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Synthesis of a chiral micelle-like dendrimer with phenylene dendrons and a 1,1′-binaphthyl core

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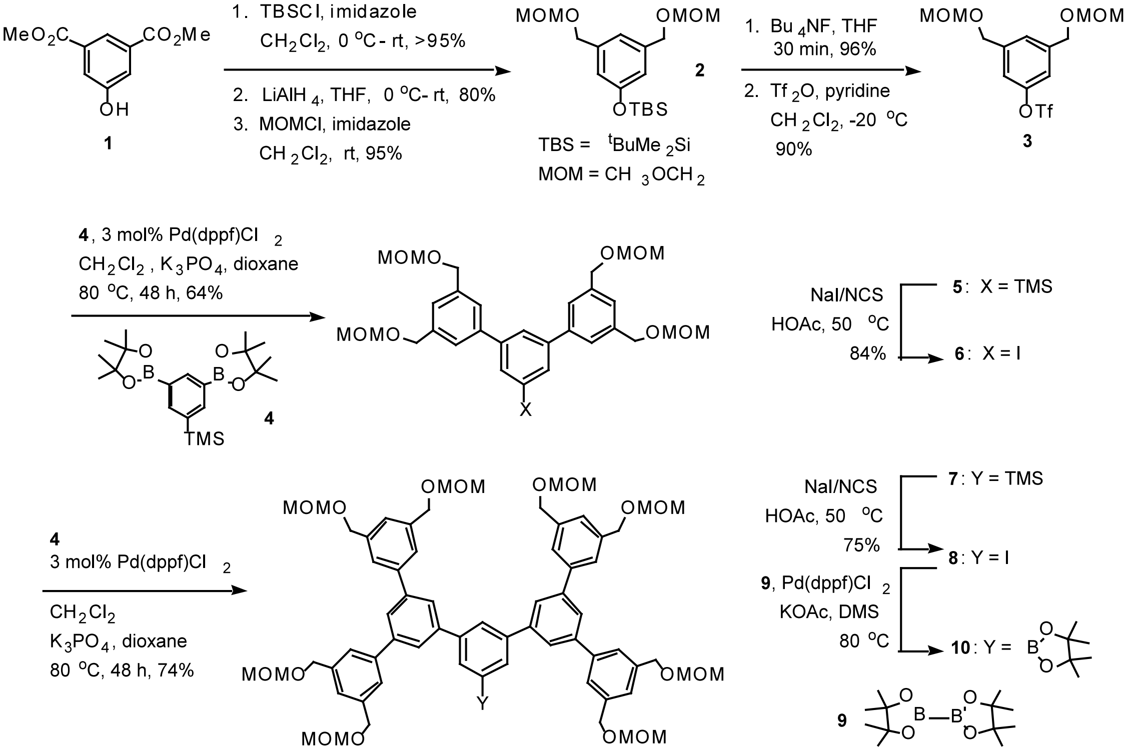
Abstract—A novel chiral micelle-like dendrimer has been synthesized. This dendrimer contains a chiral binaphthyl core, *meta*-phenylene dendrons, and hydrophilic polyhydroxyl periphery groups. It is soluble in highly polar solvents such H_2O/THF, MeOH/THF, EtOH/THF and DMSO, but insoluble in EtOAc, CH_2Cl_2 and $CHCl_3$. The study by UV–vis absorption spectroscopy reveals that the dendrimer may have a tighter conformation in a less polar solvent than in a more polar solvent. This dendrimer shows strong fluorescence in solution. © 2001 Published by Elsevier Science Ltd.

In the past two decades, a tremendous amount of study has been carried out on dendritic materials.[1–3] Unlike conventional polymers, dendrimers have well defined structures with specific shape, size and surface functional groups. By introducing hydrophilic peripheral groups to the hydrophobic branches and cores of dendrimers, materials of micelle-like structures have been designed and synthesized.[4,5] Application of these uni-



Scheme 1. Synthesis of the highly functionalized second generation dendron **10**.

Keywords: chiral dendrimer; unimolecular micelle.

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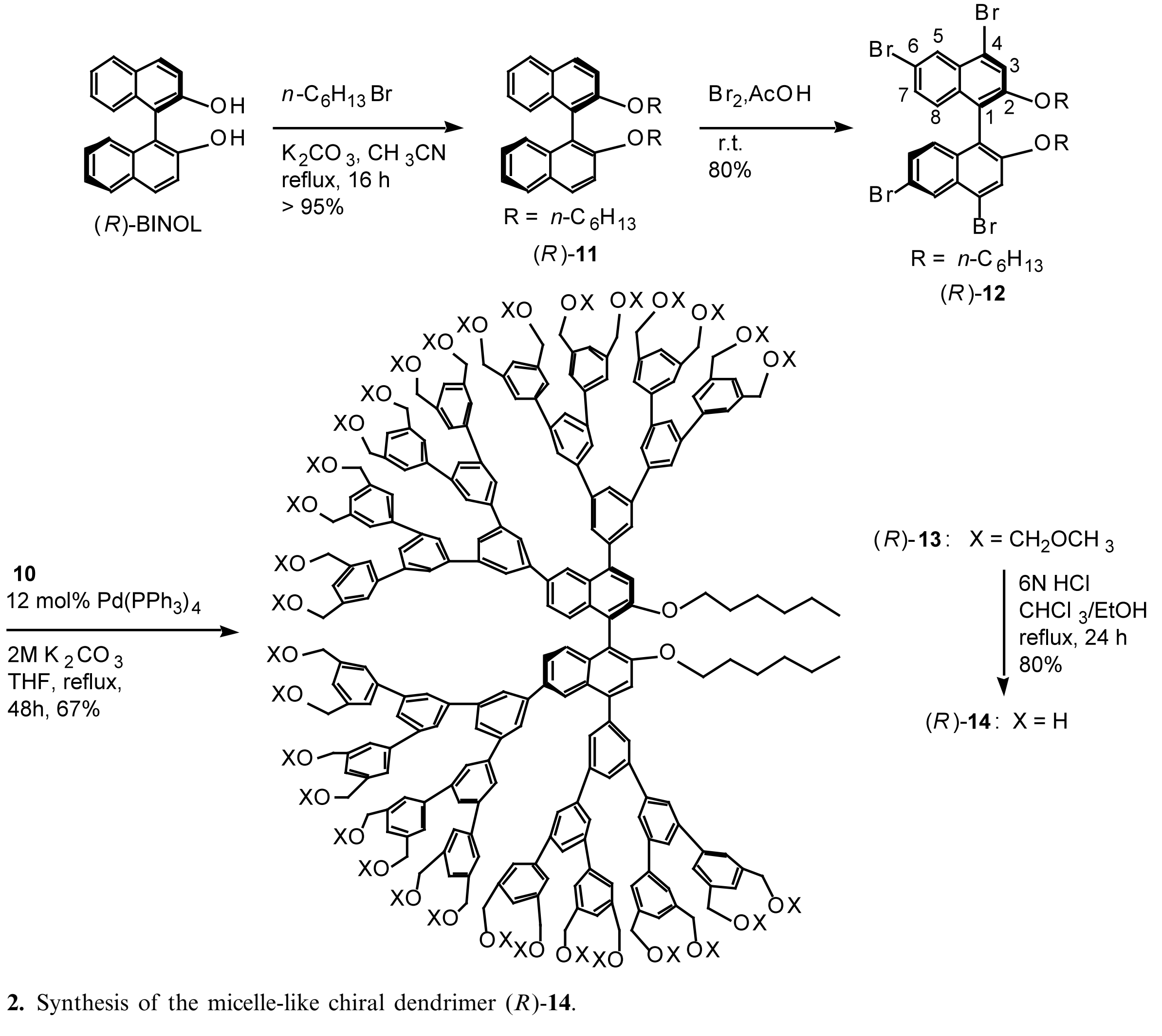
molecular micelles in areas such as drug delivery and medical image is under active investigation. This type of dendritic hosts not only can solubilize organic drug molecules in aqueous media by inclusion, but also provides a much more stable structure than the normal micelles that are susceptible to disintegration with the change of concentration, pH, temperature and other factors.[6] Because of the covalent bonds in dendrimers, their micelle-like structures will remain intact before bond cleavage. Chiral dendritic micelles have also been synthesized.[7,8] These materials are potentially useful for molecular recognition and chiral sensing in highly polar media. Recently, we have studied the use of optically active light harvesting dendrimers to build highly sensitive fluorescent sensors for the enantioselective recognition of chiral organic compounds.[9] In order to carry out such recognition in solvents of high polarity, we have synthesized a novel micelle-like chiral dendrimer that contains polyhydroxyl periphery groups, cross-conjugated phenylene dendrons, and a chiral binaphthyl core.[10] Herein, the synthesis and characterization of this material is reported.

Highly functionalized *meta*-phenylene-based dendrons were prepared for the synthesis of the desired dendrimer (Scheme 1). The commercially available compound **1** was first protected with TBS group. Then, the two ester groups were reduced with $LiAlH_4$ and the resulting two hydroxyl groups were protected with MOM groups to give **2**. The TBS group of **2** was removed with Bu_4NF and the resulting phenol hydroxyl group was converted to a triflate to form **3**. This compound was coupled with diborate **4** in the presence of $Pd(dppf)Cl_2$ to give the first generation dendron **5**.[11] The TMS group of **5** was converted to an iodide by reacting with NaI and NCS to form **6**.[12a] The Suzuki coupling of **6** with **4** gave the second generation dendron **7**.[11] Conversion of the TMS group of **7** to an iodide produced compound **8** which was then reacted with **9** to give the desired second generation dendritic borate **10**.[11a,12b,13]

Following our previously established procedure, optically pure (*R*)-1,1′-bi-2-naphthol [(*R*)-BINOL] was first alkylated to (*R*)-**11** which was then converted to the 4,4′,6,6′-tetrabrominated compound (*R*)-**12** (Scheme 2).[9] The Suzuki coupling of (*R*)-**12** with dendron **10** was catalyzed by $Pd(PPh_3)_4$ over 4 d to give dendrimer (*R*)-**13** in 67% yield.[14,15] The ^1H NMR spectrum of (*R*)-**13** was consistent with its structure. A singlet at δ 8.44 ppm was assigned to H-5 of the binaphthyl unit



Scheme 2. Synthesis of the micelle-like chiral dendrimer (*R*)-**14**.

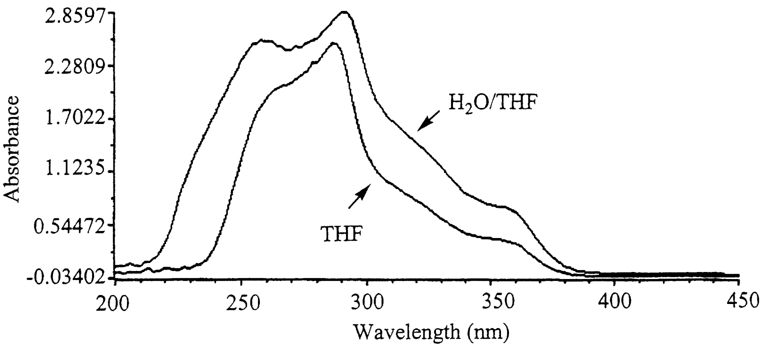


Figure 1. UV spectra of (*R*)-**14** in THF and H_2O/THF.

indicating a C_2-symmetric structure. Two singlet peaks at δ 3.31 and 3.33 containing 96 protons corresponded to the $(OCH_2OC\underline{H}_3)_{32}$ groups on the periphery. Four singlet peaks at δ 4.55, 4.51, 4.61 and 4.64 ppm were assigned to the protons of the $(Ar\text{-}C\underline{H}_2OC\underline{H}_2OCH_3)_{32}$ groups. After this dendrimer was treated with 6N HCl in $CHCl_3$ and EtOH under reflux to remove the MOM groups, the desired second generation micelle-like chiral dendrimer (*R*)-**14** was obtained.[14] The ^1H NMR spectrum of (*R*)-**14** was compared with that of (*R*)-**13**. It showed that the $\text{-}OC\underline{H}_2OC\underline{H}_3$ signals in (*R*)-**13** disappeared and a new singlet appeared at δ 4.51 with 64 protons corresponding to the $(ArC\underline{H}_2OH)_{32}$ groups of (*R*)-**14**. This indicates that all the MOM groups of (*R*)-**13** were completely hydrolyzed. The ^{13}C NMR spectrum of (*R*)-**14** also supported the structure. In the ^{13}C NMR spectrum, a strong peak at δ 62.97 was observed for the carbons of the $(Ar\text{-}\underline{C}H_2OH)_{32}$ groups. The MOM group carbon signals at δ 95.76 and 55.30 of (*R*)-**13** completely disappeared.

The matrix-assisted laser desorption/ionization (MALDI) mass spectrum of (*R*)-**14** showed the base peak at 3566 matching the calculated value for $M+Na^+$. Additional peaks at 3610 and 3626 might be assigned to the inclusion complexes (*R*)-**14**+Na^++EtOH and (*R*)-**14**+Na^++HOAc respectively probably formed during the preparation of the dendrimer. Dendrimer (*R*)-**14** was found to be more soluble in a mixed solvent of H_2O/THF (3:1) than in pure THF. It can also be dissolved in other highly polar solvents such as DMSO, EtOH/THF, and MeOH/THF, but insoluble in EtOAc, CH_2Cl_2, and $CHCl_3$.

The UV spectrum of (*R*)-**14** in THF displayed absorption λ_{max} at 260 (sh), 288, 310 (sh), and 361 (sh) nm (Fig. 1). When the solvent was changed to H_2O/THF (3:1), the absorption signals became much broader. The absorption band width at $\varepsilon/2$ increased from 52 nm in THF to 89 nm in H_2O/THF with very little changes in the peak positions. This large increase in absorption band width as the polarity of the solvent increases indicates that the dendrimer might have a much tighter conformation in THF than in H_2O/THF probably due to different degree of inter- versus intramolecular hydrogen bonds.[16] The dendrimer was strongly fluorescent in both THF and H_2O/THF with an emission maximum at 407 nm. This micelle-like dendrimer is potentially useful for the optical recognition of chiral organic molecules in highly polar media.

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13. Preparation and characterization of dendron **10**: In dry-box, a flask was charged with KOAc (294 mg, 3.0 mmol), tetraalkoxydiboron **9** (254 mg, 1.00 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (25 mg, 0.03 mmol). The mixture was then combined with a degassed solution of **8** (1.1 g, 0.88 mmol) in anhydrous DMSO (5 mL) under nitrogen. After stirred at 80°C for 8 h, the reaction mixture was cooled to room temperature and was poured into a mixture of EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: EtOAc:hexane = 1:2) to give **10**. This compound contained a small amount of pinacol that was difficult to remove. It was directly used for the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, $J = 1.8$ Hz, 2H), 8.03 (s, 1H), 7.84 (d, $J = 1.8$ Hz, 4H), 7.79 (s, 2H), 7.61 (d, $J = 1.2$ Hz, 8H), 7.39 (s, 4H), 4.74 (s, 16H), 4.69 (s, 16H), 3.43 (s, 24H), 1.39 (s, 12H).
14. Preparation and characterization of dendrimer (*R*)-**14**: (a) Under nitrogen, to a flask charged with (*R*)-**12** (76 mg, 0.10 mmol), **10** (822 mg, 0.64 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) was added degassed THF (5 mL) and K_2CO_3 (2 M, 2 mL, 4.00 mmol). The mixture was heated at reflux for 48 h. After cooled down to room temperature, the reaction solution was poured into a mixture of EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with EtOAc and EtOH (50:1) to give (*R*)-**13** (330 mg, 0.067 mmol) as a yellow solid in 67% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 2H), 8.01–7.63 (m, 42H), 7.55 (s, 16H), 7.49 (s, 16H), 7.32 (s, 8H), 7.29 (s, 8H), 4.65, 4.62, 4.58, 4.55 (4 singlet, 128H), 4.08 (s, 4H), 1.50 (br), 1.01 (br), 0.57 (br). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.38, 142.34, 142.07, 141.67, 141.15, 138.77, 136.64, 134.27, 128.48, 127.66, 126.96, 126.33, 126.03, 125.49, 124.43, 117.78, 95.76, 69.74, 68.95, 55.30, 31.22, 29.31, 25.31, 22.45, 13.82. (b) To a solution of (*R*)-**13** (300 mg, 0.06 mmol) in EtOH (ca. 30 mL) and $CHCl_3$ (20 mL) was added 6N HCl (20 mL). After heated at reflux for 24 h, the solvent was evaporated, and the resulting mixture was dissolved in a mixture of THF and EtOH and precipitated with the addition of hexane to give (*R*)-**14** (170 mg, 0.05 mmol) as a white solid in 80% yield. ^1H NMR (DMSO, 300 MHz) δ 8.40 (br), 8.02 (br), 8.04 (br), 7.93–7.70 (m), 7.59 (s, 16H), 7.53 (s, 16H), 7.30 (s, 8H), 7.27 (s, 8H), 5.19 (m, 32H), 4.51 (br, 64H), 4.20 (br), 1.46 (br), 0.97 (br), 0.49 (br). ^{13}C NMR (DMSO, 75 MHz) δ 154.09, 143.00, 142.20, 141.86, 141.52, 141.23, 139.48, 133.70, 128.22, 126.87, 124.83, 124.42, 124.08, 123.57, 119.07, 117.70, 68.86, 62.97, 30.75, 28.92, 24.94, 21.99, 13.56. MS (MALDI) m/z 3566 ($M+Na^+$, 100).
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