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京大附図

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)

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General Introduction

Helical structures are often encountered in natural products such as polyamiloise, polypeptides and nucleic acids, which are stabilized through hydrogen bonds, disulfide linkages, hydrophobic interactions, and metal coordination.¹⁾ 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,²⁾ helicates³⁾ and helixanes.⁴⁾ Among them, helicenes containing more than six benzene rings (carbohelicenes) or seven heterocyclic rings (heterohelicenes) possess rigid helical framework^{2,5)} and are very stable toward acids, bases, and relatively high temperature.⁶⁾

Ever since the first synthesis of hexahelicene and its optical resolution by Newman and Lednicer in 1955,⁷⁾ 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,⁸⁾ molecular recognition,⁹⁾ and asymmetric synthesis.¹⁰⁾ In 1968, Wynberg and his co-workers reported the synthesis of a wide variety of heterohelicenes by photocyclization of 1,2-diarylethylene.^{11,12)} 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),^{7,13)} (ii) crystal picking,⁸⁾ or (iii) microscale separation by chiral column of high performance liquid chromatography (HPLC).¹⁴⁾ Although photosynthesis by circularly polarized light¹⁵⁾ or in chiral solvents¹⁶⁾ 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,¹⁷⁾ but the diastereoselectivities of photocyclization are low to moderate and the resolution of the diastereoisomers by column chromatography is very difficult.¹⁸⁾ 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'-binaphthyl 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.¹⁹⁾ 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 1969.²⁰⁾ 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,²¹⁾ 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.^{9d,13,22)}

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.

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Abstract

The diastereocontrolled photocyclization of 1,2-diarylethylene (**3**) derived from (1*R*,2*S*,3*R*,4*S*)-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, $[\alpha]_D$ 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

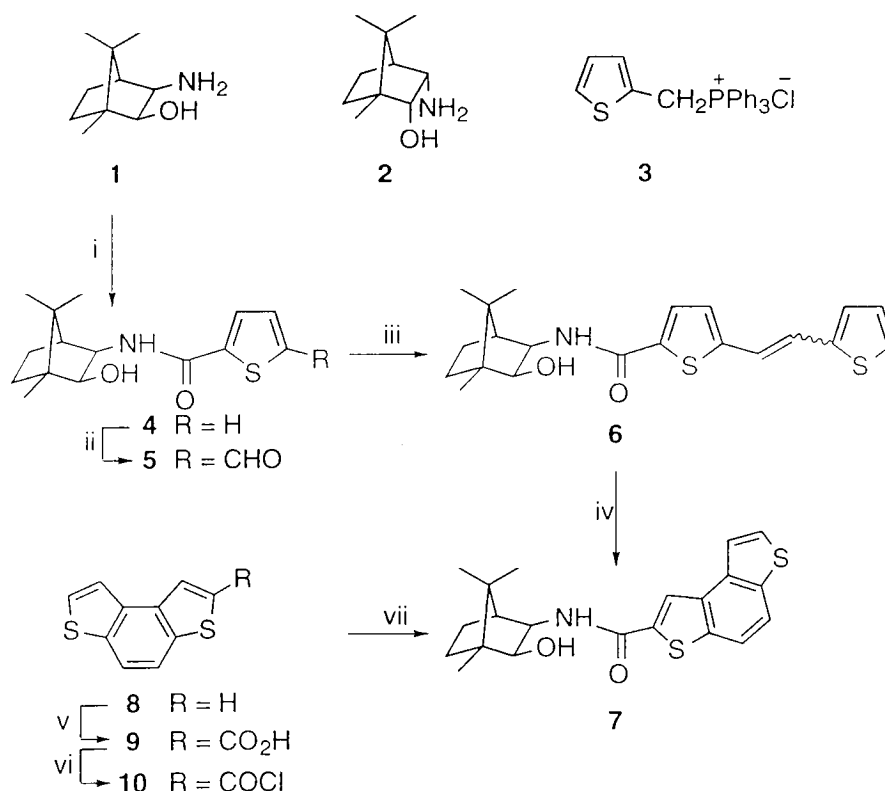
Among the artificially prepared helical molecules such as helicenes, helicates¹⁾ and helixanes,²⁾ helicene frameworks are thermally and photochemically stable. Therefore, functionalized helicenes with high optical purity are of great interest with respect of new chiral ligands and auxiliaries, chiral stationary phases,³⁾ or nonlinear optical materials.⁴⁾ 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,^{5,6,7)} crystal picking,⁸⁾ or microscale separation by chiral column of high performance liquid chromatography (HPLC).⁹⁾ 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-1*H*-benz[*e*]indene-8-carboxamide.¹⁰⁾ This chapter describes the diastereocontrolled synthesis of monofunctionalized [1]benzothieno[5,4-*b*]naphtho[1',2':4,5]thieno[3,2-

e][1]benzothiophene derivatives using (1*R*,2*S*,3*R*,4*S*)-3-amino-2-hydroxybornane (abbreviated as *exo*-amino alcohol) and (1*R*,2*R*,3*S*,4*S*)-3-amino-2-hydroxybornane (abbreviated as *endo*-amino alcohol) as chiral auxiliaries. The strategies for the synthesis of the optically active heterohelices consist of carboxamide-induced remote lithiation and diastereo-selective photocyclization of 1,2-diarylethylenes prepared by the Wittig reaction. The X-ray crystal structure of *N*-[(1*R*,2*R*,3*S*,4*S*)-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

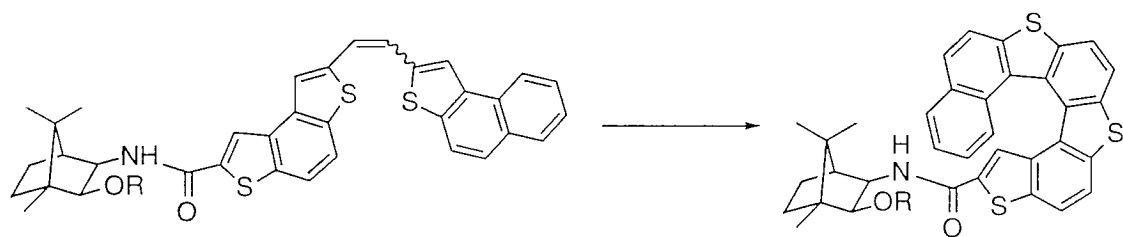
Scheme 1



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) *hν*, I₂, benzene, 54%; (v) BuLi, ether, room temperature, CO₂ (solid), 44%; (vi) SOCl₂, benzene; (vii) **1**, pyridine, 4-dimethylaminopyridine (DMAP), CH₂Cl₂, 75%.

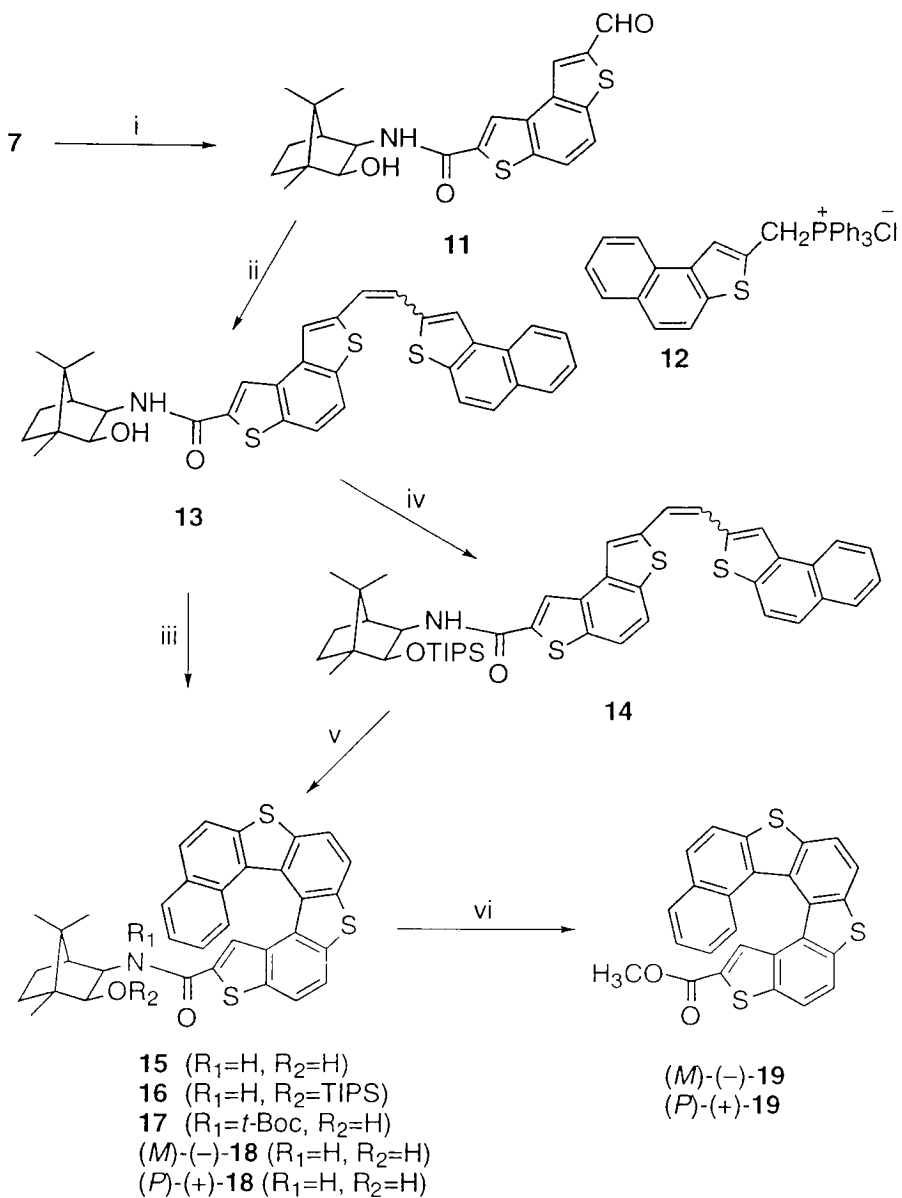
from secondary *exo*-amino alcohol **1** and 2-thiophenecarbonyl chloride¹¹⁾ at $-15\text{ }^{\circ}\text{C}$ in tetrahydrofuran (THF), 5-lithio-species was obtained exclusively¹²⁾ and trapped with *N,N*-dimethylformamide (DMF) to give 5-formylthiophene-carboxamide (**5**) in 79 % yield.¹²⁾ The Wittig reaction of **5** with thienyltriphenylphosphonium 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'*]dithiophenecarbonyl chloride (**10**) derived from benzo[1,2-*b*:4,3-*b'*]dithiophene (**8**)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*]thienylmethyltriphenylphosphonium chloride (**12**). Photocyclization of **13** in the presence of propylene oxide and a stoichiometric amount of iodine in benzene (0.60 mM) under argon¹⁴⁾ gave the desired [7]heterohelicene **15** in 57 % yield as a mixture of the diastereoisomers (45:55).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,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**

Table 1 The ratio of the diastereoisomers produced by photocyclization

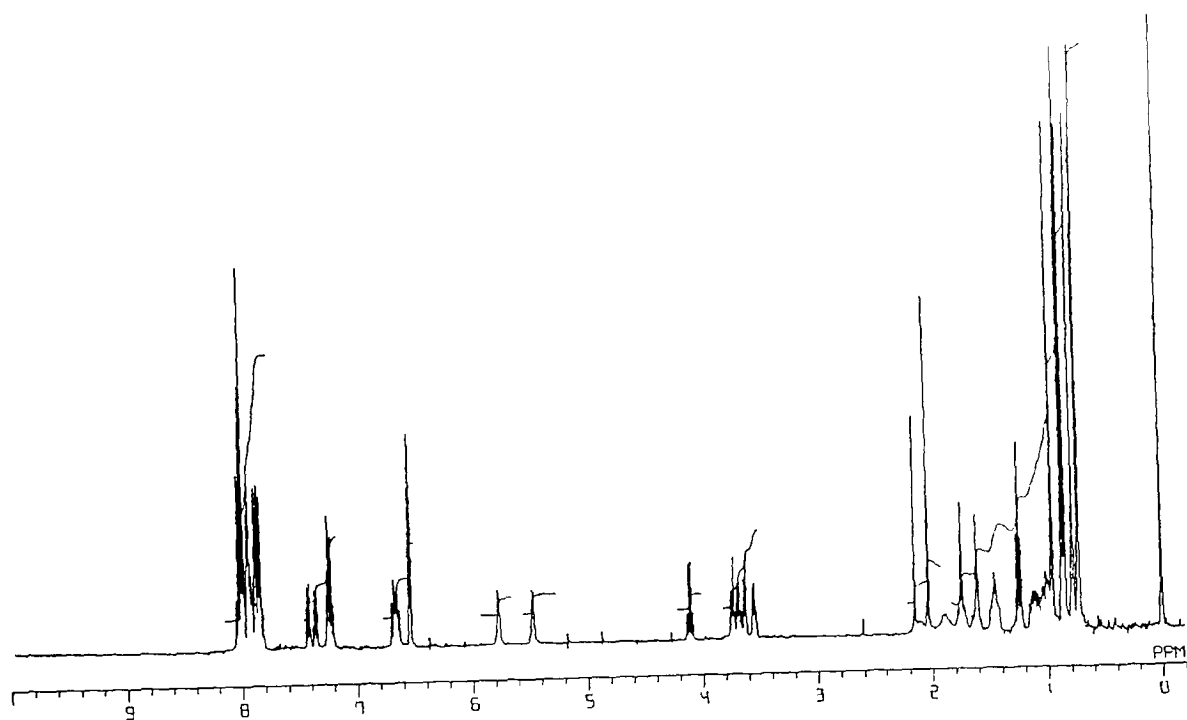


R	(-):(+)	Yield (%)	Conc. (mM)
H	55:45	57	0.60
H	53:47	91	0.31
Si(<i>i</i> -Pr) ₃	68:32	60	0.62

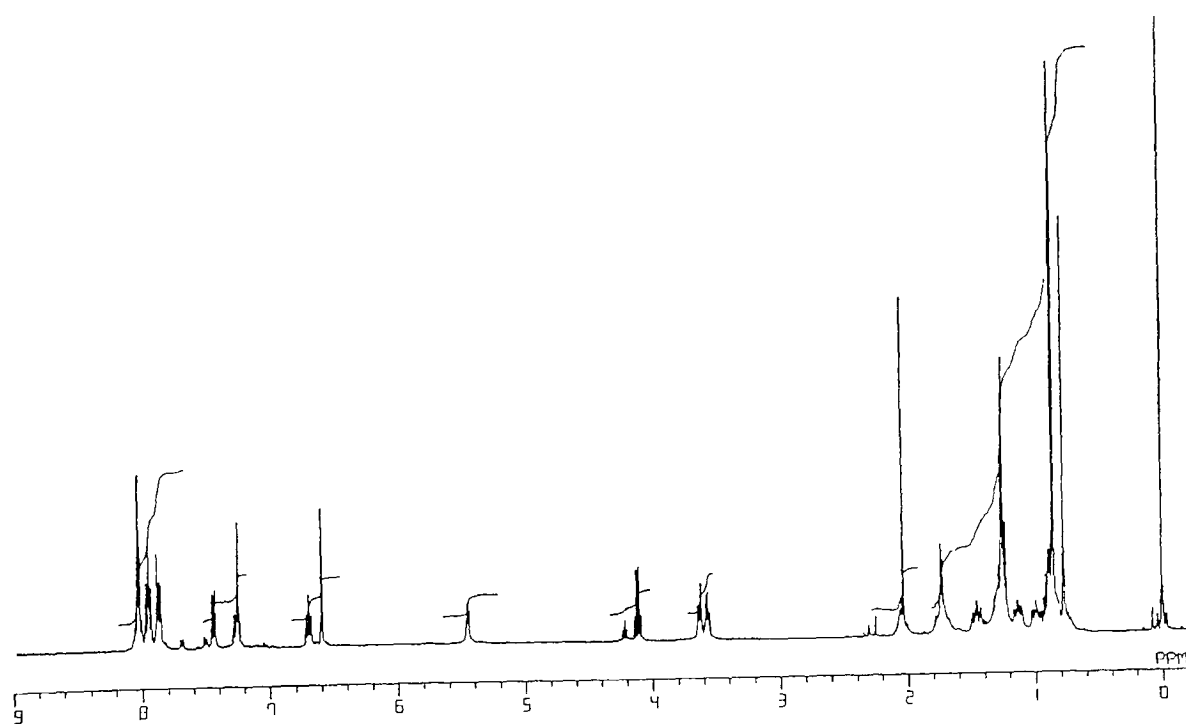
Scheme 2



Reagents and conditions: (i) LDA, THF, $-15\text{ }^{\circ}\text{C}$, DMF, 79%; (ii) **12**, $t\text{-BuOK}$, MeOH, THF, 83%; (iii) $h\nu$, I_2 , propylene oxide, benzene, 91%; (iv) $(i\text{-Pr})_3\text{SiOTf}$, 2,6-lutidine, CH_2Cl_2 , 100%; (v) (a) $h\nu$, I_2 , propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF, 61%; (vi) (a) $(t\text{-BuO}_2\text{C})_2\text{O}$, Et_3N , DMAP, CH_2Cl_2 , 76%; (b) CH_3ONa , MeOH, THF, 16%.



(a) helicene carboxamide [(*PM*)-(±)-**18**]



(b) (-)-helicene carboxamide [(*M*)-(-)-**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.¹⁵⁾ 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*-butoxycarbonylation¹⁷⁾ and subsequent methanolysis¹⁸⁾ of **17** to afford (-)-2-methoxycarbonyl[7]heterohelicene, (*M*)-(-)-**19**, in 16 % yield along with helicene-carboxamide, (*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,

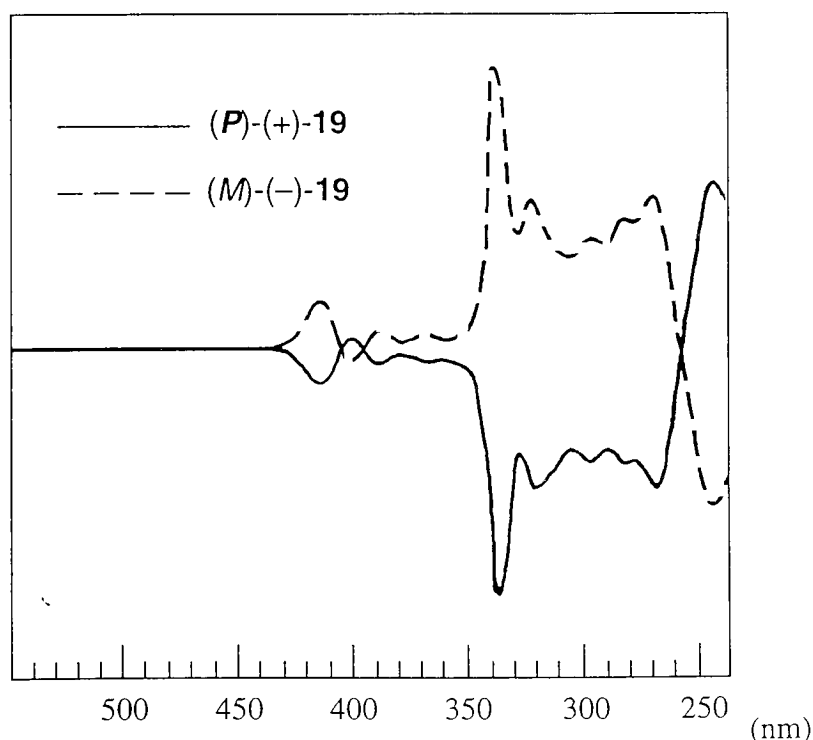


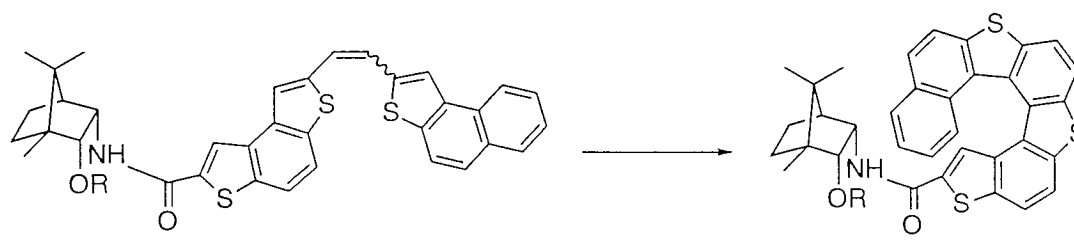
Figure 2 CD spectra of (*P*)-(+)- and (*M*)-(-)-heterohelicenes **19**

leading to the formation of helicene-carboxamide **15**.¹⁹⁾ The optical rotation of (*M*)-(-)-**19** obtained from (*M*)-(-)-**18** was $[\alpha]_D -2770$ (c 0.053, CHCl₃), whose absolute value was in good agreement with that of the enantiomer derived from (*P*)-(+)-**18**, $[\alpha]_D +2830$ (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

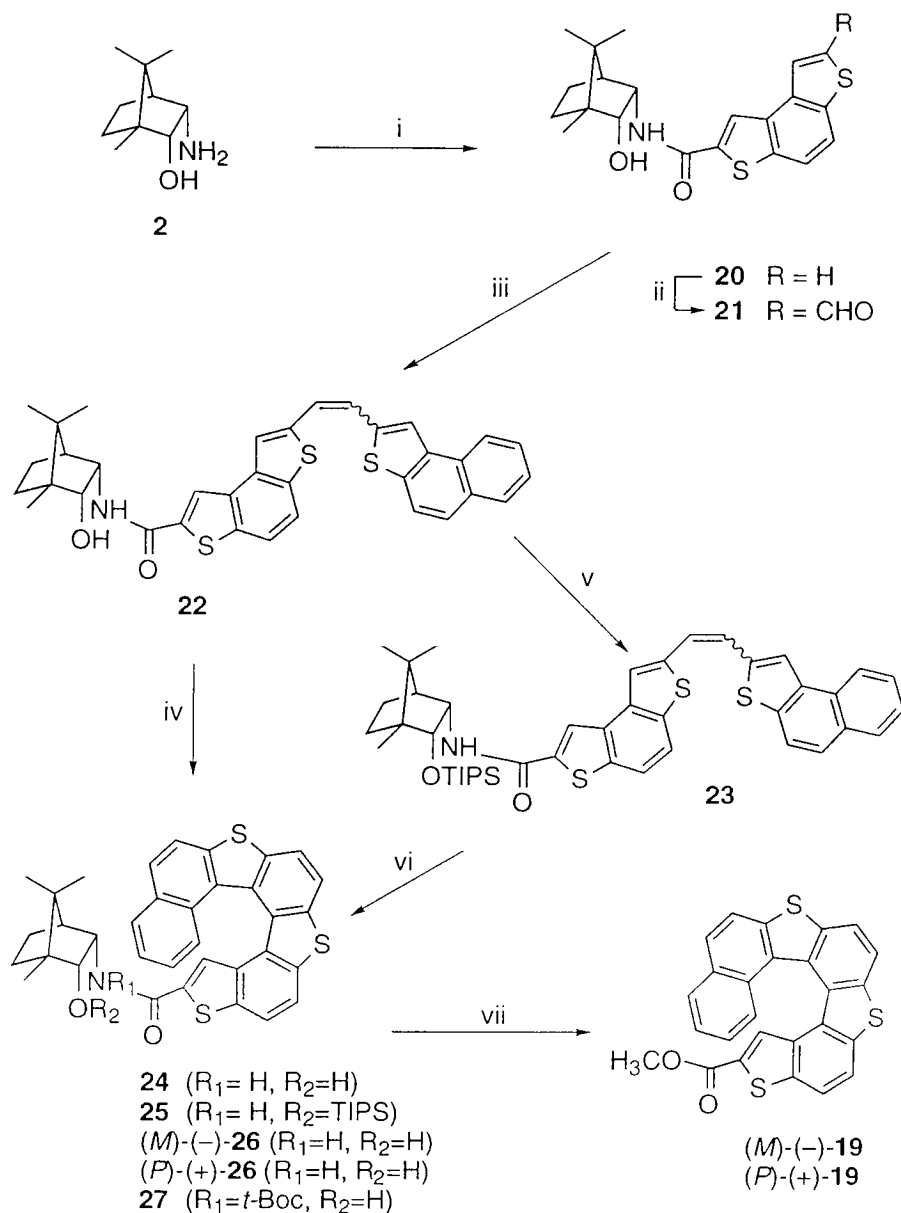
The synthesis of heterohelicenes was next carried out using *endo*-amino alcohol **2** as a chiral auxiliary. The carboxamide **20** was prepared from **2** and 2-benzo[1,2-*b*:4,3-*b'*]dithiophenecarbonyl chloride (**10**). Alpha-lithiation of the terminal thiophene ring of **20** was carried out under 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 2 The ratio of the diastereoisomers produced by photocyclization



R	(-):(+)	Yield (%)	Conc. (mM)
H	50:50	91	0.24
Si(<i>i</i> -Pr) ₃	25:75	96	0.30

Scheme 3



Reagents and conditions: (i) **10**, pyridine, DMAP, CH₂Cl₂, 73%; (ii) LDA, THF, -15 °C, DMF, 82%; (iii) *t*-BuOK, MeOH, THF, 81%; (iv) *hν*, I₂, propylene oxide, benzene, 91%; (v) (*i*-Pr)₃SiOTf, 2,6-lutidine, CH₂Cl₂, 100%; (vi) (a) *hν*, I₂, propylene oxide, benzene; (b) tetrabutylammonium fluoride, THF, 85%; (vii) (a) (*t*-BuO₂C)₂O, Et₃N, DMAP, CH₂Cl₂, 76%; (b) CH₃ONa, MeOH, THF, 16%.

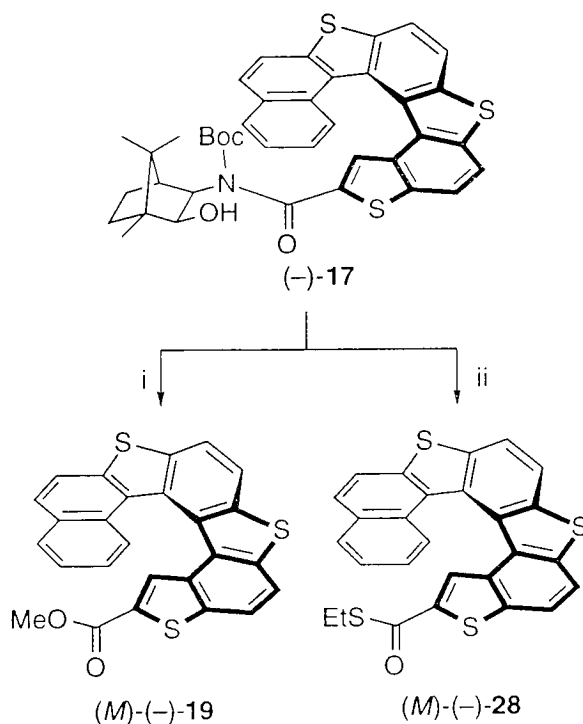
auxiliary from the major diastereomer (*P*)-(+)-**27** gave (+)-methyl ester **19** (Scheme 3). These results indicate that the diastereoselectivity is controlled by the use of the diastereomeric chiral auxiliaries such as *exo*-amino alcohol and its *endo*-isomer.

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.

Synthesis of Optically Pure [7]Thiaheterohelicene Derivatives

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 triethyloxonium tetrafluoroborate²⁰⁾ or potassium *t*-butoxide²¹⁾ were failed. However, we found that the reaction of the *N*-Boc amide (*M*)-(-)-**17** with lithium ethylmercaptide²²⁾ at 0°C

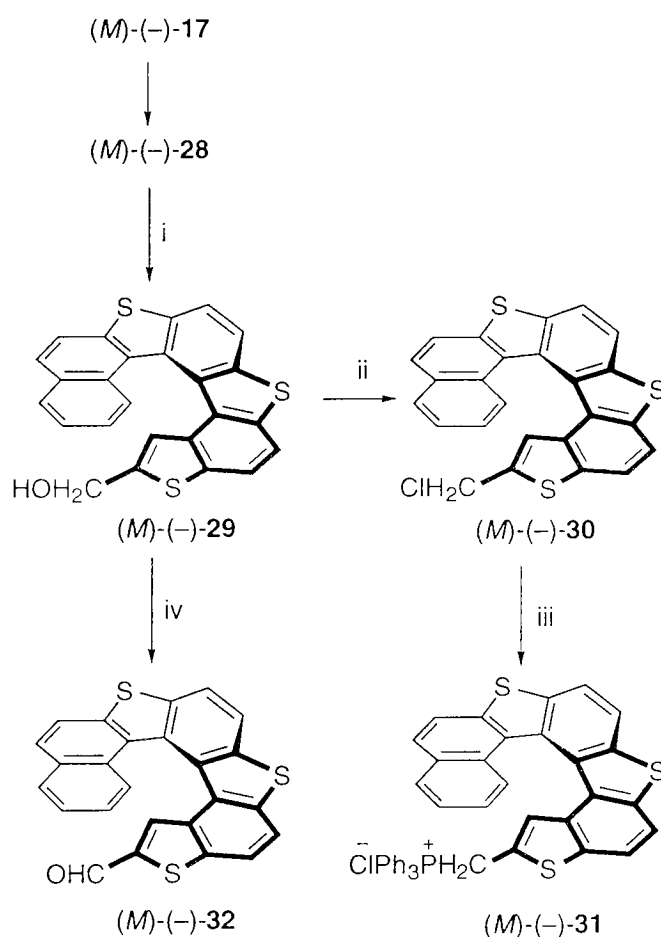
Scheme 4



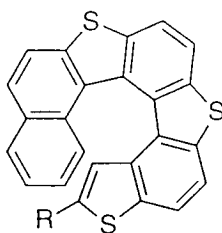
Reagents and conditions: (i), MeONa, MeOH, THF, 16%;
 (ii), EtSLi, THF, 82%.

gave helicene-thioester (*M*)-(-)-**28** in 82% yield (Scheme 4). Reduction of (*M*)-(-)-**28** by LiAlH_4 gave (hydroxymethyl)helicene (*M*)-(-)-**29** in 83% yield (Scheme 5), which was converted to (chloromethyl)helicene (*M*)-(-)-**30** by SOCl_2 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 in good agreement with those of (*M*)-(-)-isomers as shown in Table 3.

Scheme 5



Reagents and conditions: (i) LiAlH_4 , THF, 83%; (ii) SOCl_2 , benzene, 100%; (iii) PPh_3 , CH_3CN , 90%; (iv) pyridinium dichromate, CH_2Cl_2 , 90%.

Table 3 Specific Optical rotations of [7]thiaheterohelicene derivatives

R	[α] _D (concentration in CHCl ₃)	
	(<i>P</i>)-isomer	(<i>M</i>)-isomer
COSEt (28)	+2330 (0.100)	−2280 (0.100)
CH ₂ OH (29)	+1970 (0.053)	−2020 (0.046)
CH ₂ Cl (30)	+1920 (0.040)	−1930 (0.021)
CH ₂ P ⁺ Ph ₃ Cl [−] (31)	+1450 (0.050)	−1490 (0.021)
CHO (32)	+2900 (0.052)	−2830 (0.052)

Molecular Structure and Crystal Packing of the Functionalized [7]Heterohelicene

Crystals of (*P*)-(+)-**24** used for the X-ray measurement were obtained in orthorhombic form with the space group $P2_12_12_1$ 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.²³⁾ 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 $\cdots$ H bond causes a shift of $\nu_{\text{C=O}}$ 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.²⁴⁾

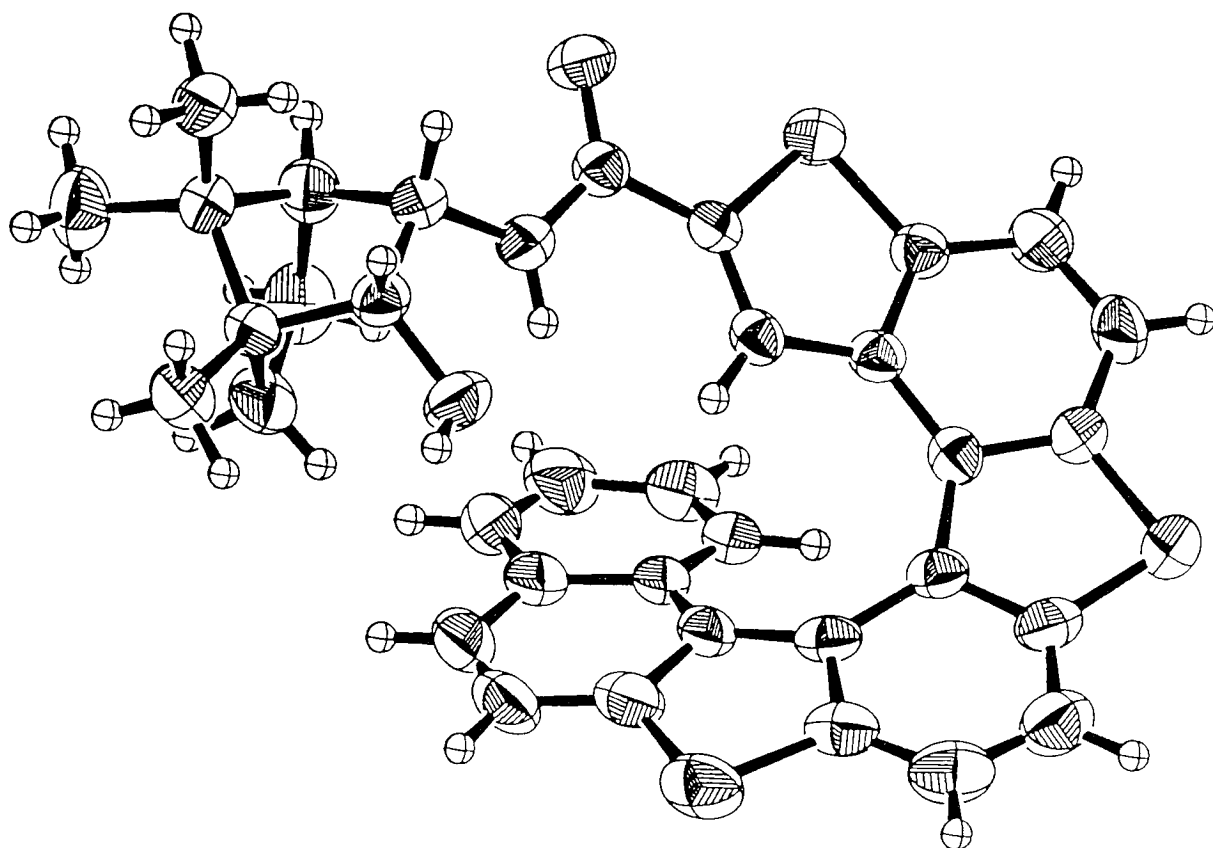


Figure 3 ORTEP view of heterohelicene (*P*)-(+)-24

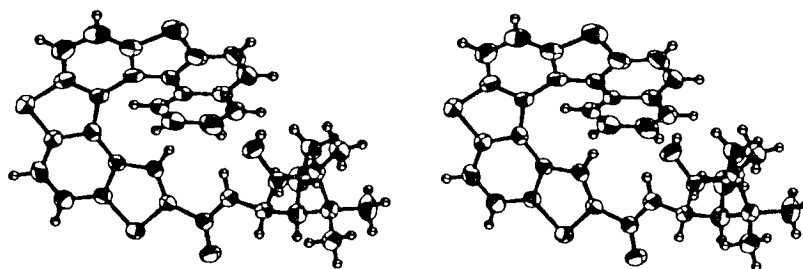


Figure 4 stereoview of heterohelicene (*P*)-(+)-24

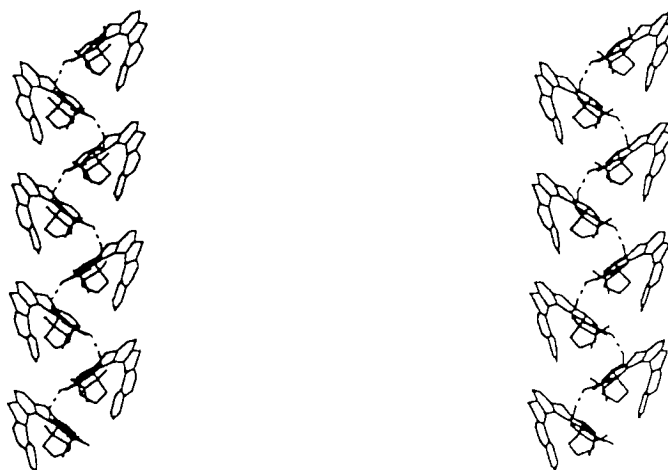
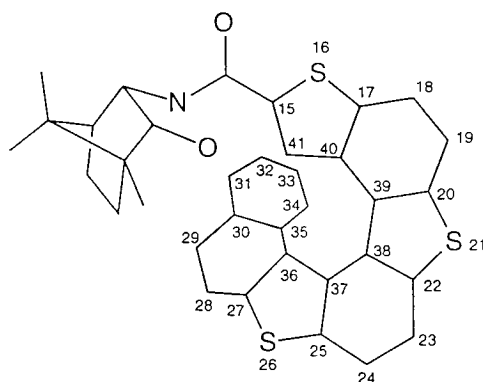


Figure 5 Helical network constructed by hydrogen bond

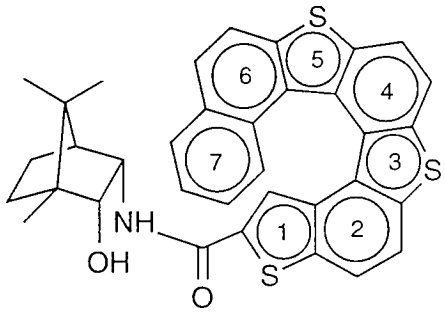
Table 4 Selected C-C bond lengths



C-C bond	length(Å)
C(32)-C(15)	4.561
C(32)-C(41)	4.383
C(32)-C(40)	4.795
C(33)-C(15)	4.204
C(33)-C(41)	3.796
C(34)-C(15)	3.918
C(34)-C(41)	3.109
C(34)-C(40)	3.048

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



The chemical structure shows a helicene core consisting of seven fused rings, numbered 1 to 7. Rings 1 and 2 are thiophene rings, while rings 3 through 7 are benzene rings. The molecule is substituted with a complex side chain at position 1, which includes a hydroxyl group (OH), an amide group (NH), and a carbonyl group (C=O). The rings are numbered 1 through 7 in a clockwise direction starting from the bottom thiophene ring.

plane	angle (degrees)
plane (1) plane (2)	11.42
plane (2) plane (3)	9.99
plane (3) plane (4)	9.97
plane (4) plane (5)	9.64
plane (5) plane (6)	6.26
plane (6) plane (7)	10.50
plane (1) plane (7)	47.33

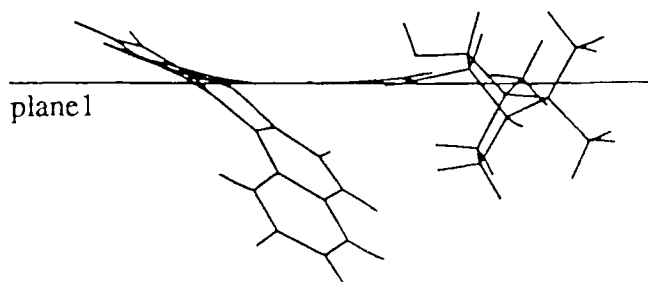


Figure 6 Side-view of helicene (*P*)-(+)-24

Chiral Optical Nonlinearity of [7]Thiaeterohelicene

Recently organic nonlinear optical materials have received considerable attention.²⁵⁾ 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.²⁶⁾ 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^{26a)} (Table 6). The effect of nonlinear rotation of the polarization plane is called “chiral optical nonlinearity” (Figure 7).

Table 6 Chiral optical nonlinearity of (*M*)-(–)-**19**

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

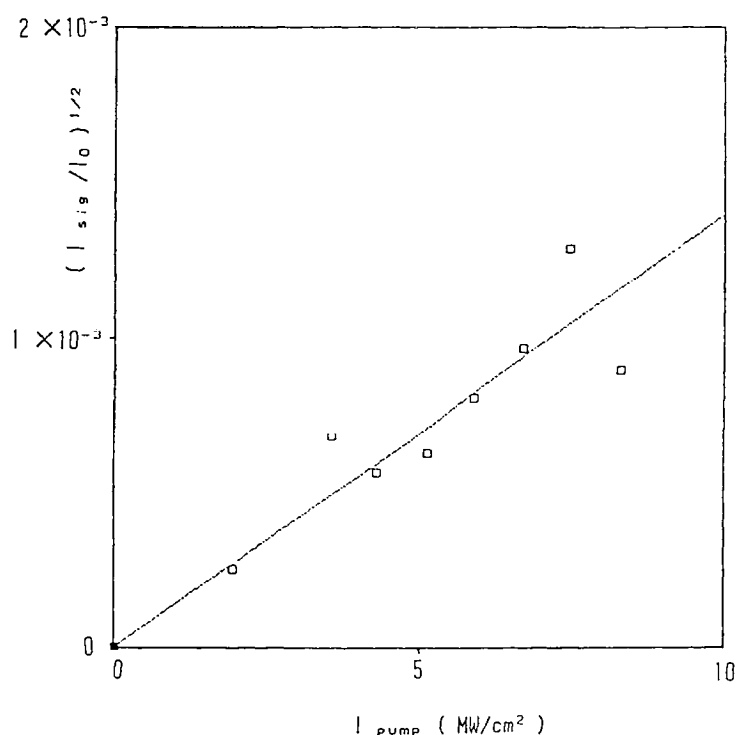


Figure 7 Chiral nonlinearity of helecene (*M*)-(-)-**19**

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; $[\alpha]_D$ 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*-[(1*R*,2*S*,3*R*,4*S*)-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 2 h 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 Na₂SO₄ 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; ¹H NMR (CDCl₃) δ 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, *J* 4.0, 1H), 2.07 (d, *J* 4.8, 1H), 3.82 (m, 2H), 6.99 (m, 1H), 7.54 (d, *J* 3.9, 1H), 7.71 (d, *J* 3.9, 1H), 9.93 (s, 1H); IR (KBr) 3400, 2950, 1665, 1645, 1530, 1510, 1445, 1210, 820 cm⁻¹; Anal. Calcd for C₁₆H₂₁NO₃S: C, 62.52; H, 6.84; N, 4.56. Found: C, 62.57; H, 7.08; N, 4.41.

***N*-[(1*R*,2*S*,3*R*,4*S*)-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 CH₂Cl₂ was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over Na₂SO₄ 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; ¹H NMR (CDCl₃) δ 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, *J* 4.4, 1H), 2.23 (br s, 1H), 3.94 (m, 2H), 6.96 (m, 1H), 6.91-7.09 (m, 5H), 7.34 (d, *J* 3.9, 1H); IR (KBr) 3385, 2955, 1625, 1535, 1520, 1495, 1280, 930 cm⁻¹; Anal. Calcd for C₂₁H₂₅NO₂S₂: 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 CO₂ in ether, and the mixture was stirred until solid CO₂ 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 CH₂Cl₂. The combined organic extracts were washed with brine and dried over Na₂SO₄ 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; ¹H NMR (CDCl₃) δ 7.66 (d, *J* 5.2, 1H), 7.77 (d, *J* 5.2, 1H), 7.82 (d, *J* 9.1, 1H), 7.97 (d, *J* 9.1, 1H), 8.53 (s, 1H); IR (KBr) 2800 (br), 1675, 1515, 1285, 1265, 1180, 1150, 750, 700 cm⁻¹; Anal. Calcd for C₁₁H₆O₂S₂: 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 Na₂S₂O₃ and extracted with benzene. The combined organic extracts were washed with aqueous NaHCO₃, 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 (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, 2H), 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.

***N*-[*(1R,2S,3R,4S)*-2-(Triisopropylsilyl)oxy-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 (**14**).**

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.

***N*-[*(1R,2S,3R,4S)*-2-Hydroxy-1,7,7-trimethylbicyclo-[2.2.1]-heptan-3-yl][1]benzothieno[5,4-*b*]naphtho[1',2':4,5]thieno[3,2-*e*][1]-benzothiophene-2-carboxamide (**15**).**

(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 % $\text{Na}_2\text{S}_2\text{O}_3$ 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_2SO_4 . The solvents were 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; ^1H 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, 7H); IR (KBr) 3375, 2950, 1645, 1620, 1520, 1480, 1150, 800, 785, 745, 525 cm^{-1} ; Anal. Calcd for $\text{C}_{35}\text{H}_{29}\text{NO}_2\text{S}_3$ C, 71.04; H, 4.94; N, 2.37. Found: C, 70.88; H, 4.98; N, 2.26.; $[\alpha]_{\text{D}} -2380$ (c 0.052, CHCl_3).

(*P*)-(+)-**18**: m.p. 189-192 °C; ^1H NMR (CDCl_3) δ 0.74 (s, 6H), 0.98 (s, 3H), 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, 7H); IR (KBr) 3385, 2950, 1635, 1520, 1480, 1150, 800, 785 cm^{-1} ; Anal. Calcd for $\text{C}_{35}\text{H}_{29}\text{NO}_2\text{S}_3$ C, 71.04; H, 4.94; N, 2.37. Found: C, 70.76; H, 5.18; N, 2.50.; $[\alpha]_{\text{D}} +2070$ (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 % $\text{Na}_2\text{S}_2\text{O}_3$ solution and the aqueous phase was extracted with benzene. The combined organic extracts were washed with saturated aqueous NaHCO_3 , brine and dried (Na_2SO_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)-(-)-Methyl [1]Benzothieno[5,4-b]naphtho[1',2':4,5]thieno-[3,2-e][1]benzothiophene-2-carboxylate ((M)-(-)-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*)-(-)-**15** (29.4 mg, 68 %) and methyl ester (*M*)-(-)-**19** as a yellow solid (5.3 mg, 16 %).

m.p. 229-231 °C; ¹HNMR (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 C₂₆H₁₄O₂S₃ C, 68.70; H, 3.10. Found: C, 68.67; H, 3.37.; [α]_D -2770 (c 0.053, CHCl₃).

***N*-[(1*R*,2*R*,3*S*,4*S*)-2-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

with brine and dried (Na_2SO_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; ^1H NMR (CDCl_3) δ 0.96 (s, 6H), 1.02 (s, 3H), 1.17 (m, 1H), 1.52 (m, 2H), 1.92 (m, 1H), 2.13 (t, J 4.2, 1H), 4.18 (d, J 8.8, 1H), 4.41 (m, 1H), 7.02 (d, J 6.5, 1H), 7.51 (d, J 8.8, 1H), 7.65 (d, J 8.8, 1H), 7.90 (s, 1H); IR (KBr) 3350, 1620, 1525, 1345, 1105, 1030, 700 cm^{-1} ; Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_2\text{S}_2$ 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-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-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_2SO_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; ^1H NMR (CD_3SOCD_3) δ 0.86 (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, 1H), 7.56 (d, J 6.1, 1H), 8.11 (d, J 8.9, 1H), 8.20 (d, J 8.9, 1H), 8.80 (s, 1H), 8.98 (s, 1H), 10.19 (s, 1H); IR (KBr) 3350, 2955, 1670, 1640, 1540, 1520, 1250, 1130 cm^{-1} ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{NO}_3\text{S}_2$ 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-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 (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_2Cl_2 and dried *in vacuo* to give olefin **22** as orange

powder (0.78 g, 81 %). An analytically pure sample of **22** was obtained by recrystallization from CHCl_3 .

m.p. 308-310 °C (dec.); ^1H NMR (CD_3SOCD_3) 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 $\text{C}_{35}\text{H}_{31}\text{NO}_2\text{S}_3$ C, 70.79; H, 5.26; N, 2.36. Found: C, 70.61; H, 5.28; N, 2.44.

***N*-[*(1R,2R,3S,4S)*-2-(Triisopropylsilyl)oxy-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 (**23**).**

To a stirred suspension of **22** (0.31 g, 0.52 mmol) in 40 mL of dry CH_2Cl_2 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 NaHCO_3 , brine and dried over Na_2SO_4 . 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 (CDCl_3) 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, J 5.2, 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 $\text{C}_{44}\text{H}_{51}\text{NO}_2\text{S}_3\text{Si}$ C, 70.45; H, 6.85; N, 1.87. Found: C, 69.94; H, 6.90; N, 1.86.

***N*-[*(1R,2R,3S,4S)*-2-Hydroxy-1,7,7-trimethylbicyclo-[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**).**

(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 % $\text{Na}_2\text{S}_2\text{O}_3$ 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_2SO_4 .

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).

S-Ethyl [1]Benzothieno[5,4-b]naphtho[1'2':4,5]thieno[3,2-e][1]-benzothiophene-2-carboxylate (28).

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%).

¹NMR (CDCl₃) δ 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 C₂₇H₁₆OS₄ C, 66.91; H, 3.33. Found: C, 66.85; H, 3.45.; (*P*)-(+)-**28**: [α]_D +2330 (c 0.100, CHCl₃); (*M*)-(-)-**28**: [α]_D -2280 (c 0.100, CHCl₃).

2-(Hydroxymethyl)[1]benzothieno[5,4-b]naphtho[1'2':4,5]thieno[3,2-e][1]benzothiophene (29).

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 CHCl₃. The organic phase was washed with brine and dried over MgSO₄. 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; ¹NMR (CDCl₃) δ 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 C₂₅H₁₄OS₃ C, 70.39; H, 3.31. Found: C, 70.33; H, 3.21.; (*P*)-(+)-**29**: [α]_D +1970 (c 0.053, CHCl₃); (*M*)-(-)-**29**: [α]_D -2020 (c 0.046, CHCl₃).

2-Chloromethyl[1]benzothieno[5,4-b]naphtho[1'2':4,5]thieno[3,2-e][1]benzothiophene (30).

To a stirred solution of alcohol **29** (90.1 mg, 0.212 mmol) in 5 mL of benzene was added thionyl chloride (0.20 mL, 2.1 mmol) at room temperature, and the reaction mixture was stirred over night. The solvent was evaporated and the residue was chromatographed on silica using hexane-ethyl acetate (20:1) as the eluent to give chloride **30** as a yellow solid (95.2 mg, 100%).

¹NMR (CDCl₃) δ 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 C₂₅H₁₃ClS₃ C, 67.47; H, 2.94. Found: C, 67.24; H, 3.12.; (*P*)-(+)-**30**: [α]_D +1920 (c 0.040, CHCl₃); (*M*)-(-)-**30**: [α]_D -1930 (c 0.021, CHCl₃).

2-(Triphenylphosphonio)methyl[1]benzothieno[5,4-b]naphtho[1'2':4,5]thieno[3,2-e][1]benzothiophene chloride (31).

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 CH₂Cl₂-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.); ¹NMR (CDCl₃) 3.48 (dd, *J* 7.5, 6.7, 2H), 5.57 (d, *J* 4.1, 1H), 6.7 (m, 2H), 7.3-7.7 (m, 16H), 7.9-8.1 (m, 7H); IR (KBr) 3040, 2750, 1440, 1110 cm⁻¹; (*P*)-(+)-**31**: [α]_D +1450 (c 0.050, CHCl₃); (*M*)-(–)-**31**: [α]_D –1490 (c 0.021, CHCl₃).

[1]Benzothieno[5,4-*b*]naphtho[1'2':4,5]thieno[3,2-*e*][1]benzo-thiophene-2-carbaldehyde (32**).**

To a stirred suspension of pyridinium dichromate (37.6 mg, 0.100 mmol) in 3 mL of CH₂Cl₂ was added a solution of alcohol **29** (21.3 mg, 0.050 mmol) in 3 mL of CH₂Cl₂ 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 MgSO₄. 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; ¹NMR (CDCl₃) 6.71 (ddd, *J* 8.2, 7.0, 1.2, 1H), 6.92 (s, 1H), 7.28 (ddd, *J* 8.1, 6.9, 1.2, 1H), 7.37 (d, *J* 8.4, 1H), 7.9-8.1 (m, 7H), 9.00 (s, 1H); Anal. Calcd for C₂₅H₁₂OS₃ C, 70.72; H, 2.85. Found: C, 70.97; H, 2.75.; (*P*)-(+)-**32**: [α]_D +2900 (c 0.052, CHCl₃); (*M*)-(–)-**32**: [α]_D –2830 (c 0.052, CHCl₃).

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: C₃₅H₂₉NO₂S₃, *M* = 591.80, crystal system, orthorhombic, space group, P2₁2₁2₁ (#19), *a* = 20.305(1), *b* = 14.830(2), *c* = 9.859(1) Å, *V* = 2968.8(4) Å³, *F*(000) = 1240.00, *Z* = 4, *μ* = 25.40 cm⁻¹, *D*_c = 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 ω–2θ scan technique to a maximum 2θ 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 statistics. Neutral atom scattering factors were taken from Cromer and Waber. Anomalous dispersion effects were included in F_{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.

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Abstract

Optically active bifunctionalized [7]thiaheterohelicene was synthesized using (1*R*, 2*R*, 3*S*, 4*S*)-*endo*-3-amino-*endo*-2-hydroxybornane as a chiral element. The photocyclo-dehydrogenation of 1,2-diarylethylene prepared from benzo-dithiophenecarboxaldehyde **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 C_2 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*)-($\pm$)-**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 C_2 symmetry, because the presence of a C_2 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-macrocyclic

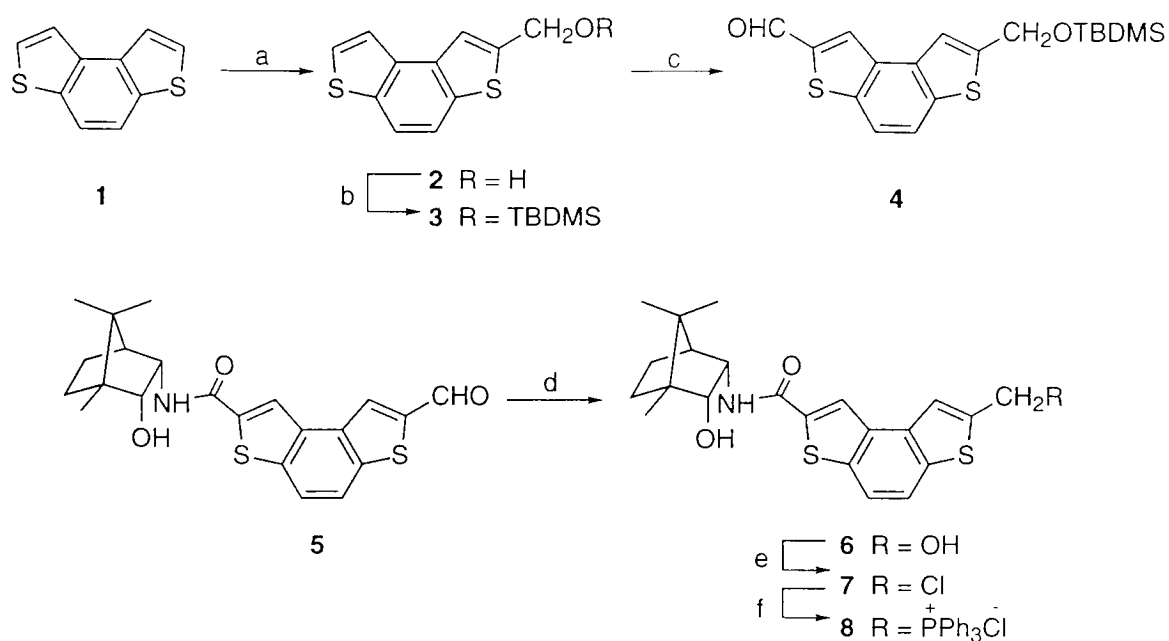
receptors with a helicene backbone like helicopodands, which performed the molecular recognition of dicarboxylic acids with high diastereoselectivities,⁴⁾ optically active helicenes have been obtained by laborious methods such as repeated recrystallizations of racemic helicene-complexes with chiral electron acceptors⁵⁾ or chiral amines,⁶⁾ crystal picking,⁷⁾ or separation by HPLC.⁸⁾ For these reasons, the asymmetric synthesis using those helicenes as chiral elements have never been evaluated.³⁾

This chapter describes a convergent synthesis of chiral bifunctionalized [7]heterohelicenes possessing C_2 symmetry by the use of bicyclic amino alcohols derived from D-camphor as a chiral auxiliary.⁹⁾ The method consists of (i) construction of benzodithiophenecarboxaldehyde and optically active phosphonium salt by regioselective α -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°C , 2-lithio species was obtained exclusively,¹⁰⁾ 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°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 procedure¹¹⁾ 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.

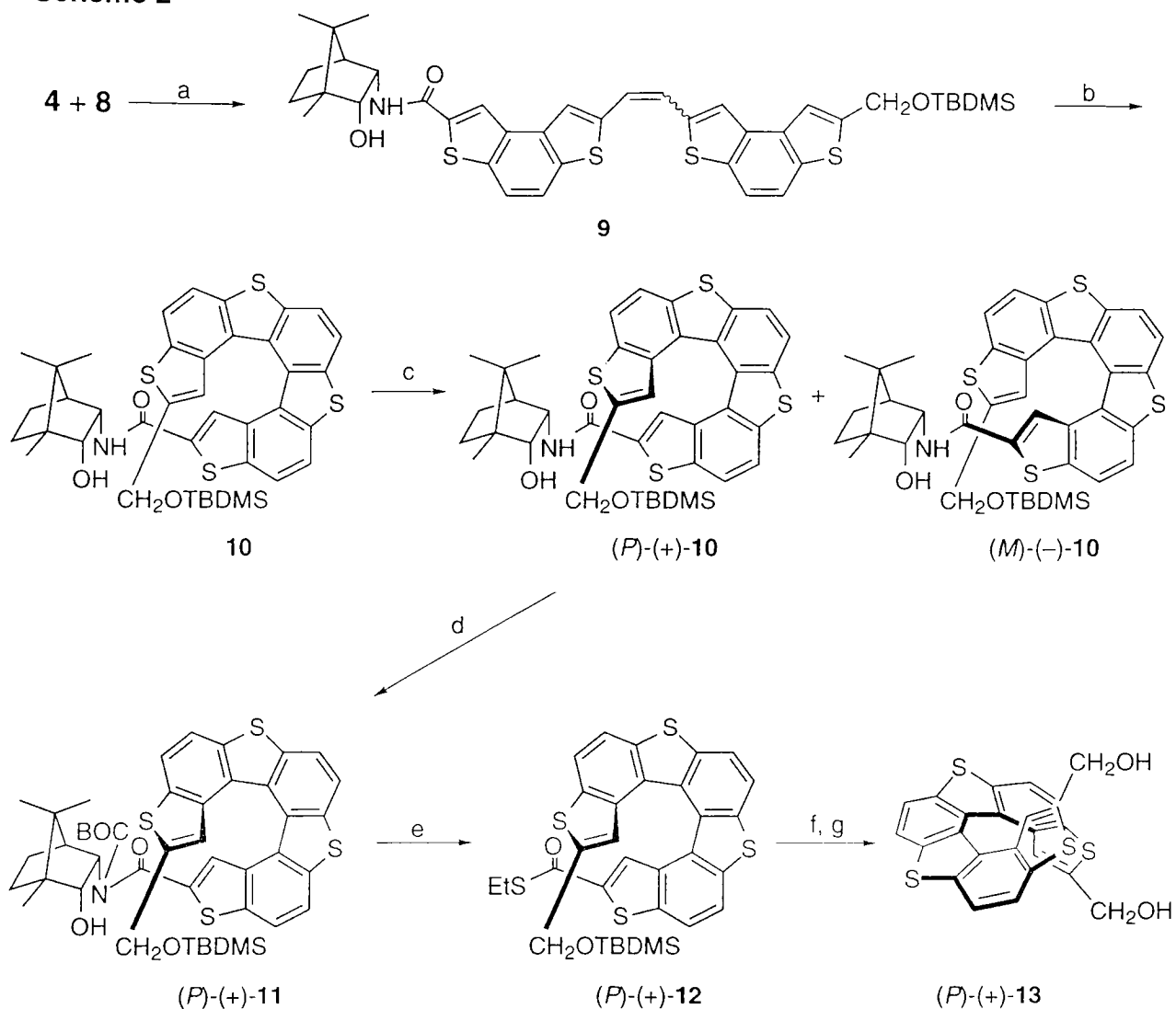
Scheme 1



Reagents and Conditions: (a) BuLi, THF, -78°C , $(\text{CH}_2\text{O})_n$, 70%; (b) TBDMSCl, imidazole, DMF, r.t., 98%; (c) BuLi, TMEDA, THF, -78°C , DMF, 81%; (d) NaBH_4 , EtOH-THF, r.t., 99%; (e) NCS, dimethyl sulfide, CH_2Cl_2 , -10°C , 82%; (f) PPh_3 , benzene, reflux, 78%.

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-workers¹²⁾ provided bifunctionalized [7]heterohelicene **10** in 77 % yield as a mixture of the diastereoisomers (38:62).^{13,14)} 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*-butoxycarbonylation¹⁵⁾ was smoothly carried out by di-*t*-butyldicarbonate at room temperature to give **11** in 70 % yield, methanolysis¹⁵⁾ of **11** completely gave the starting carboxamide **10**. Hydride reduction of **11** by lithium aluminum hydride¹⁶⁾ or Super Hydride^{®17)} afforded complex mixtures. Transesterification of **11** to the corresponding thioester according to a modification¹⁸⁾ 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 TBAF¹⁹⁾ in THF, and reduction by DIBAL in CH_2Cl_2 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**.²⁰⁾ The optical purity of (*P*)-(+)-**13** was

Scheme 2



Reagents and Conditions: (a) *t*-BuOK, MeOH-THF, r.t., 79%; (b) *hν*, I₂, propylene oxide, benzene, r.t., 77%; (c) column chromatography on silica gel; (d) (*t*-BuO₂C)₂O, DMAP, CH₂Cl₂, r.t., 70%; (e) EtSLi, THF, 50°C; (f) TBAF, THF, r.t.; (g) DIBAL, CH₂Cl₂, r.t.

determined to be *ca.* 96 % ee by HPLC analysis.²¹⁾ By a similar procedure, the antipode (*M*)-(-)-**13** was also obtained from (*M*)-(-)-**10** in *ca.* 96 % ee.

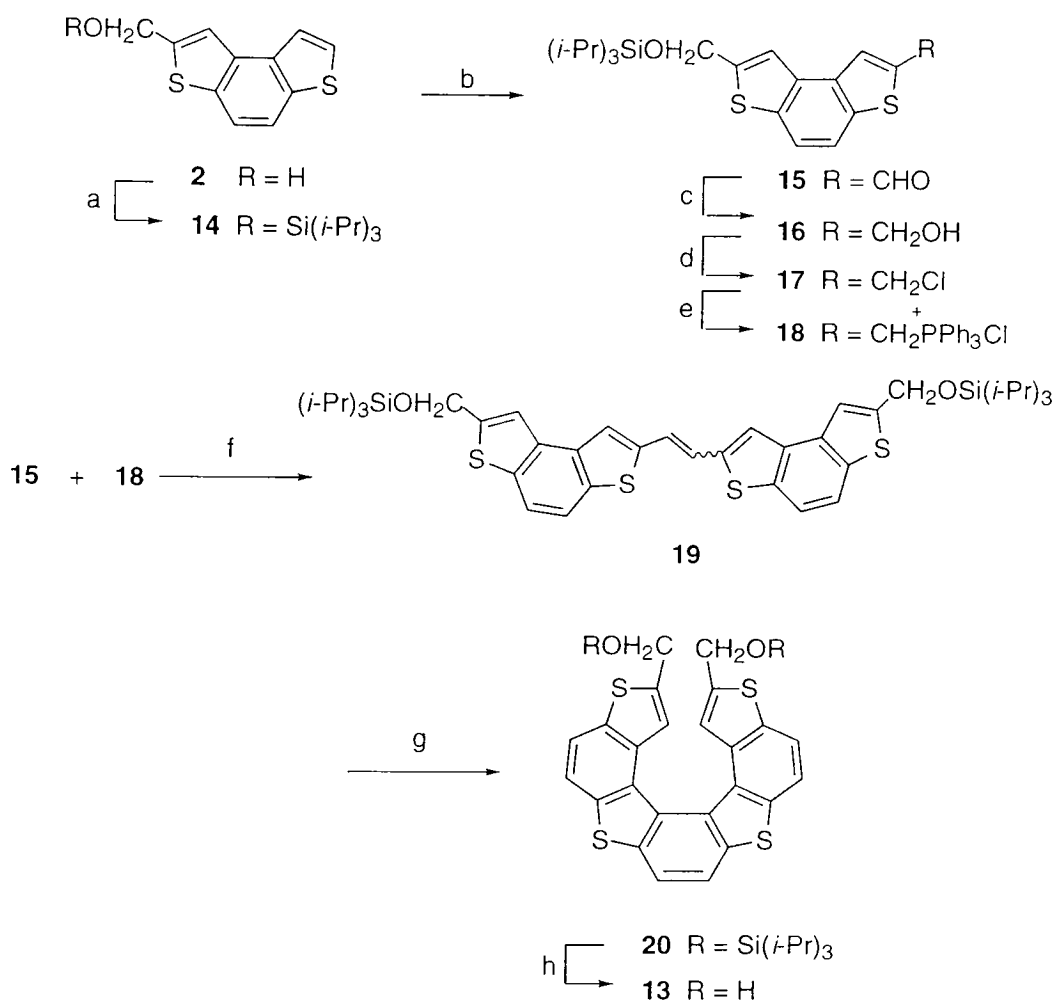
Lipase-Catalyzed Resolution of Bis(hydroxymethyl)[7]thiaheterohelicene

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,^{12,22)} 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 method¹²⁾ 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',N'*-tetramethylsuccinamide²³⁾ or brucine²⁴⁾ was unsuccessful, lipase-catalyzed transesterification in the presence of vinyl acetate was found to be effective for optical resolution.²⁵⁾ 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

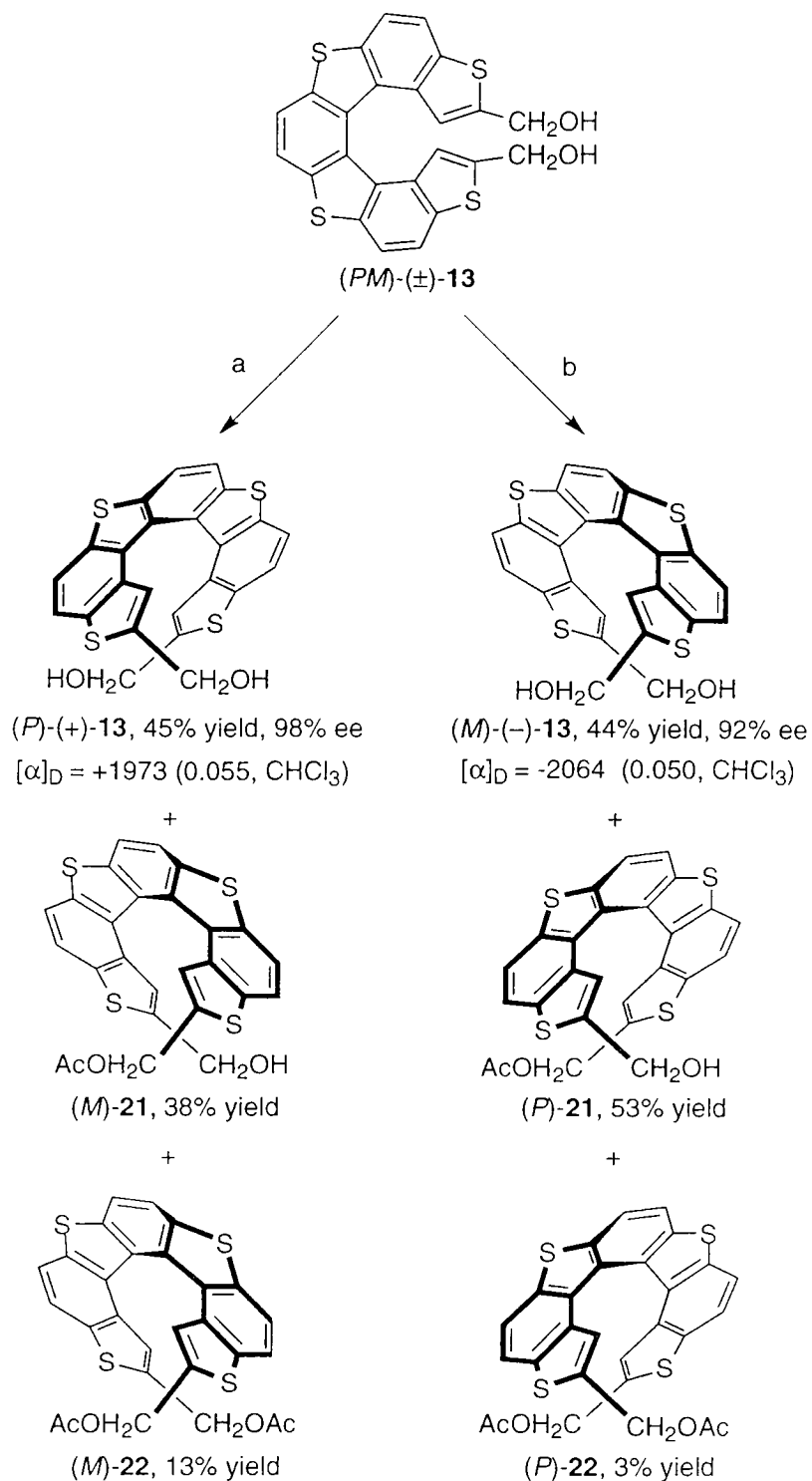
Scheme 3



Reagents and Conditions: (a) (*i*-Pr)₃SiOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 98%; (b) BuLi, TMEDA, DMF, THF, -78 °C, 97%; (c) NaBH₄, MeOH-THF, r.t.; (d) SOCl₂, pyridine, benzene, 0 °C; (e) Ph₃P, benzene, reflux, 65% (from **15**); (f) *t*-BuOK, MeOH-THF, 0 °C, 73%; (g) *hν*, I₂, propylene oxide, benzene, r.t., 66%; (h) Bu₄NF, THF, 0 °C, 93%.

(*P*)-(+)-**13** (44.7 mg, 45 % yield) 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*)-(+)-**13** was $[\alpha]_{\text{D}} +1973$ (c 0.055, CHCl₃). Hydrolysis of the monoacetate (*M*)-**21** by NaOH in methanol gave (*M*)-(–)-**13** with 80 % ee and the diacetate (*M*)-**22** gave the same enantiomer with 95 % ee.

Scheme 4



Reagents and Conditions: (a) lipase PS, vinyl acetate, MS 4A, CH₂Cl₂; (b) CAL, vinyl acetate, CH₂Cl₂.

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) 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*)-($\pm$)-**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

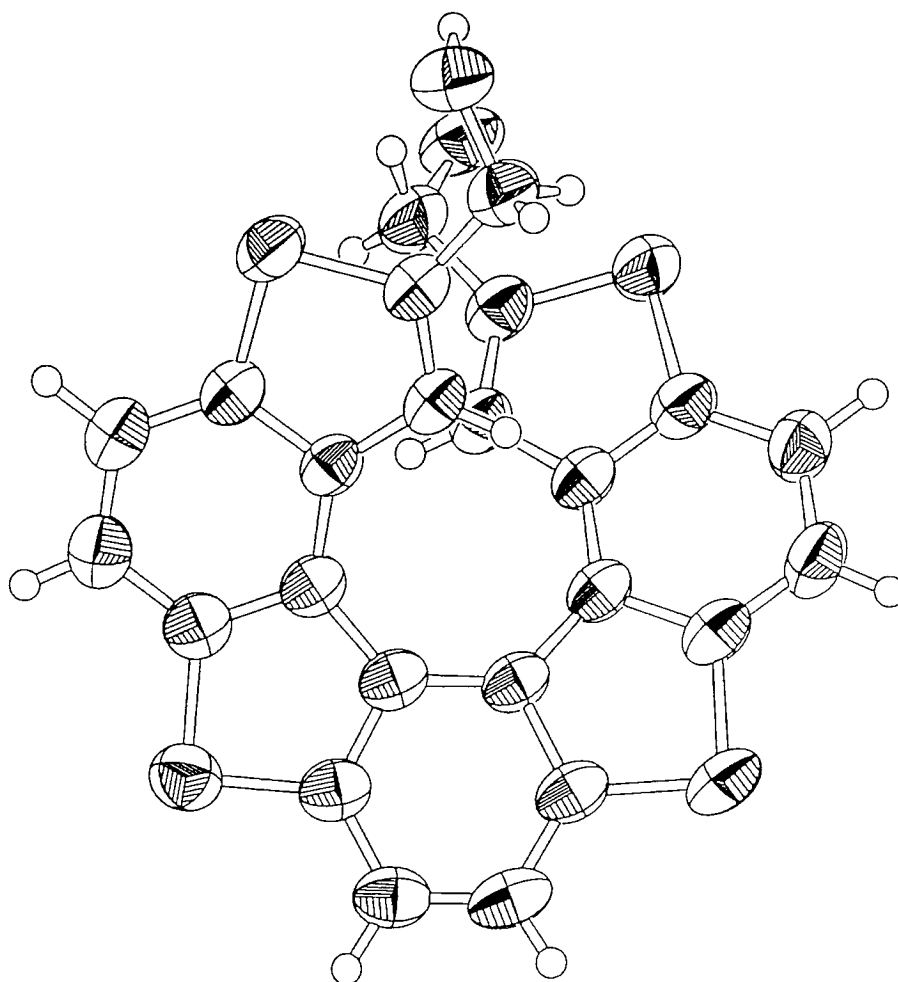


Figure 1 ORTEP view of heteroheliceediol **13**

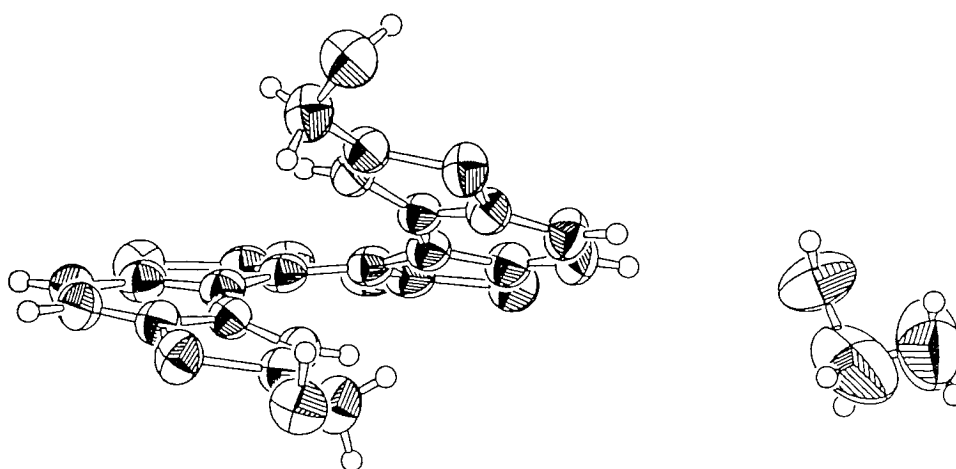


Figure 2 ORTEP sideview of heteroheliceediol **13**

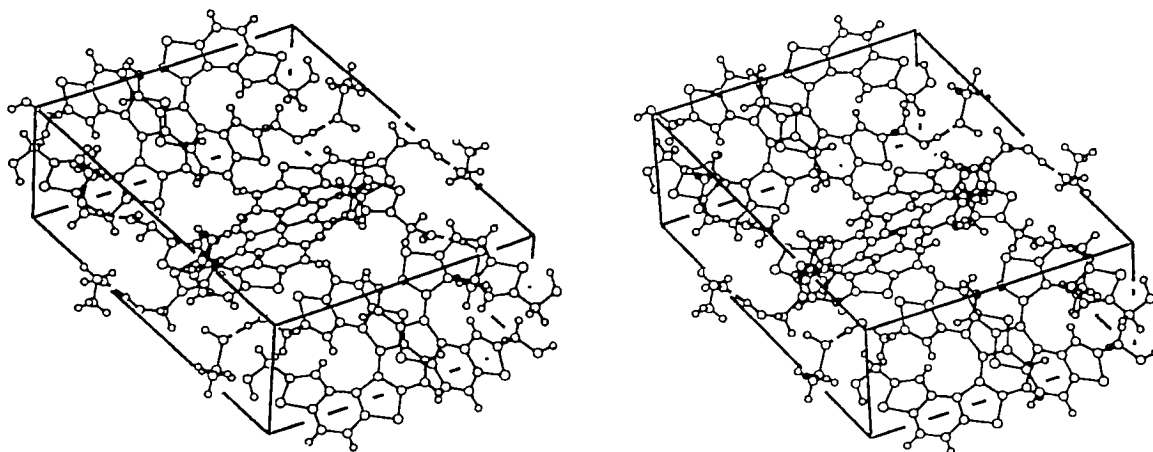


Figure 3 ORTEP view of **13**·EtOH clathrate

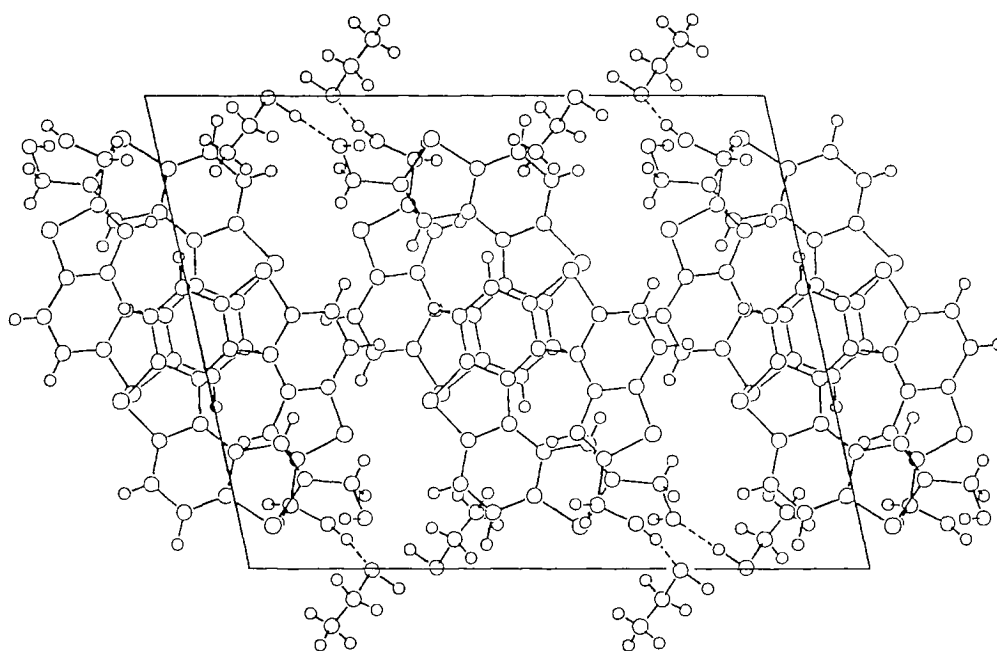
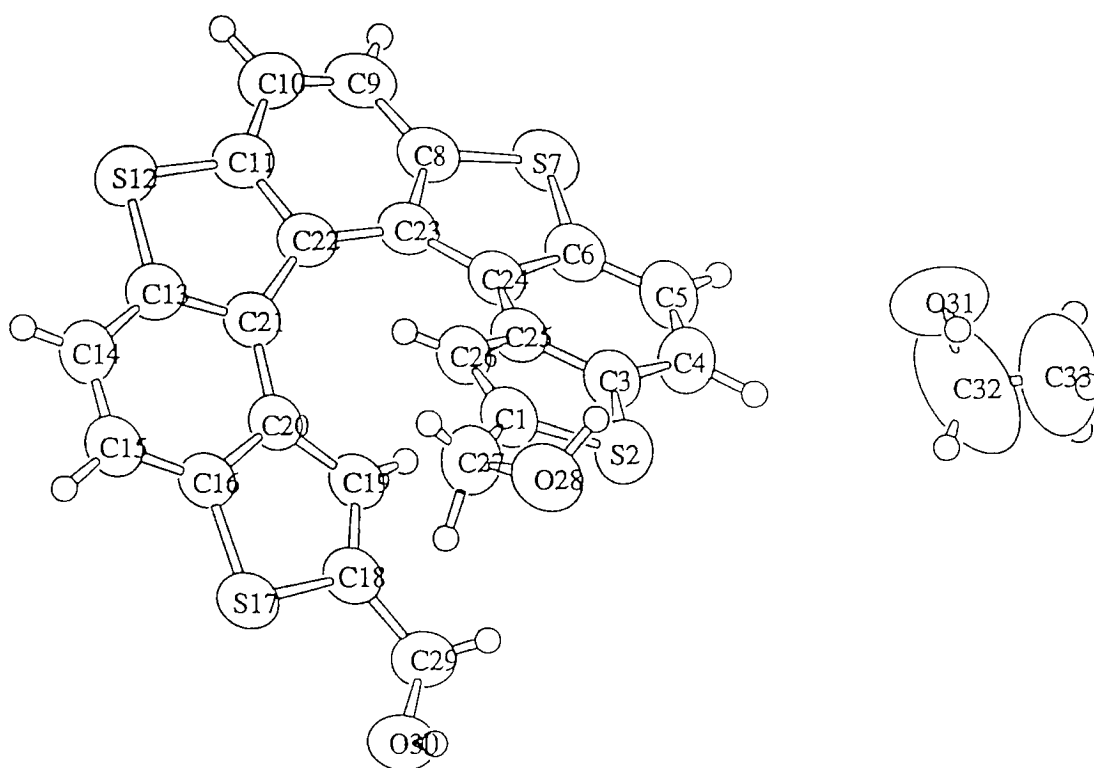


Figure 4 Heterohelicene diol **13**·EtOH clathrate as viewed along the *b* axis

Å of the C(3)-C(4) bond length of thiophene (Table 1).²⁶⁾ The angles between two adjacent rings vary from -9.33° 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 $\cdots$ C distance is 4.73 Å of C(27) $\cdots$ C(29) and two oxygen atoms, [O(28) $\cdots$ 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 ¹H 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



C-C bond	length(Å)
C(4)-C(5)	1.36
C(9)-C(10)	1.36
C(14)-C(15)	1.36
C(20)-C(21)	1.44
C(22)-C(23)	1.43
C(24)-C(25)	1.42

Table 2 Dihedral Angles between two adjacent planes (degree).

plane	1	2	3	4	5	6
2	8.3					
3	15.3	8.3				
4	24.7	19.5	11.6			
5	146.4	151.2	159.1	170.7		
6	143.1	146.6	153.8	165.2	7.1	
7	142.0	143.9	150.0	160.3	14.0	7.3

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.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 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]_D values are given in 10⁻¹deg·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 $-78\text{ }^{\circ}\text{C}$ and stirred for 1 h at $-78\text{ }^{\circ}\text{C}$. The resulting light gray suspension was allowed to warm to $0\text{ }^{\circ}\text{C}$. 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 CH_2Cl_2 . The combined organic extracts were washed with aqueous NaHCO_3 , brine, and dried over Na_2SO_4 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. $117\text{--}118\text{ }^{\circ}\text{C}$; $^1\text{H NMR}$ (CDCl_3) 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, 825, 795, 765, 700 cm^{-1} ; Anal. Calcd for $\text{C}_{11}\text{H}_8\text{OS}_2$: 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 NaHCO_3 , brine and dried over Na_2SO_4 . 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. $72\text{--}73\text{ }^{\circ}\text{C}$; $^1\text{H NMR}$ (CDCl_3) 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, 1050, 835, 775, 695 cm^{-1} ; Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{OS}_2\text{Si}$: 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 $-78\text{ }^{\circ}\text{C}$ and stirred for 2 h at $-78\text{ }^{\circ}\text{C}$. 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*-[(1*R*,2*R*,3*S*,4*S*)-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 C₂₂H₂₅NO₃S₂: C, 63.58; H, 6.06; N, 3.37. Found: C, 63.48; H, 6.12; N, 3.35.

***N*-[(1*R*,2*R*,3*S*,4*S*)-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 $-20\text{ }^{\circ}\text{C}$, and a suspension of **6** (0.82 g, 1.97 mmol) in 40 mL of CH_2Cl_2 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 CH_2Cl_2 . The combined organic extracts were washed with brine and dried over Na_2SO_4 . 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 CH_2Cl_2 -methanol (100:1) as eluent to give chloride **7** as a white solid (0.70 g, 82 %).

m.p. $212\text{--}215\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3) 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 $\text{C}_{22}\text{H}_{24}\text{ClNO}_2\text{S}_2$: C, 60.88; H, 5.57; N, 3.23. Found: C, 60.85; H, 5.61; N, 3.15.

***N*-[(1*R*,2*R*,3*S*,4*S*)-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 CH_2Cl_2 -methanol (20:1) as eluent to give phosphonium salt **8** as a pale yellow solid (0.64 g, 78 %).

m.p. $190\text{--}193\text{ }^{\circ}\text{C}$ (dec.); ^1H NMR (CDCl_3) 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*-[(1*R*,2*R*,3*S*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-yl]-5-[2-(5-*t*-butyldimethylsiloxymethyl-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 $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was allowed to warm to $0\text{ }^{\circ}\text{C}$. To the resulting white solution was added a solution of (*P*)-(+)-**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_2SO_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*)-(+)-**12** as a yellow solid.

^1H 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 $0\text{ }^{\circ}\text{C}$ 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. $50\text{--}51\text{ }^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.08-1.29 (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, 1H), 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 $\text{C}_{20}\text{H}_{28}\text{OS}_2\text{Si}$: 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 $-78\text{ }^{\circ}\text{C}$ 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 $-78\text{ }^{\circ}\text{C}$. 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 °C; 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 C₄₂H₅₆O₂S₄Si₂: 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 $\text{Na}_2\text{S}_2\text{O}_3$, aqueous NaHCO_3 , brine and dried over Na_2SO_4 . 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; $^1\text{H NMR}$ (CDCl_3) 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 $\text{C}_{42}\text{H}_{54}\text{O}_2\text{S}_4\text{Si}_2$: 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 CH_2Cl_2 . The organic phase was washed with dilute hydrochloric acid, saturated aqueous NaHCO_3 , and brine, and dried over MgSO_4 . 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; $^1\text{H NMR}$ (CDCl_3) 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 $\text{C}_{24}\text{H}_{14}\text{O}_2\text{S}_4 \cdot \text{C}_2\text{H}_5\text{OH}$: 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)-($\pm$)-**13** (101.2 mg, 0.219 mmol) in 100 mL of CH_2Cl_2 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.

$[\alpha]_D +1973$ (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*)-($\pm$)-**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.

$[\alpha]_D -1965$ (c 0.050, CHCl₃) (92 % ee)

Structure solution and refinement of (*PM*)-($\pm$)-**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, *D*_c = 1.324 gcm⁻³. All measurements were made on a Rigaku AFC7R diffractometer with Cu-K α radiation and a 12kW rotating anode generator. The data were collected at a temperature of 20 ± 1 °C using ω -2 θ scan technique to a maximum 2 θ value of 120.1°. Of the 3828 reflections which were collected, 3671 were unique (*R*_{int} = 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* > 3.00 σ (*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 statistics 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 $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley. The

values for the mass attenuation coefficients are those of Creagh and Hubbel. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

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a right-handed *P* helicity, the (–)-enantiomers a left-handed (*M*) helicity.^{3,9)} 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.

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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 π -excessive thiophene and π -deficient pyridine units were prepared by the use of *exo*-3-amino-2-hydroxybornane as a chiral auxiliary. This procedure consists of separation of the helical diastereomers prepared by photocyclization of 1,2-diarylethylenes 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

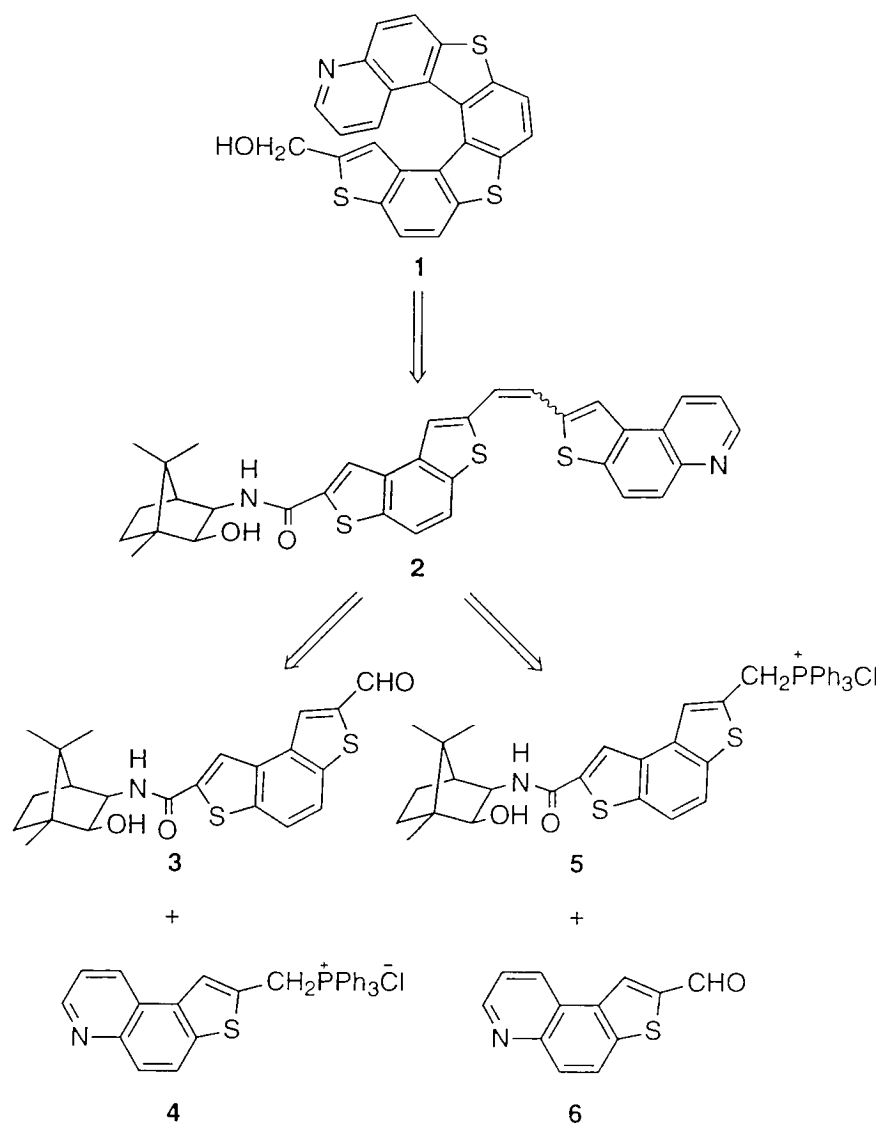
Since the first synthesis of hexahelicene ([6]helicene) which was made up of *ortho*-condensed six benzene rings by Newman in 1955,¹⁾ the helical aromatic molecules have received considerable attention because of unique helical non-planar π -electron system and of their very high rotational values.^{2,3)} The helicenes containing more than six benzene rings (carbohelicenes) or seven heterocyclic rings (heterohelicenes) possess rigid helical framework^{2a,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 heterohelices⁹⁾ by the use of *exo*- and *endo*-3-amino-2-hydroxybornane as chiral auxiliaries,¹⁰⁾ which provides various types of optically pure functionalized heterohelices.¹¹⁾ 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 -excessive thiophene and π -deficient 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 heterohelices are also described in this chapter.

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

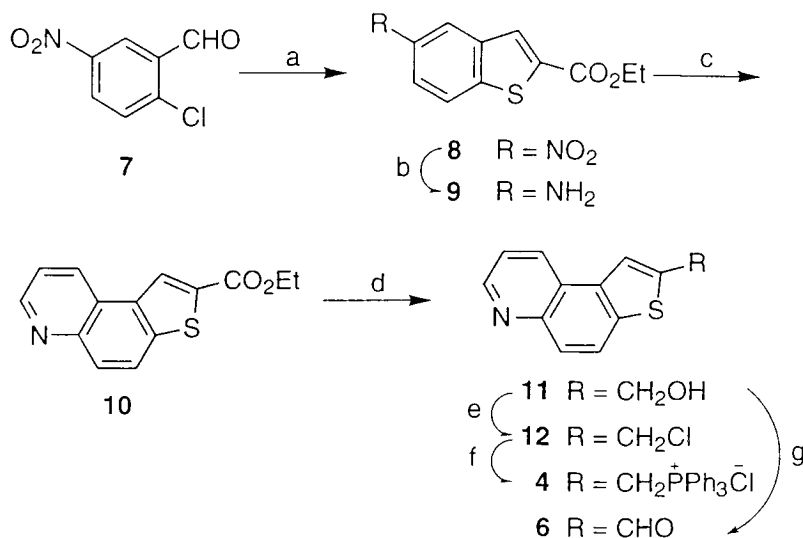
Our strategy for the synthesis of **1** bases upon the regioselective synthesis of olefin **2**, in which the thiophene appendages not only lead to the regioselective α -functionalization¹²⁾ of the ring systems, they can also participate in the regioselective photocyclization at their β -positions.^{4,13)} The pyridine nitrogen in the chiral helix 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,^{9b)} thieno[3,2-f]quinoline derivatives like **10** could not be obtained from the corresponding 1,2-diarylolefin by photocyclization.¹⁴⁾ We devised an improved method using Skraup type reaction¹⁵⁾ 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%

Scheme 1



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 LiAlH_4 provided alcohol **11**, which was converted into chloride **12** with SOCl_2 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 CH_2Cl_2 in 65% yield.

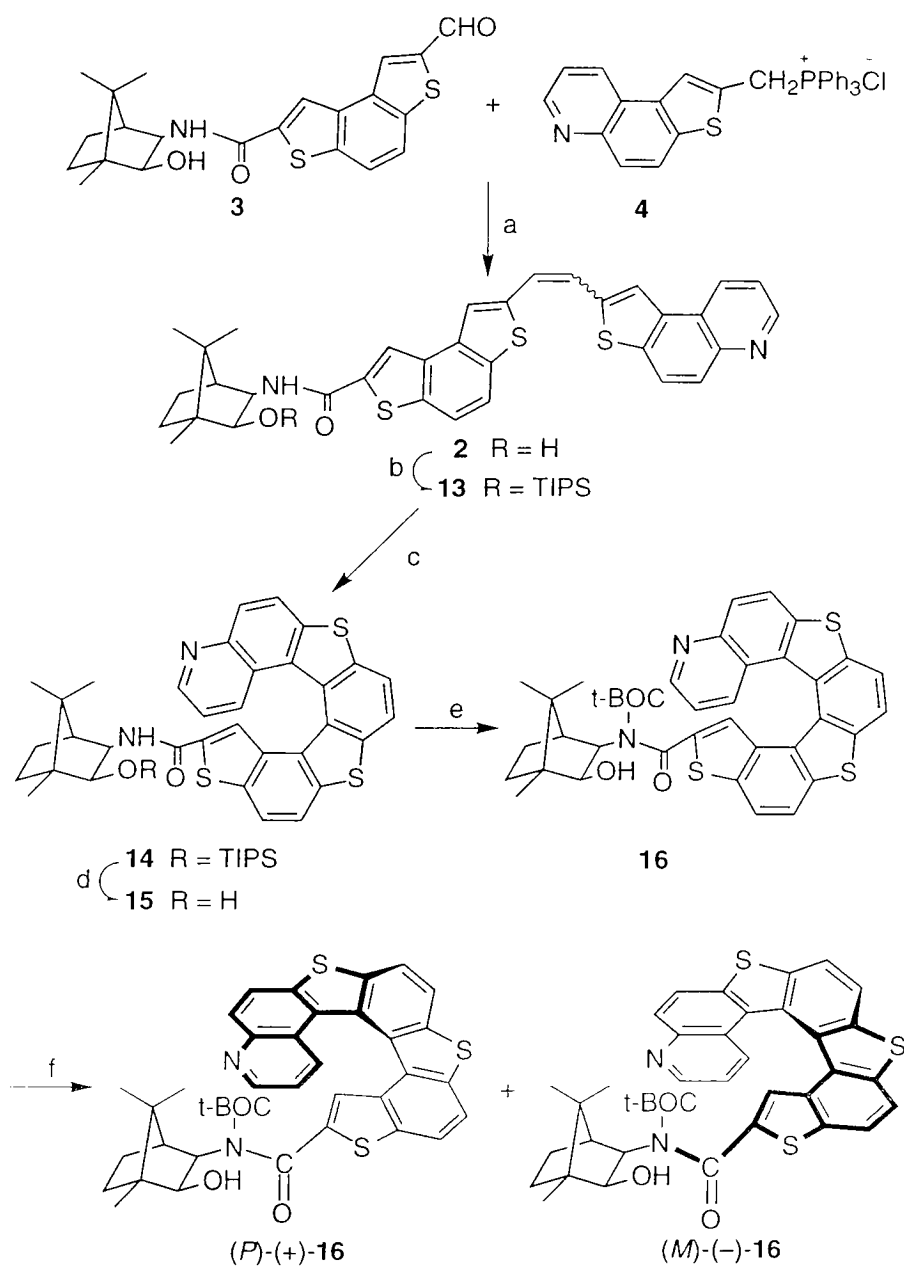
Scheme 2



Reagents and conditions: (a) HSCH₂CO₂Et, K₂CO₃, DMF, 88%; (b) iron powder, HCl, ethanol, 84%; (c) (i) H₂SO₄, glycerol, sodium *m*-benzenesulfonate, H₃BO₃; (ii) cat. H₂SO₄, ethanol, 73%; (d) LiAlH₄, THF, 91%; (e) SOCl₂, Et₃N, 74%; (f) PPh₃, benzene, 94%; (g) PDC, CH₂Cl₂, 65%.

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 ether¹⁶⁾ **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 atmosphere¹⁷⁾ 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

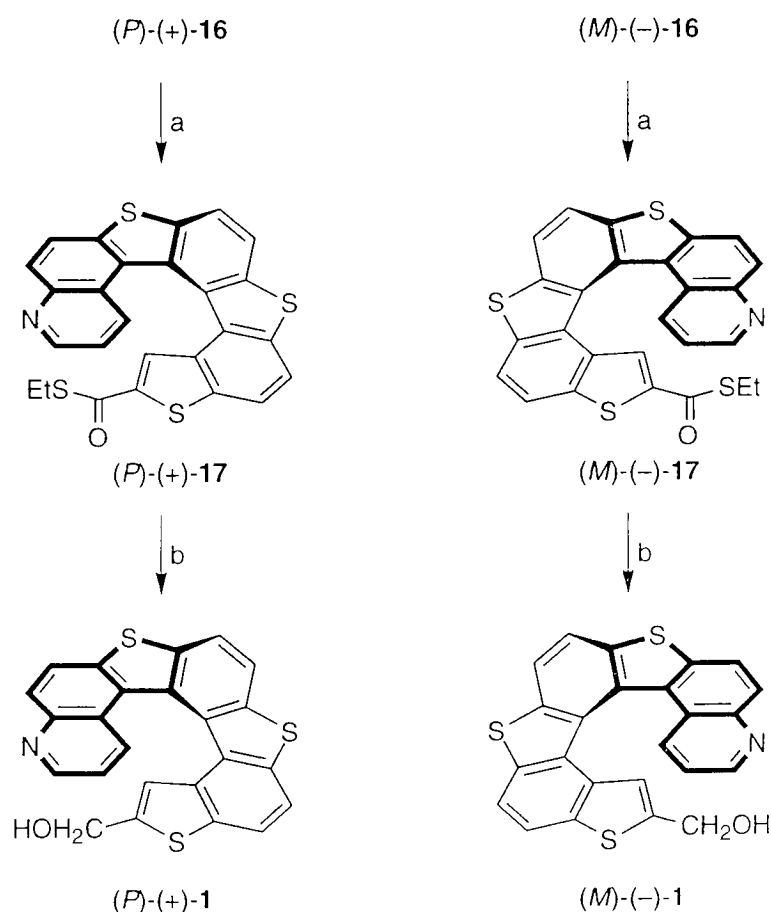


Reagents and conditions: (a) *t*-BuOK, THF, methanol, 89%; (b) triisopropylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH₂Cl₂, 94%; (c) *hν*, iodine, propylene oxide, argon, benzene, 73%; (d) TBAF, THF, 96%; (e) di-*t*-butyl dicarbonate, DMAP, CH₂Cl₂, 83%; (f) column chromatography on silica gel.

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



Reagents and conditions: (a) EtSLi, 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*-butoxy-carbonylation 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

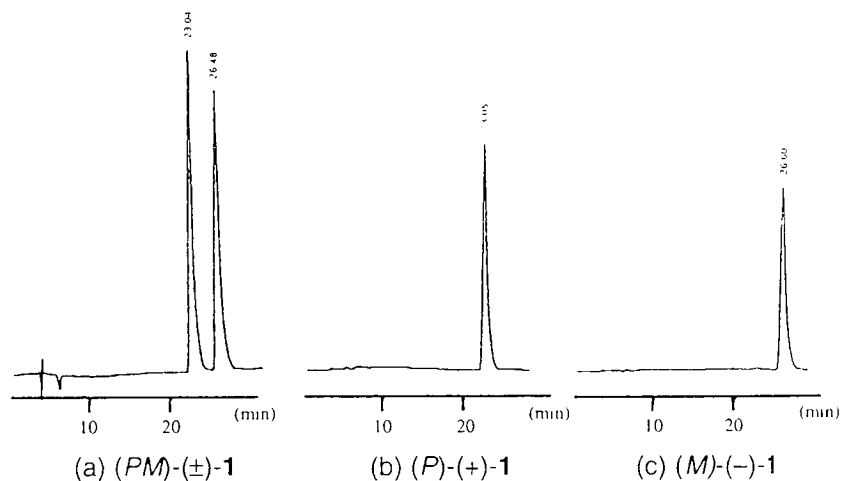


Figure 1 HPLC chromatograms of heterohelicenes **1**

Column : SUMICHIRAL OA-2000I (4.6 mm i.d. × 25 cm)

Eluent : hexane / 1,2-dichloroethane / methanol (100:100:3)

Flow rate : 1 mL/min, Detector : 254 nm

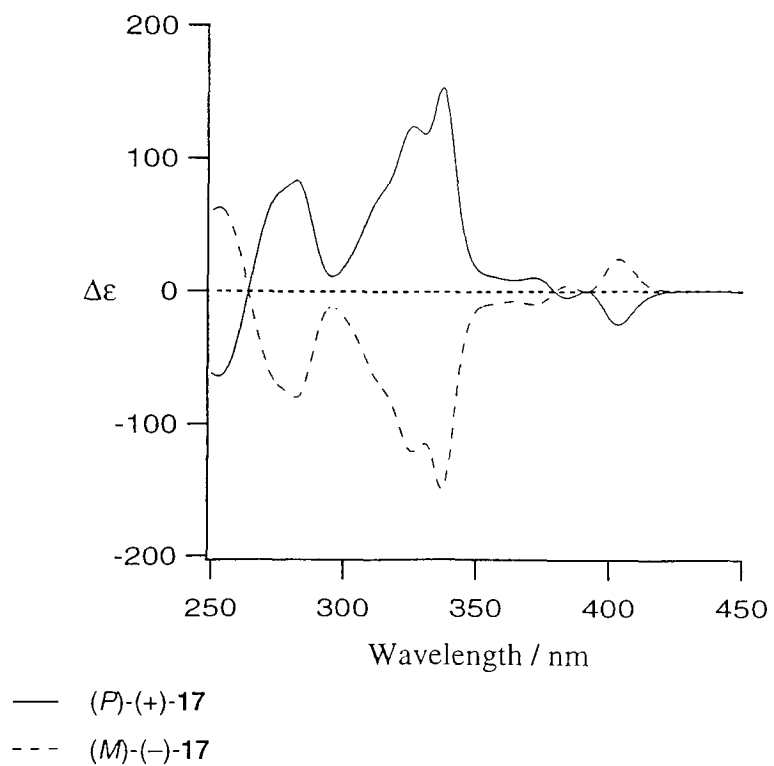


Figure 2 CD spectra of (*P*)-(+)-17 and (*M*)-(-)-17 in chloroform

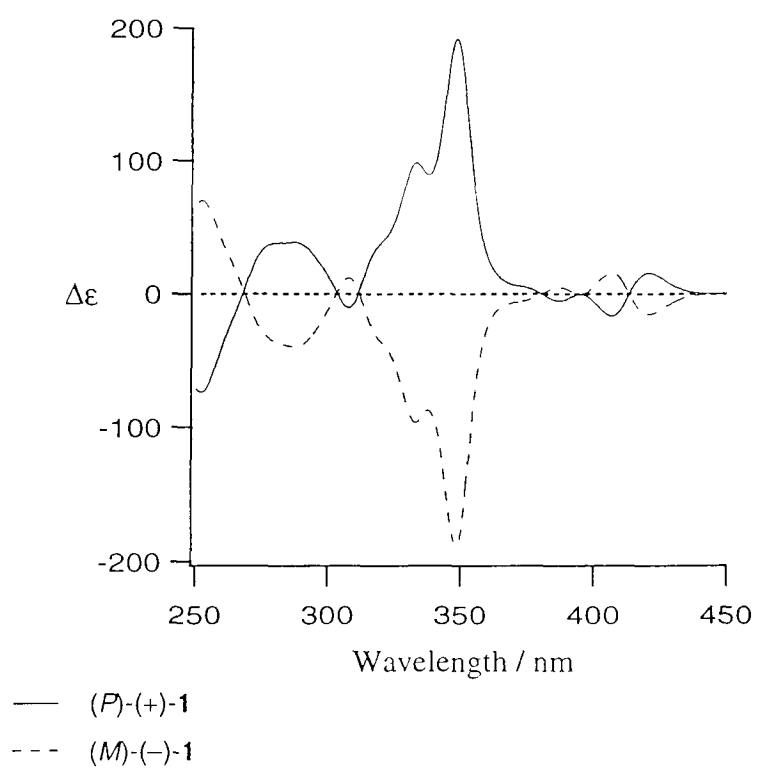


Figure 3 CD spectra of (*P*)-(+)-1 and (*M*)-(-)-1 in chloroform

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-*c*][1]benzothiophene-2-carboxylate, whose absolute configuration was determined by X-ray structural analysis of the precursor.^{9b,23)} 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*.^{2c,24)}

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**: $\Delta\delta(\text{ppm}) = +1.59$ (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 (δ 6.66 ppm) in **1** is almost the same as that of 2-H in benzo[*c*]phenanthro[1,2-*f*]quinoline (δ 6.57 ppm),²⁵⁾ but it is at higher field than that of 2-H in naphtho[1',2':4,5]thieno-[3,2-*a*]-4,7-phenanthroline (δ 7.05 ppm).²⁶⁾ 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.

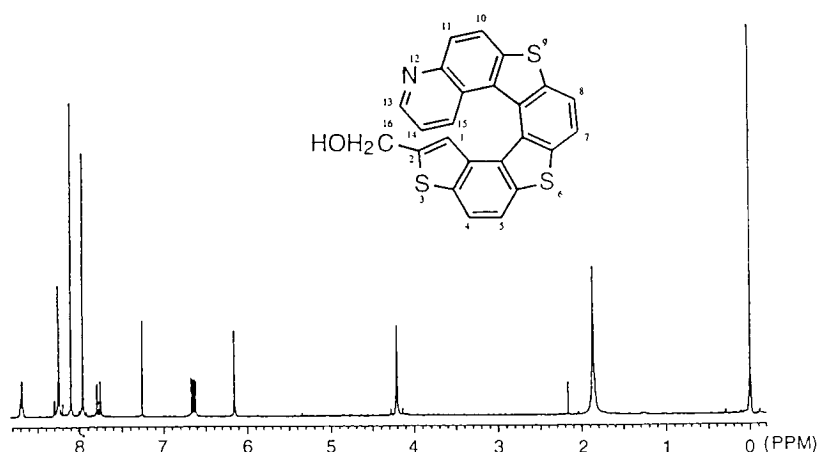


Figure 4 NMR spectrum of heterohelicene **1**.

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 micro crystalline materials, which were not suitable for X-ray analysis. The single crystal of the heterohelicene (*PM*)-($\pm$)-**1** was obtained by slow recrystallization from CHCl_3 . The results are shown in Figure 5. Although the crystal contains disordered guest CHCl_3 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

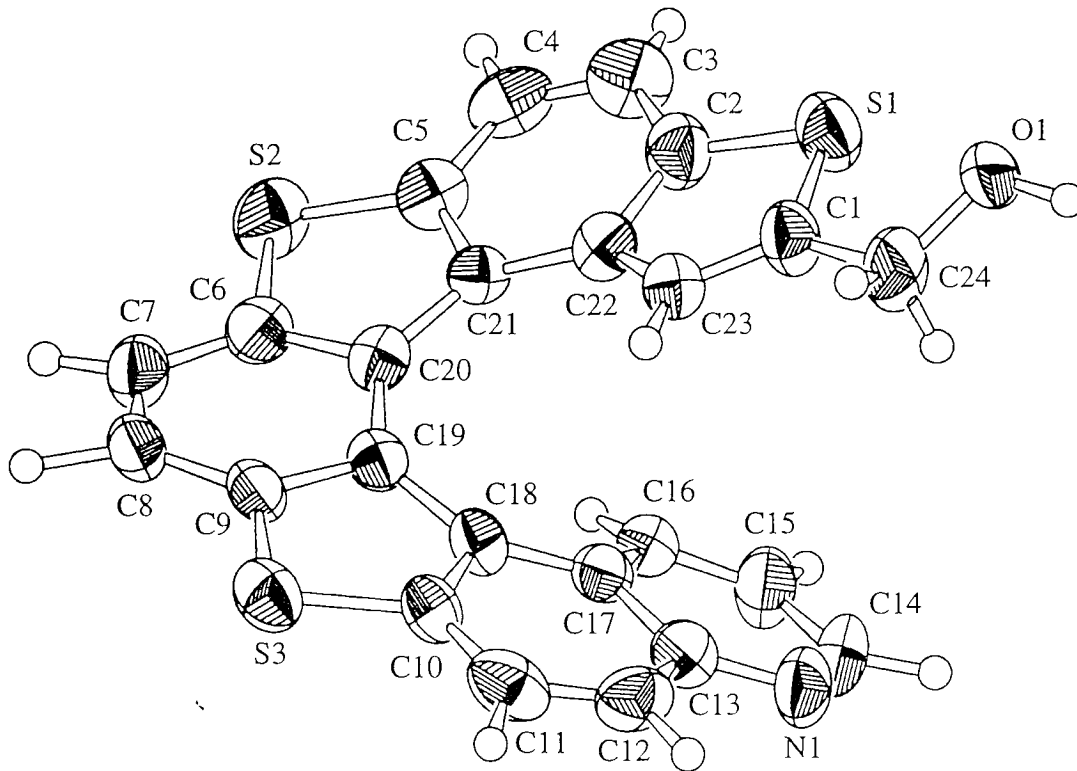


Figure 5 ORTEP view of heterohelicene **1**

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 1 Dihedral Angles between two adjacent planes (degree).

plane	1(T)	2(B)	3(T)	4(B)	5(T)	6(B)
2(B)	6.2					
3(T)	10.3	7.4				
4(B)	21.1	20.2	12.9			
5(T)	30.0	29.2	21.9	9.1		
6(B)	37.8	38.1	31.0	18.3	10.0	
7(P)	45.3	46.9	40.4	28.4	21.2	11.7

(T:thiophene; B:benzene)

Table 2 Selected C-C bond lengths

C-C bond	length(Å)
C(3)-C(4)	1.38
C(7)-C(8)	1.34
C(11)-C(12)	1.34
C(17)-C(18)	1.40
C(19)-C(20)	1.42
C(21)-C(22)	1.42

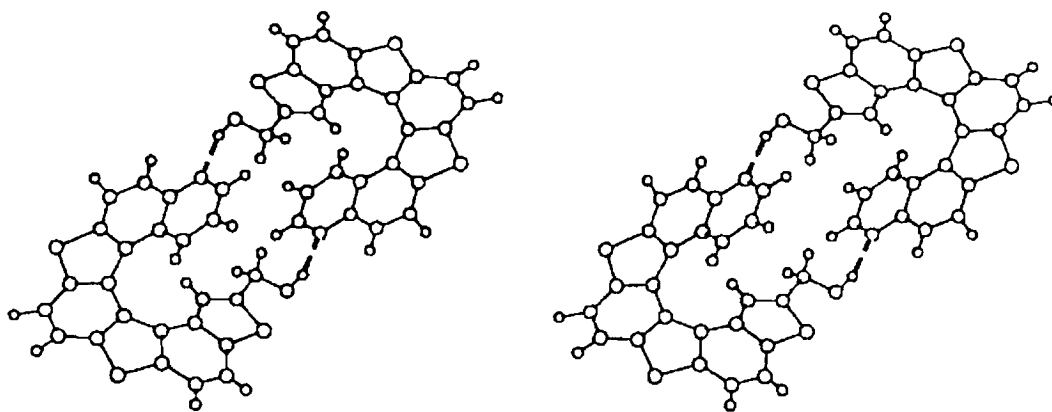


Figure 6 Stereoview of hydrogen bonded binary aggregate

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.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 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]_D 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, *J* 7.2, 3H), 4.45 (q, *J* 7.2, 2H), 7.99 (d, *J* 8.9, 1H), 8.17 (s, 1H), 8.30 (dd, *J* 8.9, 2.2, 1H), 8.78 (d, *J* 2.2, 1H); IR (KBr) 1694, 1534, 1341, 1302, 1273, 1073, 1053, 831, 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, *J* 7.2, 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.

Ethyl Thieno[3,2-f]quinoline-2-carboxylate (10).

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; $^1\text{H NMR}$ (CDCl_3) δ 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, 804, 758, 741 cm^{-1} ; Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_2\text{S}$: C, 65.35; H, 4.31; N, 5.44%. Found: C, 65.39; H, 4.29; N, 5.43.

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_2SO_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; $^1\text{H NMR}$ (CDCl_3) δ 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 $\text{C}_{12}\text{H}_9\text{NOS}$: C, 66.95; H, 4.21; N, 6.51. Found: C, 66.86; H, 4.20; N, 6.46.

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_2SO_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; $^1\text{H NMR}$ (CDCl_3) δ 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 $\text{C}_{12}\text{H}_8\text{ClNS}$: C, 61.67; H, 3.45; N, 5.99. Found: C, 61.55; H, 3.44; N, 5.95.

(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.); ¹H NMR (CDCl₃) δ 6.29 (s, 1H), 6.36 (s, 1H), 7.46 (dd, *J* 8.4, 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 C₃₀H₂₃ClNPS·2H₂O: C, 67.73; H, 5.12; N, 2.63. Found: C, 68.30; H, 5.09; N, 2.61.

Thieno[3,2-f]quinoline-2-carboxaldehyde (6).

To a stirred suspension of alcohol **11** (1.38 g, 5.90 mmol) in dry CH₂Cl₂ 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 Na₂SO₄. 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; ¹H NMR (CDCl₃) δ 7.61 (dd, *J* 8.2, 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 C₁₂H₇NOS: C, 67.59; H, 3.31; N, 6.57. Found: C, 67.48; H, 3.23; N 6.53.

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-(Triisopropylsilyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl]-5-[2-(2-thieno[3,2-f]quinolyl)ethenyl]benzo[1,2-*b*:4,3-*b'*]dithiophene-2-carboxamide (13).**

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 CH₂Cl₂ were added 2,6-lutidine

(0.48 mL, 4 mmol) and triisopropylsilyl trifluoromethanesulfonate (0.90 mL, 3.3 mmol) at $-20\text{ }^{\circ}\text{C}$, and the mixture was stirred overnight at room temperature. The resulting orange solution was washed with water and brine, and dried over Na_2SO_4 . 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. $135\text{--}137\text{ }^{\circ}\text{C}$ (dec.); ^1H NMR (CDCl_3) 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 $\text{C}_{43}\text{H}_{50}\text{N}_2\text{O}_2\text{S}_3\text{Si}$: C, 68.76; H, 6.71; N, 3.73. Found: C, 68.50; H, 7.12; N, 3.37.

***N*-[**(1*R*, 2*S*, 3*R*, 4*S*)-2-(Triisopropylsilyloxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl**][**1**]benzothieno[5',4':2,3][**1**]benzothieno-[4',5':4,5]thieno[3,2-*f*]quinoline-2-carboxamide (**14**).**

Method A : Olefin **13** (0.20 g, 0.27 mmol) and iodine (0.11 g, 0.40 mmol) were dissolved in 1.6L 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 $\text{Na}_2\text{S}_2\text{O}_3$, aqueous NaHCO_3 and brine, and dried over Na_2SO_4 . 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%).

***N*-[(1*R*,2*S*,3*R*,4*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl][1]benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-*f*]quinoline-2-carboxamide (**15**).**

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*-*t*-Butoxycarbonyl-*N*-[(1*R*,2*S*,3*R*,4*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-3-yl][1]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 dicarbodate (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: ¹H 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, 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: ¹H 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 $\text{C}_{39}\text{H}_{36}\text{N}_2\text{O}_4\text{S}_3$: C, 67.60; H, 5.24; N, 4.04. Found: C, 67.38; H, 5.24; N, 3.93.

S-Ethyl [1]Benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-f]quinoline-2-carboxylate (17).

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 Na_2SO_4 . 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. $194\text{--}195^\circ\text{C}$; ^1H NMR (CDCl_3) 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 $\text{C}_{26}\text{H}_{15}\text{NOS}_4$: C, 64.30; H, 3.11; N, 2.88. Found: C, 64.25; H, 3.16; N, 2.92; (*P*)-(+)-**17** $[\alpha]_{\text{D}} = +2670$ (c 0.0500, CHCl_3), (*M*)-(–)-**17** $[\alpha]_{\text{D}} = -2620$ (c 0.0499, CHCl_3).

2-(Hydroxymethyl)[1]benzothieno[5',4':2,3][1]benzothieno[4',5':4,5]thieno[3,2-f]quinoline (1).

To a stirred solution of the thioester **17** (28.0 mg, 0.065 mmol) in 5 mL of dry THF was added LiAlH_4 (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 Na_2SO_4 . 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. $246\text{--}247^\circ\text{C}$; ^1H NMR (CDCl_3) 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 $\text{C}_{24}\text{H}_{13}\text{NOS}_3$: C, 67.42; H, 3.06; N, 3.28. Found: C, 67.35; H, 3.00; N, 3.16; (*P*)-(+)-**1**: $[\alpha]_{\text{D}} = +2150$ (c 0.0503, CHCl_3), (*M*)-(–)-**1**: $[\alpha]_{\text{D}} = -2140$ (c 0.0503, CHCl_3).

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

A crystal of dimensions $0.40 \times 0.06 \times 0.40$ mm was used for X-ray crystallography. Crystal data: $\text{C}_{25}\text{H}_{14}\text{NOS}_3\text{Cl}_3$, $M = 546.93$, crystal system, monoclinic, space group, $P2_1/a$ (#14), $a = 7.568(3)$, $b = 20.912(2)$, $c = 15.031(3)$ Å, $\beta = 100.93(3)^\circ$, $V = 2335.9(9)$ Å³, $F(000) = 1112.00$, $Z = 4$, $\mu = 62.26$ cm^{-1} , $D_c = 1.555$ gcm^{-3} . All measurements were made on a Rigaku AFC7R diffractometer with Cu-K α 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 3899 reflections which were collected, 3596 were unique ($R_{\text{int}} = 0.030$). 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 ($I > 3.00\sigma(I)$) 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 $R_w = 0.156$, respectively. The weighting scheme was based on counting statistics 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 $\Delta f'$ 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.

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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-isopropylloxazolin-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-isopropylloxazolin-2-yl)-7-methylbenzo[1,2-b:4,3-b']dithiophene and (*S*)-1-tributylstannyl-2-(4-isopropylloxazolin-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.

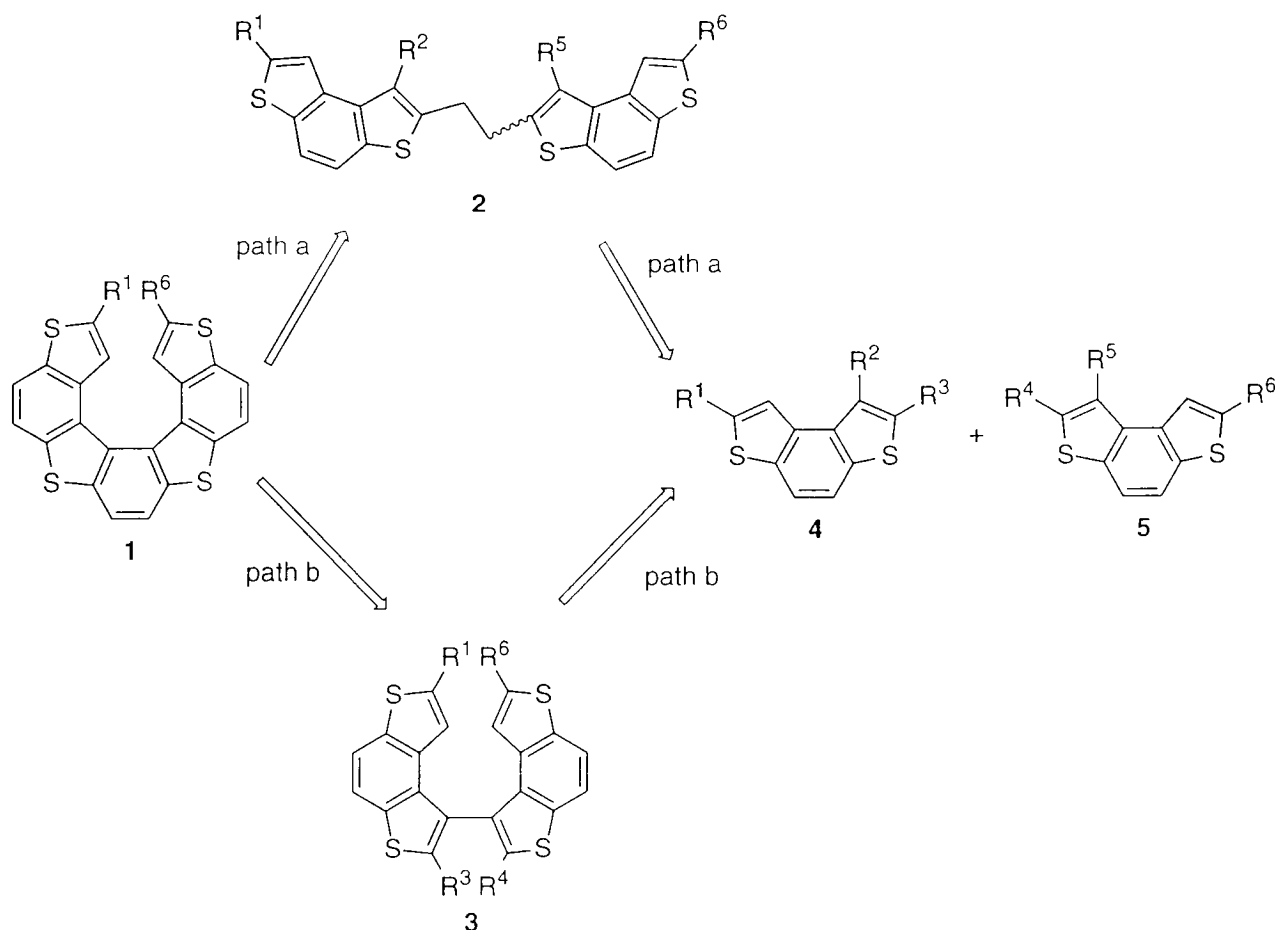
Introduction

Since the first synthesis and optical resolution of hexahelicene ([6]helicene) by Newman in 1955,¹⁾ the helical aromatic molecules have received considerable attention because of unique non-planar π -electron system and of their very high rotational values.²⁾ 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:^{3,4)} (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 I_2 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 $S_1 \rightarrow T_1$ intersystem crossing. Several non-photocyclization methods for synthesis of helicenes have been reported, including the Friedel-Crafts acylation,¹⁾ the intramolecular oxidative cyclization,⁵⁾ the cyclization of

ammonium or phosphonium salts,⁶⁾ the acid or base-catalyzed condensation reactions.^{7,8,9)} Katz and his co-workers have recently found an efficient non-photocyclization procedure using benzoquinone as a dienophile in the Diels-Alder reaction.¹⁰⁾ 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.

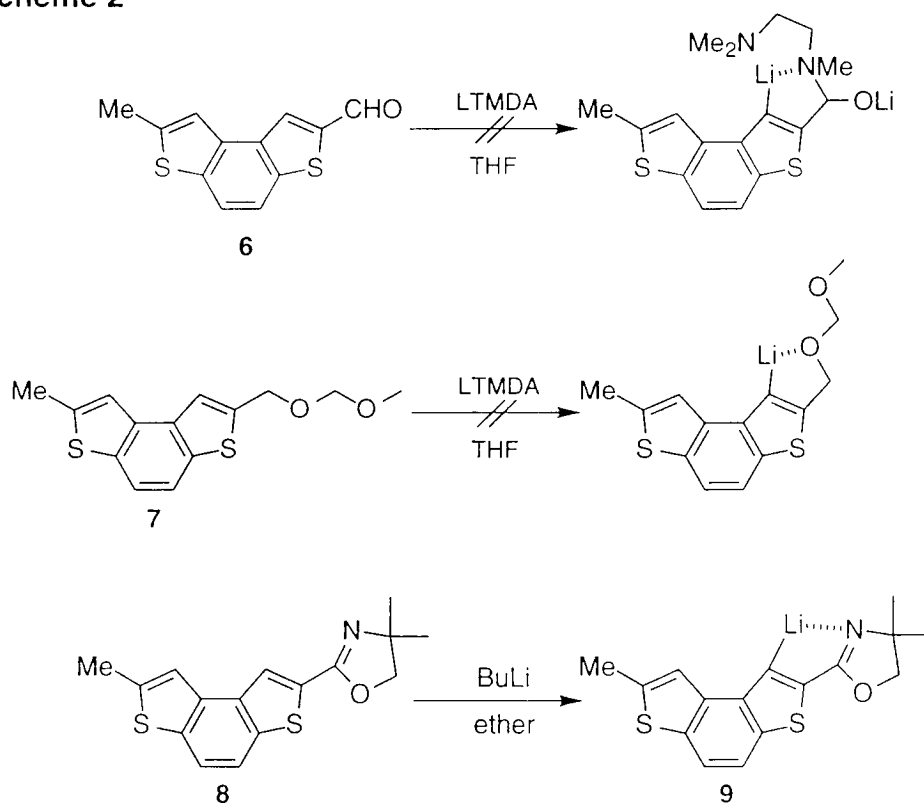
Scheme 1



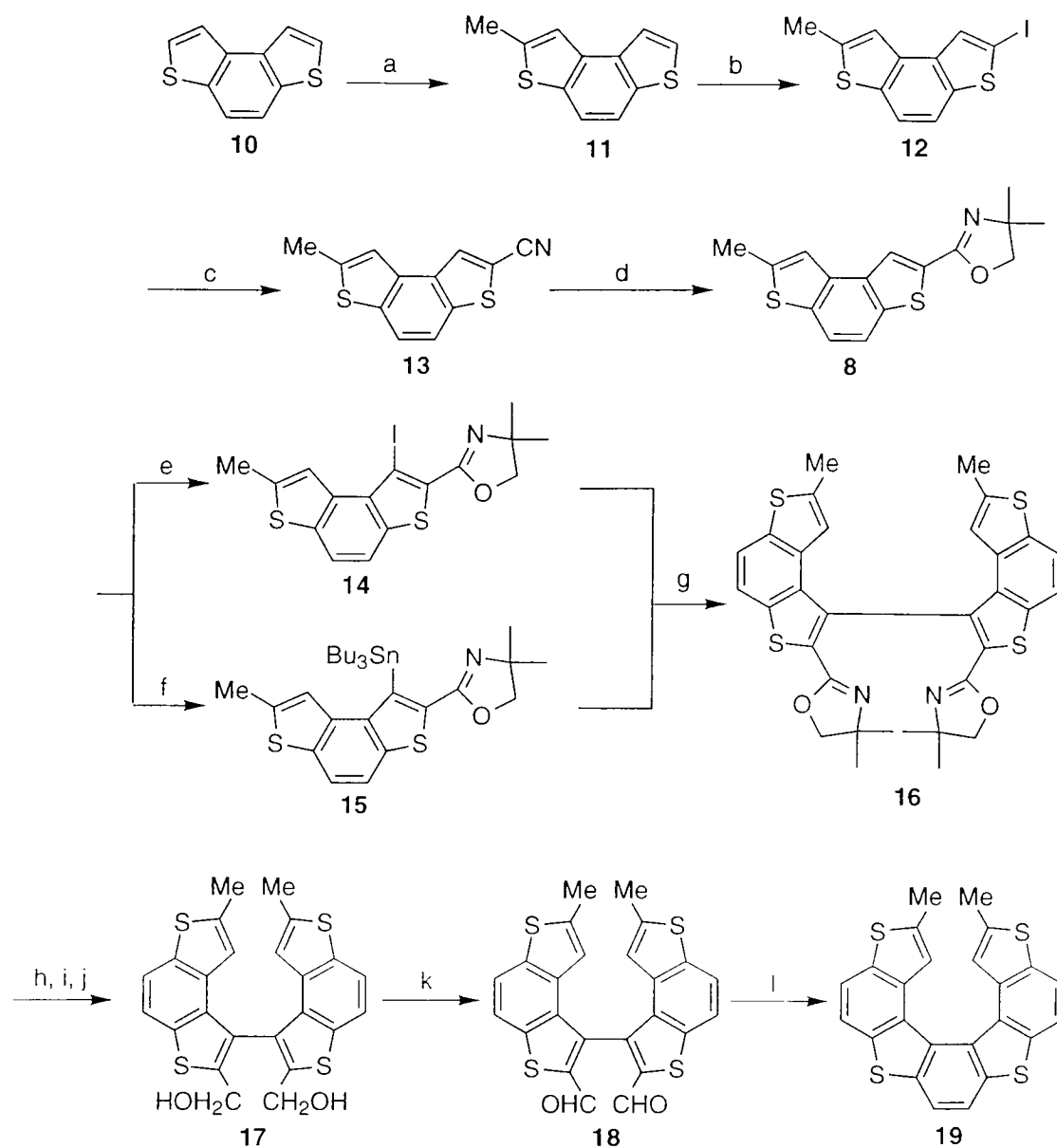
Synthesis of Racemic Disubstituted [7]Thiaheterohelicene

Our initial experiments aimed at the lithiation of the 3-position of 2-formyl-7-methylbenzo[1,2-b:4,3-b']dithiophene¹¹⁾ (**6**) using lithiated *N,N,N'*-trimethylethylenediamine (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).¹³⁾ However, we observed that the introduction of an *ortho*-directing oxazoline moiety¹⁴⁾ 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°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 3



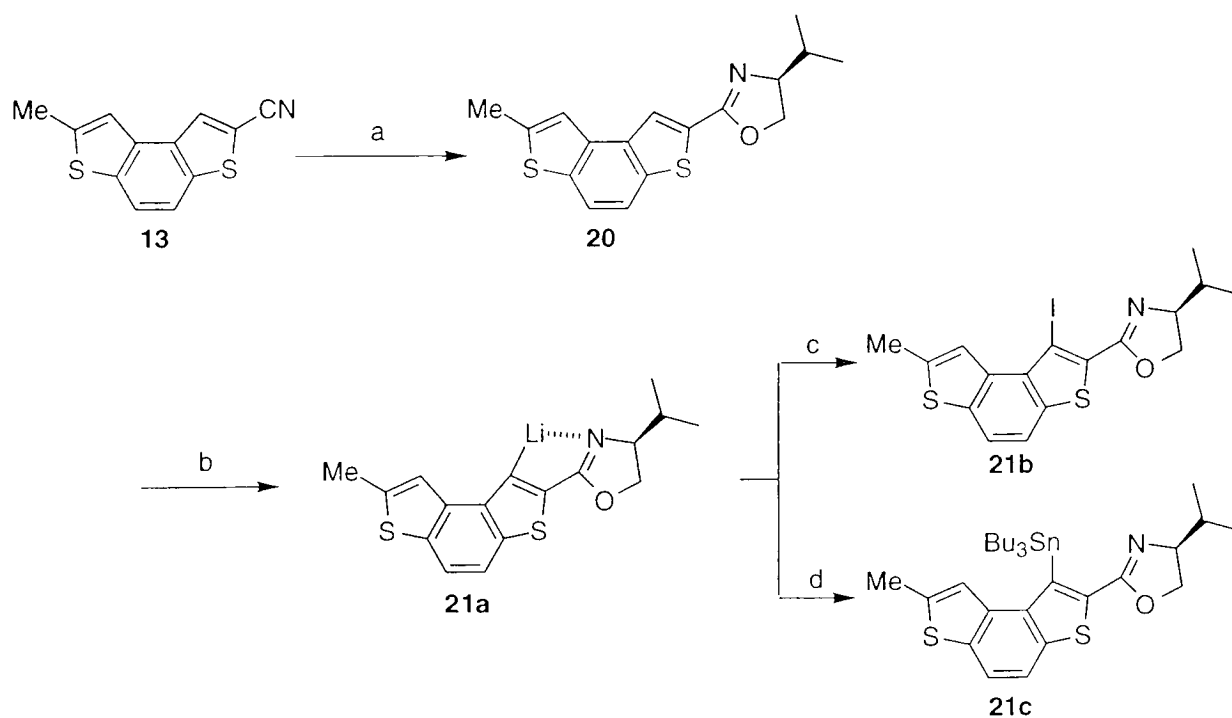
Reagents and conditions: (a) (i) BuLi, THF; (ii) MeI; (b) BuLi, THF; (ii) iodine; (c) copper(I) cyanide, DMF, 74% from 10; (d) 2-amino-2-methyl-1-propanol, cat. zinc chloride, chlorobenzene, 95%; (e) (i) BuLi, ether; (ii) iodine, 95%; (f) (i) BuLi, ether; (ii) chlorotributyltin, 91%; (g) cat. $\text{PdCl}_2(\text{PPh}_3)_2$, THF, 62%; (h) TFA, sodium sulfate, THF, H_2O ; (i) acetic anhydride, pyridine, CH_2Cl_2 ; (j) LiAlH_4 , THF, 71%; (k) PCC, CH_2Cl_2 , 94%; (l) $\text{TiCl}_3\cdot\text{DME}_{1.5}$, Zn-Cu, DME, 78%.

The cross-coupling reaction¹⁶⁾ between **14** and **15** smoothly proceeded in the presence of 5 mol% of $\text{PdCl}_2(\text{PPh}_3)_2$ 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.¹⁴⁾ Finally, the intramolecular McMurry coupling reaction¹⁷⁾ using $\text{TiCl}_3/\text{Zn-Cu}$ gave 2,13-dimethyl[7]thiaheterohelicene **19** in 32% yield. When $\text{TiCl}_3 \cdot \text{DME}_{1.5}/\text{Zn-Cu}$ ¹⁸⁾ was used in the McMurry coupling reaction, the yield of **19** was increased to 78%. The protons (δ 6.43) on C(1) and C(14) of **19**, and those (δ 5.96) on C(8) and C(8') of **18** resonate at higher field than the proton (δ 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.²⁾

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.

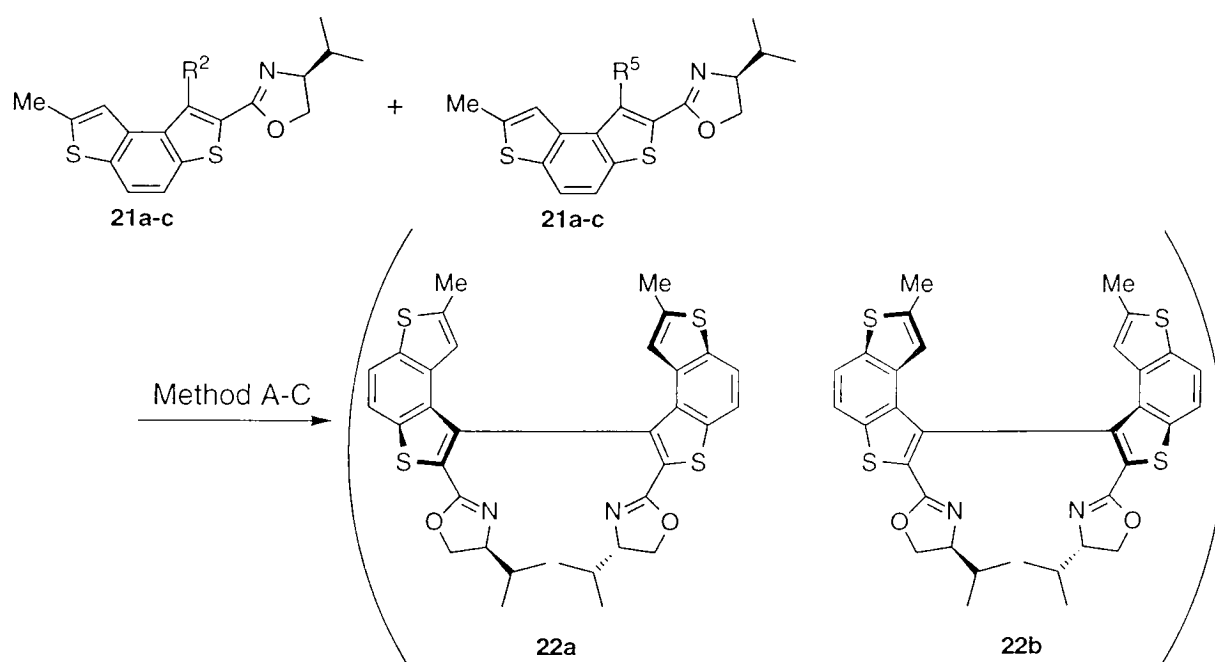
Scheme 4



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 coupling¹⁹⁾ of iodide **21b** smoothly proceeded in the presence of activated copper powder²⁰⁾ 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.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

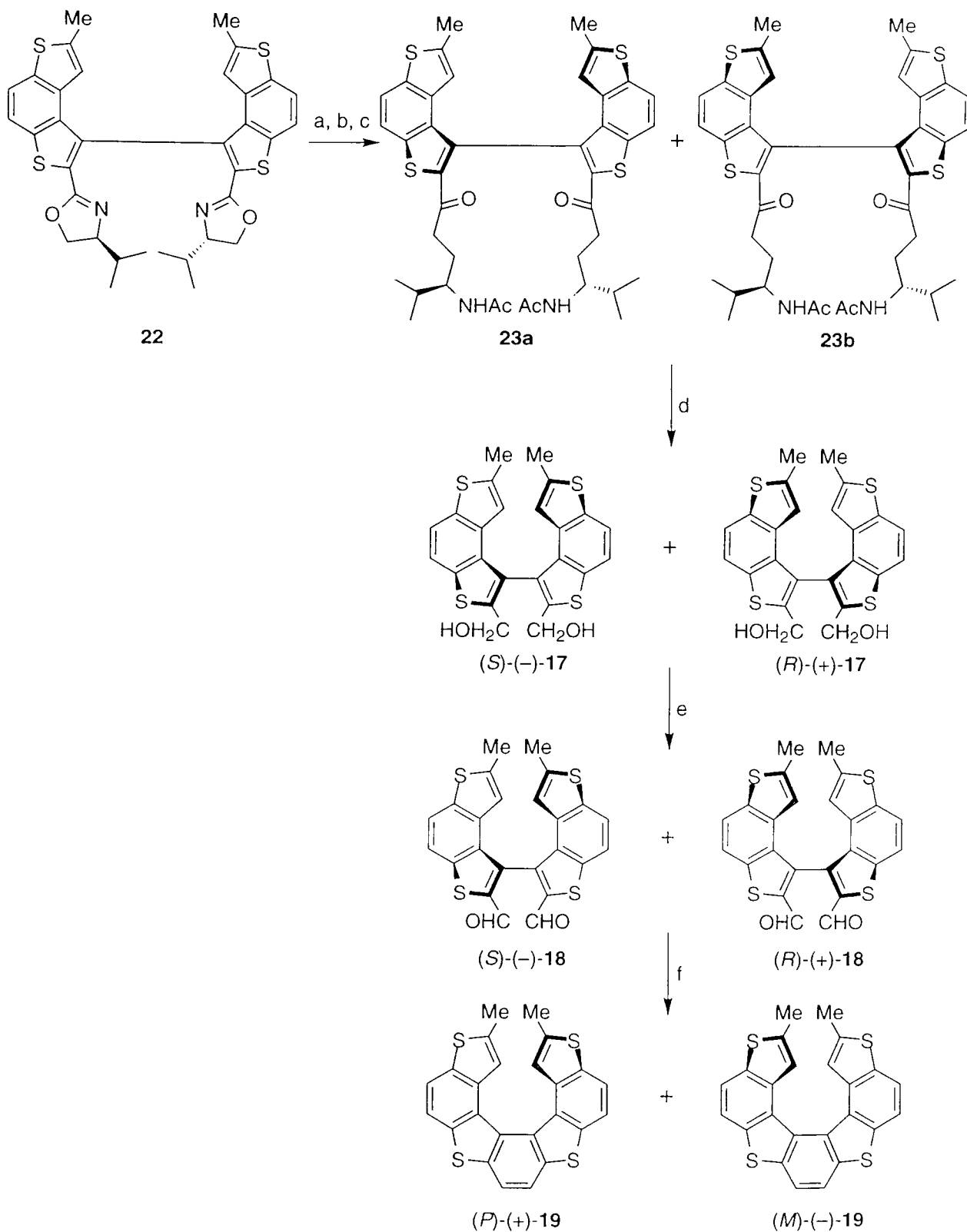
Table 1



Method	R ²	R ⁵	Mediator	Solvent	Yield(%)	22a : 22b
A	I	I	Cu	DMF	99	2.0 : 1
B	SnBu ₃	I	PdCl ₂ (PPh ₃) ₂	THF	68	2.9 : 1
C	Li	Li	CuCl ₂	ether	51 ^a	1 : 1.4

a) 22% of the protonated product (**20**) was obtained.

Scheme 5



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-DME_{1.5}, Zn-Cu, DME.

derivative **21c** catalyzed by $\text{PdCl}_2(\text{PPh}_3)_2$ 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 CuCl_2 .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 LiAlH_4 . The optical rotation of (–)-**17** was $[\alpha]_D -48.6$ (c 1.00, CHCl_3), whose absolute value was in good agreement with that of the enantiomer derived from minor diastereomer **23b**,

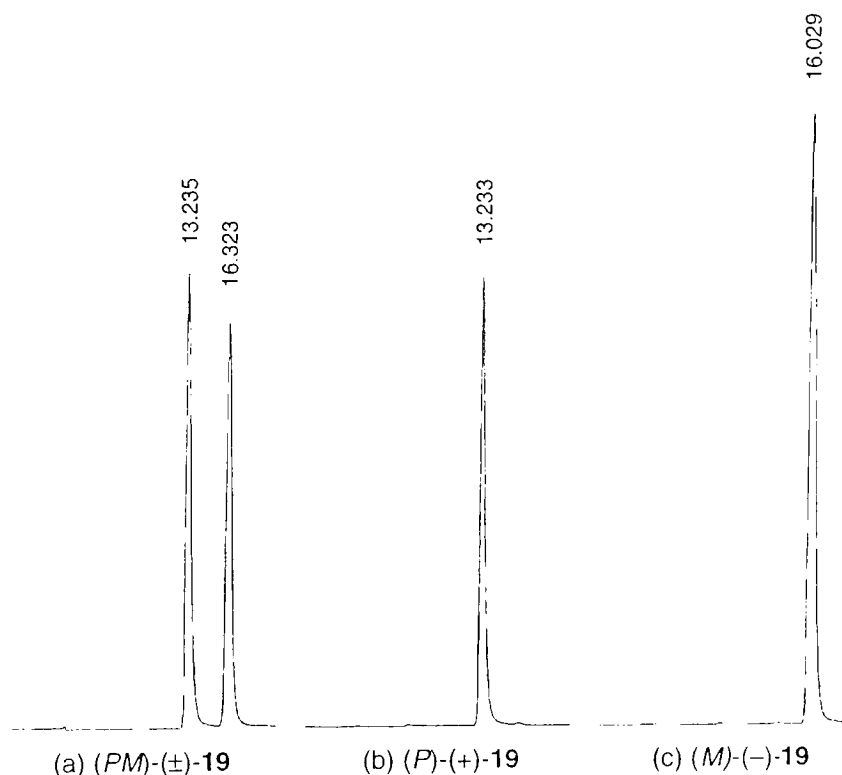


Figure 1 HPLC chromatograms of heterohelices **19**

Column : CHIRALCEL OD (4.6 mm i.d. × 25 cm)

Eluent : hexane / ethanol (100 : 0.2)

Flow rate : 1 mL/min, Detector : 254 nm

$[\alpha]_D +49.3$ (c 1.01, CHCl_3). The diol (–)- and (+)-**17** were oxidized by PCC to afford the corresponding dialdehyde (–)- and (+)-**18**, and each optical rotation was $[\alpha]_D -325$ (c 1.01, CHCl_3) and $[\alpha]_D +320$ (c 1.01, CHCl_3), respectively. The intramolecular McMurry coupling reaction using $\text{TiCl}_3 \cdot \text{DME}_{1.5}/\text{Zn-Cu}$ 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*,^{2,23)} 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 naphthyloxazoline 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 $[\alpha]_D +2720$ (c 0.0557, CHCl_3) and $[\alpha]_D -2690$ (c 0.0569, CHCl_3), respectively, and these values were much higher than those of biaryl derivatives **17** and **18**.

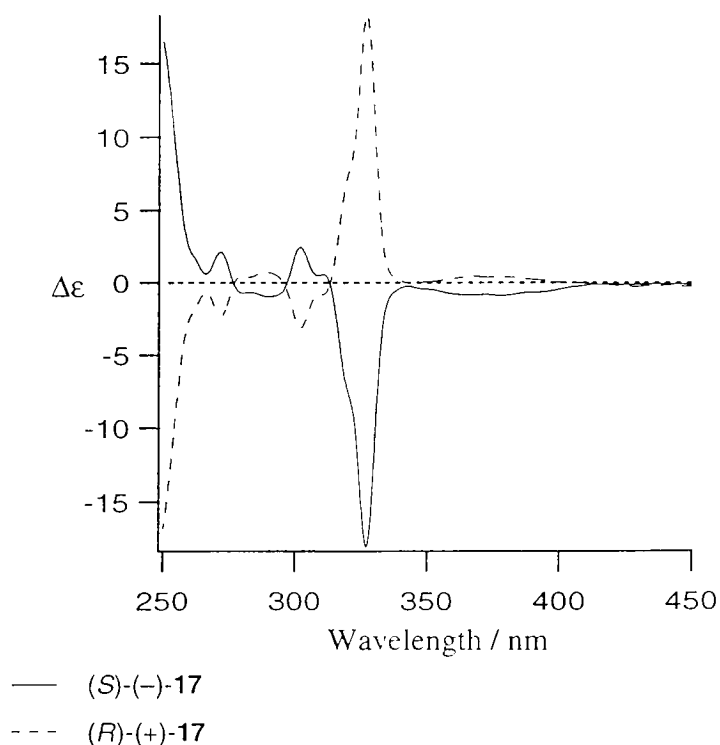


Figure 2 CD spectra of (*S*)-(-)-**17** and (*R*)-(+)-**17** in chloroform

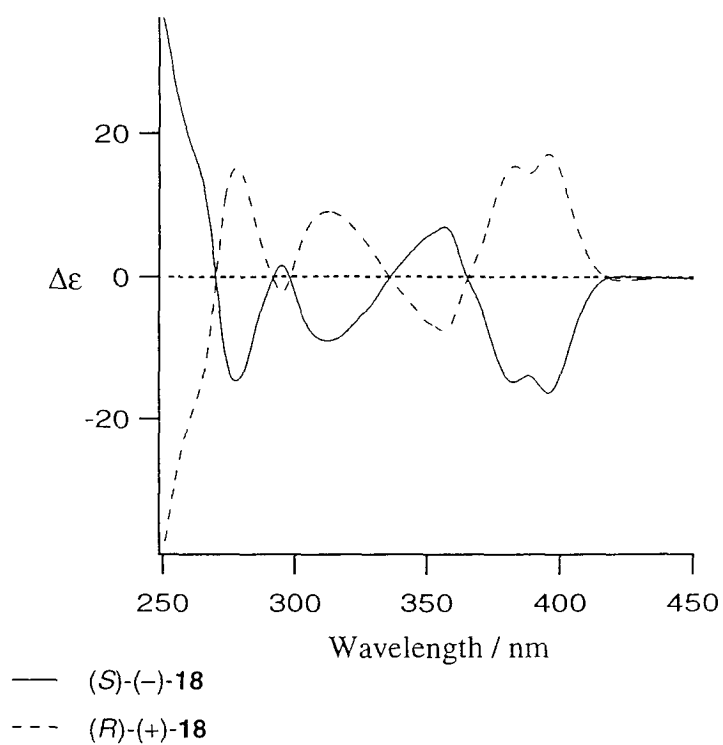


Figure 3 CD spectra of (S)-(-)-18 and (R)-(+)-18 in chloroform

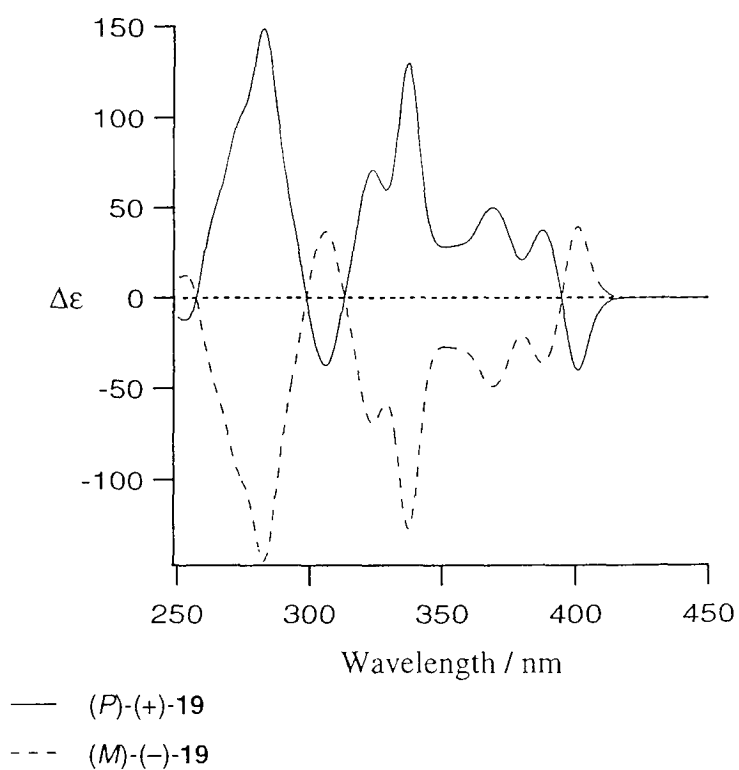


Figure 4 CD spectra of (P)-(+)-19 and (M)-(-)-19 in chloroform

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 moiety¹¹⁾ 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 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; $[\alpha]_D$ values are given in 10⁻¹deg·cm²·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_2SO_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°C under argon, and the mixture was stirred for 1 h at -78°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_2SO_3 , brine, dried over Na_2SO_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 unseparable 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** (3.11 g, 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°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_2SO_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. $120-122^\circ\text{C}$; ^1H NMR (CDCl_3) δ 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 $\text{C}_{12}\text{H}_7\text{NS}_2$: 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°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 CHCl_3 . The solution was washed with brine, and dried over Na_2SO_4 . 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; $^1\text{H NMR}$ (CDCl_3) 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 $\text{C}_{16}\text{H}_{15}\text{NOS}_2$: 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 Na_2SO_3 , brine, and dried over Na_2SO_4 . 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; $^1\text{H NMR}$ (CDCl_3) 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 $\text{C}_{16}\text{H}_{14}\text{INOS}_2$: 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 Na_2SO_4 . The solvent was evaporated and the residue was purified by GPC using CHCl_3 as eluent to give tin compound **15** as pale yellow oil (1.51 g, 91 %).

^1H NMR (CDCl_3) 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 $\text{PdCl}_2(\text{PPh}_3)_2$ (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 Na_2SO_4 . 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 (CDCl_3) 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 $\text{C}_{32}\text{H}_{28}\text{N}_2\text{O}_2\text{S}_4$: 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 Na_2SO_4 , 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 CH_2Cl_2 . 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 Na_2SO_4 . 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 LiAlH_4 (0.25 g, 6.55 mmol), and stirred at room temperature. The reaction was quenched by diluted HCl at 0°C, and diluted with CHCl_3 . The organic phase was separated, washed with brine, and dried over Na_2SO_4 . The solvent was evaporated, and the residue was passed through short column of silica gel using CHCl_3 -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); ¹H NMR (CDCl₃) δ 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 C₂₄H₁₈O₂S₄: C, 61.77; H, 3.89; N, 0. Found: C, 61.64; H, 3.87; N, 0; (*S*)-(–)-**17**: [α]_D –48.6 (c 1.00, CHCl₃); (*R*-(+)-**17**: [α]_D +49.3 (c 1.01, CHCl₃).

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 CH₂Cl₂ 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 Na₂CO₃ solution and brine, and dried over Na₂SO₄. The solvent was evaporated and the residue was recrystallized from CHCl₃ to give dialdehyde **18** (0.39 g, 94 %) as a yellow solid.

m.p. 280-281 °C; ¹H NMR (CDCl₃) δ 2.32 (d, *J* 1.1, 6H), 5.96 (br s, 2H), 7.89 (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, 662, 515 cm⁻¹; Anal. Calcd for C₂₄H₁₄O₂S₄: C, 62.31; H, 3.05. Found: C, 62.52; H, 3.00; (*S*)-(–)-**18**: [α]_D –325 (c 1.01, CHCl₃); (*R*-(+)-**18**: [α]_D +320 (c 1.01, CHCl₃).

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 TiCl₃(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 CHCl₃, and filtrated through celite pad. The filtrate was washed with water and brine, and dried over Na₂SO₄. 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; ¹H NMR (CDCl₃) δ 2.14 (d, *J* 1.1, 6H), 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 C₂₄H₁₄S₄: C, 66.94; H, 3.28. Found:

C, 67.19; H, 3.27; (*P*)-(+)-**19** : $[\alpha]_D^{25} +2720$ (c 0.0557, CHCl₃); (*M*)-(–)-**19** : $[\alpha]_D^{25} -2690$ (c 0.0569, CHCl₃).

(*S*)-2-(4-Isopropylloxazolin-2-yl)-7-methylbenzo[1,2-*b*:4,3-*b'*]-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-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 CHCl₃. The solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate and brine, and dried over Na₂SO₄. 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; ¹H NMR (CDCl₃) δ 0.96 (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, 1354, 1184, 1038, 945, 860, 833, 793, 492 cm⁻¹; Anal. Calcd for C₁₇H₁₇NOS₂: C, 64.73; H, 5.43; N, 4.44. Found: C, 64.75; H, 5.50; N, 4.32.

(*S*)-1-Iodo-2-(4-isopropylloxazolin-2-yl)-7-methylbenzo[1,2-*b*:4,3-*b'*]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 Na₂SO₃, and dried over Na₂SO₄. 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; ¹H NMR (CDCl₃) δ 1.00 (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 C₁₇H₁₆INOS₂: C, 46.26; H, 3.65; N, 3.17. Found: C, 46.32; H, 3.66; N, 3.12.

(S)-1-Tributylstannyl-2-(4-isopropylloxazolin-2-yl)-7-methyl-benzo[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 $-78\text{ }^{\circ}\text{C}$ under argon, and the mixture was stirred for 1 h at $-78\text{ }^{\circ}\text{C}$. 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 Na_2SO_4 . The solvent was evaporated and the residue was purified GPC using CHCl_3 as eluent to give tin compound **21c** as pale yellow oil (0.18 g, 79 %).

^1H NMR (CDCl_3) 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)-isopropylloxazolin-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 copper²⁰⁾ (0.96 g, 15 mmol). The mixture was heated at $100\text{ }^{\circ}\text{C}$ for 1h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with aqueous ammonia and brine, and dried over Na_2SO_4 . 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 $\text{PdCl}_2(\text{PPh}_3)_2$ (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 Na_2SO_4 . 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 $\text{C}_{38}\text{H}_{40}\text{N}_2\text{O}_6\text{S}_4$: 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 $^{\circ}\text{C}$; ^1H 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 $\text{C}_{38}\text{H}_{40}\text{N}_2\text{O}_6\text{S}_4$: C, 60.94; H, 5.38; N, 3.74. Found: C, 60.76; H, 5.73; N, 3.52.

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