First Preparation and Structural Determination of Optically Pure Cyclic Polysulfides, 6,10-Diethyl Trithiolo[*h*]benzopentathiepin Monooxides

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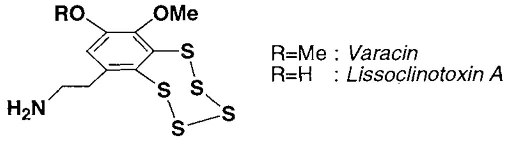
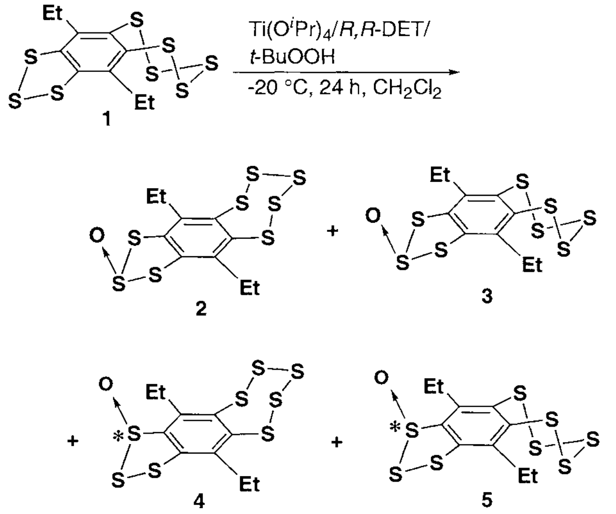
Optically pure cyclic polysulfides, 6,10-diethyl trithiolo[*h*]benzopentathiepin 7-oxides (**4**) and (**5**) were prepared by asymmetric oxidation of 6,10-diethyl trithiolo[*h*]benzopentathiepin. The structure of **4** and **5** was determined by X-ray crystallographic analysis and the configuration was confirmed as *R* configuration on the sulfinyl sulfur atoms.

Unsymmetrically substituted benzopentathiepins, *Varacin* and *Lissoclinotoxin A*, which have antitumor and antifungal activities, constitute a chiral molecule because of the slow inversion of the pentathiepin ring.[1] Recently, we and Nakayama reported the first experimental determination of the inversion energy of the pentathiepin and pentathiepan rings, respectively, which reveal that the ring inversion of these polysulfide rings proceeds very slowly at room temperature.[2,3,4] Although two diastereomers were prepared by treatment of *Varacin* with a chiral auxiliary, only one isomer was isolated and detected by ^{1}H-NMR.[1f] In order to prepare a chiral molecule from benzopentathiepin derivatives, asymmetric oxidation of 6,10-diethyl trithiolo[*h*]benzopentathiepin (**1**) was performed by a Sharpless reagent[5] to produce the optically active trithiole monooxides; hence, the diastereomers, 6,10-diethyl trithiolo[*h*]benzopentathiepin 7-oxides (**4**) and (**5**) were isolated as optically pure crystals, respectively. This paper reports the preparation, isolation, and structure determination of optically pure benzopentathiepins **4** and **5**.



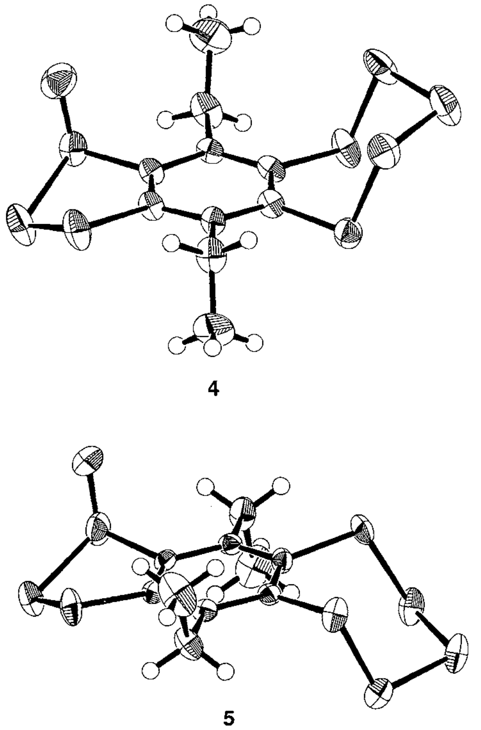
The compound **1** (580 mg, 1.5 mmol) which was obtained by treatment of tetrabromo-*p*-diethylbenzene with elemental sulfur in liquid ammonia[6] was oxidized by a reagent consisted of Ti(O^{i}Pr)$_4$/*R*,*R*-DET/*t*-BuOOH in CH$_2$Cl$_2$ (120 ml) at -20 °C under Ar for 24 h (Scheme 1). The reactants, **1**/Ti(O^{i}Pr)$_4$/*R*,*R*-DET/*t*-BuOOH were in the ratio of 1:2:4:4,[7] which gave a best result in the asymmetric oxidation, since the oxidation reaction of **1** proceeded slowly under these reaction condition. Then, sodium sulfite (1.26 g) and brine (50 ml) were added to the solution, and the solution was stirred vigorously for 1 h. After usual work-up and separation of the Ti complex and *R*,*R*-DET by filtration, the products were purified by column chromatography (silica gel: particle size 20-40 µm, *n*-hexane:CHCl$_3$=1:1). Four monooxides, 6,10-diethyl trithiolo[*h*]benzopentathiepin 8-oxides (**2**) and (**3**), and the 7-oxides **4** and **5** were obtained similarly to the oxidation of **1** with MCPBA.[2] In these monooxides, **2** and **3** are the conformational isomers with respect to the pentathiepin ring and hence are not chiral, while **4** and **5** which are unsymmetrically substituted benzopentathiepins are the diastereomer with respect to the conformation of the pentathiepin ring and the configuration of the sulfinyl sulfur atom. The compounds **4** and **5** could be separated easily by column chromatography in 18% (108 mg) and 23% (141 mg) yields, respectively. Meanwhile, **2** and **3** were obtained as a mixture in 29% (177 mg) yield. In spite of using a large amount of an oxidizing reagent, the corresponding bissulfoxide and sulfone were not obtained in the reaction.

After column chromatography, the specific rotation $[\alpha]_D$ of **4** and **5** was measured by radiation with a Na lamp in CHCl$_3$; $[\alpha]_D^{19}$=-613° (c=0.130) for **4** and $[\alpha]_D^{20}$=-971° (c=0.282) for **5**. Each compound, **4** and **5**, should contain an enantiomer. To examine $[\alpha]_D$ of the optically pure product, **4** was purified by recrystallization from *n*-hexane:CH$_2$Cl$_2$=1:1 at -20 °C to give optically pure yellow crystals. The purification of **5** was also performed by the identical recrystallization. Then $[\alpha]_D$ of **4** and **5** was measured in CHCl$_3$ and established as $[\alpha]_D^{20}$=-775° (c=0.204) for **4** and $[\alpha]_D^{19}$=-1364° (c=0.161) for **5**. On the other hand, the diastereomeric excess of these compounds was determined by measurement of 400 MHz ^{1}H-NMR using Eu(hfc)$_3$ as *de*=100% for **4** and *de*=98% for **5**.



Scheme 1. **1** : Ti(O^{i}Pr)$_4$: *R*,*R*-DET : *t*-BuOOH = 1 : 2 : 4 : 4; **2+3**: 29%; **4**: 18%; **5**: 23%.

It is important to demonstrate the structure and correct configuration of the sulfinyl groups. Therefore, X-ray crystallographic analysis of optically pure **4** and **5** was carried out with CuKα radiation to determine the absolute configuration



4

5

Figure 1. The ORTEP Drawing of **4** and **5**.

on the sulfinyl sulfur atom.[8] As shown in Figure 1, **4** and **5** have the oxygen atom on the trithiole ring, not on the pentathiepin ring. The oxygen atoms coordinated to the sulfur atoms of **4** and **5** are located on the *axial* position of the trithiole ring. Furthermore, the oxygen atom of **4** is on the *syn* side to the pentathiepin ring, and that of **5** exists on the *anti* side to the pentathiepin ring, suggesting that $[\alpha]_D$ of **4** and **5** was affected by the orientation of the pentathiepin ring. On the other hand, the configuration of **4** and **5** is *R* configuration on the sulfinyl sulfur atoms, respectively, which is verified by the value of x defined by Flack for determination of the absolute configuration; *R* configuration: x=0.03(1) for **4**, *R* configuration: x=-0.009(1) for **5**.[9] These results reveal that **4** and **5** both have *R* configuration on the sulfinyl sulfur atoms.

The compounds **4** and **5** were stable at -20 °C and no isomerization was observed at this temperature, while the epimerization of the sulfinyl groups and the ring inversion of the pentathiepin rings were found to proceed slowly at room temperature.[2,10] Further investigation with respect to the epimerization of **4** and **5** is now in progress in this laboratory.

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7 The rate of the oxidation reaction decreases in the presence of one equivalent of H_2O.

8 For X-ray crystallographic analysis, the data collection was made on a Rigaku AFC7R diffractometer with filtered CuKa radiation, and all calculations for structure solution were performed using the teXsan crystallographic software package of Molecular Structure Corporation (1985 and 1992); The crystal data for **4**: monoclinic, $P2_1$ (#4), a=8.832(2) Å, b=7.727(2) Å, c=11.685(2) Å, β=99.40(1)°, V=786.7(3) Å^3, Z=2, D_{calc}=1.700 g/cm^3, μ(CuKα)=104.09 cm^{-1}, 3051 reflections collected: 1546 unique reflection (R_{int}=0.058), 2664 [I>1.50σ(I)] used in the refinement, R=0.065 (R_w=0.085), GOF=1.18; The crystal data for **5**: orthorhombic, $P2_12_12_1$ (#19), a=18.793(2) Å, b=20.675(2) Å, c=8.091(2) Å, V=3143.8(7) Å^3, Z=8, D_{calc}=1.701 g/cm^3, μ(CuKα)=104.19 cm^{-1}, 6321 reflections collected: 3269 unique reflection (R_{int}=0.050), 5665 [I>1.50σ(I)] used in the refinement, R=0.051 (R_w=0.069), GOF=1.27.

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