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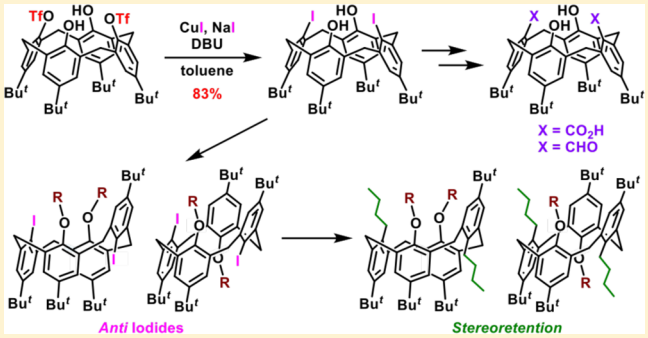
1,3-Diiodocalix[4]arene: Synthesis by Ullmann-Type Iodination of 1,3-Bistriflate Ester of Calix[4]arene, Conformational Analysis, and Transformation into 1,3-Dicarboxy-, Diformyl-, and Dialkylcalix[4]arenes

Shinya Tanaka,* Takafumi Umetsu, Satoru Nebuya, Naoya Morohashi, and Tetsutaro Hattori*

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, 6-6-11 Aramaki-Aoba, Aoba-ku, Sendai 980-8579, Japan

Supporting Information

ABSTRACT: A facile synthesis of 1,3-diiodocalix[4]arene **6** has been achieved by copper-catalyzed iodination of the 1,3-bistriflate ester **2a** of *p-tert*-butylcalix[4]arene. After protection of the hydroxy groups with iodomethane, diiodide **6** is subjected to halogen−lithium exchange with butyllithium, followed by carbonation with CO_2 or formylation with *N*-formylpiperidine and subsequent deprotection of the hydroxy groups to give novel dicarboxylic acid **11** or dialdehyde **16** in practical yields. The iodo groups of diiodide **6** pass through the calixarene macrocycle; the activation free energy for the conversion of the more stable syn conformer $\mathbf{6}_{syn}$ to the less stable anti conformer $\mathbf{6}_{anti}$ is $\Delta G^{\ddagger}$ = 104 kJ mol^{-1} at 298 K. Dialdehyde **16** shows fast self-exchange between two equivalent species with a cone conformation, $\Delta G^{\ddagger}$, being 63.2 kJ mol^{-1}. Dicarboxylic acid **11** adopts a cone conformation and forms a dimer in solution as suggested by ^{1}H NMR and X-ray crystallographic analyses. The arrangement of the iodide groups of compound **6** can be fixed predominantly to anti (**17a** and **17b**) by introducing bulky alkyl groups (e.g., propyl groups) onto the hydroxy groups. The stereospecific alkylation of the iodo groups of the resulting di-O-alkylated *anti*-1,3-diiodides provides access to the *anti*-1,3-dialkylcalixarenes **19**, which is otherwise difficult to obtain.



INTRODUCTION

Calixarenes (e.g., **1a**) and thiacalixarenes (e.g., **1b**), which are cyclic oligomers of phenols bridged at the ortho−ortho positions by methylene and epithio groups, respectively, are one of the most important building blocks in supramolecular chemistry.[1,2] A number of derivatives have been prepared via etherification or esterification of the hydroxy groups and/or electrophilic aromatic substitutions at the positions para to the hydroxy groups. However, displacement of the hydroxy groups with other functional groups by cleaving the aryl−oxygen bonds is difficult, because of steric hindrance caused by the sterically crowded cyclic structure and the presence of coordinative functional groups.[3] Although C−O bond cleavage in aryl triflates using a palladium or nickel catalyst is one of the most reliable methods of replacing phenolic hydroxy groups,[4] such reactions have been unsuccessful in the case of calixarenes,[5] with the exception of the Sonogashira coupling of 1,3-bistriflate ester **2a**, reported by Georghiou and co-workers.[6] We recently found that mono- (**3a** and **3b**) and 1,3-diaminocalixarenes (**4a** and **4b**) can be prepared via Ullmann-type amination or amidation of 1,3-bistriflate **2a** and its sulfur-bridged analogue **2b**.[7] We reasoned that copper phenoxide complexes formed between bistriflates **2** and Cu$^+$ assist the otherwise difficult oxidative addition of Ar−OTf bonds of the calixarenes. There are a wide variety of copper-assisted cross-coupling reactions for generating C−heteroatom bonds, as well as C−C bonds,[8] and therefore our protocol should have good potential for producing a range of X,O-hybrid calixarenes. We succeeded in preparing 1,3-diphosphonic acid **5a** via the Ullmann-type phosphonation of bistriflate **2a** with diethyl phosphite;[9] this is the first example of the introduction of phosphorus-containing groups into the lower rim of calixarene **1** by cleaving the aryl−oxygen bonds. In solvent extraction experiments with rare-earth metal ions, diphosphonic acid **5a** exhibited excellent extraction selectivity, which exactly reflected the order of the ion radii (r). For example, 90% of Yb^{3+} (r = 98.5 pm) was extracted at pH 1.61, whereas hardly any Eu^{3+} (r = 106.6 pm) or La^{3+} (r = 116.0 pm) was extracted under the same conditions;[10] the performance was superior to that of propylene-linked diphosphonic acid **5b**.[11] To make better use of the structural features of calixarenes by directly introducing functional groups onto the calix skeletons as shown in this example, we are studying methods to synthesize X,O-hybrid

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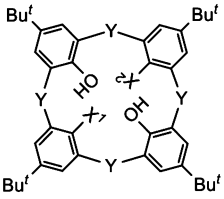
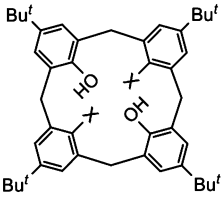
calixarenes via Ullmann-type reactions. Among such entities, 1,3-dihalogenated ones are of particular interest, as they would be good intermediates for preparing various derivatives that cannot be prepared by Ullmann-type reactions, because halogens can be transformed into various functional groups via halogen−metal exchange, followed by nucleophilic reactions.[12] To date, halo groups have been directly introduced into the narrow rims of calixarenes using the Sandmeyer reaction.[13] Biali and co-workers converted the amino group of monoaminocalix[5]arene to chloro, bromo, and iodo groups.[13a] We also synthesized mono-, 1,3-di-, and tetraiodothiacalix[4]-arenes from the corresponding aminothiacalix[4]arenes.[13b] However, the Sandmeyer reaction often suffers from low yields because of side reactions, such as hydrogenation. If 1,3-bistriflate **2** can be readily halogenated to 1,3-dihalocalixarenes, the range of narrow-rim substituents of calixarene **1** would be greatly expanded. Although the iodo group, having the highest reactivity among halo groups, is most useful for this purpose, this transformation is particularly difficult, because the nucleofugacity of the iodo group is comparable to, or greater than, that of the TfO group.[14] During the course of the study on the Sonogashira coupling of 1,3-bistriflate **2a**, Georghiou and co-workers found that mono- and 1,3-diiodocalixarenes were produced as unexpected byproducts in the coupling reaction.[6] However, the reaction requires 10 mol % of palladium catalyst and a large excess of CuI, and therefore a more sophisticated method is needed. Here, we report an efficient method for preparing 1,3-diiodide **6** by a catalytic Ullmann-type reaction and transformation of the iodo groups of **6** into carboxy, formyl, and alkyl groups via halogen−lithium exchange. The conformational analysis of the resulting X,O-hybrid calixarenes is also reported.



a; Y = CH_2, **b**; Y = S



5a : X = $P(O)(OH)_2$

5b : X = $O(CH_2)_3P(O)(OH)_2$

6 : X = I

	X^1	X^2
1	OH	OH
2	OTf	OTf
3	NH_2	OH
4	NH_2	NH_2

RESULTS AND DISCUSSION

Optimization of Ullmann-Type Iodination of 1,3-Bistriflate 2a. First, we explored the reaction conditions for the Ullmann-type iodination of 1,3-bistriflate **2a** by modifying the optimized conditions for a previously reported amination.[7b] The treatment of bistriflate **2a** with a stoichiometric amount of CuI in the presence of K_3PO_4 in toluene at room temperature resulted in quantitative recovery of the substrate (Table 1, entry 1). Replacement of the base with Cs_2CO_3, triethylamine, 2,6-lutidine, and imidazole did not give the desired 1,3-diiodide **6** (entries 2−5). However, when DBU was used, the substrate was completely consumed and 1,3-diiodide **6** was obtained in 28% yield, with a small amount of monotriflate **8** (5%) and a number of unidentified byproducts (entry 6). The replacement of the solvent by polar aprotic solvents, i.e., DMF and DMSO, resulted in decomposition of the substrate, giving monotriflate **8** as the main product (entries 7 and 8). Although use of a combination of DBU and toluene was effective for the present iodination, the product selectivity was not sufficient. We reasoned that another iodine source is required to suppress the side reactions caused by CuI. As expected, the addition of 4.0 molar equiv of KI greatly improved the selectivity, giving diiodide **6** in 63% yield (entry 9). We then tried the catalytic use of CuI. It was found that the iodination is sensitive to the reaction temperature under catalytic conditions. When the amount of CuI was reduced to 0.2 molar equiv, no reaction took place at room temperature (entry 10), whereas diiodide **6** was obtained in 45% yield at 35 °C (entry 11); the reaction carried out at a higher temperature gave the desired product in reduced yield, accompanied by many byproducts, consuming the entire substrate within 1 h (entry 12). Tetramethylammonium iodide and NaI served as iodine sources at 35 °C, but their efficiencies were inferior to that of KI (compare entries 13 and 15 with entry 11). However, NaI was used in subsequent reactions, because it reduced byproduct formation and, consequently, improved the diiodide yield by prolonging the reaction time (entry 16). It has often been reported that coordinative additives such as ethylene glycol, *N*,*N*′-dimethylethylenediamine, and 2,2′-bipyridine accelerate catalytic Ullmann-type reactions.[8] However, their addition reduced the diiodide yield and the product selectivity (compare entries 17−19 with entry 16). Increasing the amount of CuI to 1.0 molar equiv was very effective, giving diiodide **6** in a maximum yield of 83% (entry 20), while stoichiometric use of CuI promoted side reactions (entry 21).

Transformation of Iodo Groups of 1,3-Diiodide 6 into Carboxy and Formyl Groups. Compound **6** has iodo groups that are easily convertible to other functional groups, and therefore it is a good intermediate for the synthesis of various hybrid-type calix[4]arenes. We attempted the transformation of the iodo groups into carboxy groups (Scheme 1). After protection of the hydroxy groups with iodomethane (**9**), the diiodide was subjected to halogen−lithium exchange with butyllithium, followed by carbonation to give *O*-methyl-protected diacid **10** in 70% yield. Demethylation of diether **10** with HBr was accompanied by lactonization, giving a mixture of the desired diacid **11** and diester **12**. The mixture was subjected to alkaline hydrolysis, without purification, to furnish 1,3-dicarboxylic acid **11** in 76% yield based on diether **10**.

Next, the formylation of O-methylated diiodide **9** was examined (Table 2). The organodilithium species generated from diiodide **9** and butyllithium was treated with DMF at −78 °C to room temperature to give the desired dialdehyde **13** in low yield, accompanied by the formation of partially reduced aldehyde **14** and direduced product **15** (entry 1). The addition of TMEDA hardly affected the product distribution (entry 2). This suggests that the low dialdehyde yield is attributable not to the nucleophilicity of the organolithium species but to the steric bulk of the calixarene backbone, which prevents the formylation reagent from approaching the lithium center. Replacement of DMF with less sterically hindered *N*-formylpyrrolidine and *N*-formylpiperidine slightly improved the dialdehyde yield at the expense of the formation of the direduced product **15** (entries 3 and 4), but ethyl formate and ethyl orthoformate facilitated undesired protonation (entries 6 and 7). We reasoned that the formation of reduced products **14** and **15** was attributable to

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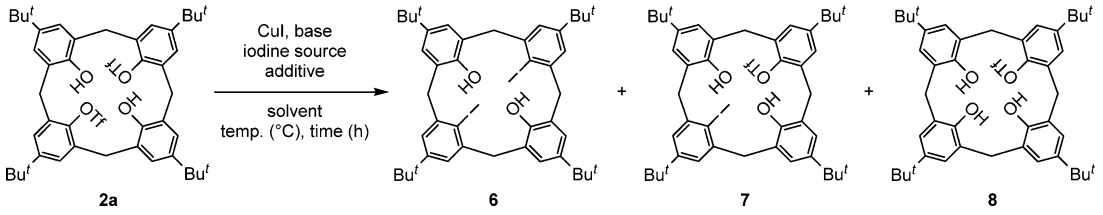
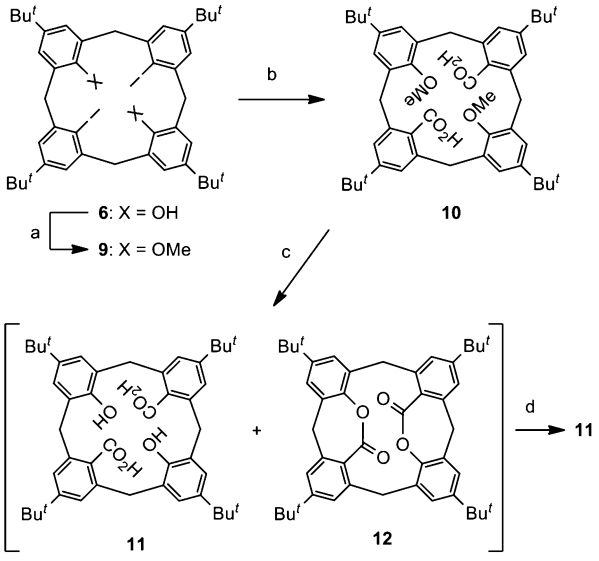
Table 1. Optimization of Ullmann-Type Iodination of 1,3-Bistriflate 2a[a]



								yield (%)[d]			
entry	CuI[b]	base[c]	iodine source	additive[c] (equiv)[b]	solvent	temp (°C)	time (h)	6	7	8	2a
1	2.2	K_3PO_4	–	–	toluene	r.t.	12	n.d.	n.d.	n.d.	>99
2	2.2	Cs_2CO_3	–	–	toluene	r.t.	12	n.d.	n.d.	n.d.	>99
3	2.2	Et_3N	–	–	toluene	r.t.	12	n.d.	n.d.	n.d.	>99
4	2.2	Lu	–	–	toluene	r.t.	12	n.d.	n.d.	n.d.	>99
5	2.2	Im	–	–	toluene	r.t.	12	n.d.	n.d.	n.d.	>99
6	2.2	DBU	–	–	toluene	r.t.	12	28	n.d.	5	n.d.
7	2.2	DBU	–	–	DMF	r.t.	12	n.d.	n.d.	21	n.d.
8	2.2	DBU	–	–	DMSO	r.t.	12	n.d.	n.d.	49	n.d.
9	2.2	DBU	KI	–	toluene	r.t.	12	63	n.d.	n.d.	8
10	0.2	DBU	KI	–	toluene	r.t.	24	n.d.	n.d.	n.d.	>99
11	0.2	DBU	KI	–	toluene	35	24	45	7	26	10
12	0.2	DBU	KI	–	toluene	50	1	19	trace	n.d.	n.d.
13	0.2	DBU	Me_4NI	–	toluene	35	24	10	n.d.	29	n.d.
14	0.2	DBU	LiI	–	toluene	35	24	n.d.	n.d.	n.d.	>99
15	0.2	DBU	NaI	–	toluene	35	24	29	19	7	40
16	0.2	DBU	NaI	–	toluene	35	48	55	10	6	17
17	0.2	DBU	NaI	EG (3.0)	toluene	35	48	20	17	9	39
18	0.2	DBU	NaI	DMEDA (0.2)	toluene	35	48	29	14	8	29
19	0.2	DBU	NaI	bpy (0.2)	toluene	35	48	50	9	3	17
20	1.0	DBU	NaI	–	toluene	35	12	83	trace	5	trace
21	2.0	DBU	NaI	–	toluene	35	12	60	trace	1	n.d.

[a]Reaction conditions: **2b** (0.219 mmol), CuI, base (2.0 molar equiv), iodine source (4.0 molar equiv), additive, toluene (10 mL). [b]Molar equivalents. [c]Abbreviations: Lu = 2,6-lutidine, Im = imidazole, EG = ethylene glycol, DMEDA = *N*,*N*′-dimethylethylenediamine, bpy = 2,2′-bipyridine. [d]Isolated yield.

Scheme 1. Synthesis of 1,3-Dicarboxylic Acid 11 from 1,3-Diiodide 6[a]



[a]Reagents and conditions: (a) NaH (8.0 molar equiv), MeI (20 molar equiv), DMF, 60 °C, 97%; (b) BuLi (3.0 molar equiv), THF, −78 °C to rt; then CO_2 bubbling, 70%; (c) 8.8 M HBr, AcOH, reflux; (d) 2 M NaOH, THF/EtOH, reflux; then 2 M HCl, 76%.

abstraction of the α-hydrogen of THF by the lithium species. We then tested various solvents (entries 8−10), among which diethyl ether exhibited the best performance, giving dialdehyde **13** in 45% yield. Prolongation of the reaction time improved the yield (entry 11), and a maximum yield of 60% was finally achieved by addition of MS4A (entry 12). Removal of the methyl groups of dialdehyde **13** with sodium octanethiolate furnished hydroxy-free 1,3-dialdehyde **16** in 91% yield (Scheme 2).

Fixation of Iodo Groups of 1,3-Diiodide 6 to Anti Conformation and Their Stereospecific Conversion to Alkyl Groups. The ^1H NMR spectrum of O-methylated diiodide **9**, recorded in $CDCl_3$ at −40 °C, showed that compound **9** exists as a mixture of five conformational isomers (Figure S1 in Supporting Information). Line broadening and coalescence of signals were observed with increasing temperature. This indicates that the iodo groups can pass through the calixarene macrocycle, forming conformational isomers originating from the syn and anti arrangements of the two iodo groups with respect to the mean plane defined by the macrocycle. We assumed that interconversion among the conformational isomers could be prevented by replacing the methyl groups with bulky substituents, and that the resulting stereoisomers would be useful for stereospecific transformations of the iodo groups. The hydroxy groups of diiodide **6** were then etherified with bulky bromoalkanes. The reaction of diiodide **6** with 1-bromopropane and 2-bromopropane in DMF

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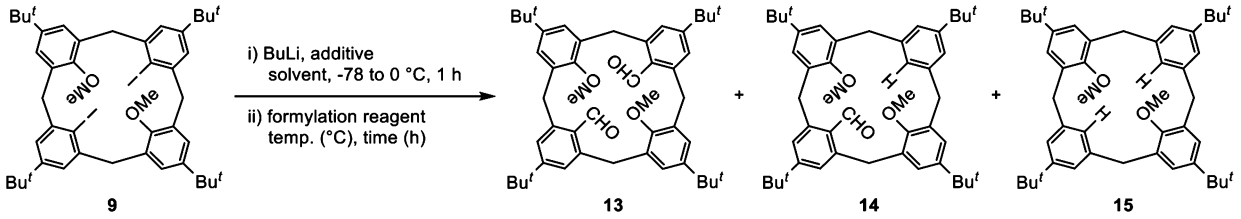
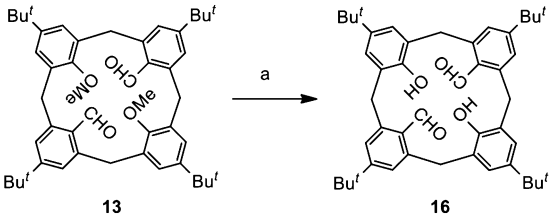
Table 2. Formylation of O-Methylated 1,3-Diiodide 9[a]



						yield (%)[b]		
entry	formylation reagent	solvent	additive	temp (°C)	time (h)	13	14	15
1	DMF	THF	–	−78 → r.t.	1	6	47	7
2	DMF	THF	TMEDA	−78 → r.t.	1	12	50	13
3	C_4H_8NCHO	THF	–	−78 → r.t.	1	18	42	n.d.
4	$C_5H_{10}NCHO$	THF	–	−78 → r.t.	1	19	56	n.d.
5	$C_5H_{10}NCHO$	THF	TMEDA	−78 → r.t.	1	18	54	n.d.
6	HCO_2Et	THF	–	−78 → r.t.	1	21	25	21
7	$HC(OEt)_3$	THF	–	−78 → r.t.	1	n.d.	n.d.	56
8	$C_5H_{10}NCHO$	toluene	–	0 → r.t.	1	34	28	n.d.
9	$C_5H_{10}NCHO$	hexane	–	0 → r.t.	1	43	25	n.d.
10	$C_5H_{10}NCHO$	Et_2O	–	0 → r.t.	1	45	28	n.d.
11	$C_5H_{10}NCHO$	Et_2O	–	0 → r.t.	12	51	27	n.d.
12[c]	$C_5H_{10}NCHO$	Et_2O	MS4A	0 → r.t.	12	60	36	n.d.

[a]Reaction conditions: (i) **9** (0.056 mmol), BuLi (3.0 molar equiv), solvent (1.5 mL), additive (3.0 molar equiv), −78 to 0 °C, 1 h; (ii) formylation reagent (10 molar equiv), temp (°C), time (h). [b]Isolated yield. [c]**9** (1.12 mmol), MS4A (1.00 g), Et_2O (30 mL) were used.

Scheme 2. Demethylation of Diether 13 to Hydroxy-Free Dialdehyde 16[a]

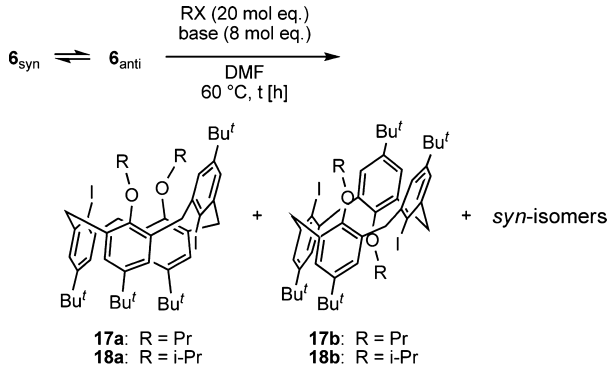


[a]Reagents and conditions: (a) $C_8H_{17}SNa$ (8.0 mol equiv), DMF, 130 °C, 1 h, 91%.

at 60 °C in the presence of NaH proceeded smoothly to give dipropyl ether **17** and diisopropyl ether **18**, respectively, as mixtures of stereoisomers (Table 3, entries 1 and 2); anti isomers were mainly obtained, with syn/anti ratios of 1/>9. The replacement of NaH with other bases hardly affected the product distribution (entries 3 and 4).

The stereochemistries of the isomers of **17** and **18** were determined by ^{1}H NMR analysis, exemplified by the case of dipropyl ether **17**, described below. A stereoisomeric mixture of dipropyl ether **17** obtained by the reaction of diiodide **6** with 1-bromopropane appeared as a single spot on TLC, but ^{1}H NMR analysis revealed that it consisted of four stereoisomers. The ^{1}H NMR spectrum of the major component, i.e., **17a**, exhibited three singlets, with integrated intensity ratios of 1:1:2 (9H, 9H, and 18H) for the *tert*-butyl protons, a pair of doublets (2H each) and two singlets (2H each) for the aryl protons, and one triplet for the terminal methyl protons of the propyl groups (6H); the spectroscopic pattern unambiguously identifies this isomer as the *anti*-1,3-diiodide with a partial cone conformation. The component present in the second largest amount, i.e., **17b**, exhibited two singlets (18H each) for the *tert*-butyl protons, two pairs each of doublets (2H each) for the aryl and bridging methylene protons, and one triplet (6H) for the

Table 3. Etherification of 1,3-Diiodide 6 with Bulky Bromoalkanes



entry	RX	base	time (h)	yield (%)[a]	anti/syn[b]	a/b[b]
1	PrBr	NaH	12	97	90:10	61:39
2	i-PrBr	NaH	12	98	97:3	55:45
3	i-PrBr	K_3PO_4	24	92	98:2	59:41
4	i-PrBr	Cs_2CO_3	24	91	98:2	55:45

[a]Chromatographic yield of isomer mixture. [b]Determined by ^{1}H NMR analysis.

terminal methyl protons of the propyl groups in the ^{1}H NMR spectrum, unambiguously identifying this isomer as the *anti*-1,3-diiodide with a 1,2-alternate conformation. The remaining two minor isomers are therefore the *syn*-1,3-diiodies, but they could not be fully characterized because of severe overlapping of their signals with the other signals.

The stereoisomeric mixture of dipropyl ether **17** could not be separated chromatographically. However, repeated crystallization of the mixture from chloroform−methanol gave the anti isomer **17a** with 88% purity. In addition, the other anti isomer, **17b**, was obtained with 96% purity by evaporating the mother liquid of the first crystallization, followed by recrystallizing the residue from the same solvent. The purities of these crystals

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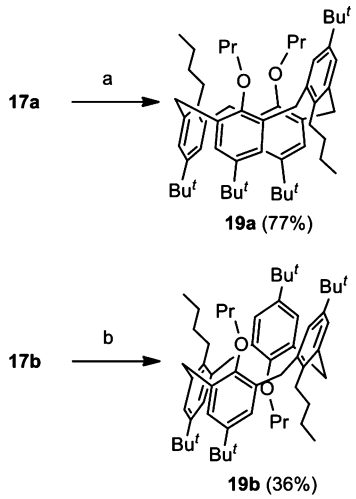
were not improved further, though these isomers did not isomerize even by heating their toluene solutions at 100 °C for 24 h.

Stereoselective synthesis of anti-1,3-disubstituted calix[4]arenes is generally very difficult.[15] For example, it is well-known that the dialkylation of the phenolic hydroxy groups of calixarene **1** with alkyl halides in the presence of a base selectively affords syn-1,3-di-O-alkylated compounds by virtue of a circular network of intramolecular hydrogen bonds in the monoalkylated intermediates.[16] The synthesis of anti-1,3-di-*O*-alkylated calixarenes therefore requires a troublesome protection−deprotection process.[15a,b,d] We also reported that the S_NAr reaction of a stereoisomer (*rctt*) of tetra-*O*-methylsulfinylcalix[4]arenes with lithium benzylamide exclusively gave a *syn*-1,3-di(benzylamino)sulfinylcalix[4]arene.[3i] We thought that di-O-propylated *anti*-1,3-diiodides **17a** and **17b** would be useful precursors for the preparation of anti-1,3-disubstituted calixarenes via stereospecific substitution reactions of the iodo groups. In an attempt to achieve this reaction, the individual stereoisomers **17a** and **17b** were subjected to halogen−lithium exchange, followed by alkylation with 1-iodobutane (Scheme 3). These reactions gave dibutylated compounds **19a** and **19b**

Scheme 3. Stereospecific Alkylation of *anti*-1,3-Diiodides 17a and 17b[a]



[a]Reagents and conditions: (a) BuLi (3.0 molar equiv), hexane, −78 to 40 °C, 2 h, then BuI (10 molar equiv), r.t., 3 h; (b) BuLi (3.0 molar equiv), Et_2O, −78 to 0 °C, 1 h, then BuI (10 molar equiv), r.t., 3 h.

in 77% and 36% yields, respectively, as single stereoisomers. The ^{1}H NMR spectrum of compound **19a** exhibited three singlets with integrated intensity ratios of 1:1:2 (9H, 9H, and 18H) for the *tert*-butyl protons, a pair of doublets (2H each) and two singlets (2H each) for the aryl protons, and two sets of signals corresponding to the butyl protons; the spectroscopic pattern unambiguously identified this compound as *anti*-1,3-dibutylcalixarene with a partial cone conformation. In contrast, compound **19b** exhibited two singlets (18H each) for the *tert*-butyl protons, two pairs of doublets for the aryl protons (2H each), and one set each of signals corresponding to the propoxy and butyl protons; the magnetic equivalences corresponded to *anti*-1,3-dibutylcalixarene with a 1,2-alternate conformation. The stereospecific transformations of the iodo groups of *anti*-1,3-diiodides **17a** and **17b** into butyl groups were therefore achieved.

Conformational Analysis of 1,3-Diiodide 6, Dicarboxylic Acid 11, and Dialdehyde 16. A crystalline sample of diiodide **6** was freshly dissolved in $CDCl_3$ and subjected to variable-temperature NMR analysis (Figure 1). The spectrum obtained at room temperature exhibited two singlets (18H each) for the *tert*-butyl protons, a pair of doublets (4H each) for the bridging methylene protons, and two singlets (4H each) for the aryl protons (Figure 1a); the magnetic equivalences suggest a C_{2v}-symmetric structure. With increasing temperature, another set of signals with the same spectroscopic pattern appeared, and their integrated intensities were increased; the equilibrium ratio of the latter to the former was 1:9 at 55 °C (Figure 1b). It can be easily deduced that this spectroscopic change arises from interconversion between the syn ($\mathbf{6}_{syn}$) and anti arrangements ($\mathbf{6}_{anti}$) of the two iodo groups (eq 1). The

$$\mathbf{6}_{syn} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{6}_{anti} \quad (1)$$

C_{2v}-symmetric spectroscopic pattern of $\mathbf{6}_{anti}$ can be rationalized by self-exchange between two equivalent species with a partial cone or 1,2-alternate conformation, resulting from fast inversion of the two phenol units on the NMR time scale; $\mathbf{6}_{syn}$ adopts a 1,3-alternate conformation with C_{2v}-symmetry, in accord with its X-ray structure (vide infra). A similar spectroscopic change was observed even at room temperature when a solution of a single isomer in $CDCl_3$ was left for 24 h; the molar ratio of the two conformers was 94:6.

Single crystals suitable for X-ray crystallographic analysis were obtained by slow vapor diffusion of methanol into a solution of diiodide **6** in dichloromethane. The X-ray structure shows that diiodide **6** adopts a 1,3-alternate conformation with a syn arrangement of the two iodo groups (Figure 2). The ^{1}H NMR spectrum of a sample prepared by dissolving the single crystals in $CDCl_3$ was identical to that of the major isomer in the variable-temperature NMR analysis (Figure 1). This strongly suggests that the major component in the syn/anti interconversion of diiodide **6** is a syn conformer ($\mathbf{6}_{syn}$) and the minor one is an anti conformer ($\mathbf{6}_{anti}$).

The kinetic parameters for the forward reaction of the interconversion of diiodide **6** (eq 1) were determined as follows. If the rate constant for the forward reaction from $\mathbf{6}_{syn}$ to $\mathbf{6}_{anti}$, the rate constant for the reverse reaction from $\mathbf{6}_{anti}$ to $\mathbf{6}_{syn}$, and the apparent rate constant for the forward reaction (eq 2) are defined as k_1, k_{-1}, and k, respectively, eq 3 can be derived from the rate equation (see Supporting Information).

$$k = k_1 + k_{-1} \quad (2)$$

$$\frac{[\mathbf{6}_{syn}] - [\mathbf{6}_{syn}]_\infty}{[\mathbf{6}_{syn}]_0 - [\mathbf{6}_{syn}]_\infty} = e^{-kt} \quad (3)$$

If the left side of the equation is defined as C, eq 3 can be rearranged to eq 4.

$$\ln C = -kt \quad (4)$$

The changes in the ratio of $\mathbf{6}_{anti}$ to $\mathbf{6}_{syn}$ with time (t) were analyzed at different temperatures, using ^{1}H NMR spectroscopy (Figure S2 in Supporting Information), and the k value was determined at each temperature as the slope of the ln C vs t plot (Figure 3). The equilibrium constant K was determined at each temperature by ^{1}H NMR analysis (Figure S2 in Supporting Information). The k and K values were used to calculate k_1 from eq 2 and the relation $K = k_1/k_{-1}$. Based on the

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J. Org. Chem. 2015, 80, 1070−1081

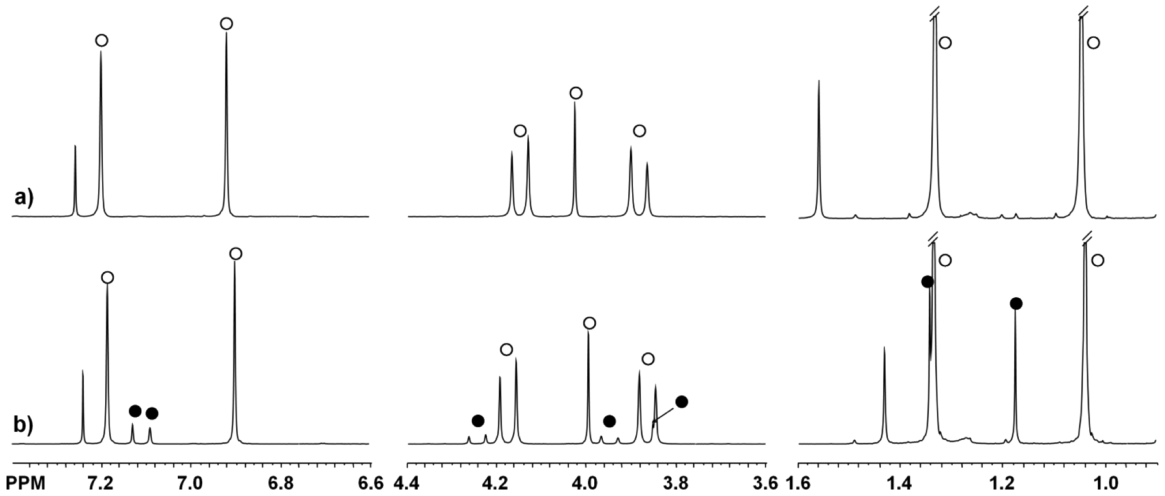

Figure 1. ^{1}H NMR spectra of 1,3-diiodide **6**: (a) freshly dissolved in $CDCl_3$ at 23 °C and (b) after equilibrium was reached at 55 °C. Signals assigned to the original conformer and the newly observed conformer are denoted by ○ and ●, respectively.

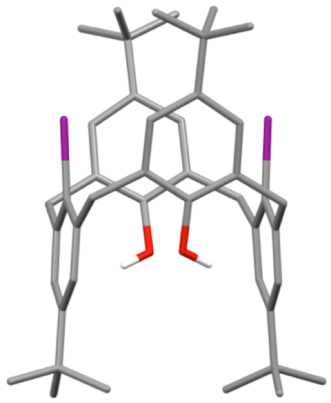

Figure 2. X-ray structure of 1,3-diiodide **6**. Hydrogen atoms except for those in HO groups and solvent molecules are omitted for clarity.

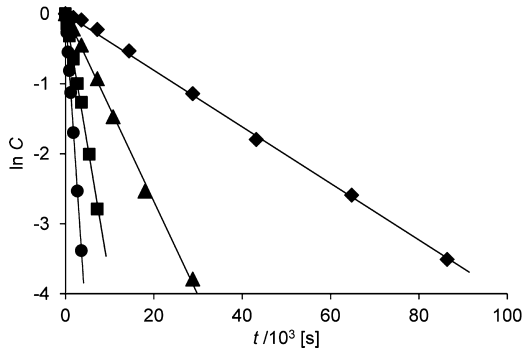

Figure 3. ln *C* vs *t* plots for conformational changes of conformer $\mathbf{6}_{syn}$ in $CDCl_3$ at 296 K (♦), 308 K (▲), 318 K (■), and 328 K (●).

Eyring plot, the activation enthalpy and entropy for the forward reaction were found to be $\Delta H^{\ddagger}$ = 90.7 kJ mol^{-1} and $\Delta S^{\ddagger}$ = −46.0 J mol^{-1} K^{-1}, respectively (Figure 4). The activation free energy at 298 K was therefore calculated to be $\Delta G^{\ddagger}$ = 104 kJ mol^{-1}. Blixt and Detellier reported the kinetic parameters for the conformational changes of tetra-*O*-methylcalix[4]arene; the $\Delta H^{\ddagger}$ values for the conversion of a partial cone conformer to 1,2-alternate, cone, and 1,3-alternate conformers are 59, 61, and 56 kJ mol^{-1}, respectively, and the $\Delta S^{\ddagger}$ values for the same changes are −70, −16, and −29 J mol^{-1} K^{-1}, respectively.[17]

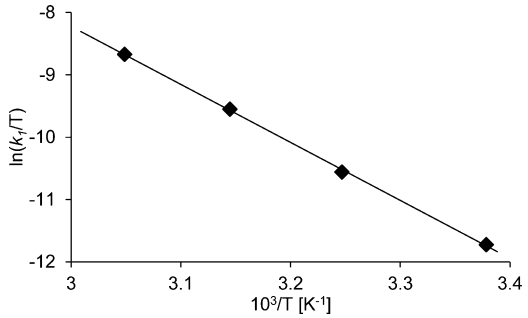

Figure 4. Eyring plot for conformational changes of conformer $\mathbf{6}_{syn}$ in $CDCl_3$.

From these values, the activation free energies at 298 K were calculated to be 65−80 kJ mol^{-1}. A comparison of the $\Delta G^{\ddagger}$ values of these two compounds indicates that it is far more difficult for the iodo group than for the methoxy group to pass through the calixarene ring.

The enthalpy and entropy differences between conformers $\mathbf{6}_{syn}$ and $\mathbf{6}_{anti}$ were determined, using a van't Hoff plot, to be ΔH = 11.5 kJ mol^{-1} and ΔS = 17.0 J mol^{-1} K^{-1}, respectively (Figure 5). These values enabled us to calculate the free energy difference between the conformers, giving ΔG = 6.44 kJ mol^{-1} at 298 K. This value falls within the range of the ΔG values (5.4−9.2 kJ mol^{-1}) between two of the four conformers of tetra-*O*-methylcalix[4]arene.[18] It is therefore concluded that

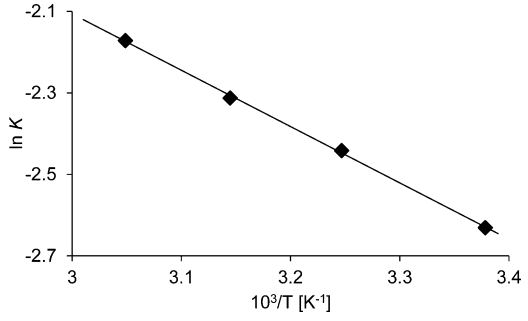

Figure 5. van't Hoff plot for equilibrium between conformers $\mathbf{6}_{syn}$ and $\mathbf{6}_{anti}$ in $CDCl_3$.

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J. Org. Chem. 2015, 80, 1070−1081

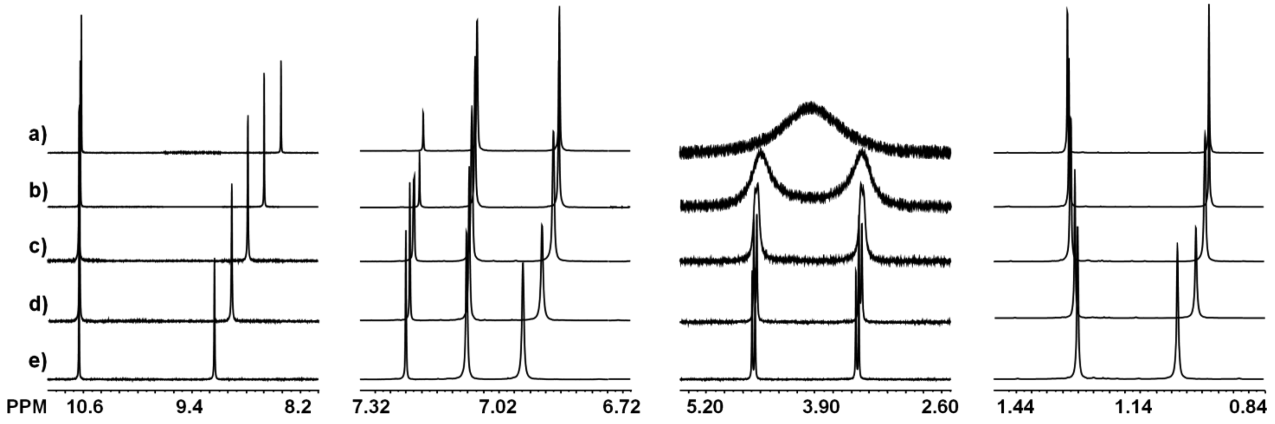

Figure 6. ^{1}H NMR spectra of 1,3-dialdehyde **16** in $CDCl_3$ at (a) 333 K, (b) 313 K, (c) 293 K, (d) 273 K, and (e) 253 K.

despite the slow interconversion rate, the difference between the conformational stabilities of conformers $\mathbf{6}_{syn}$ and $\mathbf{6}_{anti}$ is comparable to those among the four conformers of tetra-*O*-methylcalix[4]arene.

The ^{1}H NMR spectrum of dialdehyde **16** in $CDCl_3$ showed two singlets (18H each) for the *tert*-butyl protons, a pair of doublets (4H each) for the bridging methylene protons, two singlets (4H each) for the aryl protons, and one singlet (2H) for the formyl protons; the magnetic equivalences suggest a C_{2v}-symmetric structure, i.e., a cone or 1,3-alternate conformation. The hydroxy protons resonated in a low magnetic field at 9.14 ppm, which suggests the formation of intramolecular hydrogen bonds with neighboring carbonyl oxygens. This was supported by the fact that the C═O stretching vibration of dialdehyde **16** appeared at a wavenumber (1674 cm^{-1}) lower than that of the O-methylated derivative **13** (1682 cm^{-1}) in IR spectra recorded in chloroform. These observations indicate that dialdehyde **16** adopts a cone conformation in solution. To obtain further information on the intramolecular hydrogen bonds between the hydroxy and formyl groups, X-ray crystallographic analysis was performed on a single crystal obtained by slow vapor diffusion of ethyl acetate into a chloroform solution of dialdehyde **16**. It was found that dialdehyde **16** adopts a highly symmetric cone conformation and an ethyl acetate molecule is included in the cavity. However, severe disorder between the formyl and hydroxy groups prevented us from analyzing the intramolecular hydrogen bonds. In variable-temperature NMR analysis, the methylene signals, which split into two doublets near and below room temperature, approached each other with increasing temperature and coalesced at about 333 °C, but the other signals did not change their peak shapes (Figure 6). This observation can be explained by self-exchange between the two equivalent species with a cone conformation via the through-the-annulus rotation of the hydroxy and formyl groups.[19] The rate constants k for the exchange process were determined using the complete-line-shape method (Figure 7);[20] at each temperature, the simulation was in reasonable agreement with the recorded spectrum. Based on an Eyring plot, the activation enthalpy and entropy were determined to be $\Delta H^{\ddagger}$ =71.3 kJ mol^{-1} and $\Delta S^{\ddagger}$ = 27.2 J mol^{-1} K^{-1}, respectively (Figure 8). The activation free energy at 298 K was therefore calculated to be $\Delta G^{\ddagger}$ = 63.2 kJ mol^{-1}. This $\Delta G^{\ddagger}$ value was a little smaller than that reported for self-exchange between the cone conformers of calixarene **1** (68.7 kJ mol^{-1}),[21] indicating that the replacement of the two distal hydroxy groups of **1** with formyl groups decreases the activation free energy of the through-the-annulus rotation of the lower-rim substituents. This is probably because of the weakness of the circular hydrogen-bond network of dialdehyde **16**.

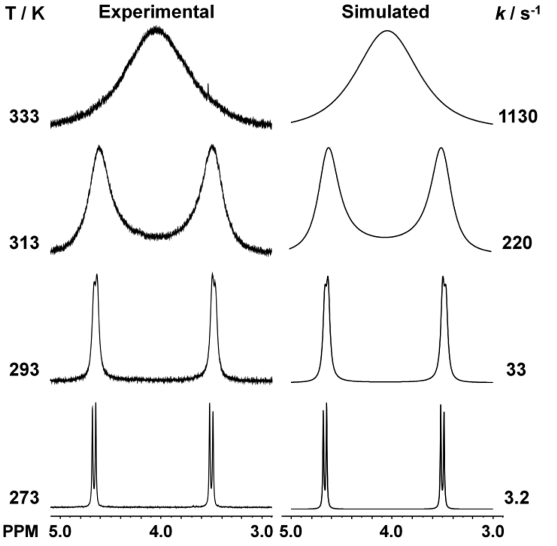

Figure 7. Experimental and simulated ^{1}H NMR signals of methylene protons of 1,3-dialdehyde **16** as functions of temperature.

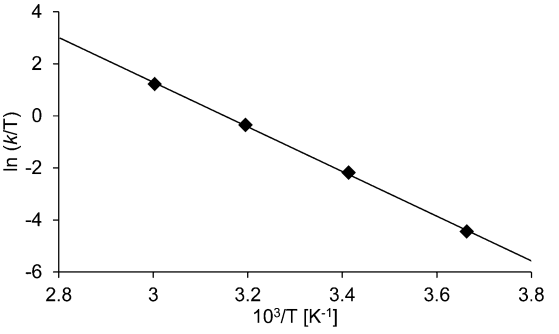

Figure 8. Eyring plot for conformational changes of 1,3-dialdehyde **16** in $CDCl_3$.

The ^{1}H NMR spectrum of dicarboxylic acid **11** exhibited two singlets (18H each) for the *tert*-butyl protons, two singlets (4H each) for the aryl protons, and a pair of doublets (4H each) for the bridging methylene protons; the magnetic equivalences suggest a C_{2v}-symmetric structure, i.e., a cone or 1,3-alternate conformation. X-ray structural analysis of a single crystal, which

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J. Org. Chem. 2015, 80, 1070−1081

was prepared by slow diffusion of hexane vapor into a solution of dicarboxylic acid **11** in ethyl acetate, revealed that the compound adopts a pinched-cone conformation (Figure 9). An

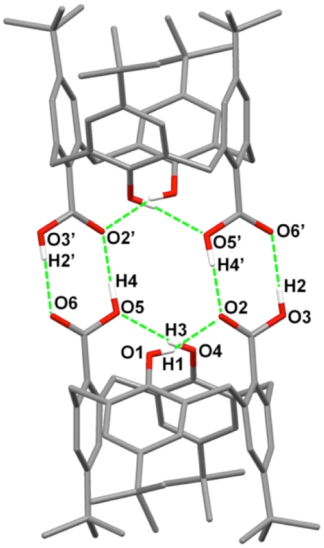

Figure 9. X-ray structure of 1,3-dicarboxylic acid **11**. Hydrogen atoms except for those in HO groups and solvent molecules are omitted for clarity. Selected distances and angles: O1−H1 = 0.749 Å, H1···O2 = 1.984 Å, O1···O2 = 2.693 Å, O1−H1···O2 = 158.33°, O4−H3 = 0.772 Å, H3···O5 = 2.074 Å, O4···O5 = 2.826 Å, O4−H3···O5 = 164.50°, O3−H2 = 0.811 Å, H1···O6′ = 1.892 Å, O3···O6′ = 2.699 Å, O3−H2···O6′ = 172.66°, O5−H4 = 0.919 Å, H4···O2′ = 1.707 Å, O5···O2′ = 2.626 Å, O5−H4···O2′ = 178.52°.

intramolecular hydrogen bond is observed between adjacent hydroxy and carboxy groups. Furthermore, intermolecular hydrogen bonds are created between the carboxy groups of two calixarene molecules, through which the two molecules are connected in a tail-to-tail manner to form a dimer. Unlike dialdehyde **16**, dicarboxylic acid **11** did not exhibit any significant changes in variable-temperature NMR analysis, regardless of the solvent used. This, combined with the X-ray structure, suggests that dicarboxylic acid **11** also forms a dimer in solution, having a structure similar to that observed in the crystal, with the aid of intra- and intermolecular hydrogen bonds.

CONCLUSION

We have established a highly efficient method for the preparation of 1,3-diiodide **6** via a catalytic Ullmann-type iodination. The compound served as a useful precursor of dicarboxylic acid **11**, dialdehyde **16**, and *anti*-1,3-dialkylcalixarenes **19**. This strongly suggests that diiodide **6** has great potential as an intermediate for synthesis of a library of various X,O-hybrid calix[4]arenes. The information on the conformational behaviors of diiodide **6**, dicarboxylic acid **11**, and dialdehyde **16** obtained in this study will be useful in using these compounds as host molecules and as building blocks for designing more elaborate host molecules. Further studies on the performance of dicarboxylic acid **11** as a metal extractant and the development of ion sensors using dialdehyde **16** as a building block are in progress.

EXPERIMENTAL SECTION

General. Melting points were taken with a micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with tetramethylsilane as an internal standard and $CDCl_3$ as a solvent unless otherwise noted. Silica gel (63−200 μm) was used for column chromatography and TLC. Water- and air-sensitive reactions were routinely carried out under nitrogen. Toluene and hexane were distilled from sodium diphenyl ketyl. DMF and DBU were distilled from calcium hydride. *N*-Formylpiperidine was distilled after drying over molecular sieves 4A. Dry THF and dry diethyl ether were used as purchased. Bistriflate **2a** was prepared according to the literature procedure.[5a]

Typical Procedure for Iodination of 1,3-Bistriflate 2a (Entry 20 in Table 1). A suspension of 1,3-bistriflate **2a** (200 mg, 0.219 mmol), CuI (42.3 mg, 0.222 mmol), NaI (131 mg, 1.18 mmol), and DBU (d = 1.02; 65.5 μL, 0.438 mmol) in toluene (10 mL) was stirred at 35 °C for 12 h. After cooling, the mixture was dissolved by addition of saturated aqueous NH_4Cl (10 mL), 2 M HCl (20 mL), and chloroform (30 mL). After the two layers were separated, the aqueous layer was extracted with chloroform. The combined organic layer was washed with saturated aqueous Na_2SO_3, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with chloroform−hexane (1:1) as an eluent to give diiodide **6** (157 mg, 83%) and monotriflate **8** (8.8 mg, 5%).

*5,11,17,23-Tetra-tert-butyl-26,28-diiodopentacyclo-[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 (**6**).* Colorless powder, mp 239−241 °C; IR (KBr) 3514, 2959, 2905, 2866, 1481, 1439, 1393, 1362, 1003, 872 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.05 (s, 18H), 1.33 (s, 18H), 3.89 (d, 4H, J = 14.6 Hz), 4.03 (s, 2H), 4.15 (d, 2H, J = 14.6 Hz), 6.92 (s, 4H), 7.20 (s, 4H); ^{13}C NMR (100 MHz) δ 31.3, 32.0, 34.3, 45.7, 103.2, 126.5, 127.5, 128.7, 142.1, 144.0, 150.5, 152.0; MS (FAB) m/z 869 M^{+}. Anal. Calcd for $C_{44}H_{54}I_2O_2$: C, 60.83; H, 6.27. Found: C, 60.73; H, 6.37.

Compounds **7** and **8** are known compounds. The NMR spectra of the samples are essentially identical with those reported in the literature.[6]

*5,11,17,23-Tetra-tert-butyl-25,27-diiodo-26,28-dimethoxypenta-cyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9, 11,13-(27),15,17,19(26),21,23-dodecaene (**9**).* A suspension of diiodide **6** (1.10 g, 1.27 mmol) and NaH (60% suspension in mineral oil; 400 mg, 10.0 mmol) in DMF (65 mL) was stirred at room temperature for 30 min. To the mixture was added iodomethane (d = 2.29; 1.53 mL, 24.6 mmol), and the mixture was stirred at 60 °C for 12 h. After cooling, the reaction was quenched with 2 M HCl and the mixture was extracted with chloroform. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with chloroform as an eluent to give diether **9** (1.11 g, 97%) as a colorless powder, mp 239−242 °C; IR (KBr) 2955, 2932, 2905, 2862, 2820, 1481, 1458, 1427, 1404, 1362, 1308, 1250, 1207, 1173, 1107, 1007, 868 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.77−1.48 (m, 36H), 3.09−4.54 (m, 14H), 6.44−7.56 (m, 8H); ^{13}C NMR (100 MHz) δ 30.8, 31.2, 31.3, 31.38, 31.43, 31.5, 31.6, 31.7, 33.6, 33.76, 33.82, 34.0, 34.1, 34.15, 34.19, 41.6, 42.8, 43.0, 43.6, 46.3, 46.5, 47.1, 57.5, 60.4, 61.4, 62.8, 63.4, 99.3, 101.6, 102.3, 102.6, 104.8, 105.1, 124.3, 124.6, 124.7, 125.0, 125.5, 125.6, 125.8, 125.9, 126.1, 126.2, 127.6, 128.8, 130.8, 131.3, 131.9, 134.6, 134.8, 135.5, 135.8, 142.8, 142.9, 143.0, 143.6, 143.8, 144.3, 144.6, 144.9, 145.0, 145.3, 146.1, 147.8, 148.1, 148.2, 148.4, 154.9, 155.1, 156.0, 156.3; MS (FAB) m/z 896 (M + H)$^{+}$. Anal. Calcd for $C_{46}H_{58}I_2O_2$: C, 61.61; H, 6.52. Found: C, 61.67; H, 6.60.

*5,11,17,23-Tetra-tert-butyl-26,28-dimethoxypentacyclo-[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-dicarboxylic Acid (**10**).* To a stirred solution of compound **9** (1.00 g, 1.12 mmol) in dry THF (60 mL) was added dropwise butyllithium (2.6 M in hexane; 1.3 mL, 3.4 mmol) at −78 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. Then, CO_2 was bubbled into the mixture via a needle for 3 h. The reaction was quenched with 2 M HCl, and the two layers were separated. The aqueous layer was

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extracted with chloroform, and the combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from hexane−ethyl acetate to give dicarboxylic acid **10** (558 mg). The mother liquid was evaporated, and the residue was purified by column chromatography with hexane−ethyl acetate (1:1) as an eluent to give an additional crop of dicarboxylic acid **10** (10.4 mg) for a total yield of 568 mg (70%) as a colorless powder, mp 305−307 °C; IR (KBr) 3214, 3067, 2967, 2909, 2870, 2839, 2500, 2481, 2427, 2369, 2346, 1748, 1605, 1489, 1462, 1416, 1393, 1362, 1346, 1296, 1204, 1107, 984, 876 cm^{-1}; ^1H NMR (400 MHz) δ 0.85 (s, 18H), 1.35 (s, 18H), 3.55 (d, 4H, J = 13.8 Hz), 3.96 (s, 6H), 4.29 (d, 4H, J = 13.8 Hz), 6.68 (s, 4H), 7.24 (s, 4H), 11.64 (br s, 2H); ^{13}C NMR (100 MHz) δ 30.9, 31.9, 34.4, 34.7, 35.2, 63.4, 125.6, 127.0, 129.0, 135.0, 137.7, 148.8, 152.1, 153.4, 169.8; MS (FAB) m/z 756 $(M + Na)^+$. Anal. Calcd for $C_{48}H_{60}O_6$: C, 78.65; H, 8.25. Found: C, 78.63; H, 8.37.

*5,11,17,23-Tetra-tert-butyl-26,28-dihydroxypentacyclo-[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-dicarboxylic Acid (**11**).* To a solution of *O*-methyl-protected diacid **10** (200 mg, 0.273 mmol) in acetic acid (15 mL) was added 8.8 M HBr (15 mL, 132 mmol), and the mixture was refluxed for 4 h. After cooling, the mixture was extracted with chloroform, and the extract was washed with saturated aqueous Na_2SO_3, dried over $MgSO_4$, and evaporated to leave a residue (195 mg), which was dissolved by addition of THF (10 mL) and ethanol (10 mL). To the solution was added 2 M NaOH (17.5 mL), and the mixture was refluxed for 14 h. After cooling, the mixture was quenched with 2 M HCl and the two layers were separated. The aqueous layer was extracted with chloroform, and the combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from hexane−ethyl acetate to give 1,3-dicarboxylic acid **11** (127 mg). The mother liquid was evaporated, and the residue was purified by column chromatography with ethyl acetate as an eluent to give an additional crop of diacid **11** (19.3 mg) for a total yield of 146 mg (76%) as a colorless powder, mp 293−297 °C (decomp); IR (KBr) 3220, 2963, 2868, 1670, 1489, 1362, 1292, 1269, 1234, 1209, 963, 874 cm^{-1}; ^1H NMR (400 MHz; acetone-d_6) δ 0.93 (s, 18H), 1.32 (s, 18H), 3.53 (d, 4H, J = 13.3 Hz), 4.50 (d, 4H, J = 13.3 Hz), 6.93 (s, 4H), 7.21 (s, 4H), 9.54 (br, 2H); ^{13}C NMR (100 MHz; acetone-d_6) δ 30.0, 32.1, 34.4, 34.8, 36.1, 126.3, 126.5, 128.3, 128.5, 139.8, 141.4, 152.5, 174.2; MS (FAB) m/z 728 $(M + Na)^+$. Anal. Calcd for $C_{46}H_{58}O_7$ (**15**·H_2O): C, 76.42; H, 8.09. Found: C, 76.28; H, 7.84.

In a separate run, the reaction mixture obtained by the acid treatment of compound **10** (vide supra) was purified by column chromatography with dichloromethane−ethyl acetate (50:1) as an eluent to give the following lactone.

*4,4′:7,7′-Dimethylenebis(2,9-di-tert-butyldibenzo[b,e]oxepin-6-(11H)-one) (**12**).* Colorless powder, mp >360 °C; IR (KBr) 2962, 2905, 2870, 1740, 1606, 1479, 1364, 1293, 1272, 1242, 1187, 1121, 1045, 868, 729 cm^{-1}; ^1H NMR (400 MHz) δ 1.25 (s, 18H), 1.27 (s, 18H), 3.40 (d, 2H, J = 13.9 Hz), 3.59 (d, 2H, J = 13.3 Hz), 4.19 (d, 2H, J = 13.9 Hz), 5.44 (d, 2H, J = 13.3 Hz), 6.94−7.02 (m, 4H), 7.40 (d, 2H, J = 2.2 Hz), 7.54 (d, 2H, J = 1.5 Hz); ^{13}C NMR (100 MHz) δ 31.0, 31.1, 31.3, 34.3, 34.8, 38.8, 121.7, 123.5, 124.9, 126.3, 126.9, 131.4, 131.6, 142.4, 142.7, 146.1, 147.7, 154.8, 164.8; MS (FAB) m/z 692 $(M + Na)^+$; HRMS (ESI-FTICR) calcd for $C_{46}H_{52}O_4$ $(M + Na)^+$ 691.3763, found 691.3758.

Typical Procedure for Formylation of O-Methylated 1,3-Diiodide 9 (Entry 12 in Table 2). To a suspension of compound **9** (1.00 g, 1.12 mmol) and molecular sieves 4A (1.00 g) in dry diethyl ether (30 mL) was added dropwise butyllithium (2.6 M in hexane; 1.3 mL, 3.4 mmol) at −78 °C with stirring. The mixture was allowed to warm to 0 °C and stirred at this temperature for 1 h. To the mixture was added *N*-formylpiperidine (1.3 mL, 11.7 mmol), and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with 2 M HCl and the two layers were separated. The aqueous layer was extracted with chloroform, and the combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with hexane−ethyl acetate (5:1) as an eluent to give dialdehyde **13** (475 mg, 60%) and monoaldehyde **14** (271 mg, 36%).

*5,11,17,23-Tetra-tert-butyl-26,28-dimethoxypentacyclo-[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-dicarbaldehyde (**13**).* Colorless powder, mp 296−299 °C; IR (KBr) 2959, 1686, 1605, 1362, 1485, 1223, 1203, 1011, 876 cm^{-1}; ^1H NMR (400 MHz) (a 6:5 equilibrium mixture of two conformers) δ 0.96 (br, 18H, the major conformer), 1.15 (s, 18H, the major conformer), 1.30 (s, 18H, the major conformer), 1.36 (s, 18H, the major conformer), 3.20 (s, 6H, the major conformer), 3.45 (br d, 4H, the major conformer), 3.68 (s, 6H, the major conformer), 3.76 (br d, 4H, the major conformer), 4.21 (br d, 4H, the major conformer), 4.43 (br d, 4H, the major conformer), 6.81 (br s, 4H, the major conformer), 7.00 (s, 4H, the major conformer), 7.16 (s, 4H, the major conformer), 7.18 (s, 4H, the major conformer), 9.89 (s, 2H, the minor conformer), 10.77 (br, 2H, the major conformer); ^{13}C NMR (100 MHz) δ 30.6, 30.8, 31.5, 33.6, 34.1, 34.17, 34.19, 34.3, 36.1, 59.4, 60.8, 125.3, 125.9, 126.0, 126.8, 131.6, 132.3, 134.2, 135.0, 140.3, 140.6, 146.4, 146.7, 152.7, 154.4, 154.9, 196.9, 198.4; MS (FAB) m/z 723 $(M + Na)^+$. Anal. Calcd for $C_{48}H_{60}O_4$: C, 82.24; H, 8.63. Found: C, 82.07; H, 8.71.

*5,11,17,23-Tetra-tert-butyl-26,28-dimethoxypentacyclo-[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-carbaldehyde (**14**).* Colorless powder, mp 177−179 °C; IR (KBr) 2959, 1690, 1601, 1481, 1362, 1207, 1111, 1011, 872, 721 cm^{-1}; ^1H NMR (400 MHz) (a 2:1 equilibrium mixture of two conformers) δ 1.00−1.45 (br, 36H, the minor conformer), 1.18 (s, 9H, the major conformer), 1.27 (s, 9H, the major conformer), 1.33 (s, 18H, the major conformer), 2.00−4.66 (m, 14H each, the major and minor confomers), 6.20 (s, 1H, the major conformer), 6.67−7.42 (m, 8H each, the major and minor confomers), 10.33 (s, 1H, the major conformer); ^{13}C NMR (100 MHz) δ 29.7, 31.1, 31.3, 31.4, 31.5, 34.0, 34.1, 34.43, 34.47, 34.52 34.6, 60.2, 122.8, 123.3, 125.4, 134.3, 142.0, 150.5, 153.4, 198.9; MS (FAB) m/z 674 $(M + H)^+$. Anal. Calcd for $C_{47}H_{60}O_3$: C, 83.88; H, 8.99. Found: C, 83.85; H, 9.22.

*5,11,17,23-Tetra-tert-butyl-25,27-dimethoxypentacyclo-[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 (**15**).* Colorless powder, mp 231−233 °C; IR (KBr) 2959, 2461, 1601, 1481, 1362, 1254, 1207, 1011, 880, 714 cm^{-1}; ^1H NMR (400 MHz) (a 5:1 equilibrium mixture of two conformers) δ 1.14 (s, 18H, the major conformer), 1.17 (s, 18H, the minor conformer), 1.35 (s, 18H, the minor conformer), 1.37 (s, 18H, the major conformer), 3.01 (s, 6H, the major conformer), 3.20 (s, 6H, the minor conformer), 3.59 (d, 4H, the major conformer, J = 15.0 Hz), 3.71 (d, 4H, the minor conformer, J = 15.8 Hz), 4.14 (d, 4H, the minor conformer, J = 15.8 Hz), 4.18 (d, 4H, the major conformer, J = 15.0 Hz), 5.95 (s, 2H, the minor conformer), 6.30 (s, 2H, the major conformer), 6.90 (s, 4H, the major conformer), 6.93 (s, 4H, the minor conformer), 7.13 (s, 4H, the minor conformer), 7.16 (s, 4H, the major conformer); ^{13}C NMR (100 MHz) δ 31.3, 31.5, 34.0, 34.1, 34.4, 34.5, 35.8, 37.3, 60.6, 61.3, 122.9, 123.7, 126.0, 126.7, 127.3, 132.2, 133.4, 141.5, 142.2, 146.2, 146.7, 150.1, 150.6, 153.9, 154.9; MS (FAB) m/z 644 M^+; HRMS (ESI-FTICR) calcd for $C_{46}H_{60}O_2$ $(M + Na)^+$ 667.4491, found 667.4486.

*5,11,17,23-Tetra-tert-butyl-26,28-dihydroxypentacyclo-[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-dicarbaldehyde (**16**).* To a solution of 1-octanethiol (592 μL, 3.41 mmol) in DMF (12 mL) was added sodium hydride (60 wt % in mineral oil, 92.2 mg, 2.31 mmol) at 0 °C, and the mixture was stirred at 50 °C for 1 h. To the mixture was added diether **13** (201 mg, 0.286 mmol), and the mixture was stirred at 130 °C for 1 h. After cooling, the reaction was quenched with 2 M HCl and the mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was crystallized from hexane−ethyl acetate to give hydroxy-free dialdehyde **16** (163 mg). The mother liquid was evaporated and the residue was purified by TLC with hexane−ethyl acetate (5:1) as a developer to give an additional crop of dialdehyde **16** (10.7 mg) for a total yield of 174 mg (91%) as a colorless powder, mp 227−228 °C; IR (KBr) 3244, 2959, 1678, 1605, 1489, 1362, 1281, 1223, 876, 775,

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679 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.95 (s, 18H), 1.30 (s, 18H), 3.47 (d, 4H, J = 11.0 Hz), 4.64 (d, 4H, J = 11.0 Hz), 6.90 (s, 4H), 7.11 (s, 4H), 8.79 (s, 2H), 10.64 (s, 2H); ^{13}C NMR (100 MHz) δ 30.4, 31.7, 33.9, 34.1, 34.5, 125.6, 126.3, 126.4, 128.4, 141.8, 142.0, 150.8, 155.3, 197.3; MS (FAB) m/z 672 M$^+$. Anal. Calcd for $C_{46}H_{56}O_4$: C, 82.10; H, 8.39. Found: C, 81.93; H, 8.51.

Typical Procedure for Etherification of 1,3-Diiodide 6 (Entry 1 in Table 2). A suspension of diiodide **6** (50.3 mg, 57.9 μmol) and NaH (60% suspension in mineral oil; 18.4 mg, 0.460 mmol) in DMF (3 mL) was stirred at room temperature for 30 min. To the mixture was added 1-bromopropane (d = 1.35; 105 μL, 1.15 mmol), and the mixture was stirred at 60 °C for 12 h. The reaction was quenched with 2 M HCl, and the mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by TLC with chloroform−hexane (2:5) as a developer to give dipropyl ether **17** as a mixture of stereoisomers (53.6 mg, 97%). The ratio of the stereoisomers was determined to be 55:35:10 (**17a**/**17b**/syn isomers) by ^{1}H NMR analysis.

Each stereoisomer of **17a** and **17b** could be enriched by crystallization. Thus, the same reaction was carried out using the diiodide **6** (1.00 g, 1.15 mmol) to give a crude mixture of stereoisomers (1.11 g, **17a**/**17b**/syn isomers = 52:36:12). It was crystallized from chloroform−methanol to give **17a**-enriched crystals (706 mg, **17a**/**17b**/syn isomers = 77:14:9), which were further recrystallized twice from the same solvent to give compound **17a** with 88% purity (508 mg, 46%, **17a**/**17b**/syn isomers = 88:3:9). On the other hand, the mother liquid of the first crystallization was evaporated to leave a residue, which was recrystallized twice from chloroform−methanol to give compound **17b** with 96% purity (207 mg, 19%, **17a**/**17b** = 4:96).

Similarly, a crude mixture of stereoisomers (699 mg, **18a**/**18b**/syn isomers = 53:44:3) obtained by carrying out the etherification of diiodide **6** (500 mg, 0.576 mmol) with 2-bromopropane on a preparative scale was recrystallized twice from chloroform−methanol to give compound **18a** with 87% purity (290 mg, 53%, **18a**/**18b**/syn isomers = 87:8:5). The mother liquid of the first crystallization was evaporated and the residue was recrystallized twice from chloroform−methanol to give compound **18b** with 98% purity (94.8 mg, 17%, **18a**/**18b** = 2:98).

*5,11,17,23-Tetra-tert-butyl-25,27-diiodo-26,28-dipropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Diiodo Isomer with a Partial Cone Conformation (**17a**).* Colorless powder, 88% purity, mp 348−350 °C; IR (KBr) 2961, 2931, 2907, 2874, 1478, 1437, 1391, 1362, 1198, 1040, 1005, 873 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.05 (s, 18H), 1.12 (t, 6H, J = 14.8 Hz), 1.35 (s, 9H), 1.39 (s, 9H), 1.78−1.90 (m, 2H), 1.93−2.07 (m, 2H), 3.55 (d, 2H, J = 12.9 Hz), 3.56 (t, 2H, J = 15.0 Hz), 3.73 (d, 2H, J = 13.3 Hz), 3.78 (t, 2H, J = 15.0 Hz), 4.09 (d, 2H, J = 13.3 Hz), 4.10 (d, 2H, J = 12.9 Hz), 6.59 (d, 2H, J = 2.5 Hz), 7.12 (s, 2H), 7.34 (d, 2H, J = 2.5 Hz), 7.39 (s, 2H); ^{13}C NMR (100 MHz) δ 11.3, 24.1, 31.3, 31.4, 31.7, 33.8, 34.19, 34.23, 41.6, 44.6, 76.9, 102.2, 103.1, 124.3, 125.8, 128.8, 129.3, 130.0, 130.4, 142.6, 142.8, 146.7, 147.2, 149.4, 154.0; MS (FAB) m/z 952 M$^+$. Anal. Calcd for $C_{50}H_{66}I_2O_2$: C, 63.02; H, 6.98. Found: C, 63.19; H, 7.15.

*5,11,17,23-Tetra-tert-butyl-25,27-diiodo-26,28-dipropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Diiodo Isomer with a 1,2-Alternate Conformation (**17b**).* Colorless powder, 96% purity, mp 210−212 °C; IR (KBr) 2959, 2953, 2905, 2872, 1479, 1472, 1433, 1393, 1362, 1283, 1200, 1109, 1044, 1009, 964, 868 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.70 (t, 6H, J = 13.5 Hz), 1.24 (s, 18H), 1.32 (s, 18H), 3.21−3.28 (m, 2H), 3.29−3.37 (m, 2H), 3.52 (d, 2H, J = 13.1 Hz), 3.78 (t, 2H), 3.86 (d, 2H, J = 15.8 Hz), 4.09 (t, 2H), 4.16 (d, 2H, J = 15.8 Hz), 4.25 (d, 2H, J = 13.1 Hz), 6.98 (d, 2H, J = 2.4 Hz), 7.10 (d, 2H, J = 2.5 Hz), 7.13 (d, 2H, J = 2.5 Hz), 7.24 (d, 2H, J = 2.4 Hz); ^{13}C NMR (100 MHz) δ 10.2, 22.5, 31.4, 31.5, 34.0, 34.1, 41.7, 46.6, 76.0, 103.1, 125.5, 125.7, 126.5, 128.7, 130.9, 133.0, 142.4, 144.2, 144.6, 148.1, 154.0; MS (FAB) m/z 952 M$^+$. Anal. Calcd for $C_{50}H_{66}I_2O_2$: C, 63.02; H, 6.98. Found: C, 63.02; H, 7.04.

*5,11,17,23-Tetra-tert-butyl-25,27-diiodo-26,28-diisopropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Diiodo Isomer with a Partial Cone Conformation (**18a**).* Colorless powder, 87% purity, mp 231−233 °C; IR (KBr) 2965, 2924, 2866, 2361, 2332, 1478, 1464, 1437, 1424, 1364, 1198, 1136, 1107, 1005, 945, 872 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.05 (s, 18H), 1.26 (d, 6H, J = 6.1 Hz), 1.36 (s, 9H), 1.41 (s, 9H), 1.44 (d, 6H, J = 6.1 Hz), 3.55 (d, 2H, J = 13.0 Hz), 3.69 (d, 2H, J = 13.3 Hz), 3.90 (m, 2H), 4.03 (d, 2H, J = 13.0 Hz), 4.15 (d, 2H, J = 13.3 Hz), 6.58 (d, 2H, J = 2.5 Hz), 7.12 (s, 2H), 7.32 (d, 2H, J = 2.5 Hz), 7.43 (s, 2H); ^{13}C NMR (100 MHz) δ 22.6, 23.1, 31.3, 31.4, 31.8, 33.7, 34.2, 42.3, 45.0, 77.1, 102.4, 103.4, 124.2, 125.7, 128.6, 128.9, 130.7, 130.9, 142.4, 142.6, 146.7, 147.1, 149.3, 152.5; MS (FAB) m/z 952 M$^+$; HRMS (ESI-FTICR) calcd for $C_{50}H_{66}I_2O_2$ (M + Na)$^+$ 975.3050, found 975.3044.

*5,11,17,23-Tetra-tert-butyl-25,27-diiodo-26,28-diisopropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Diiodo Isomer with a 1,2-Alternate Conformation (**18b**).* Colorless powder, 98% purity, mp 261−263 °C; IR (KBr) 2965, 2930, 2903, 2866, 1479, 1464, 1433, 1379, 1364, 1236, 1198, 1142, 1109, 1105, 941, 868 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.55 (d, 6H, J = 6.1 Hz), 1.14 (d, 6H, J = 6.1 Hz), 1.25 (s, 18H), 1.30 (s, 18H), 3.52 (d, 2H, J = 13.1 Hz), 3.64 (m, 2H), 3.83 (d, 2H, J = 15.8 Hz), 4.19 (d, 2H, J = 15.8 Hz), 4.28 (d, 2H, J = 13.1 Hz), 7.00 (d, 2H, J = 2.4 Hz), 7.10 (d, 2H, J = 2.2 Hz), 7.11 (d, 2H, J = 2.2 Hz), 7.21 (d, 2H, J = 2.4 Hz); ^{13}C NMR (100 MHz) δ 21.9, 22.3, 31.4, 31.5, 34.0, 42.3, 47.0, 75.6, 103.0, 125.6, 127.2, 128.4, 131.1, 133.5, 142.2, 143.6, 144.5, 148.1, 152.2; MS (FAB) m/z 952 M$^+$. Anal. Calcd for $C_{50}H_{66}I_2O_2$: C, 63.02; H, 6.98. Found: C, 62.91; H, 7.01.

*25,27-Dibutyl-5,11,17,23-tetra-tert-butyl-26,28-dipropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Dibutyl Isomer with a Partial Cone Conformation (**19a**).* To a suspension of *anti*-1,3-diiodide **17a** (83% purity; 50.2 mg, 43.8 μmol) in dry hexane (1.5 mL) was added dropwise butyllithium (1.6 M in hexane; 98.0 μL, 0.154 mmol) at −78 °C with stirring, and the mixture was gradually warmed to 40 °C over a period of 1 h and stirred for a further 1 h at this temperature. After cooling, 1-iodobutane (d = 1.62; 59.8 μL, 0.525 mmol) was added to the mixture, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with 2 M HCl, and the mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography with chloroform−hexane (2:5) as an eluent to give anti-1,3-dibutylated compound **19a** (29.7 mg). ^{1}H NMR analysis of the sample revealed that it contained 8% (w/w) of 1-butyl-3-iodocalix[4]arene, and therefore the yield of compound **19a** was calculated to be 27.3 mg (77%). The monobutylated compound could be removed from the sample as follows: The above-mentioned reaction was repeated several times to give a sample of compound **19a** (99.4 mg) containing 7% (w/w) of 1-butyl-3-iodocalix[4]arene. The sample was dissolved in dry THF and cooled to −78 °C. To the solution was added dropwise butyllithium (2.6 M in hexane; 47.0 μL, 122 μmol), and the mixture was allowed to warm to room temperature. After stirring for 1 h, the reaction was quenched with 2 M HCl, and the mixture was extracted with chloroform. The extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by TLC with chloroform−hexane (2:5) as a developer, and the desired fraction was crystallized from chloroform−methanol to give compound **19a** (57.8 mg, 63% based on **19a** used for purification) as a colorless powder with >99% purity, mp 299−301 °C; IR (KBr) 2961, 2936, 2872, 1479, 1458, 1362, 1196, 1009, 872 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.73−0.86 (m, 6H), 1.01 (t, 6H, J = 14.9 Hz), 0.97−1.07 (m, 2H), 1.05 (s, 18H), 1.13−1.26 (m, 6H), 1.34 (s, 9H), 1.41 (s, 9H), 1.81−1.94 (m, 6H), 2.01 (m, 2H), 3.21 (d, 2H, J = 12.8 Hz), 3.55 (m, 2H), 3.63 (d, 2H, J = 14.0 Hz), 3.85 (m, 2H), 3.89 (d, 2H, J = 14.0 Hz), 4.06 (d, 2H, J = 12.8 Hz), 6.78 (d, 2H, J = 2.3 Hz), 6.89 (d, 2H, J = 2.3 Hz), 7.06 (s, 2H), 7.23 (s, 2H); ^{13}C NMR (100 MHz) δ 10.6, 14.5, 14.6, 23.3, 23.7, 23.9, 24.5, 26.4, 31.2, 31.4, 31.6, 32.5, 33.3, 33.7, 34.0, 34.1, 34.8, 40.4, 76.8, 124.8, 126.0, 126.4, 128.1, 133.4, 133.9, 137.8, 138.0, 138.4, 140.9, 144.0 144.7, 146.8, 153.1; MS (FAB) m/z 812 M$^+$; HRMS

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J. Org. Chem. 2015, 80, 1070−1081

(ESI-FTICR) calcd for $C_{58}H_{84}O_2$ $(M + Na)^+$ 835.6369, found 835.6364.

*25,27-Dibutyl-5,11,17,23-tetra-tert-butyl-26,28-dipropoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octa-cosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene, anti-Dibutyl Isomer with a 1,2-Alternate Conformation (**19b**).* This compound was prepared by a similar procedure to that used for the preparation of compound **19a**. To a solution of *anti*-1,3-diiodide **17b** (95% purity; 51.0 mg, 50.9 μmol) in dry diethyl ether (1.5 mL) was added dropwise butyllithium (1.6 M in hexane; 98.0 μL, 0.154 mmol) at −78 °C, and the mixture was stirred at 0 °C for 1 h. To the mixture was added 1-iodobutane (*d* = 1.62; 59.8 μL, 0.525 mmol), and the resulting mixture was allowed to warm to room temperature and stirred for 3 h. After the workup, the crude product was purified by column chromatography with chloroform−hexane (2:5) as an eluent to give anti-1,3-dibutylated compound **19b** (16.9 mg). ^{1}H NMR analysis of the sample revealed that it contained 4% (w/w) of monobutylated compound, and therefore the yield of compound **19b** was calculated to be 16.2 mg (36%). Further purification of the sample (41.8 mg, containing 5% (w/w) of 1-butyl-3-iodocalix[4]arene) by the reduction of the byproduct, followed by TLC, and subsequent crystallization (vide supra) gave compound **19b** (22.6 mg, 57% based on **19b** used for purification) as a colorless powder with >99% purity, mp 266−268 °C; IR (KBr) 2963, 2932, 2872, 1472, 1460, 1362, 1204, 1013, 868 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.63 (t, 6H, J = 14.9 Hz), 0.71 (t, 6H, J = 14.2 Hz), 0.77−1.20 (m, 12H), 1.27 (s, 18H), 1.30 (s, 18H), 1.72 (m, 2H), 2.28 (m, 2H), 3.29 (d, 2H, J = 12.9 Hz), 3.32 (m, 2H), 3.47 (m, 2H), 3.90 (d, 2H, J = 16.2 Hz), 3.99 (d, 2H, J = 16.2 Hz), 4.02 (d, 2H, J = 12.9 Hz), 6.97 (d, 2H, J = 2.0 Hz), 7.03 (d, 2H, J = 2.4 Hz), 7.09 (d, 2H, J = 2.0 Hz), 7.22 (d, 2H, J = 2.4 Hz); ^{13}C NMR (100 MHz) δ 10.0, 14.2, 22.3, 23.1, 26.5, 31.51, 31.53, 32.9, 33.3, 33.9, 34.0, 41.9, 75.0, 125.2, 125.7, 125.9, 126.7, 132.9, 135.1, 136.9, 137.9, 139.5, 144.7, 145.7, 153.5; MS (FAB) m/z 812 M^+; HRMS (ESI-FTICR) calcd for $C_{58}H_{84}O_2$ $(M + Na)^+$ 835.6369, found 835.6364.

Single Crystal X-ray Diffraction Studies. Single-crystal X-ray diffraction data were collected with a CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å), employing a monochromator and a fine-focus rotating anode as radiation source. Data integration and reduction were performed with the SAINT and XPREP software, and the absorption correction was performed by the semiempirical method with SADABS.[22] The structure was solved by the direct method using SHELXS-97 and refined by using least-squares methods on F^2 with SHELXL-97.[23] All calculations were performed using Yadokari-XG 2009.[24]

Data for Compound $\mathbf{6}\cdot(CH_2Cl_2)_{1.5}$. $C_{45.5}H_{57}Cl_3I_2O_2$, fw = 996.06, monoclinic, $C2/c$, a = 19.5977(17) Å, b = 22.0686(17) Å, c = 12.5591(10) Å, β = 126.4940(10)°, V = 4366.7(6) Å^3, Z = 4, T = 173(2) K, 12191 reflections measured, 4962 independent reflections, 4467 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0250, wR_2 = 0.0623 (observed), R_1 = 0.0289, wR_2 = 0.0649 (all data).

Data for Compound $\mathbf{11}\cdot CH_3CO_2C_2H_5$. $C_{50}H_{64}O_8$, fw =793.01, monoclinic, $P2_1/c$, a = 12.199(3) Å, b = 30.881(8) Å, c = 11.905(3) Å, β = 95.153(4)°, V = 4466.9(19) Å^3, Z = 4, T = 100(2) K, 24785 reflections measured, 10040 independent reflections, 6131 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0764, wR_2 = 0.1806 (observed), R_1 = 0.764, wR_2 = 0.1806 (all data).

Data for Compound $\mathbf{16}\cdot CH_3CO_2C_2H_5$. $C_{50}H_{64}O_6$, fw =761.01, tetragonal, $P4/n$, a = 12.7930(15) Å, b = 12.7930(15) Å, c = 13.1300(15) Å, V = 2148.9(4) Å^3, Z = 2, T = 100(2) K, 11953 reflections measured, 2478 independent reflections, 2097 reflections were observed ($I > 2\sigma(I)$), R_1 = 0.0891, wR_2 = 0.2362 (observed), R_1 = 0.0998, wR_2 = 0.2463 (all data).

■ ASSOCIATED CONTENT

Supporting Information

CIF files for compounds $\mathbf{6}\cdot(CH_2Cl_2)_{1.5}$, $\mathbf{11}\cdot CH_3CO_2C_2H_5$, and $\mathbf{16}\cdot CH_3CO_2C_2H_5$, derivation of eq 3, time course of $[\mathbf{6}_{anti}]/[\mathbf{6}_{syn}]$ for conformational change of conformer $\mathbf{6}_{syn}$, NMR spectral charts for the compounds synthesized, and crystal structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tanaka@orgsynth.che.tohoku.ac.jp.

*E-mail: hattori@orgsynth.che.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

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