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Syntheses of New Isomers from p-t-Butylcalix[4]arene. Strategies for Regioselective Alkylation on the Lower Rim

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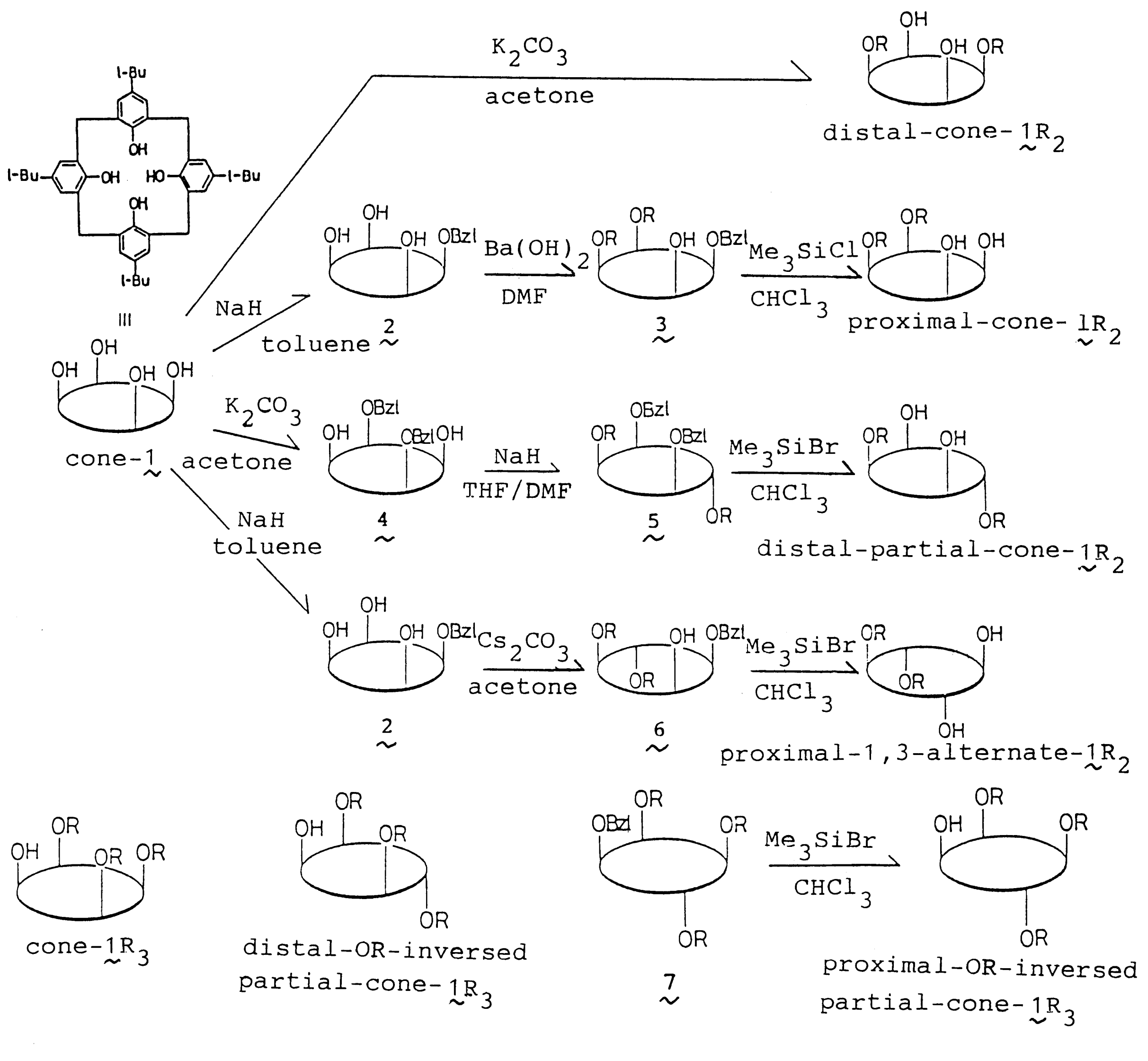
By using a protection-deprotection technique and metal template effects, a number of new regio- and conformational isomers were synthesized.

p-t-Butylcalix[4]arene (**1**) and its derivatives are a class of macrocyclic compounds having a cavity in the center and four functionalizable OH groups on the lower rim. The architecture renders calix[4]arenes a very intriguing class of host molecules, particularly when four OH groups are suitably functionalized. However, the systematic study has still been very limited. For example, the synthesis of 1,3-disubstituted calix[4]arene (distal-cone-**1**R_2) has been reported,1-4) but that of 1,2-disubstituted calix[4]arene (proximal-cone-**1**R_2) is not reported5) although the compound has been long-awaited by theoretical chemists.6) After trial-and-error experiments, we have found several versatile methods which are useful as strategies for the syntheses of new stereomers: (i) monosubstituted p-t-butylcalix[4]arene (**1**R) can be synthesized in toluene by the control of a **1**/RX (alkyl halogen) ratio,7) (ii) the reaction of **1** and RX in the presence of M_2CO_3 (M = Na or K) in acetone selectively affords distal-cone-**1**R_2,3,4) (iii) the reaction in the presence of Cs_2CO_3 affords either **1**R_3 or **1**R_4 (depending on a **1**/RX ratio), the products being the mixture of partial cone and 1,3-alternate4) and (iv) the reaction in the presence of $Ba(OH)_2$ affords only cone-**1**R_3.4,7) By the combination of these strategies with a protection-deprotection method using a benzyl group, newly introduced in this paper, we can now synthesize a number of regio- and conformational isomers from **1**.8)

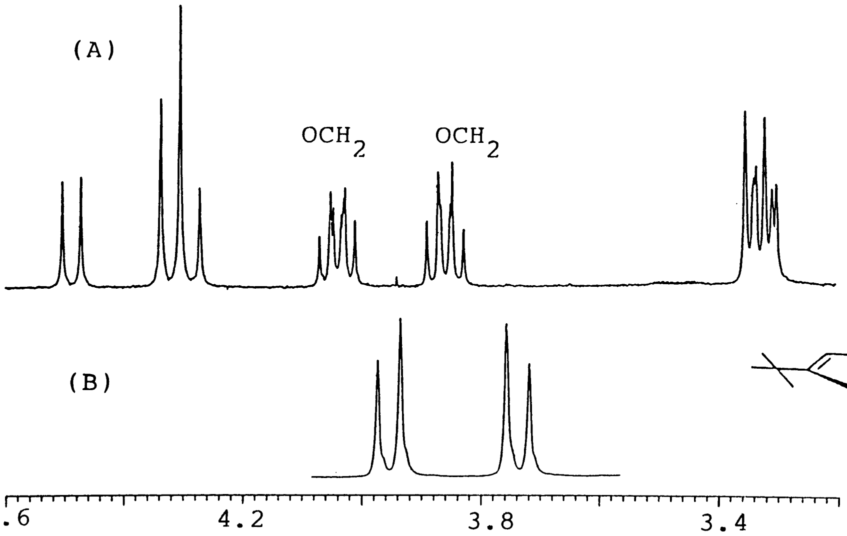
We here demonstrate the syntheses with propyl bromide as an alkylation reagent because the propyl group is bulky enough to inhibit the oxygen-through-the-annulus rotation.4,9) As shown in Scheme 1, distal-cone-**1**Pr_2 was readily synthesized from **1** and propyl bromide in acetone in the presence of K_2CO_3 (strategy (ii)): mp 247-249 °C, yield 79%.



Scheme 1.

Proximal-cone-1Pr$_2$ was synthesized via three steps: protection of one OH group with a benzyl group (2: strategy (i)), dipropylation of 2 with propyl bromide in the presence of Ba(OH)$_2$ (3: strategy (iv)), and debenzylation with Me$_3$SiCl: 2, mp 205-207 °C, yield 67%; 3(R=Pr), mp 193-195 °C, yield 67%; proximal-cone-1Pr$_2$, mp 119-121 °C, yield 78%.

Distal-partial-cone-1Pr$_2$ was also synthesized via three steps: dibenzylation of 1 in acetone in the presence of K$_2$CO$_3$ (4: strategy (ii)), dipropylation of 4 in acetone in the presence of Cs$_2$CO$_3$ (5: strategy (iii)), and debenzylation with Me$_3$SiBr: 4, mp 234-235 °C, yield 98%; 5(R=Pr), mp 228-230 °C, yield 67%; distal-partial-cone-1Pr$_2$: mp 286-287 °C, yield 90%.



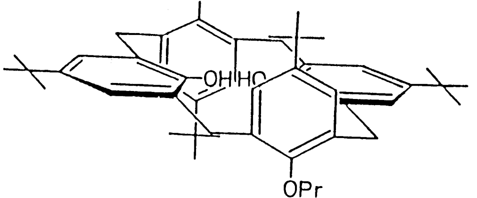


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Fig. 1. Partial ^{1}H NMR spectra for the ArCH$_2$Ar protons: (A) proximal-cone-**1**Pr$_2$, (B) distal-partial-cone-**1**Pr$_2$ (CDCl$_3$, 25 °C)

Proximal-1,3-alternate-**1**Pr$_2$ was synthesized by dipropylation of **2** in the presence of Cs$_2$CO$_3$ (strategy (iii)) followed by debenzylation with Me$_3$SiBr: **6**, mp 104-105 °C, yield 72%; proximal-1,3-alternate-**1**Pr$_2$, mp 203-204 °C, yield 98%.

Cone-**1**Pr$_3$ was synthesized in one pot from **1** with Ba(OH)$_2$ as base: mp 194-196 °C, yield 63%. When Cs$_2$CO$_3$ was used as base, the product contained 59% of partial-cone-**1**Pr$_3$ (analyzed by HPLC). This was isolated by a preparative TLC method: mp 169-171 °C, yield 48%. The ^{1}H NMR spectrum (Cl$_2$CDCDCl$_2$, 25 °C) showed that two phenol units are equivalent and one phenol unit is inversed (t-Bu groups appear at 1.16, 1.22, and 1.39 ppm in a 1:2:1 ratio and a CH$_3$ group in the inversed phenol unit appears at -0.65 ppm). This pattern is commensurate with distal-OPr-inversed partial-cone-**1**Pr$_3$.

Proximal-OPr-inversed partial-cone-**1**Pr$_3$ can be synthesized via a benzyl-protected intermediate (**7**): that is, tripropylation of **2** with propyl bromide followed by debenzylation with Me$_3$SiBr: mp 120-121 °C, yield 69%. The ^{1}H NMR spectrum (CDCl$_3$, 25 °C) showed four peaks for t-Bu groups, indicating that four phenol units are all unequivalent.10)

The ^{1}H NMR spectrum of distal-cone-**1**Pr$_2$ with C_{2v} symmetry is very simple (CDCl$_3$, 25 °C): the ArCH$_2$Ar protons appear as a pair of doublets (3.29 and 4.25 ppm, J=12.82 Hz). On the other hand, that of proximal-cone-**1**Pr$_2$ is fairly complex (Fig. 1A): the ArCH$_2$Ar protons appear as three pair of doublets in a 1:1:2 ratio. This split pattern supports the proximally-disubstituted cone structure.

More interesting is the ^{1}H NMR spectrum of distal-partial-cone-**1**Pr$_2$ (CDCl$_3$, 25 °C). As shown in Fig. 1B, the ArCH$_2$Ar protons appear as a pair of doublets and the difference in the chemical shifts ($\Delta\delta$ = 0.22 ppm) is relatively small. According to Gutsche,[11)] the $\Delta\delta$ becomes smaller when the phenol unit is flattened. Hence, the spectrum suggests the idea that two unalkylated phenol units are flattened, probably, to form intramolecular hydrogen bonds (as in **8**). In **8**, the four methylene groups are all equivalent.

In conclusion, the present paper demonstrated new strategies useful for the syntheses of a number of new isomers.

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References

1)C. D. Gutsche, B. Dhawan, J. A. Levine, K. H. No, and L. J. Bauer, Tetrahedron, 39, 409(1983).

2)D. N. Reinhoudt, S. Harkema, R. Ungaro, and E. Ghidini, J. Am. Chem. Soc., 109, 4761(1987).

3)K. No and M. Hong, J. Chem. Soc., Chem. Commun., 1990, 572.

4)K. Iwamoto, K. Fujimoto, T. Matsuda, and S. Shinkai, Tetrahedron Lett., in press

5)An Italian group (F. Bottino, L. Giunta, and S. Pappalardo, J. Org. Chem., 54, 5407(1989)) reported that the reaction of 1H$_4$ and 2-chloromethylpyridine in the presence of NaH gives the proximally-disbstituted product in 65-70% yields, but we could not reproduce their results.

6)P. J. Grootenhuis, P. A. Kollmam, L. C. Groenen, D. N. Reinhoudt, G. J. van Hummel, F. Ugozzoli, and G. D. Andreetti, J. Am. Chem. Soc., 112, 4165(1990).

7)K. Iwamoto, A. Yanagi, T. Arimura, T. Matsuda, and S. Shinkai, Chem. Lett., 1990, 1901.

8)All new compounds reported herein were identified by IR and ^{1}H NMR spectroscopic evidences and elemental analyses.

9)K. Araki, K. Iwamoto, S. Shinkai, and T. Matsuda, Chem. Lett., 1989, 1747.

10)This is a new class of ring-originating optical isomers. In fact, this can be optically resolved by an HPLC method with a chiral packing column.

11)C. D. Gutsche, "Calixarenes," Royal Society of Chemistry, Cambridge, 1989.

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