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# Novel chiral cyclic polysulfides with a biphenyl backbone: investigation of atropisomerism and pentathiepin ring inversion

Ryu Sato*, Ashraful Alam, Hidetoshi Ohta, Ko-ei Mori, Yuki Sato, Masayoshi Okawa, Masashi Tada, Shiduko Nakajo, Satoshi Ogawa, Tatsuya Yamamoto

*Department of Chemical Engineering, Faculty of Engineering, Iwate University, Morioka 020-8551, Japan*

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**Abstract**

Novel axially chiral benzopolysulfides were synthesized on biaryls by sulfurization of dithiastannoles. Pentathiepin, trithiole, and trithiole 2-oxide rings were observed as single isomer on 1,1′-biaryls. The rotational energy barrier of chiral axis was increased by incorporation of a methyl group at *ortho*-position. In that case, both trithiole oxide and pentathiepin rings appeared as diastereomer. *ortho*-Tolyl functionality was also replaced by naphthyl moiety to create more rotational hindrance. Chiral axis was incorporated at the neighborhood of polysulfide functionality by Suzuki–Miyaura cross-coupling reaction. Calculated rotational energy barriers were very much consistent with experimental observations to show atropisomerism. Energy barrier for the inversion of pentathiepin ring was experimentally determined by variable temperature $^1$H NMR. The kinetic data suggested that pentathiepin ring inversion was prompt in solution. Insufficient rotational energy barriers of chiral axis and pentathiepin ring inversion make substantially impossible to separate optically pure diastereomer even by chiral chromatography [Preliminary report: Sato, R.; Ohta, H.; Yamamoto T.; Nakajo, S.; Ogawa, S.; Alam, A. *Tetrahedron Lett.* **2007**, *48*, 4991–4994.].


*Keywords:* Axial chirality; Diastereomer; Biphenyl backbone; Pentathiepin; Ring inversion

## 1. Introduction

Rotationally hindered biaryls with rigid chiral frameworks appeared as the most successful reagents and catalysts in modern synthetic chemistry.[2] Axially chiral biaryls are of importance not only as chiral ligands in asymmetric reactions but also for biologically active natural products. Axially chiral molecules are widely found in nature and exhibit a broad range of biological activities and therefore a continuous effort has been devoted to their synthesis.[3] The rotation about the σ-bond of 1,1′-biaryls and its derivatives is an important designing factor to generate atropisomerism. Syntheses of cyclic polysulfides on rotationally hindered biaryls are extremely attractive choice, as their polysulfide derivatives are not yet explored on rotationally hindered systems.[4,5] Slow inversion of pentathiepin ring has inspired us to make polysulfide functionality on selected biaryls having substituents around the locked bond.

A small number of chiral benzopolysulfides have been reported so far. Varacin is the first naturally occurring benzopolysulfide, which showed potential antifungal and cytotoxic activities.[6] It is also reported that $^1$H NMR signals assigned to the side chain methylene proton of some varacin derivatives are complex multiplets, rather than simple one. Pentathiepin ring hinders the rotation around the side-chain bonds of varacins. Moreover, a barrier to interconversion of the low energy conformations of the pentathiepin ring induces asymmetry into the molecule, causing these protons to become diastereotopic.[7] Searle et al. also observed chirality for lissoclinotoxin A derivatives. They also quoted an interesting conclusion that asymmetric pentathiepins are chiral at least on NMR time scale although some compounds were racemized during isolation.[8] The origin of the chirality for pentathiepin is best

* Corresponding author.
*E-mail address:* rsato@iwate-u.ac.jp (R. Sato).

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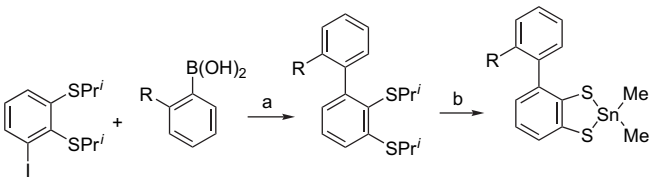
explained by slow inversion of the pentathiepin ring.[7–9] Interesting feature is that chirality is not yet observed for its trithiole or other cyclic polysulfur systems. Since then, benzopentathiepins have received considerable attention in the light of structural diversity and biological activities.[10,11] Almost all chiral benzopentathiepins were found to show biological activity and therefore we appended our attention to develop benzopenathiepin having chiral axis at the neighborhood of the pentathiepin ring.

Axial chirality is closely associated with the stereoisomers resulting from the hindered rotation about the single bond, where the barrier to rotation is high enough to allow for the isolation of the conformers. The conditions for the existence of stereoisomerisms have been defined as one where stereoisomers can be isolated and have a half-life of at least 1000 s.[12] Derivatizations of pentathiepin with chiral axis would provide atropisomeric products, which might be detectable by spectroscopy. Hence, naphthalene moiety was selectively incorporated near to polysulfide ring to give axially chiral benzopolysulfides.

## 2. Results and discussion

### 2.1. Synthesis of 2,2-dimethyl-4-phenyl-1,3,2-benzodithiastannol

The routes for the synthesis of cyclic polysulfides on 1,1′-binaphthyls are presented in Scheme 1. Reaction of 1,2-benzenedithiol with 2-iodopropane afforded 1,2-bis(isopropylthio)benzene in 79% yield.[13] Selective *ortho*-lithiation of 1,2-bis(isopropylthio)benzene with *n*-BuLi in hexane/TMEDA and successive iodination with $I_2/Et_2O$ gave 1-iodo-2,3-bis-(isopropylthio)benzene (**1**) in 66% yield, a suitable element for Suzuki–Miyaura cross-coupling reaction. Both asymmetric and symmetric C–C cross-coupling reactions were performed between **1** and boronic acid derivatives (**2** or **3**) in $DMF/H_2O$ in the presence of $CsCO_3$ as base and $Pd(PPh_3)_4$ as catalyst.[14] In the case of reaction of **1** and **2**, cross-coupling product **4** was isolated in excellent yields. The $^1H$ NMR spectrum of all isopropyl protons of **4** appeared as clear septet and doublet, respectively. The results indicated that rotation of isopropyl group occurred freely and $C_{aryl}–C_{aryl}$ bond did not affect on the rotation. Hence, compound **4** was a single isomer each. After dealkylation of isopropylthio group of compound **4** with Na/pyridine, we protected unstable dithionates with dimethyl tindichloride to give 2,2-dimethyl-4-phenyl-1,3,2-benzo dithiastannole (**6**) in 47% yield. Since the cross-coupling reaction of **1** with **2** gave successfully compound **4**, the synthesis of 2,2-dimethyl-4-(*o*-tolyl)-1,3,2-benzodithiastannole (**7**) was performed without thorough isolation of coupling intermediate 2,3-bis(isopropylthio)-2′-methylbiphenyl (**5**). As a result of such procedures, we achieved the valuable protected compound **7** from **1** and **3** in 39% yield. Spectroscopic data anticipated well for structural elucidation of the generated molecules. The energy of rotational barrier is an important criterion to resolve the racemates into diastereomer. Thus, it was sufficiently increased by adding one methyl group near to rotational axis.

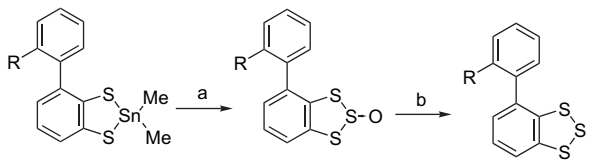



**1** **2** (R = H) **3** (R = Me) **4** (R = H) **5** (R = Me) **6** (R = H) **7** (R = Me)

Scheme 1. (a)$Pd(PPh_3)_4$ (2 mol %), $CsCO_3$ (1 equiv), $DMF/H_2O$, 120 °C, 6 h; (b) (i) Na (excess)/pyridine, reflux, 2 h, (ii) $NaBH_4$/THF/EtOH, (iii) $H_3O^+$, (iv) $Me_2SnCl_2$.

### 2.2. Synthesis of trithiole ring on 1,1′-biphenyl

Stannoles **6** and **7** were converted into corresponding trithiole 2-oxide by a common procedure quantitatively (Scheme 2).[1] Compound **8** was a single isomer. However, for increasing the rotational energy barrier of $C_{aryl}–C_{aryl}$ bond by incorporation of a methyl group, its derivative **9** appeared as diastereomer.[15] It has been pointed out that enantiomerically stable biaryls require at least three *ortho*-substituents to avoid the racemization due to the rotation around the internal bond of biaryls.[16] Compound **9** having two *ortho*-substituents on the biphenyl backbone was observed as diastereomer.[17] In general, those biphenyls in which the *mono*-substituted aromatic ring had an $sp^3$ carbon at the *ortho*-position were stable toward racemization.[18] For example, methyl group significantly retards racemization. On the other hand, electron withdrawing *ortho*-substituent group also inhibits the racemization process.[19] Sulfinyl oxygen withdraws electron from aromatic ring. Hence, although compound **9** is a di-*ortho*-substituted biphenyl, it showed diastereomeric character. However, rotational energy barrier was too low to separate optically pure diastereomer by chromatography. Compound **9** lost its diastereomerism upon reduction of sulfinyl oxygen with $SmI_2$ in THF. The evidences for generation of diastereomerism are shown in Figure 1. Methyl protons of **9** showed two singlets at 2.09 and 2.19 ppm in $^1H$ NMR. The peaks indicated that compound **11** was a single isomer due to loss of sulfinyl oxygen. Axial or equatorial arrangements of sulfinyl oxygen in respect of methyl group can promote the chirality. Observation of **9** in solution for a long time reveals the variation of diastereomeric ratio. The ring inversion of trithiole 2-oxide is not so prompt and it seems to help the molecule to separate into two isomers.




**6** (R=H) **7** (R= Me) **8** (R=H) **9** (R= Me) **10** (R=H) **11** (R= Me)

Scheme 2. (a) $SOCl_2$/THF, rt, 0.5 h; (b) TMSOTf/THF, $SmI_2$, −78 °C, 15 min.

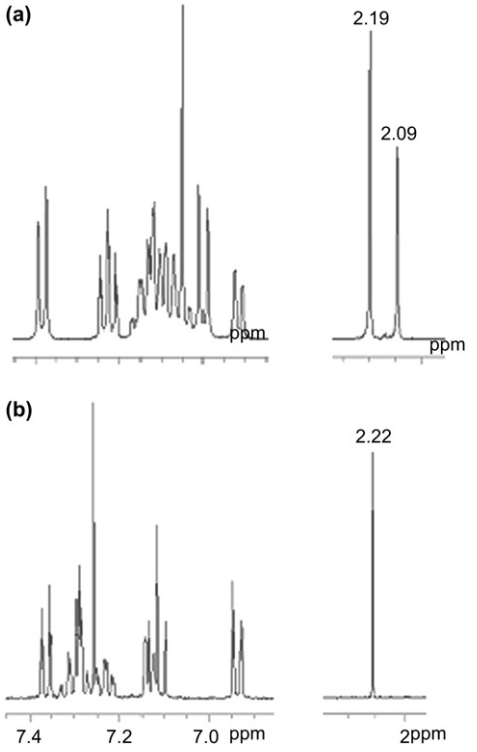
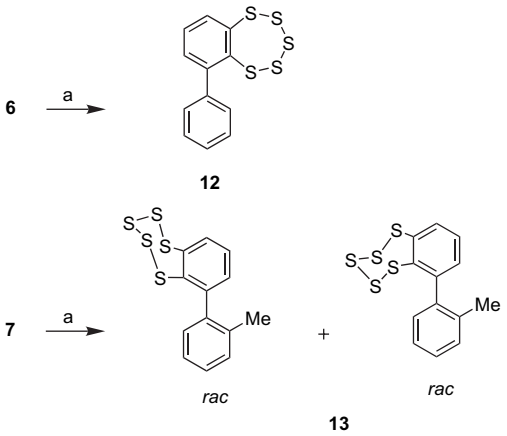



Figure 1. $^{1}$H NMR spectra of (a) compound **9** and (b) compound **11**.

Even by chiral chromatographic separation of **9**, we noticed their mutual interconversion by rotation around the biphenyl bond. In fact, starting from one enriched fraction of **9**, the same equilibrium ratio was reached in $CCl_4$ solution. Partial recrystallization at low temperature also did not afford any suitable optically pure single crystal.

### *2.3. Synthesis of pentathiepin ring on 1,1′-biphenyl*

Stannoles **6** and **7** were treated with $S_2Cl_2$ in THF to give stable pentathiepin rings (Scheme 3). 6-Phenylbenzopentathiepin (**12**) was isolated as a single isomer in 36% yield.[4,20] Pentathiepin ring in **12** does not interfere about the rotation of chiral axis. In another hand, formation of two diastereomers (**13**) was observed for the reaction of **7** at 1:1 isomeric ratio determined by NMR measurement in 53% yield. The central bond rotation was hindered for introduction of both methyl group and pentathiepin ring (Fig. 2). In $^{1}$H NMR, methyl protons appeared at 1.99 and 2.17 ppm as two singlets. In $^{13}$C NMR, methyl carbons also appeared at 20.26 and 20.86 ppm. These two diastereomers were always in equilibrium in solution. Therefore, the isolation of diastereoisomer as an optically active form is substantially impossible. The products **13** have low rotational energy barrier and one isomer exhibits fast pentathiepin ring inversion to another in the experimental conditions. Diastereomeric peaks were also calculated by B3LYP/6-31G(d) level for each optically pure isomer and the calculations were very much consistent with the experimental values. The calculated values were summarized in Table 1. NMR time scale for the isomerization of **13** was sufficient to trace diastereomer.




Scheme 3. (a) $S_2Cl_2$ (1.5 equiv)/$CH_2Cl_2$, rt, 1 h.

One fundamental question arises about atropisomerism. What are the determining factors for generation of diastereomerism for axially chiral benzopentathiepin, either rotation hindrance or pentathiepin ring geometry? Observation of diastereomerism for its different derivatives by NMR reveals that

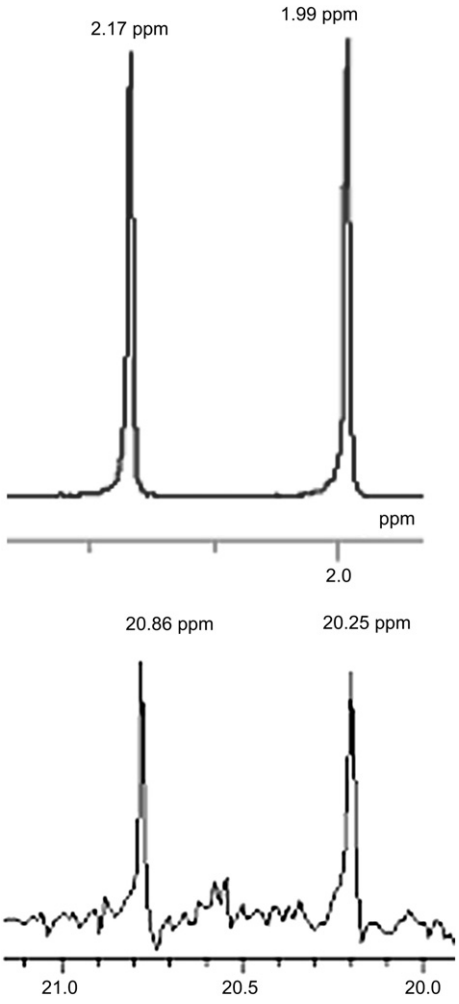



Figure 2. Partial $^{1}$H (upper) and $^{13}$C (lower) NMR peaks of methyl group of **13** clearly showed diastereomer due to the combination of both axial chirality and pentathiepin ring inversion.

Table 1
Experimental and calculated $^{13}C$ and $^{1}H$ NMR chemical shift values (ppm) of **13**

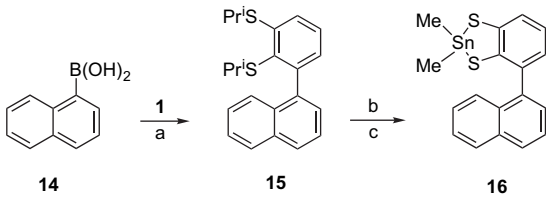
| | Expt.[a] | Calcd |
|---|---|---|
| $^{13}C$ NMR | 20.25 | 20.33[b] |
| | 20.86 | 20.76[b] |
| $^{1}H$ NMR | 2.17 | 2.14[c] |
| | 1.99 | 1.92[c] |

[a] The NMR spectra were measured in $CDCl_3$ by using TMS as an internal standard.
[b] The calculated chemical shifts were difference of C magnetic shielding tensor of **13** calculated by GIAO-HF/6-311+G(2d,p)//B3LYP/6-31G(d).
[c] The calculated chemical shifts were difference of H magnetic shielding tensor of **13** calculated by GIAO-HF/6-311+G(2d,p)//B3LYP/6-31G(d).

rotational energy barriers are vital for generation of atropisomer but pentathiepin ring inversion makes it impossible to isolate as pure form.

### 2.4. Incorporation of axial chirality on cyclic polysulfides by naphthyl moiety

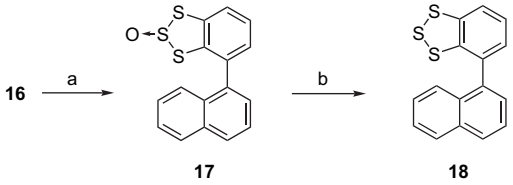
Asymmetric Suzuki–Miyaura cross-coupling reaction also enabled for the successful features of naphthyl moiety. Compound **1** was utilized as aromatic halide component for the cross-coupling reaction. Typical reaction was performed quantitatively between **1** and **14** in DMF/$H_2O$ in the presence of $CsCO_3$ as base and $Pd(PPh_3)_4$ as catalyst (Scheme 4). In $^{1}H$ NMR spectra, compound **15** gave two AB type doublets at $\delta$ 1.44 and 1.46 ppm for methyl protons of one isopropyl group, which is located adjacent to naphthalene moiety. Restricted rotation of isopropyl moiety near to naphthalene made the protons to be magnetically nonequivalent. On the contrary, the outer isopropyl group gave only sharp doublet for all six methyl protons due to their free rotation. After dealkylation of isopropylthio group of compound **15** with Na/pyridine, we protected unstable dithionates with dimethyl tindichloride to give 2,2-dimethyl-4-naphthyl-1,3,2-benzodithiastannole (**16**) in 53% yield.




Scheme 4. (a) $Pd(PPh_3)_4$ (2 mol %), $CsCO_3$ (1 equiv), DMF/$H_2O$, 120 °C, 6 h; (b) (i) Na (excess)/pyridine, reflux, 2 h, (ii) NaBH4/THF/EtOH, (iii) $H_3O^+$; (c) $Me_2SnCl_2$.

### 2.5. Synthesis of five-membered rings having axial chirality

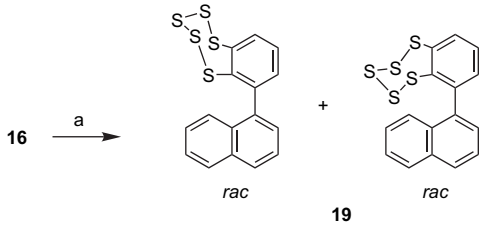
Stannole **16** was converted to 4-(1-naphthyl)-1,2,3-benzotrithiole 2-oxide (**17**) quantitatively according to Scheme 5. In IR spectra, strong sulfinyl group stretching vibration was observed at 1104 $cm^{-1}$. Subsequent reduction of **17** with TMSOTf/$SmI_2$ in THF at −78 °C yielded 4-(1-naphthyl)-1,2,3-benzotrithiole (**18**) in 26% yield as a single product. Although, compound **18** was isolated as a single product but its 2-oxide (**17**) was a diastereomeric mixture, as evident by $^{1}H$ NMR spectra. Electron withdrawing sulfinyl functionality generated enantiomerism as like as compound **9**. Difficult inversion behavior of **9** makes the molecule into diastereomer. Five-membered trithiole ring has one conformational state.[21] An appearance of complex multiplets of **17** in $^{1}H$ NMR spectra also implied that it existed as a diastereomeric mixture at least in NMR time scale.




Scheme 5. (a) $SOCl_2$/THF, rt, 0.5 h; (b) TMSOTf/THF, $SmI_2$, −78 °C, 15 min.

### 2.6. Synthesis of pentathiepin rings having axial chirality

Our main focus was to explore pentathiepin ring having axial chirality. Therefore, compound **16** was treated with 1.5 equiv of $S_2Cl_2$ in $CH_2Cl_2$ in the presence of $BF_3\cdot OEt_2$ to give **19** in overall 53% yield (Scheme 6).[4,20] Diastereomeric peaks were clearly observed for **19** by $^{1}H$ NMR. One doublet at $\delta$ 7.15 ppm and another double doublet at $\delta$ 7.23 ppm appeared in 45:55 isomeric ratios by indicating two distinct products. Peaks for each optically pure isomer were assigned after partial separation of mixture by Gel Permeation Liquid Chromatography (GPLC). Each enriched fraction was also tried to resolve by partial recrystallization at $<-20$ °C. Previously, this separation technique showed effectiveness for separation of optically active pentathiepin derivatives.[9] Compound **19** has low crystallinity and polarizability. Thus, partial recrystallization failed to isolate individual isomer.




Scheme 6. (a) $S_2Cl_2$ (1.5 equiv)/$BF_3\cdot OEt_2$, $CH_2Cl_2$, rt, 1 h.

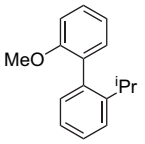
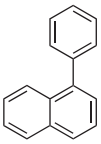
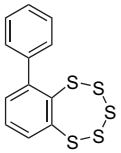
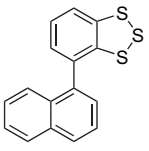
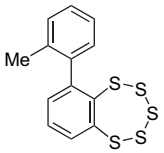
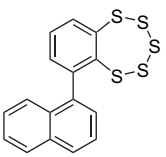
The separated enriched fraction from each chromatogram was collected from GPLC column but the product was a mixture rather than a pure diastereomer. Further attempts of partial recrystallization also did not afford single product. In course of time, the minor diastereomer was observed more in the solution. After two days, one separated fraction was completely back to original mixture. In solution, diastereomer (**19a** or **19b**) cannot exist as pure state for slow reversible inversion of the pentathiepin ring. Restricted rotation of chiral axis

and conformation of pentathiepin rings made each optically pure diastereomer (**19a** or **19b**) into enantiomer. $^{1}H$ and $^{13}C$ NMR spectra were, however, not perfectly assigned for these compounds because of their difficult resolution properties. Optically pure benzopentathiepin was yet resolved by any author and all previous assignments were also on the basis of NMR signals after partial separation.

### 2.7. Theoretical rotational energy barriers of 1,1′-binaphthyl

Calculated rotational energy barriers are presented in Table 2. For compound **19**, the value was ca. 25.49 kcal mol$^{-1}$ and it was high enough to generate corresponding diastereomerism. Naphthyl moiety acted as like as asymmetric chiral center in respect of benzopentathiepin ring. Although for the most part stable atropisomers are *ortho*–*ortho*′ tetrasubstituted biaryls,[15] a sufficient high rotational barrier about the biaryl linkage has been shown in few congested di- or trisubstituted biphenyls. The twisting of biphenyl skeleton can be induced by pentathiepin and trithiole oxide giving rise to optically active atropisomers as diastereoisomeric mixtures. Rotational energy barriers are crucial factor to generate atropisomers. Therefore, compound **12** has very low rotational energy (11.7 kcal/mol) barrier hence experimentally diastereoisomerism was not yet observed in NMR time scale. The rotational energy barriers are generally increased due to addition of methoxy and isopropyl groups at *ortho*-positions. For incorporation of one methyl group in **12**, the theoretical rotational energy barrier was increased from 11.7 to 23.8 kcal/mol. The value was high enough to form diastereomer. As a consequence, the similar atropisomerisms were also observed for 1-phenylnaphthalenepolysulfides. Sulfinyl oxygen also increases the rotational energy barriers by inductive effect. Detailed calculations of various types of 1,1′-binaphthyl having cyclic polysulfides moieties revealed that more than 20 kcal/mol rotational energy barrier is required for atropisomerism.

Table 2
Calculated biaryl rotational energy barriers of polysulfur derivatives of 1,1′-binaphthyls

| Compound | Relative energy (kcal/mol$^{-1}$) | Compound | Relative energy (kcal/mol$^{-1}$) |
|---|---|---|---|
|  | 19.2 |  | 11.8 |
|  | 11.7 |  | 19.0 |
|  | 23.8 |  | 25.5 |

Calculated by B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level (energy difference between the most stable conformer and the transition state of the aryl–aryl rotation).

### 2.8. Conformational analysis of diastereomer *19* by variable temperature $^{1}H$ NMR

Compound **19a** and **19b** are the conformational isomers. Since the pentathiepin rings existed along with the naphthyl moiety as chiral auxiliary, these two molecules are diastereomers in respect to the conformation of pentathiepin rings and locked axis.[22] One pure isomer (**19a** or **19b**) was almost isolated by GPLC analysis but once collected from column, the compound started to transform into mixture. But in solid state, both isomers were found stable. Measurements of $^{1}H$ NMR of approximately pure isomer of **19a** in $CDCl_3$ solution after every 5 h interval revealed that the compounds were isomerized to each other in solution. Isomerization can only be stopped by solid-state preservation or incubation of sample at low temperature. Therefore, in order to verify the inversion energy of pentathiepin ring experimentally and to accumulate data for activation parameters of the molecule, its isomerization was monitored at 303, 308, 313, and 318 K. Typically the results of isomerization of **19** are shown in Figure 3. The calculated kinetic parameters are presented in Table 3. The isomerization of these compounds was first order. Furthermore, as shown in Figure 4, the Eyring treatment of the rate constant of **19**, obtained at those temperatures, enabled us to calculate the activation parameters of the molecule. All thermodynamic parameters $^{298}\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ of **19** are calculated. The value of $^{298}\Delta G^{*}$ was about 24.28 kcal/mol, suggesting

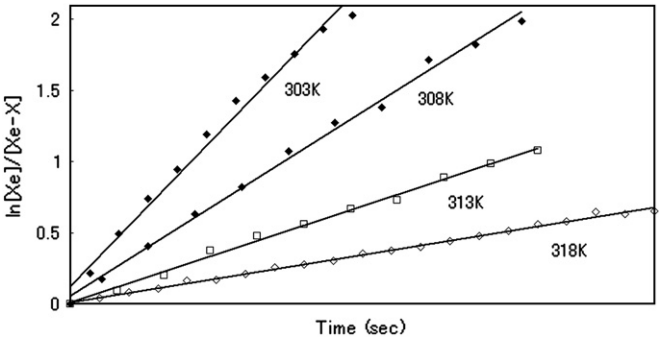



Figure 3. The representative kinetic data for the inversion of the pentathiepin ring of compound **19**; [Xe]: equilibrium concentration; [Xe–X]: concentration as a function of time.

Table 3
Kinetic and thermodynamic parameters of compound **19**

| | |
|---|---|
| 303 K | $(1.79\pm0.053)\times10^{-5}$ s$^{-1}$ |
| 308 K | $(3.74\pm0.023)\times10^{-5}$ s$^{-1}$ |
| 313 K | $(7.08\pm0.017)\times10^{-5}$ s$^{-1}$ |
| 318 K | $(11.61\pm0.328)\times10^{-5}$ s$^{-1}$ |
| $\Delta G^{**}$ | 24.28±0.015 kcal/mol |
| $\Delta H^{**}$ | 23.32±0.021 kcal/mol |
| $\Delta S^{**}$ | −3.199±0.123 eu |

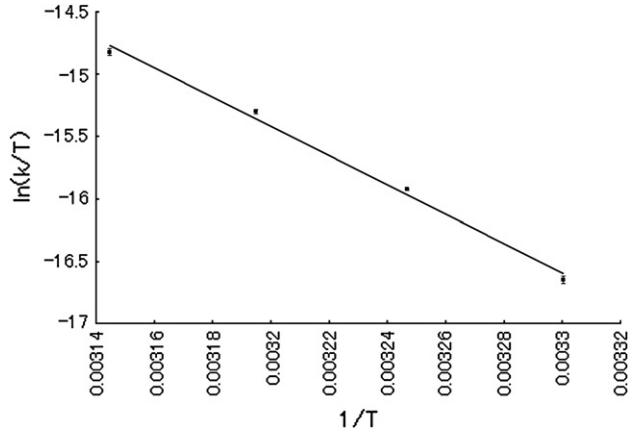



Figure 4. Eyring treatment with the standard deviation for the inversion of the pentathiepin ring of **19**.

that the inversion of pentathiepin ring proceeds at room temperature. The value of $\Delta S^{\neq}$ also suggested that the isomerization was due to the pentathiepin ring inversion. The inversion of the ring proceeded fast at higher temperature in polar solvents. Therefore, chiral chromatographic separation method was also unable to isolate diastereomer.[9]

## 3. Conclusion

Two reasons are notable concerning generation of diastereomerism. The energy barriers for the inversion of pentathiepin ring in solution and the NMR time scale are adequate to recognize them. Secondary, high rotational energy barrier of central bond acted as chiral auxiliary to resolve them into diastereomer. In addition, theoretical calculations and variable temperature $^1$H NMR experiments provided sufficient support to trace the atropisomers for all axially chiral cyclic benzopolysulfides.

## 4. Experimental

### 4.1. General

Melting points were measured with a MEL-TEMP capillary melting point apparatus and are uncorrected. $^1$H (400 MHz) and $^{13}$C (101 MHz) NMR spectra were recorded on a Bruker AC-400P instrument with $CDCl_3$ as a solvent. $^1$H NMR chemical shifts are given in relative parts per million from internal TMS. $^{13}$C NMR chemical shifts are given in relative parts per million from the internal $CDCl_3$. Mass spectra are recorded with a Hitachi M-2000 or JEOL JMS SX 102 spectrometer under electron ionization (70 eV). IR spectra were recorded on KBr disk with a JASCO FT/IR-7300 spectrometer. Hexane, $CH_2Cl_2$, THF, and DMF were freshly distilled according to standard laboratory procedure prior to use. Commercial grade TMEDA was purified by atmospheric distillation before use. All chemicals were reagent grades and were used without further purification unless otherwise stated. Wakogel C-200 was used for silica gel column chromatography. Elemental analyses were recorded using Yanaco MT-5 apparatus at the elemental analysis division of Iwate University. Chiral chromatographic separation was attempted in Daicel Chemical Industries, Ltd., Japan.

### 4.2. 1,2-Bis(isopropylthio)benzene[13]

Colorless oil; bp 128–130 °C (3.0 Torr); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.33 (d, 12H, $J$=6.5 Hz, $CH_3$), 3.49 (sept, 2H, $J$=6.5 Hz, CH), 7.05–7.44 (m, 4H, ArH).

### 4.3. 1-Iodo-2,3-bis(isopropylthio)benzene (*1*)

1,2-Bis(isopropylthio)benzene (7.47 g, 33 mmol) was dissolved in the dry hexane (75 ml) in 200 ml three-neck reactor. The solution was cooled down to 0 °C. TMEDA (8.6 ml, 59 mmol) was added into the reaction mixture. *n*-BuLi (2.67 M, 18.5 ml, 49.5 mmol) was slowly added into the reaction mixture under constant stirring. The reaction mixture was stirred for 2 h at the same temperature. Iodine (12.56 g, 49.5 mmol) was dissolved in dry ether. The iodine solution was slowly added into the reaction mixture. The reaction mixture was further stirred for 18 h at room temperature. The solution was neutralized and extracted with $CH_2Cl_2$. Running a silica gel column chromatography by using hexane as eluent gave product **1** (7.90 g) in 66% yield. Colorless oil, bp 122–125 °C (0.5 Torr); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.29 (d, 6H, $J$=6.7 Hz, $CH_3$), 1.38 (d, 6H, $J$=6.7 Hz, $CH_3$), 3.42 (sept, 1H, $J$=6.7 Hz, CH), 3.58 (sept, 1H, $J$=6.7 Hz, ArH), 6.90 (dd, 1H, $J$=7.9, 7.9 Hz, ArH), 7.19 (dd, 1H, $J$=7.9, 0.9 Hz, ArH), 7.70 (dd, 1H, $J$=7.9, 0.9 Hz, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 22.5, 22.9, 36.5, 40.5, 112.5, 126.0, 130.0, 135.8, 136.4, 146.0; IR (neat) 2962, 2922, 2864, 1538, 1420, 1239, 1190, 1154, 1051, 768, 737 cm$^{-1}$; MS (70 eV) *m/z* 352 $[M]^+$. Anal. Calcd for $C_{12}H_{17}IS_2$: C, 40.91; H, 4.86. Found: C, 41.30; H, 4.97.

### 4.4. 2,3-Bis(isopropylthio)biphenyl (*4*)

Compound **1** (1.58 g, 4.5 mmol), phenylboronic acid (0.54 g, 4.5 mmol), $CsCO_3$ (1.46 g, 4.5 mmol), and $Pd(PPh_3)_4$ (0.26 g, 0.23 mmol) were placed in a reactor fitted with a condenser under nitrogen atmosphere. Predried DMF (15 ml) was added into the reaction mixture. The reaction mixture was refluxed for 24 h by placing it in oil bath. The reactor was cooled down to room temperature and quenched with water. The product was extracted with $CH_2Cl_2$ after acidification by dilute HCl. The extracted solution was dried over $MgSO_4$ and excess solvent was removed by evaporation. The remaining DMF was separated by distillation. Running a silica gel column chromatography by using hexane as eluent gave pure product **4** (1.11 g, 82% yield). Colorless oil; bp 134.0–135.2 °C (0.4 Torr); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.97 (d, 6H, $J$=6.8 Hz, $CH_3$), 1.42 (d, 6H, $J$=6.7 Hz, $CH_3$), 2.93 (sept, 1H, $J$=6.8 Hz, CH), 3.51 (sept, 1H, $J$=6.7, CH), 7.06–7.39 (m, 8H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 22.7, 22.8, 35.9, 39.0, 125.1, 126.8, 126.9, 127.5, 128.3, 129.7, 130.9, 141.8, 145.0, 148.2; IR (neat) 2961, 1549, 788 cm$^{-1}$; MS

(70 eV) *m/z* 302 $[M]^+$; Anal. Calcd for $C_{18}H_{22}S_2$: C, 71.47; H, 7.33. Found: C, 71.84; H, 7.48.

### 4.5. 2,3-Bis(isopropylthio)-2′-methylbiphenyl (**5**)

The synthetic procedure of **5** was as same as that of product **4** from products **1** and **3**. $^1$H NMR (60 MHz, $CDCl_3$) $\delta$ 1.05–1.40 (m, 12H, $CH_3$,), 2.08 (s, 3H, $CH_3$), 3.07–3.47 (m, 2H, CH), 6.95–7.58 (m, 7H, ArH); IR (neat) 3057, 2961, 1738, 1550, 1444, 1238, 754 $cm^{-1}$. This compound was used to the next reaction without further purification.

### 4.6. 2,2-Dimethyl-4-phenyl-1,3,2-benzodithiastannole (**6**)

Product **4** (0.90 g, 3.0 mmol) was taken in a reactor fitted with a condenser under nitrogen atmosphere. Pyridine (20 ml) was added into the reactor. Carefully cut metallic sodium (0.31 g, 13.5 mmol) was also placed in it. The reaction mixture was refluxed for 2 h by placing in oil bath. The reactor was cooled down to 0 °C and the reaction mixture was quenched with methanol and water. The reaction mixture was further acidified with dilute HCl and extracted with ether. The remaining solvent was removed by evaporation. The generated dithiol was again dissolved in dry THF and the reaction mixture was reduced with $NaBH_4$ at room temperature. The reaction mixture was further quenched with water, acidified with HCl up to pH=7–8 and protected with $Me_2SnCl_2$. The generated stannole was extracted with $CH_2Cl_2$ and dried over anhydrous $MgSO_4$. Running a silica gel column chromatography by using solvent $CHCl_3$/hexane at 1:1 ratio gave product **6** (0.53 g, 47% yield). Colorless powder; mp 208.3–209.1 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.94 (s, 6H, $CH_3$), 6.85–6.96 (m, 2H, ArH), 7.32–7.48 (m, 6H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 2.3, 123.9, 126.3, 127.3, 127.9, 129.0, 129.1, 137.4, 139.0, 143.3, 143.4; IR (KBr) 3052, 1381, 781 $cm^{-1}$; MS (70 eV) *m/z* 366 $[M]^+$. Anal. Calcd for $C_{14}H_{14}S_2Sn$: C, 46.06; H, 3.87. Found: C, 45.88; H, 3.86.

### 4.7. 2,2-Dimethyl-4-(o-tolyl)-1,3,2-benzodithiastannole (**7**)

The synthetic procedure of stannole **7** from compound **5** was as same as that of product **6** (39% yield). Colorless needles; mp 200.7–201.1 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.93 (s, 6H, $CH_3$), 2.13 (s, 3H, $CH_3$), 6.77 (dd, *J*=0.9, 7.4 Hz, 1H, ArH), 6.96 (dd, *J*=7.4, 7.7 Hz, 1H, ArH), 7.12–7.30 (m, 4H, ArH), 7.48 (dd, *J*=0.9, 7.7 Hz, 1H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 2.1, 2.3, 19.8, 123.9, 125.6, 127.6, 128.8, 129.0, 129.8, 135.9, 138.1, 138.5, 142.9; IR (KBr) 3456, 1383, 754 $cm^{-1}$; MS (70 eV) *m/z* 381 $[M]^+$. Anal. Calcd for $C_{15}H_{16}S_2Sn$: C, 47.52; H, 4.25. Found: C, 47.58, H, 4.31.

### 4.8. 4-Phenyl-1,2,3-benzotrithiol 2-oxide (**8**)

Product **6** (0.36 g, 1.0 mmol) was dissolved in dry THF (4.0 ml) under air and the reaction mixture was cooled down to 0 °C. Under constant stirring, $SOCl_2$ (0.078 ml, 1.1 mmol) was slowly added into the reaction mixture under constant stirring. The mixture was stirred for 0.5 h, extracted with $CH_2Cl_2$, dried over anhydrous $MgSO_4$. The solvent was removed under vacuum. The product was separated by silica gel column chromatography by using $CHCl_3$ as solvent (0.26 g, 98% yield).

Yellow powder; mp 120.6–121.2 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (dd, 1H, *J*=1.0, 7.8 Hz, ArH), 7.41–7.46 (m, 5H, ArH), 7.43 (t, 1H, *J*=7.8 Hz, ArH), 7.59 (dd, 1H, *J*=1.0, 7.8 Hz, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 123.4, 127.8, 128.1, 128.4, 128.6, 128.7, 135.5, 136.2, 139.7, 140.8; IR (KBr) 1102 $cm^{-1}$ (S=O); MS (70 eV) *m/z* 264 $[M]^+$. Anal. Calcd for $C_{12}H_8OS_3$: C, 54.51; H, 3.05. Found: C, 54.35; H, 3.10.

### 4.9. 4-(o-Tolyl)-1,2,3-benzotrithiole 2-oxide (**9**)

The synthetic procedure from **7** was as same as that of product **8** (97% yield).

Yellow powder; mp 79.9–81.5 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.09–2.19 [s×2, 6H (2.09:2.19 ppm=1:1.5), $CH_3$], 7.12 (d, 1H, *J*=7.4 Hz, ArH), 7.20 (dd, 2H, *J*=0.7, 7.4 Hz, ArH), 7.27–7.37 (m, 8H, ArH), 7.42 (dd, 1H, *J*=1.5, 7.9 Hz, ArH), 7.44 (dd, 1H, *J*=1.5, 7.4 Hz, ArH), 7.58 (d, 2H, *J*=7.9 Hz, ArH); IR (KBr) 1123 $cm^{-1}$ (S=O); MS (70 eV) *m/z* $[278]^+$. Anal. Calcd for $C_{13}H_{10}OS_3$: C, 56.08; H, 3.62. Found: C, 56.28; H, 3.66.

### 4.10. 4-Phenyl-1,2,3-benzotrithiole (**10**)

The product **8** (0.22 g, 0.75 mmol) was dissolved in dry THF (20 ml). The solution was cooled down to −78 °C. TMSOTf (0.13 ml, 0.75 mmol) solution was added into the reactor and the reaction mixture was stirred for 10 min at the same temperature. A solution of $SmI_2$ in dry THF (0.1 M) was added into the reaction mixture. The solution was stirred for more than 1.0 h at the same temperature. After checking the progress of reaction by TLC, the mixture was quenched with water and the product was extracted with $CH_2Cl_2$. Running a silica gel column chromatography by using hexane as solvent gave pure product (0.04 g, 16% yield).

Yellow powder; mp 71.4–73.6 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.10–7.15 (m, 2H, ArH), 7.38–7.46 (m, 6H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 122.6, 126.9, 128.1, 128.30, 128.33, 128.5, 139.4, 141.1, 141.3, 142.3; IR (KBr): 3449, 1438, 799, 756 $cm^{-1}$; MS (70 eV) *m/z* 248 $[M]^+$. Anal. Calcd for $C_{12}H_8S_3$: C, 58.03; H, 3.25. Found: C, 58.28; H, 3.26.

### 4.11. 4-(o-Tolyl)-1,2,3-benzotrithiole (**11**)

The synthetic procedure from trithiole 2-oxide **9** was as same as that of product **10** (13% yield). Yellow powder; mp 152.0–153.3 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.21 (s, 3H, $CH_3$), 6.93–6.95 (m, 1H, ArH), 7.10–7.15 (m, 2H, ArH), 7.21–7.37 (m, 4H,ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 122.8, 126.8, 128.1, 128.2, 128.7, 128.5, 139.4, 140.1, 141.3, 142.5; IR (KBr) 3449, 1438, 799, 756 $cm^{-1}$; MS

(70 eV) *m/z* 262 $[M]^+$; Anal. Calcd for $C_{13}H_{10}S_3$: C, 59.50; H, 3.84. Found: C, 59.55; H, 3.94.

### 4.12. 6-Phenyl-1,2,3,4,5-benzopentathiepin (**12**)

Stannole **6** (0.36 g, 1.0 mmol) was dissolved in $CH_2Cl_2$ (10 ml) in 50 ml reactor under nitrogen atmosphere. The reaction mixture was cooled down to 0 °C. Sulfur chloride (0.12 ml, 1.5 mmol) was slowly added into the reaction mixture at the same temperature. The reaction mixture was stirred for 1 h at room temperature. The mixture was quenched with water and acidified with HCl. The generated product was extracted with $CH_2Cl_2$ and dried over $MgSO_4$. The excess solvents were removed by vacuum. Running a silica gel column chromatography by using hexane as solvent afforded product **12** (0.11 g, 36% yield).Yellow powder; mp 88.1–89.6 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.26–7.30 (m, 2H, ArH), 7.32–7.37 (m, 2H, ArH), 7.39–7.45 (m, 3H, ArH), 7.84–7.87 (m, 1H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 127.7, 128.0, 128.1, 128.5, 129.62, 129.68, 132.6, 135.1, 145.3, 149.1; IR (neat): 3368, 1439, 800, 757 $cm^{-1}$; MS (70 eV) *m/z* 312 $[M]^+$. Anal. Calcd for $C_{12}H_8S_5$: C, 46.12; H, 2.58. Found: C, 46.40; H, 2.95.

### 4.13. 6-(o-Tolyl)-1,2,3,4,5-benzopentathiepin (**13**)

The synthetic procedure was as same as that of product **12** (53% yield). Diastereomeric mixture; yellow powder; mp 88.2–89.0 °C (decomp.); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.99 (s, $CH_3$), 2.17 (s, $CH_3$), 6.91–7.37 (m, ArH), 7.87–7.89 (m, ArH); IR (KBr): 3449, 1379, 750 $cm^{-1}$; MS (70 eV) *m/z* $[326]^+$. Anal. Calcd for $C_{13}H_{10}S_5$: C, 47.82; H, 3.09. Found: C 48.02, H, 3.20.

### 4.14. 1-[2,3-Bis(isopropylthio)phenyl]naphthalene (**15**)

The synthetic procedure was as same as that of product **4** (95% yield). Colorless solid; mp 87 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.90 (d, 6H, $J$=6.7 Hz, $CH_3$), 1.44 (d, 3H, $J$=4.6 Hz, $CH_3$), 1.46 (d, 3H, $J$=4.6 Hz, $CH_3$), 3.05 (sept, 1H, $J$=6.7 Hz, CH), 3.56 (sept, 1H, $J$=6.7 Hz, CH), 7.09–7.11 (m, 1H, ArH), 7.33–7.37 (m, 4H, ArH), 7.42–7.51 (m, 3H, ArH), 7.84–7.88 (m, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 22.7, 22.8, 23.0, 35.9, 38.9, 124.8, 125.5, 125.5, 125.8, 126.2, 127.2, 127.5, 127.6, 128.0, 128.2, 132.2, 132.5, 133.2, 139.6, 145.0, 146.8; IR (neat) 3053, 2962, 2924, 2864, 1551, 1444, 1385, 1241, 1154, 803, 783, 734, 635 $cm^{-1}$; MS (70 eV) *m/z* 352 $[M]^+$. Anal. Calcd for $C_{22}H_{24}S_2$: C, 74.95; H, 6.86. Found: C, 74.94; H, 6.98.

### 4.15. 2,2-Dimethyl-4-(1-naphthyl)- 1,3,2-benzodithiastannole (**16**)

The synthetic procedure was as same as that of product **6** (53% yield). Colorless solid; mp 219–221 °C (decomp.); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.87 (s, 6H, $CH_3$), 6.89–6.91 (m, 1H, ArH), 6.99–7.03 (m, 1H, ArH), 7.36–7.42 (m, 2H, ArH), 7.44–7.48 (m, 1H, ArH), 7.50–7.58 (m, 3H, ArH), 7.86–7.89 (m, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 2.04, 123.9, 125.4, 125.7, 125.9, 126.3, 126.7, 127.0, 127.9, 128.2, 129.3, 131.6, 133.7, 139.0, 139.1, 141.1, 141.7; IR (KBr): 3048, 1383, 779 $cm^{-1}$; MS (70 eV) *m/z* 416 $[M]^+$. Anal. Calcd for $C_{18}H_{16}S_2Sn$: C, 52.07; H, 3.88. Found: C, 52.38; H, 4.00.

### 4.16. 4-(1-Naphthyl)-1,2,3-benzotrithiole 2-oxide (**17**)

The synthetic procedure was as same as that of product **8** (98% yield). Yellow solid; mp 185–186 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35–7.56 (m, 3H, ArH), 7.64–7.69 (m, 5H, ArH), 7.91–7.95 (m, 2H, ArH); IR (KBr) 1392, 1104 (S=O), 782 $cm^{-1}$; MS (70 eV) *m/z* 314 $[M]^+$. Anal. Calcd for $C_{16}H_{10}OS_3$: C, 61.11; H, 3.21. Found: C, 61.11; H, 3.32.

### 4.17. 4-(1-Naphthyl)-1,2,3-benzotrithiole (**18**)

The synthetic procedure was as same as that of product **10** (26% yield). Orange needles; mp 107–109 °C (decomp.); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.10–7.12 (m, 1H, ArH), 7.16–7.20 (m, 1H, ArH), 7.35–7.37 (m, 1H, ArH), 7.45–7.54 (m, 4H, ArH), 7.60–7.63 (m, 1H, ArH), 7.90–7.93 (m, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 122.7, 125.2, 125.6, 126.2, 126.5, 126.6, 128.4, 128.9, 129.3, 129.3, 130.6, 133.6, 137.3, 138.8, 141.0, 142.7; IR (KBr) 3043, 1387, 777 $cm^{-1}$; UV ($n$-$C_6H_{14}$) $\lambda_{max}$ 222 ($\varepsilon$ $5.7\times10^4$), 284 ($\varepsilon$ $1.1\times10^4$) nm; MS (70 eV) *m/z* 298 $[M]^+$. Anal. Calcd for $C_{16}H_{10}S_3$: C, 64.39; H, 3.38. Found: C, 64.41; H, 3.65.

### 4.18. 6-(1-Naphthyl)-1,2,3,4,5-benzopentathiepin (**19**)[1]

Stannole **16** (0.20 g, 0.48 mmol) was dissolved in $CH_2Cl_2$ (10 ml) containing $BF_3\cdot OEt_2$ (0.48 mmol, 0.06 ml) in 50 ml reactor under nitrogen atmosphere. The reaction mixture was cooled down to 0 °C. Sulfur chloride (0.06 ml, 0.72 mmol) was slowly added into the reaction mixture at the same temperature. The reaction mixture was stirred for 1 h at room temperature. The mixture was quenched with water and acidified with HCl. The generated product was extracted with $CH_2Cl_2$ and dried over $MgSO_4$. The excess solvents were removed by vacuum. Running a silica gel column chromatography by using hexane as solvent afforded product **19** (0.09 g, 53% yield). Yellow solid; mp 60–63 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15–7.17 (m, 1H, ArH), 7.34–7.44 (m, 1H, ArH), 7.40–7.44 (m, 1H, ArH), 7.47–7.53 (m, 4H, ArH), 7.90–7.93 (m, 2H, ArH), 7.97–7.98 (m, 1H, ArH); IR (KBr) 3043, 1507, 1393, 799, 775 $cm^{-1}$; UV ($n$-$C_6H_{14}$) $\lambda_{max}$ 213 ($\varepsilon$ $5.1\times10^4$), 217 ($\varepsilon$ $5.1\times10^4$), 285 ($\varepsilon$ $7.7\times10^3$) nm; MS (70 eV) *m/z* 362 $[M]^+$. Anal. Calcd for $C_{16}H_{10}S_5$: C, 53.00; H, 2.78. Found: C, 52.84; H, 3.02.

### 4.19. Attempts for isolation of diastereomer

All the diastereomers were attempted to separate by partial recystallization at cryogenic temperature. GPLC column was

also run to separate the diastereomeric mixture and after a long recycling time two fractions were almost separated. The isolated each enriched fraction was subjected to recrystallize at $<-20\ ^{\circ}C$ but the process did not afford any single isomer. However, in course of time, the minor diastereomer appeared more in the solution. Observation of one enriched fraction for 24 h in solution gave 1:1 diastereomeric mixture again. The mixture was also attempted to separate by chiral chromatography in Daicel Chemical Industries Ltd., Japan but the attempts were also unable to separate the diastereomer.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.014.

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