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Synthesis and Determination of the Absolute Configuration of Chiral Tetracosanaphthalenes

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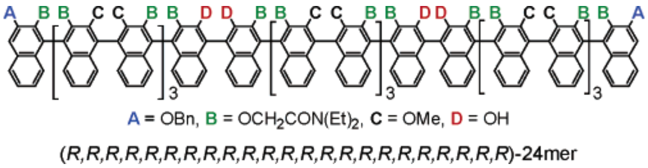
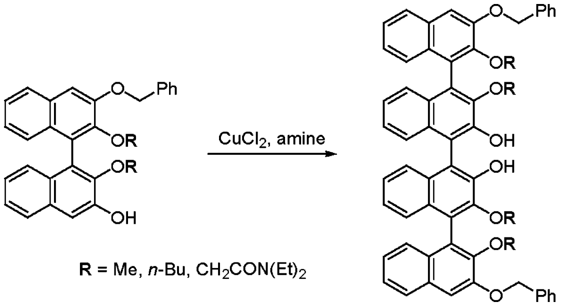


Tetracosanaphthalenes with diethylaminocarbonylmethoxy side chains were constructed by bottom-up synthesis, and their absolute configurations were determined by an exciton chirality method.

Chiral binaphthalene skeletons as in BINAP[1] and BINOL[2] have characteristic features: (1) they provide a large asymmetric space and (2) the dihedral angle can be adjusted by hinge movement to construct a suitable chiral environment. Therefore, binaphthalene skeletons have made extremely large contributions not only as catalysts for asymmetric synthesis but also as convenient fragments in the field of supramolecular chemistry. However, ternaphthalenes[3] in which a naphthalene unit is added to a binaphthalene and/or higher-order oligonaphthalene[4] have received almost no attention, including methods for their synthesis, despite their unique structures. We have focused on oligonaphthalenes and previously reported the bottom-up synthesis of optically active oligonaphthalenes using a repeating dimerization reaction of 2,3-(dioxyfunctionalized)naphthalenes that have several types of side chains, and we have determined the chirality of the newly formed axial bond.[5] The pathway for the induction of axial chirality in the dimerization reaction is controlled by the kind of side chain on naphthalene, which seemingly does not influence chiral induction (Scheme 1).[5g]

SCHEME 1. Oxidative Dimerization of Binaphthalenes



To be more precise, (1) for methoxy groups on naphthalene, diastereoselectivity was caused by epimerization of the newly formed axis together with diastereoselective crystallization,[5b,6] (2) for a diethylaminocarbonylmethoxy group, a rapid coupling reaction with high diastereoselectivity and slow epimerization of the newly formed axial bond led to a product under kinetic control, and (3) for an *n*-butoxy group, axial chirality was under thermodynamic control. We have been examining how many naphthalene units can be precisely connected through the above three methods.[5b] In the case of methoxy groups on naphthalene, the construction of a chiral 16mer was the upper limit due to its low solubility. In this paper, we report the challenging synthesis of a 24mer possessing amide groups and the determination of chirality.

The synthetic route is shown in Scheme 2. Two central hydroxy groups of (*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**1** were treated with K_2CO_3 and methyl iodide to give the corresponding methyl ether **2** in 100% yield. Mono deprotection of benzyl ethers on the top or bottom of naphthalene rings was performed using a palladium carbon catalyst to obtain the desired mono-ol **3** in 32% yield, as well as recovered material **2** (13%) and over-reacted diol **4**[5e] (19%). It was difficult to separate these compounds even using PTLC. At this stage, a fraction that mainly contained diol **4** was reacted with benzyl bromide (1 equiv) and K_2CO_3 to give mono-ol **3** (28%), **2** (17%), and diol **4** (18%). By repeating this process, a sufficient amount of mono-ol **3** that contained a small amount of diol **4** was obtained. HPLC analysis of the fraction revealed that mono-ol **3** and diol **4** were present in a ratio of

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[1] Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801−1836.

[2] (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155−3211. (b) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857−897.

[3] (a) Hayashi, T.; Hayashizaki, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 215−218. (b) Harada, N.; Hiyoshi, N.; Vassilev, V. P.; Hayashi, T. *Chirality* **1997**, *9*, 623−625.

[4] (a) Bělohradský, M.; Buděšínský, M.; Günterová, J.; Hodačová, J.; Holý, P.; Závada, J.; Císařová, I.; Podlaha, J. *J. Org. Chem.* **1996**, *61*, 1205−1210. (b) Sugimura, T.; Kurita, S.; Inoue, S.; Fujita, M.; Okuyama, T.; Tai, A. *Enantiomer* **2001**, *6*, 35−42. (c) Chow, H.-F.; Wan, C.-W. *J. Org. Chem.* **2001**, *66*, 5042−5047. (d) Habaue, S.; Seko, T.; Okamoto, Y. *Macromolecules* **2002**, *35*, 2437−2439. (e) Habaue, S.; Seko, T.; Okamoto, Y. *Macromolecules* **2003**, *36*, 2604−2608. (f) Temma, T.; Hatano, B.; Habaue, S. *Tetrahedron* **2006**, *62*, 8559−8563.

[5] (a) Fuji, K.; Furuta, T.; Tanaka, K. *Org. Lett.* **2001**, *3*, 169−171. (b) Tsubaki, K.; Miura, M.; Morikawa, H.; Tanaka, H.; Kawabata, T.; Furuta, T.; Tanaka, K.; Fuji, K. *J. Am Chem. Soc.* **2003**, *125*, 16200−16201. (c) Furuta, T.; Tanaka, K.; Tsubaki, K.; Fuji, K. *Tetrahedron* **2004**, *60*, 4431−4441. (d) Tsubaki, K.; Miura, M.; Nakamura, A.; Kawabata, T. *Tetrahedron Lett.* **2006**, *47*, 1241−1244. (e) Tsubaki, K.; Takaishi, K.; Tanaka, H.; Miura, M.; Kawabata, T. *Org. Lett.* **2006**, *8*, 2587−2590. (f) Takaishi, K.; Tsubaki, K.; Tanaka, H.; Miura, M.; Kawabata, T. *YAKUGAKU ZASSHI* **2006**, *126*, 779−787. (g) Tsubaki, K.; Tanaka, H.; Takaishi, K.; Miura, M.; Morikawa, H.; Furuta, T.; Tanaka, K.; Fuji, K.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *J. Org. Chem.* **2006**, *71*, 6579−6587. (h) Pieraccini, S.; Ferrarini, A.; Fuji, K.; Gottarelli, G.; Lena, S.; Tsubaki, K.; Spada, G. P. *Chem. Eur. J.* **2006**, *12*, 1121−1126.

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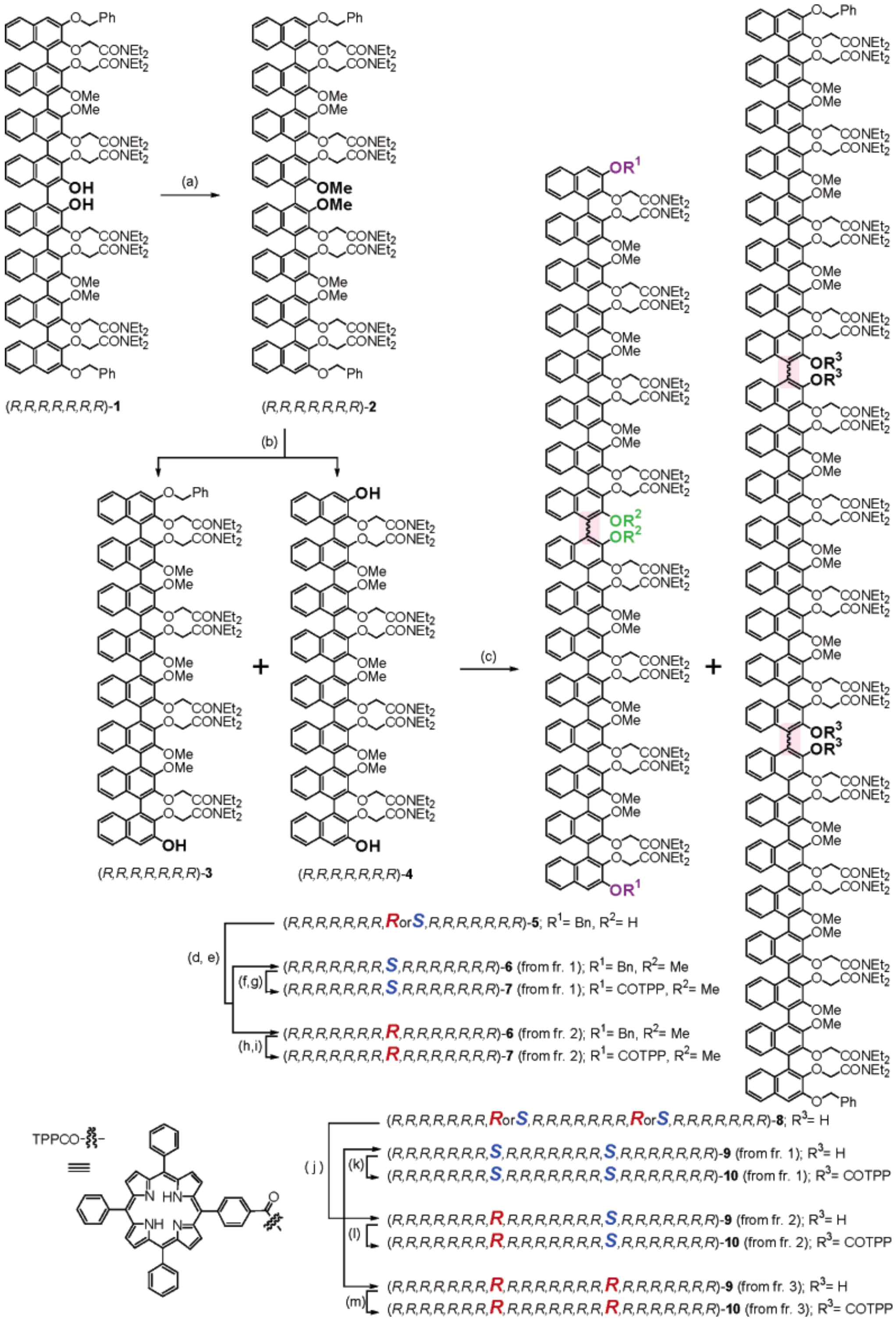
SCHEME 2. Synthesis of Chiral Tetracosanaphthalenes[a]



[a] Conditions: (a) MeI, K_2CO_3, 100%; (b) Pd/C, H_2, **3** (32%), **4** [5e] (19%), recovered **2** (13%); (c) $CuCl_2$, *i*-propylamine, **5** (37% based on **3**), **9** (60% based on **4**), recovered **3** (24% based on **3**); (d) MeI, K_2CO_3, 88%; (e) recycling preparative HPLC, fraction 1 (33%), fraction 2 (30%); (f) Pd/C, H_2, 81%; (g) $TPPCO_2H$, WSC, DMAP, 65%; (h) Pd/C, H_2, 94%; (i) $TPPCO_2H$, WSC, DMAP, 95%; (j) recycling preparative HPLC, fraction 1 (41%), fraction 2 (12%), fraction 3 (15%); (k) $TPPCO_2H$, WSC, DMAP, 85%; (l) $TPPCO_2H$, WSC, DMAP, 42%; (m) $TPPCO_2H$, WSC, DMAP, 33%.

about 94:6.[7] The mixture of **3** and **4** was treated under copper(II) and *i*-propylamine-promoted oxidative coupling conditions.[6,8] The reactivity of the oligonaphthalenes in the coupling reaction decreased as the number of naphthalene units increased. Therefore, 12.5 equiv of *i*-propylamine and 10.0 equiv of $CuCl_2$ were used for coupling of the substrate **3**. Since the starting mono-ol **3** contained a small amount of diol **4**, unexpected 24mer **8** formed through three-component coupling was obtained as well as the regular homo coupling product 16mer **5**. These 16mers **5** (37% based on mono-ol **3**), 24mers **8** (60% based on

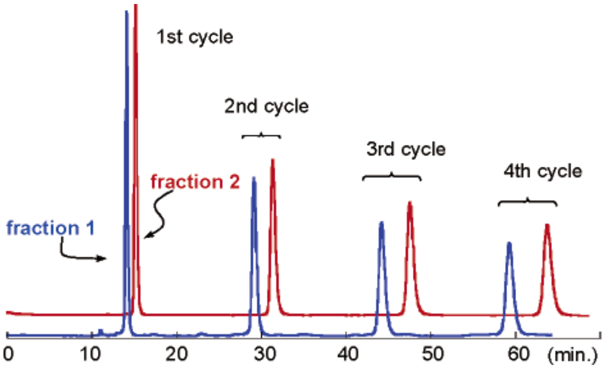


FIGURE 1. Recycling HPLC chart of diastereomer **6**. Conditions: COSMOSIL 5SL-II 20 × 250 mm (nacalai tesque), eluent; EtOAc/EtOH = 8/2, 5 mL/min. Fraction 1 (blue): (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**6**. Fraction 2 (red): (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**6**.

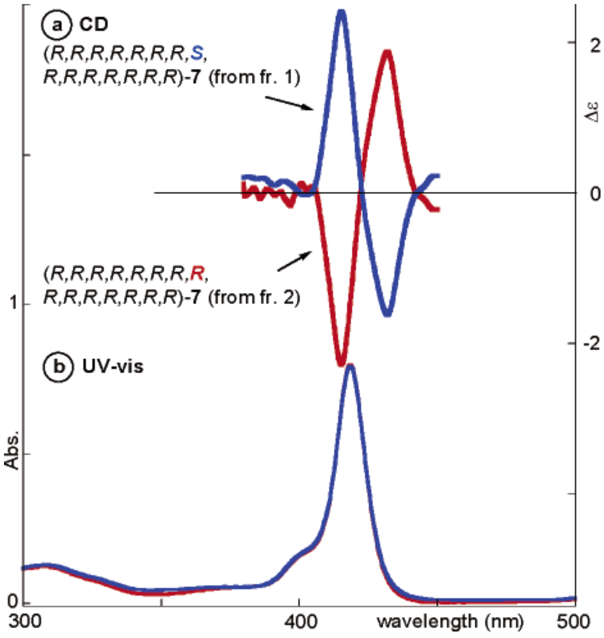


FIGURE 2. CD (a) and UV−vis (b) spectra of (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)- and (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**7**. Conditions: CH_2Cl_2, 1 × 10^{-5} M, 25 °C, light-path length = 1 mm.

diol **4**), and recovered 8mer **3** (24% based on mono-ol **3**) could be separated as diastereomeric mixtures by GPC. The 16mers **5** were followed by methylation of the central two hydroxy groups (88%), and two kinds of diastereomer **6** could be separated into single diastereomers by recycling preparative HPLC to give fraction 1 (33%) and fraction 2 (30%) (Figure 1). After reductive removal of the top and bottom benzyl groups (81−94%), the tetraphenylporphyrins (TPPs) were connected to generate scaffolding hydroxy groups to give **7** (65−95%) for determination of the newly formed axial bond.

To determine the absolute configuration of oligonaphthalenes, we have developed a convenient method that is based on long-range exciton-coupled CD of oligonaphthalenes with two TPPs on the top and bottom naphthalene rings. Thus, the sense of the CD derived from the Soret band of the two TPPs should reflect the torsion of the entire molecule and should reveal the chirality of the target central axial bond.[5e,9,10] The UV and CD spectra of TPP-16mer **7** are shown in Figure 2. The TPP-16mer **7** derived from **6**, which was the first fraction in recycling HPLC (abbreviated as **7** (from fraction 1)), had a negative split-Cotton effect, which indicated that the absolute configuration of the target axis should be *S*. TPP-16mer **7** from **6** at a longer retention time showed a positive Cotton effect, and the chirality of the axis was determined to be *R*.

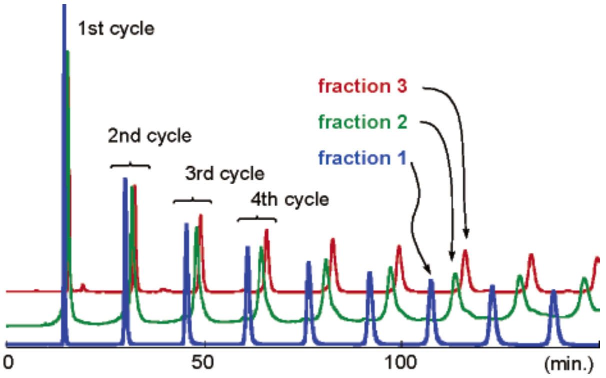


FIGURE 3. Recycling HPLC chart of diastereomer **9**. Conditions: COSMOSIL 5SL-II 20 × 250 mm (nacalai tesque), eluent; EtOAc/EtOH = 8/2, 5 mL/min. Fraction 1 (blue): (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**9**. Fraction 2 (green): (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**9**. Fraction 3 (red): (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**9**.

The 24mer (confirmed by MALDI-TOF mass) should be obtained as three kinds of diastereomers **9**, due to the generation of two new chiral axial bonds. In fact, during separation of that fraction by preparative recycling HPLC, three peaks were observed, and these could be separated into fraction 1 (41%), fraction 2 (12%), and fraction 3 (15%) (Figure 3).

It was expected that it would be difficult to determine the absolute configuration of the two axes in these oligonaphthalenes. The above method, which is based on the Cotton effect of the two TPPs on the top and bottom of naphthalenes, could not be used for these 24mers because (1) the amplitudes of CD are in inverse proportion to the square of the distance of the excitons,[9b] and (2) there are two axes for which the absolute configuration should be determined. Therefore, we searched for a new method to determine the absolute configuration of the

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(6) (a) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261−3262. (b) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313−3319. (c) Smrčina, M.; Lorenc, M.; Hanuš, V.; Sedmera, P.; Kočovský, P. *J. Org. Chem*. **1992**, *57*, 1917−1920. (d) Smrčina, M.; Poláková, J.; Vyskočil, S.; Kočovský, P. *J. Org. Chem*. **1993**, *58*, 4534−4538. (e) Zhang, Y.; Yeung, S.-M.; Wu, H.; Heller, D. P.; Wu, C.; Wulff, W. D. *Org. Lett*. **2003**, *5*, 1813−1816.

(7) See Supporting Information.

(8) (a) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983−7984. (b) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S. *Tetrahedron Lett.* **1995**, *36*, 9519−9520. (c) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.; Noji, M.; Koga, K. *J. Org. Chem*. **1999**, *64*, 2264−2271. (d) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett*. **2001**, *3*, 1137−1140. (e) Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem*. **2003**, *68*, 5500−5511. (f) Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *Angew. Chem., Int. Ed*. **2003**, *42*, 2168−2170. (g) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc*. **2003**, *125*, 6856−6857.

(9) (a) Berova, N., Nakanishi, K., Woody, R. W., Eds. *Circular Dichroism: Principles and Applications*, 2nd ed.; Wiley-VCH: New York, 2000. (b) Harada, N.; Chen, S.-M. L.; Nakanishi, K. *J. Am. Chem. Soc*. **1975**, *97*, 5345−5352. (c) Matile, S.; Berova, N.; Nakanishi, K.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc*. **1995**, *117*, 7021−7022. (d) Matile, S.; Berova, N.; Nakanishi, K.; Fleischhauer, J.; Woody, R. W. *J. Am. Chem. Soc*. **1996**, *118*, 5198−5206.

(10) Application of the exciton chirality method to 16mers **7**. See Supporting Information.

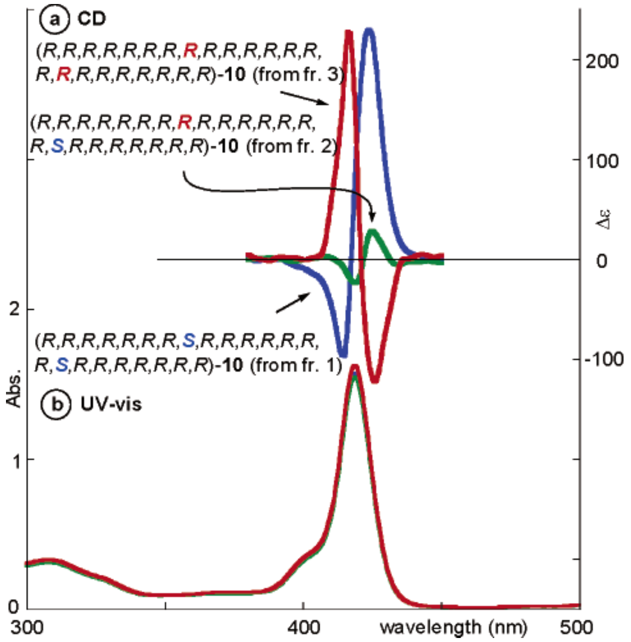

FIGURE 4. CD (a) and UV−vis (b) spectra of (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-, (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-, and (*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**10**. Conditions: CH_2Cl_2, 1×10^{-5} M, 25 °C, light-path length = 1 mm.

24mer, including two unknown axes. In our earliest investigations of oligonaphthalenes, we developed an efficient system based on a CD exciton chirality method.[5b] We focused on the two free hydroxy groups, which ride over the chirality of the unknown axial bond, and chose pyrene as an exciter. Since steric hindrance prohibited the introduction of 1-pyrene carboxylic acid to the scaffolding hydroxy groups, 1-pyrenebutyric acid was selected at that time. Thus, it was thought that bulky functional groups such as TPP carboxylic acid could not be introduced into the scaffolding hydroxy groups. However, to our surprise, the condensation of TPP carboxylic acid and four target hydroxy groups on 24mer **9** proceeded smoothly under WSC/DMAP conditions to give the corresponding tetrakis-TPP-24mer **10** in yields of 33−85%.

The UV and CD spectra of three kinds of tetrakis-TPP-24mer **10** are shown in Figure 4. In the UV spectra, the similar shape and absorbance of Soret bands (ϵ = ca. 1.6×10^6) indicated that these compounds were diastereomeric and had four TPPs. From the CD spectra, tetrakis-TPP-24mer **10**, which was obtained from the fraction 1 in the HPLC of **9**, shows a large positive CD at around 420 nm. Thus, the target axial chiralities should be *R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*. Similarly, tetrakis-TPP-24mer **10** from the third fraction shows a large negative CD and is assigned the chiralities *R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*. Furthermore, the weak amplitude on CD in the second fraction was assigned the chiralities of *R*,*R*,*R*,*R*,*R*,*R*,*R*,***R***,*R*,*R*,*R*,*R*,*R*,*R*,*R*,***S***,*R*,*R*,*R*,*R*,*R*,*R*,*R*.

In conclusion, we succeeded in the bottom-up synthesis of 24mer naphthalenes that had amide groups on their side chains and determined their absolute configurations. For oligonaphthalenes with amide side chains, 24mer is the upper limit for the scope of this synthesis and especially isolation. The construction of remaining oligonaphthalenes with butoxy side chains is under investigation.

Experimental Section

Synthesis of 16mer 5 and 24mer 8: To a mixture of $CuCl_2$ (43 mg, 0.32 mmol) in methanol (1.0 mL) was added *i*-propylamine (34 μL, 0.40 mmol) under an argon atmosphere at room temperature. After 1 h, a solution of (*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**3** (70.7 mg, 30 μmol) and (*R*,*R*,*R*,*R*,*R*,*R*,*R*)-**4** (4.3 mg, 2 μmol) in dichloromethane (1.0 mL) was added, and the reaction mixture was stirred for 11 h at room temperature. The reaction mixture was poured into a mixed solvent of 0.1 M hydrochloric acid solution and chloroform. The organic layer was washed successively with 0.1 M hydrochloric acid solution, water, and brine, dried over sodium sulfate, and evaporated to give a residue. The residue was purified by recycling preparative HPLC connected to a JAIGEL-1H (20 × 600 mm) and JAIGEL-2H (20 × 600 mm) under a flow rate of 3.5 mL/min with $CHCl_3$ detected by UV (254 nm) to give a diastereomeric mixture of 16mer **5** (35 mg, 37% based of **3**), a diastereomeric mixture of 24mer **8** (8 mg, 60% based of **4**), and recovered **3** (29 mg, 24%).

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Supporting Information Available: Full experimental details, characterization data of all new compounds, and the HPLC chart of the mixture of mono-ol **3** and diol **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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