JOC*Note*

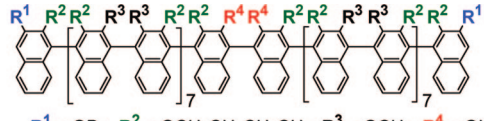
Synthesis of Chiral Dotriacontanaphthalenes: How Many Naphthalene Units Are We Able To Elaborately Connect?

Daisuke Sue,[†] Kazuto Takaishi,[†,‡] Takunori Harada,[§] Reiko Kuroda,[§,||] Takeo Kawabata,[†] and Kazunori Tsubaki*[,⊥]

Institute for Chemical Research, Kyoto University, JST ERATO-SORST Kuroda Chiromorphology Team, Graduate School of Arts and Sciences, The University of Tokyo, and Graduate School of Life and Environmental Science, Kyoto Prefectural University

tsubaki@kpu.ac.jp

Received March 2, 2009



R^1 = OBn, R^2 = $OCH_2CH_2CH_2CH_3$, R^3 = OCH_3, R^4 = OH

(*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-32mer

(*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-dotriacontanaphthalenes **32A**−**E** alternately possessing butoxy and methoxy side chains were precisely constructed through a bottom-up synthesis, and their absolute configurations and fluorescence quantum yields were determined.

There are two major synthetic routes for constructing over-nanosized molecules promising new functional materials. One is the polymer synthesis method, and the other is a bottom-up synthesis procedure beginning with small building blocks. Although these two approaches have both merits and demerits, the notable merit of the bottom-up synthesis is that complicated molecules can be precisely constructed without a molecular-weight distribution.[1]

We have focused on optically active (especially helical) rod-shaped oligo(2,3-dioxyfunctionalized)naphthalenes, which are connected at their 1,4-positions in $CuCl_2$/amine-promoted oxidative coupling reactions.[2,3] Through our previous investigations, we have revealed that (1) the newly formed axis bond between naphthalene rings is easily epimerized under the coupling conditions employed (the other axis bonds are not epimerized under the same conditions)[3] and (2) the high diastereoselectivities in the oxidative homocoupling reactions are induced via three different pathways controlled by the substituents on the 2,3-positions of the naphthalene rings (i.e., epimerization of the axis along with diastereoselective crystallization, thermodynamic, and kinetic control pathways).[2c,d] Our current challenge is to determine how many naphthalene units can be elaborately constructed by repeated homocoupling reactions via the above three pathways. In the case of the naphthalene unit with a methoxy group where diastereoselectivity is caused by epimerization of the newly formed axis along with diastereoselective crystallization, the synthesis of chiral 16mers are the upper limit because of their low solubilities.[2c] Furthermore, for a naphthalene unit with a diethylaminocarbonylmethoxy group in which a rapid coupling reaction with a high homochiral diastereoselectivity and slow epimerization of the newly formed axis leads to a kinetically controlled product, the construction of 24mers is the upper limit because of their low stabilities and the difficulty of isolations.[2g] Herein, we report our last endeavor in the synthesis of oligonaphthalenes with *n*-butoxy side chains where axial chirality is induced under thermodynamic control, and the high solubilities and stabilities are attributed to the side chains.

Scheme 1 outlines the synthesis for chiral oligonaphthalenes with a butoxy substituent on naphthalene. Starting (*S*)-**2** (total ca. 170 g) was treated with $CuCl_2$ in the presence of isopropylamine to afford quaternaphthalene **4A** as a diastereomeric mixture with respect to the newly formed central axis. The mixture was separated by column chromatography on SiO_2 to give all-(*S*)-**4A** (57% yield) as the major product and hetero-(*S*,*R*,*S*)-**4A** (11% yield) as the minor fraction in total of 68% yield and 68% diastereo excess (de). To determine the absolute configuration,[2e,g,4] each diastereomeric **4A** was condensed with tetraphenylporphyrin carboxylic acid ($TPPCO_2H$) under WSC/DMAP conditions to afford all-(*S*)-**4B** and hetero-**4B** in 79% and 62% yields, respectively. Methylation of the central hydroxy groups of all-(*S*)-**4A** (96% yield), followed by mono deprotection of the bottom benzyl group by Pd/C and H_2 provided all-(*S*)-**4D** (46% yield). Repeating the process sequence, octina-

[†] Kyoto University.
[‡] Present address: Supramolecular Science Laboratory, RIKEN (The Institute of Physical and Chemical Research).
[§] JST ERATO-SORST Kuroda Chiromorphology Team.
[||] The University of Tokyo.
[⊥] Kyoto Prefectural University.

(1) For bottom-up construction of giant molecules: (a) Aratani, N.; Osuka, A.; Kim, Y. H.; Jeong, D. H.; Kim, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1458–1462. (b) Izumi, T.; Kobashi, S.; Takimiya, K.; Aso, Y.; Otsubo, T. *J. Am. Chem. Soc.* **2003**, *125*, 5286–5287. (c) Aratani, N.; Takagi, A.; Yanagawa, Y.; Matsumoto, T.; Kawai, T.; Yoon, Z. S.; Kim, D.; Osuka, A. *Chem.—Eur. J.* **2005**, *11*, 3389–3404.

(2) (a) Tsubaki, K. *Org. Biomol. Chem.* **2007**, *5*, 2179–2188. (b) Takaishi, K.; Tsubaki, K.; Tanaka, H.; Miura, M.; Kawabata, T. *Yakugaku Zasshi* **2006**, *126*, 779–787. (c) Tsubaki, K.; Miura, M.; Morikawa, H.; Tanaka, H.; Kawabata, T.; Furuta, T.; Tanaka, K.; Fuji, K. *J. Am. Chem. Soc.* **2003**, *125*, 16200–16201. (d) 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. (e) Tsubaki, K.; Takaishi, K.; Tanaka, H.; Miura, M.; Kawabata, T. *Org. Lett.* **2006**, *8*, 2587–2590. (f) Tsubaki, K.; Miura, M.; Nakamura, A.; Kawabata, T. *Tetrahedron Lett.* **2006**, *47*, 1241–1244. (g) Tsubaki, K.; Takaishi, K.; Sue, D.; Kawabata, T. *J. Org. Chem.* **2007**, *72*, 4238–4241. (h) Tsubaki, K.; Takaishi, K.; Sue, D.; Matsuda, K.; Kanemitsu, Y.; Kawabata, T. *J. Org. Chem.* **2008**, *73*, 4279–4282.

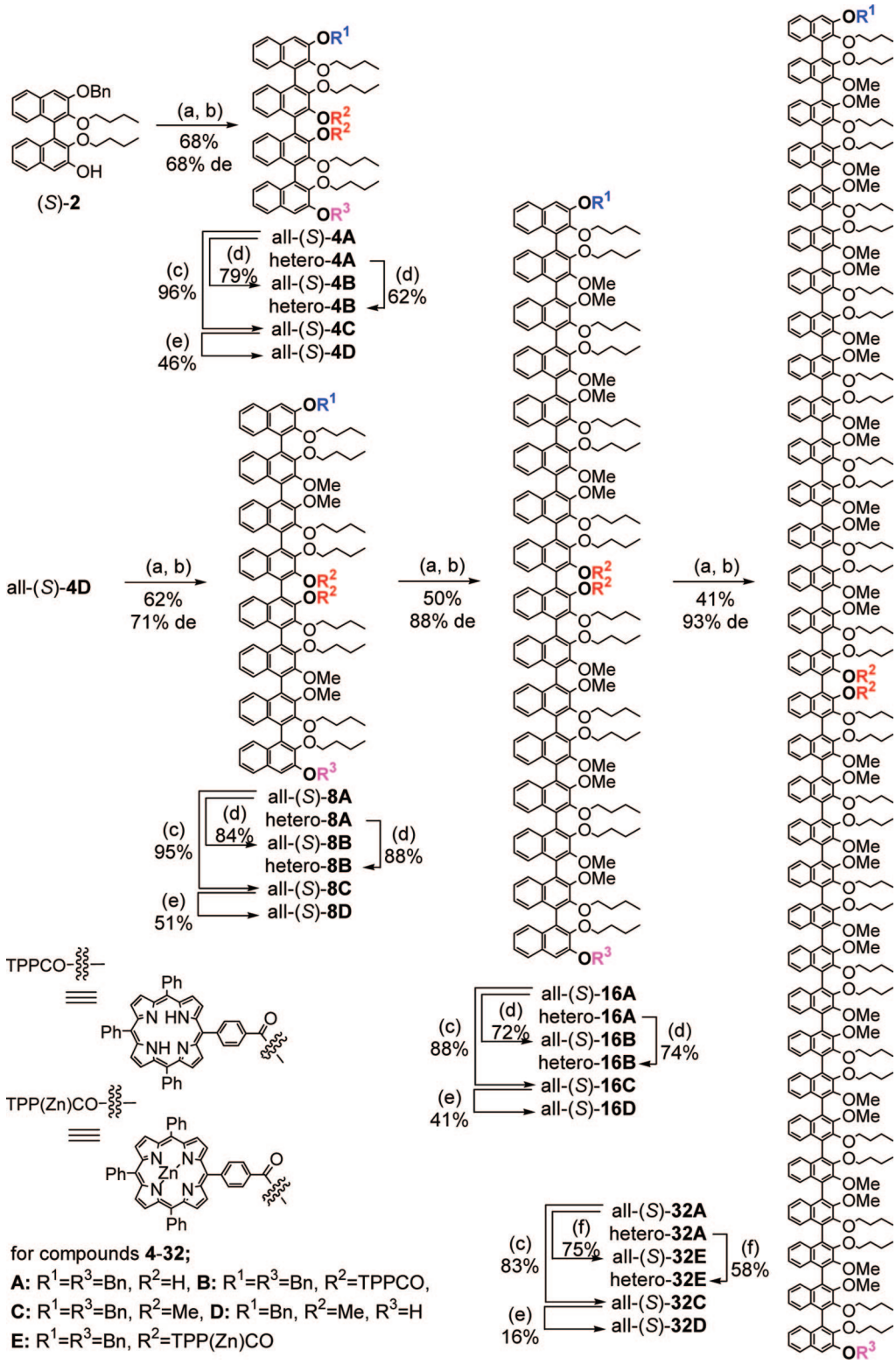
(3) (a) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261–3262. (b) Brussee, J.; Groenendijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313–3319. (c) Smrčina, M.; Lorenc, M.; Hanuš, V.; Sedmera, P.; Kočovský, P. *J. Org. Chem.* **1992**, *57*, 1917–1920. (d) Smrčina, M.; Poláková, J.; Vyskočil, S.; Kočovský, P. *J. Org. Chem.* **1993**, *58*, 4534–4538. (e) Habaue, S.; Seko, T.; Okamoto, Y. *Macromolecules* **2003**, *36*, 2604–2608.

(4) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257–263. (b) Matile, S.; Berova, N.; Nakanishi, K.; Novkova, S.; Philipova, I.; Blagoev, B. *J. Am. Chem. Soc.* **1995**, *117*, 7021–7022.

(5) We tried several times to measure HRMS and/or elemental analysis of **32E**s; however, because of their huge molecular weights and chemical instabilities, the attempts were not fruitful.

10.1021/jo900463t CCC: $40.75
Published on Web 04/16/2009

SCHEME 1. Synthetic Route for the Oligonaphthalenes[a]



[a] Conditions: (a) $CuCl_2$, *iso*-$PrNH_2$, (b) separation of diastereomers, (c) MeI, K_2CO_3, (d) $TPPCO_2H$, WSC, DMAP, (e) H_2, Pd/C or $Pd(OH)_2$, and (f) $TPP(Zn)CO_2H$, WSC, DMAP.

phthalenes **8A**−**D**, hexadecanaphthalenes **16A**−**D**, and dotriacontanaphthalenes **32A**−**E** were also constructed. In the case of **32E**, Zn−tetraphenylporphyrin carboxylic acid ($TPP(Zn)CO_2H$) was introduced instead of $TPPCO_2H$ because of the latter's chemical stability.[5] It is noteworthy that the diastereoselectivities in the homocoupling reaction of all-(*S*)-substrates (**2**, **4D**, **8D**, and **16D**) increased from 68%, 71%, and 88% to 93% de as the number of naphthalene units increased, whereas the corresponding chemical yields decreased from 68%, 62%, and 50% to 41%. As expected, separation of the

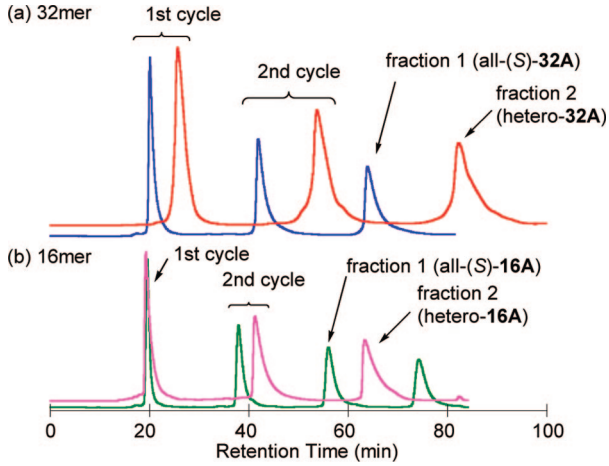


FIGURE 1. Recycling HPLC chart of (a) diastereomer **32A** and (b) diastereomer **16A**. Conditions: COSMOSIL 5SL-II 20 × 250 mm (Nacalai Tesque). (a) Eluent; $CHCl_3/Et_2O$ = 50/1, 3 mL/min. Fraction 1 (blue): all-(*S*)-**32A**. Fraction 2 (red): hetero-**32A**. (b) Eluent; $CHCl_3/Et_2O$ = 100/1, 3.3 mL/min. Fraction 1 (green): all-(*S*)-**16A**. Fraction 1 (purple): hetero-**16A**.

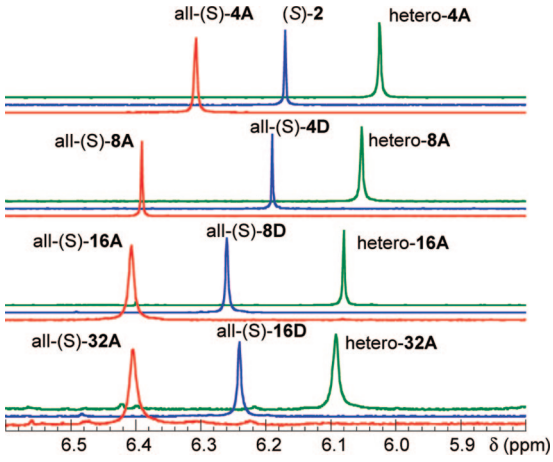


FIGURE 2. Partial ^{1}H NMR (400 MHz) spectra of oligonaphthalenes with the hydroxy group in $CDCl_3$ at 20 °C.

diastereomeric mixtures of **4A**, **8A**, **16A**, and **32A** into single diastereomers became more difficult as the number of naphthalene units increased. The synthesis of higher order oligonaphthalenes using all-(*S*)-**32D** as a starting material was also attempted. After purifying and separating the products of the coupling reaction by gel permeation chromatography (GPC) and recycling HPLC on silica gel, a probable fraction could be isolated. However, NMR analysis of benzylic and hydroxy protons indicated that the fraction was still composed of several materials (Supporting Information, Figure SI-1). Thus, the upper limit of oligonaphthalenes with butoxy side chains was determined to be 32mers because of the difficulty of isolation and separation.

The purity and separation of diastereomeric **16A** and **32A** were confirmed using both recycling HPLC (Figure 1) and ^{1}H NMR (two sharp single signals corresponding to the methylene proton in the top and bottom benzyl groups and the phenolic proton in central hydroxy groups). Figure 2 shows the ^{1}H NMR spectra of the oligonaphthalenes with a hydroxy group (**A** and **D** series). The signals, which are ascribed to the hydroxy proton, appeared near 6.0−6.4 ppm, and the sample concentration did not affect chemical shifts of these signals (Supporting Information, Figure SI-2). Compared to the chemical shifts of the hydroxy proton in oligonaphthalenes with a mono hydroxy group at the bottom, which is the starting material of the corresponding homocoupling reaction, and those of the central hydroxy groups of products, the hydroxy proton for the all-(*S*)-oligonaphthalene was at a lower magnetic field, while that of the hetero-oligonaphthalene appeared at a higher magnetic field. These results indicate that the absolute configuration of the newly formed axis can be predicted on the basis of the corresponding chemical shifts and the purity of the product can also be verified.

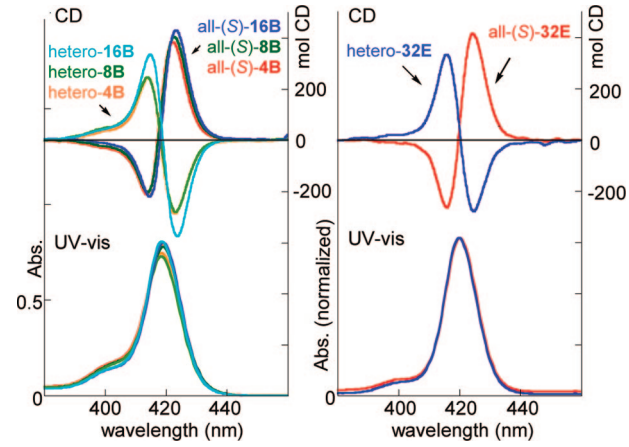


FIGURE 3. CD and UV−vis spectra of the oligonaphthalenes with two TPPs. Left: CD and UV−vis spectra of **4B**, **8B**, and **16B**. Conditions: CH_2Cl_2, $c = 1.0 \times 10^{-5}$ M, 20 °C, light path length = 1 mm. Right: CD and UV−vis spectra of **32E**. Because it is difficult to accurately weigh **32E** because of the static electricity charge as well as tiny amounts of **32E**, the concentrations of the samples were calculated on the basis of the molar absorbance coefficient (ε) of $TPP(Zn)CO_2H$ (ε = 523 000).

To determine the absolute configuration of the newly formed axis, we applied the CD exciton chirality method to the oligonaphthalenes with two TPPs. 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.[2e,g,4] The UV and CD spectra of TPP−oligonaphthalenes are shown in Figure 3. The TPP−oligonaphthalene showed a positive split Cotton effect, which indicated that the absolute configuration of the target axis should be *S*.

Using systematically constructed oligonaphthalenes, which have two hydroxy groups in the center (all-(*S*)-**4A**, all-(*S*)-**8A**, all-(*S*)-**16A**, and all-(*S*)-**32A**), the fluorescence quantum yields were measured (Figure 4). When the oligonaphthalenes were excited at 320 nm, the intensity of the fluorescence increased as the number of naphthalene units increased. Interestingly, the fluorescence quantum yields were nearly independent of the number of naphthalene units (Φ_{320} = 0.152 (all-(*S*)-**4A**), Φ_{320} = 0.225 (all-(*S*)-**8A**), Φ_{320} = 0.212 (all-(*S*)-**16A**), and Φ_{320} = 0.231 (all-(*S*)-**32A**)). In our previous study on oligonaphthalenes with methoxy substituents, the quantum yields of these compounds increased as the number of naphthalene units increased (from 20% to 82%).[2f] Even in the cases of the oligonaphthalene **C** series, the quantum yields were about 50% (Φ_{320} = 0.486 (all-(*S*)-**4C**), Φ_{320} = 0.535 (all-(*S*)-**8C**), Φ_{320} = 0.467 (all-(*S*)-**16C**), and Φ_{320} = 0.445 (all-(*S*)-**32C**); Figure SI-3 of Supporting Information). These results indicate that the quantum yields of these oligonaphthalenes are affected by the mobility of the substituent on the side chain.

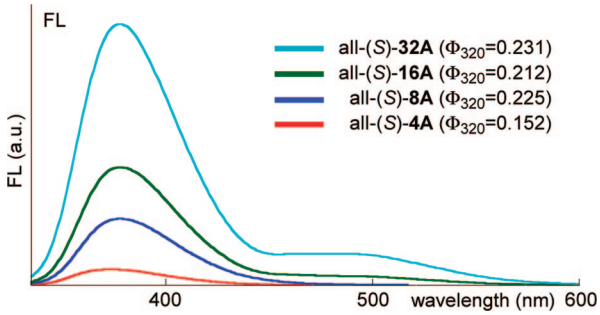


FIGURE 4. Fluorescence spectra of all-(*S*)-**4A**, **8A**, **16A**, and **32A**. Conditions: CH_2Cl_2, 20 °C, light path length = 10 mm. λ_{ext} = 320 nm. Fluorescence quantum yield (Φ) excited at 320 nm using a solution of quinine sulfate in 1 N H_2SO_4 as a reference standard (Φ = 0.546) in parentheses.

In conclusion, the last challenge in constructing optically active oligonaphthalenes among three different pathways, that is, a thermodynamic one, was completed. The chirality of the newly formed axis in the 32mers, which were the upper limit because of technical isolation or separation problems, could be unambiguously determined by the CD exciton chirality method. The corresponding 32mers, which are the highest examples of oligonaphthalenes, maintained a sufficient solubility against various kinds of organic solvents, and thus, their properties should be suitable to contribute to the field of materials chemistry. Therefore, we plan to shift our attention to developing new intrinsic functions of these oligonaphthalenes such as selective solubilization of carbon nanotubes.

Experimental Section

Synthesis of 16A. To a mixture of $CuCl_2$ (29 mg, 216.6 μmol) in methanol (1 mL) was added *i*-propylamine (23 μL, 270.8 μmol) under argon atmosphere under ice-bath cooling. After 45 min, a solution of all-(*S*)-**8D** (204.8 mg, 108.3 μmol) in dichloromethane (1 mL) was added, and the reaction mixture was stirred for 5 h at 0 °C to rt. The reaction mixture was poured into the mixed solvent of 1 M hydrochloric acid solution and $CHCl_3$. The aqueous layer was extracted with chloroform (twice). The organic layer was combined, washed with brine, dried over sodium sulfate, and evaporated to give a residue. The residue was purified by column chromatography (SiO_2 hexane/chloroform/ethyl acetate = 10:1:1) to afford to all-(*S*)-**16A** (96.6 mg, 47%) and hetero-**16A** (17.5 mg, 5.4%).

Acknowledgment. This study was partly supported by a Grant-in-Aid for Scientific Research (KAKENHI) (17659004) and the Japan Securities Scholarship Foundation (JSSF).

Supporting Information Available: Full experimental details and characterization data of all new compounds, Figures SI 1−4. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900463T