<table>
<thead>
<tr>
<th>Title</th>
<th>STUDIES ON SYNTHESIS OF OPTICALLY PURE HETEROHELICENES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Osuga, Hideji</td>
</tr>
<tr>
<td>Citation</td>
<td>Kyoto University</td>
</tr>
<tr>
<td>Issue Date</td>
<td>1997-03-24</td>
</tr>
<tr>
<td>URL</td>
<td><a href="https://doi.org/10.11501/3123279">https://doi.org/10.11501/3123279</a></td>
</tr>
<tr>
<td>Type</td>
<td>Thesis or Dissertation</td>
</tr>
<tr>
<td>Textversion</td>
<td>author</td>
</tr>
</tbody>
</table>
学位申請論文

大須賀秀次
STUDIES ON SYNTHESIS OF OPTICALLY PURE HETEROHELICENES

（光学的に純粋なヘテロヘリセンの合成に関する研究）

1997

京都大学大学院
理学研究科化学専攻
有機合成化学分科

大須賀 秀次
Contents

General Introduction 1


Chapter 3. Synthesis and Crystal Structure of Chiral Bifunctional Helicenes with \( \pi \)-deficient Pyridine and \( \pi \)-Excessive Thiophene Units. 58

Chapter 4 A novel Route to Optically Active Disubstituted Heterohelicene via Biaryl- and Carbonyl-coupling Reactions. 79

List of Publications 99

Acknowledgements 101
General Introduction

Helical structures are often encountered in natural products such as polyamiloose, polypeptides and nucleic acids, which are stabilized through hydrogen bonds, disulfide linkages, hydrophobic interactions, and metal coordination. These compounds possess inherent chirality which is related with the screw sense of helicity, i.e., a right-handed helix (P) and a left-handed helix (M). The artificially prepared helical compounds are known as helicenes, helicates and helixanes. Among them, helicenes containing more than six benzene rings (carbohelicenes) or seven heterocyclic rings (heterohelicenes) possess rigid helical framework and are very stable toward acids, bases, and relatively high temperature.

Ever since the first synthesis of hexahelicene and its optical resolution by Newman and Lednicer in 1955, the chemistry of helicenes has attracted a great deal of attention because of their very high rotational values and their unique helical structures. Chiral functionalized helicenes and their heterocyclic analogs are of great interest in material research, molecular recognition, and asymmetric synthesis. In 1968, Wynberg and his co-workers reported the synthesis of a wide variety of heterohelicenes by photocyclization of 1,2-diarylethylene. The preparation of optically active helicenes, however, still requires laborious methods such as (i) the repeated recrystallizations of diastereomeric π-complexes derived from racemic helicenes and optically active compounds like 2-(2,4,5,7-tetranitro-9-fluorenylideneaminoxy)propionic acid (TAPA), (ii) crystal picking, or (iii) microscale separation by chiral column of high performance liquid chromatography (HPLC). Although photosynthesis by circularly polarized light or in chiral solvents is a very attractive method for chiral helicenes, the enantioselectivities are very low, ranging from 0 to 3.0%. Asymmetric synthesis using a chiral auxiliary such as a menthyl ester has been developed, but the diastereoselectivities of photocyclization are low to moderate and the resolution of the diastereoisomers by column chromatography is very difficult. Little progress has been made toward the development of asymmetric synthesis of chiral helicenes for these reasons. This is a striking contrast to the 1,1'-binaphtyl derivatives, which are often used as chiral ligands or chiral auxiliaries in organic synthesis. Katz and his coworkers have recently found an efficient non-photocyclization procedure using benzoquinone as a dienophile in the Diels-Alder reaction. They obtained optically active helical quinone using (−)-camphanoyl chloride as a chiral auxiliary for optical resolution, but only the
specific helicenes were obtained by this method.

The first structural elucidation of helicenes by X-ray analysis was reported in 1969. The relationship between the absolute configuration and the rotational value of [6]heterohelicene was established by Wynberg in 1971: (+)-hexahelicene has a right-handed helicity, the (−)-enantiomer a left-handed helicity, but the crystal data and the structural data of the helicene were not indicated. So far, there are only a few reports describing the crystal structures of functionalized helicenes.

This thesis deals with the three different effective methods of the synthesis of functionalized [7]thiaheterohelicenes. The important features of these methods are as follows: (i) The optically pure functionalized heterohelicenes were obtained by photocyclization of 1,2-diarylethylene using bicyclic amino alcohols as chiral auxiliaries. (ii) Both enantiomers of bis(hydroxymethyl)[7]thiaheterohelicene were prepared by lipase-catalyzed transesterification. (iii) The optically active disubstituted heterohelicenes were synthesized without using photocyclization. The crystal structures of thiaheterohelicenes are also described in this thesis.

References
8) (a) Ashitaka, H.; Yokoh, Y.; Shimizu, R.; Yokozawa, T.; Morita, K.; Suehiro, T.; Matsumoto, Y. Nonlinear Optics 1993, 4, 281; (b) Morita, K.; Suehiro, T.; Yokoh,


(c) Lochmüller, C. H.; Ryall, R. R. J. Chromatogr. 1978, 150, 511; (d) Nakagawa, H.;
1903; (e) Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y.; Chikamatsu, H.;

Chem. Soc.* 1971, 93, 2353; (b) Bernstein, W. J.; Calvin, M.; Buchardt, O. *J. Am.
Chem. Soc.* 1972, 94, 494; (c) Kagan, H.; Moradpour, A.; Nicou, J. F.; Balvoie,
G.; Martin, R. H.; Cosyn, J. P. *Tetrahedron Lett.* 1971, 2479; (d) Bernstein, W. J.;
Calvin, M. *Tetrahedron Lett.* 1972, 2195; (e) Bernstein, W. J.; Calvin, M.; Buchardt,


Belg.* 1975, 84, 1033; (b) Cochez, Y.; Martin, R. H.; Jespers, J. *Isr. J. Chem.* 1976,

18) (a) Martin, R. H.; Libert, V. *J. Chem. Res. (S)*, 1980, 131; (b) Martin, R. H.;


1470.

92, 7218; (b) Groen, M. B.; Wynberg, H. *J. Am. Chem. Soc.* 1971, 93, 2968; (c)
Lightner, D. A.; Helfelfinger, D. T.; Frank, G. W.; Powers, T. W.; Trueblood, K. N.

1991, 56, 6787.
Chapter 1


Abstract

The diastereocntrolled photocyclization of 1,2-diarylethylene (3) derived from (1R,2S,3R,4S)-3-amino-2-hydroxybornane as a chiral auxiliary has been employed as the key step in the synthesis of functionalized chiral helicenes containing (ethylthio)carbonyl, hydroxymethyl, chloromethyl, formyl and (triphenylphosphonio)methyl groups at the 2-position of [1]benzothieno[5,4-b]-naphtho[1’2’:4,5]thieno[3,2-e][1]benzothiophene. These chiral helicenes show very high rotational values, $[\alpha]_b$ 1450-2900, and the absolute configuration of [7](heterohelicene)carboxamide possessing a positive rotational value has been determined as P, a right-handed helicity by X-ray crystallographic method. In the crystal lattice, the hydrogen bond between OH of the 3-amino-2-hydroxybornane moiety and the carbonyl oxygen located on the adjacent molecule forms a helical network. The interplanar angle between the terminal rings of the helicene is 47.3°, and the shortest nonbonded C-C distance is 3.05 Å.

Introduction

Among the artificially prepared helical molecules such as helicenes, helicates and helixanes, helicene frameworks are thermally and photochemically stable. Therefore, functionalized helicenes with high optical purity are of great interest with respect of new chiral ligands and auxiliaries, chiral stationary phases, or nonlinear optical materials. The preparation of the chiral helicenes, however, requires laborious methods such as repeated recrystallizations of the diastereomeric π complex derived from racemic helicenes and optically active compounds like TAPA, crystal picking, or microscale separation by chiral column of high performance liquid chromatography (HPLC). An efficient diastereoselective synthesis of chiral carbohelicenes has been recently reported by Katz and his co-workers who utilize optically active 3-(t-butyldimethylsilyl)oxy-2,3-dihydro-1H-benz[e]indene-8-carboxamide. This chapter describes the diastereocntrolled synthesis of monofunctionalized [1]benzothieno[5,4-b]naphtho[1’,2’:4,5]thieno[3,2-
benzothiophene derivatives using (1R,2S,3R,4S)-3-amino-2-hydroxybornane (abbreviated as *exo*-amino alcohol) and (1R,2R,3S,4S)-3-amino-2-hydroxybornane (abbreviated as *endo*-amino alcohol) as chiral auxiliaries. The strategies for the synthesis of the optically active heterohelicenes consist of carboxamide-induced remote lithiation and diastereo-selective photocyclization of 1,2-diarylethenes prepared by the Wittig reaction. The X-ray crystal structure of N-[(1R,2R,3S,4S)-2-hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]heptan-3-yl][1]benzothieno[5,4-b]naphtho[1',2':4,5]thieno[3,2-e][1]benzothiophene-2-carboxamide (24) are also reported in this chapter.

**Synthesis of Optically Pure Heterohelicene by Use of *exo*-Amino Alcohol as Chiral Auxiliary**

When lithium diisopropylamide (LDA) was treated with amide 4 prepared

![Scheme 1](image)

Reagents and conditions: (i) 2-thiophenecarbonyl chloride, CH₂Cl₂, pyridine, 76%; (ii) LDA, THF, -15 °C, DMF, 79%; (iii) 3, t-BuOK, MeOH, THF, 76%; (iv) hv, I₂, benzene, 54%; (v) BuLi, ether, room temperature, CO₂ (solid), 44%; (vi) SOCl₂, benzene; (vii) 1, pyridine, 4-dimethylaminopyridine (DMAP), CH₂Cl₂, 75%.
from secondary exo-amino alcohol 1 and 2-thiophencarbonyl chloride\textsuperscript{11} at −15 °C in tetrahydrofuran (THF), 5-lithio-species was obtained exclusively\textsuperscript{12} and trapped with N,N-dimethylformamide (DMF) to give 5-formylthiophene-carboxamide (5) in 79 % yield.\textsuperscript{12} The Wittig reaction of 5 with thienyltriphénylphosphonium chloride (3) and subsequent photocyclization of the resulting 1,2-dithienylethylene 6 gave benzodithiophenecarboxamide (7) in 54 % yield. The carboxamide 7 was also prepared from 1 and 2-benzo[1,2-b:4,3-b']dithiophencarbonyl chloride (10) derived from benzo[1,2-b:4,3-b']dithiophene (8)\textsuperscript{13} (Scheme 1). Alpha-lithiation of the terminal thiophene ring of 7 was carried out under similar conditions to those for the amide 4 and the lithio-species was treated with DMF to afford 11 in 79 % yield. The aldehyde 11 was converted into 1,2-diarylethylene 13 in 83 % yield by the Wittig reaction with 2-naphtho[2,1-b]thienylmethyltriphénylphosphonium chloride (12). Photocyclization of 13 in the presence of propylene oxide and a stoichiometric amount of iodine in benzene (0.60 mM) under argon\textsuperscript{14} gave the desired [7]heterohelicene 15 in 57 % yield as a mixture of the diastereoisomers (45:55).\textsuperscript{15} The chemical yield of the helicene 15 was improved to 91 % without significant change of the diastereoselectivity (47:53), when the reaction was carried out in more dilute condition (0.31 mM). The use of the triisopropylsilyl ether 14 prepared from 13 and triisopropylsilyl trifluoromethanesulfonate,\textsuperscript{16} provided a better diastereoselectivity (32:68) in this photocyclization (Table 1). Desilylation of the corresponding helicene 16 with tetrabutylammonium fluoride in THF gave 15 in 60 % yield from the olefin 14 (Scheme 2). Separation of the diastereoisomers of 15

\begin{table}
\begin{center}
\textbf{Table 1} The ratio of the diastereoisomers produced by photocyclization
\end{center}
\begin{tabular}{llll}
\hline
R & (-):(+) & Yield (%) & Conc. (mM) \\
\hline
H & 55:45 & 57 & 0.60 \\
H & 53:47 & 91 & 0.31 \\
Si(i-Pr)\textsubscript{3} & 68:32 & 60 & 0.62 \\
\hline
\end{tabular}
\end{table}
Scheme 2

Reagents and conditions: (i) LDA, THF, -15 °C, DMF, 79%; (ii) 12, t-BuOK, MeOH, THF, 83%; (iii) hv, I₂, propylene oxide, benzene, 91%; (iv) (i-Pr)₃SiOTf, 2,6-lutidine, CH₂Cl₂, 100%; (v) (a) hv, I₂, propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF, 61%; (vi) (a) (t-BuO₂C)₂O, Et₃N, DMAP, CH₂Cl₂, 76%; (b) CH₃ONa, MeOH, THF, 16%.
(a) helicene carboxamide $[(PM)\cdot(\pm)-18]$ 

(b) $(-)$-helicene carboxamide $[(M)\cdot(-)-18]$

**Figure 1** NMR Spectrum of Heterohelicene
was readily achieved by column chromatography on silica gel using hexane-ethyl acetate (5:1) as eluent. The optical purity of both diastereomers, (M)-(−)-18 and (P)-(+)18, was determined as >99.5 % by HPLC analysis. 1H NMR spectrum of a mixture of the diastereoisomers and that of (M)-(−)-18 are shown in Figure 1. Two sets of the diastereomeric proton peaks were detected in the chart (a) of Figure 1, indicating the presence of a mixture of diastereoisomers. In contrast, the chart (b) of Figure 1 shows only one set of peaks, which indicates the presence of only one of two diastereoisomers. It is important to note that the hydroxy function on the bicyclic moiety of the amide is crucial for chromatographic separation of the diastereomers 15, since the diastereomers 16 having O-triisopropylsilyl group were not separable by column chromatography.

Removal of the chiral auxiliary from the major diastereomer, (M)-(−)-18, was carried out by N-t-butoxycarbonylation and subsequent methanolysis of 17 to afford (−)-2-methoxycarbonyl[7]heterohelicene, (M)-(−)-19, in 16 % yield along with helicenecarboxamide, (M)-(−)-18, in 68 % yield. Similarly, (+)-methyl ester 19 was obtained from the minor isomer, (P)-(+)18. The low yield of the methyl ester 19 was probably due to the steric hindrance of the helicene moiety, since the attack of methoxide anion to carbonyl of the amide moiety is sterically hindered.

Figure 2 CD spectra of (P)-(+) and (M)-(−)-heterohelicenes 19
leading to the formation of helicenecarboxamide 15. The optical rotation of (M)-(−)-19 obtained from (M)-(−)-18 was [α]D −2770 (c 0.053, CHCl₃), whose absolute value was good agreement with that of the enantiomer derived from (P)-(−)-18, [α]D +2830 (c 0.046, CHCl₃) within the experimental error. The CD spectra of the (+)- and (−)-heterohelicenes 19 in chloroform solution are shown in Figure 2. These results indicate that both of the methyl esters 19 obtained from the diastereomers, (M)-(−)-18 and (P)-(−)-18, are enantiomerically pure.

**Synthesis of Optically Pure Heterohelicene by Use of endo-Amino Alcohol as Chiral Auxiliary**

The synthesis of heterohelicenes was next carried out using endo-amino alcohol 2 as a chiral auxiliary. The carboxamide 20 was prepared from 2 and 2-benzo[1,2-b:4,3-b']dithiophenecarbonyl chloride (10). Alpha-lithiation of the terminal thiophene ring of 20 was carried out under similar conditions to those for the amide 7 and the lithio-species was treated with DMF to afford 21 in 82 % yield. The aldehyde 21 was converted into 1,2-diarylethylene 22 in 81 % yield by the Wittig reaction with 2-naphtho[2,1-b]thienylmethyltriphenylphosphonium chloride (12). Although the photocyclization of the olefin 22 showed no diastereo-selectivity (50:50), the use of triisopropylsilyl ether 23 prepared from 22 increased the diastereoselectivity (75:25) (Table 2). Separation of the diastereoisomers 24 was performed by column chromatography on silica gel (hexane-ethyl acetate 10:1) or by recrystallization from a mixture of hexane and ethyl acetate. Removal of chiral

<table>
<thead>
<tr>
<th>R</th>
<th>(−):(+)</th>
<th>Yield (%)</th>
<th>Conc. (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>50:50</td>
<td>91</td>
<td>0.24</td>
</tr>
<tr>
<td>Si(i-Pr)₃</td>
<td>25:75</td>
<td>96</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Reagents and conditions: (i) 10, pyridine, DMAP, CH₂Cl₂, 73%; (ii) LDA, THF, -15 °C, DMF, 82%; (iii) t-BuOK, MeOH, THF, 81%; (iv) hv, I₂, propylene oxide, benzene, 91%; (v) (i-Pr)₃SiOTf, 2,6-lutidine, CH₂Cl₂, 100%; (vi) (a) hv, I₂, propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF, 85%; (vii) (a) (t-BuO₂C)₂O, Et₃N, DMAP, CH₂Cl₂, 76%; (b) CH₃ONa, MeOH, THF, 16%.
auxiliary from the major diastereomer (P)-(+)\textsuperscript{-}27 gave (+)-methyl ester 19 (Scheme 3). These results indicate that the diastereoselectivity is controlled by the use of the diastereomeric chiral auxiliaries such as exo-amino alcohol and its endo-isomer.

In order to examine whether racemization or kinetic resolution take place during the removal of chiral auxiliary, carboxamide 24 (74.6:25.4 ratio of the diastereoisomers) was converted into N-Boc derivative 27. Methanolysis of 27 gave the corresponding methyl ester 19 along with carboxamide 24 (61\%). The ratio of the diastereoisomers of the recovered carboxamide 24 was determined as 74.1:25.9 by HPLC, indicating neither racemization nor kinetic resolution occurred.


Our initial efforts to cleavage the chiral auxiliary from 17 resulted in the formation of helicene 19 in 16\% yield together with the starting helicene 18 in 68\% yield. Several attempts to remove the auxiliary using triethylxonium tetrafluoroborate\textsuperscript{20} or potassium t-butoxide\textsuperscript{21} were failed. However, we found that the reaction of the N-Boc amide (M)-(–)-17 with lithium ethylmercaptide\textsuperscript{22} at 0°C

![Scheme 4](image)

*Reagents and conditions:* (i), MeONa, MeOH, THF, 16\%; (ii), EtSLi, THF, 82\%.
gave helicene-thioester (M)-(−)-28 in 82% yield (Scheme 4). Reduction of (M)-(−)-28 by LiAlH₄ gave (hydroxymethyl)helicene (M)-(−)-29 in 83% yield (Scheme 5), which was converted to (chloromethyl)helicene (M)-(−)-30 by SOCl₂ in quantitative yield. Reaction of (M)-(−)-30 with triphenylphosphine in acetonitrile at reflux gave phosphonium salt (M)-(−)-31 in 90% yield. The (hydroxymethyl)helicene (M)-(−)-29 was then treated with pyridinium dichromate to give helicene-carboxaldehyde (M)-(−)-32 in 90% yield. By similar procedures, the corresponding P-enantiomers 28-32 were obtained from (+)-5, and the absolute values of (P)-(+)‐isomers are good agreement with those of (M)-(−)-isomers as shown in Table 3.

**Scheme 5**

\[
\begin{align*}
(M)-(−)-17 & \quad \xrightarrow{(i)} \quad (M)-(−)-28 \\
(M)-(−)-28 & \quad \xrightarrow{(i)} \quad (M)-(−)-29 \\
(M)-(−)-29 & \quad \xrightarrow{(ii)} \quad (M)-(−)-30 \\
(M)-(−)-30 & \quad \xrightarrow{(iii)} \quad (M)-(−)-31 \\
(M)-(−)-31 & \quad \xrightarrow{(iv)} \quad (M)-(−)-32
\end{align*}
\]

**Reagents and conditions:** (i) LiAlH₄, THF, 83%; (ii) SOCl₂, benzene, 100%; (iii) PPh₃, CH₃CN, 90%; (iv) pyridinium dichromate, CH₂Cl₂, 90%.
Table 3 Specific Optical rotations of [7]thiaheterohelicene derivatives

<table>
<thead>
<tr>
<th>R</th>
<th>(P)-isomer</th>
<th>(M)-isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>COSEt (28)</td>
<td>+2330 (0.100)</td>
<td>-2280 (0.100)</td>
</tr>
<tr>
<td>CH₂OH (29)</td>
<td>+1970 (0.053)</td>
<td>-2020 (0.046)</td>
</tr>
<tr>
<td>CH₂Cl (30)</td>
<td>+1920 (0.040)</td>
<td>-1930 (0.021)</td>
</tr>
<tr>
<td>CH₃P⁺Ph₃Cl (31)</td>
<td>+1450 (0.050)</td>
<td>-1490 (0.021)</td>
</tr>
<tr>
<td>CHO (32)</td>
<td>+2900 (0.052)</td>
<td>-2830 (0.052)</td>
</tr>
</tbody>
</table>


Crystals of (P)-(+)·24 used for the X-ray measurement were obtained in orthorhombic form with the space group P2₁2₁2₁ by slow crystallization from a mixture of hexane and ethyl acetate. ORTEP view of the helicene is shown in Figure 3. The stereoview (Figure 4) clearly indicates that the helicene possessing a positive rotational value has a right-handed helicity, P. This result agrees with the preliminary report that the dextrorotatory helicenes have a right-handed helicity and the levorotatory helicenes have a left-handed helicity. An interesting feature of the [7]heterohelicene derived from 3-amino-2-hydroxybornane is that the C=O oxygen of the carboxamide serves as an acceptor in the hydrogen bonding to form a helical network in the crystal lattice as illustrated in Figure 5. The presence of the intermolecular C=O···H bond causes a shift of ν₃C=O band (1640 cm⁻¹). The remarkable deformation of the aromatic rings are also recognized from the structure analysis. The inner bond distances, C(20)-C(21), C(22)-C(23), and C(24)-C(25) are lengthened to 1.42-1.45 Å compared to the bond length in benzene (1.39 Å), whereas the outer bonds, C(3)-C(4) and C(8)-C(9) are shortened to 1.36-1.37 Å (Table 4). The shortest nonbonded carbon-carbon distance is 3.05 Å between C(19) and C(25), which is same as the distance (3.05 Å) in hexahelicene.
Figure 3 ORTEP view of heterohelicene (P)-(+)-24

Figure 4 stereoview of heterohelicene (P)-(+)-24
Figure 5 Helical network constructed by hydrogen bond

Table 4 Selected C-C bond lengths

<table>
<thead>
<tr>
<th>C-C bond</th>
<th>length(Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(32)-C(15)</td>
<td>4.561</td>
</tr>
<tr>
<td>C(32)-C(41)</td>
<td>4.383</td>
</tr>
<tr>
<td>C(32)-C(40)</td>
<td>4.795</td>
</tr>
<tr>
<td>C(33)-C(15)</td>
<td>4.204</td>
</tr>
<tr>
<td>C(33)-C(41)</td>
<td>3.796</td>
</tr>
<tr>
<td>C(34)-C(15)</td>
<td>3.918</td>
</tr>
<tr>
<td>C(34)-C(41)</td>
<td>3.109</td>
</tr>
<tr>
<td>C(34)-C(40)</td>
<td>3.048</td>
</tr>
</tbody>
</table>
The dihedral angles (11.4° and 10.5°) between two adjacent planes (plane(1)-(2) and plane (6)-(7)) are larger than those (6.3°-10°) between two adjacent inner planes (Table 5). The angle between the terminal rings is 47.3°, which is much smaller than the sum (57.8°) of the angles between two adjacent rings. When the helicene molecule is projected on a plane perpendicular to the first thiophene ring (=plane (1)), the planes (2) and (3) deviate upward but the planes (4), (5), (6), and (7) deviate downward from the plane (1) (Figure 6)

Table 5 Dihedral angles between two adjacent rings

<table>
<thead>
<tr>
<th>plane</th>
<th>angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>plane (1)</td>
<td>plane (2)</td>
</tr>
<tr>
<td>plane (2)</td>
<td>plane (3)</td>
</tr>
<tr>
<td>plane (3)</td>
<td>plane (4)</td>
</tr>
<tr>
<td>plane (4)</td>
<td>plane (5)</td>
</tr>
<tr>
<td>plane (5)</td>
<td>plane (6)</td>
</tr>
<tr>
<td>plane (6)</td>
<td>plane (7)</td>
</tr>
<tr>
<td>plane (1)</td>
<td>plane (7)</td>
</tr>
</tbody>
</table>

Figure 6 Side-view of helicene (P)-(+-)-24
Chiral Optical Nonlinearity of [7]Thiaeterohelicene

Recently organic nonlinear optical materials have received considerable attention. Principles of molecular design and crystalline packing in quadratic nonlinear optics have been already elucidated and some of these are intended for practical application, however, third order nonlinear optics are still the convergence of basic research. Ashitaka and his co-workers have recently presented a new principle of nonlinear optical control of light polarization with optically active helicenes. Rotation of a probe beam polarization plane proportional to pump intensity was observed using optically pure (−)-2-methoxycarbonyl[7]heterohelicene (M)-(−)-19 near the absorption edges, and the 100 % converted $\chi^{(3)}_{\text{eff}}$ values of chiral nonlinearities thus obtained are $10^{-11} \sim 10^{-10}$ esu (0.61 wt / vol % THF, 428–431 nm). These values are several times larger than those of unsubstituted [7]thiaheterohelicene (Table 6). The effect of nonlinear rotation of the polarization plane is called “chiral optical nonlinearity” (Figure 7).

<table>
<thead>
<tr>
<th>analysis conditions</th>
<th>chiral optical nonlinearity</th>
<th>wave length (nm)</th>
<th>$\alpha_{100%}(\text{cm}^{-1})$</th>
<th>cell length (mm)</th>
<th>$\chi^{(3)}_{100%} \times 10^{-11}$ [esu]</th>
</tr>
</thead>
<tbody>
<tr>
<td>441</td>
<td>100</td>
<td>10</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>436</td>
<td>167</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>432</td>
<td>413</td>
<td>5</td>
<td>7</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>430</td>
<td>650</td>
<td>2</td>
<td>15</td>
<td>15–20</td>
<td></td>
</tr>
<tr>
<td>428</td>
<td>1100</td>
<td>2</td>
<td>20</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
Experimental

General. All reactions were carried out under an atmosphere of argon. THF was distilled under argon atmosphere from sodium benzophenone ketyl immediately before use. Ether, dichloromethane and benzene were distilled from calcium hydride and stored over 4Å molecular sieves. The hexane solution of butyllithium (Kanto Chemicals) was titrated using diphenylacetic acid.27) Melting points were determined on a Yanagimoto hotstage apparatus and are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR 8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini-200 (200 MHz) spectrometer in CDCl₃ or CD₃SOCD₃ solution with tetramethylsilane as an internal standard. J values are given in Hz. Optical rotations were measured in 1dm path length cells of 10cm³ on a JASCO Model DIP-181 polarimeter; [α]₀ values are given in 10⁻¹deg·cm²·g⁻¹. The CD spectra were recorded in chloroform at room temperature on a JASCO model J-500 recording spectropolarimeter. All photocyclizations were accomplished in a water-cooled Pyrex photoreactor using a 200-W or 500-W high-pressure mercury lamps. Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100-200 mesh was used for column chromatography. HPLC analysis was carried out with a Hitachi instrument equipped with UV detector L-4000 using...
Sumichiral OA-2500 or Shimpack CLC-SIL(M). Elemental analysis were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University. Crystal structure determinations were performed by Fujisawa pharmaceutical industry.

\[ N-[(1R,2S,3R,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-formylthiophene-2-carboxamide \] (5).

To a stirred solution of LDA [15.8 mmol, prepared from butyllithium (11.0 mL of a 1.43 M solution in hexane) and N,N’-diisopropylamine (2.2 mL)] in 30 mL of THF was added a solution of 4\[^{1b}\] (1.00 g, 3.58 mmol) in 15 mL of THF at −15 °C under argon. After 2h at 0 °C, the resulting light brown suspension was cooled to −65 °C and a solution of DMF (2.2 mL, 28.6 mmol) in 5 mL of THF was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na\(_2\)SO\(_4\) and concentrated. The crude product was chromatographed on silica (hexane-ethyl acetate (2:1)) to give aldehyde 5 as white crystals (0.87 g, 79 %).

m.p. 201-203 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.84 (s, 3H), 0.98 (s, 3H), 1.12 (s, 3H), 1.14 (m, 1H), 1.27 (m, 2H), 1.56 (m, 1H), 1.74 (m, 1H), 2.01 (d, J4.0, 1H), 2.07 (d, J4.8, 1H), 3.82 (m, 2H), 6.99 (m, 1H), 7.54 (d, J3.9, 1H), 7.71 (d, J3.9, 1H), 9.93 (s, 1H); IR (KBr) 3400, 2950, 1665, 1645, 1530, 1510, 1445, 1210, 820 cm\(^{-1}\); Anal. Calcd for C\(_{16}\)H\(_{21}\)NO\(_3\)S: C, 62.52; H, 6.84; N, 4.56. Found: C, 62.57; H, 7.08; N, 4.41.

\[ N-[(1R,2S,3R,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-[2-(2-thienyl)ethenyl]thiophene-2-carboxamide \] (6).

To a stirred solution of aldehyde 5 (0.81 g, 2.63 mmol) and phosphonium salt 3\[^{8c}\] (1.86 g, 3.95 mmol) in 40 mL of methanol was added a solution of potassium t-butoxide (0.59 g, 5.26 mmol) in 5 mL of methanol at 0 °C. After the resulting yellow suspension was stirred overnight at room temperature, the reaction was quenched by diluted hydrochloric acid and CH\(_2\)Cl\(_2\) was added. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with brine and dried over Na\(_2\)SO\(_4\) and concentrated. The crude product was recrystallized from ethanol-hexane to give olefin 6 (0.77 g, 76 %) as a yellow solid.
m.p. 220-222 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 0.84 (s, 3H), 0.98 (s, 3H), 1.10 (m, 1H), 1.14 (s, 3H), 1.26 (m, 1H), 1.54 (m, 1H), 1.76 (m, 1H), 1.96 (d, J4.4, 1H), 2.23 (br s, 1H), 3.94 (m, 2H), 6.96 (m, 1H), 6.91-7.09 (m, 5H), 7.34 (d, J3.9, 1H); IR (KBr) 3385, 2955, 1625, 1535, 1520, 1495, 1280, 930 cm\textsuperscript{-1}; Anal. Calcd for C\textsubscript{21}H\textsubscript{25}NO\textsubscript{2}S\textsubscript{2}: C, 65.08; H, 6.50; N, 3.61. Found: C, 65.03; H, 6.34; N, 3.31.

**Benzo[1,2-b:4,3-b']dithiophene-2-carboxylic acid (9).**

To a stirred solution of 8 (5.00 g, 26.3 mmol) in 150 mL of ether was added butyllithium (27.6 mmol, 17.2 mL of 1.61 M solution in hexane) at room temperature. After stirring for 15 min, the resulting light brown suspension was poured onto solid CO\textsubscript{2} in ether, and the mixture was stirred until solid CO\textsubscript{2} was disappeared. To the reaction mixture 5% NaOH solution was added, and the aqueous layer was separated and washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with CH\textsubscript{2}C\textsubscript{12}. The combined organic extracts were washed with brine and dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was recrystallized from xylene to give carboxylic acid 9 as a yellow solid (2.69 g, 44%) m.p. 263-264 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) 7.66 (d, J5.2, 1H), 7.77 (d, J5.2, 1H), 7.82 (d, J9.1, 1H), 7.97 (d, J9.1, 1H), 8.53 (s, 1H); IR (KBr) 2800 (br), 1675, 1515, 1285, 1265, 1180, 1150, 750, 700 cm\textsuperscript{-1}; Anal. Calcd for C\textsubscript{11}H\textsubscript{6}O\textsubscript{2}S\textsubscript{2}: C, 56.39; H, 2.58. Found: C, 56.59; H, 2.62.

**N-[(1R, 2S, 3R, 4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (7).**

(i) **Photocyclization:** A solution of 6 (150 mg, 0.37 mmol) and iodine (9.5 mg, 0.037 mmol) in 100 mL of benzene was irradiated under air atmosphere for 7 h at room temperature. The reaction mixture was washed with aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} and extracted with benzene. The combined organic extracts were washed with aqueous NaHCO\textsubscript{3}, brine and dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude product was chromatographed on silica (hexane-ethyl acetate (3:1)) to give amide 7 as white crystals (78 mg, 54%).

(ii) **Via acid chloride:** To a stirred suspension of 9 (0.67 g, 2.86 mmol) in 15 mL of dry benzene was added thionyl chloride (0.42 mL, 5.27 mmol), and the mixture was heated under reflux for 2 h. The solvent was distilled away from the resulting yellow solution under reduced pressure. The crude acid chloride 10 was dried in vacuo for 2 h and used without further purification. To a stirred solution of a mixture of exo-amino alcohol 1 (0.49 g, 2.86 mmol), pyridine (0.19 mL, 2.29 mmol)
and DMAP (0.14 g, 1.14 mmol) in dry 15 mL of CH₂Cl₂ was added a solution of 10 in 10 mL of dry CH₂Cl₂ at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was poured onto cold dilute hydrochloric acid and the organic layer was separated. The organic phase was washed with brine and dried over Na₂SO₄ and concentrated. The crude product was chromatographed on silica (hexane-ethyl acetate (3:1)) to give amide 7 as white crystals (0.80 g, 75 %).

m.p. 252-254 °C; ¹H NMR (CDCl₃) δ 0.86 (s, 3H), 1.02 (s, 3H), 1.12 (m, 1H), 1.18 (s, 3H), 1.27 (m, 1H), 1.58 (m, 1H), 1.80 (m, 1H), 2.00 (d, J 4.4, 1H), 2.96 (m, 1H), 3.99 (m, 1H), 7.07 (m, 1H), 7.52 (d, J 5.5, 1H), 7.56 (d, J 5.5, 1H), 7.57 (d, J 8.8, 1H), 7.72 (d, J 8.8, 1H), 7.92 (s, 1H); IR (KBr) 3300, 2950, 1620, 1540, 1520, 1495, 700 cm⁻¹; Anal. Calcd for C₂₁H₂₃NO₂S₂ C, 65.42; H, 6.01; N, 3.63. Found: C, 65.18; H, 6.15; N, 3.57.

N-[(1R,2S,3R,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-formylbenzo[1,2-b:4,3-b’]dithiophene-2-carboxamide (11).

To a stirred solution of LDA [45.7 mmol, prepared from butyllithium (29.1 mL of a 1.57 M solution in hexane) and N,N-diisopropylamine (6.4 mL)] in 60 mL of THF was added a solution of 7 (4.00 g, 10.4 mmol) in 90 mL of THF at −20 °C. After 2 h at 0 °C, the resulting dark green suspension was cooled to −65 °C and then a solution of DMF (6.5 mL, 83 mmol) in 10 mL of THF was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by aqueous ammonium chloride. The organic layer was separated and washed with brine and dried over Na₂SO₄ and concentrated. The crude product was recrystallized from ethanol to give aldehyde 11 as white crystals (3.37 g, 79 %).

m.p. 249-251 °C; ¹H NMR (CD₃SOCD₃) δ 0.80 (s, 3H), 0.92 (s, 3H), 1.09 (m, 1H), 1.13 (s, 3H), 1.20 (m, 1H), 1.49 (m, 1H), 1.69 (m, 1H), 1.91 (d, J 3.7, 1H), 3.79 (m, 2H), 5.80 (d, J 5.2, 1H), 7.63 (d, J 4.7, 1H), 8.15 (d, J 8.8, 1H), 8.21 (d, J 8.8, 1H), 8.67 (s, 1H), 9.06 (s, 1H), 10.17 (s, 1H); IR (KBr) 3400, 2950, 1670, 1635, 1540, 1520, 1485, 1250, 1130 cm⁻¹; Anal. Calcd for C₂₂H₂₃NO₃S₂ C, 63.89; H, 5.61; N, 3.39. Found: C, 63.91; H, 5.72; N, 3.45.

N-[(1R,2S,3R,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-[2-(2-naphtho[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b’]dithiophene-2-carboxamide (13).
To a stirred solution of a mixture of aldehyde 11 (1.16 g, 2.80 mmol) and phosphonium chloride 12 (1.66 g, 3.36 mmol) in a mixture of 50 mL of methanol and 30 mL of THF was added a solution of potassium t-butoxide (0.63 g, 5.60 mmol) in 8 mL of methanol at 0 °C, and the reaction mixture was stirred overnight. The precipitated product was filtered off, washed with CH₂Cl₂ and dried in vacuo to give olefin 13 as orange powder (1.38 g, 83%). An analytically pure sample of 13 was obtained by recrystallization from CHCl₃.

m.p. 289-290 °C (dec.); ¹H NMR (CD₃SOCD₃) δ 0.81 (s, 3H), 0.89-1.25 (m, 2H), 0.94 (s, 3H), 1.15 (s, 3H), 1.44-1.74 (m, 2H), 1.95 (d, J 2.5, 1H), 3.79 (m, 2H), 5.71 (d, J 3.3, 1H), 7.42 (d, J 4.3, 2H), 7.56 (m, 1H), 7.81-7.99 (m, 6H), 8.02 (s, 1H), 8.18 (d, J 4.3, 2H), 8.38 (s, 1H); IR (KBr) 3330, 2950, 1620, 1520, 1485, 1040, 805, 770 cm⁻¹; Anal. Calcd for C₃₅H₃₁NO₂S₃ C, 70.79; H, 5.26; N, 2.36. Found: C, 70.29; H, 5.29; N, 2.27.


To a stirred suspension of 13 (0.41 g, 0.68 mmol) in 40 mL of CH₂Cl₂ were added triisopropylsilyl triflate (0.24 mL, 0.88 mmol) and 2,6-lutidine (0.16 mL, 1.36 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and the suspension was stirred overnight. The reaction was quenched by addition of dilute hydrochloric acid. Brine was added and the organic phase was separated. The organic phase was washed with aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated. The crude product was chromatographed on silica (hexane-ethyl acetate (5:1)) to give olefin 14 as a yellow solid (0.51 g, 100%).

m.p. 127-130 °C; ¹H NMR (CDCl₃) δ 0.82 (s, 3H), 0.85-1.32 (m, 5H), 1.04 (s, 3H), 1.17 (d, J 5.2, 18H), 1.21 (s, 3H), 1.41-1.82 (m, 2H), 2.08 (d, J 2.6, 1H), 4.13 (m, 2H), 6.99 (d, J 3.2, 1H), 7.34 (d, J 3.8, 2H), 7.44-7.86 (m, 7H), 7.93 (d, J 8.7, 1H), 7.97 (s, 1H), 8.06 (s, 1H), 8.29 (d, J 8.7, 1H); IR (KBr) 2945, 2865, 1655, 1515, 1465, 885, 680 cm⁻¹; Anal. Calcd for C₄₄H₅₁NO₂S₃Si C, 70.45; H, 6.85; N, 1.87. Found: C, 70.04; H, 6.95; N, 2.05.

(i) From compound 13. Olefin 13 (0.30 g, 0.50 mmol) and iodine (0.13 g, 0.50 mmol) were dissolved in 1.6 L of benzene and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (12.0 mL, 250 mmol) was added to the mixture and the resulting solution was irradiated for 5 h at room temperature with argon flow. The reaction mixture was washed with 15 % Na$_2$S$_2$O$_3$ solution and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated aqueous NaHCO$_3$, brine and dried over Na$_2$SO$_4$. The solvents was evaporated and the residue was chromatographed on silica (hexane-ethyl acetate (3:1)) to give a diastereomeric mixture (43:57) of helicene 13 as a yellow solid (0.27 g, 91 %). HPLC analysis was performed by Sumichiral OA-2500. hexane / 1,2-dichloroethane / ethanol = 50:30:0.2 was used as eluent. Flash chromatography on silica (hexane-ethyl acetate (10:1-5:1)) gave 0.12 g of (P)-(+)-18 and 0.13 g of (M)-(—)-18 together with a small amount of mixed diastereomers.

(M)- (—)-18: m.p. 286-288 °C; $^1$H NMR (CDCl$_3$) δ 0.78 (s, 3H), 0.88 (s, 6H), 0.85-1.58 (m, 5H), 1.76 (d, J 3.7, 1H), 3.64 (m, 2H), 5.49 (m, 1H), 6.70 (s, 1H), 6.77 (m, 1H), 7.36 (m, 1H), 7.53 (d, J 8.3, 1H), 7.89-8.16 (m, 1H); IR (KBr) 3375, 2950, 1645, 1620, 1520, 1480, 1150, 800, 785, 745, 525 cm$^{-1}$; Anal. Calcd for C$_{35}$H$_{29}$NO$_2$S$_3$ C, 71.04; H, 4.94; N, 2.37. Found: C, 70.88; H, 4.98; N, 2.26.; [α]$_D$ -2380 (c 0.052, CHCl$_3$).

(P)-(+)-18: m.p. 189-192 °C; $^1$H NMR (CDCl$_3$) δ 0.74 (s, 3H), 0.98 (s, 6H), 0.83-1.32 (m, 4H), 1.39-1.72 (m, 2H), 3.72 (m, 2H), 5.70 (m, 1H), 6.68 (s, 1H), 6.72 (m, 1H), 7.28 (m, 1H), 7.46 (d, J 8.4, 1H), 7.88-8.14 (m, 1H); IR (KBr) 3385, 2950, 1635, 1520, 1480, 1150, 800, 785 cm$^{-1}$; Anal. Calcd for C$_{35}$H$_{29}$NO$_2$S$_3$ C, 71.04; H, 4.94; N, 2.37. Found: C, 70.76; H, 5.18; N, 2.50.; [α]$_D$ +2070 (c 0.058, CHCl$_3$).

(ii) From compound 14. Olefin 14 (0.51 g, 0.68 mmol) and iodine (0.09 g, 0.68 mmol) were dissolved in 1.1 L of benzene and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (12.0 mL, 250 mmol) was added to the mixture and the resulting solution was irradiated for 7 h at room temperature with argon flow. The reaction mixture was washed with 15 % Na$_2$S$_2$O$_3$ solution and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated aqueous NaHCO$_3$, brine and dried (Na$_2$SO$_4$) and concentrated. This material 16 was dissolved in 10 mL of dry THF and tetrabutylammonium fluoride (0.68 mL of 1M solution in THF, 0.68 mmol) was added. The mixture was stirred for 2 h at room temperature and quenched with
brine. The organic phase was separated, washed with brine and dried over Na₂SO₄.
The solvent was evaporated and the crude product was chromatographed on silica
(hexane-ethyl acetate (10:1)) to give a diastereomeric mixture (32:68) of helicene 15
as a yellow solid (0.31 g, 61 %).

\[(M)-(\text{-})\text{-Methyl \ [1]Benzothieno[5,4-b]naphtho[1',2':4,5]thieno-
[3,2-e][1]benzo[1,2-b:4,3-b']benzothiophene-2-carboxylate \ ( (M)-(\text{-})-19).}\]

To a stirred solution of 15 (88 mg, 0.15 mmol) in 3 mL of dry CH₂Cl₂ was added
DMAP (27 mg, 0.23 mmol) and triethylamine (0.03 mL, 0.23 mmol). Then a
solution of di-t-butyldicarbonate (0.10 g, 0.45 mmol) in 1 mL of dry CH₂Cl₂ was
added and the resulting solution was stirred for 1h. The solvent was evaporated and
the crude product was purified by column chromatography on silica (hexane-ethyl
acetate (5:1)) to give the N-Boc derivative 17 (78 mg, 76 %) as yellow solid. This
material was dissolved in 1 mL of dry THF and 1 mL of methanol, and sodium
methoxide (0.18 mL, 2M in methanol) was added. After the mixture was stirred
overnight at room temperature. The crude product was chromatographed on silica
(hexane-ethyl acetate (10:1)) to give \((M)-(\text{-})-15\) (29.4 mg, 68 %) and methyl ester
\((M)-(\text{-})-19\) as a yellow solid (5.3 mg, 16 %).

m.p. 229-231 °C; \(^{1}\)H NMR (CDCl₃) δ 3.62 (s, 3H), 6.70 (m, 1H), 6.98 (d, J 2.0, 1H),
7.27 (m, 1H), 7.38 (d, J 8.8, 1H), 7.96 (m, 3H), 8.06 (d, J 3.0, 2H), 8.12 (d, J 3.0, 2H);
IR (KBr) 1710, 1510, 1290, 1250, 1150 cm⁻¹; Anal. Calcd for \(\text{C}_{26}\text{H}_{14}\text{O}_{2}\text{S}_{3}\) C, 68.70;
H, 3.10. Found: C, 68.67; H, 3.37.; \([\alpha]_D\) -2770 (c 0.053, CHCl₃).

\(N-[\ (1\text{R}, 2\text{R}, 3\text{S}, 4\text{S})-2-\text{Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-
heptan-3-yl}]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide \ (20).\)

To a stirred suspension of 9 (1.00 g, 4.27 mmol) in 40 mL of dry benzene was added
thionyl chloride (0.63 mL, 8.54 mmol) and the mixture was heated under reflux for 4
h. The solvent was distilled away from the resulting yellow solution under reduced
pressure. The crude benzodithiophene carbonyl chloride 10 was dried in vacuo for
2 h and was used without further purification. To a stirred solution of a mixture of
endo-amino alcohol 2 (0.73 g, 4.27 mmol), pyridine (0.26 mL, 3.42 mmol) and
DMAP (0.21 g, 1.71 mmol) in 30 mL of dry CH₂Cl₂ was added a solution of
benzodithiophene carbonyl chloride 10 in dry CH₂Cl₂ (10 mL) at 0 °C and the mixture
was stirred at room temperature overnight. To the reaction mixture was added cold
dilute hydrochloric acid, and the aqueous layer was extracted with CH₂Cl₂ and washed

-26-
with brine and dried \((\text{Na}_2\text{SO}_4)\) and concentrated. The crude product was recrystallized from ethanol to give amide 20 as white crystals (1.20 g, 73 %).

m.p. 274-276 °C; \(\text{H} \text{NMR (CDCl}_3\) \(\delta 0.96 \text{ (s, 6H), 1.02 \text{ (s, 3H), 1.17 \text{ (m, 1H), 1.52 \text{ (m, 2H), 1.92 \text{ (m, 1H), 2.13 (t, } J 4.2, 1\text{H), 4.18 (d, } J 8.8, 1\text{H), 4.41 (m, 1H), 7.02 (d, } J 6.5, 1\text{H), 7.51 (d, } J 8.8, 1\text{H), 7.65 (d, } J 8.8, 1\text{H), 7.90 (s, 1H); IR (KBr) 3350, 1620, 1525, 1345, 1105, 1030, 700 \text{ cm}^{-1}; \) Anal. Calcd for C\(_{21}\)H\(_{23}\)NO\(_2\)S\(_2\) C, 65.42; H, 6.01; N, 3.63. Found: C, 65.38; H, 6.12; N, 3.54.

\(N-[(1R,2R,3S,4S)-2\text{-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl}]-5\text{-formylbenzo[1,2-b:4,3-b']dithiophene-2-carboxamide (21).}\)

To a stirred solution of LDA [11.4 mmol, prepared from butyllithium (7.1 mL of a 1.61 M solution in hexane) and N,N-diisopropylamine (1.6 mL)] in 30 mL of THF was added a solution of 20 (1.00 g, 2.59 mmol) in 50 mL of THF at -20 °C. After stirring for 2 h at 0 °C, the resulting dark green suspension was cooled to -65 °C and then a solution of DMF (1.6 mL, 20.7 mmol) in 8 mL of THF was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of aqueous ammonium chloride. The organic layer was separated, washed with brine and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and the crude product was recrystallized from ethanol to give aldehyde 21 as white crystals (0.88 g, 82 %).

m.p. 265-267 °C; \(\text{H} \text{NMR (CD}_3\text{SOCD}_3\) \(\delta 0.86 \text{ (s, 3H), 0.92 (s, 3H), 0.98 (s, 3H), 1.13 (m, 1H), 1.48 (m, 2H), 1.97 (m, 2H), 3.92 (m, 1H), 4.31 (m, 1H), 5.49 (d, } J 5.5, 1\text{H), 7.56 (d, } J 6.1, 1\text{H), 8.11 (d, } J 8.9, 1\text{H), 8.20 (d, } J 8.9, 1\text{H), 8.80 (s, 1H), 8.98 (s, 1H); IR (KBr) 3350, 2955, 1670, 1640, 1540, 1520, 1250, 1130 \text{ cm}^{-1}; \) Anal. Calcd for C\(_{22}\)H\(_{23}\)NO\(_2\)S\(_2\) C, 63.89; H, 5.61; N, 3.39. Found: C, 63.75; H, 5.63; N, 3.27.

\(N-[(1R,2R,3S,4S)-2\text{-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl}]-5-[2-(2\text{-naphtho[2,1-b]thienyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (22).}\)

To a stirred solution of aldehyde 21 (0.67 g, 1.62 mmol) and phosphonium chloride 12 (0.86 g, 1.73 mmol) in a mixture of 30 mL of methanol and 25 mL of THF was added a solution of potassium t-butoxide (0.37 g, 3.24 mmol) in 4 mL of methanol at 0 °C, and the reaction mixture was stirred overnight. The precipitated product was filtered off, washed with CH\(_2\)Cl\(_2\) and dried \textit{in vacuo} to give olefin 22 as orange
powder (0.78 g, 81 %). An analytically pure sample of 22 was obtained by recrystallization from CHCl₃.

m.p. 308-310 °C (dec.); ¹H NMR (CD₃SOCD₃) δ 0.87 (s, 3H), 0.93 (s, 3H), 0.99 (s, 3H), 1.14 (m, 1H), 1.51 (m, 2H), 1.99 (m, 2H), 3.93 (m, 1H), 4.31 (m, 1H), 5.48 (m, 1H), 7.43-7.72 (m, 4H), 7.82-8.05 (m, 5H), 8.18 (s, 1H), 8.40 (m, 3H), 8.60 (s, 1H).  

IR (KBr) 3380, 2950, 1630, 1520, 1490, 925, 830, 800 cm⁻¹; Anal. Calcd for C₃₅H₃₁NO₂S₃ C, 70.79; H, 5.26; N, 2.36. Found: C, 70.61; H, 5.28; N, 2.44.


To a stirred suspension of 22 (0.31 g, 0.52 mmol) in 40 mL of dry CH₂Cl₂ were added triisopropylsilyl triflate (0.18 mL, 0.67 mmol) and 2,6-lutidine (0.12 mL, 1.04 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and the suspension was stirred overnight. The reaction was quenched by addition of 5% hydrochloric acid. Brine was added and the organic phase was separated, washed with aqueous NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated and the crude product was chromatographed on silica (hexane-ethyl acetate (5:1)) to give silyl ether 23 as a yellow solid (0.40 g, 100 %).

m.p. 126-130 °C; ¹H NMR (CDCl₃) δ 0.94 (s, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 1.04-1.33 (m, 3H), 1.15 (d, J 7.3, 18H), 1.53 (m, 2H), 1.98 (m, 3H), 2.26 (m, 1H), 4.30-4.53 (m, 2H), 6.91 (d, J 5.7, 1H), 7.34 (d, J5.2, 1H), 7.43-7.86 (m, 2H), 7.62 (s, 1H), 7.70-7.85 (m, 4H), 7.93 (d, J 7.8, 1H), 7.97 (s, 1H), 8.11 (s, 1H), 8.29 (d, J 7.8, 1H); IR (KBr) 2945, 2865, 1655, 1515, 1490, 1110, 1060, 685 cm⁻¹; Anal. Calcd for C₄₄H₅₁NO₂S₃Si C, 70.45; H, 6.85; N, 1.87. Found: C, 69.94; H, 6.90; N, 1.86.


(i) From compound 22. Olefin 22 (0.15 g, 0.26 mmol) and iodine (0.068 g, 0.26 mmol) were dissolved in 1.1 L of benzene and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (6.0 mL, 125 mmol) was added to the mixture and the resulting solution was irradiated for 5 h at room temperature with argon flow. The reaction mixture was washed with 15 % Na₂S₂O₃ solution and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄.
The solvent was evaporated and the residue was chromatographed on silica (hexane-ethyl acetate (3:1)) to give the diastereomeric mixture (50:50) of helicene 24 as yellow solid (0.14 g, 91%). HPLC analysis was performed by Sumichiral OA-2500 using hexane-1,2-dichloroethane-ethanol (50:30:0.2) as the eluent.

(ii) From compound 23. Olefin 23 (0.25 g, 0.33 mmol) and iodine (0.085 g, 0.33 mmol) were dissolved in 1.1 L of benzene and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (8.0 mL, 170 mmol) was added to the mixture and the resulting solution was irradiated for 5 h at room temperature with argon flow. The reaction mixture was washed with 15 % Na₂S₂O₃ solution and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄ and concentrated. This material 25 was dissolved in 10 mL of dry THF and tetrabutylammonium fluoride (0.66 mL of 1M solution in THF, 0.66 mmol) was added. The mixture was stirred for 2 h at room temperature and quenched with brine. The organic phase was separated, washed with brine and dried over Na₂SO₄.

The solvent was evaporated and the crude product was chromatographed on silica (hexane-ethyl acetate (10:1)) to give a diastereomeric mixture (75:25) of helicene 24 (0.17 g, 85 %). Further purification of 24 by silica gel chromatography (hexane-ethyl acetate (10:1)) gave optically pure (P)-(+)-26.

m.p. 280-283 °C; ¹H NMR (CDCl₃) δ 0.89 (s, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.02-1.40 (m, 2H), 1.40 (d, J 8.0, 1H), 1.46-1.93 (m, 2H), 2.05 (t, J 4.3, 1H), 3.33 (m, 1H), 4.02 (m, 1H), 5.64 (d, J 5.4, 1H), 6.73 (s, 1H), 6.76 (m, 1H), 7.30 (m, 1H), 7.55 (d, J 8.3, 1H), 7.94 (d, J 8.3, 1H), 7.99-8.15 (m, 7H); IR (KBr) 3370, 2950, 1640, 1525, 1155, 800, 785 cm⁻¹; Anal. Calcd for C₃₅H₂₉NO₂S₃ C, 71.04; H, 4.94; N, 2.37. Found: C, 71.26; H, 4.96; N, 2.45.; [α]D +2320 (c 0.050, CHCl₃).


To a stirred solution of ethanethiol (0.075 mL, 1.0 mmol) in 4 mL of THF was added butyllithium (0.83mmol, 0.55 mL of 1.5 M solution in hexane) at -78 °C. The solution was allowed to warm to 0 °C, and a solution of N-Boc amide 17 (0.26 g, 0.376 mmol) in 6 mL of THF was added. After the mixture was stirred overnight at room temperature, the mixture was poured into 3% aqueous NaClO solution. The mixture was concentrated under reduced pressure, and the residue was dissolved in CHCl₃. The organic phase was separated, washed with brine and dried over Na₂SO₄.
The solvent was evaporated and the residue was chromatographed on silica using hexane-ethyl acetate (30:1) as eluent to give thioester 28 as a yellow solid (149 mg, 82%).

\[ ^1 \text{NMR (CDCl}_3 \] \delta 1.22 (t, J 7.6, 3H), 2.8 (m, 2H), 6.70 (dd, J 8.2, 7.2, 1H), 7.04 (s, 1H), 7.27 (dd, J 8.2 and 6.9, 1H), 7.37 (d, J 6.2, 1H), 7.9-8.1 (m, 7H); Anal. Calcd for C\(_{27}\)H\(_{16}\)O\(_4\)S\(_4\) C, 66.91; H, 3.33. Found: C, 66.85; H, 3.45.; (P)-(+-)28: [\(\alpha\)]\(_D\) +2330 (c 0.100, CHCl\(_3\)); (M)-(+-)-28: [\(\alpha\)]\(_D\) -2280 (c 0.100, CHCl\(_3\)).


To a stirred suspension of lithium aluminum hydride (130 mg, 2.70 mmol) in 5 mL of THF was added a solution of thioester 28 (130 mg, 0.269 mmol) in 5 mL of THF at 0 °, and the reaction mixture was stirred for 2 h. The reaction was quenched by careful addition of dilute hydrochloric acid, and the mixture was diluted with CHCl\(_3\). The organic phase was washed with brine and dried over MgSO\(_4\). The solvent was evaporated and the residue was chromatographed on silica using hexane-ethyl acetate (3:1) as the eluent to give alcohol 29 as a yellow solid (94.0 mg, 83%).

m.p. 189-191 °C; \(^1\)NMR (CDCl\(_3\)) \delta 0.58 (dd, J 7.9, 5.1, 1H), 4.12 (m, 2H), 6.19 (s, 1H), 6.73 (ddd, J 8.4, 7.0, 1.4, 1H), 7.33 (ddd, 8.1, 6.9, 1.2, 1H), 7.46 (d, J 8.3, 1H), 7.9-8.1 (m, 7H); IR(KBr) 3370, 3040, 2900 cm\(^{-1}\); Anal. Calcd for C\(_{25}\)H\(_{14}\)OS\(_3\) C, 70.39; H, 3.31. Found: C, 70.33; H, 3.21.; (P)-(+-)29: [\(\alpha\)]\(_D\) +1970 (c 0.053, CHCl\(_3\)); (M)-(+-)-29: [\(\alpha\)]\(_D\) -2020 (c 0.046, CHCl\(_3\)).


To a stirred solution of lithium aluminum hydride (130 mg, 2.70 mmol) in 5 mL of THF was added a solution of thioester 28 (130 mg, 0.269 mmol) in 5 mL of THF at 0 °, and the reaction mixture was stirred for 2 h. The reaction was quenched by careful addition of dilute hydrochloric acid, and the mixture was diluted with CHCl\(_3\). The organic phase was washed with brine and dried over MgSO\(_4\). The solvent was evaporated and the residue was chromatographed on silica using hexane-ethyl acetate (3:1) as the eluent to give alcohol 29 as a yellow solid (94.0 mg, 83%).

m.p. 189-191 °C; \(^1\)NMR (CDCl\(_3\)) \delta 4.10 (d, J 3.3, 2H), 6.30 (s, 1H), 6.74 (ddd, J 8.4, 7.1, 1.3, 1H), 7.3 (ddd, J 8.1, 6.9, 1.2, 1H), 7.47 (dd, J 8.5, 0.8, 1H), 7.9-8.1 (m, 7H); Anal. Calcd for C\(_{25}\)H\(_{13}\)ClS\(_3\) C, 67.47; H, 2.94. Found: C, 67.24; H, 3.12.; (P)-(+-)30: [\(\alpha\)]\(_D\) +1920 (c 0.040, CHCl\(_3\)); (M)-(+-)-30: [\(\alpha\)]\(_D\) -1930 (c 0.021, CHCl\(_3\)).

To a stirred solution of chloride 30 (96.5 mg, 0.217 mmol) in 3 mL of acetonitrile was added triphenylphosphine (274 mg, 1.08 mmol), and the mixture was heated under reflux for 36 h. The solvent was evaporated and the residue was chromatographed on silica using CH$_2$Cl$_2$-ethanol (from 1:0 to 10:1) as the eluent to give phosphonium salt 31 as a yellow solid (137.7 mg, 90%). 

m.p. 284-286 °C (dec.); $^1$NMR (CDCl$_3$) 3.48 (dd, J7.5, 6.7, 2H), 5.57 (d, J4.1, 1H), 6.7 (m, 2H), 7.3-7.7 (m, 16H), 7.9-8.1 (m, 7H); IR (KBr) 3040, 2750, 1110 cm$^{-1}$; ($P$)-(+-)31: $[\alpha]_D^{+} +1450$ (c 0.050, CHCl$_3$); ($M$)-(--)31: $[\alpha]_D^{+} -1490$ (c 0.021, CHCl$_3$).


To a stirred suspension of pyridinium dichromate (37.6 mg, 0.100 mmol) in 3 mL of CH$_2$Cl$_2$ was added a solution of alcohol 29 (21.3 mg, 0.050 mmol) in 3 mL of CH$_2$Cl$_2$ at room temperature, and the reaction mixture was stirred over night. The reaction mixture was filtrated, and the filtrate was washed with dilute hydrochloric acid, brine and dried over MgSO$_4$. The solvent was evaporated and the residue was chromatographed on silica using hexane-ethyl acetate (5:1) as the eluent to give aldehyde 32 as yellow solid (19.2 mg, 90%).

m.p. 271-273 °C; IR (KBr) 3040, 2800, 1670 cm$^{-1}$; $^1$NMR (CDCl$_3$) 6.71 (ddd, J8.2, 7.0, 1.2, 1H), 6.92 (s, 1H), 7.28 (ddd, J8.1, 6.9, 1.2, 1H), 7.37 (d, J8.4, 1H), 7.9-8.1 (m, 7H), 9.00 (s, 1H); Anal. Calcd for C$_{25}$H$_{12}$OS$_3$: C, 70.72; H, 2.85. Found: C, 70.97; H, 2.75.; ($P$)-(+-)32: $[\alpha]_D^{+} +2900$ (c 0.052, CHCl$_3$); ($M$)-(--)32: $[\alpha]_D^{+} -2830$ (c 0.052, CHCl$_3$).

Structure solution and refinement of ($P$)-(+-)24

A crystal of dimensions 0.40 × 0.30 × 0.30 mm was used for X-ray crystallography. Crystal data: C$_{35}$H$_{29}$NO$_2$S$_3$, M = 591.80, crystal system, orthorhombic, space group, P2$_1$2$_1$2$_1$ (#19), a = 20.305(1), b = 14.830(2), c = 9.859(1) Å, V = 2968.8(4) Å$^3$, F(000) = 1240.00, Z = 4, $\mu$ = 25.40 cm$^{-1}$, Dc = 1.324 gcm$^{-3}$. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-Kα radiation and a rotating anode generator. The data were collected at a temperature of 297 ± 1 K using $\omega$–2$\theta$ scan technique to a maximum 2$\theta$ value of 130°. Of the 2943 reflections which were collected, 2895 were unique ($R_{int}$ = 0.008). The structure was solved by heavy-atom Patterson methods using PATTY and expanded using Fourier techniques (DIRDIF92). The non-hydrogen atoms were refined anisotropically.
Hydrogen atoms were refined isotropically. The final cycle of the full-matrix least-squares refinement was based on 2441 observed reflections \( (I > 3.00\sigma(I)) \) and 486 variable parameters and converged with unweighted and weighted agreement factors of \( R = 0.038 \) and \( R_w = 0.031 \), respectively. The weighting scheme was based on counting statics. Neutral atom scattering factors were taken from Cromer and Waber. Anomalous dispersion effects were included in \( F_{\text{calc}} \); the values for \( \Delta f' \) and \( \Delta f'' \) were those of Creagh and McAuley. The values for the mass attenuations were those of Creagh and Hubbel. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

References and Notes


17) Separation of the diastereoisomers of heterohelicene by column chromatography was easily performed at the stage of the N-Boc derivatives 17.


Chapter 2

Synthesis of Optically Active Bis(hydroxymethyl)[7]thiaheterohelicene.

Helical Crystal Structure of Helicene-Ethanol Clathrate.

Abstract

Optically active bifunctionalized [7]thiaheterohelicene was synthesized using (1R, 2R, 3S, 4S)-endo-3-amino-endo-2-hydroxybornane as a chiral element. The photocyclo-dehydrogenation of 1,2-diarylethylene prepared from benzodithiophenecarboxaldehyde 4 and optically active phosphonium salt 8 gave a 38:62 mixture of the chromatographically separable diastereomers of [7]thiaheterohelicene. The removal of the chiral auxiliary from the diastereomers was readily achieved by thiolysis and subsequent desilylation and reduction gave new helical ligands possessing C₂ symmetry, (P)- and (M)-2,13-bis(hydroxymethyl)dithieno[3,2-e:3',2'-e']benzo[1,2-b:4,3-b']bis[1]benzothiophenes. Both enantiomers of bis(hydroxymethyl)heterohelicene 13 of high optical purity were obtained by lipase-catalyzed transesterification of racemic diol, (PM)-(±)-13.

The racemic bis(hydroxymethyl)heterohelicene 13 affords a crystalline inclusion complex with ethanol having a 1:1 host-guest ratio self-assembled through a helical network of hydrogen bonds. The X-ray crystal structure analysis unambiguously showed a highly organized supramolecular structure.

Introduction

Chiral bifunctionalized ligands have been successfully used as chiral catalysis or auxiliaries in asymmetric synthesis.¹ A great deal of efforts have particularly devoted to the rational design of chiral molecules with C₂ symmetry, because the presence of a C₂ symmetry axis within chiral complexes can reduce the number of possible competing diastereomeric transition states.² On the other hand, little is known about chiral ligands with helical structures due to the difficulties in their syntheses and optical instability. Hence, the chiral bifunctionalized helicenes which have rigid structures and optical stability are very attractive chiral ligands from a view point of asymmetric synthesis. Although a variety of racemic carbohelicenes and heterohelicenes have been prepared,³ including a new class of non-macroyclic
receptors with a helicene backbone like helicopodands, which performed the molecular recognition of dicarboxylic acids with high diastereoselectivities, optically active helicenes have been obtained by laborious methods such as repeated recrystallizations of racemic helicene-complexes with chiral electron acceptors or chiral amines, crystal picking, or separation by HPLC. For these reasons, the asymmetric synthesis using those helicenes as chiral elements have never been evaluated.

This chapter describes a convergent synthesis of chiral bifunctionalized [7]heterohelicenes possessing \( \text{C}_2 \) symmetry by the use of bicyclic amino alcohols derived from D-camphor as a chiral auxiliary. The method consists of (i) construction of benzodithiophenecarboxaldehyde and optically active phosphonium salt by regioselective \( \alpha \)-lithiation of benzodithiophene moiety, (ii) coupling of these two units and photocyclodehydrogenation of the resulting 1,2-diarylethylene. It is important to note that the protection of the benzylic hydroxy group of the 1,2-diarylethylene by silyl ether increases solubility in organic solvents, otherwise it often leads to difficulty in purification of helicenes and decreases the reactivity in the photocyclization of olefins.

**Synthesis of Optically Active Bis(hydroxymethyl)[7]thiaheterohelicene by Use of Bicyclic Amino Alcohol**

When benzo[1,2-b:4,3-b']dithiophene 1\(^{7c}\) was treated with butyllithium at \(-78^\circ\text{C} \), 2-lithio species was obtained exclusively, which was trapped with solid paraformaldehyde to give 2-hydroxymethyl compound 2 in 70 % yield. The alcohol 2 was treated with \( t \)-butyldimethylchlorosilane to give the corresponding silyl ether 3 in 98 % yield. Alpha-lithiation of the terminal thiophene ring of 3 was carried out under similar conditions to those for 1 and the lithio-species thus obtained were treated with DMF at \(-78^\circ\text{C} \) to afford 4 in 81 % yield. Phosphonium salt 8 was prepared from aldehyde 5\(^{9}\) in three steps. Reduction of 5 was achieved by sodium borohydride at room temperature to give 6 in almost quantitative yield. Chlorination of the benzylic hydroxy group of 6 was carried out according to the Corey procedure\(^{10}\) to give benzylic chloride 7 in 82 % yield. Reaction of the chloride 7 and triphenylphosphine in benzene at reflux gave phosphonium chloride 8 in 78 % isolated yield.
The aldehyde 4 was converted into 1,2-diarylethylene 9 in 79% yield by the Wittig reaction with the phosphonium chloride 8. Photocyclization of 9 by a method reported by Katz and his co-workers" provided bifunctionalized [7]heterohelicene 10 in 77% yield as a mixture of the diastereoisomers (38:62). It should be emphasized that the diastereoisomers 10 was readily separated by column chromatography. Removal of the chiral auxiliary from 10, however, proved to be very difficult because of its highly congested structure. Although N-t-butoxycarbonylation was smoothly carried out by di-t-butyldicarbonate at room temperature to give 11 in 70% yield, methanolysis of 11 completely gave the starting carboxamide 10. Hydride reduction of 11 by lithium aluminum hydride or Super Hydride afforded complex mixtures. Transesterification of 11 to the corresponding thioester according to a modification of the Damon procedure was found to be an effective method. N-Boc derivative (P)-(+)11 was treated with EtSLi in a sealed flask at 50 °C to afford the thioester (P)-(+)12 and subsequent desilylation by TBAF in THF, and reduction by DIBAL in CH₂Cl₂ gave 2,13-bis(hydroxymethyl)dithieno[3,2-e:3′,2′-e′]benzo[1,2-b:4,3-b′]bis[1]benzothiophene, (P)-(+)13 in 20% yield from (P)-(+)11. The optical purity of (P)-(+)13 was
determined to be ca. 96 % ee by HPLC analysis.\textsuperscript{211} By a similar procedure, the antipode \((M)-(\textendash)-13\) was also obtained from \((M)-(\textendash)-10\) in ca. 96 % ee.
Lipase-Catalyzed Resolution of Bis(hydroxymethyl)[7]thiaheterohelicene

Since photocyclization of 1,2-diarylethylenes depends on various factors such as the type of light source and its positioning, the transparency of the material, the purity of the reactants and the solvents, the scale of the reaction, the substrate structure, the concentration of the material, the presence of I₂ and propylene oxide or oxygen, and the reaction temperature, the previously described route to 2,13-bis(hydroxymethyl)[7]heterohelicene with high optical purity by cyclization of two 3-ring units is highly efficient. However, heterohelicene diols (P)-(+)·13 and (M)-(−)·13, were not obtained in high yield, and there is still a need for more efficient method for the synthesis of optically active diol 13. Thus, optical resolution of the racemic diol (PM)-(±)-13 was carried out as a complementary method.

Racemic 2,13-bis(hydroxymethyl)[7]thiaheterohelicene 13 was obtained from readily available 1-hydroxymethyl[1,2-b:4,3-b']benzodithiophene (2). The hydroxy group of 2 was protected by triisopropylsilyl triflate to give silyl ether 14 in 98 % yield. Treatment of 14 with butyllithium at −78 °C afforded 5-lithio species exclusively, which was trapped with DMF to give aldehyde 15 in 67 % yield. Phosphonium salt 18 was prepared from aldehyde 15 in three steps. Thus, reduction of 15 was achieved by NaBH₄ at room temperature to give alcohol 16 in almost quantitative yield. Chlorination of the hydroxy group and subsequent treatment with triphenylphosphine in benzene gave 18 in 65 % overall yield. The Wittig reaction of 15 with 18 was carried out with t-BuOK in MeOH-THF to give 1,2-diarylethylene 19 in 73 % yield. Photocyclization of the olefin 19 by the Katz’s method provided 2,13-bis(triisopropylsilyloxy)methyl-[7]thiaheterohelicene 20 in 66 % yield. Desilylation by TBAF in THF gave the desired 2,13-bis(hydroxymethyl)dithieno[3,2-e:3',2'-e']benzo[1,2-b:4,3-b']bis[1]benzodithiophene, (PM)-(±)-13, in 59% yield.

Although several attempts to resolve racemic 2,13-bis(hydroxymethyl)[7]-thiaheterohelicene, (PM)-(±)-13, using (R,R)-(−)-N,N',N'-tetramethylsuccinamide or brucine was unsuccessful, lipase-catalyzed transesterification in the presence of vinyl acetate was found to be effective for optical resolution. Thus, the reaction of (PM)-(±)-13 (100 mg) with the lipase from Pseudomonas cepacia (Amano PS, 2.99 g) in CH₂Cl₂ (100 mL) in the presence of molecular sieves 4A (4.37 g) at room temperature was terminated close to the 50 % esterification point (25 h), giving
Scheme 3

\( \text{ROH}_2\text{C} \quad \text{S} \quad \text{S} \quad \text{H} \quad \text{S} \quad \text{S} \quad \text{OH}_2\text{C} \)

(a) \((i-\text{Pr})_3\text{SiOTf}, 2,6\)-lutidine, \(\text{CH}_2\text{Cl}_2\), 0 °C, 98%; (b) \(\text{BuLi}, \text{TMEDA}, \text{DMF}, \text{THF}, -78 \degree \text{C}, 97%\); (c) \(\text{NaBH}_4, \text{MeOH}-\text{THF}, \text{r.t.}\); (d) \(\text{SOCl}_2, \text{pyridine}, \text{benzene}, 0 \degree \text{C}\); (e) \(\text{Ph}_3\text{P}, \text{benzene, reflux, 65\% (from 15)}\); (f) \(\text{t-BuOK, MeOH-THF, 0 \degree \text{C}, 73\%}\); (g) \(\text{hv}, \text{I}_2, \text{propylene oxide, benzene, r.t., 66\%}\); (h) \(\text{Bu}_4\text{NF, THF, 0 \degree \text{C, 93\%.}}\)

\((P)-(+)\text{-13} (44.7 \text{ mg, 45 \% yield}) \text{ in 98 \% ee and the corresponding monoacetate (M)-21 (40.9 mg, 38 \% yield) and diacetate (M)-22 (15.1 mg, 13 \% yield) which were readily separated by silica gel chromatography. The rotational value of (P)-(+)\text{-13 was } [\alpha]_D +1973 (c 0.055, \text{CHCl}_3). \) Hydrolysis of the monoacetate (M)-21 by \(\text{NaOH in methanol gave (M)-(--)13 with 80 \% ee and the diacetate (M)-22 gave the same enantiomer with 95 \% ee.} \)
In contrast, the transesterification of racemic helicene (PM)-(±)-13 (100 mg) with the lipase from Candida antarctica (Nova CAL, 0.5 g) gave (M)-(−)-13 (43.7 mg, 44% yield) with 92% ee and the corresponding monoacetate (P)-21 (57.8 mg, 53% yield).
yield) and diacetate (P)-22 (3.4 mg, 3 % yield). The rotational value of (M)-(−)-13 was \([\alpha]_D -1965\) (c 0.050, CHCl₃). It is noteworthy that, when (P)-13 of 60 % ee was carefully recrystallized from CH₂Cl₂-hexane, yellow crystals were obtained, which showed no enantiomeric excess. From the filtrate, (P)-13 was obtained in 95 % ee.

This procedure is operationally very simple, providing both enantiomers of 2,13-bis(hydroxymethyl)dithieno[3,2-e;3′,2′-e’]benzo[1,2-b:4,3-b’]bis[1]benzothiophenes, (P)-(+)–13 and (M)-(−)-13, of high optical purity on a 40-mg or larger scale.

**X-ray Structural Analysis of Helicene-Ethanol Clathrate**

When racemic bis(hydroxymethyl)[7]thiaheterohelicene (PM)-(±)-13 was recrystallized from ethanol, yellow crystals were obtained. NMR spectrum showed that the crystals contained ethanol with a 1:1 ratio. The complex is remarkably stable at room temperature, and releases ethanol at 100 °C and decomposes at 178-183 °C. The inclusion of ethanol was also confirmed by the X-ray structure analysis (Figures 1 and 2) which unambiguously showed highly organized structure (Figure 3).

The helicenediol 13 of same helicity are aligned in a stacking column along the crystallographic b direction by intermolecular hydrogen bonds. Two stacking columns of same helicity are interlocked by the ethanol molecules through hydrogen bonds, giving either a right-handed strand of [(P)-9][EtOH] or a left-handed strand of [(M)-9][EtOH]. The central benzene ring of (P)-helicenediol in a strand and that of (M)-enantiomer in a neighboring strand are placed in a face-to-face orientation with an average distance of 4.33 Å (Figure 4). Within the helicenediol 13 itself, four thiophene rings and three benzene rings constitute a full turn of the helix and the terminal thiophene rings are spread away with an interplanar angle of 38°. The distortion from planarity influences double bond character and thus bond lengths. The C-C distances of the outer rings C(4)-C(5), C(9)-C(10) and C(14)-C(15) are shortened to 1.36 Å and the inner bond C(20)-C(21), C(22)-C(23) and C(24)-C(25) are lengthened to 1.42-1.44 Å, compared to the bond length (1.39 Å) in benzene. The inner C-C bond lengths in the thiophene rings are lengthened to 1.46 Å from 1.42 Å.
Figure 1 ORTEP view of heterohelicidol 13

Figure 2 ORTEP sideview of heterohelicidol 13
Figure 3 ORTEP view of 13-EtOH clathrate

Figure 4 Heterohelicene diol13-EtOH clathrate as viewed along the b axis

Å of the C(3)-C(4) bond length of thiophene (Table 1). The angles between two adjacent rings vary from $-9.33^\circ$ to $+11.63^\circ$, which indicates that the strain seems mainly to be localized in the inner aromatic rings, giving rise to an irregular screw of the helicene (Table 2). The longest nonbonded C···C distance is 4.73 Å of C(27)···C(29) and two oxygen atoms, [O(28)···O(30)] are separated by 5.70 Å. On
the other hand, the shortest nonbonded C⋯C distance is 2.94 Å of C(19)⋯C(26), which is smaller than the sum of the Van der Waals radii of two CH₂ groups. The deviation from planarity in the solid state is also confirmed by 'H NMR spectroscopy in chloroform solution. Thus, the resonance of protons (δ 6.60) on C(19) and C(26) shown in Figure 4 is at higher field than a proton (δ 7.55) on C(1) of 2,5-bis(hydroxymethyl)benzo[1,2-b:4,3-b']dithiophene. This upfield shift indicates that these protons experience the shielding of the terminal overlapping thiophene rings.

Table 1 Selected C-C bond lengths

<table>
<thead>
<tr>
<th>C-C bond</th>
<th>length(Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4)-C(5)</td>
<td>1.36</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.36</td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.36</td>
</tr>
<tr>
<td>C(20)-C(21)</td>
<td>1.44</td>
</tr>
<tr>
<td>C(22)-C(23)</td>
<td>1.43</td>
</tr>
<tr>
<td>C(24)-C(25)</td>
<td>1.42</td>
</tr>
</tbody>
</table>
Table 2 Dihedral Angles between two adjacent planes (degree).

<table>
<thead>
<tr>
<th>plane</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15.3</td>
<td>8.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>24.7</td>
<td>19.5</td>
<td>11.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>146.4</td>
<td>151.2</td>
<td>159.1</td>
<td>170.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>143.1</td>
<td>146.6</td>
<td>153.8</td>
<td>165.2</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>142.0</td>
<td>143.9</td>
<td>150.0</td>
<td>160.3</td>
<td>14.0</td>
<td>7.3</td>
</tr>
</tbody>
</table>

The above results suggest that the inclusion of guest molecules within a helical network is possible. Since optically pure 13 can be prepared by lipase-catalyzed transesterification, there is also a potential for chiral recognition of racemic guests based on helicity.

**Experimental**

**General.** All reactions were carried out under an atmosphere of argon. THF was distilled under argon atmosphere from sodium benzophenone ketyl immediately before use. Ether, dichloromethane and benzene were distilled from calcium hydride and stored over 4A molecular sieves. The hexane solution of butyllithium (Kanto Chemicals) was titrated using diphenylacetic acid. Melting points were determined on a Yanagimoto hotstage apparatus and are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR 8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini-200 (200 MHz) spectrometer in CDCl₃ solution with tetramethylsilane as an internal standard. J values are given in Hz. Optical rotations were measured in 1dm path length cells of 10cm³ on a JASCO Model DIP-181 polarimeter; [α]₀ values are given in 10⁻¹ deg.cm².g⁻¹. All photocyclizations were accomplished in a water-cooled Pyrex photoreactor using a 500-W high-pressure mercury lamps. Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100-200 mesh was used for column chromatography. Elemental analysis were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.
2-Hydroxymethylbenzo[1,2-b:4,3-b’]dithiophene (2).
To a stirred solution of 1 (1.90 g, 10 mmol) in 70 mL of THF was added butyllithium (6.5 mL of 1.56 M solution in hexane) at —78 °C and stirred for 1 h at —78 °C. The resulting light gray suspension was allowed to warm to 0 °C. To the reaction mixture was added paraformaldehyde (0.90 g, 30 mmol) and stirred at room temperature overnight. The reaction was quenched by saturated ammonium chloride and 5 % hydrochloric acid, and separated aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with aqueous NaHCO₃, brine, and dried over Na₂SO₄ and concentrated. The residue was chromatographed on silica gel using hexane-ethyl acetate (2:1) as eluent to give alcohol 2 as a white solid (1.54 g, 70 %).

m.p. 117-118 °C; ¹H NMR (CDCl₃) δ 2.02 (t, J 4.4, 1H), 5.01 (d, J 4.4, 2H), 7.55 (d, J 5.4, 1H), 7.60 (s, 1H), 7.65 (d, J 5.4, 1H), 7.74 (d, J 8.8, 1H), 7.81 (d, J 8.8, 1H); IR (KBr) 3245, 1185, 1125, 1040, 1010, 840, 795, 765, 700 cm⁻¹; Anal. Calcd for C₁₁H₈O₂S₂: C, 59.97; H, 3.66. Found: C, 60.04; H, 3.74.

2-(t-Butyldimethylsiloxymethyl)benzo[1,2-b:4,3-b’]dithiophene (3).
To a stirred solution of 2 (1.33 g, 6.04 mmol) in dry 5 mL of DMF was added imidazole (1.13 g, 15.10 mmol) and t-butyldimethylchlorosilane (0.96g, 6.07 mmol) and stirred for 2h at room temperature. The reaction was quenched by dilute hydrochloric acid. The reaction mixture was diluted with ethyl acetate, and the organic phase was washed with NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (20:1) as eluent to give silyl ether 3 as a white solid (1.97 g, 98 %).

m.p. 72-73 °C; ¹H NMR (CDCl₃) δ 0.16 (s, 6H), 0.97 (s, 9H), 5.05 (d, J 1.1, 2H), 7.51 (s, 1H), 7.54 (d, J 5.7, 1H), 7.66 (d, J 5.7, 1H), 7.74 (d, J 8.8, 1H), 7.78 (d, J 8.8, 1H); IR (KBr) 2925, 2855, 1470, 1250, 1135, 1090, 835, 775, 695 cm⁻¹; Anal. Calcd for C₁₇H₂₂O₂S₂Si: C, 61.03; H, 6.63. Found: C, 60.94; H, 6.69.

5-(t-Butyldimethylsiloxymethyl)-2-formylbenzo[1,2-b:4,3-b’]-dithiophene (4).
To a stirred solution of 3 (1.36 g, 4.07 mmol) in 40 mL of THF were successively added TMEDA (0.92 mL, 6.10 mmol) and butyllithium (4.6 mL of 1.36 M solution in hexane) at —78 °C and stirred for 2 h at —78 °C. To the resulting green solution was added a solution of DMF (1.4 mL, 17.04 mmol) in 5 mL of THF at —78
°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated ammonium chloride and 5 % hydrochloric acid. The organic layer was separated and aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with aqueous NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as eluent to give aldehyde 4 as a yellow solid (1.20 g, 81%).

m.p. 79-81 °C; ¹H NMR (CDCl₃) δ 0.17 (s, 6H), 0.98 (s, 9H), 5.07 (s, 2H), 7.57 (s, 1H), 7.77 (d, J 8.8, 1H), 7.91 (d, J 8.8, 1H), 8.33 (s, 1H), 10.15 (s, 1H); IR (KBr) 2925, 2855, 1675, 1665, 1365, 1335, 1250, 1135, 1075, 840, 775 cm⁻¹; Anal. Calcd for C₁₈H₂₂O₂S₂Si: C, 59.63; H, 6.12. Found: C, 59.61; H, 6.11.

N-[(1R, 2R, 3S, 4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-hydroxymethylbenzo[1,2-b:4,3-b']dithiophene-2-carboxamide (6).
To a stirred solution of 5 (2.14 g, 5.18 mmol) in a mixture of 100 mL of THF and 100 mL of ethanol was added sodium borohydride (0.98 g, 25.90 mmol) at room temperature. The resulting white suspension was stirred for 4 h at room temperature. The reaction was quenched by the dropwise addition of 10 % hydrochloric acid. The reaction mixture was concentrated in reduced pressure and dissolved in CH₂Cl₂. The organic phase was washed with brine, dried over Na₂SO₄, and concentrated. The residue was recrystallized from ethyl acetate, and the mother liquor was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (1:2) as eluent to give alcohol 6 as white crystals (2.13 g, 99%).

m.p. 186-188 °C; ¹H NMR (CDCl₃) δ 0.95 (s, 3H), 0.96 (s, 3H), 1.02 (s, 3H), 1.18-1.59 (m, 3H), 1.91 (m, 1H), 2.18 (m, 1H), 2.32 (br s, 1H), 2.61 (br s, 1H), 4.15 (m, 1H), 4.41 (m, 1H), 4.99 (s, 2H), 6.97 (d, J 6.5, 1H), 7.45 (s, 1H), 7.58 (d, J 8.4, 1H), 7.69 (d, J 8.4, 1H), 7.92 (s, 1H); IR (KBr) 3400, 2950, 1630, 1525, 1185, 1125, 1105, 1050, 1020, 545 cm⁻¹; Anal. Calcd for C₁₉H₂₅NO₃S₂: C, 63.58; H, 6.06; N, 3.37. Found: C, 63.48; H, 6.12; N, 3.35.

N-[(1R, 2R; 3S, 4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-chloromethylbenzo[1,2-b:4,3-b']dithiophene-2-carboxamide (7).
To a stirred solution of N-chlorosuccinimide (0.58 g, 4.33 mmol) in 20 mL of CH₂Cl₂ was added dimethyl sulfide (0.37 mL, 4.90 mmol) dropwise at 0 °C. The white
suspension was cooled to −20 °C, and a suspension of 6 (0.82 g, 1.97 mmol) in 40 mL of CH₂Cl₂ was gradually added over 30 min. The resulting pale yellow suspension was allowed to warm to room temperature and stirred overnight. The reaction was quenched by brine, and the reaction mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over Na₂SO₄. The solvent was evaporated and the residue was recrystallized from ethyl acetate. The mother liquor was evaporated and the residue was chromatographed on silica gel using CH₂Cl₂-methanol (100:1) as eluent to give chloride 7 as a white solid (0.70 g, 82%).

m.p. 212-215 °C; ¹H NMR (CDCl₃) δ 0.95 (s, 3H), 0.96 (s, 3H), 1.02 (s, 3H), 1.27 (m, 1H), 1.53 (m, 2H), 1.92 (m, 1H), 2.16 (m, 1H), 2.61 (br s, 1H), 4.17 (m, 1H), 4.52 (m, 1H), 4.93 (s, 2H), 7.00 (d, J 4.1, 1H), 7.55 (s, 1H), 7.60 (d, J 8.8, 1H), 7.65 (d, J 8.8, 1H), 7.87 (s, 1H); IR (KBr) 3400, 2953, 1645, 1525, 1255, 1195, 1050, 785, 725, 690, 660 cm⁻¹; Anal. Calcd for C₂₂H₂₄ClNO₂S₂: C, 60.88; H, 5.57; N, 3.23. Found: C, 60.85; H, 5.61; N, 3.15.

N-[(1R,2R,3S,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-2-triphenylphosphiniomethylbenzo[1,2-b:4,3-b']-dithiophene-2-carboxamide (8).

To a stirred suspension of 7 (0.51 g, 1.18 mmol) in 5 mL of benzene was added triphenylphosphine (0.34 g, 1.30 mmol) and the mixture was heated under reflux for 48 h. The solvent was evaporated and the residue was chromatographed on silica gel using CH₂Cl₂-methanol (20:1) as eluent to give phosphonium salt 8 as a pale yellow solid (0.64 g, 78%).

m.p. 190-193 °C (dec.); ¹H NMR (CDCl₃) δ 0.94 (s, 6H), 1.00 (s, 3H), 1.22 (m, 1H), 1.53 (m, 2H), 1.98 (m, 1H), 2.11 (m, 1H), 4.13 (m, 1H), 4.35 (m, 1H), 5.82 (m, 2H), 7.11 (d, J 8.7, 1H), 7.23 (d, J 8.7, 1H), 7.59-7.78 (m, 16H), 8.36 (s, 1H); IR (KBr) 3300, 2950, 1640, 1520, 1485, 1435, 1115, 730, 690, 500 cm⁻¹.

N-[(1R,2R,3S,4S)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-[2-(5-t-butyldimethylsiloxyethyl-2-benzo[1,2-b:4,3-b']dithiophenyl)ethenyl]benzo[1,2-b:4,3-b']dithiophene-2-carboxamide (9).

To a stirred solution of aldehyde 4 (0.26 g, 0.72 mmol) and phosphonium chloride 8 (0.50 g, 0.72 mmol) in a mixture of 10 mL of methanol and 5 mL of THF was added a solution of t-BuOK (0.16 g, 1.44 mmol) in 2 mL of methanol at room temperature,
butyllithium (0.55 mL of a 1.5 M solution in hexane) at −78 °C and the reaction mixture was allowed to warm to 0 °C. To the resulting white solution was added a solution of (P)-(+)\textbf{-11} (35.5 mg) in 10 mL of THF and the mixture was stirred overnight at room temperature. The reaction was quenched by aqueous sodium hydroxide and separated aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate (10:1) as eluent to give thioester (P)-(+)\textbf{-12} as a yellow solid.

$^1$H NMR (CDCl$_3$) δ 0.14 (s, 3H), 0.16 (s, 3H), 0.93 (s, 9H), 1.32 (t, J 7.5, 3H), 3.02 (q, J 7.5, 2H), 3.76 (d, J 6.5, 1H), 4.22 (d, J 10.4, 1H), 4.62 (d, J 6.5, 1H), 4.75 (d, J 10.4, 1H), 7.30-7.73 (m, 4H), 8.01 (s, 2H).

2-(Triisopropylsiloxymethyl)benzo[1,2-b:4,3-b’]dithiophene (14). To a stirred solution of 2-(hydroxymethyl)benzo[1,2-b:4,3-b’]dithiophene 2 (1.97 g, 8.94 mmol) in 30 mL of dichloromethane were added 2,6-lutidine (2.39 g, 22.35 mmol) and triisopropylsilyl triflate (3.60 g, 9.21 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by aqueous sodium carbonate and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine and dried over MgSO$_4$. The solvent was evaporated and the residue was chromatographed on silica gel using hexane as eluent to give silyl ether 14 as a white solid (3.29 g, 98 %).

m.p. 50-51 °C; $^1$H NMR (CDCl$_3$) δ1.08-1.29 (m, 21H), 5.13 (d, J 1.1, 2H), 7.51 (t, J 1.0, 1H), 7.51 (d, J 5.3, 1H), 7.64 (d, J 5.5, H), 7.72 (d, J 9.3, 1H), 7.77 (d, J 8.1, 1H); IR (KBr) 2959, 2940, 2863, 2350, 2330, 1458, 1372, 1130, 1082, 1067, 1015, 994, 882, 830, 801, 760, 695 cm$^{-1}$; Anal. Calcd for C$_{20}$H$_{28}$OS$_2$Si: C, 63.78; H, 7.49. Found: C, 63.80; H, 7.50.

2-(Triisopropylsiloxymethyl)-5-formylbenzo[1,2-b:4,3-b’]dithiophene (15). To a stirred solution of 14 (3.24 g, 8.63 mmol) in 40 mL of THF were successively added TMEDA (1.50 g, 12.94 mmol) and butyllithium (7.56 mL of 1.37 M solution in hexane) at −78 °C and the mixture was stirred for 5 h. To a resulting green solution was added a solution of DMF (3.15 g, 43.15 mmol) in 5.0 mL of THF at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight.
5-(Triisopropylsiloxymethyl)-2-benzo[1,2-b:4,3-b']dithiophenyl-methyltriphenylphosphonium Chloride (18).

To a stirred solution of 17 (4.32 g, 10.16 mmol) in 20 mL of benzene was added triphenylphosphine (4.48 g, 16.84 mmol) and the mixture was heated under reflux for 2 h. The solvent was evaporated and the residue was washed with diethyl ether to give phosphonium salt 18 (3.30 g, 47 %) as an off-white solid. The filtrate was concentrated and the residue was chromatographed on silica gel using dichloromethane-methanol (10:1) as eluent to give 18 (1.10 g, 16 %).

m.p. 159-161 °C; ¹H NMR (CDCl₃) δ 1.08-1.29 (m, 21H), 5.07 (d, J 1.1, 2H), 6.09 (d, J 14.2, 2H), 7.37-7.89 (m, 19H); IR (KBr) 2944, 2867, 1464, 1439, 1339, 1184, 1132, 1113, 1067, 997, 884, 785, 720, 689, 507 cm⁻¹.

5-[5-(Triisopropylsiloxymethyl)-2-benzo[1,2-b:4,3-b']-dithiophenyl]ethenyl-2-(triisopropylsiloxymethyl)benzo[1,2-b:4,3-b']dithiophene (19).

Aldehyde 15 (2.95 g, 7.25 mmol) and phosphonium salt 18 (5.36 g, 7.80 mmol) were dissolved in a mixture of 20 mL of THF and 100 mL methanol. To the solution was added a solution of t-BuOK (1.17 g, 10.42 mmol) in 20 mL of methanol at 0 °C. The resulting yellow suspension was stirred for 2 h. The reaction was quenched by dilute hydrochloric acid. The precipitate was filtrated, washed with methanol, and dried in vacuo to give olefin 19 (4.83 g, 86 %) as a yellow solid.

m.p. 197-199 ºC; ¹H NMR (CDCl₃) δ 1.09-1.29 (m, 42H), 5.14 (d, J 1.1, 4H), 7.30 (s, 2H), 7.48 (d, J 1.1, 2H), 7.61 (s, 2H), 7.66 (d, J 9.0, 2H), 7.74 (d, J 9.0, 2H); IR (KBr) 2942, 2865, 1635, 1460, 1372, 1183, 1129, 1084, 1067, 995, 882, 835, 824, 797, 783, 685 cm⁻¹; Anal. Calcd for C₄₂H₆₆O₂S₄Si₂: C, 64.90; H, 7.26. Found: C, 64.82; H, 7.42.

2,13-Di(triisopropylsiloxymethyl)dithieno[3,2-e:3',2'-e']benzo-[1,2-b:4,3-b']bis[1]benzothiophene (20).

Olefin 19 (0.20 g, 0.25 mmol) and iodine (0.10 g, 0.39 mmol) were dissolved in 1.7 L of benzene and argon was bubbled through the stirred solution for 1.5 h before photo-irradiation. The photo-reactor was cooled to 0 °C and propylene oxide (9.0 mL, 0.13 mol) was added to the mixture. The solution was irradiated for 2 h with argon flow. After most of the substrate was consumed (checked by TLC), the olefin 19 (0.20 g, 0.25 mmol) and iodine (0.10 g, 0.39 mmol) was added and the reaction mixture was irradiated for 2 h. This procedure was repeated eight times, and 1.68 g
(2.16 mmol) of the olefin 19 was used in total. The reaction mixture was successively washed with aqueous Na₂S₂O₃, aqueous NaHCO₃, brine and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (100:1) as eluent to give helicene 20 as a pale yellow solid (1.15 g, 66 %).

m.p. 164-167 °C; ¹H NMR (CDCl₃) δ 0.93-1.13 (m, 42H), 4.53 (dd, J 1.1, 13.4, 2H), 4.60 (dd, J = 1.1, 13.5, 2H), 6.56 (t, J 1.1, 2H), 7.88 (d, J 8.6, 2H), 7.97 (d, J 9.0, 2H), 7.99 (s, 2H); IR (KBr) 2942, 2890, 2865, 1460, 1416, 1364, 1321, 1298, 1244, 1198, 1134, 1092, 1067, 995, 918, 884, 849, 789, 735, 687 cm⁻¹; Anal. Calcd for C₄₂H₇₄O₂S₄Si₂: C, 65.06; H, 7.02. Found: C, 65.43; H, 7.07.

2,13-Bis(hydroxymethyl)dithieno[3,2-e:3’,2’-e’]benzo[1,2-b:4,3-b’]bis[1]benzothiophene (13).

To a stirred solution of 20 (0.185 g, 0.239 mmol) in 7.0 mL of THF was added a solution of tetrabutylammonium fluoride (0.5 mL of 1 M solution in THF) at 0 °C and the solution was stirred at room temperature for 5 h. The reaction was quenched by brine, and the mixture was diluted with CH₂Cl₂. The organic phase was washed with dilute hydrochloric acid, saturated aqueous NaHCO₃, and brine, and dried over MgSO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (2:1) as eluent to give diol 13 as a yellow solid (0.108 g, 98 %). Recrystallization from ethanol gave an analytically pure sample.

m.p. 179-181 °C; ¹H NMR (CDCl₃) δ 1.72 (dd, J 4.8, 8.0, 2H), 4.27 (2H, dd, J 4.8, 13.1), 4.46 (dd, J 8.0, 13.1, 2H), 6.59 (s, 2H), 7.97 (d, J 8.0, 2H), 8.02 (d, J 8.0, 2H), 8.06 (s, 2H); Anal. Calcd for C₂₄H₁₄O₂S₄•C₂H₅OH: C, 62.30; H, 3.05. Found (recrystallized from EtOH): C, 61.46; H, 3.76.

(P)-(+) -2,13-Bis(hydroxymethyl)dithieno[3,2-e:3’,2’-e’]benzo[1,2-b:4,3-b’]bis[1]benzothiophene ( (P)-13).

To a stirred solution of (PM)-(±)-13 (101.2 mg, 0.219 mmol) in 100 mL of CH₂Cl₂ were added molecular sieves 4A (4.37 g), PCL (2.99 g, 60 u/mg), and vinyl acetate (2.0 mL, 21.7 mmol), and the reaction mixture was stirred at 30 °C. The reaction was terminated close to the 50 % esterification point (25 h) by filtration of lipase. The solvent was evaporated and the following column chromatography on silica gel gave (P)-helicenediol (P)-(+) -13 (44.7 mg, 44 %) in 98 % ee along with monoacetate 21 (40.9 mg, 37 %) and diacetate 22 (15.1 mg, 13 %). Hydrolysis of 21 (40.9 mg) by catalytic amounts of 0.1 N aqueous NaOH (1 mL) in 10 mL of methanol gave
(M)-(−)-13 (35.6 mg) in 77% ee. In a similar way, the hydrolysis of 22 (15.1 mg) afforded (M)-(−)-13 (12.1 mg) in 94% ee.

[α]_D +1973 (c 0.055, CHCl₃) (98% ee)

(M)-(−)-2,13-Bis(hydroxymethyl)dithieno[3,2-e:3’,2’-e’]benzo-[1,2-b:4,3-b’]bis[1]benzothiophene ((M)-13).

To a stirred solution of (PM)-(±)-13 (100.3 mg, 0.217 mmol) in 100 mL of CH₂Cl₂ were added CAL (0.50 g, 70 u/mg) and vinyl acetate (2.0 mL, 21.7 mmol), and the reaction mixture was stirred at 30 °C. The reaction was terminated close to the 50% esterification point (9.5 h) by filtration of lipase. The solvent was evaporated and the following column chromatography on silica gel gave (M)-(−)-13 (43.7 mg, 44%) in 92% ee along with monoacetate 21 (57.8 mg, 53%) and diacetate 22 (3.4 mg, 3%).

Hydrolysis of 21 (57.8 mg) by catalytic amounts of 0.1 N aqueous NaOH (1 mL) in 10 mL of methanol gave (P)-(−)-13 in 67% ee. In a similar way, the hydrolysis of 22 (3.4 mg) afforded (P)-(−)-13 in 89% ee.

[α]_D −1965 (c 0.050, CHCl₃) (92% ee)

Structure solution and refinement of (PM)-(±)-13

A crystal of dimensions 0.20 × 0.10 × 0.60 mm was used for X-ray crystallography. Crystal data: C₂₆H₂₀O₃S₄, M = 508.68, crystal system, monoclinic, space group, P2₁/c (#14), a = 15.028(2), b = 8.046(2), c = 19.369(2) Å, β = 102.779(7)°, V = 2284.0(5) Å³, F(000) = 1056.00, Z = 4, μ = 40.52 cm⁻¹, Dc = 1.324 g cm⁻³. All measurements were made on a Rigaku AFC7R diffractometer with Cu-Kα radiation and a 12kW rotating anode generator. The data were collected at a temperature of 20 ± 1 °C using ω–2θ scan technique to a maximum 2θ value of 120.1°. Of the 3828 reflections which were collected, 3671 were unique (R_ex = 0.026). The structure was solved by direct methods using SAPI91 and expanded using Fourier techniques (DIRDIF92). The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, the rest were included in fixed positions. The final cycle of the full-matrix least-squares refinement was based on 2792 observed reflections (I > 3.00σ(I)) and 347 variable parameters and converged with unweighted and weighted agreement factors of R = 0.046 and R_w = 0.055, respectively. The weighting scheme was based on counting statics and included a factor (p = 0.020) to downweight the intense reflections. Neutral atom scattering factors were taken from Cromer and Waber. Anomalous dispersion effects were included in F.calc; the values for Δf' and Δf'' were those of Creagh and McAuley.
values for the mass attenuation coefficients are those of Creagh an Hubbel. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

References and Notes
13) The decrease of the mass numbers from 743 to 741 during the photo-reaction clearly indicates the formation of [7]heterohelicene.
14) The ratio of the diastereoisomers was determined by HPLC using Shim-pack CLC-SIL(M) (eluent: hexane/ethanol = 100/1). On the basis of an X-ray determination, (+)-carbohelicenes and (+)-heterohelicenes have been shown to possess
a right-handed $P$ helicity, the $(-)$-enantiomers a left-handed ($M$) helicity. Since
the optical rotational value (several thousands degrees) of helicenes are very high
compared to that of the amino alcohol used as a chiral auxiliary, the signs of the
optical rotations of the diastereomers (10 and 11) arise from the helicity of the
helicenes (12 and 13). In this context, the absolute configurations ($P$ or $M$) of the
diastereomers indicate those of the helicenes themselves.

18) (a) Damon, R. E.; Coppola, G. M. Tetrahedron Lett. 1990, 31, 2849; (b) Evans,
20) $^1$H NMR of 13 : $\delta$ 1.71 (br s, 2H), 4.27 (d, $J_{12.8}$, 2H), 4.46 (d, $J_{13.5}$, 2H), 6.60
(s, 2H), 7.97 (d, $J_{8.7}$, 2H), 8.02 (d, $J_{8.7}$, 2H), 8.07 (s, 2H).
21) Sumichiral OA-2000 was used and 1,2-dichloroethane/ethanol = 100/1 was used as
an eluent.
25) For a recent review: see, (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Man
Zwanenburg, B. Tetrahedron 1991, 47, 7409; (c) Guanti, G.; Banfi, L.; Riva, R.
Tetrahedron:Asymmetry 1994, 5, 9; (d) Hof, R. P.; Kellog, R. M.
(g) Itoh, T.; Chika, J-I.; Takagi, Y.; Nishiyama, S. J. Org. Chem. 1993, 58, 5717. (h)
Chapter 3

Synthesis and Crystal structure of Chiral Bifunctional Helicenes with \( \pi \)-Deficient Pyridine and \( \pi \)-Excessive Thiophene Units.

Abstract

Optically active 2(hydroxymethyl)- and 2-(ethylthiocarbonyl)[1]-benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-f]quinolines (1 and 17) containing of \( \pi \)-excessive thiophene and \( \pi \)-deficient pyridine units were prepared by the use of \textit{exo}-3-amino-2-hydroxybornane as a chiral auxiliary. This procedure consists of separation of the helical diastereomers prepared by photocyclization of 1,2-diarylethlenes and removal of the chiral auxiliary by thiolate anion. Large scale preparation of the helicenes can be accomplished by a modified procedure of the photocyclization reaction. Optical purities of both enantiomers of the heterohelicenes were >99.5\%, and the absolute configurations of 1 and 17 were determined by comparison of CD spectra.

The X-ray structure analysis of the racemic \((PM)\)-(\pm\)-1 indicates the presence of the hydrogen bonded binary aggregation between the enantiomeric \(P\) and \(M\) molecules in the crystal packing.

Introduction

Since the first synthesis of hexahelicene ([6]helicene) which was made up of \textit{ortho}-condensed six benzene rings by Newman in 1955,\(^1\) the helical aromatic molecules have received considerable attention because of unique helical non-planar \(\pi\)-electron system and of their very high rotational values.\(^2,3\)\) The helicenes containing more than six benzene rings (carbohelicenes) or seven heterocyclic rings (heterohelicenes) possess rigid helical framework\(^2,4\) and are very stable toward acids, bases, and relatively high temperature.\(^5\) For this reason, chiral functionalized analogues are promising candidates for chiral ligands and auxiliaries in asymmetric syntheses. The syntheses of chiral helicenes, however, requires laborious methods such as (i) repeated recrystallization of diastereomeric charge transfer complexes derived from 2-(2,4,5,7-tetranitro-9-fluorenylideneamino-oxy)propionic acid (TAPA),\(^1,6\) (ii) crystal picking of racemic mixtures,\(^7\) or (iii) separation by chiral column using High-Performance Liquid Chromatography (HPLC).\(^8\)
Recently we have developed an efficient method for the synthesis of optically active monofunctionalized heterohelicenes by the use of exo- and endo-3-amino-2-hydroxybornane as chiral auxiliaries, which provides various types of optically pure functionalized heterohelicenes. This chapter describes the synthesis of potentially more valuable bifunctionalized heterohelicene such as 2-(hydroxymethyl)- and 2-(ethylthiocarbonyl)[1]benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-f]quinoline (1) and (17) consisted of π-deficient thiophene and π-excessive pyridine rings, as well as a practical method for the preparation of a large amount of heterohelicene by modifying photocyclization of diaryl olefins. The optical properties of the resulting heterohelicenes are also described in this chapter.

Synthesis of Chiral Bifunctional Helicenes with π-Deficient and π-Excessive Thiophene Units

Our strategy for the synthesis of 1 bases upon the regioselective synthesis of olefin 2, in which the thiophene appendages not only lead to the regioselective α-functionalization of the ring systems, they can also participate in the regioselective photocyclization at their β-positions. The pyridine nitrogen in the chiral helicene can serve as a hydrogen acceptor as well as a metal chelating agent for chirality recognition. Two routes are possible in the preparation of olefin 2 (Scheme 1), a precursor of the desired heterohelicene which was readily obtained by the Wittig reactions of 3 and 4, or 5 and 6. Although benzo[1,2-b:4,3-b']dithiophene derivatives 3 and 5 possessing a chiral auxiliary derived from D-camphor have already been reported, thiieno[3,2-f]quinoline derivatives like 10 could not be obtained from the corresponding 1,2-diarylolefin by photocyclization. We devised an improved method using Skraup type reaction as shown in Scheme 2. Thus, reaction of 2-chloro-5-nitrobenzaldehyde 7 and ethyl mercaptoacetate in the presence of potassium carbonate in DMF smoothly proceeded at room temperature to give 5-nitrobenzo[b]thiophene-2-carboxylate 8 in 88% yield. Selective reduction of the nitro group of 8 was accomplished by iron powder and hydrochloric acid in absolute ethanol to afford ethyl 5-aminobenzo[b]thiophene-2-carboxylate 9 in 96%
yield. The resulting amine 9 was then treated with a mixture of glycerol and concentrated sulfuric acid in the presence of sodium m-nitrobenzenesulfonate and boric acid, and the reaction mixture was esterified by acidic ethanol to give the desired ethyl thieno[3,2-f]quinoline-2-carboxylate 10 in 73% yield. Reduction of 10 with LiAlH₄ provided alcohol 11, which was converted into chloride 12 with SOCl₂ in the presence of triethylamine. Reaction of 12 and triphenylphosphine in refluxing benzene gave phosphonium salt 4 in 94% yield and aldehyde 6 was obtained by oxidation of 11 with pyridinium dichromate (PDC) in CH₂Cl₂ in 65% yield.
Scheme 2

The Wittig reactions of 3 with 4 and of 5 with 6 gave 2 in 84% and 76% yields, respectively. The olefin 2, however, has low solubility in common organic solvents, which hampered subsequent manipulations. In order to improve the solubility of the olefin, 2 was converted into the corresponding triisopropylsilyl ether\(^{16}\) 13 in 94% yield. The silyl ether 13 was dissolved in benzene (0.30 g in 1.6 L of benzene, 0.25 mM) and irradiated with a high-pressure mercury lamp in the presence of a stoichiometric amount of iodine and excess amount of propylene oxide under inert atmosphere\(^{17}\) to give helicene 14 in 59% yield as a mixture of diastereoisomers in a ratio of 38:62 determined by HPLC analysis.\(^{18}\) Since the yield of helicene by intramolecular photocyclization reaction is highly dependent on the concentration of starting material, the dilute solution should be used in this reaction. Thus, photocyclization performed in more dilute solution (0.20 g in 1.6 L of benzene, 0.17
Scheme 3

Reagents and conditions: (a) t-BuOK, THF, methanol, 89%; (b) triisopropylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH2Cl2, 94%; (c) hν; iodine, propylene oxide, argon, benzene, 73%; (d) TBAF, THF, 96%; (e) di-t-butyl dicarbonate, DMAP, CH2Cl2, 83%; (f) column chromatography on silica gel.

mM) increased the yield of 14 to 73% (diastereoisomer ratio 37:63). If the heterohelicene 14 is stable under conditions using intense irradiation of UV light, the olefin 13 can be added in the same vessel containing 14 after the photocyclization.
Thus, 13 (0.20 g) dissolved in 1.6 L of benzene (0.17 mM) was irradiated with a high-pressure mercury lamp under the conditions as described above. After the olefin 13 was consumed as judged by TLC, additional portions of 13 (0.20 g, 0.27 mmol) and iodine (0.40 mmol) were added into the reaction mixture and the irradiation was repeated. After this procedure was repeated six times, 0.70 g of heterohelicene 14 was obtained in 59% yield from olefin 12; total amount was 1.20 g (1.62 mmol) and the diastereomer ratio of 14 37:63. This procedure can be successfully applied to other photocyclization reaction using a catalytic amount of

**Scheme 4**

![Scheme 4](image)

**Reagents and conditions:** (a) EtSiLi, THF, 89%; (b) LiAlH₄, THF, 85%
iodine. Thus, the photocyclization of 1,2-di(2-thienyl)ethene (2.88 g, 15 mmol) in 1.7 L of benzene (9.5 mM) containing 0.45 mmol of I₂ was repeated four times to give 9.50 g (50 mmol) of benzo[1,2-b:4,3-b']dithiophene in 83 % yield.¹⁹

The diastereomers of the helicene could be separated by silica-gel column chromatography after desilylation with TBAF and subsequent N-t-butoxycarbonylation by di-t-butyl dicarbonate. Optical purities of both diastereomers, (+)-16 and (-)-16, were determined as >99.5% by HPLC analysis.²⁰ Removal of chiral auxiliary was successfully carried out by transformation of 16 to the corresponding thioester 17 by LiSEt in THF.¹¹,²¹ Optical rotation of (-)-17 obtained from the major diastereomer, (-)-16, was -2620 (c 0.0499, CHCl₃), whose absolute value has good agreement with that of the enantiomer (+)-17 obtained from (+)-16, +2670 (c 0.0500, CHCl₃). Both enantiomers of the thioester were converted into the corresponding alcohols by reduction with LiAlH₄ in 85% yield. Optical rotations of (-)-1 and (+)-1 were -2140 (c 0.0503, CHCl₃) and +2150 (c 0.0503, CHCl₃), respectively, and their optical purities were determined to be >99.5% by HPLC analysis (Figure 1).²² The CD spectra of thioester 17 and alcohol 1 (Figure 2

Figure 1 HPLC chromatograms of heterohelicenes 1
Column : SUMICHIRAL OA-2000I (4.6 mm i.d. x 25 cm)
Eluent : hexane / 1,2-dichloroethane / methanol (100:100:3)
Flow rate : 1 mL/min, Detector : 254 nm
Figure 2  CD spectra of (P)-(+)-17 and (M)-(−)-17 in chloroform

Figure 3  CD spectra of (P)-(+)-1 and (M)-(−)-1 in chloroform
and Figure 3) clearly indicate that (+)-17 and (+)-1 have same helicity as that of the
(P)-(+) -methyl[1]benzothieno[5,4-b]naphtho[1',2':4,5]thieno[3,2-e][1]benzothiophene-2-carboxylate, whose absolute configuration was determined by X-ray
structural analysis of the precursor. Thus, it is clearly shown that (+)-1 has a
helicity of P, and (−)-1 has that of M. This result agrees with the fact that the
levorotatory helicenes have the same M- helicity, and vice versa.

The deviation from planarity of the helicene 1 could be confirmed by NMR
analysis (Figure 4). The chemical shifts for 1-H, 14-H and 16-H in the spectrum of 1
show large upfield shifts compared to the chemical shifts of the alcohol 11 : $\Delta\delta$(ppm) = +1.59 (1-H), +0.83 (14-H), +0.83 (16-H). This suggests that the helical structure
exerted these protons in the anisotropic region of the aromatic rings of the same
molecule. The chemical shift for 14-H ($\delta$ 6.66 ppm) in 1 is almost the same as that of
2-H in benzo[c]phenanthro[1,2-f]quinoline ($\delta$ 6.57 ppm), but it is at higher field than
that of 2-H in naphtho[1',2':4,5]thieno-[3,2-a]-4,7-phenanthroline ($\delta$ 7.05 ppm). These results indicate that the heterohelicene 1 has a full turn of helix such as
benzo[c]phenanthro[1,2-f]quinoline, since the chemical shifts for the protons in
terminal aromatic rings are dependent on the degree of overlapping of both terminal
rings.

![Figure 4 NMR spectrum of heterohelicene 1.](image-url)
Crystal Structure of Bifunctional Heterohelicene

In order to confirm the structure and the absolute configuration of the optically active bifunctional heterohelicene with pyridine ring \((P)-(+)\)-1 or \((M)-(-)\)-1, several attempts to obtain single crystal for X-ray structure analysis were carried out. However, slow recrystallization from various solvents only gave microcrystalline materials, which were not suitable for X-ray analysis. The single crystal of the heterohelicene \((PM)-(\pm)\)-1 was obtained by slow recrystallization from CHCl₃. The results are shown in Figure 5. Although the crystal contains disordered guest CHCl₃ molecules in its cavity and the unweighted and weighted agreement factors are 0.113 and 0.156, respectively, the temperature factors were small and the structure of the helicene molecule was well confirmed. The dihedral angles between two

\[
\begin{align*}
S2 & \quad S5 \quad 04 \quad 3 \quad 2 \\
C7 & \quad C6 \quad C21 \quad C22 \quad C23 \\
C20 & \quad C19 \quad C18 \quad C17 \quad C16 \\
S3 & \quad S10 \quad C11 \quad C12 \quad C13 \\
C14 & \quad C15 \quad N1
\end{align*}
\]

Figure 5 ORTEP view of heterohelicene 1
adjacent planes (Table 1) are between 6.2 and 12.9°. The results clearly indicate that
the strain seems to be localized in the inner aromatic rings. Thus, the outer bonds
C(3)-C(4), C(7)-C(8), and C(11)-C(12) are shortened to 1.34-1.38 Å to the bond
length in benzene (1.39 Å), while the inner bond distances C(17)-C(18), C(19)-C(20),
and C(21)-C(22) are lengthened to 1.40-1.43 Å. The dihedral angles between the
terminal rings is 45.3°, which is larger than that of bis(hydroxymethyl)-
[7]thiaheterohelicene (38°).28) It is interesting to note that the binary aggregation by
hydrogen bond between P and M molecules was found in the crystal packing (Figure
6).

<table>
<thead>
<tr>
<th>plane</th>
<th>1(T)</th>
<th>2(B)</th>
<th>3(T)</th>
<th>4(B)</th>
<th>5(T)</th>
<th>6(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(B)</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3(T)</td>
<td>10.3</td>
<td>7.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4(B)</td>
<td>21.1</td>
<td>20.2</td>
<td>12.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5(T)</td>
<td>30.0</td>
<td>29.2</td>
<td>21.9</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6(B)</td>
<td>37.8</td>
<td>38.1</td>
<td>31.0</td>
<td>18.3</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>7(P)</td>
<td>45.3</td>
<td>46.9</td>
<td>40.4</td>
<td>28.4</td>
<td>21.2</td>
<td>11.7</td>
</tr>
</tbody>
</table>

(T: thiophene; B: benzene)

Table 2 Selected C-C bond lengths

<table>
<thead>
<tr>
<th>C-C bond</th>
<th>length(Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(3)-C(4)</td>
<td>1.38</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.34</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.34</td>
</tr>
<tr>
<td>C(17)-C(18)</td>
<td>1.40</td>
</tr>
<tr>
<td>C(19)-C(20)</td>
<td>1.42</td>
</tr>
<tr>
<td>C(21)-C(22)</td>
<td>1.42</td>
</tr>
</tbody>
</table>
Experimental

**General:** All reactions were carried out under an atmosphere of argon. THF and ether were distilled under argon atmosphere from sodium benzophenone ketyl immediately before use. Dichloromethane and benzene were distilled from calcium hydride and stored over 4Å molecular sieves. The hexane solution of butyllithium (Kanto Chemicals) was titrated using diphenylacetic acid. Melting points were determined on a Yanagimoto hotstage apparatus and are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR 8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini-200 (200 MHz) spectrometer in CDCl₃ with tetramethylsilane as an internal standard, and J values are given in Hz. The CD spectra are recorded on a JASCO Model J-720W recording spectropolarimeter in CHCl₃. Optical rotation was measured in 1 dm lengths cells of 10cm³ on a JASCO Model DIP-181 polarimeter; [α]₀ values are given in 10⁻¹deg·cm²·g⁻¹. Photocyclization reactions were performed in a water-cooled pyrex photoreactor using an Eikosha 500-W high-pressure mercury lamp. Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100-200 mesh was used for column chromatography. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.

**Ethyl 5-Nitrobenzo[b]thiophene-2-carboxylate (8).**
To a stirred solution of 5-nitro-2-chlorobenzaldehyde (18.56 g, 100 mmol) in 200 mL of dry DMF was added anhydrous K₂CO₃ (16.59 g, 120 mmol) and ethyl thioglycolate.
(11.0 mL, 100 mmol) at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was then poured into ice water and the solid was collected, washed with water, and dried in vacuo. The solid was recrystallized from ethyl acetate to give 8 as white needles (22.01 g, 88%).

m.p. 162-165 °C; ¹H NMR (CDCl₃) δ 1.44 (t, J7.2, 3H), 4.45 (q, J7.2, 2H), 7.99 (d, J 8.9, 1H), 8.17 (s, 1H), 8.30 (dd, J 8.9, 2.2, 1H), 8.78 (d, J2.2, 1H); IR (KBr) 1694, 1534, 1341, 1302, 1273, 1073, 760, 741 cm⁻¹; Anal. Calcd for C₁₁H₉NO₄S: C, 52.58; H, 3.61; N, 5.57. Found: C, 52.67; H, 3.55; N, 5.55.

Ethyl 5-Aminobenzo[b]thiophene-2-carboxylate (9).

To a stirred suspension of 8 (11.30 g, 45 mmol) in 450 mL of ethanol was added 27 g of iron powder, and the mixture was heated under reflux. To the stirred suspension was added 27 mL of concentrated hydrochloric acid dropwise and stirred for additional 1 h under reflux. The reaction mixture was filtrated and the filtrate was evaporated. The residue was dissolved in CH₂Cl₂, successively washed with water, NaHCO₃ solution, and brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was recrystallized from hexane-ethyl acetate to give 9 as a yellow solid (9.60 g, 96%).

m.p. 80-81 °C; ¹H NMR (CDCl₃) δ 1.40 (t, J 7.2, 3H), 3.76 (br s, 2H), 4.38 (q, J7.2, 2H), 6.89 (dd, J 8.7, 2.3, 1H), 7.11 (d, J 2.3, 1H), 7.61 (d, J 8.7, 1H), 7.86 (s, 1H); IR (KBr) 3382, 1674, 1636, 1522, 1302, 1293, 1240, 1156, 1076, 762 cm⁻¹; Anal. Calcd for C₁₁H₁₁NO₂S: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.84; H, 5.02; N, 6.32.


This compound was prepared according to the literature procedure.¹⁵) Amine 9 (8.93 g, 40.4 mmol) was treated with glycerol (11.52 g, 125.1 mmol), sodium m-nitrobenzenesulfonate (4.54 g, 20.2 mmol), boric acid (1.90 g, 30.67 mmol), and concentrated sulfuric acid (12.27 g, 125.1 mmol), and the mixture was heated at 170 °C for 1 h and then was cooled. Dry benzene (100 ML) was added and water was removed by azeotropic distillation. The excess of benzene was evaporated and dried in vacuo. To this reaction mixture, 100 mL of ethanol and concentrated sulfuric acid (1.7 mL) were added and the mixture was heated under reflux overnight. The solvent was evaporated and water was added to the mixture. The mixture was made alkaline by NaOH, extracted with ethyl acetate, washed with brine, and dried with Na₂SO₄. The solvent was evaporated, and the residue was recrystallized from hexane-ethyl acetate to give the product 10 as white needles (73 %, 29.3 mmol).
m.p. 140-142 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 1.45\) (t, \(J 7.1\), 2H), 4.46 (q, \(J 7.1\), 2H), 7.57 (dd, \(J 8.3\), 4.4, 1H), 8.06 (d, \(J 9.3\), 1H), 8.12 (d, \(J 9.3\), 1H), 8.65 (dd, \(J 8.3\), 1.6, 1H), 8.66 (s, 1H), 8.98 (dd, \(J 4.4\), 1.6, 1H); IR (KBr) 1717, 1563, 1509, 1289, 1254, 1080, 1017, 758, 741 cm\(^{-1}\); Anal. Calcd for C\(_{14}\)H\(_{11}\)NO\(_2\)S: C, 65.35; H, 4.31; N, 5.44%. Found: C, 65.39; H, 4.29; N, 5.43.

\textbf{2-(Hydroxymethyl)thieno[3,2-f]quinoline (11).}

To a stirred solution of ester 10 (1.29 g, 5.0 mmol) in 30 mL of dry THF was added LiAlH\(_4\) (0.19 g, 5.0 mmol) at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction was quenched by careful addition of water, and the reaction mixture was filtrated through celite pad, and successively washed with CHCl\(_3\). The organic phase was separated and washed with brine, and dried over Na\(_2\)SO\(_4\). The solvent was evaporated, and the residue was recrystallized from ethyl acetate to give alcohol 11 as white needles (0.98 g, 91%).
m.p. 164-165 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 2.63\) (br s, 1H), 5.05 (s, 2H), 7.49 (dd, \(J 4.3\), 8.3, 1H), 7.78 (s, 1H), 7.94 (d, \(J 8.9\), 1H), 8.03 (d, \(J 8.9\), 1H), 8.52 (dd, \(J 8.3\), 1.7, 1H), 8.91 (dd, \(J 4.3\), 1.7, 1H); IR (KBr) 3399, 3252, 2953, 1610, 1528, 1483, 1275, 1179, 1032, 600 cm\(^{-1}\); Anal. Calcd for C\(_{12}\)H\(_9\)NOS: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.86; H, 4.20; N, 6.46.

\textbf{2-(Chloromethyl)thieno[3,2-f]quinoline (12).}

To a stirred suspension of alcohol 11 (0.65 g, 3 mmol) in 50 mL of dry benzene was added thionyl chloride (0.45 mL, 6 mmol) and triethylamine (2 mL, 15 mmol), and the reaction mixture was heated under reflux for 2 h. Then the dark brown suspension was filtrated through celite pad and washed with benzene. The filtrate was successively washed with water and brine, and dried over Na\(_2\)SO\(_4\). The solvent was evaporated, and the residue was chromatographed on silica gel using hexane-ethyl acetate (3:1) as eluent to give chloride 12 as a white solid (0.52 g, 74%).
m.p. 104-106 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 4.98\) (s, 2H), 7.52 (dd, \(J 8.4\), 4.3, 1H), 7.94 (s, 1H), 8.00 (d, \(J 9.2\), 1H), 8.06 (d, \(J 9.2\), 1H), 8.56 (dd, \(J 8.4\), 1.8, 1H), 8.95 (dd, \(J 4.3\), 1.8, 1H); IR (KBr) 3023, 1568, 1495, 1252, 1186, 1153, 803, 704, 658, 642 cm\(^{-1}\); Anal. Calcd for C\(_{12}\)H\(_8\)C\(_1\)NS: C, 61.67; H, 3.45; N, 5.99. Found: C, 61.55; H, 3.44; N, 5.95.

\textbf{(2-Thieno[3,2-f]quinolylmethyl)triphenylphosphonium Chloride (4).}

To a stirred solution of chloride 12 (0.52 g, 2.23 mmol) in 10 mL of dry benzene was
added triphenylphosphine (1.75 g, 6.69 mmol), and the mixture was heated under reflux overnight. The resulting precipitation was filtrated and washed with dry ether, and the filtrate was concentrated in vacuo. The residue was dissolved in 5 mL of dry benzene, and the mixture was heated under reflux for additional 2 days. The resulting precipitation was filtrated again, and washed with dry ether. The combined phosphonium salt was dried in vacuo (1.04 g, 94%), and was used without further purification.

m.p. 238-240 °C(dec.); $^1$H NMR (CDCl$_3$) δ 6.29 (s, 1H), 6.36 (s, 1H), 7.46 (dd, J8.4, 4.4, 1H), 7.56-7.93 (m, 17H), 8.33 (d, J 3.8, 1H), 8.56 (dd, J 8.4, 1.5, 1H), 8.88 (dd, J 4.4, 1.5, 1H); IR (KBr) 3400, 1491, 1439, 1111, 839, 818, 720, 689, 581, 509 cm$^{-1}$; Anal. Calcd for C$_{30}$H$_{23}$ClNPS·2H$_2$O: C, 67.73; H, 5.12; N, 2.63. Found: C, 68.30; H, 5.09; N, 2.61.

To a stirred suspension of alcohol 11 (1.38 g, 5.90 mmol) in dry CH$_2$Cl$_2$ was added PDC (4.44 g, 11.8 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was filtrated through celite pad, and the filtrate was washed with water and brine, and dried over Na$_2$SO$_4$. The solvent was evaporated, and the residue was recrystallized from ethyl acetate to give aldehyde 6 as white needles (0.89 g, 65%).

m.p. 212-213 °C; $^1$H NMR (CDCl$_3$) δ 7.61 (dd, J8.2, 4.4, 1H), 8.11 (d, J 9.3, 1H), 8.17 (d, J 9.3, 1H), 8.63 (s, 1H), 8.66 (dd, J 8.2, 1.7, 1H), 9.01 (dd, J 4.4, 1.7, 1H), 10.20 (s, 1H); IR (KBr) 1671, 1505, 1489, 1370, 1242, 1192, 1163, 810, 666, 486 cm$^{-1}$; Anal. Calcd for C$_{12}$H$_7$NOS: C, 67.59; H, 3.31; N, 6.57. Found: C, 67.48; H, 3.23; N 6.53.

Method A (from 3 and 4): To a stirred solution of aldehyde 3 (0.83 g, 2 mmol) in 20 mL of THF and 20 mL of methanol were successively added phosphonium salt 4 (0.99 g, 2 mmol) and potassium t-butoxide (0.45 g, 4 mmol) in 5 mL of methanol at 0 °C, and the mixture was stirred overnight at room temperature. The resulting precipitate was filtrated, and sufficiently washed with methanol and benzene. The crude olefin 2 was dried in vacuo, and used without further purification.

To a stirred suspension of olefin 2 in 30 mL of dry CH$_2$Cl$_2$ were added 2,6-lutidine
(0.48 mL, 4 mmol) and triisopropylsilyl trifluoromethanesulfonate (0.90 mL, 3.3 mmol) at −20 °C, and the mixture was stirred overnight at room temperature. The resulting orange solution was washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was chromatographed on silica gel to give the silylated product 13 as a yellow solid (1.26 g, 84%).

**Method B** (from 5 and 6): Reaction procedure is almost the same as described above. From aldehyde 6 (0.13 g, 0.6 mmol) and phosphonium salt 5 (0.42 g, 0.6 mmol), olefin 13 was obtained as a yellow solid (0.34 g, 76%).

m.p. 135-137 °C (dec.); ¹H NMR (CDCl₃) δ 0.83 (s, 3H), 0.85-2.36 (m, 8H) 1.03 (s, 3H), 1.14 (d, J 5.2, 18H), 1.21 (s, 3H), 4.03-4.22 (m, 2H), 6.97(d, J 6.0, 1H), 7.34 (s, 2H), 7.52 (dd, J 8.4, 4.4, 1H), 7.61 (s, 1H), 7.76-8.06 (m, 6H), 8.58 (dd, J 8.4, 1.5, 1H), 8.94 (dd, J 4.4, 1.5, 1H); IR (KBr) 2944, 2865, 1653, 1516, 1460, 1364, 1053, 884, 830, 681 cm⁻¹; Anal. Calcd for C₄₃H₅₀N₂O₂SiS₃: C, 68.76; H, 6.71; N, 3.73. Found: C, 68.50; H, 7.12; N, 3.37.


**Method A**: Olefin 13 (0.20 g, 0.27 mmol) and iodine (0.11 g, 0.40 mmol) were dissolved in 1.6 L of benzene, and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (9.3 mL, 133 mmol) was added to the mixture and the resulting solution was irradiated for 15 h at room temperature with argon flow. The reaction mixture was washed with aqueous Na₂S₂O₅, aqueous NaHCO₃ and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was chromatographed on silica gel using hexane-ethyl acetate to give diastereomeric mixture (37:63) of heterohelicene 14 as a yellow solid (0.14 g, 73%).

**Method B**: Olefin 13 (0.20 g, 0.27 mmol) and iodine (0.11 g, 0.40 mmol) were dissolved in 1.6 L of benzene, and argon was bubbled through the stirred solution for 2 h before photo-irradiation. Propylene oxide (9.3 mL, 133 mmol) was added to the mixture and the resulting solution was irradiated at room temperature with argon flow. When most of the substrate was consumed (judged by TLC), the irradiation was stopped and the additional substrates, olefin 13 and iodine were dissolved in the above reaction mixture. The procedures were repeated six times, and olefin 1.20 g (1.62 mmol) of 13 was used in total. The reaction time was varied in each step. While the substrate was consumed by irradiation for 10 h in the first step, it took 24 h
to complete the reaction in the final one. The diastereomeric mixture (37:63) of heterohelicene 14 was obtained as a yellow solid (0.70 g, 59%).


To a stirred solution of diastereomeric mixture of helicene 14 (0.67 g, 0.89 mmol) in 10 mL of THF was added TBAF (1.8 mL of a 1 M solution in THF) at room temperature, and the mixture was stirred overnight. The reaction mixture was concentrated in vacuo, and the residue was dissolved in CHCl₃, washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was chromatographed on silica gel to give the desilylated helicene 15 as a yellow solid (0.50 g, 96%).

\[ N\cdot-t\cdot Butoxycarbonyl\cdot N\cdot[(1R,2S,3R,4S)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-f]quinoline-2-carboxamide \] (16).

To a stirred solution of diastereomeric mixture of helicene 15 (0.50 g, 0.85 mmol) in 20 mL of dry CH₂Cl₂ were added 4-dimethylaminopyridine (DMAP) (0.21 g, 1.7 mmol) and di-t-butyl dicarbobate (0.74 g, 3.4 mmol) at room temperature, and the mixture was stirred overnight. The reaction mixture was washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was passed through the short column on silica gel using hexane-ethyl acetate (2:1) as eluent to give a diastereomeric mixture of the t-Boc-helicene 16 as a yellow solid (0.49 g, 83%). The column chromatography on silica gel using hexane-ethyl acetate (10:1 - 5:1) as eluent gave both of the pure diastereomer \((P)-(+)-16\) (0.12 g, 0.17 mmol) and \((M)-(−)-16\) (0.20 g, 0.29 mmol) as optically pure form.

\((P)-(+)-16\) : m.p. 156-158 °C: ³¹H NMR (CDCl₃) δ 0.88 (s, 3H), 0.89 (s, 3H), 1.05-1.83 (m, 5H), 1.07 (s, 3H), 1.35 (s, 9H), 3.99 (t, J 8.4, 1H), 4.70 (d, J 8.4, 1H), 5.73 (d, J 7.7, 1H), 6.62 (dd, J 8.8, 4.2, 1H), 6.89 (s, 1H), 7.77 (dd, J 8.8, 1.6, 1H), 7.97 (d, J 8.4, 1H), 8.08 (d, J 8.4, 1H), 8.10 (d, J 8.4, 1H), 8.15 (d, J 8.4, 1H), 8.28 (s, 2H), 8.71 (dd, J 4.2, 1.6, 1H); IR (KBr) 2950, 2360, 1748, 1645, 1541, 1470, 1277, 1254, 1150, 1102, 805 cm⁻¹; Anal. Calcd for C₃₉H₃₆N₂O₄S₃: C, 67.60; H, 5.24; N, 4.04. Found: C, 67.86; H, 5.15; N, 3.91.

\((M)-(−)-16\) : m.p. 160-162 °C: ³¹H NMR (CDCl₃) δ 0.67 (s, 3H), 0.72-1.02 (m, 1H), 0.79 (s, 3H), 0.92 (s, 3H), 1.09 (s, 9H), 1.05-1.89 (m, 4H), 4.07 (t, J 7.7. 1H), 4.61 (d,
J 7.7, 1H), 5.16 (d, J 8.1, 1H), 6.65 (dd, J 8.2, 4.2, 1H), 6.68 (s, 1H), 7.42 (dd, J 8.2, 1.6, 1H), 8.02 (d, J 8.6, 1H), 8.08 (d, J 8.6, 1H), 8.27 (d, J 9.0, 1H), 8.35 (d, J 9.0, 1H), 8.74 (dd, J 4.2, 1.6, 1H), 9.15 (s, 2H); IR (KBr) 2957, 2360, 1748, 1665, 1655, 1522, 1275, 1254, 1155, 806 cm⁻¹; Anal. Calcd for C₃₉H₃₆N₂O₄S₃: C, 67.60; H, 5.24; N, 4.04. Found: C, 67.38; H, 5.24; N, 3.93.


To a stirred solution of ethanethiol (0.13 mL, 2 mmol) in 5 mL of dry THF was added butyllithium (0.67 mL of a 1.50 M solution in hexane, 1 mmol) at —78 °C, and the mixture was allowed to warm to room temperature and stirred for 1 h at room temperature. To the resulting white suspension was added t-Boc-helicene 17 (47.6 mg, 0.069 mmol) in 5 mL of dry THF at room temperature, and the mixture was stirred overnight. The reaction mixture was washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) to give thioester 17 as a yellow solid (29.9 mg, 89%).

m.p. 194-195 °C; ¹H NMR (CDCl₃) δ 1.21 (t, J 7.4, 3H), 2.85 (q, J 7.4, 2H), 6.64 (dd, J 8.6, 4.2, 1H), 7.13 (d, J 0.9, 1H), 7.75 (dd, J 8.6, 1.3, 1H), 8.01 (dd, J 8.6, 0.9, 1H), 8.11 (d, J 8.6, 1H), 8.12 (d, J 8.4, 1H), 8.17 (d, J 8.4, 1H), 8.28 (d, J 8.9, 1H), 8.31 (d, J 8.9, 1H), 8.70 (dd, J 4.2, 1.3, 1H); IR (KBr) 1657, 1626, 1495, 1298, 1190, 1138, 866, 823, 804, 790 cm⁻¹; Anal. Calcd for C₂₅H₁₅NOS₄: C, 64.30; H, 3.11; N, 2.88. Found: C, 64.25; H, 3.16; N, 2.92; (P)-(+) 17 [α]D = +2670 (c 0.0500, CHCl₃), (M)-(−) 17 [α]D = −2620 (c 0.0499, CHCl₃).


To a stirred solution of the thioester 17 (28.0 mg, 0.065 mmol) in 5 mL of dry THF was added LiAlH₄ (10 mg, 0.26 mmol) at room temperature, and the mixture was for 1 h at room temperature. The reaction was quenched by careful addition of water, and the reaction mixture was filtrated through celite pad. The organic phase was separated from the filtrate, and washed with water and brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was chromatographed on silica gel using hexane-ethyl acetate (1:2) to give alcohol 1 as a yellow solid (23.8 mg, 85%).

m.p. 246-247 °C; ¹H NMR (CDCl₃) δ 1.79 (br s, 1H), 4.18 (d, J 14.4, 1H), 4.26 (d, J 14.4, 1H), 6.19 (s, 1H), 6.66 (dd, J 8.5, 4.3, 1H), 7.79 (dd, J 8.5, 1.6, 1H), 7.95 (d,
J 8.0, 1H), 7.99 (d, J 8.0, 1H), 8.11 (s, 2H), 8.21 (d, J 8.9, 1H), 8.27 (d, J 8.9, 1H), 8.69 (dd, J 4.3, 1.6, 1H); IR (KBr) 3220, 2800, 1495, 1298, 1154, 1127, 1105, 1044, 812, 779 cm⁻¹; Anal. Calcd for C₂₅H₁₄NOS₃: C, 67.42; H, 3.06; N, 3.28. Found: C, 67.35; H, 3.00; N, 3.16; (P)-(+) - 1: [α]D = +2150 (c 0.0503, CHCl₃), (M) - (−) - 1: [α]D = −2140 (c 0.0503, CHCl₃).

Structure Solution and Refinement of (PM) - (±) - 1

A crystal of dimensions 0.40 × 0.06 × 0.40 mm was used for X-ray crystallography. Crystal data: C₂₅H₁₄NOS₃Cl₃, M = 546.93, crystal system, monoclinic, space group, P2₁/a (#14), a = 7.568(3), b = 20.912(2), c = 15.031(3) Å, α = 100.93(3)°, V = 2335.9(9) Å³, F(000) = 1112.00, Z = 4, μ = 62.26 cm⁻¹, Dc = 1.555 gcm⁻³. All measurements were made on a Rigaku AFC7R diffractometer with Cu-Kα radiation and a 12kW rotating anode generator. The data were collected at a temperature of 20 ± 1 °C using θ–2θ scan technique to a maximum 2θ value of 120.1°. Of the 3899 reflections which were collected, 3596 were unique (Rint = 0.030). The structure was solved by direct methods and expanded using Fourier techniques (SAPI91). Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final cycle of the full-matrix least-squares refinement was based on 2286 observed reflections (I > 3.00σ(I)) and 263 variable parameters and converged (largest parameter was 2.23 times its end) with unweighted and weighted agreement factors of R = 0.113 and Rw = 0.156, respectively. The weighting scheme was based on counting statics and a included a factor (ρ=0.020) to downweight the intense reflections. Neutral atom scattering factors were taken from Cromer and Waber. Anomalous dispersion effects were included in Fcalc; the values for Δf’ and Δf’’ were those of Creagh and McAuley. The values for the mass attenuations were those of Creagh an Hubbel. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

References and Notes


18) The ratio of the diastereoisomers was determined by HPLC using Shim-Pack CLC-SIL(M) (eluent : hexane/ethanol = 100:3).


20) The ratio of the diastereoisomers was determined by HPLC using Shim-Pack CLC-SIL(M) (eluent : hexane/ethanol = 100:5).


22) The optical purities of the enantiomers were determined by HPLC using Sumichiral OA-2000I (eluent : hexane/1,2-dichloroethane/methanol = 100:100:3).


Chapter 4  A Novel Route to Optically Active Disubstituted Heterohelicene via Biaryl- and Carbonyl coupling Reactions.

Abstract
A new non-photochemical synthesis of optically active disubstituted heterohelicene is described. Directed metalation was accomplished at the 1-position of (S)-2-(4-isopropyloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']dithiophene was accomplished by the use of BuLi in ether to give the organolithium species, which upon treatment with iodine and chlorotributyltin, gave (S)-1-iodo-2-(4-isopropyloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']dithiophene and (S)-1-tributylstannyl-2-(4-isopropyloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']-dithiophene in high yields. Several types of asymmetric coupling reactions between them and the following separation by column chromatography on silica gel gave the optically pure biaryl compound. The intramolecular McMurry coupling reaction gave optically pure 2,13-dimethyl[7]thiaheterohelicene.

Introduction
Since the first synthesis and optical resolution of hexahelicene ([6]helicene) by Newman in 1955, the helical aromatic molecules have received considerable attention because of unique non-planar π-electron system and of their very high rotational values. In the synthesis of these overcrowding aromatic molecules, oxidative photocyclization of 1,2-diarylethylenes is a crucial step, but the process has several drawbacks and limitations: (i) The reaction usually requires dilute conditions in order to prevent photodimerizations. (ii) The products usually absorb more strongly than do the olefins under the UV irradiation. (iii) The oxidative photocyclization reaction is not compatible with acid sensitive functional groups because of generation of HI during dehydrogenation of the corresponding dihydro intermediates by I₂ and (4) the olefins having nitro and amino functional groups are not employed for photocyclization because the singlet electronic state, which leads to ring closure, decays by the S₁→T₁ intersystem crossing. Several non-phocyclization methods for synthesis of helicenes have been reported, including the Friedel-Crafts acylation, the intramolecular oxidative cyclization, the cyclization of
ammonium or phosphonium salts, the acid or base-catalyzed condensation reactions. Katz and his co-workers have recently found an efficient non-photocyclization procedure using benzoquinone as a dienophile in the Diels-Alder reaction. They obtained optically active helical quinone using (−)-camphanoyl chloride as a chiral auxiliary for optical resolution. However, there is still a need for complementary methods which proceed under mild conditions and extend the range of application.

This chapter describes a non-photochemical route to bifunctionalized heterohelicene, which utilizes the coupling reaction between two aryl units, 4 and 5, and then the intramolecular McMurry coupling between the R³ and R⁴ substituents of the biaryl skeleton 3 (Scheme 1; path b). In photochemical pathway (path a), the two aryl moieties at first connected at R³ and R⁴ by a vinylene bridge, and the resulting 1,2-diarylethylene 2 are subjected to cyclization between the R² and R⁵ groups.

Scheme 1

Our initial experiments aimed at the lithiation of the 3-position of 2-formyl-7-methylbenzo[1,2-b:4,3-b’]dithiophene\(^{11}\) (6) using lithiated \(N,N,N’\)-trimethyl-ethylenediamine (LTMDA)\(^{12}\) were unsuccessful and aldehyde 6 was recovered. The lithiation of methoxymethyl ether 7 by butyllithium in THF also did not produce 3-lithio species, and only the starting material 7 was obtained (Scheme 2).\(^{12}\) However, we observed that the introduction of an ortho-directing oxazoline moiety\(^{12}\) at the 1-position of 7-methylbenzo[1,2-b:4,3-b’]dithiophene (8) led to a facile generation of the organolithium species 9. The oxazoline 8 was prepared from the corresponding cyanide 13,\(^{15}\) which was readily available from 10 by methylalation, iodination and subsequent cyanidation in 74% overall yield. Treatment of oxazoline 8 with BuLi in ether at \(-78^\circ\text{C}\), followed by trapping the lithium anion with iodine and chlorotributyltin, gave iodide 14 and tin compound 15 in 95% and 91% yields, respectively.

Scheme 2

![Scheme 2](image-url)
Scheme 3

Reagents and conditions: (a) (i) BuLi, THF; (ii) Mel; (b) BuLi, THF; (ii) iodine; (c) copper(I) cyanide, DMF, 74% from 10; (d) 2-amino-2-methyl-1-propanol, cat. zinc chloride, chlorobenzene, 95%; (e) (i) BuLi, ether; (ii) iodine, 95%; (f) (i) BuLi, ether; (ii) chlorotributyltin, 91%; (g) cat. PdCl₂(PPh₃)₂, THF, 62%; (h) TFA, sodium sulfate, THF, H₂O; (i) acetic anhydride, pyridine, CH₂Cl₂; (j) LiAlH₄, THF, 71%; (k) PCC, CH₂Cl₂, 94%; (l) TiCl₃·DME₁.₅, Zn-Cu, DME, 78%.
The cross-coupling reaction\textsuperscript{16} between 14 and 15 smoothly proceeded in the presence of 5 mol\% of PdCl\(_2\)(PPh\(_3\))\(_2\) to afford the biaryl compound 16 in 62\% yield. The oxazoline moiety was transformed into the corresponding dialdehyde 18 via oxidation of diol 17 by PCC.\textsuperscript{14} Finally, the intramolecular McMurry coupling reaction\textsuperscript{17} using TiCl\(_3\)/Zn-Cu gave 2,13-dimethyl[7]thiaheterohelicene 19 in 32\% yield. When TiCl\(_3\)-DME\(_{1.5}\)/Zn-Cu\textsuperscript{18} was used in the McMurry coupling reaction, the yield of 19 was increased to 78\%. The protons (\(\delta\) 6.43) on C(1) and C(14) of 19, and those (\(\delta\) 5.96) on C(8) and C(8') of 18 resonate at higher field than the proton (\(\delta\) 7.32) on C(1) of 11. This implies that the former protons are in the region of a shielding zone exerted by the helical aromatic structure.\textsuperscript{23}

**Synthesis of Optically Active Disubstituted [7]Thiaheterohelicene**

In order to apply this non-photochemical route to the synthesis of optically active helicenes, chiral oxazoline derivatives were subjected to the coupling reaction. Chiral oxazoline 20 were prepared from nitrile 13 by use of L-valinol in 89\% yield.

---

**Scheme 4**

- **Reagents and conditions:** (a) L-Valinol, cat. zinc chloride, chlorobenzene, 89\%; (b) (i) BuLi, ether; (c) iodine, 91\%; (d) chlorotributyltin, 79\%
When the oxazoline 20 was treated with BuLi under the same condition as for the lithiation of achiral derivative 8, litho-species 21a was readily generated, which upon treatment with iodine and chlorotributyltin, iodide 21b and tin compound 21c were obtained in 91% and 79% yields, respectively. The results of asymmetric coupling reactions using the oxazoline derivatives 21a-c are shown in Table 1. The asymmetric Ullmann coupling\(^\text{19}^\text{1}\) of iodide 21b smoothly proceeded in the presence of activated copper powder\(^\text{20}\) in DMF at 100 °C, and a mixture of the diastereoisomers of biaryl 22 was obtained in nearly quantitative yield. The ratio of the diastereomers was confirmed as 2.0:1 by HPLC analysis.\(^\text{21}\) Recrystallization of the diastereomeric mixture of 22 from hexane-ethyl acetate gave diastereomERICally pure compound (>98% de) in 41% yield. The Stille coupling between the iodide 21b and the tin

Table 1

<table>
<thead>
<tr>
<th>Method</th>
<th>(R^2)</th>
<th>(R^5)</th>
<th>Mediator</th>
<th>Solvent</th>
<th>Yield(%)</th>
<th>(22a : 22b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>I</td>
<td>I</td>
<td>Cu</td>
<td>DMF</td>
<td>99</td>
<td>2.0:1</td>
</tr>
<tr>
<td>B</td>
<td>SnBu(_3)</td>
<td>I</td>
<td>PdCl(_2)(PPh(_3))(_2)</td>
<td>THF</td>
<td>68</td>
<td>2.9:1</td>
</tr>
<tr>
<td>C</td>
<td>Li</td>
<td>Li</td>
<td>CuCl(_2)</td>
<td>ether</td>
<td>51(^\text{a})</td>
<td>1:1.4</td>
</tr>
</tbody>
</table>

\(^{a}\) 22% of the protonated product (20) was obtained.
Reagents and conditions: (a) TFA, sodium sulfate, THF, H₂O; (b) acetic anhydride, pyridine, CH₂Cl₂; (c) silica gel column chromatography, 96%; (d) LiAlH₄, THF, 86%; (e) PCC, CH₂Cl₂; (f) TiCl₃·DME₁.₅, Zn-Cu, DME.
derivative 21c catalyzed by PdCl₂(PPh₃)₂ gave a diastereomeric mixture of 22 (2.9:1) in 68% yield. It is interesting to note that the stereoselectivity was found to be reversed (the ratio of the diastereomers 1:1.4), when the coupling reaction of the organolithium compound 21a was carried out by CuCl₂.²² Although the mechanistic details of the stereoselectivity are not clear at present, this provides a very useful method for the preparation of sterically hindered diaryl compounds.

In order to obtain optically pure biaryl compound, the diastereomeric mixture of bisoxazoline 22 was transformed into ester amide 23 by partial hydrolysis with trifluoroacetic acid and following acetylation with acetic anhydride. Diastereomers of ester amide 23 were readily separated by column chromatography on silica gel using chloroform-ethanol as an eluent. Treatment of 23a derived from the major isomer in the Ullmann coupling gave the corresponding diol (−)-17 by LiAlH₄. The optical rotation of (−)-17 was [α]ᵣ = −48.6 (c 1.00, CHCl₃), whose absolute value was good agreement with that of the enantiomer derived from minor diastereomer 23b.

![HPLC chromatograms of heterohelicenes 19](image)

**Figure 1** HPLC chromatograms of heterohelicenes 19

Column: CHIRALCEL OD (4.6 mm i.d. × 25 cm)
Eluent: hexane/ethanol (100:0.2)
Flow rate: 1 mL/min, Detector: 254 nm
([α]₀ +49.3 (c 1.01, CHCl₃). The diol (−)- and (+)-17 were oxidized by PCC to afford the corresponding dialdehyde (−)- and (+)-18, and each optical rotation was [α]₀ −325 (c 1.01, CHCl₃) and [α]₀ +320 (c 1.01, CHCl₃), respectively. The intramolecular McMurry coupling reaction using TiCl₃-DME₅/Zn-Cu gave (+)-19 in 52% from (−)-18 and (−)-19 in 53% from (+)-18. Since it is known that all of the levorotatory helicenes have the same helicity M, and vice versa,²²³ the absolute configurations of the obtained dimethyl helicene (−)- and (−)-19 were confirmed as P and M, respectively. The optical purity of the helicene (P)-(+) and (M)-(−)-19 are determined as >99% (Figure 1) by HPLC analysis using Chiralcel OD.²⁴ The results indicate that all of the biaryl and helicene derivatives do not racemize in these reaction conditions. If the C-C bond of the biaryl compounds would not rotate during the McMurry coupling reaction, the absolute configuration of the biaryl compounds 23a, (−)-17 and (−)-18 derived from major diastereoisomer 22a in Ullmann coupling were confirmed as (S). The assignment agrees with the results of the asymmetric Ullmann coupling of naphtyloxazoline bromide reported by Meyers,¹⁹ and this is also supported by the CD spectrum of 17, 18 and 19. The optical rotation of the dimethylheterohelicenes 19 were [α]₀ +2720 (c 0.0557, CHCl₃) and [α]₀ −2690 (c 0.0569, CHCl₃), respectively, and these values were much higher than those of biaryl derivatives 17 and 18.

![Figure 2](image-url)  
**Figure 2**  CD spectra of (S)-(−)-17 and (R)-(+)17 in chloroform
Figure 3 CD spectra of \( (S)-(\_\_)-18 \) and \( (R)-(\_\_)-18 \) in chloroform

Figure 4 CD spectra of \( (P)-(\_\_)-19 \) and \( (M)-(\_\_)-19 \) in chloroform
In summary, we have developed a practical non-photochemical method for optically active disubstituted thiaheterohelicenes using asymmetric coupling reaction and the intramolecular McMurry coupling reactions as the key steps. The methyl groups of 18 can be easily converted to other functionalities such as the bromomethyl moiety\(^{11}\) and are thus appropriate for further synthetic studies. The high diastereoselectivities of the coupling reactions should be developed, when the isopropyl group in the oxazoline ring are converted into more hindered alkyl groups.\(^{19}\)

**Experimental**

**General.** All reactions were carried out under an atmosphere of argon. THF and ether were distilled under argon atmosphere from sodium benzophenone ketyl immediately before use. Dichloromethane and benzene were distilled from calcium hydride and stored over 4Å molecular sieves. The hexane solution of butyllithium (Kanto Chemicals) was titrated using diphenylacetic acid.\(^{25}\) Melting points were determined on a Yanagimoto hotstage apparatus and are not corrected. IR spectra were recorded on a SHIMADZU FT IR DR 8000/8100 infrared spectrometer. NMR spectra were obtained with a Varian Gemini-200 (200 MHz) spectrometer in CDCl\(_3\) with tetramethylsilane as an internal standard, and J values are given in Hz. The CD spectra are recorded on a JASCO Model J-720W recording spectropolarimeter in CHCl\(_3\). Optical rotation was measured in 1 dm lengths cells of 10cm\(^3\) on a JASCO Model DIP-181 polarimeter; \([\alpha]_D\) values are given in 10\(^{-1}\)deg\-cm\(^2\)\-g\(^{-1}\). Thin layer chromatography was performed by using Merck precoated silica gel sheets 60F-254. Silica gel (Wakogel) of the size 100-200 mesh was used for column chromatography. Elemental analysis were performed by the Microanalytical Laboratory, operated by the Institute for Chemical Research, Kyoto University.

**2-Methylbenzo[1,2-b:4,3-b']dithiophene (11).**

To a stirred solution of 10 (1.90 g, 10 mmol) in 50 mL of dry THF was added butyllithium (10.2 mmol, 6.6 mL of 1.53 M solution in hexane) at −78 °C under argon, and the mixture was stirred for 1h at −78°C. To the resulting yellow solution, 0.69 mL of methyl iodide (11 mmol) in 5 mL of THF was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride, and the organic phase was
separated, washed with brine, dried over Na$_2$SO$_4$. The solvent was evaporated, and
the residue was chromatographed on silica gel using hexane as the eluent, and the
crude product was obtained as white solid (2.00 g, crude yield 98 %). Although
NMR spectrum indicate the existence of a slight amount (<10%) of dimethyl
derivative, this compound was used in the following reaction without further
purification.

2-Iodo-7-Methylbenzo[1,2-b:4,3-b']dithiophene (12).
To a stirred solution of 11 (2.00 g, crude 9.8 mmol) in 50 mL of dry THF was added
butyllithium (11 mmol, 7.0 mL of 1.53 M solution in hexane) at $-78 \ ^\circ C$ under argon,
and the mixture was stirred for 1h at $-78 \ ^\circ C$. To the resulting yellow solution, 2.92
g of iodine (11.5 mmol) in 5 mL of THF was added. The reaction mixture was
allowed to warm to room temperature and stirred for 2 h. The reaction was
quenched by saturated aqueous ammonium chloride. The organic phase was
separated, subsequently washed with aqueous Na$_2$SO$_3$, brine, dried over Na$_2$SO$_4$.
The solvent was evaporated, and the residue was chromatographed on silica gel using
hexane as the eluent to give the crude product as white solid (3.11 g, crude yield 96 %).
Although the unseparatable impurity still remains in the obtained white solid, this
compound was used in the following reaction without further purification.

7-Methylbenzo[1,2-b:4,3-b']dithiophene-2-carbonitrile (13).
A mixture of 12 (3.11g, crude 9.4 mmol) and copper(I) cyanide (1.10 g, 11 mmol) in
15 mL of dry DMF was heated with stirring at 100 \ ^\circ C for 12 h. The resulting dark
brown suspension was poured into excess of aqueous ammonium solution to
decompose the complex, and was diluted with ethyl acetate. The organic phase was
separated, washed with brine, and dried over Na$_2$SO$_4$. The solvent was evaporated, and the residue was recrystallized from hexane-ethyl acetate to give nitrile 13 as white
needles (1.70 g, 74 % from 10).
m.p. 120-122 \ ^\circ C; \ ^1H NMR (CDCl$_3$) $\delta$ 2.69 (d, J 1.2, 3H), 7.36 (br s, 1H), 7.67 (d, J 9.1, 1H), 7.86 (d, J 9.1, 1H), 8.14 (s, 1H); IR (KBr) 2210, 1339, 1186, 1117, 858,
833, 779, 534, 478, 448 cm$^{-1}$; Anal. Calcd for C$_{12}$H$_7$NS$_2$: C, 62.85; H, 3.08; N, 6.11.
Found: C, 62.77; H, 2.93; N, 6.26.

2-(4,4-dimethyloxazolin-2-yl)-7-Methylbenzo[1,2-b:4,3-b']-dithiophene (8).
In a 50 mL two-necked flask, zinc chloride (60 mg, 0.44 mmol, 11 mol%) was heated
at 300 \ ^\circ C under high vacuum for 1 h and cooled under argon. After cooling to room
temperature, nitrile 13 (0.90 g, 3.92 mmol), 2-amino-2-methyl-1-propanol (0.70 g, 7.84 mmol) and chlorobenzene (10 mL) were added. The mixture was heated under reflux for 36 h. The solvent was removed under reduced pressure, and the residue was dissolved in CHCl₃. The solution was washed with brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) as eluent to give oxazoline 8 as white needles (1.12 g, 95%).

m.p. 174-176 °C; ¹H NMR (CDCl₃) δ 1.34 (s, 6H), 2.67 (d, J 1.2, 3H), 4.18 (s, 2H), 7.34 (br s, 1H), 7.68 (d, J 8.6, 1H), 7.75 (d, J 8.6, 1H), 8.13 (s, 1H); IR (KBr) 3650, 1647, 1512, 1366, 1312, 1181, 1026, 797, 702, 484 cm⁻¹; Anal. Calcd for C₁₆H₁₅NOS₂: C, 63.75; H, 5.02; N, 4.65. Found: C, 63.54; H, 4.97; N, 4.55.

1-Iodo-2-(4,4-dimethyloxazolin-2-yl)-7-Methylbenzo[1,2-b:4,3-b']dithiophene (14).

To a stirred solution of 8 (0.80 g, 2.65 mmol) in dry ether (100 mL) was added butyllithium (3.98 mmol, 2.65 mL of 1.50 M solution in hexane) at -78 °C under argon, and the mixture was stirred for 2 h at -78 °C. To the resulting yellow solution, 1.08 g of iodine (4.24 mmol) in 10 mL of ether was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by saturated aqueous ammonium chloride. The organic phase was separated, washed with aqueous Na₂SO₃, brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as eluent to give iodide 14 as white needles (1.07 g, 95%).

m.p. 157-158 °C; ¹H NMR (CDCl₃) δ 1.45 (s, 6H), 2.71 (d, J 1.1, 3H), 4.20 (s, 2H), 7.69 (d, J 8.5, 1H), 7.81 (d, J 8.5, 1H), 8.90 (br s, 1H); IR (KBr) 2980, 1649, 1489, 1348, 1289, 1034, 976, 943, 785, 484 cm⁻¹; Anal. Calcd for C₁₆H₁₄INOS₂: C, 44.97; H, 3.30; N, 3.28. Found: C, 44.61; H, 3.24; N, 3.20.

1-Tributylstannyl-2-(4,4-dimethyloxazolin-2-yl)-7-Methylbenzo[1,2-b:4,3-b']dithiophene (15).

To a stirred solution of 8 (0.85 g, 2.82 mmol) in 100 mL of dry ether was added butyllithium (4.23 mmol, 2.77 mL of 1.53 M solution in hexane) at -78 °C under argon, and the mixture was stirred for 2 h at -78 °C. To the resulting yellow solution, 1.22 mL of tributyltin chloride (4.51 mmol) in 5 mL of ether was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride. The organic
phase was separated, washed with brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was purified by GPC using CHCl₃ as eluent to give tin compound 15 as pale yellow oil (1.51 g, 91%).

1H NMR (CDCl₃) δ 0.85 (t, J 7.2, 9H), 1.22-2.13 (m, 18H), 1.43 (s, 6H), 2.66 (d, J 1.1, 3H), 4.15 (s, 2H), 7.42 (br s, 1H), 7.70 (d, J 8.6, 1H), 7.75 (d, J 8.6, 1H).

2,2′-Bis(4,4-dimethyloxazolin-2-yl)-7,7′-dimethyl-1,1′-bi[benzo-[1,2-b:4,3-b′]dithiophene] (16).

To a stirred solution of catalytic amount of PdCl₂(PPh₃)₂ (86.3 mg, 0.12 mmol, 5 mol%) in 20 mL of dry THF was added iodide 14 (1.07 g, 2.50 mmol) and tin compound 15 (1.45 g, 2.46 mmol) under argon. The mixture was heated under reflux for 60 h. The reaction mixture was diluted with ethyl acetate, washed with brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) as eluent to give biaryl 16 as a white solid (0.92 g, 62%).

m.p. 261-263 °C; 1H NMR (CDCl₃) δ 1.13 (s, 6H), 1.19 (s, 6H), 2.28 (d, J 1.1, 6H), 3.52 (d, J 8.1, 2H), 3.71 (d, J 8.1, 2H), 6.04 (br s, 2H), 7.77 (s, 4H); IR (KBr) 2971, 1636, 1499, 1308, 1188, 1124, 1034, 939, 810, 486 cm⁻¹; Anal. Calcd for C₃₂H₂₈N₂O₂S₄: C, 63.97; H, 4.70; N, 4.66. Found: C, 63.87; H, 4.73; N, 4.54.

2,2′-bis(hydroxymethyl)-7,7′-dimethyl-1,1′-bi[benzo[1,2-b:4,3-b′]dithiophene] (17).

To a stirred solution of biaryl 16 (0.79 g, 1.31 mmol) in 30 mL of THF was added 1.5 mL of water, 20 g of Na₂SO₄, and 2 mL of trifluoroacetic acid, and the suspension was stirred overnight at room temperature. After filtration, the solvent was removed under reduced pressure, and the resulting residue was dissolved in 20 mL of dry CH₂Cl₂. To the stirred solution was added 4 mL of pyridine and 4 mL of acetic anhydride, and the mixture was stirred overnight at room temperature. The reaction mixture was subsequently washed with dilute hydrochloric acid, brine, and dried over Na₂SO₄. The solvent was evaporated and dried in vacuo, and the residue was dissolved in 10 mL of dry THF. To the stirred solution was added LiAlH₄ (0.25 g, 6.55 mmol), and stirred at room temperature. The reaction was quenched by diluted HCl at 0°C, and diluted with CHCl₃. The organic phase was separated, washed with brine, and dried over Na₂SO₄. The solvent was evaporated, and the residue was passed through short column of silica gel using CHCl₃-MeOH (100:3) as
the eluent. The solvent was evaporated, and the residue was recrystallized from THF-hexane to give diol 17 as a white solid (0.44 g, 71%).
m.p. 265-268 °C (dec); $^1$H NMR (CDCl$_3$) $\delta$ 2.27 (d, J 1.1, 6H), 4.52 (d, J 12.7, 2H), 4.61 (d, J 12.7, 2H), 5.95 (br s, 2H), 7.75 (d, J 8.5, 2H), 7.82 (d, J 8.5, 2H); IR (KBr) 3260, 1398, 1335, 1125, 1020, 790, 513, 419 cm$^{-1}$; Anal. Calcd for C$_{24}$H$_{18}$O$_2$S$_4$: C, 61.77; H, 3.89; N, 0. Found: C, 61.64; H, 3.87; N, 0; (S)-(—)-17 : [\alpha]_D $-48.6$ (c 1.00, CHC1$_3$); (R-(+)-17 : [\alpha]_D +49.3 (c 1.01, CHCl$_3$).

2,2'-Diformyl-7,7'-dimethyl-1,1'-bi[benzo[1,2-b:4,3-b']-dithiophene] (18).
To a stirred solution of diol 17 (0.41 g, 0.88 mmol) in 30 mL of dry CH$_2$C1$_2$ was added PCC (0.57 g, 2.64 mmol), and the mixture was stirred for 2 h at room temperature. After filtration, the reaction mixture was washed with aqueous Na$_2$CO$_3$ solution and brine, and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was recrystallized from CHC1$_3$ to give dialdehyde 18 (0.39 g, 94%) as a yellow solid.
m.p. 280-281 °C; $^1$H NMR (CDCl$_3$) $\delta$ 2.32 (d, J 8.8, 2H), 7.96 (d, J 8.5, 2H), 9.68 (s, 2H); IR (KBr) 1660, 1566, 1483, 1246, 1207, 1124, 1073, 795, 562, 515 cm$^{-1}$; Anal. Calcd for C$_{24}$H$_{14}$O$_2$S$_4$: C, 62.31; H, 3.05. Found: C, 62.52; H, 3.00; (S)-(—)-18 : [\alpha]_D $-325$ (c 1.01, CHC1$_3$); (R)-(+)-18 : [\alpha]_D +320 (c 1.01, CHCl$_3$).

2,13-Dimethyldithieno[3,2-c:3', 2'-c']benzo[1,2-b:4,3-b']bis[1]-benzothiophene (19).
To a stirred suspension of TiCl$_3$(DME)$_{1.5}$ (0.50 g, 1.73 mmol) in 15 mL of dry DME was added zinc-copper couple (0.34 g, 5.18 mmol) under argon, and the mixture was heated under reflux for 1 h. Dialdehyde 18 (100 mg, 0.216 mmol) in 5 mL of DME was added dropwise over a period of 2 h. The reaction mixture was heated under reflux for an additional 36 h. After cooling, the reaction mixture was diluted with CHCl$_3$, and filtrated through celite pad. The filtrate was washed with water and brine, and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was chromatographed on silica gel using hexane as eluent to give heterohelicene 19 (72.5 mg, 73%) as a yellow solid.
m.p. 228-230 °C; $^1$H NMR (CDCl$_3$) $\delta$ 2.14 (d, J 8.4, 2H), 6.43 (br s, 2H), 7.85 (d, J 8.4, 2H), 7.95 (d, J 8.4, 2H), 7.98 (s, 2H); IR (KBr) 1375, 1320, 1296, 1204, 1152, 1125, 831, 776, 519, 477 cm$^{-1}$; Anal. Calcd for C$_{24}$H$_{14}$S$_4$: C, 66.94; H, 3.28. Found:
C, 67.19; H, 3.27;  \((P)-(+)\)-19 : \([\alpha]_D +2720 \text{ (c 0.0557, CHCl}_3\);  \((M)-(--)\)-19 : \([\alpha]_D -2690 \text{ (c 0.0569, CHCl}_3\).

\((S)-2-(4-\text{Isopropyloxazolin-2-yl})-7-\text{methylbenzo}[1,2-b:4,3-b']-\text{dithiophene (20).}\)

In a 50 mL two-necked flask, zinc chloride (0.15 g, 11 mmol, 11 mol\%) was heated at 300 °C under high vacuum for 1 h and cooled under argon. After cooling to room temperature, nitrile 13 (2.29 g, 10 mmol), \((S)-2-\text{amino-3-methyl-1-butanol (1.65 g, 16 mmol)}\) and chlorobenzene 30 mL were added. The mixture was heated under reflux for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in CHCl\(_3\). The solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate and brine, and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and the residue was recrystallized from hexane-ethyl acetate to give oxazoline 20 as white needles (2.80 g, 89 \%).

m.p. 138-139 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 0.96 \text{ (d, J 6.7, 3H), 1.06 (d, J 6.7, 3H), 1.84-2.01 (m, 1H), 2.67 (d, J 1.1, 3H), 4.10-4.26 (m, 2H), 4.40-4.55 (m, 1H), 7.34 (d, J 1.1, 1H), 7.68 (d, J 8.5, 1H), 7.75 (d, J 8.5, 1H), 8.12 (s, 1H); IR (KBr) 2980, 1646, 1509, 1493, 1254, 1184, 1038, 945, 860, 833, 793, 492 cm\(^{-1}\); Anal. Calcd for C\(_{17}\)H\(_{17}\)NOS\(_2\): C, 64.73; H, 5.43; N, 4.44. Found: C, 64.75; H, 5.50; N, 4.32.

\((S)-1-\text{Iodo-2-(4-isopropyloxazolin-2-yl)-7-methylbenzo}[1,2-b:4,3-b']\text{dithiophene (21b).}\)

To a stirred solution of 20 (1.58 g, 5.0 mmol) in dry ether (180 mL) was added butyllithium (8.0 mmol, 5.0 mL of 1.60 M solution in hexane) at −78 °C under argon, and the mixture was stirred for 1 h at −78 °C. To the resulting yellow suspension, 2.03 g of iodine (8.0 mmol) in 15 mL of ether was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by saturated aqueous ammonium chloride. The organic phase was separated and washed with brine, aqueous Na\(_2\)SO\(_3\), and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and the residue was recrystallized from hexane-ethyl acetate to give iodide 21b as white needles (2.01 g, 91 %).

m.p. 135-137 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 1.00 \text{ (d, J 6.7, 3H), 1.09 (d, J 6.7, 3H), 1.85-2.04 (m, 1H), 2.71 (d, J 1.1, 3H), 4.12-4.26 (m, 2H), 4.42-4.56 (m, 1H), 7.69 (d, J 8.6, 1H), 7.81 (d, J 8.6, 1H), 8.91 (d, J 1.1, 1H); IR (KBr) 1636, 1493, 1211, 1173, 1127, 1061, 980, 874, 830, 785 cm\(^{-1}\); Anal. Calcd for C\(_{17}\)H\(_{16}\)INOS\(_2\): C, 46.26; H, 3.65; N, 3.17. Found: C, 46.32; H, 3.66; N, 3.12.
(S)-1-Tributylstannyl-2-(4-isopropyloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']dithiophene (21c).

To a stirred solution of 20 (0.12 g, 0.37 mmol) in 30 mL of dry ether was added butyllithium (0.56 mmol, 0.35 mL of 1.62 M solution in hexane) at −78 °C under argon, and the mixture was stirred for 1 h at −78 °C. To the resulting yellow suspension, 0.17 mL of tributyltin chloride (0.60 mmol) in 5 mL of ether was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride. The organic phase was separated, washed with brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was purified GPC using CHCl₃ as eluent to give tin compound 21c as pale yellow oil (0.18 g, 79%).

1H NMR (CDCl₃) δ 0.79-1.95 (m, 34H), 2.65 (d, J 1.1, 3H), 4.00-4.22 (m, 2H), 4.40-4.55 (m, 1H), 7.42 (d, J 1.1, 1H), 7.70 (d, J 8.7, 1H), 7.75 (d, J 8.7, 1H).

2,2'-Bis(4-(S)-isopropyloxazolin-2-yl)-7,7'-dimethyl-1,1'-bi-benzo[1,2-b:4,3-b']dithiophene (22).

Method A (Ullmann coupling) : To a stirred solution of 21b (1.33 g, 3 mmol) in 15 mL of dry DMF was added freshly activated copper (0.96 g, 15 mmol). The mixture was heated at 100 °C for 1 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with aqueous ammonia and brine, and dried over Na₂SO₄. The ratio of the diastereomer was determined as 2.0:1 by HPLC analysis. The solvent was evaporated and the residue was recrystallized from hexane/ethyl acetate to give diastereomerically pure (>98% de) bisoxazoline 22a as pale yellow crystals (0.39 g, 41%). The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) to give 0.55 g (58%) of as a mixture of diastereoisomers (1:1.4).

Method B (Stille coupling) : To a stirred solution of catalytic amount of PdCl₂(PPh₃)₂ (20.5 mg, 29.2 µmol, 10 mol%) in 5 mL of dry THF was added iodide 21b (129 mg, 0.292 mmol) and tin compound 21c (177 mg, 0.292 mmol) under argon. The mixture was heated under reflux for 24 h. The reaction mixture was diluted with ethyl acetate, washed with brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) as eluent to give 124 mg (68 %) of bisoxazoline 22 as a mixture of diastereoisomers (2.9:1).
Method C (coupling reaction catalyzed by CuCl₂): To a stirred solution of 20 (158 mg, 0.50 mmol) in 20 mL of dry ether was added butyllithium (0.80 mmol, 0.50 mL of 1.60 M solution in hexane) at −78 °C under argon, and the mixture was stirred for 2 h at −78 °C. To the resulting yellow suspension, 0.20 g of anhydrous CuCl₂ (1.5 mmol) was added. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by saturated aqueous ammonium chloride. The organic phase was separated and washed with dilute hydrochloric acid, aqueous sodium carbonate and brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on silica gel using hexane-ethyl acetate (5:1) as eluent to give 79 mg (51%) of bisoxazoline 22 as a mixture of diastereoisomers (1:1.4).

(S)-22: m.p. 244-247 °C; ¹H NMR (CDCl₃) δ 0.69 (d, J 6.7, 6H), 0.71 (d, J 6.7, 6H), 1.48-1.69 (m, 2H), 2.26 (d, J 1.1, 6H), 3.73-4.00 (m, 6H), 5.94 (br s, 2H), 7.77 (s, 4H); IR (KBr) 2955, 1640, 1509, 1350, 1229, 1173, 1127, 1071, 980, 781 cm⁻¹; Anal. Calcd for C₃₄H₃₂N₂O₂S₄·0.5H₂O: C, 64.02; H, 5.21; N, 4.39. Found: C, 64.02; H, 5.10; N, 4.25.

Bis(2-(S)-acetamido-3-methyl-1-butyl) 7,7’-dimethyl-1,1’-bi-[benzo[1,2-b:4,3-b’]dithiophene]-2,2’-dicarboxylate (23). To a stirred solution of a mixture of diastereomers (1:1.4) of bisoxazoline 22 (0.55 g, 0.88 mmol) in 20 mL of THF was added 1 mL of water, 11 g of Na₂SO₄, and 2.2 mL (28 mmol) of trifluoroacetic acid, and the suspension was stirred overnight at room temperature. After filtration, the solvent was removed under reduced pressure and dried in vacuo, and the resulting residue was dissolved in 20 mL of dry CH₂Cl₂. To the stirred solution was added 4 mL of pyridine and 4 mL of acetic anhydride, and the mixture was stirred overnight at room temperature. The reaction mixture was washed with diluted HCl, brine, and dried over Na₂SO₄. The solvent was evaporated to give crude ester amide 22 (0.65 g, 99%). The diastereoisomer was chromatographed on silica gel using chloroform-ethanol (100:0.2) to give ester amide (R)-22 (0.33 g 50%) and (S)-22 (0.25 g, 38%) together with a small amount of mixed diastereomers (0.05 g, 8%).

(R)-22: m.p. 132-135 °C; ¹H NMR (CDCl₃) δ 0.59-0.75 (m, 12H), 0.83-0.92 (m, 2H), 1.26 (d, J 2.4, 4H), 1.49 (d, J 1.0, 6H), 2.32 (s, 6H), 3.51-3.63 (m, 2H), 4.00 (dd, J 11.5, 3.0, 2H), 4.17 (dd, J 11.5, 3.0, 2H), 4.22 (d, J 9.5, 2H), 5.78 (d, J 1.0, 2H), 7.86 (d, J 8.6, 2H), 7.92 (d, J 8.6, 2H); IR (KBr) 3293, 2961, 1701, 1655, 1540, 1489.
1291, 1229, 1115, 1084 cm$^{-1}$; Anal. Calcd for C$_{38}$H$_{40}$N$_2$O$_6$S$_4$: C, 60.94; H, 5.38; N, 3.74. Found: C, 61.48; H, 5.97; N, 3.46.

(S)-22: m.p. 115-118 °C; $^1$H NMR (CDCl$_3$) δ 0.23 (d, J 6.6, 6H), 0.47 (d, J 6.6, 6H), 0.82-0.92 (m, 2H), 1.26 (d, J 2.4, 4H), 1.96 (d, J 1.0, 6H), 2.33 (s, 6H), 3.41-3.53 (m, 2H), 3.95 (dd, J 11.6, 2.6, 2H), 4.17 (dd, J 11.6, 2.6, 2H), 4.67 (d, J 9.5, 2H), 5.84 (d, J 1.0, 2H), 7.86 (d, J 8.7, 2H), 7.93 (d, J 8.6, 2H); IR (KBr) 3293, 2961, 1699, 1653, 1545, 1489, 1289, 1229, 1115, 1082 cm$^{-1}$; Anal. Calcd for C$_{38}$H$_{40}$N$_2$O$_6$S$_4$: C, 60.94; H, 5.38; N, 3.74. Found: C, 60.76; H, 5.73; N, 3.52.

References and Notes


13) Gschwend, H. W.; Rodriguez, H. R. Org. React. 26, 1
21) The ratio of the diastereoisomers was determined by HPLC using Shim-Pack CLC-SIL(M) (eluent : hexane/2-propanol = 100:1)
24) The optical purities of the enantiomers were determined by HPLC using Chiralcel OD (eluent : hexane/ethanol = 100:0.2).
List of Publications

1. An Efficient Synthetic Method for Optically Pure Heterohelicenes
   Tanaka, K.; Osuga, H.; Suzuki, H.; Kishida, H.

2. Diastereoccontrolled Synthesis of Optically Pure Functionalized Heterohelicenes
   Tanaka, K.; Osuga, H.; Suzuki, H.

   Tanaka, K.; Osuga, H.; Shogase, Y.; Suzuki, H.

4. Enantioselective Synthesis of Helical Molecules: Lipase-Catalyzed Resolution of
   Bis(hydroxymethyl)[7]thiaheterohelicene
   Tanaka, K.; Shogase, Y.; Osuga, H.; Suzuki, H.; Nakamura, K.

5. Complexation with Helical Molecules: Helical Crystal Structure of
   Bis(hydroxymethyl)[7]thiaheterohelicene-Ethanol Clathrate

6. Synthesis and Crystal Structure of Chiral Bifunctional Helicenes with π-Deficient
   Pyridine and π-Excessive Thiophene Units
   Tanaka, K.; Kitahara, Y.; Suzuki, H.; Osuga, H.; Kawai, Y.

   *Enantiomer* in press.

8. A Novel Route to Disubstituted [7]Thiaheterohelicene via Biaryl- and Carbonyl-
Coupling Reactions
Tanaka, K.; Suzuki, H.; Osuga, H.

9. Practical Synthesis of Optically Pure Bifunctionalized Heterohelicenes
Osuga, H.; Suzuki, H.; Tanaka, K.

**Other Publications**
1. 総説 カルボヘリセン、ヘテロヘリセンおよびその類縁化合物－合成と反応
有機合成化学協会誌 **1994**, 52, 1020.
大須賀秀次、鈴木仁美

2. Stereocontrolled Diels-Alder Reactions with Chiral Tricyclic Oxazolidinones
Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H.

3. Stereocontrolled Cyclopropanation of α,β-Unsaturated Carboxamides Derived from Bicyclic Amino Alcohols
Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H.
Acknowledgements

I would like to express grateful acknowledgements to Professor Hitomi Suzuki and Associate Professor Kazuhiko Tanaka for their continuous guidance, discussion and encouragement during the course of these works. I also wish to thank Dr. Yoshihiro Matano and Dr. Naoki Komatsu for their helpful suggestion and discussion.

I wish gratefully to express appreciation to Associate Professor Kaoru Nakamura, Institute for Chemical Research, Kyoto University, for helpful suggestion and discussion on the lipase-catalysed reaction. I deeply thank Dr. Yasushi Kawai, Institute for Chemical Research, Kyoto University, for X-ray structure analysis and his valuable suggestion. I wish to thank Mr. Keisuke Imai, Fuzisawa Pharmaceutical Co., Ltd., for X-ray structure analysis. I wish to express appreciation to Mr. Hiroshi Kishida, Sumitomo Chemical Co., Ltd., for HPLC analysis. I also thank Mrs. Toshiko Hirano for elemental analysis.

I am also grateful to all the past and present members of the laboratory for their assistance, especially Dr. Takashi Murashima and Dr. Toshihiro Murafuji for their useful suggestions and encouragements. I am grateful to Mr Koji Koyama, Miss Yuka Shogase, Mr. Kazuyuki Somemiya, graduate students Yoshinori Kitahara, Takuji Kume, and undergraduate student Tadashi Takimoto for their useful suggestions and kind cooperation. I wish to thank graduate students Takeji Enya, Tohru Ikegami, Hajime Abe, Tadashi Mori, and Takehiko Kawakami for their so kind cooperation.