

## Chiral Tetrakis(2-thienyl)methane Derivative: A Possible Precursor for Cryptochiral Tetraalkylmethanes

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(5-Acetyl-2-thienyl)(5-benzoyl-2-thienyl)(5-bromo-2-thienyl)-(5-cyano-2-thienyl)methane has been synthesized as the first chiral tetrakis(2-thienyl)methane derivative. This compound can be resolved by chiral HPLC. Since Raney nickel reduction of tetrakis(2-thienyl)methane derivatives gave tetraalkylmethane derivatives, chiral tetrakis(2-thienyl)methane derivatives will be good precursors for a number of cryptochiral tetraalkylmethanes and their derivatives.

Cryptochirality means the “hidden” chirality of such compounds that are virtually optically inactive in spite of inherently chiral molecular structure.<sup>1</sup> Chiral tetraalkylmethanes do not contain any functional groups, and they can be classified as cryptochiral compounds. These cryptochiral tetraalkylmethanes have been studied for several decades in relation to their optical activity,<sup>2</sup> chiral discrimination,<sup>3</sup> and absolute configuration determination.<sup>4</sup> Recently, we reported the synthesis and chiroptical properties of phenyl(2-pyridyl)(3-pyridyl)(4-pyridyl)methane as the first chiral molecule based on a tetraarylmethane framework (Chart 1).<sup>5</sup> Now we have devised another type of chiral molecule based on a tetraarylmethane framework; chirality is introduced by the four different substituents on a symmetrical tetraarylmethane core. We chose tetrakis(2-thienyl)methane<sup>6</sup> (Th<sub>4</sub>C) as the core unit. It is expected that a number of cryptochiral tetraalkylmethanes and their derivatives could be systematically synthesized by Raney nickel reduction of the corresponding chiral Th<sub>4</sub>C derivatives. In addition, optical resolution and absolute configuration determination of Th<sub>4</sub>C derivatives would be more practical than those of tetraalkylmethane itself. Therefore, chiral Th<sub>4</sub>C derivatives are interesting not only in their own chiroptical properties, which would be dependent upon their substituents, but also as promising precursors of enantiomerically pure cryptochiral tetraalkylmethane derivatives. We now report the synthesis and chiroptical properties of **1** as the first example of a chiral Th<sub>4</sub>C derivative. Raney nickel reduction of Th<sub>4</sub>C is also presented.

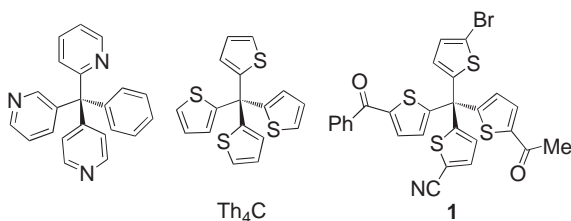
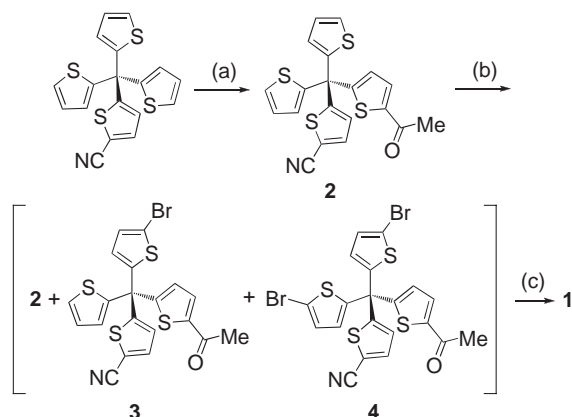


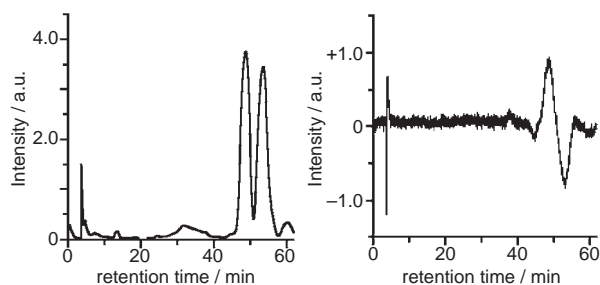
Chart 1.



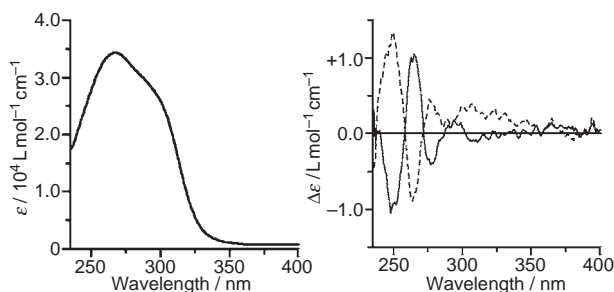
**Scheme 1.** Synthesis of **1**. Reagents and conditions: (a) CH<sub>3</sub>COCl (1.0 equiv), SnCl<sub>4</sub> (1.0 equiv), CS<sub>2</sub>, rt, 2 h, 56%; (b) NBS (1.0 equiv), DMF, in the dark, rt, 24 h; (c) PhCOCl (20 equiv), AlCl<sub>3</sub> (20 equiv), rt, 20 h, 35% (2 steps).

The synthesis of **1** is illustrated in Scheme 1. Friedel–Crafts acylation of (5-cyano-2-thienyl)tris(2-thienyl)methane<sup>6b</sup> afforded **2** in 56% yield. Bromination of **2** with NBS in DMF afforded a mixture of the starting material **2**, mono-brominated compound **3**, and di-brominated compound **4**. Since the purification of **3** was difficult, the crude product was used without further purification. Thus, the mixture containing **3** was treated with excess benzoyl chloride and AlCl<sub>3</sub> to afford a mixture of **4**, monobenzoylelated product **1**, and dibenzoylelated product. The target chiral molecule **1** in turn, was purified by column chromatography on silica gel. Identification of **1** was achieved by EI-MS, NMR, and elemental analysis.<sup>7,8</sup>

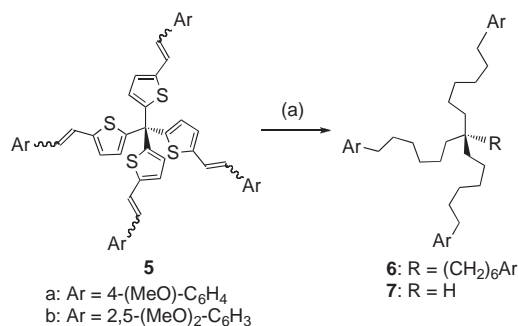
The enantiomeric pair of **1** was successfully resolved by chiral HPLC with a CHIRALPAK AS-H column (Figure 1). As expected, the electronic CD spectra of the two fractions in acetonitrile (Figure 2) are mirror images of each other. In order to assign the absolute configuration of **1**, we attempted to calculate the electronic CD curve for comparison with the experimental CD spectra.<sup>5,9</sup> However, a standard molecular-mechanics conformational analysis with MMFF94S<sup>10</sup> gave as many as 663 stable conformations within 20.25 kJ mol<sup>-1</sup>, which correspond to the various rotamers not only around the four C–aryl bonds but also around the single bonds in acetyl and benzoyl groups. The population of the most stable conformer was estimated to be only 1.7% at room temperature. Accordingly, it was practically impossible to achieve the absolute configuration determination of **1** by calculation of the CD curve.



**Figure 1.** Chromatogram for the enantiomeric separation of **1**. Left: UV detection ( $\lambda = 275$  nm). Right: CD detection ( $\lambda = 275$  nm). Conditions: column; CHIRALPAK AS-H, eluent; hexane/ethanol = 90:10 (v/v), flow rate;  $1.0 \text{ mL min}^{-1}$ , temperature;  $35^\circ\text{C}$ ,  $t_1 = 49.5$  min,  $t_2 = 51.5$  min.



**Figure 2.** Left: UV-vis spectrum of **1** in acetonitrile. Right: CD spectra of the enantiomeric pair of **1** in acetonitrile. The first and second eluted fractions are plotted as solid and dashed lines, respectively.



**Scheme 2.** Raney nickel reduction of Th<sub>4</sub>C derivative **5**. Reagents and conditions: (a) Raney nickel W7 (50 equiv),  $0.3 \text{ MPa H}_2$ , ethanol-benzene,  $85^\circ\text{C}$ , 5 h, **6a** (40%), **7a** (27%), **6b** (53%), and **7b** (24%).

Providing for the reduction of chiral Th<sub>4</sub>C derivative **1**, Raney nickel reduction of **5** was examined as a model experiment for the synthesis of tetraalkylmethane from the corresponding Th<sub>4</sub>C derivative (**Scheme 2**). Since we studied the Raney nickel reduction of tris(2-thienyl)methane derivatives,<sup>11</sup> we applied similar conditions to the reduction of **5**. For convenient UV-detection by TLC analysis and the assignment of NMR chemical shifts of the products, methoxyphenyl groups were attached at the terminals of the Th<sub>4</sub>C framework. When an isomeric mixture of **5** was treated with excess Raney nickel under medium pressure of hydrogen, the tetraalkylmethane derivative **6** was obtained in moderate yield accompanied by the correspond-

ing trialkylmethane derivative **7**, produced by the hydrogenolysis of one C-C bond of the central carbon atom in **5**.<sup>12</sup>

In summary, we have synthesized the first chiral Th<sub>4</sub>C derivative **1** and enclosed chiroptical properties of **1**. We have also shown that Raney nickel reduction of **5** gives tetraalkylmethane derivative **6** in moderate yield. These results would open the way to a number of optically pure samples of cryptochiral tetraalkylmethanes and their derivatives. Synthesis of other chiral Th<sub>4</sub>C derivatives, absolute configuration determination and Raney nickel reduction of **1** are now under investigation.

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- Spectroscopic data for **1**: pale yellow solid; mp  $61.5\text{--}62.5^\circ\text{C}$ ; EIMS  $m/z$  (rel intensity) 595 ( $\text{M}^+$ , <sup>81</sup>Br, 100), 593 ( $\text{M}^+$ , <sup>79</sup>Br, 81), 552 ( $[\text{M} - \text{CH}_3\text{CO}]^+$ , <sup>81</sup>Br, 61), 550 ( $[\text{M} - \text{CH}_3\text{CO}]^+$ , <sup>79</sup>Br, 45), 514 ( $[\text{M} - \text{Br}]^+$ , 85), 490 ( $[\text{M} - \text{PhCO}]^+$ , <sup>81</sup>Br, 33), 488 ( $[\text{M} - \text{PhCO}]^+$ , <sup>79</sup>Br, 31); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  2.55 (s, 3H), 6.84 (d,  $J = 4.0$  Hz, 1H), 7.02 (d,  $J = 4.0$  Hz, 1H), 7.13 (d,  $J = 4.0$  Hz, 1H), 7.14 (d,  $J = 4.0$  Hz, 1H), 7.15 (d,  $J = 4.0$  Hz, 1H), 7.49–7.52 (m, 2H), 7.55 (d,  $J = 4.0$  Hz, 1H), 7.56 (d,  $J = 4.0$  Hz, 1H), 7.61 (d,  $J = 4.0$  Hz, 1H), 7.59–7.63 (m, 1H), 7.84–7.86 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  26.57, 54.26, 110.58, 113.43, 114.10, 128.60, 128.64, 128.96, 128.99, 129.20, 129.23, 130.03, 131.87, 132.68, 134.17, 137.28, 137.41, 143.81, 144.59, 149.70, 157.25, 157.26, 157.47, 187.96, 190.57; Anal. Calcd for C<sub>27</sub>H<sub>16</sub>BrNO<sub>2</sub>S<sub>4</sub>: C, 54.54; H, 2.71; N, 2.36%. Found: C, 54.22; H, 2.98; N, 2.34%.
- Full assignment of the <sup>1</sup>H and <sup>13</sup>C NMR spectra was achieved by the acquisition of heteronuclear multiple-quantum correlation (HMQC) and heteronuclear multiple-bond correlation (HMBC) spectra.<sup>13</sup>
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- Experimental details of the Raney nickel reduction of **5** and spectroscopic data of the products are described in the Supporting Information.
- Supporting Information is also available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.