Pergamon

Tetrahedron 58 (2002) 6405–6412

TETRAHEDRON

Hedathiosulfonic acids A and B, novel thiosulfonic acids from the deep-sea urchin *Echinocardium cordatum*

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Received 1 April 2002; revised 24 May 2002; accepted 25 May 2002

In honor of Professor Yoshito Kishi on the occasion of his award of the prestigious Tetrahedron Prize

Abstract—Hedathiosulfonic acids A and B were isolated from the deep-sea urchin *Echinocardium cordatum* and were determined to be novel 6-undecanethiosulfonic acids by 2D NMR, HRMS, and methylation reaction. The stereostructure of hedathiosulfonic acid A was determined by the analysis of its degradation product, a cyclic β-hydroxysulfone. Hedathiosulfonic acids exhibited acute toxicity. We carried out various model reactions of the olefinic compounds with thiosulfonic acids and proved that, as is the case with natural products, synthesized thiosulfonic acid possessing a carbon–carbon double bond was converted into β-hydroxysulfone in the presence of oxygen.

1. Introduction

In our continuing search for marine bioactive compounds, we have directed our attention to the deep-sea invertebrates. Because the deep-sea organisms survive in severe environments with features such as the absence of light, low levels of oxygen, and high pressure, it is likely that they produce different compounds from those that shallow water organisms produce. With advances in deep ocean technology, the study of numerous bioactive compounds from the bottom feeders has been possible. For example, nortopsentins from the sponge *Spongosorites ruetzleri*, γ-indomycinone from a *Streptomyces* sp., and guaymasol from a *Bacillus* sp. have been reported.[1] We have previously reported the isolation and structural determination of hedathiosulfonic acids A (**1**) and B (**2**) from the deposit-feeding deep-sea heart urchin *Echinocardium cordatum* (Fig. 1).[2] Although many substances that contain sulfur atoms such as sulfonic acids, thiols, and sulfides have been isolated from echinoderms, there have been no previous reports of a thiosulfonic acid like the hedathiosulfonic acids.[3] Recently, the bacteria *Thiothrix* sp., which can oxidize sulfide, have been reported as symbionts in invertebrates from sulfur-rich habitats.[4] A symbiotic relationship has also been demonstrated between *Thiothrix* sp. and *E. cordatum*.[5] Therefore, the genus *Thiothrix* is probably the actual source of hedathiosulfonic acids. We report here the detailed isolation and structure determination of **1** and **2**, along with details of our studies of the model reactions using the thiosulfonic acids.

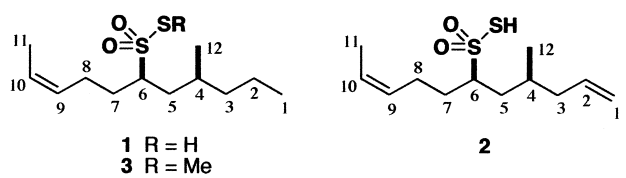

Figure 1. Structures of hedathiosulfonic acids A (**1**) and B (**2**).

2. Results and discussion

2.1. Isolation and structural determination

The aqueous 80% EtOH extract of the deep-sea urchin *E. cordatum,* collected at a depth of 400 m off the Heda coast of the Izu Peninsula, Japan, was partitioned between EtOAc and H_2O. The EtOAc-soluble fraction was subjected to fractionation guided by acute toxicity against mice using column chromatography and reversed-phase HPLC to give hedathiosulfonic acids A (**1**, 0.0037% yield based on wet wt) and B (**2**, 0.0046% yield based on wet wt) as colorless oils. Hedathiosulfonic acids A (**1**) and B (**2**) exhibited low acute toxicity against mice, with LD_{99}s of 0.39 and 0.36 g/kg, respectively.

The fluorescent X-ray analysis of hedathiosulfonic acid A (**1**) suggested the presence of two sulfur atoms. The molecular formula of **1** was determined to be $C_{12}H_{24}O_2S_2$

Keywords: natural thiosulfonic acid; isolation; structure determination; model reaction.

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0040–4020/02/$ - see front matter
PII: S0040-4020(02)00654-3

Table 1. NMR data for hedathiosulfonic acid A (**1**) and B (**2**) in CD_3OD

Atom	Hedathiosulfonic acid A (**1**)		Atom	Hedathiosulfonic acid B (**2**)	
	$^1H^a$	$^{13}C^b$		$^1H^a$	$^{13}C^b$
1	0.91 t (7.2), 3H	14.7 q	1a	4.98 br d (17.4)	116.2 t
			1b	5.01 br d (10.1)	
2a	1.32 m	20.9 t	2	5.83 ddt (10.1, 17.4, 7.2)	138.4 d
2b	1.44 m				
3a	1.11 m	40.1 t	3a	1.88 m	42.1 t
3b	1.39 m		3b	2.19 m	
4	1.78 m	31.8 d	4	1.88 m	32.1 d
5a	1.31 m	39.9 t	5a	1.34 ddd (6.3, 6.6, 14.5)	39.5 t
5b	2.11 ddd (5.3, 7.3, 14.3)		5b	2.13 ddd (5.8, 6.7, 14.5)	
6	2.86 dq (5.3, 5.1)	70.8 d	6	2.88 ddt (6.3, 5.8, 5.9)	70.7 d
7a	1.58 m	32.7 t	7a	1.57 m	32.7 t
7b	2.18 m		7b	2.19 m	
8a	2.23 ddt (7.7, 14.5, 7.2)	25.9 t	8a	2.23 ddt (7.2, 14.6, 7.6)	25.8 t
8b	2.30 ddt (8.1, 14.5, 8.0)		8b	2.29 m	
9	5.40 br ddd (7.7, 8.1, 10.9)	131.3 d	9	5.40 dddq (6.7, 7.2, 10.6, 1.7)	131.2 d
10	5.47 br dq (10.9, 6.7)	125.3 d	10	5.47 br dq (10.6, 6.7)	125.3 d
11	1.63 d (6.7), 3H	13.0 q	11	1.63 br d (6.7), 3H	13.1 q
12	0.92 d (6.6), 3H	20.6 q	12	0.93 d (6.2), 3H	20.2 q

[a] Recorded at 800 MHz. Coupling constants (Hz) are in parentheses.
[b] Recorded at 201 MHz. Multiplicity was based on HMQC spectrum.

by HRFABMS (*m/z* 309.0951, calcd for $C_{12}H_{23}Na_2O_2S_2$, 309.0935). The NMR data for **1** are summarized in Table 1. The ^1H NMR, ^{13}C NMR, and HMQC spectra of **1** showed the presence of three methyl carbons, five methylene carbons, two methine carbons, and two olefinic methine carbons (δ_C 125.3, 131.3). Based on the chemical shift, it was clarified that one methine carbon was attached to an oxygenated sulfur atom (δ_H 2.86, δ_C 70.8). A detailed analysis of the COSY spectrum enabled us to elucidate the entire carbon framework. The geometry of the C-9 olefin was determined to be 9*Z* based on the magnitude of $J_{9,10}=10.9$ Hz. Furthermore, to determine the functional group (S_2O_2H) at C-6, we methylated hedathiosulfonic acid A (**1**) with $Me_2SO_4-Et_3N$ to give methyl thiosulfonate **3**. The chemical shifts of an additional methyl group (δ_H 2.67, δ_C 17.5) in **3** suggested that this methyl carbon was attached to an non-oxygenated sulfur atom. As a result, we determined the gross structure of hedathiosulfonic acid A as **1**, possessing a thiosulfonic acid functionality.

The ^1H NMR spectrum of hedathiosulfonic acid B (**2**) resembled that of hedathiosulfonic acid A (**1**), but the presence of three additional vinyl protons (δ_H 4.98, 5.01, 5.83) and the molecular formula of **2** determined by HRFABMS (*m/z* 307.0761, calcd for $C_{12}H_{21}Na_2O_2S_2$, 307.0778) suggested that **2** was a dehydro derivative of **1**. The NMR data for **2** are summarized in Table 1. We determined that the geometry of the C-9 olefin is 9*Z* based on the magnitude of $J_{9,10}=10.6$ Hz. As expected, the gross structure of hedathiosulfonic acid B was determined to be **2** by similar analyses of COSY, HMQC, and HMBC spectra.

Hedathiosulfonic acid A (**1**) was unstable in air and gradually decomposed into sulfonic acid **4**, five-membered cyclic sulfone **5**, and six-membered cyclic sulfone **7** (Fig. 2). The NMR data for these three compounds are summarized in Table 2. The gross structures of **4**, **5**, and **7** were determined using the 2D NMR and the mass spectra. To confirm the position of the hydroxyl group, sulfones **5** and **7** were converted into 3,5-dinitrobenzoate **6** and acetate **8**, respectively. The oxymethine protons in both **6** ($\delta_{H\text{-}10}$ 5.66) and **8** ($\delta_{H\text{-}9}$ 4.80) were shifted to more than 1 ppm downfield from those in **5** and **7**, respectively.

Since the stereochemistiy in hedathiosulfonic acid A (**1**) could not be deduced by the spectroscopic analysis, that of the sulfone **7** was determined as follows (Fig. 3). As the six-membered sulfone ring part, the magnitude of $J_{8a,9}=10.0$ Hz, $J_{8b,9}=3.9$ Hz, and $J_{9,10}=10.0$ Hz suggested that H-8a and H-9, H-9 and H-10 were located in *anti* arrangement, respectively, and that H-8b and H-9 were located in *gauche* arrangement. In the NOE experiments (600 MHz) on **7**, NOEs were observed for H-6/H-8a and H-10, H-9/H-7a, and H-10/H-8a. These results suggested that the protons H-6, H-7a, H-8a, H-9, and H-10 were oriented in *anti* arrangements with respect to the six-membered sulfone ring with the chair conformation. As the alkyl side chain part, the magnitude of $J_{5a,6}=7.2$ Hz and $J_{5b,6}=5.4$ Hz suggested that H-5a and H-6 were in *anti* arrangement and that H-5b and H-6 were in *gauche* arrangement. The stereochemistry of C-4 was not determined clearly because of the subtle difference of the magnitude of $J_{4,5a}=8.0$ Hz and $J_{4,5b}=7.3$ Hz. In the NOE

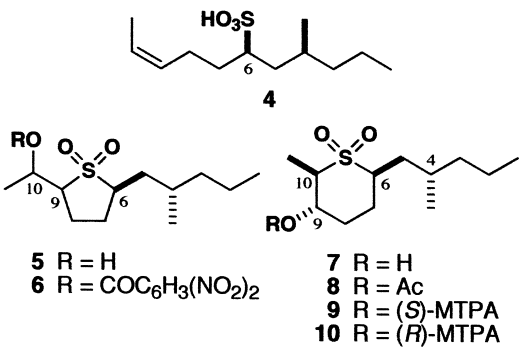


Figure 2. The degraded compounds from hedathiosulfonic acid A (**1**) and related compounds.

Table 2. NMR data for compounds **4**, **5**, and **7** in CD_3OD

Atom	**4**		**5**[a]		**7**	
	^1H[b]	^{13}C[c]	^1H[b]	^{13}C[c]	^1H[d]	^{13}C[e]
1	0.91 t (7.3), 3H	14.7 q	0.91 t (7.3), 3H	14.5 q	0.92 t (7.3), 3H	14.6 q
2a	1.35 m	21.0 t	1.32 m	20.9 t	1.30 m	20.7 t
2b	1.46 m		1.40 m		1.41 m	
3a	1.10 m	40.2 t	1.16 m	40.4 t	1.11 m	39.6 t
3b	1.37 m		1.32 m		1.34 m	
4	1.78 dq (12.9, 6.8)	31.6 d	1.71 m	31.3 d	1.75 dq (7.3, 6.6)	31.0 d
5a	1.30 m	39.4 t	1.37 m	36.2 t	1.22 dt (14.0, 7.1)	34.3 t
5b	1.91 m		1.84 m		1.95 ddd (5.4, 7.3, 14.0)	
6	2.73 dq (5.9, 5.9)	58.7 d	3.08 ddt (5.9, 14.5, 6.2)	61.5 d	3.03 m	59.0 d
7a	1.55 m	32.1 t	1.60 dq (12.9, 5.9)	28.7 t	1.56 m	27.6 t
7b	1.99 m		2.27 m		2.02 ddt (2.7, 13.9, 7.0)	
8a	2.21 ddt (7.0, 15.0, 7.5)	25.6 t	1.98 m	24.0 t	1.58 m	34.9 t
8b	2.28 ddt (7.0, 15.0, 7.5)		2.29 m		2.08 ddt (2.7, 12.8, 4.0)	
9	5.39 m	131.2 d	2.89 ddd (6.3, 7.7, 10.6)	68.6 d	3.51 dt (4.0, 10.5)	72.2 d
10	5.46 m	125.3 d	4.07 dq (6.3, 6.3)	66.3 d	2.92 dq (10.5, 6.6)	64.1 d
11	1.63 d (7.6), 3H	18.1 q	1.30 d (6.3), 3H	22.0 q	1.41 d (6.6), 3H	6.9 q
12	0.92 d (6.4), 3H	20.4 q	0.96 d (6.6), 3H	19.9 q	0.96 d (6.6), 3H	20.3 q

[a] Compound **5** was isolated as a mixture of two diastereomers (2:1 ratio), detected by the NMR analysis. The data for the major diastereomer were described.
[b] Recorded at 600 MHz. Coupling constants (Hz) are in parentheses.
[c] Recorded at 150 MHz. Multiplicity was based on DEPT analysis.
[d] Recorded at 800 MHz. Coupling constants (Hz) are in parentheses.
[e] Recorded at 201 MHz. Multiplicity was based on HMQC spectrum.

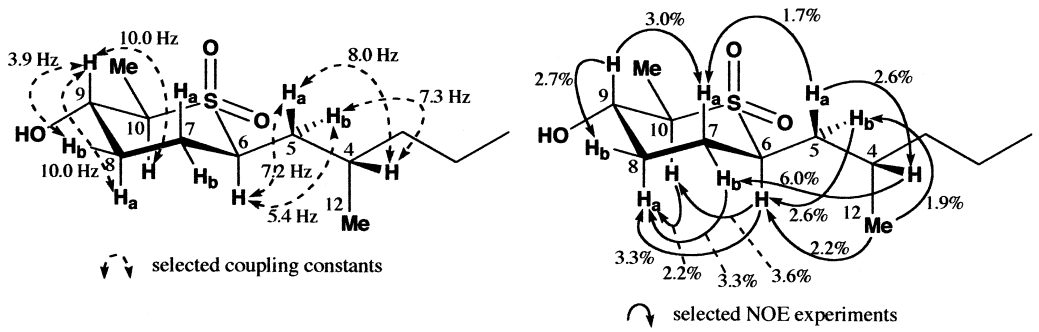


Figure 3. Relative stereochemistry of sulfone **7**.

experiments on **7**, NOEs were observed for H-5a/H-7a and H-12/H-6. In particular, irradiation of the signal at H-4 strongly enhanced the signal for H-7b (6.0%). These results suggested that the single bond rotation between C-4 and C-5 was restricted in part and that one of the stable conformations of **7** was as shown in Fig. 3. Therefore, the relative stereochemistry in the six-membered cyclic sulfone **7** was suggested to be 4*S**, 6*R**, 9*S**, and 10*R**.

The relative stereochemistry in the five-membered cyclic sulfone **5**, isolated as a mixture of two diastereomers (2:1 ratio), was determined using 3,5-dinitrobenzoyl derivative **6** as follows (Fig. 4). As the major diastereomer of **6**, the NOESY correlations for H-6/H-7b and H-8a, H-7a/H-5a, H-8b, and H-9, H-7b/H-8a, and H-8b/H-9 suggested that the protons H-6 and H-9 were oriented in *anti* arrangements with respect to the sulfone ring. As the minor diastereomer of **6**, the NOESY correlations for H-6/H-7a, H-8b, and H-9, H-8b/H-7a and H-9 suggested that the protons H-6 and H-9 were oriented in *syn* arrangements with respect to the sulfone ring. The stereochemistries of C-4 and C-10 in both diastereomers of **6** were not determined, however, because of the single bond rotations in the side chain part. Therefore,

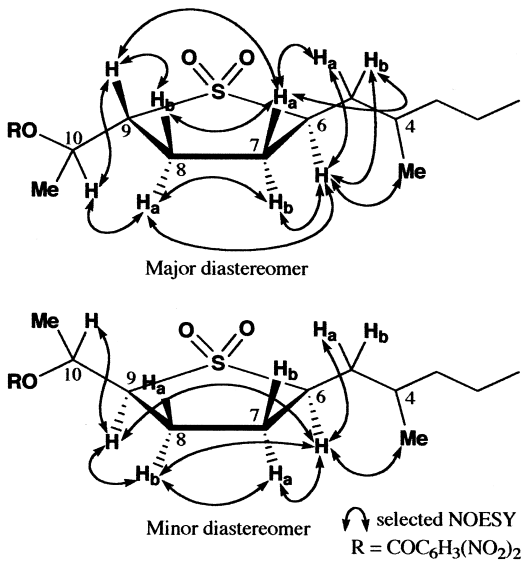
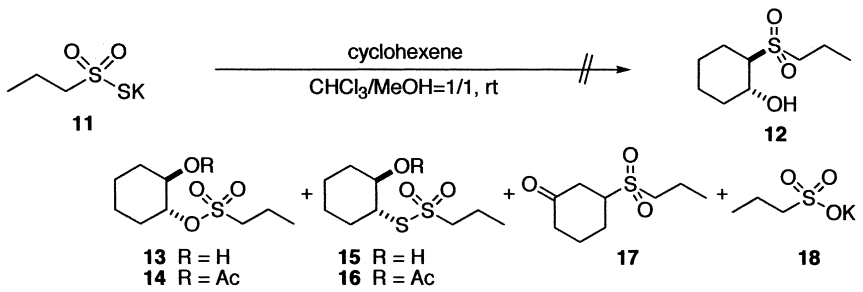


Figure 4. Relative stereochemistry of sulfone **6**.

Table 3. Reactions of thiosulfonic acid potassium salt **11** with cyclohexene



Entry	Amount of cyclohexene (equiv.)	Time (h)	Conditions	Products (%)[a]				Recovered **11** (%)[a]
				13	**15**	**17**	**18**	
1	67	24.5	Under air	11	7	–	52	
2[b]	77	22	Under air	–	9	6	76	
3[c]	83	23	Under air	–	–	–	–	94
4	175	15	Under O_2	6	16	2	71	
5[c]	128	36	Under O_2	–	–	–	–	66

[a] Isolated yields.
[b] Starting material **11** was treated with TFA before use.
[c] 5 equiv. of BHT were added.

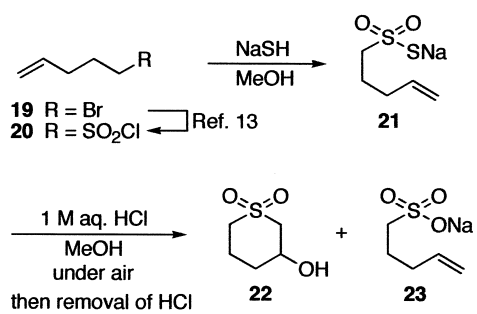
the relative stereochemistry in the sulfone **5** was established to be 6*R* *, 9*R* * for the major diastereomer and 6*R* *, 9*S* * for minor one.

The absolute stereochemistry in **7** was determined using the modified Mosher's method.[6] Treatment of the sulfone **7** with (*R*)- or (*S*)-MTPAC1 gave (*S*)- or (*R*)-MTPA esters **9** and **10**, respectively. The ^{1}H NMR signals of the two MTPA esters **9** and **10** were assigned on the basis of the 2D NMR spectra, and the $\Delta\delta$ values ($\delta_S - \delta_R$, ppm) were then calculated. The results indicated that the absolute stereochemistry of C-9 was 9*S*, and that the absolute stereochemistry in **7** was suggested to be 4*S*, 6*R*, 9*S*, and 10*R*. Based on these results, the absolute stereochemistry in hedathiosulfonic acid A (**1**) was established to be 4*S* and 6*R*.

2.2. Model reactions with the synthesized thiosulfonic acids

The compounds containing sulfonyl groups, such as sulfonyl halides, sulfonyl cyanides, sulfonyl thiocyanides, selenosulfonates, and thiosulfonates, are common precursors of sulfonyl radicals, which are useful for their ability to add to carbon–carbon multiple bonds in organic synthesis.[7,8] In addition, the sulfur–sulfur bonds of thiosulfonates are known to be cleaved in thermal conditions without the addition of radical initiator or UV irradiation.[9] Therefore, we expected that thiosulfonic acids would also leave sulfonyl radicals, and that cyclic sulfones **5** and **7** were formed from hedathiosulfonic acid A (**1**) via the intramolecular addition of sulfonyl radicals into carbon–carbon double bonds. To investigate the reaction mechanisms, we examined intermolecular reactions using *n*-propylthiosulfonic acid potassium salt (**11**) (Table 3). Treatment of **11** with cyclohexene in $CHCl_3$–MeOH (1:1, v/v) in air gave several unexpected adducts, β-hydroxysulfonate **13**, β-hydroxythiosulfonate **15**, and sulfonic acid potassium salt **18** (entry 1). Compounds **13** and **15** were converted into acetates **14** and **16**, respectively. The HMBC correlations from the oxymethine protones in **14** (δ_H 4.83) and in **16** (δ_H 4.74) into the carbonyl carbons in **14** (δ_C 170.8) and in **16** (δ_C 170.6) confirmed that products **13** and **15** each possessed a hydroxyl group, respectively. Treatment of **11** with trifluoroacetic acid before the reaction afforded mainly **18**, and γ-ketosulfone **17** was also formed (entry 2).[10] Under an oxygen atmosphere, degradation of **11** was more accelerated (entry 4). Under any conditions, however, no β-hydroxysulfones such as **12** were obtained. It should be noted that thiosulfonic acid reacted with cyclohexene even in the absence of moisture. In addition, a couple of radical intermediates must be associated with those reactions because thiosulfonic acid sodium salt **11** was recovered in the presence of radical scavengers (entries 3 and 5).

We also examined intramolecular reactions (Scheme 1). Several intramolecular additions of δ-unsaturated thiyl and sulfonyl radicals have also been reported.[9,11,12] The addition of NaSH to 4-pentenesulfonyl chloride (**20**), which was synthesized from 4-pentene-1-bromide (**19**)[13] by King's method, gave thiosulfonic acid sodium salt **21** (85%). Although **21** was stable under air for more than 2 weeks in MeOH, the addition of aqueous hydrochloric acid led to β-hydroxysulfone **22** (15%) and sulfonic acid **23** (43%).[14,15] Treatment of compound **21** with trifluoroacetic acid followed by standing in the solvent-free condition under



Scheme 1.

an oxygen atmosphere also gave compound **22** (23%). In any case, however, five-membered hydroxysulfone was not detected. From 4-pentenylthiyl radical both the five- and six-membered sulfides have been synthesized in the ratio of 1:19.[11] The predominance of the larger ring has been explained by the reversibility of the addition of the thiyl radical into carbon–carbon double bonds. These results suggested that thiosulfonic acid sodium salt **21** could also be cyclized under thermodynamic control.[16]

The degradation reaction of **1** into the cyclic sulfones **5** and **7** was reproduced by synthetic analogs. In trying to understand the mechanism of the novel degraded reaction from hedathiosulfonic acid A (**1**) into sulfones **5** and **7**, we assumed that sulfonyl radicals were generated by the cleavage of sulfur–sulfur bonds of thiosulfonic acids followed by 5-*exo* or 6-*endo* cyclization and oxidation. Since the protones H-9 and H-10 in **7** are oriented in *anti* arrangement, the stereospecificity in C-9 should be lost during the cyclization. It should be noted that sulfones **5** and **7** could result in the cyclization of those radical intermediates under thermodynamic control.

3. Conclusion

Hedathiosulfonic acids A (**1**) and B (**2**) were isolated from the deep-sea urchin *E. cordatum*, and were determined to be novel 6-undecanethiosulfonic acids by 2D NMR, HRMS, and methylation reaction. The stereostructure of **1** was elucidated by the spectroscopic analysis of its degradation product **7**. Regarding model reactions of the decomposition of hedathiosulfonic acid A (**1**), the synthetic analog, thiosulfonic acid **21**, was converted into β-hydroxysulfone **22** in acidic conditions. Further mechanistic studies on these reactions are in progress.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. All solvents were purified by a standard procedure before use. The starting materials were azeotropically dried with benzene before use. All reactions were conducted under a nitrogen atmosphere unless otherwise noted. Fuji silysia silica gel BW-820 MH and Nacalai Tesque Cosmosil 75C_{18}-OPN were used for column chromatography. Merck precoated silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC). Fluorescent X-ray spectra was recorded on a Horiba EMAX-5770W instrument. Optical rotations were measured with a JASCO DIP-1000 polarimeter. IR spectra were recorded on a JASCO FT/IR-230 spectrometer in chloroform. NMR spectra were recorded on a JEOL JNM-A400 (400 MHz for ^{1}H and 100 MHz for ^{13}C), a JEOL JNM-A600 (600 MHz for ^{1}H and 150 MHz for ^{13}C), or a JEOL JNM-ECP800 (800 MHz for ^{1}H and 201 MHz for ^{13}C) instrument. The chemical shifts were referenced to the solvent peaks: δ_H 3.31 (residual C*H*D_2OD) and δ_C 49.0 for CD_3OD, δ_H 7.26 (residual C*H*Cl_3) and δ_C 77.0 for $CDCl_3$. Mass spectra (FABMS) were recorded on a JEOL JMS-LG2000 spectrometer. The matrix used in FABMS analysis was *m*-nitrobenzyl alcohol.

4.2. Isolation and structure determination of hedathiosulfonic acids A and B

The whole parts including shells (10.9 kg, wet wt) of the urchin *E. cordatum*, collected at a depth of 400 m off the Heda coast of the Izu Peninsula, Japan, were crushed in a blender in aqueous 80% EtOH and extracted with the same solvent (20 L) for 3 days. The alcoholic extract was concentrated and partitioned between EtOAc (3×1 L) and H_2O (2 L). The EtOAc extracts (29.8 g) showed an acute toxicity against ddY mice (i.p. injection), which were subjected to fractionation guided by the toxicity. One-eleventh of the oily residue was chromatographed on ODS (60 g, MeOH–H_2O, 60:40→85:15→95:5→100:0). A half of the early fraction (343 mg) was separated by six rounds of HPLC (Develosil ODS HG-5, 20×250 mm, 50% aqueous MeOH, 5 mL/min, UV 205 nm) to give hedathiosulfonic acids A (**1**) (18.2 mg; LD_{99} 0.39 mg/kg) and B (**2**) (22.4 mg; LD_{99} 0.36 mg/kg) as colorless oils.

4.2.1. Hedathiosulfonic acid A (1). $[\alpha]_D^{26}=+2.1°$ (*c* 0.073, MeOH); IR ($CHCl_3$) 3580–3260 (br), 1180, 1060 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; MS (FAB) *m/z* 309 $(M-H+2Na)^+$; HRMS (FAB) calcd for $C_{12}H_{23}Na_2O_2S_2$ $(M-H+2Na)^+$ 309.0935, found 309.0951.

4.2.2. Hedathiosulfonic acid B (2). $[\alpha]_D^{26}=-2.2°$ (*c* 0.28, MeOH); IR ($CHCl_3$) 3520–3240 (br), 1640, 1180, 1060 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; MS (FAB) *m/z* 307 $(M-H+2Na)^+$; HRMS (FAB) calcd for $C_{12}H_{21}Na_2O_2S_2$ $(M-H+2Na)^+$ 307.0778, found 307.0761.

4.2.3. Procedure for methylation of hedathiosulfonic acid A (1). To a solution of hedathiosulfonic acid A (**1**) 5.6 mg (21 μmol) in CH_2Cl_2 (0.50 mL) was added triethylamine 0.05 mL (0.36 mmol). The mixture was cooled to 0°C, and dimethylsulfonic acid 0.10 mL (1.1 mmol) was added. After the resulting mixture was stirred at room temperature for 74 h, the mixture was diluted with EtOAc (15 mL), washed with brine (5 mL), dried, and concentrated. The residual oil was purified by column chromatography on silica gel (0.5 g, $CHCl_3$–MeOH, 10:0→9:1→4:1) and on ODS gel (0.2 g, MeOH–H_2O, 9:1), and HPLC was performed (YMC ODS-AQ, 4.6×150 mm, 80% aqueous MeOH, 1 mL/min, UV 215 nm) to give methyl thiosulfonate **3** (5.9 mg, quant.) as a colorless oil: $[\alpha]_D^{28}=+1.0°$ (*c* 0.28, MeOH); IR ($CHCl_3$) 1460, 1330, 1300, 1120 cm^{-1}; ^{1}H NMR (800 MHz, CD_3OD) δ 5.55 (1H, dtq, *J*=11.0, 1.4, 6.8 Hz), 5.38 (1H, dtq, *J*=11.0, 7.3, 1.8 Hz), 3.30 (1H, m), 2.66 (3H, s), 2.33 (1H, ddt, *J*=15.0, 6.8, 6.8 Hz), 2.23 (1H, ddt, *J*=15.0, 6.8, 6.8 Hz), 2.07 (1H, dddd, *J*=5.1, 6.8, 8.8, 14.5 Hz), 1.96 (1H, ddd, *J*=5.5, 7.0, 14.3 Hz), 1.75 (1H, m), 1.72 (1H, ddt, *J*=8.8, 14.5, 6.8 Hz), 1.64 (3H, d, *J*=6.8 Hz), 1.46 (1H, ddd, *J*=5.1, 7.0, 14.3 Hz), 1.42 (1H, m), 1.35 (1H, m), 1.31 (1H, m), 1.15 (1H, m), 0.96 (3H, d, *J*=6.6 Hz), 0.92 (3H, t, *J*=7.3 Hz); ^{13}C NMR (201 MHz, CD_3OD) δ 129.2 (d, C9), 126.0 (d, C10), 68.5 (d, C6), 39.0 (t, C3), 37.0 (t, C5), 30.1

(d, C4), 30.0 (t, C7), 23.8 (t, C8), 19.9 (t, C2), 18.9 (q, C12), 17.5 (q, C13), 13.3 (q, C1), 11.5 (q, C11); MS (FAB) *m/z* 279 $(M+H)^+$; HRMS (FAB) calcd for $C_{13}H_{27}O_2S_2$ $(M+H)^+$ 279.1453, found 279.1458.

4.3. Degraded compounds from hedathiosulfonic acid A (1) and related compounds

4.3.1. Isolation of the degraded compounds 4, 5, and 7. The whole parts including shells (4.8 kg, wet wt) of *E. cordatum* were crushed, extracted, and partitioned as described in Section 2.1. The EtOAc extracts (14.8 g) were chromatographed on silica gel (300 g, benzene–acetone, 9:1→7:1→0:1, then MeOH). The eluates of acetone (2.1 g) contained hedathiosulfonic acid (**1**) as a major component. When stocked in air for 1 month, compound **1** was decomposed to give **4**, **5**, and **7** as new components, which were detected by the analyses of TLC and NMR spectra. Two-thirds of the fractions were chromatographed on silica gel (25 g, benzene–acetone, 1:0→3:2→0:1, then MeOH) to give four additional fractions (fractions I–IV). Fraction II (0.44 g) was purified by column chromatography on silica gel ((1) 9 g, *n*-hexane–EtOAc, 7:3→1:1→3:7→1:9; (2) 9 g, $CHCl_3$–MeOH, 60:1→50:1→20:1) to give five-membered sulfone **5** (99.2 mg) as a colorless oil. Fraction III (0.36 g) was separated by column chromatography on silica gel ((1) 10 g, $CHCl_3$–MeOH, 15:1→9:1→16:3→7:2; (2) 2.5 g, $CHCl_3$–MeOH, 15:1→7:2; (3) 1.5 g, acetone–MeOH, 1:1→0:1), and by ODS gel (1.0 g, MeOH–H_2O, 1:9→3:7→5:5→7:3→0:1). The 30% aqueous MeOH fraction (15.0 mg) was purified by HPLC ((1) Develosil ODS MG-5, 20×250 mm, 60% aqueous MeOH, 5 mL/min, UV 205 nm; (2) Develosil ODS HG-5, 20×250 mm, 30% aqueous MeOH, 5 mL/min, UV 205 nm) to give six-membered sulfone **7** (4.5 mg) as a colorless oil. Fraction IV (0.42 g) was purified by column chromatography on ODS gel (10.0 g, MeOH–H_2O, 1:9→2:8→3:7→5:5→0:1) and on silica gel (4 g, $CHCl_3$–MeOH, 1:0→7:1→14:5→0:1) to give sulfonic acid **4** (0.22 g) as a colorless oil.

4.3.2. Sulfonic acid 4. $[\alpha]_D^{28}=-1.7°$ (*c* 0.70, MeOH); IR ($CHCl_3$) 3600–3100 (br), 1460, 1160, 1020 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; MS (FAB) *m/z* 271 $(M+Na)^+$; HRMS (FAB) calcd for $C_{12}H_{24}NaO_3S$ $(M+Na)^+$ 271.1344, found 271.1317.

4.3.3. Five-membered sulfone 5. IR ($CHCl_3$) 3600–3480 (br), 1160, 1460, 1300, 1280, 1110 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; MS (FAB) *m/z* 271 $(M+Na)^+$; HRMS (FAB) calcd for $C_{12}H_{24}NaO_3S$ $(M+Na)^+$ 271.1344, found 271.1353.

4.3.4. Six-membered sulfone 7. $[\alpha]_D^{28}=+4.1°$ (*c* 0.23, MeOH); IR ($CHCl_3$) 3640–3300 (br), 1600, 1460, 1300, 1130 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; MS (FAB) *m/z* 271 $(M+Na)^+$; HRMS (FAB) calcd for $C_{12}H_{24}NaO_3S$ $(M+Na)^+$ 271.1344, found 271.1349.

4.3.5. 3,5-Dinitrobenzoate 6. To a solution of five-membered sulfone **5** 5.0 mg (20 μmol) in pyridine (1.0 mL) cooled to 0°C was added 3,5-dinitrobenzoyl chloride (102 mg, 0.44 mmol), and the mixture was stirred at room temperature for 22.5 h. The reaction mixture was diluted with toluene (5.0 mL) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel ((1) 3.0 g, hexane–EtOAc, 5:1→3:1→1:1; (2) 0.5 g, benzene–acetone, 1:0→30:1→0:1) to give 3,5-dinitrobenzoate **6** (6.5 mg, 75%, 2:1 diastereomer mixture) as a colorless oil: IR ($CHCl_3$) 1735, 1630, 1550, 1460, 1340, 1280, 1160 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) (noted only the signal of the major diastereomer) δ 9.25 (1H, br d, *J*=12.1 Hz), 9.14–9.11 (2H, m), 5.66 (1H, dq, *J*=12.0, 6.2 Hz), 3.26 (1H, dt, *J*=12.0, 7.4 Hz), 3.06 (1H, m), 2.40–2.33 (2H, m), 2.04 (1H, m), 1.94 (1H, m), 1.74–1.65 (2H, m), 1.62 (3H, d, *J*=7.8 Hz), 1.41–1.31 (2H, m), 1.31–1.23 (2H, m), 1.12 (1H, m), 0.92 (3H, d, *J*=6.6 Hz), 0.87 (3H, t, *J*=7.1 Hz); MS (FAB) *m/z* 443 $(M+H)^+$; HRMS (FAB) calcd for $C_{19}H_{27}N_2O_8S$ $(M+H)^+$ 443.1488, found 443.1464.

4.3.6. Acetate 8. To a solution of six-membered sulfone **7** 0.5 mg (2.0 μmol) in pyridine (0.2 mL) cooled to 0°C was added Ac_2O (0.1 mL, 1.1 mmol), and the mixture was stirred at room temperature for 37.5 h. The reaction mixture was diluted with toluene (5.0 mL) and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (0.4 g, hexane–EtOAc, 1:1→MeOH) to give acetate **8** (0.3 mg, 51%) as a colorless oil: $[\alpha]_D^{28}=+17°$ (*c* 0.023, MeOH); IR ($CHCl_3$) 1750, 1310, 1140 cm^{-1}; ^1H NMR (800 MHz, CD_3OD) δ 4.80 (1H, dt, *J*=4.0, 12.3 Hz), 3.29 (1H, dq, *J*=12.3, 6.9 Hz), 3.15 (1H, m), 2.35 (3H, s), 2.11 (1H, ddt, *J*=15.2, 4.1 Hz), 2.08 (1H, m), 1.96 (1H, ddd, *J*=6.2, 7.7, 14.0 Hz), 1.76 (1H, m), 1.70 (1H, ddt, *J*=3.6, 15.2, 14.3 Hz), 1.62 (1H, ddt, *J*=2.8, 16.6, 14.3 Hz), 1.41 (1H, m), 1.34 (1H, m), 1.32 (3H, d, *J*=6.9 Hz), 1.30 (1H, m), 1.25 (1H, dt, *J*=7.3, 14.0 Hz), 1.11 (1H, m), 0.97 (3H, d, *J*=6.6 Hz), 0.92 (3H, t, *J*=7.2 Hz); MS (FAB) *m/z* 313 $(M+Na)^+$; HRMS (FAB) calcd for $C_{14}H_{26}NaO_4S$ $(M+Na)^+$ 313.1450, found 313.1450.

4.3.7. (*S*)-MTPA ester 9. A colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48 (2H, d, *J*=7.9 Hz), 7.44–7.40 (3H, m), 5.03 (1H, dt, *J*=3.5, 11.0 Hz), 3.51 (3H, s), 3.06 (1H, dq, *J*=11.0, 6.8 Hz), 2.82 (1H, m), 2.31 (1H, ddt, *J*=3.5, 13.2, 6.0 Hz), 2.06 (1H, m), 2.03 (1H, m), 1.76 (1H, ddt, *J*=3.5, 16.7, 13.6 Hz), 1.69 (1H, m), 1.52 (1H, m), 1.38 (1H, m), 1.38 (3H, d, *J*=6.8 Hz), 1.32 (1H, ddd, *J*=6.4, 8.2, 14.5 Hz), 1.25 (1H, m), 1.24 (1H, m), 1.07 (1H, m), 0.95 (3H, d, *J*=6.6 Hz), 0.88 (3H, t, *J*=7.2 Hz); MS (FAB) *m/z* 465 $(M+H)^+$; HRMS (FAB) calcd for $C_{22}H_{32}F_3O_5S$ $(M+H)^+$ 465.1923, found 465.1947.

4.3.8. (*R*)-MTPA ester 10. A colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (2H, d, *J*=8.2 Hz), 7.44–7.39 (3H, m), 5.06 (1H, dt, *J*=3.6, 11.2 Hz), 3.55 (3H, s), 3.05 (1H, dq, *J*=11.2, 6.7 Hz), 2.84 (1H, m), 2.37 (1H, ddt, *J*=3.6, 12.6, 7.3 Hz), 2.06 (1H, m), 2.05 (1H, m), 1.78 (1H, ddt, *J*=3.6, 15.0, 12.6 Hz), 1.71 (1H, m), 1.65 (1H, m), 1.40 (1H, m), 1.33 (1H, m), 1.28 (1H, m), 1.25 (1H, m), 1.22 (3H, d, *J*=6.7 Hz), 1.08 (1H, m), 0.95 (3H, d, *J*=6.6 Hz), 0.89 (3H, t, *J*=7.2 Hz); MS (FAB) *m/z* 465 $(M+H)^+$; HRMS (FAB) calcd for $C_{22}H_{32}F_3O_5S$ $(M+H)^+$ 465.1923, found 465.1945.

4.4. Reactions of *n*-propylthiosulfonic acid potassium salt (11) with cyclohexene

4.4.1. Under air (Table 3, entry 1). To a solution of **11** 7.8 mg (44 μmol) in $CHCl_3$–MeOH (1:1, v/v, 0.3 mL) cyclohexene (0.3 mL, 3.0 mmol) was added under air, and the mixture was stirred at room temperature for 24.5 h. The reaction mixture was concentrated, and the residual oil was separated by column chromatography on silica gel (0.5 g, EtOAc→MeOH). The eluates of MeOH were purified by column chromatography on silica gel (0.5 g, acetone→MeOH) to give sulfonic acid potassium salt **18** (3.8 mg, 52%) as a colorless powder. The eluates of EtOAc were purified by column chromatography on silica gel ((1) 2.0 g, benzene–acetone, 50:1→30:1→20:1→10:1→0:1; (2) 0.5 g, $CHCl_3$→acetone→MeOH) and by TLC on silica gel (200×100×0.50 mm, *n*-hexane–EtOAc, 1:1) to give sulfonate **13** (1.1 mg, 11%) and thiosulfonate **15** (0.7 mg, 6.6%) as colorless oils.

4.4.2. Under an oxygen atmosphere (Table 3, entry 4). To a solution of **11** 5.0 mg (28 μmol) in $CHCl_3$–MeOH (1:1, v/v, 0.3 mL) cyclohexene (0.50 mL, 4.9 mmol) was added under a nitrogen atmosphere, and oxygen gas was bubbled into the mixture for 5 min. The mixture was stirred at room temperature for 15 h, and then the reaction mixture was concentrated. The residual oil was separated by column chromatography on silica gel ((1) 0.5 g, EtOAc→MeOH; (2) 0.5 g, *n*-hexane–EtOAc, 4:1→3:1→2:1→3:2→0:1; (3) 0.5 g, *n*-hexane–EtOAc, 4:1→3:1→2:1→0:1; (4) 0.5 g, $CHCl_3$) and by TLC on silica gel ((1) 70×70×0.25 mm, *n*-hexane–EtOAc, 1:1; (2) 100×200×0.25 mm, *n*-hexane–EtOAc, 3:2) to give sulfonate **13** (0.40 mg, 6.4%), thiosulfonate **15** (1.1 mg, 16%), γ-ketosulfone **17** (0.1 mg, 1.8%), and sulfonic acid potassium salt **18** (2.9 mg, 71%) as colorless oils.

4.4.3. Sulfonate 13. IR ($CHCl_3$) 3640–3480 (br), 1450, 1360, 1340, 1180 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 4.43 (1H, ddd, *J*=4.9, 8.8, 12.0 Hz), 3.60 (1H, m), 3.15 (2H, m), 2.17 (1H, m), 2.09 (1H, m), 1.93 (2H, dq, *J*=15.0, 7.7 Hz), 1.76 (1H, m), 1.72 (1H, m), 1.53 (1H, ddt, *J*=4.0, 11.4, 12.8 Hz), 1.35 (1H, ddt, *J*=3.7, 10.8, 12.0 Hz), 1.31 (1H, dtt, *J*=12.8, 3.3, 12.8 Hz), 1.26 (1H, dtt, *J*=12.0, 3.3, 12.0 Hz), 1.08 (3H, t, *J*=7.7 Hz); ^{13}C NMR (201 MHz, $CDCl_3$) δ 85.9 (d), 72.7 (d), 53.0 (t), 33.2 (t), 31.6 (t), 24.2 (t), 23.6 (t), 17.6 (t), 13.0 (q); MS (FAB) *m/z* 245 $(M+Na)^+$; HRMS (FAB) calcd for $C_9H_{18}NaO_4S$ $(M+Na)^+$ 245.0824, found 245.0854.

4.4.4. Thiosulfonate 15. IR ($CHCl_3$) 3640–3480 (br), 1450, 1320, 1130 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 3.49 (1H, m), 3.47 (1H, m), 3.41 (1H, ddd, *J*=6.5, 9.2, 13.6 Hz), 3.25 (1H, ddd, *J*=4.0, 9.9, 12.6 Hz), 2.27 (1H, m), 2.14 (1H, m), 1.97 (2H, m), 1.79 (1H, m), 1.76 (1H, m), 1.54 (1H, ddt, *J*=3.6, 12.6, 12.6 Hz), 1.39 (1H, m), 1.36 (1H, m), 1.31 (1H, dtt, *J*=12.8, 3.2, 12.8 Hz), 1.08 (3H, t, *J*=7.5 Hz); ^{13}C NMR (201 MHz, $CDCl_3$) δ 73.7 (d), 64.6 (t), 58.6 (d), 35.4 (t), 33.3 (t), 26.2 (t), 24.2 (t), 17.8 (t), 13.0 (q); MS (FAB) *m/z* 261 $(M+Na)^+$; HRMS (FAB) calcd for $C_9H_{18}NaO_3S_2$ $(M+Na)^+$ 261.0595, found 261.0578.

4.4.5. Acetate 14. Compound **14** was synthesized from sulfonate **13** as described above (see Section 4.3.6) (71%) as a colorless oil: IR ($CHCl_3$) 1730, 1360, 1340, 1160 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 4.83 (1H, ddd, *J*=4.8, 8.9, 10.3 Hz), 4.58 (1H, ddd, *J*=5.1, 8.9, 11.0 Hz), 3.06 (2H, dt, *J*=9.1, 6.6 Hz), 2.22 (1H, m), 2.08 (3H, s), 1.88 (2H, tq, *J*=6.6, 7.6 Hz), 1.77 (1H, m), 1.72 (1H, m), 1.62 (1H, m), 1.39 (1H, m), 1.36–1.31 (2H, m), 1.06 (3H, t, *J*=7.6 Hz); ^{13}C NMR (201 MHz) δ 170.8 (CH_3CO_2–); MS (FAB) *m/z* 265 $(M+H)^+$; HRMS (FAB) calcd for $C_{11}H_{21}O_5S$ $(M+H)^+$ 265.1110, found 265.1122.

4.4.6. Acetate 16. Compound **16** was synthesized from thiosulfonate **15** as described above (see Section 4.3.6) (56%) as a colorless oil: IR ($CHCl_3$) 1730, 1360, 1340, 1160 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$) δ 4.74 (1H, dt, *J*=4.4, 9.8 Hz), 3.43 (1H, dt, *J*=4.4, 9.8 Hz), 3.34 (2H, ddd, *J*=2.6, 5.8, 9.8 Hz), 2.33 (1H, m), 2.09 (3H, s), 1.96 (2H, m), 1.75 (1H, m), 1.73–1.68 (2H, m), 1.49 (1H, m), 1.45–1.35 (2H, m), 1.09 (3H, t, *J*=7.4 Hz); ^{13}C NMR (201 MHz) δ 170.6 (CH_3CO_2–); MS (FAB) *m/z* 281 $(M+H)^+$; HRMS (FAB) calcd for $C_{11}H_{21}O_4S_2$ $(M+H)^+$ 281.0881, found 281.0877.

4.5. Intramolecular cyclization of thiosulfonic acid 21 into β-hydroxysulfone 22

4.5.1. Preparation of 4-pentenethiosulfonic acid sodium salt (21). A mixture of 4-pentenesulfonyl chloride (**20**) 634 mg (3.76 mmol) and sodium hydrosulfide 1.06 g (18.9 mmol) in MeOH (8 mL) was stirred at room temperature for 8 h. The reaction mixture was filtered on cotton, and the residue was washed with MeOH (5 mL). The filtrate and washings were combined and concentrated. The residual powder was purified by column chromatography on silica gel ((1) 50 g, EtOAc→acetone→MeOH; (2) 30 g, acetone→MeOH) to give 4-pentenethiosulfonic acid sodium salt (**21**) (613 mg, 85%) as a colorless powder: Mp 236–239°C; IR (KBr) 3470 (br), 1640, 1170, 1075 cm^{-1}; ^1H NMR (800 MHz, CD_3OD) δ 5.83 (1H, ddt, *J*=16.9, 10.2, 7.7 Hz), 5.06 (1H, br dd, *J*=16.9, 2.3 Hz), 4.99 (1H, br dd, *J*=10.2, 2.3 Hz), 3.15 (2H, t, *J*=7.7 Hz), 2.19 (2H, br tt, *J*=7.4, 7.0 Hz), 2.01 (1H, tt, *J*=7.7, 7.4 Hz); ^{13}C NMR (201 MHz, CD_3OD) δ 139.0 (d), 115.7 (t), 66.4 (t), 33.3 (t), 25.7 (t); MS (FAB) *m/z* 211 $(M+Na)^+$; HRMS (FAB) calcd for $C_5H_{10}NaO_2S_2$ $(M+Na)^+$ 210.9839, found 210.9847.

4.5.2. Intramolecular cyclization of compound 21. *Method A*. To a solution of thiosulfonic acid sodium salt **21** 9.0 mg (48 μmol) in MeOH (1 mL) aqueous hydrochloric acid (1 M, 0.1 mL) was added under an oxygen atmosphere. The reaction mixture was stirred at room temperature for 4 days and then concentrated. The residual powder was purified by column chromatography on silica gel (0.5 g, $CHCl_3$–MeOH, 19:1→9:1→0:1) and by TLC on silica gel (200×100×0.50 mm, $CHCl_3$–MeOH, 9:1) to give β-hydroxysulfone **22** (1.1 mg, 15%) and sulfonic acid sodium salt **23** (3.5 mg, 43%) as colorless powders, respectively.

Method B. A mixture of **21** 6.1 mg (32 μmol) and trifluoroacetic acid (1 mL) was concentrated in vacuo. The residue was stocked at room temperature under an oxygen

atmosphere for 7 days. The reaction mixture was purified as described above to give **22** (1.1 mg, 23%) and **23** (2.1 mg, 38%).

Acknowledgments

This work was supported in part by Grants-in-Aid for Scientific Research (No. 11558079) and Scientific Research on Priority Areas (A) (No. 12045235) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are indebted to Wako Pure Chemical Industries, Ltd, and Banyu Pharmaceutical Co., Ltd, for their financial support. We thank Professors R. Noyori and M. Kitamura (COE, Nagoya University) for allowing us to use the NMR instruments. We also thank Dr T. Matsumoto (Nagoya University) for the measurement of the fluorescent X-ray analysis.

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