EFFICIENT SYNTHESIS AND BIOLOGICAL PROPERTIES OF NEW BENZOPENTATHIEPINS

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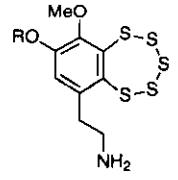
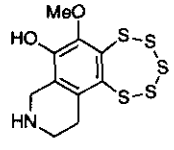
Abstract - New 6,7-dimethoxybenzopentathiepin and 6-(2-aminoethyl)benzopentathiepin, which are partial structures of varacin, were synthesized from 1,2-dimethoxybenzene and 1,2-benzenedithiol respectively.

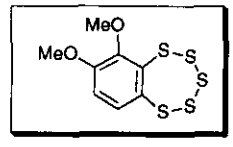
Recently, the characteristic chemical properties of cyclic polysulfides have attracted wide attention in the field of organosulfur chemistry.[1] We have also reported new methods for the synthesis of benzopentathiepins[2] and the related compounds.[3] Furthermore, we have found many reactions for providing 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]



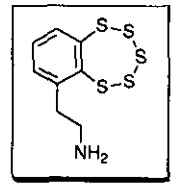
Varacin R = Me
Lissoclinotoxin A R = H



Lissoclinotoxin B



A

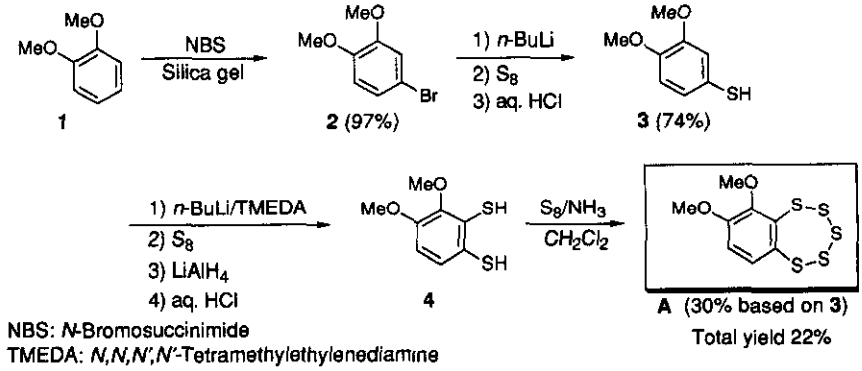


B

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; ^{1}H 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}C{^{1}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 $C_8H_8O_2S_5$: C, 32.41; H, 2.72. Found: C, 32.19; H, 2.66.

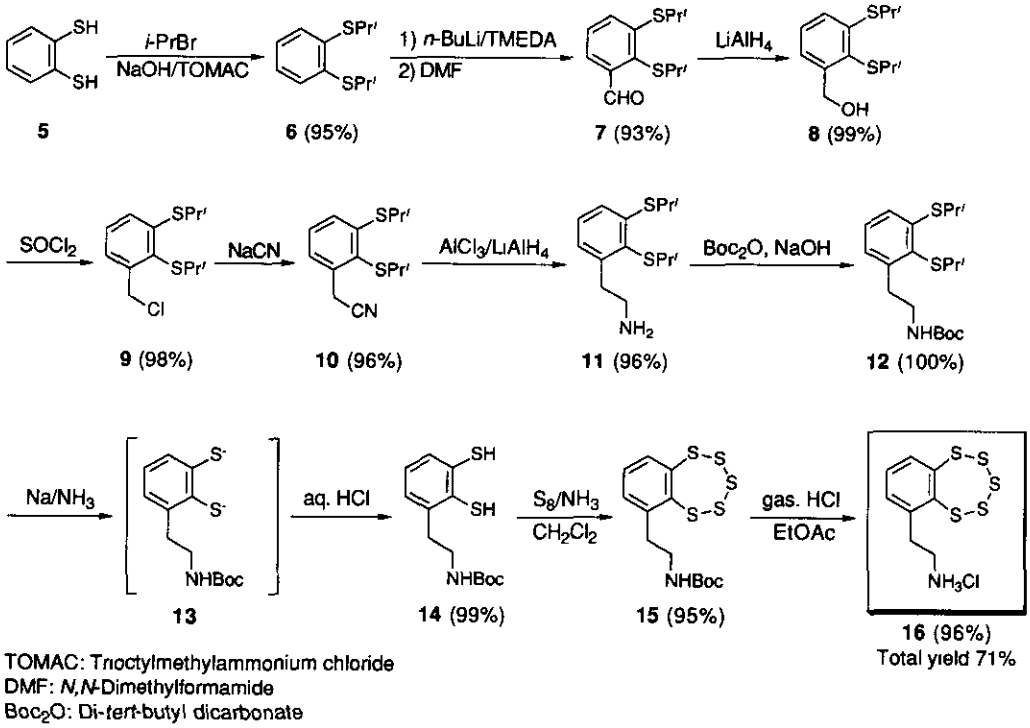


Scheme 1

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 $LiAlH_4/AlCl_3$ 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.); ^{1}H 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 $C_8H_{10}NClS_5$: C, 30.41; H, 3.19; N, 4.43. Found: C, 30.27; H, 3.09; N, 4.26.

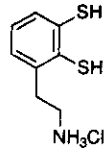


Scheme 2

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 μg/mL toward HeLa S_3 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}, μg/ml HeLa S_3
6,7-Dimethoxybenzopentathiepin (**A**)	6.12
6-[2-[*N*-(*tert*-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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ACKNOWLEDGEMENTS

This work was partially supported by Grant-in Aid for Scientific Research (No. 05554015) from the Ministry of Education, Science and Culture, Japan.

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

Received, 31st January, 1995