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Proximal *O*,*O*′-capped calix[4]arenes with a disiloxane bridge as highly efficient synthetic intermediates for 1,2-dialkylation at the lower rim

Fumitaka Narumi,[a,*] Naoya Morohashi,[b] Nobuji Matsumura,[b] Nobuhiko Iki,[b] Hiroshi Kameyama[a] and Sotaro Miyano[b,*]

[a]*Department of Basic Sciences, School of Science and Engineering, Ishinomaki Senshu University, 1 Shinmito, Minamisakai, Ishinomaki 986-8580, Japan*

[b]*Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan*

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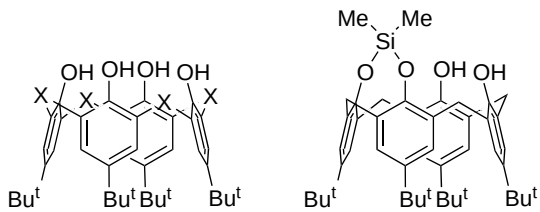
Abstract—Treatment of calix[4]arenes with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane using imidazole as a base yielded *O*,*O*′-bridged calixarenes in excellent yields, which were subsequently treated with an alkyl halide/base to give *O*″,*O*‴-dialkylated products in high yields. These were, in turn, amenable to fluoride-promoted quantitative desilylation, thus providing an efficient method for the net proximal dialkylation of calix[4]arenes at the lower rim. © 2002 Elsevier Science Ltd. All rights reserved.

In the last two decades, calix[4]arenes have been one of the most extensively investigated molecular platforms for the construction of synthetic receptors in molecular recognition and supramolecular chemistry.[1,2] This is mainly due to the synthetic availability of large quantities of the parent macrocycles, especially *p*-*tert*-butylcalix[4]arene (**C1**),[3] and their ready modifications at the phenolic hydroxy groups (lower rim) as well as at the *para* positions (upper rim) to introduce a variety of substituents to develop varying functions.[4,5] However, during the course of our study on the development of new functions of thiacalix[4]arenes (e.g. **T1**),[6–8] we realized that regioselective *O*,*O*′-difunctionalization at the neighboring phenolic hydroxy groups of the calix[4]arene class compounds has not yet been sufficiently explored, and development of a general method for such transformations would be highly desirable because they would provide very useful building blocks for the design of synthetic receptors.[9–12]

One plausible approach to accomplish the above objective may be to block two neighboring hydroxy groups out of the four by bridging them with a proper protecting unit. Although Reinhoudt and co-workers proposed *O*,*O*′-bridging by reacting **C1** with phthaloyl chloride, the yield of the bridged product was only fair (30%).[13] Furthermore, the ester functionality of the protecting unit may not always be suitable for application to proximal diesterification of the remaining hydroxy groups. In this context, a paper reported by Lattman et al. attracted our attention. They reacted **C1** with dichlorodimethylsilane/triethylamine to give *O*,*O*′-dimethylsilyl-bridged product **2** in 60% yield, which, as they had expected, should be an ideal starting material for the synthesis of 1,2-disubstituted calix[4]arenes.[14] However, treatment of **2** with BuLi/CF_3SO_3Me gave not the desired *O*″,*O*‴-dimethylated product but doubly 1,2- and 3,4-silyl-bridged calix[4]arene accompanying the formation of a tetramethoxy derivative of **C1**, seemingly via the attack of the phenoxide on one **2** on the silicon on another **2**.[14] We supposed that such kind of disproportionation might have been brought about



C1 : X = CH_2
T1 : X = S

2

Keywords: *O*,*O*′-bridged calix[4]arenes; proximal dialkylation; disyloxane.

* Corresponding authors. Tel.: +81-225-22-7716; fax: +81-225-22-7746 (F.N.); tel./fax.: 81-22-217-7262 (S.M.); e-mail: fnarumi@isenshu-u.ac.jp; miyano@orgsynth.che.tohoku.ac.jp

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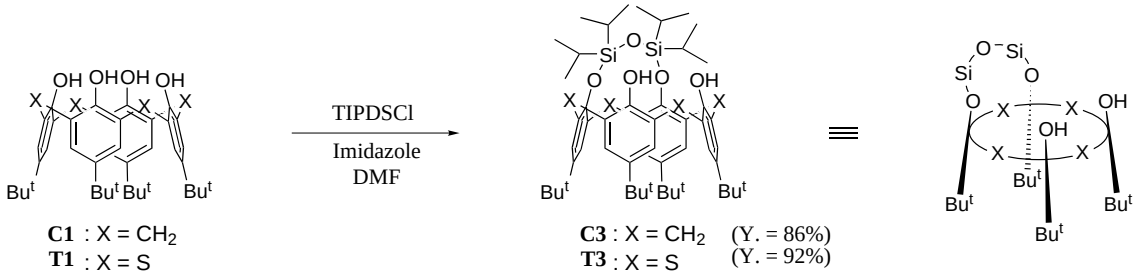
by the lability of the dimethylsilyl moiety per se as well as by the ring strain of **2**, and thus, linking of two adjacent phenolic hydroxy groups with a silyl bridge of proper chain length and robustness would make a *truly* 'ideal' *O,O′*-protected intermediate for further modification on the remaining hydroxy groups. To our pleasure, we have found that a tetraisopropyldisiloxane[15] (TIPDS) unit is a quite hopeful candidate for the *O,O′*-protection of calix[4]arenes, and herein we report a facile synthesis of proximal disiloxane-bridged calix[4]arenes **C3** and **T3** at the lower rim in excellent yields and their use as efficient synthetic intermediates for the net selective proximal dialkylation of calix[4]arenes **C1** and **T1** at the lower rim via a protection–alkylation–deprotection sequence.

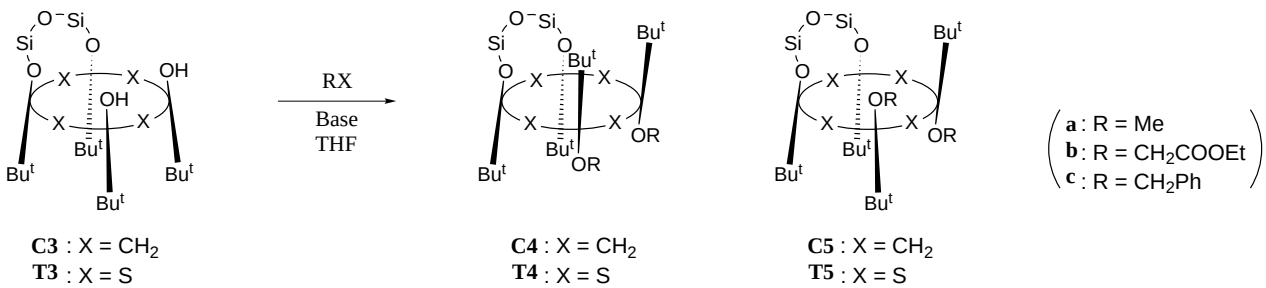
Reaction of **C1** and **T1** with an excess amount of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in the presence of imidazole in DMF for 12 h at room temperature cleanly proceeded to give the proximal disiloxane-bridged compounds **C3** and **T3** in 86 and 92% yield, respectively, after crystallization from CH_2Cl_2–MeOH (Scheme 1).[16] The identity of the former product as an intrabridged disiloxane (**C3**) is confirmed by FAB-MS (*m/z* 891 (M^+)) and ^1H NMR spectrum (500 MHz, $CDCl_3$) which showed two singlets of *tert*-butyl protons at δ 1.17 and 1.23 (each 18H) and four doublets of aryl protons at δ 6.95–7.06 (each 2H) to support the 1,2- rather than 1,3-bridged structure, as the latter should show only two kinds of singlets for the aryl protons. Furthermore, the cone conformation of **C3** was substantiated by the chemical shift difference ($\Delta\delta$) >0.9 ppm between the *exo* and *endo* geminal protons for the methylene groups between the aryl rings.[1] The proximally intrabridged structure of **T3** was also deduced from the ^1H NMR resonances of the *tert*-butyl (2×s at δ 1.16 and 1.24 (each 18H)) and aryl protons (4×d at δ 7.49–7.56 (each 2H)) as discussed for **C3**. Although **T3** lacks the bridging methylenes which have been the probe for assigning the conformation of conventional calix[4]arenes, the cone structure of **T3** was rather safely deduced by comparing the chemical shifts of the isopropyl-methyl protons of the TIPDS groups (4×d at δ 0.80–1.38 (each 6H)) with those of **C3** (4×d at δ 0.79–1.37 (each 6H)); if they had a 1,2-alternate conformation, those protons should appear in the more upfield region (ca. 0.4 ppm) because of the anisotropic deshielding effects by the 3,4-aryl nuclei (vide infra).

Although a rational explanation for the exclusive formation of the proximal *O,O′*-bridged products without any detectable amount of 1,3- or inter-bridged ones should await further investigations including X-ray structural analyses,[17] the excellent yields of the 1,2-protected compounds **C3** and **T3** without relying on high-dilution technique and/or chromatography should be quite useful from the synthetic viewpoint in calixarene chemistry as shown below.

Treatment of *O,O′*-disiloxanes **C3** and **T3** with an alkyl halide in THF in the presence of a base (Cs_2CO_3 at reflux or *tert*-BuOK at 0°C) gave the corresponding *O″,O‴*-dialkylated products in excellent yields (Scheme 2, Table 1). As an example, the reaction of **C3** with ethyl bromoacetate afforded two dialkylated products (**C4b** and **C5b**), the conformations of which were determined by ^1H and ^{13}C NMR spectra. The ^1H NMR spectra of the major component showed two singlets for the *tert*-butyl protons (δ 1.26 and 1.29 (each 18H)) and four doublets for the aromatic protons (δ 6.96–7.24 (each 2H)), indicating that this compound should be in either cone or 1,2-alternate conformation. Judging from



Scheme 1.



Scheme 2.

Table 1. Isolated yield of the products for the *O″*,*O‴*-dialkylations of **CA-2** or **TCA-2** with RX[a]

Starting material	RX	Yield (%)			
		1,2-Alternate **4**		Partial-cone **5**	
C3	MeI	**C4a**	85		–
	$BrCH_2COOEt$	**C4b**	69	**C5b**	25
	$PhCH_2Br$[b]	**C4c**	90		0
T3	MeI	**T4a**	87		–
	$BrCH_2COOEt$	**T4b**	88		Trace
	$PhCH_2Br$	**T4c**	74	**T5c**	9

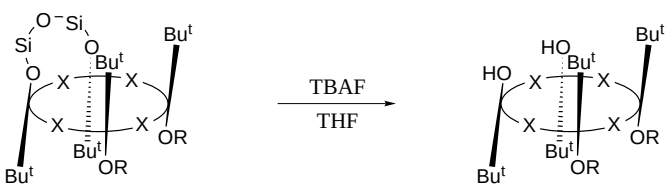
[a] RX (6 equiv.), Cs_2CO_3 (6 equiv.), THF, reflux.
[b] RX (4 equiv.), *tert*-BuOK (3 equiv.), THF, 0°C.

the bridging methylene protons appearing as three pairs of doublets of 1:2:1 intensity and the $\Delta\delta$ between the *exo* and *endo* geminal protons of the double intensity being not more than 0.5 ppm, this product is most probably the 1,2-alternate conformer **C4b**. Moreover, the ^{1}H NMR signals of this compound showed isopropyl-methyl proton signals of the TIPDS groups shifted upfield (δ 0.42, 0.80, 0.93 and 0.96 (each 6H)) as compared with those of **C3** (δ 0.79, 1.10, 1.31 and 1.37 (each 6H)), clearly indicating the anisotropic shielding effects by the 3,4-aromatic rings. De Mendoza and co-workers showed that ^{13}C NMR signals for the bridging methylene carbon atoms of calixarenes between different orientations are found at δ 37–39, while those between similar orientations appear at δ 30–32.[18] The major product (**C4b**) showed three signals at δ 33.8, 34.0, 39.2 for the bridging methylene carbons, which also supported the 1,2-alternate conformation. In contrast, the ^{1}H NMR of the minor product showed four singlets (δ 1.08, 1.09, 1.30 and 1.32 (each 9H)) for the *tert*-butyl protons and eight doublets (δ 6.85–7.24 (each 1H)) for the aromatic protons. This spectrum required that the product should be an asymmetric molecule, i.e. partial-cone conformer **C5b**.

The structures of the *O″*,*O‴*-dialkylation products other than **C4b** and **C5b** in Table 1 were similarly assigned by ^{1}H and ^{13}C NMR as above. The ^{1}H NMR spectrum of *O″*,*O‴*-dimethylated product **C4a** showed that it was fixed in the 1,2-alternate conformation in solution at room temperature, although it is known that a methoxyphenyl unit of calix[4]arenes can usually rotate by flip–flop motion via the so-called through-annulus rotation. Thus, the bulky TIPDS moiety seemed to retard the rotation of the methoxyphenyl groups of **C4a**. The conformation of thiacalix[4]arene derivatives **T4a–c** was also assigned to be 1,2-alternate structure based on the ^{1}H NMR signals of the TIPDS groups shifted upfield similar to those of **C4a–c**. The data in Table 1 demonstrates that the *O″*,*O‴*-dialkylation proceeded with high stereoselectivity to give the 1,2-alternate conformers preferentially, probably due to the steric hindrance imposed by the bulky TIPDS moiety, although the reason for the appreciable formation of **C5b** from the reaction of **C3** with the bromoacetate is not clear.

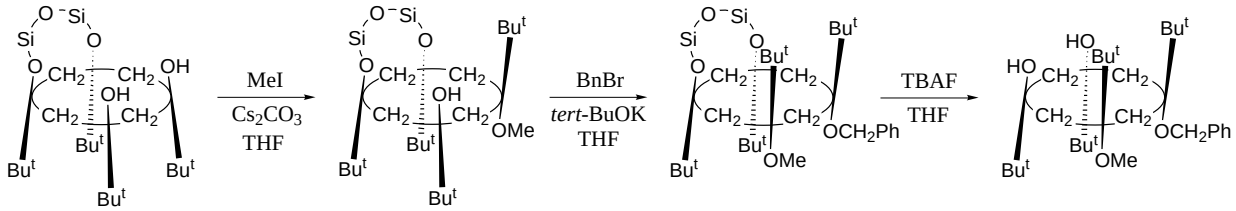
Desilylation of the disiloxane-capped calix[4]arenes **C4a–c** and **T4a–c** was carried out by a simple treatment with tetrabutylammonium fluoride (TBAF) in THF to liberate the proximal *O*,*O′*-dialkylated calix[4]arenes **C6a–c**[9,19,20] and **T6a–c**[21] quantitatively (Scheme 3). It is presumed from their ^{1}H NMR spectra that they took *syn* form in $CDCl_3$ at room temperature, except the 1,2-dimethylethers **C6a** and **T6a**, which were found to exist as mixtures of *syn* and *anti* stereoisomers.[19]

In a preliminary experiment, it was shown that the 1,2-protected calix[4]arene **C3** was amenable to monoalkylation as exemplified by treatment with 1.5 equiv. amount of methyl iodide to give monomethylated product **C7** in 98% yield (Scheme 4). Alkylation of the remaining hydroxy group of **C7** with benzyl bromide completed the *O‴*-alkylation to give **C8** (96%), deprotection of which by treatment with the fluoride ion afforded *O*-methyl-*O′*-benzyl calix[4]arene **C9** in very high yield (98%). It should be noted that **C8** and **C9** class compounds are inherently chiral due to the ring structure having two differently substituted aromatic rings neighboring each other.



R	X = CH_2	S (%)
Me	98	96
CH_2COOEt	93	93
CH_2Ph	94	93

Scheme 3.



C3 **C7** (Y. = 98%) **C8** (Y. = 96%) **C9** (Y. = 98%)

Scheme 4.

In conclusion, we have shown here that the tetraisopropyldisiloxane unit is very useful for protection of two adjacent hydroxy groups of calix[4]arenes out of the four; the *O*,*O*′-capping reaction, subsequent alkylation of the remaining hydroxy groups, and final desilylation proceed quite smoothly with excellent yields to provide an efficient method for the net proximal dialkylation of calix[4]arenes at the lower rim. Studies on the preparation and enantioseparation of inherently chiral *O*,*O*′-differently substituted calix[4]arenes by substitution at the neighboring two OH groups are now under way.

Acknowledgements

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16. To a suspension of **C1** (3.25 g, 5.01 mmol) in anhydrous DMF (50 ml) imidazole (1.02 g, 15.0 mmol) was added and stirred for 30 min. at room temperature. Then a solution of TIPDSCl (1.9 ml, 5.94 mmol) in DMF (25 ml) was added dropwise for 1 h. After stirring for an additional 11 h, the mixture was cooled to 0°C and then added 2 M HCl (100 ml). The precipitate was filtered and washed with water. The product was recrystallized from dichloromethane and methanol and dried in vacuo to get white powder **C3** (3.85 g, 86%). **T3** was obtained in a similar manner from **C3** (92%). Compound **C3**: mp 238–240°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (d, J=7.4 Hz, 6H, CH(CH_3)$_2$), 1.10 (d, J=7.4 Hz, 6H, CH(CH_3)$_2$), 1.17 (s, 18H, C(CH_3)$_3$), 1.17–1.21 (m, 2H, CH(CH$_3$)$_2$), 1.23 (s, 18H, C(CH_3)$_3$), 1.31 (d, J=7.4 Hz, 6H, CH(CH_3)$_2$), 1.37 (d, J=7.4 Hz, 6H, CH(CH_3)$_2$), 1.47–1.53 (m, 2H, CH(CH$_3$)$_2$), 3.33–3.42 (m, 4H, ArCH_2Ar), 4.20 (d, J=13.6 Hz, 1H, ArCH_2Ar), 4.55 (d, J=13.3 Hz, 1H, ArCH_2Ar), 4.60 (d, J=13.1 Hz, 2H, ArCH_2Ar), 6.95 (d, J=2.5 Hz, 2H, ArH), 6.98 (d, J=2.3 Hz, 2H, ArH), 7.02 (d, J=2.5 Hz, 2H, ArH), 7.06 (d, J=2.3 Hz, 2H, ArH), 8.66 (s, 2H, OH); FAB-MS (m/z): 891 (M^+). Compound **T3**: mp 308–310°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (d, J=7.6 Hz, 6H, CH(CH_3)$_2$), 1.14–1.20 (m, 14H, CH(CH_3)$_2$), 1.16 (s, 18H, C(CH_3)$_3$), 1.24 (s, 18H, C(CH_3)$_3$), 1.32–1.39 (m, 2H, CH(CH$_3$)$_2$), 1.38 (d, J=2.1 Hz, 6H, CH(CH_3)$_2$), 7.49 (d, J=2.5 Hz, 2H, ArH), 7.51 (d, J=2.5 Hz, 2H, ArH), 7.54–7.56 (m, 4H, ArH), 8.12 (s, 2H, OH); FAB-MS (m/z): 963 ($M+1^+$).
17. It seems that 1,3-bridging requires a rather long chain. See Ref. 13.
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21. Compound **T6b**: mp 194–195°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (s, 18H, C(CH_3)$_3$), 1.23 (s, 18H, C(CH_3)$_3$),

1.35 (t, $J=7.2$ Hz, 6H, OCH_2CH_3), 4.35–4.30 (m, 4H, OCH_2CH_3), 4.81 (d, $J=16.5$ Hz, 2H, OCH_2CO), 5.31 (d, $J=16.5$ Hz, 2H, OCH_2CO), 7.03 (d, $J=2.5$ Hz, 2H, ArH), 7.12 (d, $J=2.5$ Hz, 2H, ArH), 7.52 (d, $J=2.5$ Hz, 2H, ArH), 7.54 (d, $J=2.5$ Hz, 2H, ArH), 9.14 (s, 2H, OH); FAB-MS (m/z): 893 ($M+1^+$). Compound **T6c**: mp 114–116°C; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (s, 18H, $C(CH_3)_3$), 1.21 (s, 18H, $C(CH_3)_3$), 5.19 (d, $J=10.9$ Hz, 2H, CH_2Ph), 5.54 (d, $J=10.9$ Hz, 2H, CH_2Ph), 7.07 (d, $J=2.5$ Hz, 2H, ArH), 7.15 (d, $J=2.5$ Hz, 2H, ArH), 7.40–7.32 (m, 6H, CH_2Ph), 7.48 (d, $J=2.5$ Hz, 2H, ArH), 7.51 (d, $J=2.5$ Hz, 2H, ArH), 7.64–7.61 (m, 4H, CH_2Ph), 8.35 (s, 2H, OH); FAB-MS (m/z): 901 ($M+1^+$).