′-Dimethoxy-1,1′-binaphthalene (**2**) (3.14 g, 50 mmol) was dissolved in CH_2Cl_2 (100 mL) and stirred at 0 °C (ice/water bath). Bromine (1.13 mL, 44 mmol) was added in one portion with vigorous stirring and a stream of nitrogen was bubbled through the solution to remove the evolving HBr gas. The reaction mixture was stirred for additional 5 h while the flask was allowed to warm to room temperature. The nitrogen flow was stopped and the yellow solution was allowed to stand overnight. A 20 mL of 10% $NaHSO_3$ solution was added with a vigorous stir to quench the excess bromine. The colorless organic layer was separated, washed with 10% $NaHSO_3$ solution and water, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 3.50 g of white amorphous powder (74%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.01 (s, 2H), 7.87 (d, 2H, J=8.0 Hz), 7.44 (d, 2H, J=8.0 Hz), 7.26 (d, 2H, J=8.0 Hz), 6.92 (d, 2H, J=8.0 Hz), 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.3, 132.5, 130.4, 130.1, 129.9, 128.9, 127.1, 119.2, 117.6, 115.1, 56.7. APCI positive *m*/*z* 472.9.

4.3. (*R*)- and (*S*)-2,2′-Dimethoxy-[1,1′] binaphthalene-6,6′-dicarbaldehyde (**4**)

Under nitrogen atmosphere, 1.0 g of (*R*)-6,6′-dibromo-2,2′-dimethoxy-1,1′-binaphthalene (**3**) (2.12 mmol) was dissolved in 60 mL of dry THF. The stirred solution was cooled to −78 °C in dry ice/acetone bath, and 1.7 mL of *n*-BuLi (2.5 M in *n*-hexane, 4.25 mmol) was added slowly to keep the temperature below −70 °C. After 5–6 h of stirring at this temperature, 0.5 mL of dry *N*,*N*-dimethylformamide (6.46 mmol) was added slowly to keep the temperature below −50 °C. After stirring for 45 min at this temperature, the reaction mixture was poured into HCl/ice water (pH<1) under vigorous stirring. The mixture was extracted with 3×50 mL CH_2Cl_2. The combined organic phases were washed twice with water and dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oil. In order to obtain an analytical sample, the oil was submitted to column chromatography on silica using CH_2Cl_2 as eluting agent to give 0.52 g of white amorphous powder. Yield: 66.2%; ^{1}H NMR (400 MHz, $CDCl_3$) 10.10 (s, 2H), 8.38 (s, 2H), 8.17 (d, 2H, *J*=8.0 Hz), 7.69 (d, 2H, *J*=8.0 Hz), 7.54 (d, 2H, *J*=8.0 Hz), 7.14 (d, 2H, *J*=8.0 Hz), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 192.2, 157.7, 137.3, 135.3, 132.4, 132.0, 128.2, 126.0, 123.6, 119.0, 114.5, 56.7. APCI positive *m*/*z* 371.1 ($[M+H]^+$).

4.4. (*R*)- and (*S*)-2,2′-Dimethoxy-*N*,*N*′-dimethyl-1,1′-binaphthalene-6,6′-dimethanamine (**5**)

Methylamine (17 mL, 33% by weight, 8 M solution in absolute ethanol, 135 mmol) was added under nitrogen atmosphere to (*R*)-2,2′-dimethoxy-[1,1′]-binaphthalenyl-6,6′-dicarbaldehyde (**4**) (0.5 g, 1.25 mmol), the reaction mixture was stirred at room temperature for 18 h. Then $NaBH_4$ (0.7 g, 18.4 mmol) was added in one portion. The solution was stirred for another 2 h until the Schiff base was completely reduced to amine (monitored with TLC, silica gel, dichloromethane/petroleum ether=2:1, v/v). The solution was concentrated under reduced pressure and the residue was mixed with 50 mL water. The aqueous solution was extracted with dichloromethane (3×100 mL). The combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the amine as a white solid (0.43 g, 79.6%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (d, 2H, *J*=8.0 Hz), 7.75 (s, 2H), 7.39 (d, 2H, *J*=8.0 Hz), 7.13 (d, 2H, *J*=8.0 Hz), 7.01 (d, 2H, *J*=8.0 Hz), 3.82 (s, 4H), 3.71 (s, 6H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.0, 134.2, 133.4, 129.4, 129.2, 127.3, 127.5, 125.7, 119.6, 114.5, 94.6, 57.0, 35.7. TOF EI-MS (positive) *m*/*z* 400.2148.

4.5. (*R*)- and (*S*)- [(2,2′-Dimethoxy[1,1′-binaphthalene]-6,6′-yl)bis[methylene(methylimino)-methylene-2,1-phenylene]]boronic acid (**1**)

To a stirred solution of (*R*)-2,2′-dimethoxy-*N*,*N*′-dimethyl-[1,1′]binaphthalenyl-6,6′-dimethanamine (**5**) (200 mg, 0.30 mmol) in 30 mL of methanol at room temperature was added 2.2 equiv of 2-formylphenylboronic acid (164 mg, 1.09 mmol). The mixture was allowed to react for 2 h, at which time 10 equiv of sodium borohydride (185 mg, 4.87 mmol) was added. The mixture was stirred for an additional 1 h. The solvent was removed in vacuum, and the resulting solid was redissolved in 30 mL of water and the aqueous phrase was extracted with methylene chloride (3×50 mL). The organic phase was dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified with column chromatography (Al_2O_3, dichloromethane/methanol=50:1, v/v). A white solid was obtained (*R*-**1**) (182 mg, 54.5%). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) 7.89 (d, 2H, *J*=8.0 Hz), 7.68–7.69 (m, 2H), 7.39 (d, 2H, *J*=8.0 Hz), 7.21–7.25 (m, 6H), 7.06 (d, 4H, *J*=8.0 Hz), 6.98 (d, 2H, *J*=8.0 Hz), 3.68–3.70 (m, 14H), 2.15 (br, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 155.2, 140.5, 135.12, 132.30, 130.2, 129.5, 128.9, 128.3, 128.1, 127.8, 127.7, 126.4, 124.8, 118.4, 113.3, 62.9, 61.9, 54.9, 35.8. TOF EI-MS$^+$ 335.0063 ($[M+2H]^{2+}$), 651.0013 ($[M-H_2O+H]^+$). *S*-**1** was synthesized with similar methods. ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD) 8.00 (d, 2H, *J*=8.0 Hz), 7.81 (br, 2H), 7.49 (d, 2H, *J*=8.0 Hz), 7.29–7.34 (m, 6H), 7.16 (d, 4H, *J*=8.0 Hz), 7.08 (d, 2H, *J*=8.0 Hz), 3.79–3.81 (m, 14H), 2.31 (br, 6H). TOF EI-MS (positive) *m*/*z* 335.1179 ($[M+2H]^{2+}$), 651.2379 ($[M-H_2O+H]^+$).

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