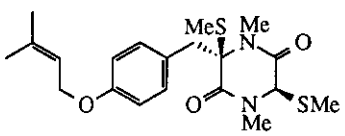
TOTAL SYNTHESES OF NATURALLY OCCURRING BIS(METHYLTHIO)SILVATIN AND ITS THREE STEREOISOMERS

Yasuchika Yonezawa, Kanetaka Shimizu, Mayumi Uchiyama, Natsuki Kagawa, and Chung-gi Shin*

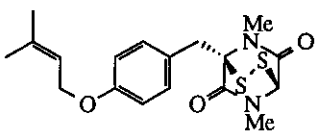
Laboratory of Organic Chemistry, Faculty of Technology, Kanagawa University, Kanagawa-ku, Yokohama 221, Japan

Abstract — Total syntheses of naturally occurring bis(methylthio)silvatin and its three stereoisomers were achieved from 1,4-dimethyl-3-(*p*-hydroxy)benzyl-2,5-piperazinedione. The configurational structures of the four stereoisomers, thus obtained, were definitely determined by the comparisons of their mps, specific rotations and NMR spectra.

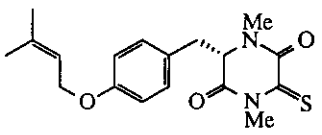
Bis(methylthio)silvatin (**1a**)[1,2] and similar two nameless products,[1,2] produced by *Gliocladium virens*, have a main cyclic dipeptide [cyclo(Gly-Tyr)] structure substituted with two methylmercapto groups at 2, 5-positions. In addition, similar natural products, dithiosilvatin (**2**) and silvathione (**3**), have been also isolated from *Aspergillus silvaticus* and structurally determined.[3] Most of the above mentioned natural products feature an interesting common substructure, 3-methyl-2-butenyl



Bis(methylthio)silvatin (**1a**)



Dithiosilvatin (**2**)



Silvathione (**3**)

Figure 1.

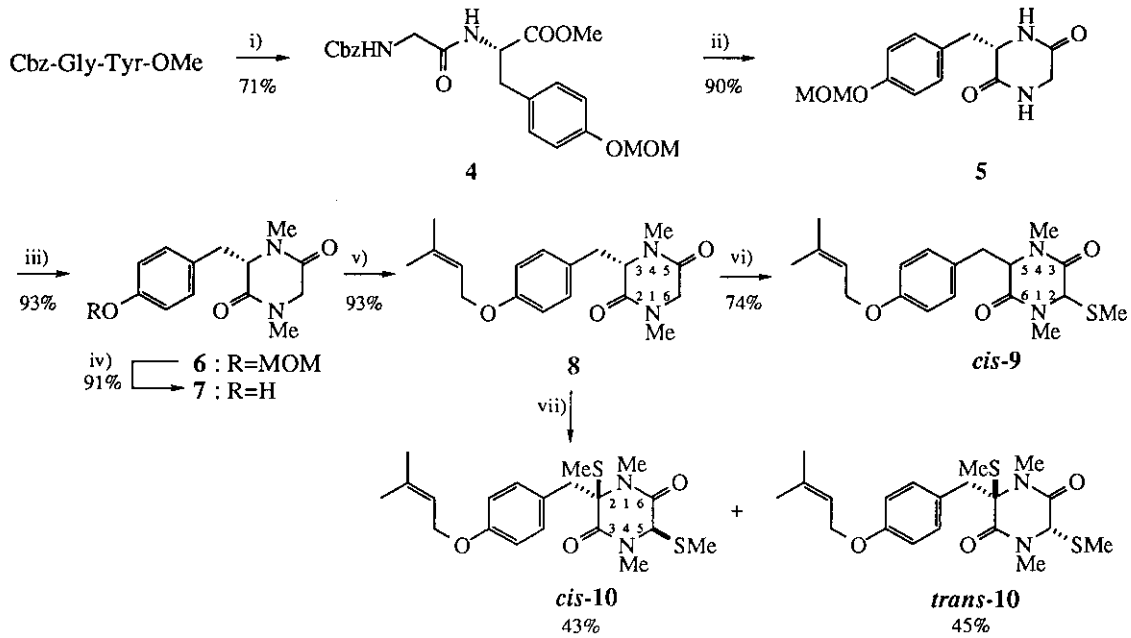
group linked to hydroxyl group of 3-(*p*-hydroxy)benzyl-PDO (2,5-piperazinedione=PDO) derivative, illustrated in Figure 1. Although the direct transformation to **1a** only by the reductive methylation of **2** with $NaBH_4$ and MeI, and the configurational confirmation has been reported,[3] the total synthesis of any natural products mentioned above has not been achieved yet. We were interested in not only the total syntheses of **1a** and its three stereoisomers, but also their structure-bioactivity relationship.

In this paper, we wish to report on the first achievement of the chiral syntheses of all of the stereoisomers (**1a-d**) from 1,4-dimethyl-3-(*p*-hydroxy)benzyl-PDO (**7**) and the definite configurational determinations.

So far, 3-[*p*-(3-methyl-2-butenyl)oxy]benzyl-PDO, which is thought to be a promising starting material for **1**, has been already synthesized by *O*-alkylation of 3-(*p*-hydroxy)benzyl-PDO with 1-bromo-3-methyl-2-butene.[2] However, the yield is a considerably low, because of the occurrence of undesirable *N*-alkylation of 1,4-positions. Accordingly, we chose the different route as follows.

First of all, *N*-benzyloxycarbonyl (Cbz)-Gly-Tyr-OMe was prepared by the coupling of Cbz-Gly-OH with H-Tyr-OMe by the usual dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide (HOSu) method. Protection of the hydroxyl group with chloromethyl methyl ether (MOMCl) gave Cbz-Gly-Tyr(MOM)-OMe (**4**). Hydrogenolytic deprotection of Cbz group on 10% Pd/C gave *N*-free dipeptide as the intermediate, which was immediately cyclized with NH_3 in MeOH to afford 3-(*p*-MOMO)benzyl-PDO derivative (**5**). Subsequent *N*-methylation[4] of 1,4-positions of **5** with MeI and NaH gave the corresponding 1,4-dimethyl derivative (**6**). Then, after deprotection of MOM group of **6** with HCl/EtOAc, the obtained 1,4-dimethyl-3-(*p*-hydroxy)benzyl-PDO (**7**) was *O*-alkylated[2] with 1-bromo-3-methyl-2-butene using NaH in dimethylformamide (DMF) to give the expected 1,4-dimethyl-3-[*p*-(3-methyl-2-butenyl)oxy]benzyl-PDO (**8**)[5] in 93% yield (Scheme 1).

Furthermore, for the synthesis of 3,6-dimethylmercapto-PDO derivative, the methylthiolation of **8** was variously examined. Finally, by the method reported by Bossler and Seebach,[5] the compound (**8**) was treated with lithium *N*,*N*-diisopropylamide (LDA) (made from *N*,*N*-diisopropylamine and *n*-butyllithium in THF) and then dimethyl disulfide (Me_2S_2) in THF-hexamethylphosphoric triamide (HMPA) at -78 °C for 2 h. As the results, in the case using LDA (1.2 eq) and Me_2S_2 (2 eq) to **8**, only methylthiosilvatin (**9**) as

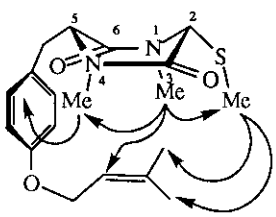


i) MOMCl, iPr$_2$NEt / CH_2Cl_2, rt, overnight, ii) 10% Pd/C, H_2 / EtOH, rt, 4 h; NH_3 / MeOH, -10 °C, 1 h, iii) MeI, NaH / DMF, rt, 3 h, iv) HCl / EtOAc, rt, 3 h, v) 1-Bromo-3-methyl-2-butene, NaH / DMF, rt, 1 h, vi) LDA (1.2 eq), Me_2S_2 (2 eq) / THF-HMPA, -78 °C, 2 h, vii) LDA (3 eq), Me_2S_2 (6 eq) / THF- HMPA, -78 °C, 2 h.

Scheme 1.

a racemate was obtained in a 74% yield. However, with increasing gradually the amounts of LDA and Me_2S_2 under similar conditions, it was found that the expected bis(methylthio)silvatin (**10**) also formed and increased, besides **9**. Consequently, in the case using LDA (3 eq) and Me_2S_2 (6 eq), the yield of **10** alone as a mixture of geometric isomers eventually reached the highest value of 88%.

Since the structure of **9** was determined to be *cis*-form[6] by the ^{1}H NMR analyses which included NOE experiments (Figure 2), the racemate was chromatographed by HPLC using hexane and 2-propanol (90:10 v/v) as the eluent under flow rate 7.6 mL/min at 40 °C by detecting UV (254 nm) absorption to give two optical isomers. The configurational structure could fully determine to be (2*R*,5*R*)-**9** and (2*S*,5*S*)-**9**, because the first fraction gave (*R*)-*N*-methyltyrosine, and the second gave (*S*)-*N*-methyltyrosine by the acid hydrolysis of each isomers. Thus obtained **9** is thought to be a very promising starting material for the synthesis of an another similar natural product, silvathione.[3]



NOE correlations are depicted with arrow.

Figure 2.

On the other hand, the compound (**10**) obtained above could be readily separated on a silica gel column using hexane and EtOAc (1 : 1 v/v) to give two kinds of diastereomers, ***cis***- and ***trans***-**10** as racemates in 45% and 43% yields, respectively. The structures of the respective geometric isomers of **10** were clearly determined by the NMR spectral analyses.

Table. Optical isomers of bis(methylthio)silvatin

Compd No.		Synthetic	Natural	From **2**
***cis*-10** (racemate)	mp / °C	88		
(2*R*,5*R*)-**1a**	mp / °C	syrup	syrup	syrup
	$[\alpha]_D$ ($CHCl_3$)	-43.0° (c 1.5)	-26.8° (c 6.8)	-43.5° (c 1.5)
(2*S*,5*S*)-**1b**	mp / °C	syrup		
	$[\alpha]_D$ ($CHCl_3$)	+44.0° (c 1.5)		
***trans*-10** (racemate)	mp / °C	113-114		
(2*R*,5*S*)-**1c**	mp / °C	133-135		130-132
	$[\alpha]_D$ ($CHCl_3$)	+27.7° (c 0.4)		+19.9° (c 1.0)
(2*S*,5*R*)-**1d**	mp / °C	130-131		
	$[\alpha]_D$ ($CHCl_3$)	-25.9° (c 0.4)		

Furthermore, similarly to the case of **9**, the optical resolution of ***cis*-10** was carried out to give (2*R*,5*R*)-**1a** and (2*S*,5*S*)-**1b**. Interestingly, the obtained optical isomers were found to be a colorless syrup, whereas the racemate was colorless crystals (mp 88 °C). On the other hand, the complete similar resolution of ***trans*-10** gave (2*R*,5*S*)-**1c** and (2*S*,5*R*)-**1d**. The melting points and specific rotations of the four optically active stereoisomers are summarized in Table 1. By the comparisons of the specific rotations, it was found that (2*R*,5*R*)-**1a** obtained by HPLC of ***cis*-10** was identical to the natural bis(methylthio)silvatin. However, the specific rotation of the naturally occurring bis(methylthio)silvatin and that of the product derived from **2**[2] were found to be considerably low.

In conclusion, it is worth-noting that synthetic (2*R*,5*R*)-**1a** and its three stereoisomers were purely obtained from 1,4-dimethyl-3-(*p*-MOMO)benzyl-PDO (**6**) *via* **8** in a short step.

EXPERIMENTAL

Melting points were determined with Yanaco Mp -J3 micro melting points apparatus, and are uncorrected. The IR spectra were recorded on Hitachi 270-30 spectrophotometer in KBr. The ^{1}H NMR and ^{13}C NMR spectra were measured with JEOL JNM-A-500 spectrometer in $CDCl_3$ solution with TMS as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-370 polarimeter in MeOH (Japan Spectroscopic Co., Ltd.). High performance liquid-chromatography (HPLC) analyses and separations were performed on CHIRALCEL OJ (0.46 cm ID x 25 cmL) and CHIRALCEL OJ (2.0 cmID x 25 cmL) (TOSOH 8010 system), respectively.

***N*-Cbz-Gly-Tyr(MOM)-OMe (4):** To a solution of Cbz-Gly-Tyr-OMe (13.6 g, 35.9 mmol) in CH_2Cl_2 (150 mL) were added drop by drop, with stirring, MOMCl (9.5 mL, 125 mmol) and *N*,*N*-diisopropylethylamine (24.4 mL, 143 mmol) at 0 °C for 6 h. After stirring continuously at rt overnight, the reaction mixture was concentrated in vacuo to give a residual syrup, which was poured into EtOAc (200 mL). The resulting solution was washed twice with 10% citric acid (200 mL x 2), twice with saturated $NaHCO_3$ (200 mL x 2), and brine (200 mL) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 2 v/v) to give **4** as colorless syrup. Yield 10.6 g (71%). $[\alpha]_D^{24}$ +50.2° (c 1.3, MeOH). IR: 3328, 3250, 1737, 1710, 1671 cm^{-1}. ^{1}H NMR: δ 3.03 (d, 2H, Tyr's β-H, *J*=5.7 Hz), 3.45 (s, 3H, $-OCH_3$), 3.70 (s, 3H, $-COOCH_3$), 3.83 (m, 2H, Gly's α-H), 4.83 (dt, 1H, Tyr's α-H, *J*=5.7 and 7.9 Hz), 5.11 (s, 4H, $-OCH_2O-$ and Ph-CH_2-), 5.48 (br s, 1H, NH), 6.53 (br d, 1H, NH, *J*=7.9 Hz), 6.85-7.05 (m, 4H, Tyr's Ph-H), 7.23-7.47 (m, 5H, Cbz's Ph-H). *Anal.* Calcd for $C_{22}H_{26}N_2O_7$: C, 61.39; H, 6.09; N, 6.51. Found: C, 61.22; H, 6.23; N, 6.55.

3-(*p*-MOMO)benzyl-2,5-piperazinedione (5): A suspension of **4** (4.73 g, 11.4 mmol) and 10% Pd/C (470 mg) in EtOH (50 mL) was stirred under H_2 stream at rt for 4 h. After removal of Pd/C, the

filtrate was concentrated in vacuo to give a residue, which was dissolved in MeOH (50 mL). The resulting solution was saturated with NH_3 gas at -10 °C for 1 h to give colorless crystals. Recrystallization from MeOH gave **5** as colorless needles. Yield 2.70g (90%). mp 236 °C (decomp). $[\alpha]_D^{25}$ +3.3° (c 1.0, AcOH). IR: 3196, 3052, 2990, 2930, 1674, 1620, 1515 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.82 (dd, 1H, Ph-CH_2-, *J*=5.0 and 13.5 Hz), 2.85 (d, 1H, 6-Ha, *J*=17.5 Hz), 3.03 (dd, 1H, Ph-CH_2-, *J*=4.6 and 13.5 Hz), 3.36 (s, 3H, -OCH_3), 3.37 (d, 1H, 6-Hb, *J*=17.5 Hz), 4.02 (dd, 1H, 3-H, *J*=4.6 and 5.0 Hz), 5.15 (s, 2H, -OCH_2O-), 6.93 (d, 2H, Ph-H, *J*=8.6 Hz), 7.08 (d, 2H, Ph-H, *J*=8.6 Hz), 7.89 (br s, 1H, NH), 8.13 (br s, 1H, NH). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: 58.71; H, 6.51; N, 10.55.

1,4-Dimethyl-3-(*p*-MOMO)benzyl-2,5-piperazinedione (6): To a solution of **5** (2.70 g, 10.2 mmol) in DMF (50 mL) were added, with stirring, NaH (1.07 g, 24.5 mmol, 55% in oil) at -10 °C for 30 min and then MeI (3.81 mL, 61.2 mmol). After stirring at -10 °C for 30 min and then at rt for 3 h, the resulting solution was concentrated in vacuo to give a residue, which was dissolved in ethyl acetate (100 mL). The solution was washed with brine (30 mL) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crystals, which were recrystallized from a mixture of hexane and ethyl acetate to give **5** as colorless needles. Yield 2.38 g (80%). mp 77-78 °C. $[\alpha]_D^{24}$ +36.1° (c 1.0, MeOH). IR: 2932, 1662, 1512 cm^{-1}. ^1H NMR: δ 2.41 (d, 1H, 6-Ha, *J*=17.1 Hz), 2.74 (s, 3H, NCH_3), 3.04 (dd, 1H, Ph-CH_2-, *J*=4.4 and 14.2 Hz), 3.06 (s, 3H, NCH_3), 3.23 (dd, 1H, Ph-CH_2-, *J*=3.4 and 14.2 Hz), 3.34 (d, 1H, 6-Hb, *J*=17.1 Hz), 3.46 (s, 3H, -OCH_3), 4.15 (dd, 1H, 3-H, *J*=3.4 and 4.4 Hz), 5.12 (d, 1H, OCH_2O-, *J*=6.8 Hz), 5.18 (d, 1H, OCH_2O-, *J*=6.8 Hz), 6.96 (s, 4H, Ph-H). *Anal.* Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.95; N, 9.58. Found: C, 61.36; H, 6.95; N, 9.46.

1,4-Dimethyl-3-(*p*-hydroxy)benzyl-2,5-piperazinedione (7): A solution of **6** (5.0 g, 12.2 mmol) in EtOAc (50 mL) saturated with gaseous HCl was stirred at rt for 1 h. The resulting solution was concentrated in vacuo to give residual crystals, which were recrystallized from AcOH to give **7** as colorless needles. Yield 2.75 g (91%). mp 224 °C (decomp). $[\alpha]_D^{24}$ +3.4° (c 1.0, 28% NH_4OH). IR: 3298, 2926, 1662, 1614, 1593, 1512 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.22 (d, 1H, 6-Ha, *J*=17.1 Hz), 2.63 (s,

3H, NCH_3), 2.90 (s, 3H, NCH_3), 2.96 (s, 2H, Ph-CH_2-*J*=3.7 Hz), 3.42 (d, 1H, 6-Hb, *J*=17.1 Hz), 4.18 (t, 1H, 3-H, *J*=3.7 Hz), 6.72 (m, 4H, Ph-H), 9.40 (s, 1H, Ph-OH). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.29. Found: C,62.50; H, 6.49; N, 11.70.

1,4-Dimethyl-3-[*p*-(3-methyl-2-butenyl)oxy]benzyl-2,5-piperazinedione (8): To a solution of **7** (700 mg, 2.82 mmol) in DMF (10 mL) were added, with stirring, NaH (148 mg, 3.38 mmol, 55% in oil) at -10 °C for 30 min and then 1-bromo-3-methyl-2-butene (110 mL, 8.46 mmol). After stirring at -10 °C for 30 min and then at rt for 1 h, the reaction mixture was poured into ice water (50 mL) and extracted five times with EtOAc (10 mL x 5). The combined extracts were washed twice with brine (30 mL x 2). The resulting solution was dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give crude crystals, which were recrystallized from a mixture of hexane and EtOAc to give **8** as colorless needles. Yield 809 mg (82%). mp 121-123 °C. $[\alpha]_D^{24}$ -4.2° (c 0.5, MeOH). IR: 3310, 2926, 1662, 1614, 1512 cm^{-1}. ^1H NMR: δ 1.74 (s, 3H,Me), 1.18 (s, 3H, Me), 2.37 (d, 1H, 6-Ha, *J*=17.1 Hz), 2.73 (s, 3H, NMe), 3.03 (dd, 1H, Ph-CH_2-, *J*=4.4 and 14.2 Hz), 3.06 (s, 3H, NMe), 3.22 (dd, 1H, Ph-CH_2-, *J*=3.4 and 14.2 Hz), 3.33 (d, 1H, 6-Hb, *J*=17.1 Hz), 4.15 (dd, 1H, 3-H, *J*=3.4 and 4.4 Hz), 4.48 (d, 2H, -OCH_2CH=, *J*=6.8 Hz), 5.46 (t, 1H, -OCH$_2$C*H*=, *J*=6.8 Hz), 6.75-6.97 (m, 4H, Ph-H). *Anal.* Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85. Found: C, 67.91; H, 7.97; N, 8.35.

Methylthiosilvatin (*cis*-9): To a solution of *N*,*N*-diisopropylamine (0.36 mL, 21.65 mmol) in THF (15 mL) was added a solution of 1.6 M *n*-butyllithium in hexane (1.66 mL, 2.65 mmol) under Ar stream at -78 °C for 30 min. A solution of **8** (700 mg, 2.21 mmol) in THF (7 mL) and HMPA (1 mL) was added to the resulting solution and, after stirring for 1 h, dimethyl disulfide (0.39 mL, 4.43 mmol) was further added drp by drop at -78°C for 1 h. The reaction mixture was treated with a saturated NH_4Cl aqueous solution (20 mL) at rt for 30 min and then the organic solvent was evaporated in vacuo. The residual aqueous layer was extracted five times with EtOAc (20mL x 5) and the combined extracts were washed twice with brine and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a crude crystals, which were purified on silica gel column using a mixture of hexane and EtOAc (1 : 2 v/v) to give colorless crystals. Recrystallization from hexane and EtOAc gave ***cis*-9** as colorless needles. Yield 593 mg

(74%). mp 106-108 °C. The obtained ***cis*-9** was resolved by HPLC using a mixture of hexane and 2-propanol (90 : 10 v/v) by the flow rate 7.6 mL min^{-1} to give two stereoisomers, (2*R*,5*R*)-**9** and (2*S*,5*S*)-**9**, respectively. (2*R*,5*R*)-**9**. $[\alpha]_D^{24}$ -108.1° (c 0.9, $CHCl_3$). (2*S*,5*S*)-**9**. $[\alpha]_D^{24}$ +106.5° (c 0.4, $CHCl_3$). IR: 3484, 2962, 2926, 1665, 1615 cm^{-1}. ^1H NMR: δ 1.73 (s, 3H, Me), 1.80 (s, 3H, Me), 2.42 (s, 3H, SMe), 2.56 (s, 3H, NMe, 3.07 (s, 3H, NMe), 3.24 (dd, 1H, Ph-CH_2-, *J*=5.4 and 13.9 Hz), 3.25 (dd,1H, Ph-CH_2-, *J*=8.9 and 13.9 Hz), 4.22 (dd, 1H, 5-H, *J*=5.4 and 8.9 Hz), 4.49 (d, 2H, -OCH_2CH=, *J*=6.6 Hz), 4.58 (s, 1H, 2-H), 5.48 (t, 1H, -OCH_2CH=, *J*=6.6 Hz), 6.88 (d, 2H, Ph-H, *J*=8.6 Hz), 6.97 (d, 2H, Ph-H, *J*=8.6 Hz). *Anal.* Calcd for $C_{19}H_{26}N_2O_3S$: C, 62.95; H, 7.23; N, 7.73C, 62.54; H, 7.20; N, 7.53. Found: C, 62.95; H, 7.23; N, 7.73.

Hydrolysis of *cis*-9: A solution of ***cis*-9** (5 mg) in 6M HCl (1 ml) in sealed tube was heated at 110 °C for 12 h. The reaction mixture was washed twice with diethyl ether (1 ml x 2) and the aqueous layer was chromatographed by HPLC using CHIRALPAK WH (0.46 mm i.d. x 25 cm) column with 0.25 mM aqueous $CuSO_4$ solution by the flow rate 1.5 mL min^{-1} at rt by detecting UV (254 nm) absorption to give (*R*)-*N*-methyltyrosine as first fraction and (*S*)-*N*-methyltyrosine as second fraction.

Bis(methylthio)silvatin (10): To a solution of *N*,*N*-diisopropylamine (1.5 mL, 11.2 mmol) in THF (25 mL) was added a solution of 1.6 M *n*-butyllithium in hexane (7.0 mL, 11.2 mmol) under Ar stream at -78 °C for 30 min. A solution of **7** (1.6 g, 3.75 mmol) in THF (15 mL) and HMPA (2 mL) was added to the resulting solution and then , after stirring for 1 h, dimethyl disulfide (2.0 mL, 22.5 mmol) was added frop by drop at -78 °C for 1 h. Similarly to the case of **9**, the obtained crystals were chromatographed on silica gel colmun to give two kinds of crystals. Crystals from the first fraction were recrystallized from hexane and cyclohexane to give ***cis*-10** as colorless needles in 45% (691 mg) yield, and the second was recrystallized from cyclohexane to give ***trans*-10** as colorles needles in 43% (670 mg) yield. The obtained ***cis*-** and ***trans*-10** were resolved by HPLC using a mixture of hexane and 2-propanol (90 : 10 v/v) by the flow rate 7.6 mL min^{-1} to give four stereoisomers, (2*R*,5*R*)-**1a**, (2*S*,5*S*)-**1b**, (2*R*,5*S*)-**1c**, and (2*S*,5*R*)-**1d**, respectively. (2*R*,5*R*)-**1a**: IR: 3454, 2968, 2920, 1668, 1659, 1614, 1580 cm^{-1}. ^1H NMR : δ 1.73 (s, 3H, $\underline{Me}_2$C=CH-), 1.79 (s, 3H, $\underline{Me}_2$C=CH-), 2.16 (s, 3H, SMe), 2.29 (s, 3H, SMe), 2.96 (s,

3H, NMe), 3.24 (s, 3H, NMe), 3.08 (d, 1H, Ph-CH_2-, J=14.0 Hz), 3.53 (d, 1H, Ph-CH_2-, J=14.0 Hz), 4.19 (s, 1H, 5-H), 4.45 (d, 2H, -OCH_2CH=, J=6.7 Hz), 5.46 (t, 1H, -OCH$_2$CH=, J=6.7 Hz), 6.78 (d, 2H, Ph-H, J=8.5 Hz), 6.97 (d, 2H, Ph-H, J=8.5 Hz). ^{13}C NMR (500 HMz, $CDCl_3$): δ 13.55, 16.20, 18.17, 25.77, 30.13, 33.44, 41.81, 64.97, 74.89, 114.59, 119.94, 125.89, 130.53, 138.18, 158.25, 164.29, 164.87. *Anal.* Calcd for $C_{20}H_{28}N_2O_3S_2$: C, 58.79; H, 6.91; N, 6.86. Found: C, 59.17; H, 6.94; N, 6.80.

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