

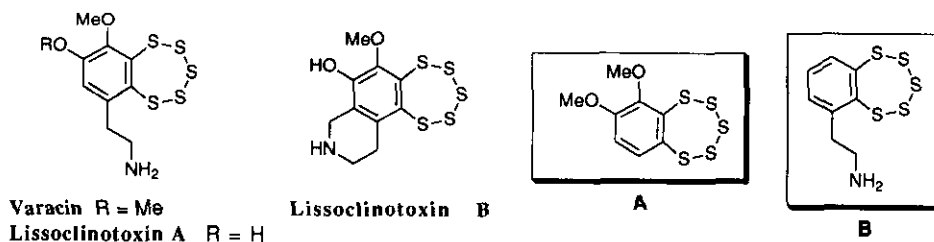
EFFICIENT SYNTHESIS AND BIOLOGICAL PROPERTIES OF NEW BENZOPENTATHIEPINS

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Abstract - New 6,7-dimethoxybenzopentathiepin and 6-(2-aminoethyl)benzopentathiepin, which are partial structures of varacin, were synthesized from 1,2-dimethoxybenzene and 1,2-benzenedithiol respectively.

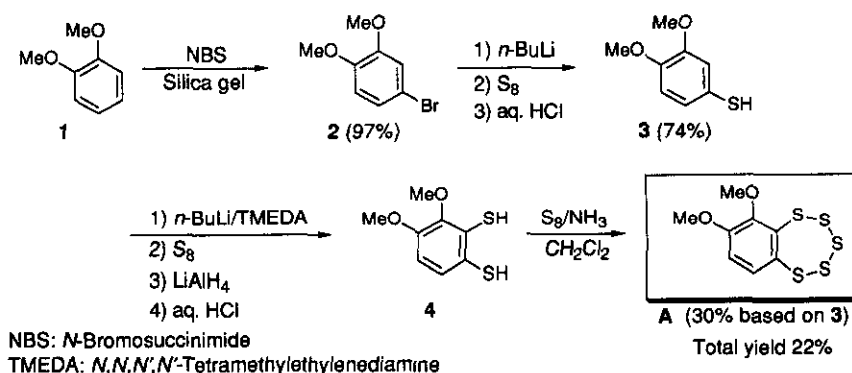
Recently, the characteristic chemical properties of cyclic polysulfides have attracted wide attention in the field of organosulfur chemistry.¹ We have also reported new methods for the synthesis of benzopentathiepins² and the related compounds.³ Furthermore, we have found many reactions for providing some heterocycles from such cyclic polysulfides.⁴ On the basis of these findings, our interests were directed to the synthesis of new biologically active benzopentathiepin, for example, varacin and lissoclinotoxins,⁵ which were found in marine natural products and the total syntheses have been recently reported.⁶ In this paper, we wish to report an efficient synthesis and the biological properties of two novel benzopentathiepins, 6,7-dimethoxybenzopentathiepin (**A**) and 6-(2-aminoethyl)benzopentathiepin (**B**), which are partial structures of varacin, using our original method with elemental sulfur and gaseous ammonia.²



Our synthetic interests focused on new benzopentathiepins related to varacin or lissoclinotoxin A and consequently we selected two new benzopentathiepins **A** and **B** that are partial structures of varacin. These compounds are very interesting in the viewpoint of biological activities. The synthesis of benzopentathiepin **A** was established from 1,2-dimethoxybenzene (**1**) as follows (Scheme 1). 1,2-Dimethoxybenzene (**1**) was brominated with *N*-bromosuccinimide in the presence of silica gel to give 4-bromo-1,2-dimethoxybenzene (**2**) in 97% yield.⁷ 3,4-Dimethoxybenzenethiol (**3**) obtained from **2** by halogen-metal exchange with *n*-BuLi following treatment with elemental sulfur (74%) was reacted with *n*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and then elemental sulfur to afford 3,4-dimethoxy-1,2-benzenedithiol (**4**).⁸ The reaction mixture containing benzenedithiol (**4**) was treated with elemental sulfur

and gaseous ammonia in dichloromethane to give 6,7-dimethoxybenzopentathiepin (**A**) in total yield 22%. The yield of **A** was rather low because of the low regioselectivity in ortho lithiation of **3**. Here, we could not find any other ring-sized product such as 4,5-dimethoxybenzotrithiole at all.

6,7-Dimethoxybenzopentathiepin (**A**): Pale yellow needles; mp 88.0-88.5 °C; ^1H nmr (400 MHz, CDCl_3) δ 3.88 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 6.82(d, $J = 8.4$ Hz, 1H, ArH), and 7.56 (d, $J = 8.4$ Hz, 1H, ArH); $^{13}\text{C}\{^1\text{H}\}$ nmr (100 MHz, CDCl_3) δ 56.2, 61.9, 112.9, 132.1, 135.6, 139.6, 150.9, and 155.0; ir (KBr) 3063, 3000, 2956, 2837, 1296, 1255, and 821 cm^{-1} ; ms (m/z) 296 (M^+); Anal. Calcd for $\text{C}_8\text{H}_8\text{O}_2\text{S}_5$: C, 32.41; H, 2.72. Found: C, 32.19; H, 2.66.

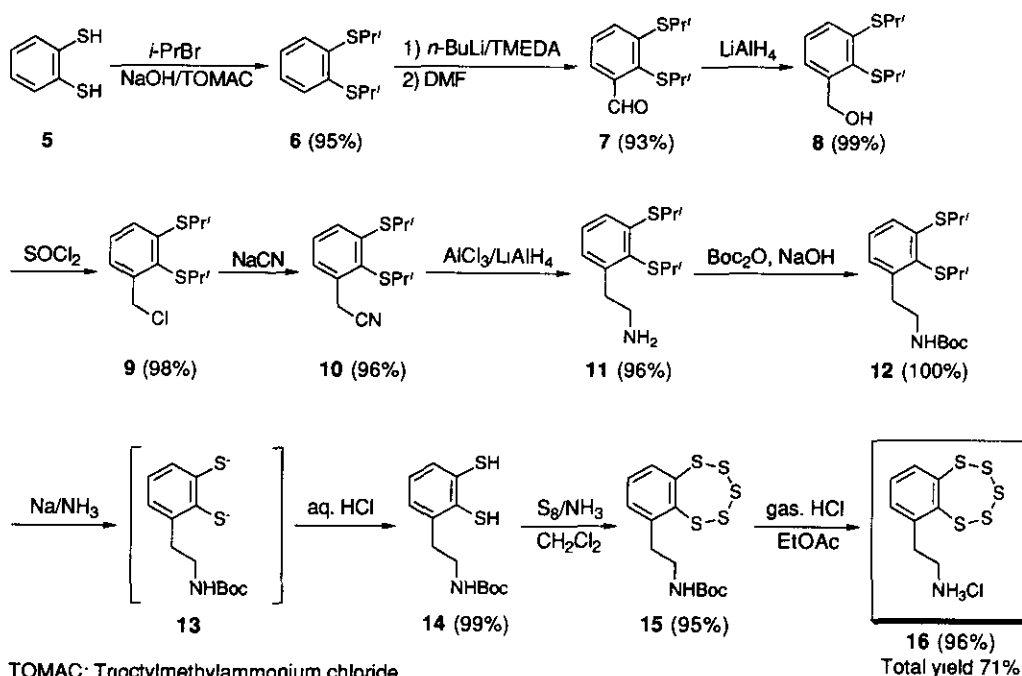


Scheme 1

Next, our synthetic interest was directed to the synthesis of new benzopentathiepin having aminoethyl group on benzene ring. Biologically interesting benzopentathiepin, 6-(2-aminoethyl)benzopentathiepin (**B**), was synthesized as follows (Scheme 2): Starting compound, 1,2-benzenedithiol (**5**) was protected with isopropyl group in the presence of NaOH and trioctylmethylammonium chloride to give 1,2-bis(isopropylthio)benzene (**6**) in 95% yield.⁹ Ortho lithiation of **6** with *n*-BuLi in the presence of TMEDA followed by treatment of the resulting lithium salt with *N,N*-dimethylformamide afforded 2,3-bis(isopropylthio)benzaldehyde (**7**) in 93% yield.¹⁰ Reduction of **7** with LiAlH_4 (99%) followed by chlorination with SOCl_2 furnished 2,3-bis(isopropylthio)benzyl chloride (**9**) in 98% yield from the corresponding alcohol (**8**).¹¹ Following treatment of **9** with NaCN (96%) and reduction with $\text{LiAlH}_4/\text{AlCl}_3$ yielded 2,3-bis(isopropylthio)phenethylamine (**11**) in 96% yield from **10**.^{12,13} Amino group of **11** was protected by treatment with di-*tert*-butyl dicarbonate to give *tert*-butyl carbamate (**12**) in 100% yield.¹⁴ The obtained **12** was reduced with Na/NH_3 to give dithiolate (**13**) and then the intermediate (**13**) was treated with aqueous HCl solution to give 3-[2-[*N*-(*tert*-butoxycarbonyl)amino]ethyl]-1,2-benzenedithiol (**14**) in 99% yield.¹⁵ The sulfurization of **14** was accomplished by our original method, that is the treatment with elemental sulfur and gaseous ammonia in dichloromethane, to give novel 6-[2-[*N*-(*tert*-butoxycarbonyl)amino]ethyl]benzopentathiepin (**15**) in 95% yield. Moreover, the treatment of **15** with gaseous HCl in ethyl acetate gave the hydrochloride salt (**16**) of 6-(2-aminoethyl)benzopentathiepin (**B**) in 96% yield (total yield 71%).¹⁶ Also in this reaction, we could not observe the formation of any other product.

6-(2-Aminoethyl)benzopentathiepin hydrochloride (**16**): Pale yellow powder; mp 195-200 °C (decomp.); ^1H nmr (400 MHz, CD_3OD) δ 3.04-3.11 (m, 2H, CH_2), 3.18-3.25 (m, 1H, CH_2), 3.29-3.36 (m, 1H, CH_2),

7.32 (t, $J = 7.7$ Hz, 1H, ArH), 7.40 (dd, $J = 1.5, 7.7$ Hz, 1H, ArH), and 7.75 (dd, $J = 1.5, 7.7$ Hz, 1H, ArH); ^{13}C { ^1H } nmr (100 MHz, CD_3OD) δ 35.0, 41.6, 132.2, 134.1, 136.5, 144.3, 144.9, and 147.2; IR (KBr) 2957 cm^{-1} ; ms (m/z) 280 ($M^+ - 35$); Anal. calcd for $\text{C}_8\text{H}_{10}\text{NCIS}_5$: C, 30.41; H, 3.19; N, 4.43. Found: C, 30.27; H, 3.09; N, 4.26.

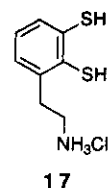


Scheme 2

It has been shown that benzopentathiepins isolated from ascidians of the genus *Lissoclinum*, varacin and lissoclinotoxins, have potent biological activities.⁵ New benzopentathiepins (A, 15, and 16) and the related compound (17) synthesized by new route mentioned above were also cytotoxic compounds and showed structural functional relationships to the cytotoxicity.¹⁷ Thus, all these compounds exhibited cytotoxicity with IC_{50} values of 6.12–0.26 $\mu\text{g}/\text{mL}$ toward HeLa S₃ cells (Table 1). Protection of the amino group and change of substituents on the benzene ring of 16 lowered the cytotoxicity. Interestingly, pentathiepin (16) showed ten times greater cytotoxicity compared with it of benzenedithiol (17). These results suggest that the pentathiepin and phenethylamine moieties play important roles on the biological activity.

Table 1. Cytotoxicity Testing Results for Synthetic Benzopentathiepins and Related Compound A, 15-17

Compd	IC_{50} , $\mu\text{g}/\text{ml}$
	HeLa S ₃
6,7-Dimethoxybenzopentathiepin (A)	6.12
6-[2-[<i>N</i> -(<i>tert</i> -Butoxycarbonyl)amino]ethyl]benzopentathiepin (15)	3.18
6-(2-Aminoethyl)benzopentathiepin hydrochloride (16)	0.26
3-(2-Aminoethyl)-1,2-benzenedithiol hydrochloride (17)	3.13



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17. Full data will be reported in a future paper.