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SYNTHESIS AND CHARACTERIZATION OF FUNCTIONALIZED BENZOPENTATHIEPINS

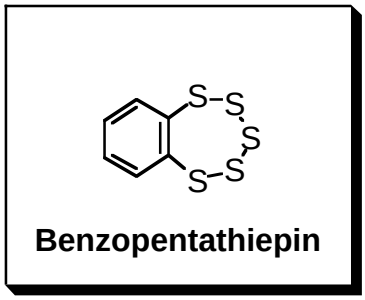
Ryu Sato,* Tetsuya Ohyama, Takatomo Kawagoe, Masaru Baba,
Shiduko Nakajo, Takeshi Kimura, and Satoshi Ogawa

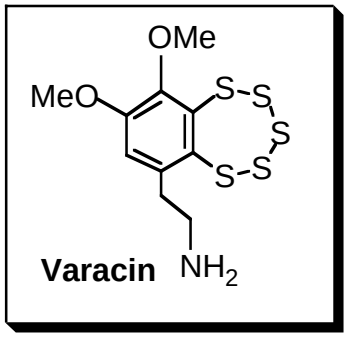
Department of Applied Chemistry, Faculty of Engineering, Iwate University
Morioka, 020-8551, Japan

Abstract-Four benzopentathiepins (**12**, **14**, **16**, and **18**) having a functional group, such as aminoethyl, pyridyl, pyrimidinyl, and thienyl groups, respectively, on the benzene ring were synthesized from 3-substituted 1,2-benzenedithiol by sulfurization with elemental sulfur in the presence of ammonia. These benzopentathiepins were characterized in the light of interaction of the pentathiepin ring with the functional group.

INTRODUCTION

For the synthesis of a typical cyclic benzopolysulfide, benzopentathiepin, which shows fungicidal activity[1], Chenard *et al*. proposed a new route by heating benzothiadiazole with elemental sulfur in the presence of 1,4-diazabicyclo[2.2.2]octane in 1985. Meanwhile Davidson *et al*. found a natural product, **varacin**,[2a] containing a benzopentathiepin framework[2b] and also succeeded in the total synthesis.[3] We have also performed the synthesis of benzopentathiepin with substituents, such as an alkyl, methoxy, and other groups, on the benzene ring, by the reaction of benzenedithiol or its synthetic equivalent with elemental sulfur in liquid ammonia.[4] Thus, many cyclic benzopolysulfides, such as benzopentathiepins and benzotrithioles, have attracted the attention of chemists in the fields of heteroatom and biological chemistry.[5]





There is, however, a significant problem to be solved: how do the substituents affect the stability of the pentathiepin ring? The interaction of the pentathiepin ring with the substituent has still not been fully elucidated chemically and also in relation to biological activity.[6] In this paper, we wish to report the

synthesis of some benzopentathiepins which have a functional group containing a nucleophilic nitrogen or sulfur atom on the benzene ring (Figure 1).[7] The interaction of the functional group with the pentathiepin ring is discussed in terms of the stability.

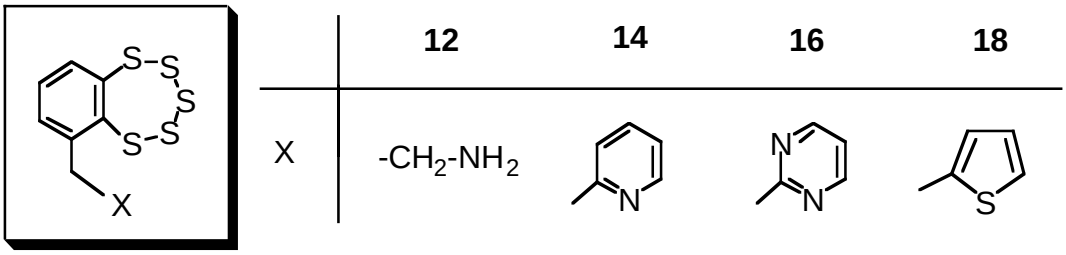
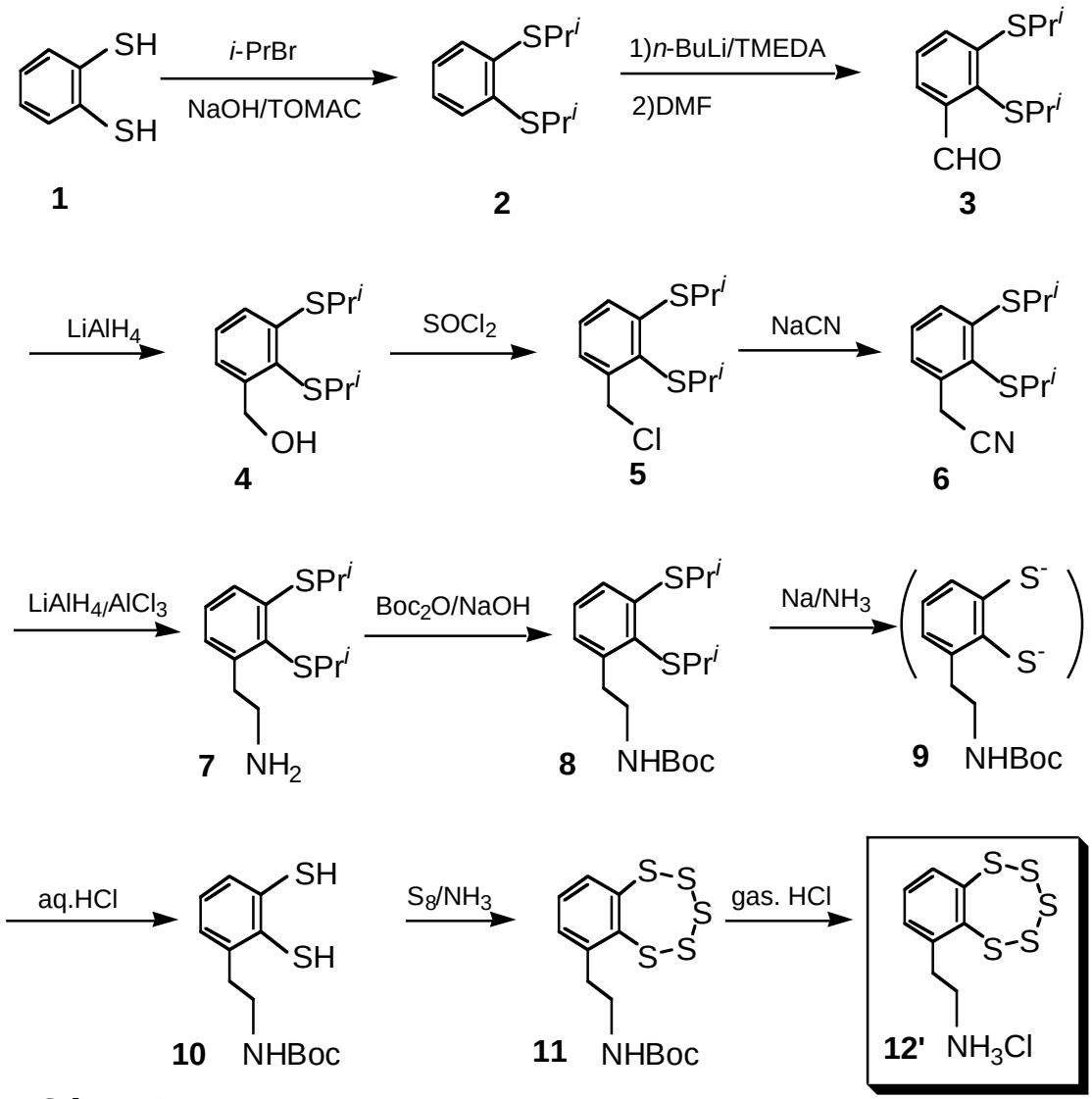


Figure 1. 6-Substituted benzopentathiepins

RESULTS AND DISCUSSION

It is well-known that a polysulfide ring such as benzopentathiepin is sensitive to a nucleophile, for example, amine and thiolate anion, accompanied by a cleavage of the sulfur–sulfur linkage[8] as well as a linear disulfide and the related polysulfides.[9] However, a benzopentathiepin framework was found in the natural product, **varacin**, having an aminoethyl group at the neighboring position to the polysulfide ring in the molecule.[2] It is noteworthy that the benzopentathiepin ring is not affected by the nucleophilic attack of an amino group, even if the inner amino group is protected with hydrogen chloride as an ammonium salt.[3] Our final aim was directed to the synthesis of benzopentathiepins having an amino group without protection by formation of an ammonium salt. The synthesis of the partial structure of **varacin**, 6-(2-aminoethyl)benzopentathiepin, was initially carried out as follows (Scheme 1). Two thiol groups of the starting compound, 1,2-benzenedithiol (**1**), were protected with an isopropyl group by reaction of isopropyl bromide in the presence of NaOH and trioctylmethylammonium chloride,[10] to give 1,2-bis(isopropylthio)benzene (**2**) in 95% yield. Ortho lithiation of **2** with *n*-BuLi in the presence of *N*,*N*,*N*‘,*N*’-tetramethylethylenediamine (**TMEDA**) followed by treatment of the resulting lithium compound with *N*,*N*-dimethylformamide afforded 2,3-bis(isopropylthio)benzaldehyde (**3**) in 93% yield.[11] Reduction of **3** with $LiAlH_4$ (99%) followed by chlorination with $SOCl_2$ furnished 2,3-bis(isopropylthio)benzyl chloride (**5**) in 98% yield *via* the corresponding alcohol (**4**).[12] Subsequent treatment of **5** with NaCN in a mixture of ethanol and water giving 1-cyanomethyl-2,3-bis(isopropylthio)benzene (**6,** 96%)[13] and the reduction of **6** with $LiAlH_4/AlCl_3$ yielded 2,3-bis(isopropylthio)phenethylamine (**7**) in 96% yield.[14] The amino group was protected by treatment with di-*tert*-butyl dicarbonate (Boc_2O), to give the carbonate (**8**) in 100% yield.[15] The obtained **8** was reduced with Na/NH_3 to dithiolate (**9**), which was treated with 10% HCl solution, to give 3-{2-[*N*-(*tert*-butoxycarbonyl)amino]ethyl}-1,2-benzenedithiol (**10**) in 99% yield. The sulfurization of **10** was accomplished by the following method, that is, the treatment with elemental sulfur in dichloromethane in the presence of ammonia gave a new benzopentathiepin, 6-{2-[*N*-(*tert*-butoxycarbonyl)amino]ethyl}-benzopentathiepin (**11**), in 95% yield. Further treatment of **11** with gaseous HCl in ethyl acetate gave the salt (**12’**) of 6-(2-aminoethyl)benzopentathiepin (**12**) in 96% yield (total yield 71% from **1**). In this

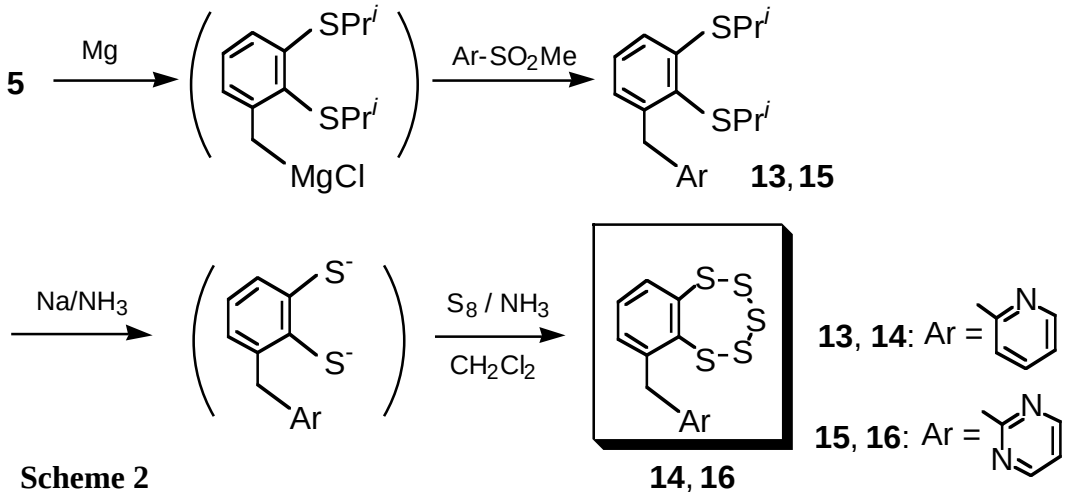


Scheme 1

reaction, we did not observe the formation of any other product.[1] However, HCl-free **12** formed by neutralization of **12'** with a base (aqueous NaOH solution) could not be isolated; it decomposed to give an insoluble polymer. This is very important for the effect of the substituent on the stability of the pentathiepin ring, because this result indicates that the pentathiepin ring is very reactive toward a free alkylamino group.

Next, we performed the introduction of a nitrogen functional group showing a weaker basicity on the benzene ring. We chose (2-pyridyl) and (2-pyrimidinyl)methyl groups as a functional group (Scheme 2). The introduction of these substituents was carried out as follows. Thus, the formation of a Grignard reagent from 2,3-bis(isopropylthio)benzyl chloride (**5**) followed by the reaction with 2-(methylsulfonyl)-pyridine[16] gave 1-[(2-pyridyl)methyl]-2,3-bis(isopropylthio)benzene (**13**) in 72% yield. Dealkylation of the alkylthio group in **13** by Birch reduction and following sulfurization with elemental sulfur in the presence of ammonia in dichloromethane afforded the desired 6-(2-pyridylmethyl)benzopentathiepin (**14**) as yellow crystals in 33% yield based on **13**. The structure of benzopentathiepin **14** was confirmed spectroscopically and finally established by elemental analysis. This compound was relatively stable in a solution of an organic solvent such as dichloromethane, but the isolated **14** from the solvent is less

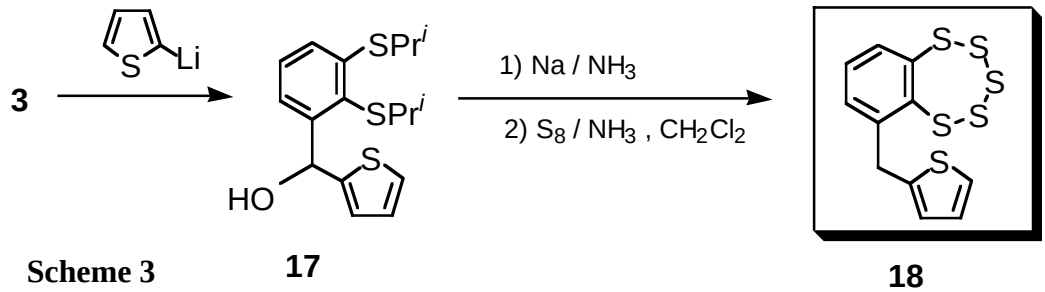
stable and decomposed slowly to an unidentified polymer.



Scheme 2

The formation of a Grignard reagent from 2,3-bis(isopropylthio)benzyl chloride (**5**) followed by reaction with 2-(methylsulfonyl)pyrimidine[16] afforded 1-(2-pyrimidinylmethyl)-2,3-bis(isopropylthio)benzene (**15**) in 59% yield. Birch reduction of compound (**15)** and following sulfurization with elemental sulfur in the presence of ammonia in dichloromethane gave a new benzopentathiepin, 6-[(2-pyrimidinyl)methy]-benzopentathiepin (**16**), as a yellow oily matter in 11% yield. Here, we wish to emphasize the stability of the pentathiepins obtained in this work. Thus, the success of the synthesis and isolation of two benzopentathiepins (**14** and **16**) points to the fact that the pentathiepin ring is stable toward the nitrogen functional group in the pyridine and pyrimidine.

Finally, our interest was focused on the synthesis of a pentathiepin having a thienyl group, which contains a thiophilic sulfide moiety. The synthetic route was established as follows (Scheme 3).



Scheme 3

The reaction of 2,3-bis(isopropylthio)benzaldehyde (**3**) with thienyl lithium[17] obtained by lithiation of thiophene afforded [2,3-bis(isopropylthio)phenyl](2-thienyl)methanol (**17**) quantitatively. Interestingly, the reduction of alcohol (**17**) with metallic sodium in liquid ammonia followed by sulfurization with elemental sulfur in the presence of ammonia in dichloromethane as a solvent gave directly the desired 6-[(2-thienyl)methyl]benzopentathiepin (**18**) as a yellow oily matter in 34% yield. The pentathiepin (**18)** could be isolated from the reaction mixture by column chromatography. According to these results, the pentathiepin ring is sufficiently stable toward the sulfide moiety in the thienyl group.

In conclusion, we have succeeded in the synthesis of four novel pentathiepins having a 2-aminoethyl, (2-pyridyl)methyl, (2-pyrimidinyl)methyl, or (2-thienyl)methyl group as the substituent on the benzene ring. In this study, we were able to confirm the stability of the pentathiepin ring toward a nucleophilic functional group containing nitrogen or sulfur.

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and were uncorrected. Elemental analyse were performed by Yanagimoto MT-3 and MT-5. IR spectra were recorded as KBr pellets or in neat using KRS-5 on a JASCO FT-7300 unit. The ^{1}H and ^{13}C NMR spectra were obtained on a Hitachi R-1500 and a Bruker AC-400P. MS spectra (EI) were recorded on a Hitachi M-2000 at 70 eV.

Synthesis of 6-(2-Aminoethyl)benzopentathiepin hydrochlorate (12')

Preparation of 1,2-Bis(isopropylthio)benzene (2) from 1

2-Bromopropane (37.9 g, 308 mmol) was added dropwise with stirring to a solution of 1,2-benzenedithiol (**1**) (14.6 g, 102 mmol), NaOH (16.4 g, 410 mmol), and trioctylmethylammonium chloride (1.25 g, 3.1 mmol) in a mixture of benzene (100 mL) and water (100 mL). After stirring for 12 h at rt, the solution was treated with ice-cold water and acidified with 10% HCl solution. The reaction mixture was extracted with benzene (3 x 50 mL) from the solution. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using $CHCl_3$ as the eluent to give **2** (22.0 g, 95%).

2: Colorless oil, bp 93-94 ˚C (0.4 Torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.33 (12H, d, *J* = 7.0 Hz, CH_3), 3.49 (2H, sept, *J* = 7.0 Hz, -CH-), 7.00-7.54 (4H, m, Ar-H). IR (neat) ν_{max} (cm^{-1}): 3053, 2961, 2924, 2864, 1571, 1444, 784. MS (EI) m/z 226 (M^+).

Preparation of 2,3-Bis(isopropylthio)benzaldehyde (3) from 2

A white suspension was obtained by addition of *n*-BuLi (33.0 mmol) in hexane (20.3 mL) and **TMEDA** (4.64 g, 102 mmol) to a solution of **2** (4.98 g, 22.0 mmol) in hexane (13 mL) under argon. To the suspension, *N*,*N*-dimethylformamide (2.41 g, 33.0 mmol) was added dropwise with stirring at 0 ˚C, and then the solution was stirred at rt for 3 h. The solution was treated with ice-cold water and neutralized by 10% HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using $CHCl_3$ as the eluent to give **3** (5.22 g, 93%).

3: Yellow oil, bp 113-114 ˚C (0.1 Torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.26 (6H, d, *J* = 7.0 Hz, CH_3), 1.39 (6H, d, *J* = 8.2 Hz, CH_3), 2.80-3.82 (2H, m, CH), 7.21-7.83 (3H, m, Ar-H), 10.83 (1H, s, CHO); IR (neat) ν_{max} (cm^{-1}): 1686(CHO). MS (EI) m/z 254 (M^+).

Preparation of 2,3-Bis(isopropylthio)benzylalcohol (4) from 3

To a solution of **3** (1.04 g, 4.10 mmol) in THF (50 mL) was added slowly $LiAlH_4$ (100 mg, 2.64 mmol), and then the solution was stirred at 3 h under reflux. The solution was treated with ice-cold water and acidified by 10% HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The product was purified

by chromatography on silica gel using $CHCl_3$ as the eluent to give **4** (1.04 g, 99%).
4: Colorless oil, bp 143 ˚C (0.4 Torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.25 (6H, d, *J* = 8.8 Hz, CH_3), 1.35 (6H, d, *J* = 8.8 Hz, CH_3), 2.60 (1H, br, OH), 3.07-3.85 (2H, m, CH), 4.84 (2H, d, *J* = 4.7 Hz, C***H***$_2$OH), 7.24 (3H, s, Ar-H); IR (neat) ν_{max} (cm^{-1}): 3383(OH). MS (EI) m/z: 256 (M^+).

Preparation of 2,3-Bis(isopropylthio)benzyl chloride(5) from 4

To a solution of **4** (1.28 g, 5 mmol) in $CHCl_3$ (5mL), $SOCl_2$ (0.71g, 6 mmol) in $CHCl_3$ (5 mL) was added dropwise, and the solution was stirred at rt for 1 h. After evaporation of $CHCl_3$ from the solution, the obtained mixture was purified by chromatography on silica gel using a mixture of hexane : benzene (3 : 1) as the eluent to give **5** (1.35 g, 98%).
5: Colorless oil, bp 106-107 ˚C (0.1 Torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ: 1.25 (6H, d, *J* = 7.0 Hz, CH_3), 1.38 (6H, d, *J* = 6.5 Hz, CH_3), 3.11-3.93 (2H, m, CH), 4.96 (2H, s, CH_2), 7.00-7.47 (3H, m, Ar-H); IR (neat) ν_{max} (cm^{-1}): 3052, 2962, 2925, 2864, 1559, 1445, 1273, 739. MS (EI) m/z: 274 (M^+).

Preparation of 2,3-Bis(isopropylthio)benzyl cyanide (6) from 5

A solution of **5** (1.38 g, 5.02 mmol) in ethanol (5 mL) was added to a solution involving NaCN (0.37 g, 7.5 mmol) in water (7 mL) and ethanol (5 mL), and the solution was stirred at 100 ˚C for 3 h. The reaction mixture was extracted with ether (3 x 50 mL) from the solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was purified by chromatography on silica gel using $CHCl_3$ as the eluent to give **6** (1.28 g, 96%).
6: Colorless oil, bp 125-127 ˚C (0.4 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (6H, d, *J* = 6.4 Hz, CH_3), 1.38 (6H, d, *J* = 6.4 Hz, CH_3), 3.49 (2H, sept, *J* = 6.4 Hz, CH), 4.10 (2H, s, CH_2), 7.04-7.48 (3H, m, Ar-H); IR (neat) ν_{max} (cm^{-1}): 2554 (CN). MS (EI) m/z: 265 (M^+).

Preparation of 2,3-Bis(isopropylthio)phenethylamine (7) from 6

A solution of **6** (1.33 g, 5 mmol) in ether (5.5 mL) was added dropwise to a suspension of $LiAlH_4$ (0.21 g, 5.5 mmol) in ether (8 mL) involving $AlCl_3$ (0.73 g, 5.5 mmol), and then the solution was stirred at rt for 1 h. The solution was treated with ice-cold water, acidified with 10% HCl solution, and basified with 10% NaOH aqueous solution. The reaction mixture was extracted with ether (3 x 50 mL) from the solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using a mixture of $CHCl_3$: MeOH (9 : 1) as the eluent to give **7** (1.29 g, 96%).
7: Colorless oil, bp 121-122 ˚C (0.3 Torr); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (6H, d, *J* = 6.4 Hz, CH_3), 1.38 (6H, d, *J* = 6.4 Hz, CH_3), 2.70-3.17 (4H, m, CH_2CH_2), 4.50 (2H, br s, NH_2) 3.48 (2H, sept, *J* = 6.4 Hz, CH), 6.58-7.48 (3H, m, Ar-H); IR (neat) ν_{max} (cm^{-1}): 3371, 3293 (NH). MS (EI) m/z: 271 (M^++1).

Preparation of 2,3-Bis(isopropylthio)-1-[2-(*N*-*tert*-butoxycarbonylamino)ethyl]benzene (8) from 7

To a solution of **7** (2.71 g, 10.1 mmol) and NaOH (0.43 g, 11.1 mmol) in a mixture of *tert*-BuOH (10 mL) and water (10 mL), di-*tert*-butyl dicarbonate (Boc_2O) (2.42 g, 11.1 mmol) in *tert*-BuOH (10 mL) was added dropwise for 1 h, and then the solution was stirred for 24 h. After careful neutralization with 10% HCl solution, the reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using CH_2Cl_2 as the eluent to give **8** (3.71 g, 100%).

8: Colorless needles, mp. 104-105 ˚C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.21 (6H, d, *J* = 6.6 Hz, CH(***CH*****$_3$**)$_2$), 1.39 (6H, d, *J* = 6.7 Hz, CH(***CH*****$_3$**)$_2$), 1.43 (9H, s, C(***CH*****$_3$**)$_3$), 3.13 (2H, t, *J* = 6.6 Hz, ***CH*****$_2$** CH_2NH), 3.34 (2H, q, *J* = 6.7 Hz, CH_2***CH*****$_2$**NH), 3.45 (1H, sept, *J* = 6.6 Hz, ***CH***$(CH_3)_2$), 3.47 (1H, sept, *J* = 6.7 Hz, ***CH***$(CH_3)_2$), 4.59 (1H, br s, NH), 7.04 (1H, d, *J* = 7.8 Hz, Ar-H), 7.11 (1H, dd, *J* = 1.2, 7.8 Hz, Ar-H), 7.21 (1H, t, *J* = 7.8 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 22.3, 28.4, 35.3, 35.7, 39.1, 41.6, 79.0, 124.4, 126.1, 128.8, 131.5, 144.9, 154.4, 155.8. IR (KBr) ν_{max} (cm^{-1}): 3360 (NH), 1687 (CO). MS (EI) m/z: 369 (M^+). *Anal*. Calcd for $C_{19}H_{31}NO_2S_2$: C; 61.74; H, 8.45; N, 3.79. Found: C, 61.34; H, 8.54; N, 3.64.

Preparation of 3-{2-[*N*-(*tert*-Butoxycarbonyl)amino]ethyl}-1,2-benzenedithiol (10) from 8 *via* Sodium 3-{2-[*N*-(*tert*-Butoxycarbonyl)amino]ethyl}-1,2-benzenedithiolate (9)

Small pieces of metallic sodium (1.38 g, 60 mg-atom) were added slowly to a solution of **8** (4.10 g, 11.1 mmol) in a mixture of THF (30 mL) and liquid ammonia (50 mL) at –78 ˚C for 1 h with stirring. After completion of the reaction, the solution was treated with NH_4Cl (0.535 g, 10 mmol) and then ammonia and THF were removed from the solution under reduced pressure. To the residue containing the reaction mixture, water (50 mL) was added, and the aqueous solution was acidified with 10% HCl solution. The reaction mixture was extracted with $CHCl_3$ (3 x 50 mL) from the solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using CH_2Cl_2 as the eluent to give **10** (3.15 g, 99%).

10: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (9H, s, C(***CH*****$_3$**)$_3$), 2.94 (2H, t, *J* = 6.8 Hz, ***CH*****$_2$** CH_2NH), 3.37 (2H, q, *J* = 6.8 Hz, CH_2C***H*****$_2$**NH), 3.79 (1H, s, SH), 3.99 (1H, s, SH), 4.73 (1H, br s, NH), 6.98-7.00 (2H, m, Ar-H), 7.27-7.30 (1H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.3, 35.9, 40.0, 79.1, 126.1, 139.3, 155.8. IR (neat) ν_{max} (cm^{-1}): 3353 (NH), 2534 (SH) 1708 (CO). MS (EI) m/z: 283 (M^+-H_2).

Synthesis of 6-{2-[N-(*tert*-Butoxycarbonyl)amino]ethyl}benzopentathiepin (11) from 10

Gaseous ammonia (10 mL as liquid ammonia) was bubbled into a solution of **10** (0.85 g, 3 mmol) and elemental sulfur (0.48 g, 15 mg-atom) in CH_2Cl_2 (300 mL) with stirring at rt. The solution was stirred until complete evaporation of ammonia under atmosphere (*ca*. 4 day). The reaction mixture, obtained by removal of CH_2Cl_2 from the solution under reduced pressure, was purified by chromatography on silica gel using CH_2Cl_2 as the eluent to give **11** (1.08 g, 95%).

11: Pale yellow plates, mp 112-114 ˚C (CH_2Cl_2 / hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.43 (9H, s, $C(CH_3)_3$), 3.11-3.24 (2H, m, C***H*****$_2$** CH_2NH), 3.29-3.40 (2H, m, CH_2C***H*****$_2$**NH), 4.64 (1H, br s, NH), 7.25 (1H, dd, *J* = 7.4, 7.6 Hz, Ar-H), 7.30 (1H, d, *J* = 7.6 Hz, ArH), 7.25 (1H, dd, *J* = 1.8, 7.4 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.4, 36.8, 41.8, 79.4, 130.1, 132.8, 134.6, 143.7, 145.3, 155.7. IR (KBr) ν_{max} (cm^{-1}): 3342 (NH), 1670 (CO). MS (EI) m/z: 315 (M^+-S_2). *Anal*. Calcd for $C_{13}H_{17}NOS_5$: C; 41.13; H, 4.51; N, 3.69. Found: C, 40.89; H, 4.49; N, 3.50.

Synthesis of 6-(2-Aminoethyl)benzopentathiepin Hydrochlorate (12') from 11

Dry gaseous HCl was bubbled into a solution of **11** (1.14 g, 3 mmol) in ethyl acetate (100 mL) sufficiently at 0 ˚C with stirring to give a yellow precipitate. The precipitate was washed with ethyl acetate (20 mL) to give a pale yellow powder (**12'**) (0.882 g, 96%).

12': Pale yellow powder, mp 195-200 ˚C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.04-3.11 (2H, m,

CH_2), 3.18-3.25 (1H, m, CH_2), 3.29-3.36 (1H, m, CH_2), 7.32 (1H, t, *J* = 7.7 Hz, Ar-H), 7.40 (1H, dd, *J* = 1.5, 7.7 Hz, Ar-H), 7.75 (1H, dd, *J* = 1.5, 7.7 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.0, 41.6, 132.2, 134.1, 136.5, 144.3, 144.9, 147.2. IR (KBr) ν_{max} (cm^{-1}): 2957 (NH_3^+). MS (EI) m/z: 280 (M^+-Cl). *Anal*. Calcd for $C_8H_{10}ClS_5$: C, 30.41; H, 3.19; N, 4.43. Found: C, 30.27; H, 3.09; N, 4.26.

Synthesis of 6-[(2-Pyridyl)methyl] and 6-[(2-Pyrimidinyl)methyl]benzopentathiepin (14 and 16) from 5 *via* 2-[2,3-Bis(isopropylthio)benzyl]pyridine and pyrimidine (13 and 15)

Preparation of 13 and 15

A few drops of 1,2-dibromoethane were added to a solution of dry ether (1 mL) containing metallic magnesium (73 mg, 3.0 mg-atom) under argon with irradiation by ultrasonic waves. After completely dissolving the magnesium, a solution of **5** (275 mg, 1.0 mmol) in dry ether (1 mL) was added to the solution. The obtained solution involving a Grignard reagent was added dropwise to a solution of 2-(methylsulfonyl)pyridine or pyrimidine (1.0 mmol) in dry ether (1.0 mL), and then the solution was heated under reflux for 12 h. The solution was treated with ice-cold water and neutralized by 10% HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using a mixture of ethyl acetate : $CHCl_3$ (3 : 1) as the eluent to give **13** (75%) or **15** (72%).

Synthesis of 14 from 13 and 16 from 15

To a solution of metallic sodium (1.84 g, 80.0 mg-atom) in liquid ammonia (25 mL), **13** or **15** (2.0 mmol) in THF (4 mL) was added dropwise at –78 ˚C, and then the solution was allowed to reflux for 30 min. The mixture obtained by evaporation of ammonia at rt was treated with methanol and water and then neutralized with 10% HCl solution. The mixture was extracted with CH_2Cl_2 (3 x 50 ml) from the aqueous solution. The organic layer was dried over $MgSO_4$ and filtered. To the solution containing 3-pyridyl or 3-pyrimidinyl-1,2-benzenedithiol, elemental sulfur (0.32 g, 10.0 mg-atom) was added, and then gaseous ammonia (20 mL as liquid ammonia) was bubbled slowly with stirring. The solution was allowed to stand with stirring for 3 days until complete evaporation of ammonia and concentrated by evaporation of CH_2Cl_2 under reduced pressure. The product was purified by chromatography on silica gel using a mixture of ethyl acetate : hexane (1 : 1) as the eluent to give **14** (33%) as yellow crystals and **16** (11%) as yellow oil.

14: mp 109 ˚C (decomp, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.44 and 4.60 (2H, ABq, *J* = 15.2 Hz, CH_2), 7.08 (1H, dd, *J* = 7.7, 2.0 Hz, Py-H), 7.12 (1H, dt, *J* = 7.7, 2.0 Hz, Py-H), 7.27 (1H, t, *J* = 7.7 Hz, Ar-H), 7.39 (1H, dd, *J* = 7.7, 1.4 Hz, Ar-H), 7.60 (1H, dt, *J* = 7.7, 1.8 Hz, Py-H), 7.76 (1H, dd, *J* = 7.7, 1.4 Hz, Ar-H), 8.54 (1H, dd, *J* = 7.7, 1.8 Hz, Py-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 44.7, 121.5, 123.3, 130.1, 133.2, 134.8, 136.6, 144.1, 145.27, 145.32, 149.5, 159.5. IR (KBr) ν_{max} (cm^{-1}): 3047, 3003, 2921, 1638, 1589, 1567, 1470, 1432, 1175, 1147, 1090, 1047, 993, 832, 747, 639, 584, 449, 403. MS (EI) m/z 263 (M^+-S_2). *Anal*. Calcd for $C_{12}H_9NS_5$: C, 44.01; H, 2.77; N, 4.28. Found: C, 44.39; H, 3.22; N, 3.97.

16: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.65 and 4.72 (2H, ABq, *J* = 15.6 Hz, CH_2), 7.13 (1H, t, *J* = 4.9 Hz, Pyrim-H), 7.29 (1H, t, *J* = 7.7 Hz, Ar-H), 7.41 (1H, dd, *J* = 7.7, 1.2 Hz, Ar-H), 7.79 (1H, dd,

J = 7.7, 1.2 Hz, Ar-H), 8.66 (2H, d, *J* = 4.9 Hz, Pyrim-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 46.1, 118.8, 130.0, 133.2, 135.1, 143.9, 145.1, 157.0, 157.3, 168.8. IR (neat) ν_{max} (cm^{-1}): 3044, 2965, 2927, 2854, 1562, 1416, 1265, 1217, 1182, 1139, 1090, 993, 840, 788, 666, 635, 603, 534, 523, 475. MS (EI) m/z: 264 (M^+-S_2). *Anal*. Calcd for $C_{11}H_8N_2S_5$: C, 40.22; H, 2.45; N, 8.53. Found: C, 40.57; H, 2.85; N, 7.93.

Synthesis of 6-[(2-Thienyl)methyl]benzopentathiepin (18) from 3 *via* [2,3-Bis(isopropylthio)phenyl]-(2-thienyl)methanol (17)

Preparation of 17 from 3

A solution of *n*-BuLi (34.6 mmol) in hexane (23 mL) was added dropwise to a solution of thiophene (2.41 g, 28.7 mmol) in THF (60 mL) at 0 ˚C with stirring. A solution of **3** (10.6 g, 41.5 mmol) in THF (40 mL) was added slowly to the solution and then stirred at rt for 2 h. The solution was treated with 10% NH_4Cl aqueous solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by chromatography on silica gel using hexane as the eluent to give **17** (9.65 g, 100%).

17: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (3H, d, *J* = 6.7 Hz, CH_3), 1.20 (3H, d, *J* = 6.7 Hz, CH_3), 1.38 (6H, d, *J* = 6.6 Hz, CH_3), 2.92 (1H, s, OH), 3.45 (1H, sept, *J* = 6.7 Hz, CH), 3.50 (1H, sept, *J* = 6.6 Hz, CH), 6.81 (1H, s, CHOH), 6.81-6.82 (1H, m, Th-H), 6.90-6.92 (1H, m, Th-H), 7.21-7.23 (2H, m, Ar-H and Th-H), 7.33 (1H, t, *J* = 7.7 Hz, Ar-H), 7.39 (1H, dd, *J* = 7.7, 1.4 Hz, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 22.7, 22.8, 22.8, 23.2, 36.0, 39.3, 70.5, 123.6, 124.9, 125.1, 126.1, 126.6, 129.2, 130.4, 145.3, 148.0, 148.4. IR (neat) ν_{max} (cm^{-1}): 3070, 2960, 2922, 2863, 1560, 1443, 1403, 1382, 1365, 1291, 1241, 1178, 1141, 1050, 831, 756, 736, 700, 508.

Synthesis of 18 from 17

A few pieces of metallic sodium (184 mg, 8.0 mg-atom) were added slowly to a solution of **17** (339 mg, 1.0 mmol) in a mixture of THF (1 mL) and liquid ammonia (10 mL) under nitrogen and stirred at –70 ˚C for 20 min. After evaporation of ammonia at rt, the solution was neutralized by 10% HCl solution. The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL) from the aqueous solution. The organic layer was dried over $MgSO_4$ and filtered. To the obtained solution containing the reaction mixture, elemental sulfur (160 mg, 5.0 mg-atom) was added slowly and then ammonia (20 mL as liquid ammonia) was bubbled at rt. The solution was allowed to stand with stirring for 3 days until complete evaporation of ammonia and concentrated by evaporation of CH_2Cl_2 under reduced pressure. The product was purified by chromatography on silica gel using hexane as the eluent to give **18** (112 mg, 34%).

18: Yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.40 (1H, d, *J* = 15.7 Hz, CH_2), 4.53 (1H, d, *J* = 15.7 Hz, CH_2), 6.72 (1H, dd, *J* = 3.4, 1.1 Hz, Th-H), 6.90 (1H, dd, *J* = 3.4, 5.2 Hz, Th-H), 7.14 (1H, dd, *J* = 5.2, 1.1 Hz, Th-H), 7.23 (1H, t, *J* = 7.6 Hz, Ar-H), 7.31 (1H, dd, *J* = 7.6, 1.4 Hz, Ar-H), 7.73 (1H, dd, *J* = 7.6, 1.4 Hz, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 36.43, 124.3, 125.6, 126.9, 130.2, 132.3, 134.8, 142.5, 143.5, 145.3, 146.2. IR (neat) ν_{max} (cm^{-1}): 3066, 2916, 1570, 1432, 1400, 1229, 1175, 1143, 1074, 1038, 908, 850, 798, 750, 697, 515, 475. MS (EI) m/z: 268 (M^+-S_2). *Anal*. Calcd for $C_{11}H_8S_6$: C, 39.73; H, 2.42. Found: C, 39.98; H, 2.66.

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