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Synthesis of novel axially chiral cyclic benzopolysulfides

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Abstract—Novel axially chiral benzopentathiepins were synthesized by sulfurization of dithiastannole. Naphthyl moiety was introduced near the pentathiepin ring by Suzuki–Miyaura cross-coupling reaction. Pentathiepins were found as diastereomeric mixture. Rotational energy barrier for C–C bond was estimated by theoretical calculation. Energy barrier for the inversion of pentathiepin ring was experimentally determined by variable temperature ^{1}H NMR.

Axial chirality represents interesting stereochemical features for modern synthetic chemistry. Axially chiral molecules are widely found in nature and exhibit a broad range of biological activities[1] and therefore a great deal of effort has been continuously devoted to their synthesis.[2]

There are many reports concerning the synthesis[3] and characterization[4] of cyclic polysulfides fused to aromatics, but only a few numbers of chiral benzopolysulfides have appeared in the literature. Davidson et al. in 1991, discovered varacin (**1**) (Fig. 1), which showed potential antifungal and cytotoxic activities.[5] They also disclosed that the ^{1}H NMR signals assigned to the side chain methylene proton are unexpectedly complex, attributing this to restricted rotation of the side chain in **1** or **2**.[6] A high barrier to interconversion of the chair conformation of the pentathiepin ring induces asymmetry into the molecule, causing these protons to become diasterotopic. At the same time, Searle et al. also observed chirality for lissoclinotoxin A derivatives **3** and **4**.[7] They also quoted an interesting conclusion that asymmetric pentathiepins are chiral at least on NMR time scale as some compounds were racemized during isolation. The origin of 'the chirality for pentathiepin and its derivatives are best explained by slow inversion of the pentathiepin ring due to the exceptionally high barrier (24.0–29.0 kcal mol^{-1}) to ring inversion.[8,9] An interesting feature is that chirality is not yet observed for its trithiole (**5**) and open ring derivatives (**6**). Since then chiral benzopolysulfides have received considerable attention in the light of structural diversity[10] and biological activities.[11] Several chiral benzopentathiepins were found to show biological activity,[6,7] and we thus appended our attention to develop benzopenathiepin having a chiral auxiliary near the polysulfide ring.

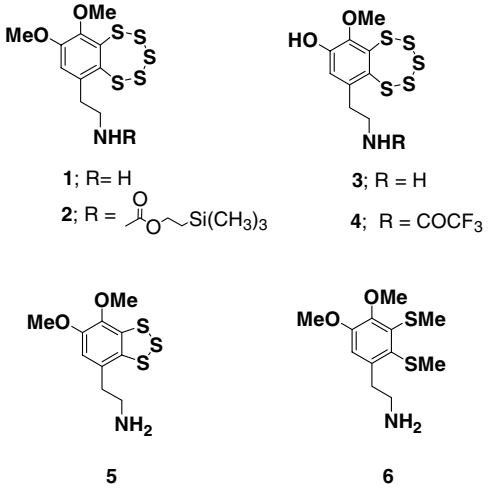

Figure 1.

Axial chirality is often associated with the stereoisomers resulting from the hindered rotation about the single bond, where the barrier to rotation is high enough to

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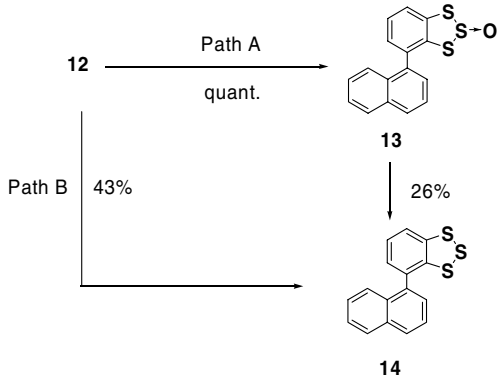
allow for the isolation of the conformers. The conditions for the existence of stereoisomerisms have been defined as one where stereoisomers can be isolated and have a half life of at least 1000 s.[12] The most extensively studied class of atropisomers is BINAP derivatives due to their high barrier to rotation. Derivatizations of benzopentathiepin with some chiral auxiliary would be expected to provide diastereomeric products, which might be separable as an optically pure isomer. Thus, the naphthalene moiety was selectively attempted to incorporate at the neighbourhood of the polysulfide ring as a C_{aryl}–$C_{naphthyl}$ functionality to give a chiral axis.

Herein, we report the novel synthesis of axially chiral cyclic benzopolysulfides. The synthesis was achieved by sulfurization followed by the Suzuki–Miyaura cross-coupling reaction as an important step. The barriers to rotation about the C_{aryl}–C_{naphyl} bond were estimated by theoretical calculations.

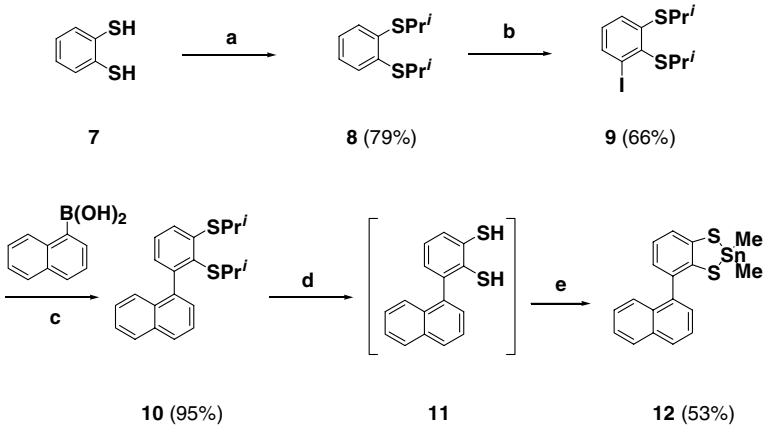
The synthetic procedure is presented in Scheme 1. The reaction of 1,2-benzenedithiol (**7**) with 2-iodopropane afforded 1,2-bis(isopropylthio)benzene (**8**) in 79% yield.[13] Lithiation of **8** with *n*-BuLi/TMEDA in hexane and successive iodination with I_2/Et_2O gave 1-iodo-2,3-bis(isopropylthio)benzene (**9**) in 66% yield, a suitable element for the Suzuki–Miyaura cross-coupling reaction having C–S bonds with an aromatic ring. Asymmetric C–C coupling reaction was performed between **9** and 1-napthaleneboronic acid in DMF/H_2O in the presence of Cs_2CO_3 as base and $Pd(PPh_3)_4$ as catalyst.[14] 1-[2,3-Bis(isopropylthio)phenyl]naphthalene (**10**) was isolated in excellent yields. In the ^1H NMR spectra, compound **10** gave two AB-type doublets at δ 1.44 and 1.46 ppm for methyl protons of one isopropyl group, which is located adjacent to the naphthalene moiety. Restricted rotation of the methyl group in the isopropyl moiety near naphthalene made the protons to be magnetically nonequivalent. On the contrary, the outer isopropyl group gave only a sharp doublet for all six methyl protons due to their free rotation. Treatment of **10** with Na/NH_3 did not, however, remove isopropyl groups to afford stable dithiols after subsequent acidification with concd HCl. Therefore, thiol groups were protected in the bulk of the reaction at neutral condition with dimethyl tin(1V)dichloride, and expectedly 4-(1-naphthyl)-2,2-dimethyl-1,3,2-benzodithiastannole (**12**) was isolated in 53% yield. Spectroscopic data anticipated well for structural elucidation of **12**.[15]

Initial attempts to get chiral benzotrithioles are presented in Scheme 2. Stannole **12** was treated with $SOCl_2$ in dry THF to afford 4-(1-naphthyl)-1,2,3-benzotrithiole 2-oxide (**13**) quantitatively, according to Path A. In the IR spectra, strong sulfinyl group stretching vibration was observed at 1104 cm^{-1}. The subsequent reduction of **13** with TMSOTf/SmI_2 in THF at −78 °C yielded 4-(1-naphthyl)-1,2,3-benzotrithiole (**14**) in 26% yield as a single isomer. According to Path B, treatment of **12** with 1.0 equiv of SCl_2 gave **14** in 43% yield. Although compound **14** was isolated as a single product, its 2-oxide (**13**) was a diastereomeric mixture, as evident from the ^1H NMR spectra. Spatial arrangements of sulfinyl oxygen around the trithiole ring and its slow inversion make the molecule into diastereomer.

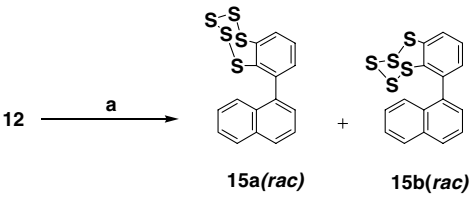
Asymmetric benzopentathiepin is a diastereomer for its two conformational states of the polysulfide ring,[9] while the corresponding benzotrithiole exists as a single isomer. The five-membered trithiole ring has one confor-



Scheme 2. Reagents and conditions: Path A (i) $SOCl_2$/THF, rt, 0.5 h, (ii) TMSOTf/THF, SmI_2, −78 °C, 15 m; (Path B) (i) SCl_2 (1.0 equiv), THF, −78 °C, 15 m.



Scheme 1. Reagents and conditions: (a) 2-iodopropane, benzene/NaOH aq., TOMAC, rt, 12 h; (b) *n*-BuLi/TMEDA, hexane, I_2/Et_2O; (c) 2 mol% $Pd(PPh_3)_4$, $CsCO_3$ (1 equiv), DMF/H_2O, 120 °C, 6 h; (d) (i) Na (excess)/pyridine, reflux, 2 h, (ii) $NaBH_4$/THF–EtOH, (iii) H_3O^+; (e) Me_2SnCl_2.



Scheme 3. Reagents and conditions: (a) S_2Cl_2 (1.5 equiv)/$BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 1 h.

mational state.[16] The appearance of complex multiplets of **13** in the ^{1}H NMR spectra also implied that it existed as a diastereomeric mixture at least on the NMR time scale. Pentathiepin having axial chirality was our main goal. Therefore, compound **12** 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 **15** in an overall 53% yield (Scheme 3).

Diastereomeric peaks were clearly observed for compound **15** by ^{1}H NMR. One doublet at δ 7.15 ppm and another double doublet at δ 7.23 ppm appeared in a 45:55 isomeric ratio by indicating two distinct products. Partial recrystallization had failed to separate the isomers. Thus, the mixture was attempted to be analyzed by gel permeation liquid chromatography (GPLC) for further resolution of diastereomers. Two isomers were almost separated after 24 h and the separated fraction was studied using ^{1}H NMR spectrum (Fig. 2). The sharp doublet at δ 7.23 ppm (marked by a circle) had almost disappeared after a long recycling of the mixture in the column while the remaining doublet had more clearly appeared.

The separated individual fraction from each chromatogram was collected but the product was a mixture rather than a pure diastereomer. Partial recrystallization of the isolated fraction at <-20 °C also did not afford a single product. Furthermore, in due course, the minor diastereomer was seen more in the solution. After two days

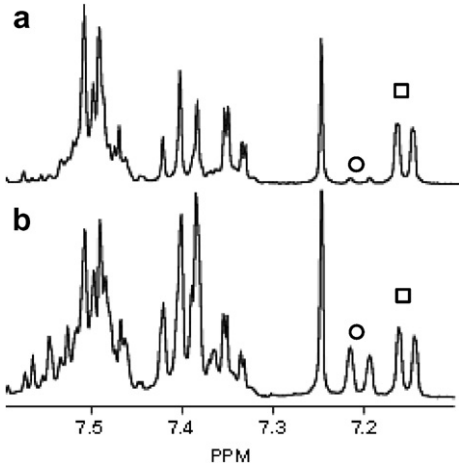


Figure 2. Partial ^{1}H NMR (400 MHz) spectra of (a) single diastereomer of **15** and (b) diastereomeric mixture of **15**. Both spectra were recorded in $CDCl_3$ at 25 °C.

Table 1. Calculated biaryl rotational energy barriers for 1-phenylnaphthalene, **14** and **15** (energy difference between the most stable conformer and the transition state of the aryl–aryl rotation)

Compound	Relative energy/kcal mol^{-1} B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d)
1-Phenylnaphthalene	11.75
14	18.97
15	25.49

the separated fraction (Fig. 2a) was back to the original mixture (Fig. 2b) again. In solution, diastereomer (**15a** or **15b**) cannot exist in the pure state for a slow reversible inversion of the pentathiepin ring. In order to verify the inversion energy of the pentathiepin ring of **15**, its isomerization was monitored by ^{1}H NMR spectroscopy at 303 K, 308 K, 313 K and 318 K. The value of $^{298}\Delta G^{\#}$ was about 24.28 kcal/mol, suggesting that the inversion of the pentathiepin ring proceeds at room temperature. Therefore, the chromatographic separation period is not sufficient for isolation of the individual diastereomer.

Restricted rotation of the chiral axis and conformation of pentathiepin rings made each optically pure diastereomer (**15a** or **15b**) into an enantiomer. Compound **13** was also a diastereomer while compound **14** was racemic. ^{1}H and ^{13}C NMR spectra were, however, not perfectly assigned for these compounds because of their incomplete resolution. Optically pure benzopentathiepin is yet to be resolved by any author and all previous assignments were also on the basis of NMR signals after partial separation.[6,7]

Two reasons are notable concerning generation of diastereomerism for **15**: (a) The energy barrier for the inversion of the pentathiepin ring from their low energy chair conformation to boat conformation and the NMR time scale is adequate to recognize them.[9,12] (b) A sufficiently high rotational energy barrier of the C_{aryl}–$C_{naphthyl}$ bond enables one to resolve them into diastereomers. Calculated rotation energy barriers are provided in Table 1. For compound **15**, the value was found to be ca. 25.49 kcal mol^{-1} and it was high enough to generate corresponding diastereomers. The naphthyl moiety acted like an asymmetric chiral center for benzopentathiepin.

In conclusion, we were successful in synthesis, characterization and partial separation of novel axially chiral benzopentathiepins. Diastereomers were detected by the analysis of ^{1}H NMR spectra, and polysulfides ring sizes were assigned by mass fragments, GPLC retention time and elemental analysis. Syntheses of axially chiral benzopentathiepins having a higher rotational energy barrier are underway.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.117.

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15. *1-[2,3-Bis(isopropylthio)phenyl]naphthalene* (**10**): colourless solid; mp 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 6.9.

4-(1-Naphthyl)-2,2-dimethyl-1,3,2-benzodithiastannole (**12**): colourless solid; mp 219–221 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-(1-Naphthyl)-1,2,3-benzotrithiole (**14**): orange needles; mp 107–109 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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}) λ_{max} 222 (ε 5.7×10^4), 284 (ε 1.1×10^4) 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.

6-(1-Naphthyl)-1,2,3,4,5-benzopentathiepin (**15**): yellow solid; mp 60–63 °C; IR (KBr) 3043, 1507, 1393, 799, 775 cm^{-1}; UV (n-C_6H_{14}) λ_{max} 213 (ε 5.1×10^4), 217 (ε 5.1×10^4), 285 (ε 7.7×10^3) 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.
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