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Fluorescent Sensors for the Enantioselective Recognition of Mandelic Acid: Signal Amplification by Dendritic Branching

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Abstract: Novel chiral bisbinaphthyl compounds have been synthesized for the enantioselective fluorescent recognition of mandelic acid. By introducing dendritic branches to the chiral receptor unit, the fluorescence signals of the receptors are significantly amplified because of the light-harvesting effect of the dendritic structure. This has greatly increased the sensitivity of the sensors in the fluorescent recognition. Study of the three generation sensors demonstrates that the generation zero sensor is the best choice for the recognition of mandelic acid because of its greatly increased fluorescence signal over the core and its high enantioselectivity. This sensor is potentially useful for the high throughput screening of chiral catalysts for the asymmetric synthesis of α-hydroxycarboxylic acids.

Introduction

Enantioselective fluorescent sensors are potentially useful for the rapid assay of the enantiomeric composition of chiral substrates. Although chiral recognition in photoluminescence has been studied for over two decades,[1−6] only recently has the development of practically useful chiral fluorescent sensors attracted research attention.[7,8] Figure 1 gives two examples of fluorophores that have exhibited good enantioselective responses toward chiral molecules. The 1,1′-binaphthyl compound was used for the recognition of certain saccharides,[7a] and the hexahelicene[7c] was used for certain amino alcohols.

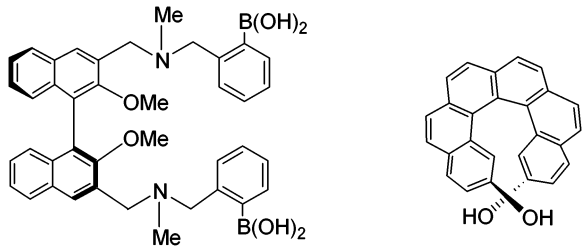

Figure 1. Two compounds used for enantioselective fluorescent recognition.

In our laboratory, we are interested in developing fluorescent sensors for the enantioselective recognition of chiral α-hydroxycarboxylic acids. α-Hydroxycarboxylic acids are found to be the structural units of many natural products and drug molecules.[9,10] They can also serve as multifunctional precursors to many organic compounds. Significant progress has been made for the synthesis of chiral α-hydroxycarboxylic acids.[9,10] One of the most efficient ways to generate optically active α-hydroxycarboxylic acids is by asymmetric catalysis. Although the traditional method to individually design and test chiral catalysts has greatly advanced the field of asymmetric catalysis,[11] a tremendous amount of trial and error is still required in this process. Thus, employing the high throughput combinatorial screening technique should significantly facilitate the search of highly enantioselective as well as practical catalysts.[12] Enantioselective fluorescent sensors would be very useful to quickly

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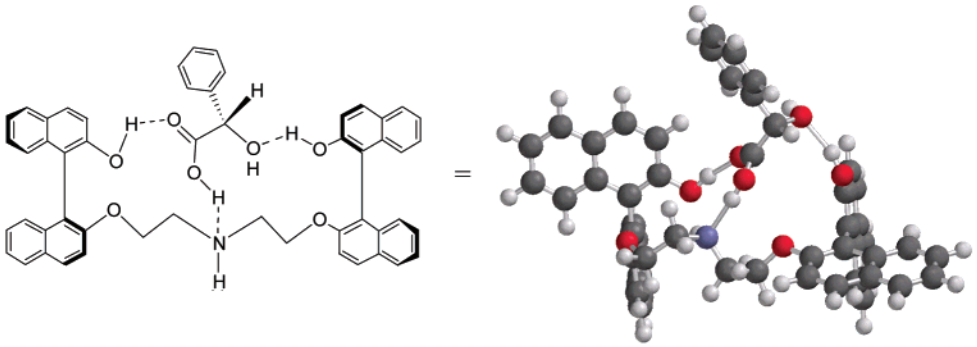
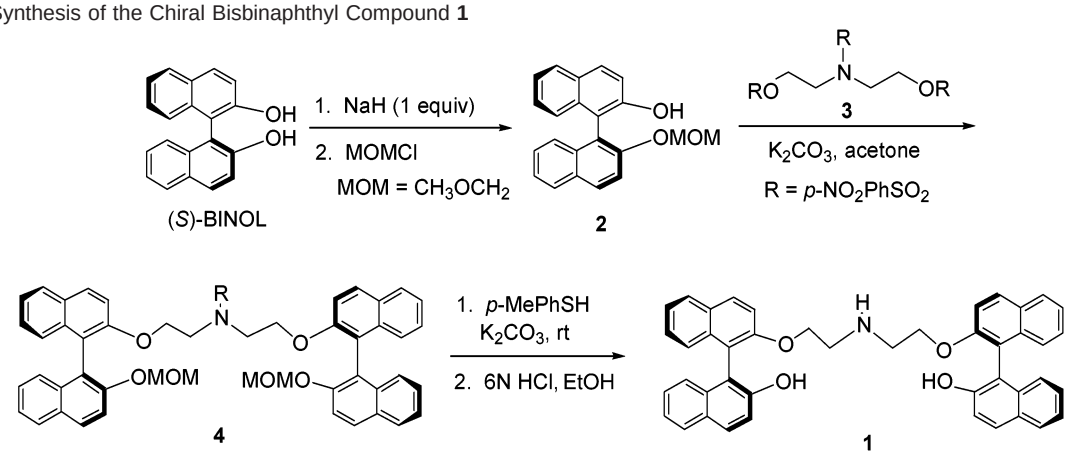


Figure 2. Proposed structure for the complex **1** + (*S*)-mandelic acid.

Scheme 1. Synthesis of the Chiral Bisbinaphthyl Compound **1**



determine the enantioselectivity of the catalysts used in a combinatorial assay because the current fluorescence microplate readers can measure the fluorescence signals of hundreds of samples in a matter of minutes. Other techniques such as electron-spray mass spectrometry, IR thermograph, and electrophosphoresis are also under development for the fast analysis of chiral compounds.[13] Using enantioselective fluorescent sensors has the advantage of being able to directly determine the substrate enantiomeric purity. We have designed and synthesized chiral bisbinaphthyl-based compounds for the enantioselective fluorescent recognition of mandelic acid, a chiral α-hydroxycarboxylic acid. We have further applied the light-harvesting effect of dendritic materials to construct sensors with largely increased fluorescent signals and thus greatly improved sensitivity. Herein, this work is reported.[14]

Results and Discussion

1. Design and Synthesis of Chiral Bisbinaphthyl-Based Fluorescent Sensors. We have designed a chiral bisbinaphthyl molecule for the fluorescent recognition of α-hydroxycarboxylic acids. The molecular modeling structure (PCSpartan-Pro with semiemperical PM3 force field) depicted in Figure 2 is a proposed hydrogen-bonded complex between the designed receptor **1** and mandelic acid. In **1**, its nitrogen lone pair electrons are positioned to quench the fluorescence of the binaphthyl units by an intramolecular photoinduced-electron-transfer (PET) process.[15,16] Thus, an α-hydroxycarboxylic acid should be able to enhance the fluorescence of **1** by protonation of its nitrogen atom. The two enantiomers of a chiral α-hydroxycarboxylic acid should form two diastereomeric complexes with **1**, giving different fluorescence responses.

Compound **1** was readily prepared according to Scheme 1. Reaction of (*S*)-1,1′-bi-2-naphthol [(*S*)-BINOL] with 1 equiv of NaH followed by treatment with MOMCl gave the mono-protected BINOL **2** in 87% yield.[17] This compound (2.4 equiv) was then reacted with **3**[18] in the presence of K_2CO_3 in refluxing acetone to form the bisbinaphthyl compound **4** in 92% yield. The *p*-nitrosulfonyl group of **4** was removed with *p*-MePhSH,[19] and the MOM groups were removed by hydrolysis with 6 N HCl to produce the desired compound **1** in 73% yield over the two steps. This compound was a white solid and soluble

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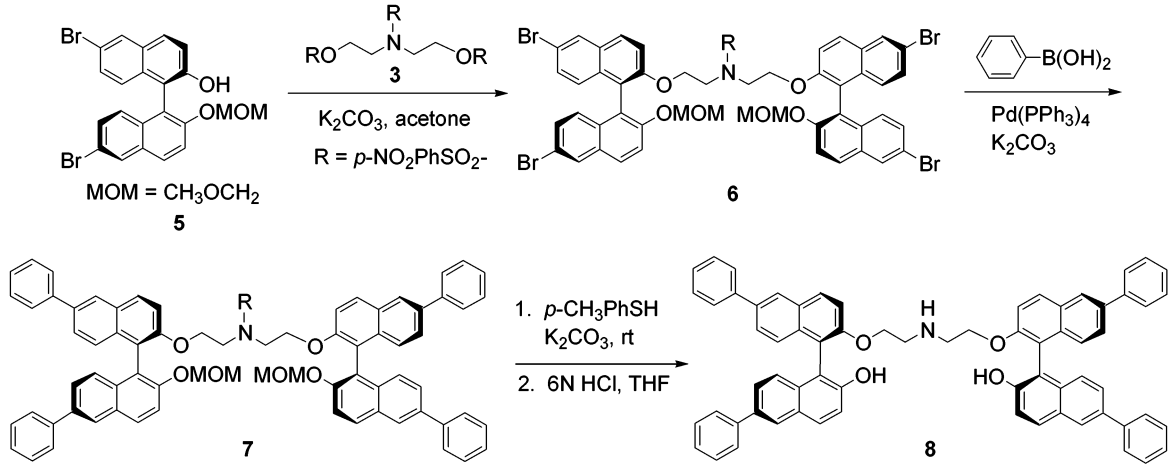
Scheme 2. Synthesis of the G0 Bisbinaphthyl Compound **8**



in most common organic solvents. Its specific optical rotation was +24.5. We also prepared the bisbinaphthyl compound starting from racemic BINOL, which gave a 1:1.8:1 mixture of three stereoisomers, that is, (*S*,*S*)-, (*R*,*S*)- and (*R*,*R*)-**1**, as determined by using an HPLC-Chiracel AD column. This indicates that in the conversion of **2** to **4**, the formation of the homodimers was only slightly faster than the formation of the heterodimer. On the basis of the HPLC analyses of the isomeric mixture and compound **1**, both the enantiomeric and the diastereomeric purities of **1** were determined to be greater than 98%.

The dendritic derivatives of **1** were synthesized to improve its fluorescence signal. Scheme 2 shows the synthesis of the tetraphenyl substituted bisbinaphthyl molecule **8**. Reaction of the monoprotected (*R*,*R*)-6,6′-dibromoBINOL **5** with **3** formed **6** in 83% yield. The Suzuki coupling[20] of **6** with phenylboronic acid introduced four phenyl rings to the 6,6′-positions of the binaphthyl units to give **7** in 80% yield. Removal of the protecting groups in **7** produced the desired compound **8** as a white solid in 70% yield. This compound is the G0 (generation zero) dendritic derivative of the bisbinaphthyl core **1**. The specific optical rotation of **8** is −251.

A different route was used to make the next generation dendritic molecule **14** because of easier purification (Scheme 3). The Suzuki coupling of 3,5-diphenylphenyl boronic acid (**9**)[21] with the (*R*,*R*)-6,6′-dibromobinaphthyl **10** generated **11** in 92% yield. Deprotection of **11** followed by monoprotection gave **12** in 74% yield. Reaction of **12** with **3** gave the bisbinaphthyl compound **13** in 88% yield. Removal of the protecting groups in **13** produced the desired G1 (generation one) dendritic molecule **14** as a white solid in 58% yield. The specific optical rotation of this compound is −179.

2. Spectroscopic Study of the Core, G0, and G1 Bisbinaphthyl Molecules. The ^{1}H and ^{13}C NMR spectra of the three generation bisbinaphthyl molecules, that is, core **1**, G0 **8**, and G1 **14**, are consistent with their C_2 symmetry. All of the three compounds displayed two signals at δ ~67 and ~47 for their $-OCH_2CH_2NH-$ units in the ^{13}C NMR spectra. High-resolution mass spectroscopic analyses confirmed their structures. The UV spectra of these compounds show that the signals at the short wavelengths (<300 nm) increased significantly with the increasing number of branching phenyl rings at the 6,6′-positions of the binaphthyl units because of the phenyl absorptions, but much smaller changes were observed at the long wavelengths. The absorption maximum wavelengths and extinguish coefficients for the compounds are 280 (16 500) and 334 (10 600) nm for the core, 263 (168 700), 297 (sh, 53 200), and 343 (sh, 9800) nm for G0, and 267 (257 100), 304 (sh, 58 600), and 343 (sh, 9800) nm for G1.

Figure 3a,b is the fluorescence spectra of the three generation compounds (3.1×10^{-6} M in methylene chloride) when excited at 270 (a) and 310 (b) nm, respectively. The dendritic benzene branches in the G0 and G1 molecules have resulted in significantly increased fluorescence. This indicates an efficient intramolecular energy transfer from the phenyl rings to the naphthyl core.[22,23]

The fluorescence intensities of these compounds are stronger when excited at 270 nm than excited at 310 nm especially for the G0 and G1 molecules because of their stronger absorptions at the shorter wavelength. The emission maxima are 372 nm for the G0 and G1 molecules and 368 nm for the core. The excitation spectra show that the most intense absorptions for the phenyl branched G0 molecule **8** and G1 molecule **14** ($c = 3.1 \times 10^{-6}$ M in methylene chloride) are at 270 nm where the phenyl rings absorb. This further supports the efficient intramolecular energy transfer of these compounds.

3. Enantioselective Fluorescent Recognition of Mandelic Acids Using the Bisbinaphthyl Compounds. We first used the bisbinaphthyl core **1** to conduct the fluorescent recognition of mandelic acid. When **1** was treated with (*R*)- or (*S*)-mandelic acid, a significant fluorescence enhancement was observed as expected due to the suppressed PET quenching upon protonation by the acid. This fluorescence enhancement was also found to be very enantioselective. As Figure 4 displays, in benzene

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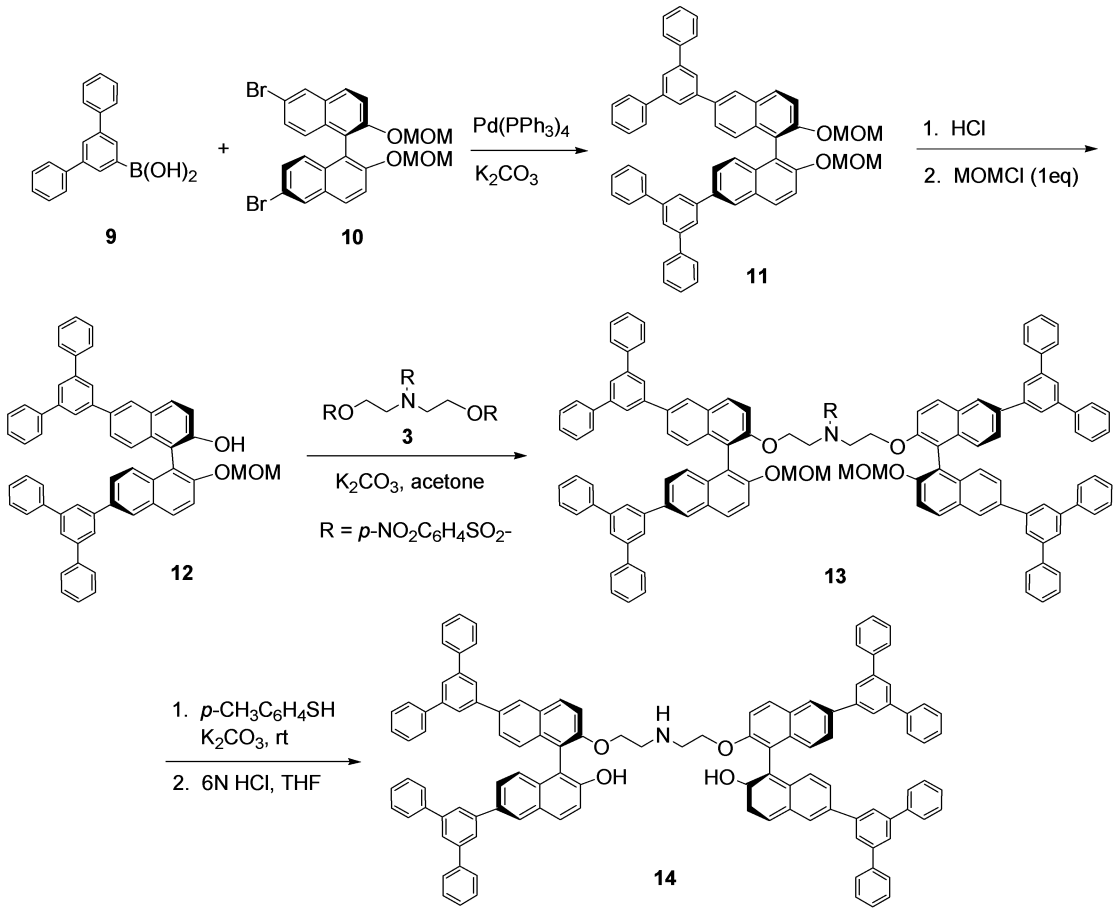
(23) The light-harvesting effect of binaphthyl-based dendrimers has been studied in fluorescence quenching but not in fluorescence enhancement.[8]

Scheme 3. Synthesis of the G1 Bisbinaphthyl Compound **14**



solution [containing 2% dimethoxyethylene (DME)], the fluorescence intensity of **1** (9.5×10^{-5} M) was increased to 2.87 times the original value by (*S*)-mandelic acid (5.0×10^{-3} M). However, (*R*)-mandelic acid (5.0×10^{-3} M) only increased the fluorescence intensity of **1** to 1.75 times. That is, the enantiomeric fluorescence difference ratio, *ef* [$ef = (I_S - I_0)/(I_R - I_0)$], is 2.49. This large difference in the enantiomeric fluorescence enhancement makes **1** a practically useful sensor for the enantioselective recognition of the chiral α-hydroxycarboxylic acid.

When **1** (9.5×10^{-5} M) was treated with mandelic acid in the concentration range of 5.0×10^{-3}–2.0×10^{-2} M, the fluorescence enhancement of the sensor followed the Benesi–Hildebrand type equation:[24]

$$\frac{I_0}{I - I_0} = \frac{b}{a - b}\left\{\frac{1}{K[\mathrm{M}]} + 1\right\}$$

where I_0 is the fluorescence intensity of the sensor in the absence of the acid, I is the fluorescence intensity in the presence of the acid, [M] is the concentration of the acid, and K is the association constant between the sensor and the acid. In the equation, a and b are constants. Figure 5 plots $I_0/(I - I_0)$ against 1/[M] according to the Benesi–Hildebrand equation. From this plot, the association constant of 1 + (*S*)-mandelic acid was found to be 348 M^{-1}, and that of 1 + (*R*)-mandelic acid was 163 M^{-1}.

The interaction of **1** with (*S*)-mandelic acid in benzene-d_6 (containing 2% DME) was studied by using ^{1}H NMR spectrometry. It was observed that the methine proton signal of (*S*)-mandelic acid at δ 5.16 was shifted downfield upon interaction with the sensor. In a 9:1 sensor/acid solution, the methine signal was observed at δ 5.28. The Job plot of the sensor in the presence of the acid is obtained by ploting the mole fraction of the acid (X) against $\Delta\delta^*X$, where $\Delta\delta$ is the chemical shift change of the acid methine proton.[25,26] A maximum at $X = 0.5$ is observed. This indicates the formation of a 1:1 complex between the sensor and the acid.

The fluorescence enhancement of the enantiomer of **1** in the presence of (*R*)- and (*S*)-mandelic acid was also studied. The enantiomer of **1**, *ent*-**1**, was prepared from (*R*)-BINOL. It was observed that (*R*)-mandelic acid enhanced the fluorescence of *ent*-**1** much greater than (*S*)-mandelic acid. There is a mirror image relationship between the fluorescence enhancement of *ent*-**1** and **1** in the presence of the two enantiomers of mandelic acid. This confirms that the observed different fluorescence enhancement between the two enantiomers of mandelic acid is indeed due to chiral recognition by the fluorescent sensor.

To gain a better understanding of the interaction between the bisbinaphthyl sensor **1** and mandelic acid, we studied the fluorescence of the sensor in the presence of the derivatives of mandelic acid where either the acid group or the hydroxyl group

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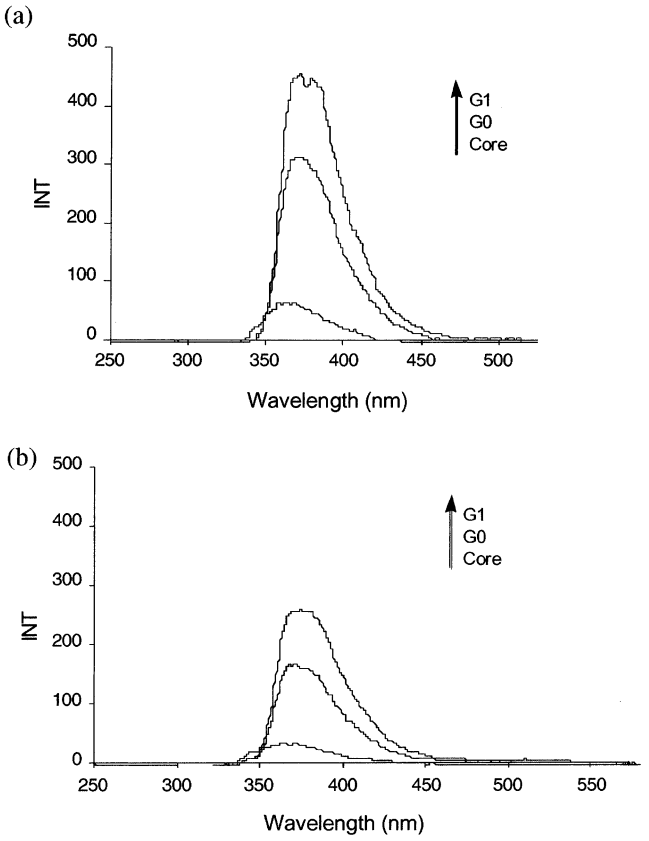
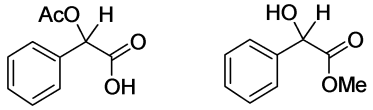


Figure 3. Fluorescence spectra of the chiral bisbinaphthyl compounds in methylene chloride when excited at 270 nm (a) and 310 nm (b), respectively.

was protected. When **1** was treated with compounds (*R*)- and (*S*)-**15** in which the α-hydroxyl group of mandelic acid was acylated, both (*R*)- and (*S*)-**15** were found to greatly enhance the fluorescence of **1** under conditions similar to the use of mandelic acid but exhibit essentially no enantioselectivity. Sensor **1** was also interacted with compound **16**, a methyl ester of mandelic acid. In the presence of racemic **16** (5.0×10^{-3} M in benzene containing 2% DME), **1** (9.5×10^{-5} M) displayed almost no fluorescence enhancement. These studies demonstrate that both the hydroxyl group and the carboxylic acid group of mandelic acid are important for the enantioselective fluorescence enhancement of the sensor. This is consistent with the proposed multiple hydrogen-bonding structure between the sensor and mandelic acid.



15 **16**

The fluorescence of **1** (9.5×10^{-5} M in benzene containing 1% DME) in the presence of mandelic acid (1.0×10^{-2} M) with various enantiomeric composition was studied. A linear relationship between I/I_0 and the percent of the *S* component of mandelic acid was observed. Thus, the enantiomeric composition of the α-hydroxycarboxylic acid can be readily determined by measuring the fluorescence intensity of sensor **1** in the presence of the substrate.

We have further studied the interaction of mandelic acid with the G0 and G1 dendritic derivatives **8** and **14**. Figure 6

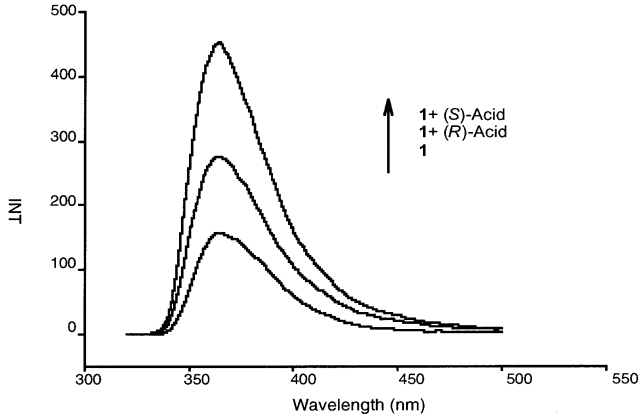


Figure 4. Fluorescence spectra of sensor 1 with and without mandelic acid ($\lambda_{exc} = 310$ nm).

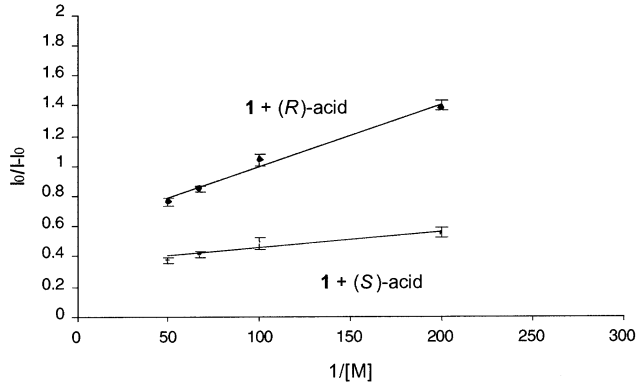


Figure 5. Benesi−Hildebrand plot of sensor **1** (9.5×10^{-5} M in benzene containing 2% DME) in the presence of mandelic acid.

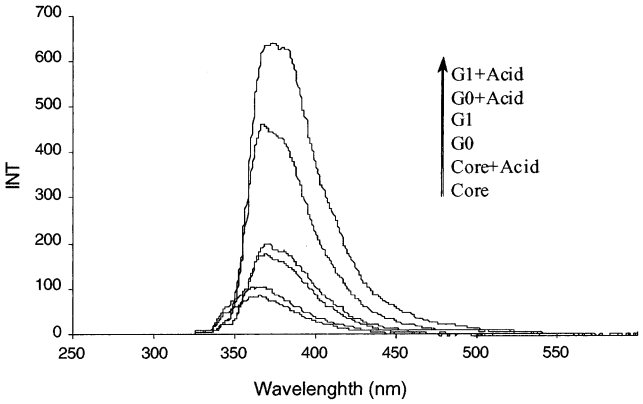


Figure 6. Comparison of the fluorescence spectra of core *ent*-**1**, G0 **8**, and G1 **14** in the presence of (*R*)-mandelic acid.

compares the fluorescence intensity of core *ent*-**1**, G0 **8**, and G1 **14** in the presence of (*R*)-mandelic acid. The concentration of all of the bisbinaphthyl compounds was 3.1×10^{-6} M. The acid concentration was 1.0×10^{-3} M, and the solvent was benzene containing 0.1% DME (the solvent used in Figure 3 was methylene chloride). As shown in Figure 6, the fluorescence enhancement ($I - I_0$) of the G0 compound in the presence of the acid is ca. 14 times that of the core, and the fluorescence enhancement of the G1 compound in the presence of the acid is ca. 22 times that of the core. This signal amplification caused by the dendritic branches makes the G0 and G1 molecules much more sensitive fluorescent sensors than the core.[23]

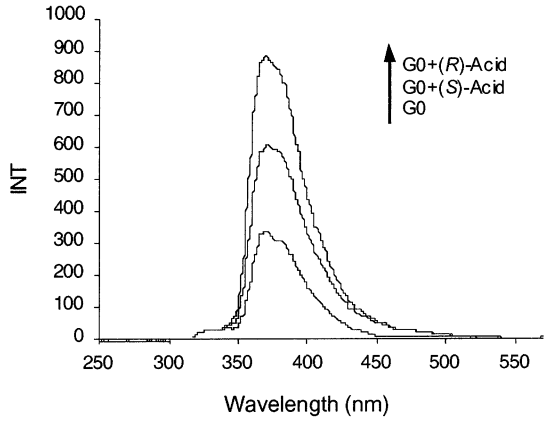


Figure 7. Fluorescence spectra of the G0 sensor **8** (3.1×10^{-6} M in benzene containing 0.1% DME) with/without (*R*)- and (*S*)-mandelic acid (1.0×10^{-3} M).

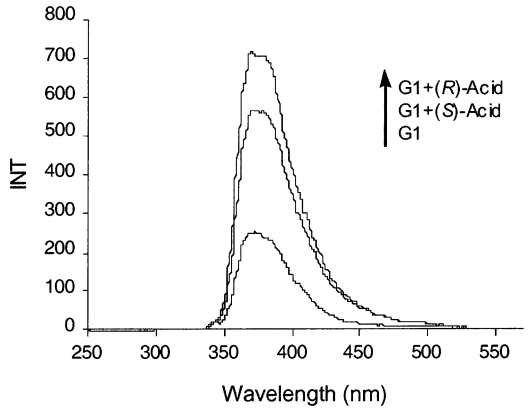


Figure 8. Fluorescence spectra of the G1 sensor **14** (3.1×10^{-6} M in benzene containing 0.1% DME) with/without (*R*)- and (*S*)-mandelic acid (1.0×10^{-3} M).

The enantioselectivity of the G0 and G1 compounds for the fluorescent recognition of mandelic acid was evaluated. Figure 7 shows the fluorescence spectra of the G0 sensor (1.0×10^{-5} M in benzene containing 0.1% DME) with/without (*R*)- and (*S*)-mandelic acid (1.0×10^{-3} M). The enantioselective fluorescent response of the G0 sensor is quite high as represented by an *ef* of 2.05.

The G1 molecule also exhibited enantioselective fluorescent responses toward (*R*)- and (*S*)-mandelic acid, and an *ef* of 1.49 was observed in Figure 8. We also found that the amount of DME in the solvent significantly influences the behavior of the sensor. Increasing the concentration of DME decreased both the fluorescent enhancement and the enantioselectivity. Thus, although it is necessary to add DME to help solubilize the acid, the amount of DME needs to be minimized.

The study of the G1 sensor shows that, although this compound has the highest fluorescence enhancement in the presence of mandelic acid, its enantioselectivity becomes smaller than those of the G0 and core sensors. Comparing the three generation sensors, we conclude that the G0 dendritic sensor is the best choice for the recognition of mandelic acid because it has the greatly increased sensitivity over the core while still maintaining a high enantioselectivity.

Summary

We have designed and synthesized a class of chiral bisbinaphthyl-based fluorescent sensors for the enantioselective recognition of mandelic acid. We have demonstrated that by introducing dendritic branches to the chiral receptor unit, the light-harvesting effect of the dendritic structure can amplify the fluorescence signals of the receptors and greatly increase their sensitivity. This study has identified the G0 bisbinaphthyl molecule as a highly sensitive as well as a highly enantioselective fluorescent sensor. Both of the enantiomers of this sensor will be used to *sequentially* interact with the resin-bound mandelic acid generated from various catalytic reactions. The relative fluorescence intensity of these two enantiomeric sensors will allow us to determine the enantiomeric composition. By doing so, the effect of the achiral acid starting materials or impurities will be excluded, because they will generate the same fluorescence enhancement for both of the enantiomeric sensors. Only the desired chiral acid with high enantiomeric purity can exhibit a large fluorescence difference when sequentially treated with the two enantiomeric sensors. In addition, because the mandelic acid is resin-bound, most other impurities will be washed away. Using this strategy, the enantioselective sensors will allow us to quickly identify the most enantioselective catalyst in a combinatorial matrix that converts a resin-bound starting material to the resin-bound mandelic acid.

Experimental Section

General Data. Melting points were uncorrected and obtained on a Mel-Temp II capillary melting point apparatus. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. NMR spectra were recorded on a Varian-300 MHz spectrometer. Chemical shifts were given in ppm relative to internal reference $CDCl_3$ (^{1}H, 7.23 ppm; ^{13}C, 77.23 ppm). Mass spectra were recorded on a LCQ Finnigan mass spectrometer. HRMS data were obtained by the University of California-Riverside mass spectroscopy facility. UV−vis spectra were recorded on a Cary 5E UV−vis−NIR spectrophotometer. Fluorescence spectra were recorded on a Perkin-Elmer LS-50B luminescence. The excitation and emission slits were set at 2.5 and 3.5 nm, respectively. The scan speed was set at 100 nm/min.

Preparation and Characterization of Bis[2-(4′-nitro-benzenesulfonyloxy)-ethyl]-4-nitro-benzenesulfonamide, the Linker Molecule 3. Under nitrogen, to a stirred solution of diethanolamine (5.25 g, 50.0 mmol), triethylamine (30 mL, 200.0 mmol), and trimethylamine hydrochloride (0.3 g, 3.3 mmol) in acetonitrile (100 mL) was slowly added 4-nitrobenzenesulfonyl chloride (97%) (38.5 g, 165 mmol) in acetonitrile (50 mL) at 0 °C. After being stirred for 3−4 h (monitored by TLC), the mixture was filtered, and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluted with 20−40% ethyl acetate in hexanes to give **3** as a white solid in 70% yield. mp 133−134 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.67 (t, J = 5.4 Hz, 4H), 4.34 (t, J = 5.4 Hz, 4H), 8.12 (d, J = 7.5 Hz, 2H), 8.21 (d, J = 7.5 Hz, 4H), 8.41 (d, J = 7.5 Hz, 2H), 8.52 (d, J = 7.5 Hz, 4H). ^{13}C NMR (acetone-d_6, 75 MHz): δ 48.5, 69.8, 125.3, 125.5, 129.5, 130.3, 141.7, 145.1, 151.2, 151.9. ESI-MS *m*/*z*: 661 $(M + 1)^+$. Anal. Calcd for $C_{22}H_{20}N_4O_{14}S_3$: C, 40.00; H, 3.05; N, 8.49. Found: C, 40.09; H, 3.01; N, 8.49.

Preparation and Characterization of (*S*,*S*)-*N*,*N*-Bis-[2-(2′-methoxymethoxy- [1,1′]binaphthalenyl-2-yloxy)-ethyl]-4-nitro-benzenesulfonamide, 4. Under nitrogen, to a 100 mL Schlenk flask were added the monoprotected (*S*)-BINOL **2** (3.3 g, 10.0 mmol), linker **3** (2.2 g, 3.3 mmol), K_2CO_3 (4.7 g, 33.0 mmol), and acetone (60 mL). The mixture was then heated at reflux for 16 h and monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature, and water (60 mL) was added. The solution was extracted with ethyl acetate (3 × 100 mL), and the organic layer was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by column chromatography on silica gel eluted with 10−30% ethyl acetate

in hexane to give **4** as a bright yellow solid in 92% yield (4.2 g). mp 102−105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.57 (m, 2H), 2.67 (m, 2H), 3.06 (s, 6H), 3.58 (m, 4H), 4.88 (d, J = 6.9 Hz, 2H), 4.99 (d, J = 6.9 Hz, 2H), 7.01−7.48 (m, 18H), 7.81−7.92 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.0, 55.9, 68.0, 95.3, 114.3, 117.5, 119.6, 121.4, 124.0, 124.3, 125.3, 125.5, 126.6, 127.8, 127.9, 129.3, 129.4, 129.6, 129.8, 133.9, 146.0, 149.4, 153.7, 154.5. ESI-MS m/z: 915 ($M + H^+$). HRMS (FAB) calcd for $C_{54}H_{46}N_2O_{10}NaS$ ($M + Na^+$): 937.2771. Found: 937.2776.

Preparation and Characterization of (*S*,*S*)-Bis-[2-(2′-hydroxy-[1,1′]binaphthalenyl-2-yloxy)-ethyl]-amine, 1. Under nitrogen, to a solution of **4** (0.914 g, 1.0 mmol) in DMF (30 mL) were added K_2CO_3 (0.420 g, 3.0 mmol) and 4-methylbenzenethiol (0.150 g, 1.2 mmol) sequentially. The mixture was stirred at room temperature for 4 h and monitored by TLC. Water (30 mL) was then added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic solution was washed sequentially with 1 N NaOH, water, and then dried over Na_2SO_4. After the solvent was removed, the residue was purified by flash chromatography on silica gel eluted with 20−40% ethyl acetate in hexane to give a nitrogen deprotected product in 94% yield. This compound (1.5 g, 2.0 mmol) was dissolved in ethanol (20 mL) and combined with 4 N HCI (10 mL). After degassed by bubbling nitrogen through, the acidic mixture was heated at 40−50 °C for 4 h. The mixture was then neutralized at room temperature with Na_2CO_3 and extracted with diethyl ether (3 × 30 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent by evaporation, the residue was passed through a short silica gel column eluted with 10% methanol in diethyl ether to afford **1** as a white powder in 78% yield. mp 120−123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.33 (m, 4H), 3.87 (m, 4H), 4.4 (br, 3H), 6.98−7.44 (m, 16H), 7.78 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 9.0 Hz, 2H), 7.98 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.5, 67.6, 115.0, 117.0, 117.9, 119.3, 123.2, 124.1, 124.9, 125.2, 126.3, 126.9, 127.9, 128.0, 129.1, 129.3, 129.5, 130.2, 133.8, 151.7, 154.3. ESI-MS m/z: 642.5 ($M + H^+$). $[\alpha]_D$ = +24.52 (c = 0.75, CH_2Cl_2). CD (THF, 1.0 × 10^{-4} M) $[\theta]_\lambda$ 6.2 × 10^4 (241 nm), −4.3 × 10^4 (223 nm). Anal. Calcd for $C_{44}H_{35}O_4N$: C, 82.34; H, 5.50; N, 2.18. Found: C, 82.32; H, 5.57; N, 2.10.

Preparation and Characterization of (*R*,*R*)-6,6′-Dibromo-2′-methoxymethoxy-[1,1′]binaphthalenyl-2-ol, 5. Under nitrogen, a 250 mL flask equipped with an addition funnel was charged with (*R*)-6,6′-dibromo-1,1′-bi-naphthol (4.44 g, 10.0 mmol), K_2CO_3 (6.90 g, 50.0 mmol), and acetone (50 mL). After the mixture was stirred at room temperature for 5 min, a solution of chloromethyl methyl ether (0.91 mL, 12.0 mmol) in acetone (50 mL) was added dropwise via the addition funnel. The mixture was stirred at room temperature for 5 h and quenched with water. Most of the solvent was then removed under vacuum, and the mixture was diluted with CH_2Cl_2. The organic layer was further washed with water and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 15−20% ethyl acetate in hexane to give **5** as a pale yellow solid in 75% yield (3.66 g). mp 60−63 °C. $[\alpha]_D$ = −90.0 (c = 0.62, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.19 (s, 3H), 4.93 (s, br, 1H), 5.08 (d, J = 6.9 Hz, 1H), 5.11 (d, J = 6.9 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 9.0 Hz, 1H), 7.29 (dd, J = 2.4, 9.0 Hz, 1H), 7.34 (d, J = 3.0 Hz, 1H), 7.37 (d, J = 2.7 Hz, 1H), 7.62 (d, J = 9.3 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 8.07 (d, J = 2.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.5, 95.1, 115.0, 117.4, 118.2, 119.0, 126.6, 126.9, 129.3, 130.0, 130.3, 130.4 (br), 130.9, 131.4, 132.4, 132.5, 151.8, 154.0. APCI-MS m/z: 457.0 ($M - OCH_3 + 2$, 100). HRMS (DEI) calcd for $C_{22}H_{16}O_3Br_2$: 485.9466. Found: 485.9483.

Preparation and Characterization of (*R*,*R*)-*N*,*N*-Bis-[2-(6,6′-dibromo-2′- methoxymethoxy-[1,1′]binaphthalenyl-2-yloxy)-ethyl]-4-nitro-benzenesulfonamide, 6. A procedure similar to the preparation of **4** was applied to make **6** from the reaction of **5** with **3**. After general workup, the crude product was purified by column chromatography on silica gel eluted with 30% ethyl acetate in hexane to give **6** as a bright yellow solid in 83% yield. mp 107−110 °C. $[\alpha]_D$ = +48.9 (c = 0.90, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47−2.55 (m, 2H), 2.68−2.76 (m, 2H), 3.07 (s, 6H), 3.51−3.66 (m, 4H), 4.87 (d, J = 6.9 Hz, 1H), 4.99 (d, J = 6.9 Hz, 1H), 6.84 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.3 Hz, 2H), 7.24 (dd, J = 1.8, 9.0 Hz, 2H), 7.29 (dd, J = 1.8, 9.0 Hz, 2H), 7.46−7.51 (m, 4H), 7.75 (d, J = 9.0 Hz, 2H), 7.85 (d, J = 9.0 Hz, 2H), 7.95−7.98 (m, 4H), 8.04 (d, J = 1.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.4, 56.3, 68.1, 95.3, 115.4, 118.2, 118.5, 119.4, 121.0, 124.3, 127.1, 127.3, 128.0, 128.8, 129.3, 130.1, 130.2 (br), 130.7, 130.9, 132.5, 145.8, 149.8, 153.2, 153.8. APCI-MS m/z: 1225.8 (M). HRMS (MALDI) calcd for $C_{54}H_{42}N_2O_{10}NaSBr_4$ ($M + Na^+$): 1252.9150. Found: 1252.9275.

Preparation and Characterization of (*R*,*R*)-*N*,*N*-Bis-[2-(2′-methoxymethoxy-6,6′-diphenyi-[1,1′]binaphthalenyl-2-yloxy)-ethyl]-4-nitro-benzenesulfonamide, 7. Under nitrogen, to a 50 mL Schlenk flask charged with **6** (615 mg, 0.5 mmol) were syringed phenylboronic acid (377 mg, 3.0 mmol) and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) in aqueous K_2CO_3 (2 M, 5 mL, degassed with nitrogen) and dry THF (10 mL). The reaction mixture was degassed again by three freeze−pump−thaw cycles and was then refluxed under nitrogen. After 2.5 days, the reaction mixture was cooled to room temperature. After most of the solvent was removed under vacuum, the mixture was diluted with CH_2Cl_2. The organic layer was washed with 1 N HCl and brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 25% ethyl acetate in hexane to give **7** as an orange solid in 80% yield (490 mg). mp 134−137 °C. $[\alpha]_D$ = +18.7 (c = 0.40, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47−2.56 (m, 2H), 2.75−2.83 (m, 2H), 3.11 (s, 6H), 3.51−3.57 (m, 2H), 3.61−3.68 (m, 2H), 4.94 (d, J = 6.6 Hz, 2H), 5.02 (d, J = 6.6 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.7 Hz, 2H), 7.28−7.41 (m, 8H), 7.45−7.57 (m, 16H), 7.69 (dd, J = 1.2, 8.1 Hz, 4H), 7.85−7.95 (m, 6H), 8.03 (s, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.1, 56.3, 68.1, 95.5, 115.0, 118.1, 119.6, 121.5, 124.2, 125.8, 126.1, 126.3, 126.5, 127.3, 127.4, 127.5, 128.0, 129.1, 129.1, 129.8, 130.2, 130.3, 133.3, 133.3, 136.8, 137.2, 140.7, 141.1, 146.1, 149.7, 153.0, 153.7. APCI-MS m/z: 1218.1 (M). HRMS (MALDI) calcd for $C_{78}H_{62}N_2O_{10}NaS$ ($M + Na^+$): 1241.4017. Found: 1241.4110.

Preparation and Characterization of (*R*,*R*)-*N*,*N*-Bis-[2-(2′-hydroxy-6,6′- diphenyl-[1,1′]binaphthalenyl-2-yloxy)-ethyl]-amine, the G0 Sensor 8. A procedure similar to the preparation of **1** was applied to make **8** from the deprotection of **7**. After general workup, the crude product was purified by column chromatography on silica gel eluted with 2−5% MeOH in ethyl acetate to give **8** as a white solid in 70% yield. mp 164−167 °C. $[\alpha]_D$ = −251.2 (c = 0.44, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.39−2.44 (m, 2H), 2.58−2.64 (m, 2H), 3.84−3.89 (m, 2H), 3.95−4.29 (m, 2H), 7.16 (d, J = 8.7 Hz, 2H), 7.26−7.42 (m, 16H), 7.48−7.53 (m, 4H), 7.41−7.60 (m, 6H), 7.70−7.73 (m, 4H), 7.91 (d, J = 8.7 Hz, 2H), 8.04 (d, J = 9.0 Hz, 2H), 8.07 (d, J = 1.8 Hz, 2H), 8.12 (d, J = 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 48.0, 67.6, 115.5, 117.5, 118.0, 120.3, 125.8, 126.0, 126.2, 126.4, 127.0, 127.2, 127.3, 127.5, 128.6, 129.0, 129.1, 129.7, 130.0, 130.9, 133.3, 136.2, 137.1, 141.1, 152.2, 154.5. APCI-MS m/z: 946.5 ($M + 1$, 100). HRMS (MALDI) calcd for $C_{68}H_{52}NO_4$ ($M + H^+$): 946.3891. Found: 946.3871.

Preparation and Characterization of (*R*)-2,2′-Bis-methoxymethoxy-6,6′-bis- [1,1′;3′,1″]terphenyl-5′-yl-[1,1′]binaphthalenyl, 11. The reaction was carried out by using **10** (935 mg, 1.8 mmol), 3,5-diphenylphenylboronic acid (**9**) (1.900 g, 4.0 mmol), $Pd(PPh_3)_4$ (203 mg, 0.2 mmol) in dry THF (16 mL), and aqueous K_2CO_3 (2 M, 12 mL). The reaction mixture was heated at reflux under nitrogen for 3 days. After general workup, the crude product was passed through a silica gel column using 25% ethyl acetate in hexane to give **11** as a white solid in 92% yield (1.34 g). mp 141−144 °C. $[\alpha]_D$ = −118.1 (c

= 0.64, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.22 (s, 6H), 5.06 (d, J = 6.6 Hz, 2H), 5.16 (d, J = 6.6 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.36−7.43 (m, 4H), 7.47−7.52 (m, 8H), 7.63−7.74 (m, 12H), 7.80 (t, J = 1.8 Hz, 2H), 7.89 (d, J = 1.5 Hz, 4H), 8.07 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.2, 95.5, 118.1, 121.3, 125.3, 125.5, 126.4, 126.5, 127.6, 127.8, 129.1, 130.1, 130.4, 133.6, 136.9, 141.4, 142.4, 142.6, 153.2. APCI-MS *m*/*z*: 830.1 (M). HRMS (FAB) calcd for $C_{60}H_{46}O_4$: 830.3396. Found: 830.3371.

Preparation and Characterization of (*R*)-2′-Methoxymethoxy-6,6′-bis- [1,1′;3′,1″]terphenyl-5′-yl-[1,1′]binaphthalenyl-2-ol, 12. Under nitrogen, to a solution of **11** (880 mg, 1.1 mmol) in EtOH (13 mL) and THF (13 mL) was added 4 N HCl (6 mL). The mixture was degassed with nitrogen and then heated at 60 °C for 24 h. After being cooled, the mixture was neutralized with aqueous $NaHCO_3$ and then evaporated under vacuum to remove most of the solvent. The remaining mixture was diluted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the crude product (720 mg) was dissolved in acetone (40 mL) in a 100 mL flask, to which K_2CO_3 (0.69 g, 5.0 mmol) was charged and a solution of chloromethyl methyl ether (0.09 mL, 1.2 mmol) in acetone (20 mL) was added dropwise via an addition funnel. The mixture was stirred at room temperature for 5 h and then quenched with water. After removal of acetone under vacuum, the remaining mixture was diluted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The resulting oil was passed through a silica gel column eluted with 25% ethyl acetate in hexane. This gave compound **12** as a pale yellow solid (620 mg) in 74% yield. mp 163−165 °C. $[\alpha]_D$ = −196.5 (c = 0.53, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.25 (s, 3H), 5.07 (s, br, 1H), 5.13 (d, J = 6.9 Hz, 1H), 5.19 (d, J = 6.9 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 7.36−7.42 (m, 6H), 7.45−7.51 (m, 8H), 7.64 (dd, J = 1.8, 9.0 Hz, 1H), 7.67−7.73 (m, 10H), 7.79 (t, J = 1.5 Hz, 1H), 7.81 (t, J = 1.5 Hz, 1H), 7.87 (d, J = 1.8 Hz, 4H), 8.02 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 1.5 Hz, 1H), 8.24 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 56.5, 95.3, 115.3, 117.7, 117.9, 118.4, 125.2, 125.5, 125.7, 126.0, 126.6 (m), 127.4, 127.6, 127.8, 127.8, 129.1, 129.6, 130.5, 130.7, 131.6, 133.4, 133.5, 136.3, 137.7, 141.3, 141.4, 142.1, 142.5, 142.6, 142.7, 151.8, 154.1. APCI-MS *m*/*z*: 725.5 (M − OCH_2OCH_3, 100). HRMS (FAB) calcd for $C_{58}H_{42}O_3$: 786.3134. Found: 786.3103.

Preparation and Characterization of (*R*,*R*)-*N*,*N*-Bis-[2-(2′-methoxymethoxy-6,6′-bis- [1,1′;3′,1″]terphenyl-5′-yl-[1,1 ′]binaphthalenyl-2-yloxy)-ethyl]-4-nitrobenzenesulfonamide, 13. A procedure similar to the preparation of **4** was applied to make **13** from the reaction of **12** with **3**. After general workup, the crude product was purified by column chromatography on silica gel eluted with 25−30% ethyl acetate in hexane to give **13** as a yellow solid in 88% yield. mp 178−180 °C. $[\alpha]_D$ = −40.9 (c = 0.56, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.51−2.58 (m, 2H), 2.73−2.84 (m, 2H), 3.11 (s, 6H), 3.51−3.65 (m, 4H), 4.95 (d, J = 6.9 Hz, 2H), 5.04 (d, J = 6.9 Hz, 2H), 7.04 (d, J = 9.3 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.26−7.64 (m, 44H), 7.69−7.74 (m, 10H), 7.78−7.81 (m, 6H), 7.84−7.88 (m, 6H), 7.96−7.99 (m, 4H), 8.19 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.0, 56.3, 68.1, 95.6, 114.9, 118.2, 119.5, 121.5, 124.2, 125.2 (m), 125.4 (m), 126.1 (m), 126.4 (m), 126.5 (m), 127.5, 127.6, 127.8, 128.0, 129.1, 129.7, 129.9, 130.3, 133.4, 133.5, 136.7, 137.0, 141.2, 141.4, 141.8, 142.3, 142.6, 142.7, 146.2, 149.7, 153.2, 153.8. APCI-MS *m*/*z*: 1828.4 (M + 2). HRMS (MALDI) calcd for $C_{126}H_{94}N_2O_{10}ONaS$ (M + Na^+): 1849.6521. Found: 1849.6475.

Preparation and Characterization of (*R*,*R*)-*N*,*N*-Bis-[2-(2′-hydroxy-6,6′-bis- [1,1′;3′,1″]terphenyl-5′-yl-[1,1′]binaphthalenyl-2-yloxy)-ethyl]-amine, the G1 Sensor 14. A procedure similar to the preparation of **1** was applied to make **14** from **13**. After general workup, the crude product was purified by column chromatography on silica gel eluted with 2−5% MeOH in ethyl acetate twice to give a pale yellow solid. This pale yellow solid was dissolved in a minimum amount of CH_2Cl_2 and further precipitated with MeOH to afford pure **14** as a white solid in 58% yield. mp 189−192 °C. $[\alpha]_D$ = −179.2 (c = 0.92, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.39−2.43 (m, 2H), 2.60−2.66 (m, 2H), 3.85−3.92 (m, 2H), 3.90−4.05 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.16−7.21 (m, 4H), 7.28−7.42 (m, 20H), 7.45−7.50 (m, 10H), 7.62−7.75 (m, 22H), 7.79 (s, 2H), 7.83−7.86 (m, 6H), 8.04 (d, J = 9.3 Hz, 2H), 8.09 (s, 2H), 8.17 (3, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 47.8, 67.4, 115.5, 117.4, 118.1, 120.3, 125.1, 125.3, 125.4, 125.8, 126.2, 126.4 (m), 126.5, 127.1, 127.6, 127.7, 127.8, 129.0, 129.1, 129.6, 130.0, 131.0, 133.4, 133.5, 136.1, 137.0, 141.3, 142.2, 142.3, 142.5, 142.7, 152.3, 154.5. APCI-MS *m*/*z*: 1554.0 (M). HRMS (MALDI) calcd for $C_{116}H_{84}NO_4$ (M + H^+): 1554.6395. Found: 1554.6392.

Preparation of Samples for Fluorescence Measurement. Materials: Sensors were purified by column chromatography and then stored in a refrigerator. The enantiomers of mandelic acid were purchased from Aldrich and recrystallized from methanol. They were then passed through a short column of silica gel (eluted with diethyl ether) and dried under vacuum. All of the solvents were either HPLC or spectroscopic grade. The benzene stock solutions of the sensors were freshly prepared for each measurement. A 0.1 M stock solution of mandelic acid was freshly prepared using benzene containing 10% (v) DME. DME was added to improve the solubility of the acid in benzene. For the fluorescence enhancement study, a sensor solution was mixed with the mandelic acid solution at room temperature in a 10 mL volumetric flask and diluted to the desired concentration. The resulting solution was allowed to stand at room temperature for 4 h before the fluorescence measurement. Because the enantioselective fluorescent recognitions were conducted in benzene solution and benzene absorbs significantly at 270 nm, excitation at 310 nm was applied to all of the fluorescence measurements unless otherwise indicated.

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Supporting Information Available: UV spectra, Job plot, and other analytical figures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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