JOC Article

Synthesis of All Stereoisomers of Sulfinylcalix[4]arenes[1]

Naoya Morohashi,*[,†,§] Hiroshi Katagiri,[†] Nobuhiko Iki,[†] Yusuke Yamane,[†] Chizuko Kabuto,[‡] Tetsutaro Hattori,[†] and Sotaro Miyano*[,†]

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan, and Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University, Aoba, Aoba-ku, Sendai 980-8578, Japan

miyano@orgsynth.che.tohoku.ac.jp; n-moro@yz.yamagata-u.ac.jp

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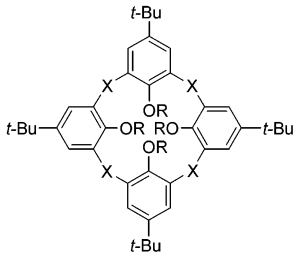
All four stereoisomers of *p-tert*-butylsulfinylcalix[4]arene [**4**(rccc), **4**(rcct), **4**(rctt), and **4**(rtct)], arising from the disposition of the four sulfinyl groups with respect to the mean plane of the four bridging sulfur atoms, have been prepared via oxidation of *p-tert*-butylthiacalix[4]arene (**2**) or its tetra-*O*-benzyl ethers **5** of defined conformations. Thus, treatment of **2** with 4.4 molar equiv of $NaBO_3 \cdot 4H_2O$ gave the rtct and rctt isomers in 27% and 17% yields, respectively, while oxidation of cone **5** ($\mathbf{5}_C$) and partial cone **5** ($\mathbf{5}_{PC}$) proceeded stereoselectively to give, after debenzylation of the resulting tetrasulfoxides **12** and **15**, the rccc and rcct isomers in 56% and 28% yields, respectively, based on **5**. The sulfinylcalix[4]arenes **4** were treated with iodomethane in the presence of a base to give the corresponding tetramethyl ethers **16**, the structures of which in regard to the disposition of the sulfinyl groups and the conformation of the phenol units were determined by X-ray crystallography. Also reported is the synthesis of all four conformational isomers of tetra-*O*-benzyl ether of **2** ($\mathbf{5}_C$, $\mathbf{5}_{PC}$, $\mathbf{5}_{1,2-A}$, and $\mathbf{5}_{1,3-A}$).

Introduction

Calix[4]arenes (e.g., **1**) are an extensively utilized molecular scaffold for synthetic receptors in supramolecular and molecular recognition chemistry.[2] This is mainly due to the availability of the basic macrocycles in substantial quantities from base-catalyzed condensation of *p*-alkylphenols with formaldehyde.[3] The macrocycles are, in turn, amenable to various modifications at the hydroxy groups (lower rim) and/or at the para positions (upper rim) of the phenolic units to bring about various functions.[2] Although modification of the bridging methylene groups or their replacement with heteroatoms such as nitrogen, phosphorus, sulfur, and the like is a highly intriguing method to alter the properties of the calix class compounds, there have been only few such attempts because of the synthetic difficulties.[4]



Replacement of any of the four bridging methylene groups by epithio groups was first reported by Sone et al. in 1993 via the stepwise joining of the component phenol units by methylene or epithio bonds followed by ultimate cyclization of the resulting acyclic tetramer.[5] However, it was not until 1997 when we disclosed a facile synthesis of 2,8,14,20-tetrathiacalix[4]arenes (e.g., **2**), by simply heating a *p*-alkylphenol with elemental sulfur in the presence of NaOH,[6] that these new members of the calix family were proved to be not a simple substitute for the parent calix[4]arenes but second-generation calixes bearing intrinsic advantages not attainable by the

* To whom correspondence should be addressed. Phone/Fax: +81-22-217-7262.
† Department of Biomolecular Engineering.
‡ Instrumental Analysis Center for Chemistry.
§ Present address: Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, Yonezawa 992-8510, Japan.

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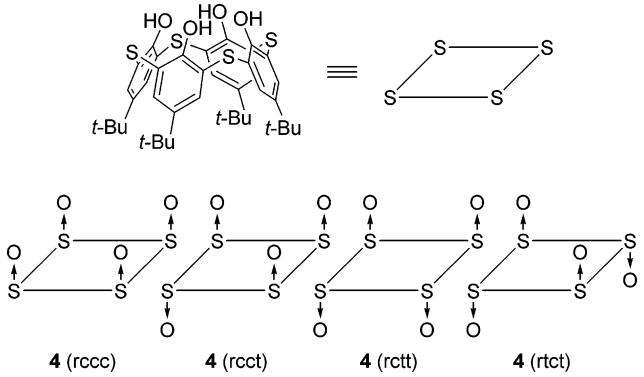

FIGURE 1. Schematic representation of four stereoisomers of **4**. Herein we use the term *cis* (c) or *trans* (t) to denote the disposition of sulfoxide oxygen with respect to reference oxygen from the mean plane containing four sulfur atoms, as suggested by Dr. V. Böhmer; see ref 7a. The isomer notation proceeds around the system in a clockwise direction from reference oxygen, which should be chosen to maximize the number of *cis*, and *cis* is preferable to *trans*.

methylene-bridged counterparts.[7] In particular, the ready oxidizability of the thio function to the sulfinyl and sulfonyl groups should be mentioned first, significantly widening the versatility of the thia-macrocycles. Thus, treatment of **2** with 8 molar equiv of $NaBO_3 \cdot 4H_2O$ gave sulfonylcalix[4]arene **3** in excellent yield.[1a,8,9] In the preparation of sulfinylcalix[4]arene **4**, the situation becomes somewhat complicated because of the possible stereoisomers due to the disposition of the four sulfinyl functions to give the rccc, rcct, rctt, and rtct isomers (Figure 1). Previously, we reported that isomer **4**(rtct) was obtained in 31% yield by direct oxidation of **2** with 4 molar equiv of $NaBO_3 \cdot 4H_2O$.[8,10]

Another noticeable feature of the sulfur-bridged calix[4]arenes is their unique metal binding ability.[11] It has been found that **2** extracts very well the so-called "soft" metal ions from an aqueous phase into an organic phase, by coordination of the bridging sulfur to the metal center with cooperative ligation of the two neighboring phenoxides to form two sets of five-membered chelates as exemplified by ^{1}H NMR spectroscopy[11] and X-ray crystallography of **2**−metal complexes.[12] On the other hand, the sulfonyl counterpart **3** prefers "hard" metal ions by coordination of the hard sulfonyl oxygen ligand.[8,13]

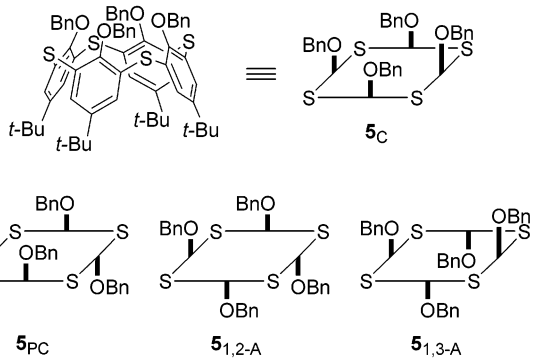

FIGURE 2. Schematic representation of all four conformational isomers of tertrabenzyl ether **5**.

It is quite interesting to note that the sulfinylcalix[4]arenes of rtct configuration [e.g., **4**(rtct)] can extract a wide variety of metal ions ranging from soft to hard.[8] It was concluded that **4**(rtct) can alternate the ligating atom between the oxygen and sulfur of the sulfinyl function depending on the hardness or softness of the metal ions to be extracted. This hypothesis was actually substantiated by X-ray crystallography of several complexes of **4**(rtct) with Pd(II)[14] and Ti(IV)[15] ions, which in turn brought about further interest in the complexation ability of isomers of **4** other than **4**(rtct) toward metal ions. Herein, as the first endeavor in this line, we report the preparation of all four stereoisomers of **4** in detail. In the course of this investigation, we needed specific conformational isomers of tetra-*O*-benzylthiacalix[4]arenes **5** as the intermediates for stereoselective synthesis of **4** of particular configurations, and the synthesis of all stereoisomers of **5** is also reported.

Results and Discussion

Synthesis of All Four Conformational Isomers of Tetra-*O*-benzyl Ether 5. Calixarene *O*-benzyl ethers of defined conformation have commonly been used as intermediates for the preparation of calixarenes of the desired conformation.[16] Therefore, it is highly desirable to have a set of all four conformational isomers of *p*-*tert*-butylthiacalix[4]arene tetra-*O*-benzyl ethers, that is, cone ($\mathbf{5}_C$), partial cone ($\mathbf{5}_{PC}$), 1,2-alternate ($\mathbf{5}_{1,2-A}$), and 1,3-alternate ($\mathbf{5}_{1,3-A}$) (Figure 2).[17] First of all, a one-step procedure for the tetra-*O*-benzylation of **2** with bromomethylbenzene was examined, varying a base, and Table 1 lists the isolated yields of the four conformational isomers of **5**. Treatment of **2** with a large excess of the bromide in THF−DMF using NaH as a base afforded a mixture containing $\mathbf{5}_C$ as the major product accompanied with small amounts of $\mathbf{5}_{PC}$ and $\mathbf{5}_{1,3-A}$ (entry 1). It can be seen that the alkali metal carbonates used significantly affected the conformational outcome of the reaction. Thus, Na_2CO_3 required the addition of NaI for the

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(9) Mislin, G.; Graf. E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *J. Chem. Soc., Chem. Commun*. **1998**, 1345.

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(12) (a) Iki, N.; Morohashi, N.; Kabuto, C.; Miyano, S. *Chem. Lett*. **1999**. 219. (b) Mislin, G.; Graf, E.; Hosseini, M. W.; Bilyk, A.; Hall, A. K.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *Chem. Commun*. **1999**, 373. (c) Bilyk, A.; Hall, A. K.; Harrowfield, J. M.; Hosseini, M. W.; Skelton, B. W.; White, A. H. *Inorg. Chem*. **2001**, *40*, 672.

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(16) See, for example: (a) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, 47, 2221. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *25*, 4325.

(17) The conformational preferences in the alkylation of thiacalix[4]arenes have been reported very recently: Lhoták, P.; Himl, M.; Stibor, I.; Petříčková, H. *Tetrahedron Lett*. **2002**, *43*, 9621.

TABLE 1. Conformer Distribution for Reaction of 2 with Bromomethylbenzene

				yield (%)[a]			
entry	base	solvent	time (h)	$\mathbf{5}_C$	$\mathbf{5}_{PC}$	$\mathbf{5}_{1,2-A}$	$\mathbf{5}_{1,3-A}$
1	NaH	THF−DMF (9:1)	2[b]	68	9	*c*	6
2[d]	Na_2CO_3	acetone	144[b]	50	12	1	2
3	K_2CO_3		48[b]	7	12	1	50
4	Cs_2CO_3		2[b]	*c*	3	1	70
5	K_2CO_3	DMF	24[e]	*c*	3	2	63

[a] Isolated yield. [b] At reflux. [c] Not detected. [d] NaI (4 molar equiv) was added. [e] At 60 °C.

bromide to react with **2** at a practical rate, giving preferentially the cone conformer in acetone, whereas K_2CO_3 and Cs_2CO_3 did not need the addition of NaI and preferred the formation of the 1,3-alternate isomer in the same solvent (entries 2−4). On the other hand, the solvent seems not to affect so much the isomer distribution as can be seen from the reaction with K_2CO_3 in DMF, which also gave the 1,3-alternate isomer selectively (entry 5). These results are in contrast to those reported by Gutsche et al., in which the one-step tetra-*O*-benzylation of methylene-bridged calix[4]arene **1** with NaH gave the cone isomer but the reaction with K_2CO_3 gave the partial cone conformer selectively.[18] Unfortunately, we could find suitable conditions for a one-step synthesis of neither $\mathbf{5}_{PC}$ nor $\mathbf{5}_{1,2-A}$, and thus these conformers were prepared by multistep procedures (vide infra).

Although it has been well-known that the conformation of conventional calix[4]arene derivatives can conveniently be assigned by relying on the ^{1}H NMR resonance pattern of the methylene groups between the phenol nuclei,[2] it is rather difficult to assign the conformation of thiacalix[4]arene derivatives because of the lack of the probing methylene moiety. However, the conformation of thiacalix[4]arenes of partial cone and 1,2-alternative can be deduced from their ^{1}H NMR resonances of the *tert*-butyl and aromatic protons. Thus, the isomer that showed three singlets for the *tert*-butyl protones [δ 0.75 (9H), 0.85 (18H), and 1.21 (9H)] and two singlets [δ 7.38 and 7.61 (each 2H)] and two doublets [δ 6.92 and 7.38 (each 2H)] for the aryl protons was safely assigned to $\mathbf{5}_{PC}$, and the other that showed one singlet for the *tert*-butyl protones [δ 1.13 (36H)] and two doublets for the aryl protons [δ 7.31 and 7.67 (each 4H)] was assigned to $\mathbf{5}_{1,2-A}$ (see Experimental Section). The distinction between the cone and 1,3-alternate conformers is very difficult, because ^{1}H NMR spectra of these conformers show quite similar resonance patterns, in which both the *tert*-butyl and aryl signals appear as singlet absorption. Eventually, the structural assignment of $\mathbf{5}_C$ and $\mathbf{5}_{1,3-A}$ relied on the X-ray analysis of $\mathbf{5}_C$ (Figure 3). It can be seen that, in the solid state, $\mathbf{5}_C$ takes a typical pinched cone structure with a C_{2v} symmetry. Therefore, the other isomer of the similar ^{1}H NMR spectrum was unambiguously assigned to be $\mathbf{5}_{1,3-A}$.

In the next step, we tried the synthesis of $\mathbf{5}_{PC}$ by a multistep procedure (Scheme 1). Treatment of **2** with bromomethylbenzene in acetone using Na_2CO_3 as the base without the addition of NaI afforded a dibenzylated product **6**, the stereo- and regiochemistry of which was assigned to be *syn*-1,3-di-*O*-benzyl ether (*syn*-1,3-**6**) on

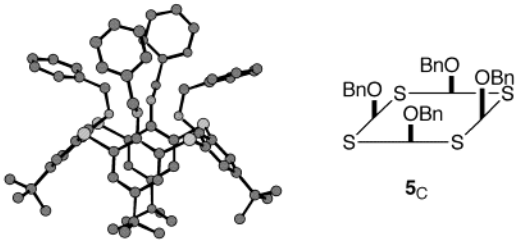
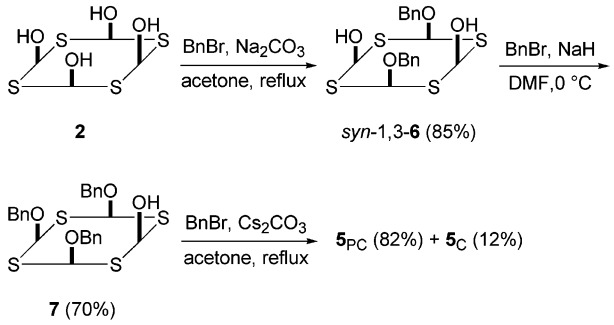


FIGURE 3. X-ray structure of $\mathbf{5}_C$. H atoms are omitted for clarity.

SCHEME 1



the basis of the ^{1}H NMR spectrum. Thus, two singlets for the *tert*-butyl protons [δ 0.79 and 1.34 (each 18H)] and two singlets for the aryl protons [δ 6.96 and 7.68 (each 4H)] ruled out the possibility of **6** to be a 1,2-regioisomer or an *anti*-1,3-isomer. Then, *syn*-1,3-**6** was further treated with the bromide (1 molar equiv) in DMF employing 1 molar equiv of NaH to afford a tribenzyl ether **7** in 70% yield, the stereochemistry of which was deducible from that of the product of the subsequent reaction. We have learned previously that in the *O*-alkylation of a mono-*O*-alkylated thiacalix[4]arene using Cs_2CO_3 as the base, the alkyl group coming in tends to replace the remaining phenolic hydroxy protons from the opposite side of the already residing alkyl groups with respect to the mean plane defined by the four S atoms.[19] By relying on this experimental generalization, tribenzyl ether **7** should most probably be converted to $\mathbf{5}_{PC}$ by treatment with an additional bromomethylbenzene in acetone using Cs_2CO_3 as the base. The fourth benzylation gave two tetrabenzyl ethers in 82% and 12% yields, respectively, the minor product of which was proved to be $\mathbf{5}_C$. Therefore, the major product should be the partial cone conformer $\mathbf{5}_{PC}$. Thus, $\mathbf{5}_{PC}$ was obtained in 49% yield via the three-step sequential benzylation of **2**.

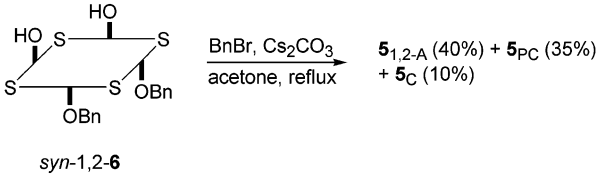
Finally, another stepwise procedure was devised for the synthesis of $\mathbf{5}_{1,2-A}$. It is conceivable that the possible intermediary di-*O*-benzyl ethers **6** to $\mathbf{5}_{1,2-A}$ should be limited to *syn*- or *anti*-1,2-**6**, or *anti*-1,3-**6**. However, it has been a common understanding in calixarene chemistry that *O*-dialkylation of a native calix[4]arene usually affords the 1,3- rather than the 1,2-isomer of *syn* conformation as the main product.[20] The preferential formation of a *syn*-1,3-conformer also stands for a disubstitution reaction of thiacalix[4]arenes as exemplified by the dibenzylation of **2** as stated above. Therefore, it should

(18) Gutsche, C. D.; Reddy P. A. *J. Org. Chem.* **1991**, *56*, 4783.

(19) Iki, N.; Narumi, F.; Fujimoto, T.; Morohashi, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2745.

(20) Chaper 5 of ref 2a,b.

SCHEME 2



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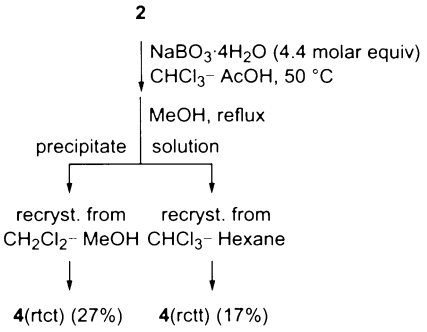


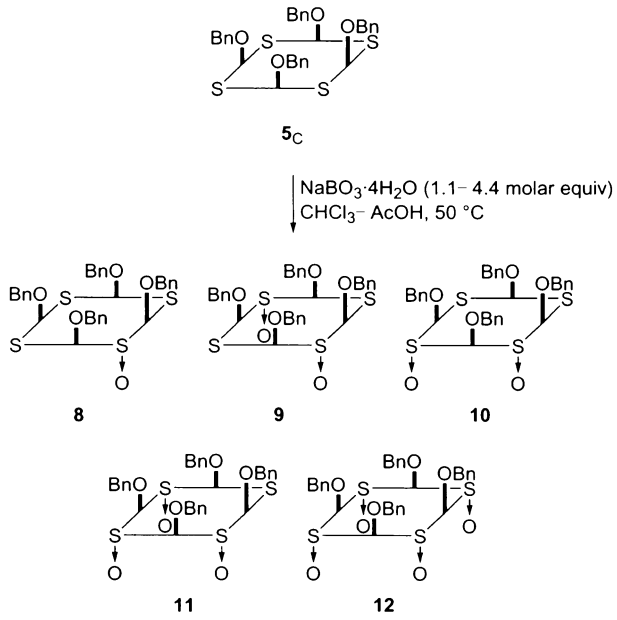
be noted that the preparation of a tetra-*O*-substituted calix[4]arene of 1,2-alternate conformation is a rather challenging task. In a previous paper,[21] we have reported a facile method for the synthesis of *syn*-1,2-di-*O*-alkylated thiacalix[4]arenes via 1,2-*O*-disiloxane-capping by treatment of **2** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in the presence of imidazole, followed by dialkylation of the two remaining phenolic hydroxy groups with an alkyl halide using Cs_2CO_3 as a base, and subsequent deprotection of the disiloxane moiety with tetrabutylammonium fluoride, which was conveniently adopted to the preparation of *syn*-1,2-**6**. The diether thus obtained in 69% yield based on the starting **2** was treated with an additional bromomethylbenzene in acetone using Cs_2CO_3 to give $\mathbf{5}_{1,2-A}$ (40%) with concomitant formation of $\mathbf{5}_{PC}$ (35%) and $\mathbf{5}_{C}$ (10%) (Scheme 2); thus, the four-step route gave $\mathbf{5}_{1,2-A}$ in a net 28% yield based on **2**.

Although several attempts to increase the selectivity of the production of the 1,2-alternate isomer of **5** were not fruitful, we could now have all the stereoisomers of tetra-*O*-benzyl ether **5** in hand in substantial amounts.

Synthesis of 4(rtct) and 4(rctt) Isomers by Oxidation of 2. Although we[1a] and others[10] have previously obtained the rtct isomer of **4** from oxidation of native **2** with $NaBO_3$ or H_2O_2, we were aware of the fact that the reaction of **2** with $NaBO_3 \cdot 4H_2O$ (4.4 molar equiv) gave a mixture containing several oxidation products. These were hardly separable by chromatography because of the decomposition of the phenolic entities on silica gel seemingly by oxidation. We revisited the reaction to improve the product yield and found that **4**(rtct) could be obtained as an insoluble part of the reaction mixture boiled in methanol (Scheme 3). Concentration of the methanol solution gave **4**(rctt) as a precipitate. Finally, spectrometrically pure samples of **4**(rtct) (27%) and **4**(rctt) (17%) were obtained by recrystallization of the solids from a dichloromethane−methanol and a chloroform−hexane solution, respectively. These results indicate that the configurations of the sulfinyl groups of **4** significantly

(21) Narumi, F.; Morohashi, N.; Matsumura, N.; Iki, N.; Kameyama, H.; Miyano, S. *Tetrahedron Lett.* **2002**, *43*, 621.

SCHEME 4



affect the solubility of the molecules; **4**(rctt) is highly soluble in methanol, whereas **4**(rtct) is essentially insoluble in hot methanol. The absolute dispositions of the four sulfinyl groups of **4**(rtct) were confirmed by X-ray crystallography,[8] and those of **4**(rctt) were determined after conversion into tetramethyl ether **16** (vide infra). It was shown by ^{1}H NMR assay that the $NaBO_3$ oxidation of **2** produced a small amount of **4**(rcct), besides **4**(rtct) and **4**(rctt), while the presence of **4**(rccc) isomer was not detectable.

Synthesis of 4(rccc) and 4(rcct) Isomers via Stereocontrolled Oxidation of Tetra-*O*-benzyl Ethers $\mathbf{5}_{C}$ and $\mathbf{5}_{PC}$, Respectively, Followed by Debenzylation. As the direct oxidation of **2** did not seem promising to obtain the rccc and rcct isomers of **4**, we then tackled a strategy to control the direction of the approach of the oxidant by introducing bulky substituents at the phenolic hydroxy groups, which are also able to freeze the flip-flop motion of the calix phenol units. We chose a benzyl moiety as the candidate because it possesses not only sufficient steric bulk to fulfill the requirements but also easiness of introduction (vide supra) and removal.[1b]

Initially, the oxidation of $\mathbf{5}_{C}$ was examined in detail (Scheme 4).[22] Oxidation of $\mathbf{5}_{C}$ with varying amounts of $NaBO_3 \cdot 4H_2O$ (1.1−4.4 molar equiv) produced mono- to tetrasulfinyl derivatives **8**−**12**, which were readily separated by chromatography on silica gel. It can be seen that the distribution of the products was mainly determined by the amounts of the oxidant (Table 2). The identities of the sulfinylcalix[4]arenes **8**−**12** were established by ^{1}H NMR and MS spectra except for the absolute stereochemistry of the sulfinyl groups, which was finally determined by X-ray crystallography on tetrasulfinylcalix[4]arene **12** (Figure 4). It can be seen that all four sulfinyl groups direct toward equatorial orientation in a down-

(22) Recently Lhoták reported the oxidation of thiacalix[4]arene tetraacetate having cone conformation to the sulfinyl derivative, the absolute stereochemistry of which was not determined: Lhoták, P. *Tetrahedron* **2001**, *57*, 4775.

TABLE 2. Oxidation of 5_C with $NaBO_3 \cdot 4H_2O$

entry	$NaBO_3 \cdot 4H_2O$ (molar equiv)	yield (%)[a] 8	9	10	11	12
1	1.1	56	21	15	*b*	*b*
2	2.2	18	32	30	11	*b*
3	3.3	*b*	23	2	57	11
4	4.4	*b*	*b*	*b*	*b*	94

[a] Isolated yield. [b] Not detected.

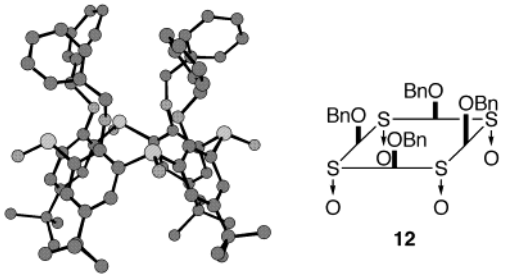
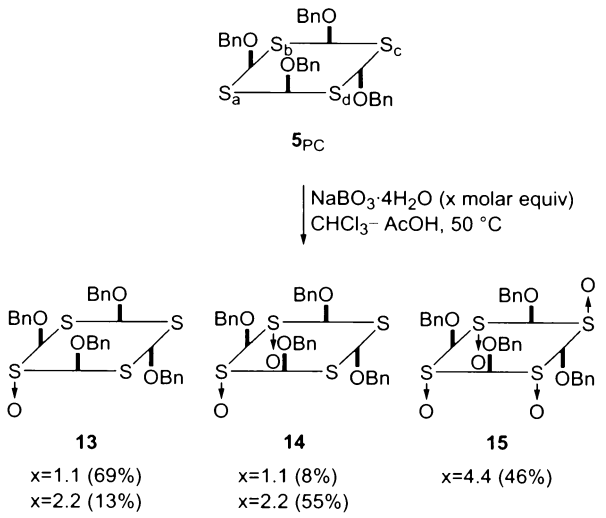


FIGURE 4. X-ray structure of **12**. H atoms and included solvents are not shown for clarity.

SCHEME 5



down-down-down manner seemingly to avoid the benzyl moieties. Considering the fact that the oxidation of $\mathbf{5}_C$ with $NaBO_3 \cdot 4H_2O$ eventually ends up in the formation of **12**, it is concluded that the disposition of the sulfinyl units of the intermediary **8**, **9**, **10**, and **11** should also be equatorial, showing that the stereochemistry of the oxidation was completely controlled by the benzyl groups.

In the next step, the oxidation of $\mathbf{5}_{PC}$ was studied in detail (Scheme 5). Oxidation of $\mathbf{5}_{PC}$ with 1.1 and 2.2 molar equiv of $NaBO_3 \cdot 4H_2O$ gave mono- and disulfinyl derivative **13** and **14** as the main products, respectively, although concomitant formation of small amounts of unidentified products was also suggested by ^1H NMR assay of the reaction mixtures. X-ray crystallography of **14** revealed that S_a and S_b of $\mathbf{5}_{PC}$ had been converted to sulfinyl groups with the oxygens disposed *anti* to the three proximal benzyl groups (Figure 5). Treatment of $\mathbf{5}_{PC}$ with $NaBO_3 \cdot 4H_2O$ (4.4 molar equiv) eventually gave **15**, which should come to **4**(rcct) after deprotection as evidenced hereinafter. These results show that the oxidizing agent attacks at first at S_a and then S_b from

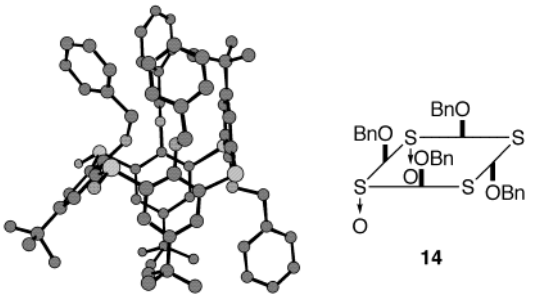


FIGURE 5. X-ray structure of **14**. H atoms and included solvents are not shown for clarity.

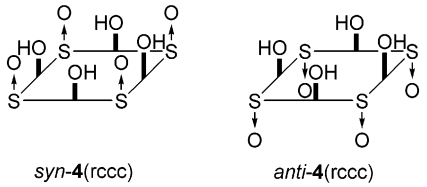
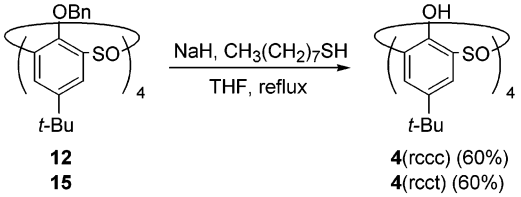


FIGURE 6. Schematic representation of *syn*- and *anti*-**4**(rccc).

SCHEME 6



the opposite side of the three *anti* benzyl groups with respect to the mean plane containing four sulfur atoms to avoid steric hindrance. Although the stereochemistry of the third oxidation step was not elucidated, the fourth oxidation seemed to avoid dipole repulsion toward the third sulfinyl, resulting in the up-and-down relationship between the third and fourth sulfinyl groups to form **15**.

Oxidation of $\mathbf{5}_{1,2-A}$ and $\mathbf{5}_{1,3-A}$ was found to give complex, hardly isolable mixtures, showing that stereocontrol of the oxidation was difficult by relying on the arrangement of the benzyl moieties in these conformational isomers.

Although iodotrimethylsilane is a conventional resource used for the deprotection of *O*-benzylated calixarenes,[14] attempted debenzylation of **12** and **15** with the iodide accompanied partial reduction of the sulfinyl groups of the resulting **4**(rccc) and **4**(rcct) to sulfide bonds. It was found, however, that sodium octane-1-thiolate was acceptable as the deprotection agent for **12** and **15**, giving **4**(rccc) (60%) and **4**(rcct) (60%), respectively (Scheme 6). Thus, synthetic methods for all four stereoisomers of *p*-*tert*-butylsulfinylcalix[4]arene **4** have now been provided.

Comparison of Spectral Properties of Stereoisomers of 4. It is interesting to compare the IR absorption of **2** with that of stereoisomers of **4**. The OH stretching absorption (ν_{OH}) of **4**(rccc) substantially shifted to a lower frequency (KBr disk, 3128 cm^{-1}) as compared to that of **2** (3324 cm^{-1}) and other stereoisomers of **4** (3188−3423 cm^{-1}), strongly indicating an increased intramolecular hydrogen bonding in **4**(rccc) compared to that in the others. The X-ray analyses have shown the presence of hydrogen bonding between the hydroxy and sulfinyl

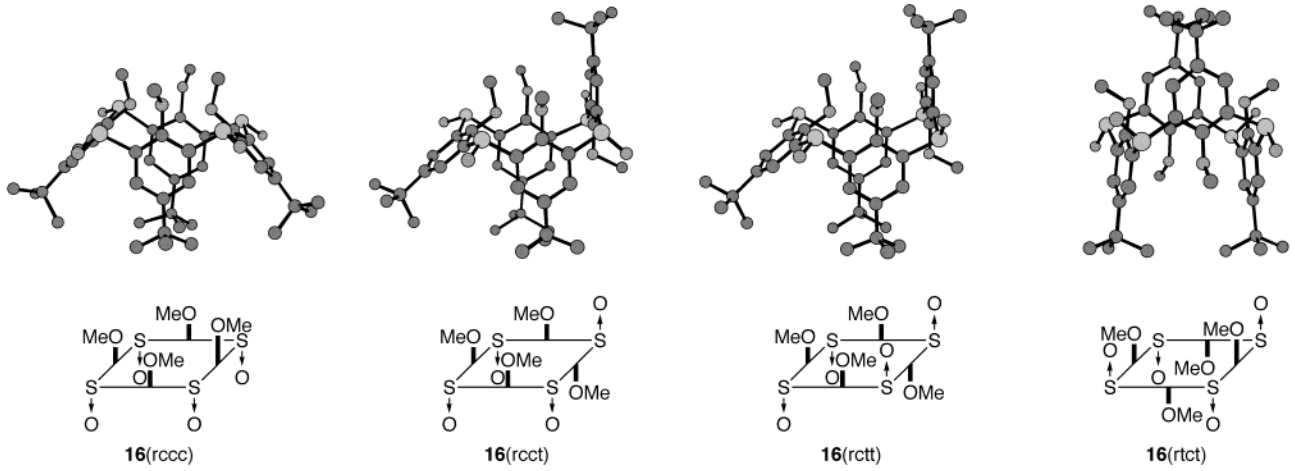


FIGURE 7. X-ray structures of **16**(rccc), **16**(rcct), **16**(rctt), and **16**(rtct). H atoms and included solvents are not shown for clarity.

groups in **4**(rtct),[7b,10] whereas circular intramolecular hydrogen bonding exists among the four hydroxy groups in **2**.[23] On the other hand, the S=O stretching absorption ($\nu_{S=O}$) of **4**(rccc) appears at 1028 cm^{-1}, falling between the absorptions of **12** (1049 cm^{-1}) and **4**(rtct) (1001 cm^{-1}) to indicate the presence of some hydrogen bonding between the hydroxy and sulfinyl groups in **4**(rccc). Therefore, the hydroxy groups of **4**(rccc) seem to form hydrogen bonding not only with adjacent hydroxy but also sulfinyl groups. Furthermore, the ^{1}H NMR spectrum of **4**(rccc) in $CDCl_3$−DMSO-d_6 showed a sharp singlet at 7.69 ppm for the aryl ring protons, indicating that they were equivalent on the NMR time scale. On the other hand, the ring protons of **4**(rtct) are nonequivalent, showing two broad peaks at 7.37 and 7.76 ppm due to the two adjacent sulfinyl groups in a *trans* relationship. From these discussions, the conformation of **4**(rccc) may tentatively be assigned as a cone structure in the solution with sulfinyl groups in a *syn* relationship to the phenolic hydroxy groups rather than an *anti* structure as depicted in Figure 6. Furthermore, **4**(rctt) and **4**(rcct) showed two $\nu_{S=O}$ peaks at 1053 and 1005 cm^{-1} and 1028 and 1003 cm^{-1}, respectively, indicating that **4**(rctt) and **4**(rcct) had more than two sulfinyl groups under different circumstances in the solid state because of the differences in the form of hydrogen bonding.

X-ray Crystallography of Tetramethyl Ethers 16. As it was very difficult to obtain single crystals of sulfinylcalix[4]arenes **4** except **4**(rtct),[7b,10] the configurations of the sulfinyl groups of all four isomers of **4** were determined after conversion into tetramethyl ether derivatives **16**. Treatment of **4** with iodomethane in THF using K_2CO_3 or Cs_2CO_3 as the base afforded tetramethyl ethers **16** in high yields (~80%). Single crystals of all stereoisomers **16** were obtained as usual, and their X-ray structural analyses were carried out (Figure 7). In the solid state, **16**(rccc) adopts a cone conformation, in which all four sulfinyl groups direct in opposite direction toward all four methoxy groups. On the other hand, **16**(rtct) adopts 1,3-alternate conformation seemingly to minimize the dipole repulsion between the sulfinyl and methoxy groups, the parent **4**(rtct) also adopting 1,3-alternate conformation as reported before.[7b,10] Furthermore, **16**(rcct) and **16**(rctt) have partial cone conformation, in which methoxy groups between two *syn* sulfinyl groups direct oppositely to them to minimize the steric hindrance and dipole repulsion between the sulfinyl and methoxy groups. From these results it seems that the configuration of the four sulfinyl groups would significantly influence the conformational arrangement of the phenol units of sulfinylcalix[4]arene derivatives.

Conclusion

We have provided here the routes for the synthesis of all four stereoisomers of *p-tert*-butylsulfinylcalix[4]arene **4**. Direct oxidation of native **2** gave the rtct and rctt isomers. On the other hand, the rcct and rccc isomers were obtained by stereocontrolled oxidation of tetrabenzyl ether **5** of defined conformations followed by debenzylation by treatment with a thiolate. The configurations of four sulfinyl groups of all four stereoisomers of **4** were confirmed after being converted into tetramethyl ether derivatives **16**. Furthermore, synthetic procedures for all four conformational isomers of tetra-*O*-benzylthiacalix[4]arene **5** were presented.

Experimental Section

General Methods. Melting points were taken using a micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent, unless otherwise noted. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. Silica gel $60GF_{254}$ was used for TLC. Silica gel columns were prepared by use of silica gel 60 (63−200 μm). Water- and air-sensitive reactions were routinely carried out under nitrogen. THF was distilled from sodium diphenyl ketyl just before use. Acetone and DMF were distilled from $CaSO_4$ and stored under nitrogen. 5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol (**2**)[6] and 27,28-dibenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26-diol (*syn*-1,2-**6**)[21] were synthe-

(23) (a) Akdas, H.; Bringel, L.; Graf, E.; Hosseini, M. W.; Mislin, G.; Pansanel, J.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1998**, *39*, 2311. (b) Iki, N.; Kabuto, C.; Fukushima, T.; Kumagai, H.; Takeya, H.; Miyanari, S.; Miyashi, T.; Miyano, S. *Tetrahedron* **2000**, *56*, 1437.

sized as described in the literatures. Densities (*d*) are given in units of g mL^{-1}.

General Procedure for the Benzylation of 2 to Conformational Isomers of 25,26,27,28-Tetrabenzyloxyl-5,-11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene (5) (Table 1). Thiacalix[4]-arene **2** was suspended in a dry solvent (ca. 50 mM solution) containing 16 molar equiv of an anhydrous alkali metal carbonate and bromomethylbenzene. To the suspension was added 4 molar equiv of NaI, if necessary (entry 2). The mixture was heated at reflux (entries 2−4) or 60 °C (entry 5) for 2−144 h. After cooling, precipitates were removed by filtration. The filtrate was poured into water and extracted with chloroform. The extract was washed with water, and the solvent was evaporated. The residual oil was triturated with methanol to give a solid, which was chromatographed on silica gel with hexane−chloroform (5:1) as the eluent. See Table 1 for the reaction conditions and the product distribution. In entry 1, the reaction was conducted as follows. A mixture of **2** (1.00 g, 1.39 mmol), NaH (534 mg, 22.3 mmol), DMF (1.5 mL), and THF (13.5 mL) was stirred at room temperature for 30 min. To the mixture was added bromomethylbenzene (3.93 g, 23.0 mmol), and the mixture was refluxed for 2 h. The reaction was quenched by addition of several drops of methanol. After most of the THF was evaporated, the residue was poured into water (50 mL) and worked up as above. Chromatographic purification of the resulting oil gave $\mathbf{5}_{C}$ (1.02 g, 68%), $\mathbf{5}_{PC}$ (134 mg, 9%), and $\mathbf{5}_{1,3-A}$ (87 mg, 6%).

Data for $\mathbf{5}_{C}$: mp 208−209.5 °C; ^{1}H NMR (500 MHz) δ 1.06 (36H, s), 5.24 (8H, s), 7.15−7.19 (12H, m), 7.22 (8H, s), 7.47−7.48 (8H, m); ^{13}C NMR (125 MHz) δ 31.2, 34.1, 76.7, 127.6, 127.7, 129.9, 133.9, 136.4, 137.4, 145.8, 158.1; FAB-MS *m*/*z* 1081 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.73; H, 6.67; S, 11.65.

Data for $\mathbf{5}_{PC}$: mp 222.5−224 °C; ^{1}H NMR (500 MHz) δ 0.75 (9H, s), 0.85 (18H, s), 1.21 (9H, s), 4.87 (2H, s), 4.92 (2H, d, *J* = 10.1 Hz), 5.08 (2H, s), 5.11 (2H, d, *J* = 10.1 Hz), 6,92 (2H, d, *J* = 2.51 Hz), 7.02−7.08 (3H, m), 7.30−7.36 (9H, m), 7.38 (2H, d, *J* = 2.51 Hz), 7.38 (2H, s), 7.39−7.43 (2H, m), 7.61 (2H, s), 7.65−7.68 (4H, m), 7.76−7.77 (2H, m); ^{13}C NMR (125 MHz) δ 30.8, 31.0, 31.3, 33.8, 33.9, 34.1, 71.1, 75.9, 77.6, 126.8, 126.9, 128.0, 128.2, 128.3, 128.4, 128.6, 128.9, 129.8, 129.9, 130.0, 133.5, 133.6, 134.2, 136.1, 137.2, 137.3, 137.6, 144.7, 145.6, 146.1, 156.3, 158.8, 160.2; FAB-MS *m*/*z* 1081 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.62; H, 6.79; S, 11.84.

Data for $\mathbf{5}_{1,2-A}$: mp 280−282 °C; ^{1}H NMR (500 MHz) δ 1.13 (36H, s), 4.50 (4H, d, *J* = 12.0 Hz), 4.70 (4H, d, *J* = 12.0 Hz), 6.58 (8H, d, *J* = 7.44 Hz), 6.94 (8H, t, *J* = 7.44 Hz), 7.05 (4H, t, *J* = 7.44 Hz), 7.31 (4H, d, *J* = 2.51 Hz), 7.67 (4H, d, *J* = 2.51 Hz); ^{13}C NMR (125 MHz) δ 31.1, 34.2, 73.4, 126.6, 127.5, 127.6, 128.8, 129.7, 129.9, 134.2, 137.4, 146.4, 157.3; FAB-MS *m*/*z* 1081 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.49; H, 6.76; S, 11.63.

Data for $\mathbf{5}_{1,3-A}$: mp 278−280 °C; ^{1}H NMR (500 MHz) δ 0.84 (36H, s), 5.07 (8H, s), 7.00−7.16 (20H, m), 7.14 (8H, s); ^{13}C NMR (125 MHz) δ 30.8, 33.8, 71.1, 126.8, 127.3, 128.0, 128.6, 129.4, 137.7, 146.0, 156.9; FAB-MS *m*/*z* 1081 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_4S_4$: C, 75.51; H, 6.71; S, 11.86. Found: C, 75.26; H, 6.70; S, 12.06.

26,28-Dibenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (*syn*-1,3-6). A mixture of thiacalix[4]arene **2** (3.00 g, 4.16 mmol), Na_2CO_3 (3.53 g, 33.3 mmol), bromomethylbenzene (5.70 g, 33.3 mmol), and dry acetone (100 mL) was refluxed for 2 d. After cooling, precipitates were removed by filtration. The filtrate was poured into water (200 mL) and extracted with chloroform. The organic layer was washed with water and evaporated to leave an oil, which was suspended in hot dichloromethane−ethanol, and the insoluble part was filtered. After the filtrate was evaporated, the residue was crystallized from dichloromethane−ethanol to give *syn*-1,3-**6** (3.18 g, 85%) as colorless crystals: mp 257−259 °C; ^{1}H NMR (500 MHz) δ 0.79 (18H, s), 1.34 (18H, s), 5.49 (4H, s), 6.96 (4H, s), 7.23−7.27 (2H, m), 7.30−7.34 (4H, m), 7.60−7.64 (4H, m), 7.68 (4H, s), 7.97 (2H, s); ^{13}C NMR (125 MHz) δ 30.8, 30.9, 34.0, 34.2, 76.4, 122.2, 128.3, 128.5, 129.0, 129.3, 132.7, 134.4, 136.7, 142.7, 148.1, 155.6, 155.8; FAB-MS *m*/*z* 901 [(M + 1)$^+$]. Anal. Calcd for $C_{54}H_{60}O_4S_4$: C, 71.96; H, 6.71; S, 14.23. Found: C, 72.03; H, 6.70; S, 14.09.

26,27,28-Tribenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,-14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-25-ol (7). NaH (60% dispersion in mineral oil; 1.4 mg, 35 μmol) was washed with dry hexane (2.0 mL) and suspended in dry DMF (3 mL). To it was added *syn*-1,3-**6** (27.7 mg, 30.7 μmol), and the mixture was stirred at room temperature for 30 min and then cooled to 0 °C. To the mixture was added bromomethylbenzene (d = 1.438; 3.7 μL, 31 μmol), and the resulting mixture was stirred at this temperature for 4 h. The mixture was quenched by addition of several drops of methanol, and the DMF was removed under reduced pressure at 60 °C. To the residue was added 2 M HCl (50 mL), and the mixture was extracted with chloroform. The organic layer was washed with water and evaporated to dryness. The residual oil was triturated with methanol to give a solid, which was purified by TLC with hexane−ethyl acetate (15:1) as the eluent to give **7** as a colorless powder (21.2 mg, 70%): mp 200−202 °C; ^{1}H NMR (500 MHz) δ 0.85 (18H, s), 1.25 (9H, s), 1.27 (9H, s), 5.14 (2H, d, *J* = 11.1 Hz), 5.14 (2H, d, *J* = 11.1 Hz), 5.37 (2H, s), 6.96 (2H, d, *J* = 2.5 Hz), 6.97 (2H, d, *J* = 2.5 Hz), 7.14−7.16 (3H, m), 7.28−7.30 (6H, m), 7.34−7.35 (2H, m), 7.49−7.50 (4H, m), 7.55 (2H, s), 7.60 (2H, s), 7.74 (1H, s); ^{13}C NMR (125 MHz) δ 30.9, 31.4, 31.4, 34.0, 34.1, 34.2, 74.7, 78.3, 121.9, 127.3, 127.4, 128.1, 128.3, 128.9, 129.2, 129.5, 129.8, 131.1, 132.4, 133.6; FAB-MS *m*/*z* 991[(M + 1)$^+$]. Anal. Calcd for $C_{61}H_{66}O_4S_4$: C, 73.90; H, 6.71; S, 12.94. Found: C, 73.82; H, 6.85; S, 13.19.

Benzylation of 7 to $\mathbf{5}_{PC}$ and $\mathbf{5}_{C}$. Tri-*O*-benzyl ether **7** (21.2 mg, 21.4 μmol) was suspended in dry acetone (4.0 mL), containing Cs_2CO_3 (34.7 mg, 107 μmol) and bromomethylbenzene (d = 1.438; 12 μL, 100 μmol), and the mixture was heated at reflux for 2 h. After cooling, precipitates were removed by filtration, and the filtrate was poured into water (50 mL). The mixture was extracted with chloroform, and the extract was washed with water. After the solvent was evaporated, the residual oil was triturated with methanol (20 mL) to give a solid, which was purified by TLC with hexane−chloroform (5:1) as the eluent to give $\mathbf{5}_{PC}$ (18.9 mg, 82%) and $\mathbf{5}_{C}$ (2.8 mg, 12%).

Dibenzylation of *syn*-1,2-6 to $\mathbf{5}_{1,2-A}$, $\mathbf{5}_{PC}$, and $\mathbf{5}_{C}$. *syn*-1,2-Di-*O*-benzyl ether **6** (40.8 mg, 45.3 μmol) was suspended in dry acetone (4.0 mL), containing Cs_2CO_3 (127 mg, 390 μmol) and bromomethylbenzene (d = 1.438; 47 μL, 400 μmol). The mixture was heated at reflux for 2 h. After cooling, precipitates were removed by filtration. The filtrate was poured into water (50 mL) and extracted with chloroform. The organic layer was washed with water and evaporated to dryness. The residual oil was triturated with methanol (20 mL) to give a solid, which was chromatographed on silica gel with hexane−chloroform (5:1) as the eluent to give $\mathbf{5}_{1,2-A}$ (19.5 mg, 40%), $\mathbf{5}_{PC}$ (17.3 mg, 35%), and $\mathbf{5}_{C}$ (4.9 mg, 10%).

Oxidation of 2 to 4(rctt) and 4(rtct). To a solution of **2** (3.00 g, 4.16 mmol) in chloroform (60 mL) were added acetic acid (90 mL) and $NaBO_3{\cdot}4H_2O$ (2.82 g, 18.3 mmol), and the mixture was heated at 50 °C for 4 h. The cooled mixture was poured into 2 M HCl (200 mL), and the aqueous layer was extracted with chloroform. The combined organic layer was washed with 6 M HCl and evaporated to leave an oil. Trituration with hexane (100 mL) gave a solid, which was suspended in boiled methanol (200 mL). The insoluble part was collected by filtration and crystallized from dichlo-

romethane−methanol to give 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiapentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene-*r*-2,*t*-8,*c*-14,*t*-20-tetraone [**4**(rtct)] as colorless crystals (890 mg, 27%): mp 295 °C (decomp); IR (KBr) 3188, 1001 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.29 (36H, s), 7.65 (8H, s), 9.30 (4H, s); ^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6 1:1) δ 1.23 (36H, s), 7.37 (4H, s), 7.76 (4H, s); ^{13}C NMR (125 MHz) δ 31.3, 34.7, 124.2 (br), 130.2 (br), 142.1, 152.8; FAB-MS *m*/*z* 785 [(M + 1)$^+$]. Anal. Calcd for $C_{40}H_{48}O_8S_4$: C, 61.20; H, 6.16; S, 16.34. Found: C, 60.88; H, 6.12; S, 16.06. On the other hand, the filtrate was evaporated, and the residue was crystallized from chloroform−hexane to give 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),-15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*t*-14,*t*-20-tetraone [**4**(rctt)] as colorless crystals (550 mg, 17%): mp 225−228 °C (decomp); IR (KBr) 3423, 1053, 1005 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.19 (18H, s), 1.24 (18H, s), 7.47 (4H, br),7.58 (4H, s); ^{13}C NMR (125 MHz, $CDCl_2CDCl_2$, 360 K) δ 31.0, 31.1, 34.5, 34.6, 125.3, 126.6 (br), 128.5, 129.0, 143.7, 143.7, 152.3, 153.3; FAB-MS *m*/*z* 785 [(M + 1)$^+$]. Anal. Calcd for $C_{40}H_{48}O_8S_4$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.17; H, 6.34; S, 16.50.

General Procedure for the Oxidation of 5_C to 8−12 (Table 2). To a solution of 5_C (50.0 mg, 46.2 μmol) in chloroform (2.0 mL) were added acetic acid (3.0 mL) and $NaBO_3$·$4H_2O$ (1.1−4.4 molar equiv), and the mixture was heated at 50 °C for 1 d. The cooled mixture was poured into water and extracted with chloroform. The extract was washed with water, and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel with hexane−ethyl acetate (4:1 or 2:1) as the eluent to give **8**−**12**. See Table 2 for the reaction conditions and the product distribution.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-2-one (8): mp 262−264 °C; IR (KBr) 1045 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.04 (18H, s), 1.11 (18H, s), 5.11 (2H, d, *J* = 11.5 Hz), 5.21 (2H, d, *J* = 11.0 Hz), 5.27 (2H, d, *J* = 11.0 Hz), 5.54 (2H, d, *J* = 11.5 Hz), 7.17−7.25 (16H, m), 7.31 (2H, d, *J* = 1.55 Hz), 7.32 (2H, d, *J* = 1.55 Hz), 7.39 (2H, d, *J* = 2.36 Hz), 7.41 (2H, d, *J* = 2.36 Hz), 7.53−7.55 (4H, m); ^{13}C NMR (125 MHz) δ 31.1, 31.2, 34.1, 34.6, 76.5, 77.5, 122.3, 128.0, 128.1, 128.1, 129.6, 129.8, 129.9, 130.2, 133.7, 134.2, 136.5, 136.9, 137.0, 139.5, 146.4, 146.8, 153.5, 158.0; FAB-MS *m*/*z* 1097 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_5S_4$: C, 74.41; H, 6.61; S, 11.69. Found: C, 74.43; H, 6.59; S, 11.59.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-14-dione (9): mp 300−301.5 °C; IR (KBr) 1043 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.09 (36H, s), 5.18 (2H, d, *J* = 11.2 Hz), 5.55 (2H, d, *J* = 11.2 Hz), 7.22−7.30 (12H, m), 7.38 (2H, d, *J* = 2.44 Hz), 7.39 (2H, d, *J* = 2.44 Hz), 7.40−7.42 (8H, m); ^{13}C NMR (125 MHz) δ 31.1, 34.6, 77.3, 122.5, 128.1, 128.3, 128.5, 129.9, 136.1, 136.6, 139.7, 147.5, 153.3; FAB-MS *m*/*z* 1113 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_6S_4$: C, 73.34; H, 6.52; S, 11.52. Found: C, 73.20; H, 6.60; S, 11.34.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8-dione (10): mp 294−296 °C; IR(KBr) 1045 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.82 (9H, s), 1.01 (9H, s), 1.26 (18H, s), 5.09 (2H, s), 5.20 (2H, d, *J* = 11.7 Hz), 5.20 (2H, s), 5.82 (2H, d, *J* = 11.7 Hz), 6.88 (2H, s), 7.15−7.36 (20H, m), 7.37 (2H, s), 7.62 (2H, d, *J* = 2.46 Hz), 7.72 (2H, d, *J* = 2.46 Hz); ^{13}C NMR (125 MHz) δ 30.8, 30.9, 31.3, 34.0, 34.8, 35.0, 75.4, 79.2, 79.5, 121.9, 125.9, 128.1, 128.3, 128.3, 128.5, 128.5, 128.9, 129.0, 129.7, 129.9, 130.0, 132.6, 135.3, 136.4, 136.6, 137.5, 139.4, 139.7, 147.0, 147.2, 148.6, 151.2, 152.8, 157.1; FAB-MS *m*/*z* 1113 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_6S_4$: C, 73.34; H, 6.52; S, 11.52. Found: C, 73.48; H, 6.71; S, 11.38.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14-trione (11): mp 311−312.5 °C; IR (KBr) 1047 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.07 (18H, s), 1.14 (18H, s), 5.18 (2H, d, *J* = 11.2 Hz), 5.19 (4H, s), 5.56 (2H, d, *J* = 11.2 Hz), 7.22−7.32 (16H, m), 7.38 (2H, d, *J* = 2.31 Hz), 7.39 (2H, d, *J* = 2.31 Hz), 7.43−7.45 (4H, m), 7.62 (2H, d, *J* = 2.39 Hz), 7.66 (2H, d, *J* = 2.39 Hz); ^{13}C NMR (125 MHz) δ 31.0, 31.1, 77.7, 78.4, 122.8, 124.6, 124.8, 128.3, 128.5, 128.5, 128.8, 129.0, 130.0, 130.0, 135.1, 135.9, 136.9, 139.0, 139.3, 139.5, 148.0, 148.9, 149.2, 153.2; FAB-MS *m*/*z* 1129 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_7S_4$: C, 72.30; H, 6.42; S, 11.36. Found: C, 72.24; H, 6.67; S, 11.30.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*c*-20-tetraone (12): mp 318−319 °C; IR (KBr) 1049 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.12 (36H, s), 5.22 (8H, s), 7.30−7.37 (20H, m), 7.63 (8H, s); ^{13}C NMR (125 MHz) δ 31.0, 35.2, 78.8, 124.9, 128.6, 129.3, 130.1, 134.8, 139.2, 148.9, 149.4; FAB-MS *m*/*z* 1145 [(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_8S_4$: C, 71.30; H, 6.34; S, 11.20. Found: C, 71.50; H, 6.35; S, 11.26.

General Procedure for the Oxidation of 5_{PC} to 13−15 (Scheme 5). Oxidation of 5_{PC} was performed by the same procedure as used for the oxidation of 5_C. See Scheme 5 for the reaction conditions and the product distribution.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaen-2-one (13): mp 259.5−261 °C; IR (KBr) 1045 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.75 (9H, s), 0.82 (9H, s), 0.93 (9H, s), 1.26 (9H, s), 4.05 (1H, d, *J* = 14.8 Hz), 4.81 (1H, d, *J* = 9.9 Hz), 5.08 (2H, s), 5.15 (1H, d, *J* = 9.9 Hz), 5.19 (1H, d, *J* = 10.4 Hz), 5.38 (1H, d, *J* = 10.4 Hz), 5.98 (1H, d, *J* = 12.8 Hz), 6.78 (1H, d, *J* = 2.51 Hz), 7.09−7.16 (5H, m), 7.13 (1H, d, *J* = 2.51 Hz), 7.25−7.30 (3H, m), 7.33 (1H, d, *J* = 2.51 Hz), 7.34−7.41 (6H, m), 7.51 (1H, d, *J* = 2.51 Hz), 7.52 (1H, d, *J* = 2.48 Hz), 7.64 (1H, d, *J* = 2.50 Hz), 7.67 (1H, d, *J* = 2.50 Hz), 7.55−7.57 (2H, m), 7.67−7.73 (4H, m), 7.72 (1H, d, *J* = 2.48 Hz); ^{13}C NMR (125 MHz) δ 30.9, 30.9, 31.3, 33.8, 33.9, 34.5, 34.7, 70.9, 75.9, 77.5, 77.9, 121.6, 123.4, 127.6, 127.7, 127.8, 128.1, 128.3, 128.4, 128.5, 128.5, 128.6, 128.9, 129.3, 129.8, 129.8, 135.5, 135.8, 136.6, 136.9, 137.3, 139.0, 146.0, 146.6, 147.4, 150.6, 155.9, 157.5, 160.0; FAB-MS *m*/*z* 1097[(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_5S_4$: C, 74.41; H, 6.61; S, 11.69. Found: C, 74.15; H, 6.94; S, 11.50.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8-dione (14): mp 267.5−269 °C; IR (KBr) 1053 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.83 (18H, s), 0.97 (9H, s), 1.32 (9H, s), 4.60 (2H, s), 5.06 (2H, s), 5.15 (2H, d, *J* = 10.5 Hz), 5.37 (2H, d, *J* = 10.5 Hz), 7.00−7.52 (20H, m), 7.05 (2H, d, *J* = 2.42 Hz), 7.45 (2H, d, *J* = 2.42 Hz), 7.68 (2H, s), 7.95 (2H, s); ^{13}C NMR (125 MHz) δ 30.8, 31.0, 31.4, 34.1, 34.4, 35.4, 73.6, 74.6, 77.4, 122.2, 123.5, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 128.7, 128.9, 129.3, 129.7, 134.7, 135.2, 135.8, 136.2, 137.2, 138.4, 138.8, 145.4, 146.3, 147.7, 148.0, 154.8, 159.4; FAB-MS *m*/*z* 1113[(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_6S_4$: C, 73.34; H, 6.52; S, 11.52. Found: C, 73.27; H, 6.54; S, 11.41.

25,26,27,28-Tetrabenzyloxyl-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*t*-20-tetraone (15): mp 303−305 °C; IR (KBr) 1053 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.83 (9H, s), 0.86 (9H, s), 0.88 (9H, s), 1.34 (9H, s), 4.40 (1H, d, *J* = 13.2 Hz), 4.66 (1H, d, *J* = 13.2 Hz), 4.93 (1H, d, *J* = 7.3 Hz), 5.13 (1H, d, *J* = 10.1 Hz), 5.17 (1H, d, *J* = 8.2 Hz), 5.29 (1H, d, *J* = 10.1 Hz), 5.54 (1H, d, *J* = 8.2 Hz), 5.56 (1H, d, *J* = 7.3 Hz), 7.05−7.07 (2H, m),

7.12 (1H, d, J = 2.40 Hz), 7.17 (1H, d, J = 2.34 Hz), 7.19−7.22 (3H, m), 7.34−7.42 (9H, m), 7.52 (1H, d, J = 2.34 Hz), 7.57−7.59 (2H, m), 7.66 (1H, d, J = 2.51 Hz), 7.70−7.81 (4H, m), 7.94 (1H, d, J = 2.40 Hz), 7.97 (1H, d, J = 2.33 Hz), 8.03 (1H, d, J = 2.33 Hz), 8.25 (1H, d, J = 2.51 Hz); ^{13}C NMR (100 MHz) δ 30.7, 30.7, 30.8, 31.3, 34.6, 34.6, 34.9, 35.5, 73.2, 80.4, 80.9, 83.0, 122.5, 122.6, 126.0, 126.1, 127.8, 127.9, 128.3, 128.8, 128.8, 128.8, 129.0, 129.1, 129.5, 130.0, 130.8, 130.9, 131.2, 131.8, 134.5, 135.1, 135.6, 135.8, 136.1, 136.2, 137.4, 137.6, 137.8, 138.1, 140.2, 144.6, 146.9, 148.1, 148.6, 149.0, 150.0, 152.6, 153.6; FAB-MS m/z 1145[(M + 1)$^+$]. Anal. Calcd for $C_{68}H_{72}O_8S_4$: C, 71.30; H, 6.34; S, 11.20. Found: C, 71.03; H, 6.39; S, 11.34.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*c*-20-tetraone [4(rccc)]. To a suspension of NaH (8.1 mg, 340 μmol) in dry THF (5 mL) was added octane-1-thiol (51.5 mg, 352 μmol), and the mixture was stirred at room temperature for 30 min. To the mixture was added **12** (49.8 mg, 43.5 μmol), and the resulting mixture was refluxed for 2 h. After cooling, the mixture was poured into ice-cold methanol (10 mL). To it was added 6 M HCl (10 mL), and the mixture was extracted with chloroform. The organic layer was evaporated to leave an oil, which was triturated with methanol. Crystallization of the resulting solid from dichloromethane−methanol gave **4**(rccc) as a colorless powder (20.5 mg, 60%): mp 316 °C (decomp); IR (KBr) 3128, 2959, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6 1:1) δ 1.14 (36H, s), 7.69 (8H, s); ^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6 1:1) δ 31.1, 34.6, 122.2, 133.0, 143.0, 150.4; FAB-MS m/z 785 [(M + 1)$^+$]. Anal. Calcd for $C_{40}H_{48}O_8S_4$: C, 61.20; H, 6.16; S, 16.34. Found: C, 60.98; H, 6.11; S, 16.09.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*t*-20-tetraone [4(rcct)]. This compound was prepared by the same procedure as used for the preparation of **4**(rccc). From **15** (2.00 g, 1.75 mmol) was obtained **4**(rcct) as a colorless powder (821 mg, 60%): mp 247−250 °C (decomp); IR (KBr) 3206, 1028, 1003 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.21 (18H, s), 1.24 (18H, s), 7.49−7.87 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$/DMSO-d_6 1:1) δ 31.4, 31.5, 35.1, 35.5, 124.4 (br), 126.8 (br), 128.2 (br), 132.8 (br), 143.9, 153.4 (br); FAB-MS m/z 785 [(M + 1)$^+$]. Anal. Calcd for $C_{40}H_{48}O_8S_4$: C, 61.20; H, 6.16; S, 16.34. Found: C, 60.97; H, 6.41; S, 16.35.

General Procedure for the Methylation of Stereoisomers of 4 to 16. A stereoisomer of **4** was suspended in dry THF (ca. 10 mM solution), containing 8.0 molar equiv of an anhydrous alkali metal carbonate [K_2CO_3 for **4**(rtct), Cs_2CO_3 for the other isomers of **4**] and 20 molar equiv of iodomethane, and the mixture was refluxed for 1 d. After cooling, precipitates were removed by filtration, and the filtrate was poured into water (50 mL). The mixture was extracted with chloroform, and the extract was washed with water. After the solvent was evaporated, the residue was chromatographed on silica gel with chloroform−ethyl acetate as the eluent to give the corresponding stereoisomer of **16**, the yield and the spectral and physical data of which are given below. Crystals suitable for X-ray analyses were grown in chloroform−methanol.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*c*-20-tetraone [16(rccc)]: yield 83%; mp 322−324 °C; IR (KBr) 1051 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.15 (36H, s), 4.18 (12H, s), 7.69 (8H, s); ^{13}C NMR (125 MHz) δ 31.0, 35.3, 63.9 (br), 124.9 (br), 138.8, 149.9 (br), 151.2 (br); FAB-MS m/z 841 [(M + 1)$^+$]. Anal. Calcd for $C_{44}H_{56}O_8S_4$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.54; H, 6.60; S, 15.03.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*c*-14,*t*-20-tetraone [16(rcct)]: yield 78%; mp 324.5−327.5 °C; IR (KBr) 1055 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.02 (9H, s), 1.07 (9H, s), 1.39 (9H, s), 1.39 (9H, s), 3.43 (3H, s), 3.88 (3H, s), 4.03 (6H, s), 7.06 (1H, br), 7.29 (1H, br), 7.81 (1H, d, J = 2.1 Hz), 7.86 (1H, d, J = 2.2 Hz), 7.97 (1H, d, J = 2.2 Hz), 8.00 (1H, d, J = 2.3 Hz), 8.06 (1H, br), 8.20 (1H, br); ^{13}C NMR (125 MHz) δ 30.8, 30.8, 31.3, 31.4, 34.7, 34.9, 34.9, 35.7, 61.6, 63.7, 64.0, 66.2, 122.5, 122.9, 125.4, 126.4, 127.6, 127.7, 130.5, 131.2, 135.3, 136.5, 136.5, 137.3, 137.6, 138.7, 138.8, 140.2, 144.4, 146.5, 148.3, 148.4, 150.1, 151.2, 152.7, 154.7; FAB-MS m/z 841[(M + 1)$^+$]. Anal. Calcd for $C_{44}H_{56}O_8S_4$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.48; H, 6.76; S, 15.56.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*c*-8,*t*-14,*t*-20-tetraone [16(rctt)]: yield 86%; mp 332.5−334 °C; IR (KBr) 1053 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.03 (18H, s), 1.38 (9H, s), 1.46 (9H, s), 3.47 (3H, s), 3.80 (3H, s), 4.07 (6H, s), 7.21 (2H, s), 7.82 (2H, s), 7.97 (2H, s), 8.12 (2H, s); ^{13}C NMR (100 MHz) δ 30.8, 31.4, 34.6, 35.3, 35.7, 61.2, 61.7, 66.3, 119.6, 122.7 (br), 125.7, 127.4, 130.9, 135.2, 136.6, 138.8, 140.2 (br), 146.8, 148.1, 148.4, 150.1, 155.0; FAB-MS m/z 841 [(M + 1)$^+$]. Anal. Calcd for $C_{44}H_{56}O_8S_4$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.55; H, 6.65; S, 15.41.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,20-tetrathiapentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-*r*-2,*t*-8,*c*-14,*t*-20-tetraone [16(rtct)]: yield 87%; mp 308.5−309 °C; IR (KBr) 1055 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.32 (36H, s), 3.92 (12H, s), 7.68 (4H, d, J = 2.4 Hz), 8.13 (4H, d, J = 2.4 Hz); ^{13}C NMR (125 MHz) δ 31.1, 34.8, 64.0, 127.4, 130.2, 136.5, 137.5, 146.7, 152.2; FAB-MS m/z 840 (M$^+$). Anal. Calcd for $C_{44}H_{56}O_8S_4$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.64; H, 6.68; S, 15.50.

X-ray Crystallography. Data were collected on a Rigaku/MSC mercury CCD diffractometer using Mo Kα radiation (λ = 0.71069 Å). The structures were solved by the direct methods and refined by the full-matrix least-squares method. All calculations were performed using the software package teXsan (v 1.10).

Data for 5$_C$: $C_{68}H_{72}O_4S_4\cdot CH_2ClCH_2Cl$, M = 1180.51, monoclinic, a = 21.617(1) Å, b = 15.6187(9) Å, c = 20.908(2) Å, β = 100.269°, V = 6946.4(8) Å^3, T = 223 K, space group $C2/c$ (No. 15), Z = 4, D_{calc} = 1.129 g/cm^3, μ(Mo Kα) = 2.57 cm^{-1}, data collection 900 images at 30.0 s, number of measured reflections = 32460 (2θ < 54.9°), independent reflections = 7795 (R_{int} = 0.022), final R = 0.059, R_w = 0.071 for 3635 observed reflections [$I_0 > 3.0\sigma(I_0)$], GOF = 1.90.

Data for 12: $C_{68}H_{72}O_8S_4\cdot H_2O\cdot CH_3CN$, M = 1204.62, tetragonal, $a = b$ = 15.8724(6) Å, c = 12.5804(9) Å, V = 3169.4(3) Å^3, T = 150 K, space group $P4/n$ (No. 85), Z = 2, D_{calc} = 1.262 g/cm^3, μ(Mo Kα) = 2.08 cm^{-1}, data collection 480 images at 30.0 s, number of measured reflections = 21745 (2θ < 54.2°), independent reflections = 3444 (R_{int} = 0.086), a symmetry-related absorption correction, final R = 0.062, R_w = 0.073 for 1568 observed reflections [$I_0 > 3.5\sigma(I_0)$], GOF = 1.56.

Data for 14: $C_{68}H_{72}O_6S_4\cdot CHCl_3$, M = 1232.93, triclinic, a = 13.6278(7) Å, b = 14.325(1) Å, c = 18.048(1) Å, α = 84.004(3)°, β = 78.644(3)°, γ = 68.0693(9)°, V = 3202.7(4) Å^3, T = 223 K, space group $P\bar{1}$(No. 2), Z = 2, D_{calc} = 1.278 g/cm^3, μ(Mo Kα) = 3.24 cm^{-1}, data collection 480 images at 30.0 s, number of measured reflections = 26431 (2θ < 52.0°), independent reflections = 11863 (R_{int} = 0.025), a symmetry-related absorption correction, final R = 0.063, R_w = 0.067 for 6854 observed reflections [$I_0 > 4.0\sigma(I_0)$], GOF = 2.21.

Data for 16(rccc): $C_{44}H_{56}O_8S_4\cdot CH_3OH\cdot H_2O$, M = 891.23, monoclinic, a = 19.650(2) Å, b = 13.8900(6) Å, c = 33.6300(5) Å, β = 91.5800(3)°, V = 9175.4(8) Å^3, T = 220 K, space group $C2/c$ (No. 15), Z = 8, D_{calc} = 1.296 g/cm^3, μ(Mo Kα) = 2.64 cm^{-1}, data collection 1024 images at 30.0 s, number of measured reflections = 31508 (2θ < 55.0°), independent reflections =

9512 (R_{int} = 0.021), final R = 0.045, R_w = 0.050 for 6328 observed reflections [$I_0 > 3.0\sigma(I_0)$], GOF = 1.36.

Data for 16(rcct): $C_{44}H_{56}O_8S_4 \cdot CHCl_3$, M = 960.54, triclinic, a = 11.430(2) Å, b = 14.940(3) Å, c = 16.120(5) Å, α = 90.730(8)°, β = 105.340(3)°, γ = 99.450(3)°, V = 2640.1841 Å^3, T = 230 K, space group $P\bar{1}$(No. 85), Z = 2, D_{calc} = 1.208 g/cm^3, μ(Mo Kα) = 3.77 cm^{-1}, data collection 480 images at 30.0 s, number of measured reflections = 20493 ($2\theta < 54.2°$), independent reflections = 10004 (R_{int} = 0.052), final R = 0.067, R_w = 0.087 for 4529 observed reflections [$I_0 > 5.0\sigma(I_0)$], GOF = 2.205.

Data for 16(rctt): $C_{44}H_{56}O_8S_4 \cdot CH_3OH$, M = 873.20, monoclinic, a = 11.2043(6) Å, b = 15.275(2) Å, c = 14.901(1) Å, β = 96.4206(9)°, V = 2534.3(4) Å^3, T = 230 K, space group $P2_1/m$ (No. 11), Z = 2, D_{calc} = 1.144 g/cm^3, μ(Mo Kα) = 2.35 cm^{-1}, data collection 750 images at 30.0 s, number of measured reflections = 21335 ($2\theta < 52°$), independent reflections = 5090 (R_{int} = 0.036), final R = 0.060, R_w = 0.075 for 2765 observed reflections [$I_0 > 3.0\sigma(I_0)$], GOF = 2.15.

Data for 16(rtct): $C_{44}H_{56}O_8S_4 \cdot CHCl_3$, M = 960.54, monoclinic, a = 15.7107(6) Å, b = 21.633(2) Å, c = 15.285(1) Å, β = 102.7716(6)°, V = 5073.4(6) Å^3, T = 230 K, space group $P2_1/n$ (No. 14), Z = 4, D_{calc} = 1.257 g/cm^3, μ(Mo Kα) = 3.92 cm^{-1}, data collection 754 images at 30.0 s, number of measured reflections = 36079 ($2\theta < 52°$), independent reflections = 9672 (R_{int} = 0.053), final R = 0.066, R_w = 0.069 for 4621 observed reflections [$I_0 > 2.0\sigma(I_0)$], GOF = 1.22.

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Supporting Information Available: CIF files for **5**$_C$, **12**, **14**, and four stereoisomers **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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