One Step Synthetic Method of Asymmetrically Substituted Calix[4]arenes: Benzoylation of Monoalkylcalix[4]arenes

Kye Chun Nam*, Jong Min Kim, and Yu Jeong Kim

Department of Chemistry, Chonnam National University, Kwangju 500-757, Korea
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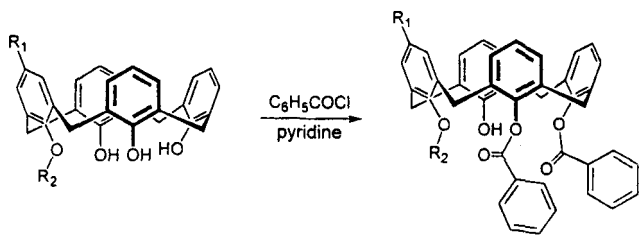
Calixarenes are cavity containing metacyclophanes which are recently utilized as a versatile host molecules.[1-3] One of the most important aspect about host-guest chemistry is molecular recognition.[4,5] Like chiral cyclodextrines, calixarenes are expected to have similar chiral recognition ability because molecular structure of calixarenes could allow the preparation of synthetic molecule with a chiral cavity.[6] If molecular asymmetry could be originated from the direct calixarene framework, the efficient chiral recognition would be expected.

Böhmer[7,8] and Vicens[9] synthesized the asymmetric calix[4] arenes by introducing the different substituents at the upper rim of calix[4]arenes. Shinkai reported[10,11] that molecular asymmetry could be directly generated by the selective lower rim alkylation. Recently, Pappalardo[12] synthesized the chiral calix[4]crown ethers from the similar strategy applied by Shinkai. Gutsche *et al.*[13] have found that calix[4]arene is only tribenzoylated when it is treated with excess benzoyl chloride in pyridine. If this behavior could be achieved from monosubstituted calix[4]arenes, the chiral ABBH type[10] calix[4]arenes could be expected if the existing substituent is not benzoyl group. From this simple benzoylation, we succeeded the another convenient method for the synthesis of the ester groups containing chiral calix[4]arenes. By introducing two large benzoyl groups at the lower rim of monosubstituted calix[4]arenes, not only the various chiral calix[4]arenes are obtained easily, but also ring inversion is inhibited. Since the monosubstituted calix[4]arenes are easily available from the selective functionalization,[14,15] this simple method could provide the efficient synthetic method for the chiral calix[4]arenes.

Treatment of monosubstituted calix[4]arenes **1a** with excess benzoyl chloride in pyridine gave the chiral calix[4] arene **2a** exclusively. Only two benzoyl groups are introduced selectively, one at the opposite and the other at the adjacent position relative to the present alkyl group, to give so called ABBH type chiral calix[4]arenes as shown in Scheme 1. Two benzoyl group might end up at both adjacent position relative to alkyl group, which can be described as a ABHB type, but we observed none of this products. It can be rationalized by the order of benzoylation. If we assumed that two benzoylation did not occur simultaneously, first benzoyl group could prefer to be introduced at the opposite side of the existing alkyl group due to steric crowd. Then the second benzoyl group will end up either side to finish a ABBH type calix[4]arene. When monoallylcalix[4]arene **1b** and monomethylcalix[4]arene **1c** treated with benzoyl chloride in pyridine, the asymmetrically substituted calix[4]arenes **2b** and **2c** produced, suggesting that the size of alkyl group did not influence the benzoylation



1 **2**

	R_1	R_2
a	H	$CH_2\phi$
b	H	$CH_2CH{=}CH_2$
c	H	CH_3
d	NO_2	$CH_2\phi$
e	NO_2	$CH_2CH{=}CH_2$
f	NO_2	CH_3

Scheme 1.

reaction. In order to introduce anion binding sites in the future, nitrated monoalkylcalix[4]arenes **1d, 1e,** and **1f** were prepared by the four step reaction from debutylated calix[4] arene such as tribenzoylation,[13] nitration, alkylation followed by the hydrolysis of benzoyl groups. These nitroalkylcalix[4]arenes also treated with benzoyl chloride in pyridine and produced the asymmetrically substituted ABBH type calix[4]arenes **2d, 2e,** and **2f** exclusively.

The ^{1}H NMR spectrum of **2a** shows the typical chiral calix[4]arene characteristics such as four pairs of doublets at δ 3.2-4.1 for the eight bridge methylene protons and the very complicated aromatic signals at around δ 6.2-8.0. The diastereotopic protons of benzylic methylene appear as a pair of doublets at δ 4.3 as expected. In order to confirm that the six asymmetrically substituted compounds **2a-2f** consist of a pair of enantiomers, we measured their ^{1}H NMR spectra in the presence of chiral shift reagents as shown in Figure 1. It was found that Pirkles reagent[16] ((S)-2, 2,2-trifluoro-1-(9-anthryl)ethanol) is very effective. In all six asymmetric compounds peaks shifted slightly upfield and split into more complicated pattern due to doubling even at 25 °C.

The conformation of **2a-2f** was deduced from the ^{13}C NMR spectra. Particularly diagnostic were the chemical shifts for the methylene carbons of these derivatives.[17] Compounds **2a-2f** show four signals for the methylene carbons, indicating that they are asymmetric compounds. For example, the ^{13}C NMR spectra of **2a** showed four signals at δ 38.01, 37.80, 31.70, and 31.11 for the methylene carbons,

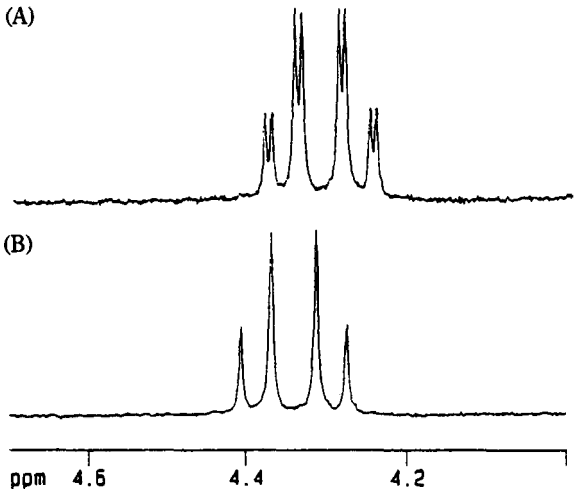


Figure 1. Partial ^{1}H NMR spectra of compound **2d** in $CDCl_3$: (A) in the absence of Pirkles reagent; (B) in the presence of Pirkles reagent (2 equiv).

suggesting that it has two *anti* and two *syn* oriented phenolic units. It can be either partial cone or 1,2-alternate conformation. Because partial cone as well as 1,2-alternate conformation have two *anti* and two *syn* oriented phenolic units. The same pattern of bridge methylene carbons signals was observed from the ^{13}C NMR spectra of **2c**, **2d**, **2e**, and **2f**. At this point we do not know the exact conformation of these compounds without X-ray diffraction analysis. But the cone conformation of **2b** was confirmed by the ^{13}C NMR analysis, which showed four methylene carbon signals at around δ 30-32 such as δ 31.80, 31.24, 30.57, and 30.47, indicating that it has only *syn* oriented phenolic units. It seems that the size of lower rim substituents as well as the presence of the upper rim substituents could influence the outcome of the conformation, but it is not conclusive at this moment. The nitro group at the upper rim of calix[4]arene will be utilized as a handle for the introduction the anion binding sites[18] for anion receptors.

In conclusion this simple procedure for introducing two benzoyl groups simultaneously into monoalkylcalix[4]arenes could open up the easy way for the synthesis of a variety of the chiral calix[4]arenes and will also provide the selective functionalization method of 1,2-position of calix[4]arene after removing the benzyl group.

Experimental

25-Alkyloxy-26,27,28-trihydroxycalix[4]arenes 1a,[15] 1b,[15] and 1c[13] were prepared by the reported procedure

5-Nitro-26-benzyloxy-25,27,28-trihydroxycalix[4]arene 1d. Nitro group was introduced into the tribenzoester calix[4]arene[13] and alkylated with benzyl bromide in the presence of K_2CO_3. Removal of benzoester with hydroxide produced **1d** in 43% four step yield from debutylated calix[4]arene. mp 245-247 °C. ^{1}H NMR ($CDCl_3$) δ 9.22 and 8.88 (two s, 3H, OH), 7.98 (s, 2H, O_2NArH), 7.70-7.40 (m, 5H, ArH from benzyl), 7.10, 7.70, and 6.97 (three d, 6H, ArH, *J*=7.5 Hz), 6.71 and 6.69 (two t, 3H, ArH, *J*=7.5 Hz), 5.26 (s, 2H, -OCH_2Ar), 4.32-3.43 (two pairs of d, 8H, $ArCH_2Ar$, *J*=13.2 and 13.8 Hz). ^{13}C NMR ($CDCl_3$) δ 156.46, 150.93, 148.64, 145.04, 136.01, 134.60, 129.53, 129.37, 129.19, 129.00, 128.85, 128.48, 128.38, 128.32, 126.56, 124.94, 122.28, and 121.22 (Ar), 79.90 (-OCH_2Ar), 31.72 and 31.69 ($ArCH_2Ar$). IR (KBr) 3308 cm^{-1} (OH), 1525 and 1348 cm^{-1} (-NO_2).

5-Nitro-26-allyloxy-25,27,28-trihydroxycalix[4]arene 1e. Following the procedure described for **1d**, **1e** was obtained in 38% four step yield from debutylated calix[4]arene. mp >175 °C dec. ^{1}H NMR ($CDCl_3$) δ 9.31 and 8.94 (two s, 3H, OH), 7.94 (s, 2H, O_2NArH), 7.10, 7.06, and 6.97 (three d, 6H, ArH, *J*=7.8 Hz), 6.73 and 6.67 (two t, 3H, ArH, *J*=7.8 Hz), 6.50-6.30 (m, 1H, -CH=), 5.80-5.50 (m, 2H, =CH_2), 4.74 (d, 2H, -OCH_2-), 4.40-3.46 (two pairs of d, 8H, $ArCH_2Ar$, *J*=13.17 and 13.85 Hz). ^{13}C NMR ($CDCl_3$) δ 156.40, 150.86, 148.67, 145.01, 135.90, 131.36, 129.39, 128.84, 128.49, 128.37, 126.59, 124.87, 122.29, and 121.26 (Ar and -CH=CH_2), 78.24 (-OCH_2-), 31.72 and 31.65 ($ArCH_2Ar$). IR (KBr) 3342 cm^{-1} (OH), 1543 and 1328 cm^{-1} (-NO_2).

5-Nitro-26-methyloxy-25,27,28-trihydroxycalix[4]arene 1f. Following the procedure described for **1d**, **1f** was obtained in 39% four step yield from debutylated calix[4]arene. mp >249 °C dec. ^{1}H NMR ($CDCl_3$) δ 9.28 and 8.95 (two s, 3H, OH), 7.93 (s, 2H, O_2NArH), 7.10, 7.07, and 6.97 (three d, 6H, ArH, *J*=7.8 Hz), 6.72 and 6.66 (two t, 3H, ArH, *J*=7.8 Hz), 4.41-3.48 (two pairs of d, 8H, $ArCH_2Ar$, *J*=13.20 and 13.82 Hz), 4.19 (s, 3H, -OCH_3). ^{13}C NMR ($CDCl_3$) δ 157.75, 150.84, 148.65, 144.99, 135.60, 129.49, 128.83, 128.50, 128.44, 128.33, 126.59, 124.95, 122.27, and 121.28 (Ar), 64.10 (-OCH_3), 31.73 and 31.35 ($ArCH_2Ar$). IR (KBr) 3300 cm^{-1} (OH), 1529 and 1346 cm^{-1} (-NO_2).

25-Benzyloxy-26,27-bisbenzoyloxy-28-hydroxycalix[4]arene 2a. To a solution of 0.30 g (0.58 mmol) of **1a** in 30 mL of pyridine, 2.0 mL (17 mmol) of benzoyl chloride was added slowly at room temperature. The reaction mixture was stirred for 18 h, and then added 50 mL of $CHCl_3$. The organic layer washed with the water, separated, and evaporated. The residue was triturated with MeOH. Recrystallization from $CHCl_3$-MeOH gave 0.25 g (59%) of colorless crystalline **2a**. mp 261-264 °C. ^{1}H NMR ($CDCl_3$) δ 7.95-6.20 (m, 28H, ArH and OH), 5.18 and 4.86 (a pair of d, 2H, -CH_2Ar, *J*=11.7 Hz), 4.04-3.24 (four pairs of d, 8H, $ArCH_2Ar$, *J*=12.9 Hz and 15.6 Hz). ^{13}C NMR ($CDCl_3$) δ 164.94, 163.55 (-CO_2-), 153.05, 152.68, 148.12, 146.72, 135.81, 133.16, 133.14, 133.05, 132.81, 132.71, 132.59, 132.47, 131.80, 130.73, 130.36, 130.30, 130.22, 129.66, 129.46, 129.35, 129.30, 129.25, 128.89, 128.68, 128.64, 128.47, 128.41, 128.14, 127.32, 126.32, 125.34, 125.26, 125.18, and 119.18 (Ar), 77.34 (-OCH_2Ar), 38.01, 37.80, 31.70, and 31.11 ($ArCH_2Ar$). IR (KBr) 3391 cm^{-1} (OH), 1731 and 1714 cm^{-1} (-CO_2-).

25-Allyloxy-26,27-bisbenzoyloxy-28-hydroxycalix[4]arene 2b. Following the procedure described for **2a** with 0.30 g of **1b**, 0.32 g (74%) of **2b** was obtained after recrystallization from $CHCl_3$-MeOH. mp 225-226 °C. ^{1}H NMR ($CDCl_3$) δ 8.74-6.45 (m, 23H, ArH and OH), 5.39-5.25 (m, 1H, -CH= from allyl), 4.89-4.82 (m, 2H, =CH_2 from allyl), 4.32-3.33 (five pairs of d, 10H, $ArCH_2Ar$ and -OCH_2-). ^{13}C NMR ($CDCl_3$) δ 166.90, 165.97 (-CO_2-), 153.27, 151.55, 147.02, 145.40, 135.96, 135.36, 133.59, 133.50,

133.38, 132.88, 132.06, 131.96, 131.92, 130.19, 129.60, 129.34, 129.18, 129.06, 128.74, 128.38, 128.09, 127.96, 127.90, 127.01, 126.03, 124.97, 124.87, 119.49, and 119.02 (Ar and -CH=CH_2), 77.84 (-OCH_2-), 31.80, 31.24, 30.57, and 30.47 ($ArCH_2Ar$). IR (KBr) 3349 cm^{-1} (OH), 1728 cm^{-1} (-CO_2-).

25-Methyloxy-26,27-bisbenzoyloxy-28-hydroxycalix[4]arene 2c. Following the procedure described for **2a** with 0.30 g of **1c**, 0.26 g (59%) of **2c** was obtained after recrystallization from $CHCl_3$-MeOH. mp >290 °C dec. ^{1}H NMR ($CDCl_3$)e δ 7.55-6.11 (m, 22H, ArH), 5.50 (s, 1H, OH), 4.03-3.42 (m, 8H, $ArCH_2Ar$), 2.94 (s, 3H, -OCH_3). ^{13}C NMR ($CDCl_3$) δ 164.85, 163.56 (-CO_2-), 156.27, 151. 59, 134.83, 134.66, 134.00, 133.77, 133.73, 133.09, 132.60, 130.41, 129.80, 129.16, 129.09, 128.99, 128.88, 128.76, 128.58, 128.51, 128.27, 127.96, 127.83, 127.73, 127.11, 126.27, 126.16, 124.03, and 120.36 (Ar), 59.28 (-OCH_3), 38.18, 36.70, 31.58, and 29.65 ($ArCH_2Ar$). IR (KBr) 3417 cm $^{-1}$ (OH), 1724 cm $^{-1}$ (-CO_2-).

5-Nitro-26-benzyloxy-25,28-bisbenzoyloxy-27-hydroxycalix[4]arene 2d. Following the procedure described for **2a** with 0.30 g of **1d**, 0.25 g (61%) of **2d** was obtained after recrystallization from $CHCl_3$-MeOH. mp >260 °C dec. ^{1}H NMR ($CDCl_3$) δ 7.95-6.20 (m, 27H, ArH and OH), 5.18 and 4.86 (a pair of d, 2H, -OCH_2Ar, J=11.7 Hz), 4.10-3.24 (four pairs of d, 8H, $ArCH_2Ar$, J=12.9 Hz and 15.6 Hz). ^{13}C NMR ($CDCl_3$) δ164.94, 163.55 (-CO_2-), 153.05, 152.68, 148.12, 146.72, 135.81, 133.16, 133.14, 133.05, 132.81, 132.71, 132.59, 132.47, 131.80, 130.73, 130.36, 130.30, 130.22, 129.66, 129.46, 129.35, 129.30, 129.25, 128.89, 128.68, 128.64, 128.47, 128.41, 128.14, 127.32, 126.32, 125.34, 125.26, 125.18, and 119.18 (Ar), 77.34 (-OCH_2Ar), 38.01, 37.80, 31.70, and 31.11 ($ArCH_2Ar$). IR (KBr) 3448 cm^{-1} (OH), 1733 and 1722 cm^{-1} (-CO_2-), 1521 and 1348 cm^{-1} (-NO_2).

5-Nitro-26-allyloxy-25,28-bisbenzoyloxy-27-hydroxycalix[4]arene 2e. Following the procedure described for **2a** with 0.30 g of **1e**, 0.24 g (57%) of **2e** was obtained after recrystallization from $CHCl_3$-MeOH. mp >210 °C dec. ^{1}H NMR ($CDCl_3$) δ 7.92-6.32 (m, 22H, ArH and OH), 6.10 (m, 1H, -CH= from allyl), 5.48-5.45 (m, 2H, CH_2 = from allyl), 4.72-4.38 (m, 2H, -OCH_2-), 4.07-3.34 (four pairs of d, 8H, $ArCH_2Ar$, J=16.2 Hz, 15.9 Hz, 14.1 Hz, and 12.9 Hz). ^{13}C NMR ($CDCl_3$) δ 164.58, 162.98 (-CO_2-), 157.75, 152.71, 147.93, 146.53, 143.75, 134.61, 134.41, 133.28, 133.16, 132.56, 131.98, 131.59, 131.06, 130.65, 130.53, 129.68, 129.37, 129.29, 129.26, 129.22, 129.00, 128.51, 128.42, 128.07, 127.39, 127.34, 125.87, 125.70, 125.16, 124.89, 124.77, 120.56, and 119.96 (Ar and -CH= CH_2), 75.42 (-OCH_2-), 37.79, 31.84, and 31.27 ($ArCH_2Ar$). IR (KBr) 3411 cm $^{-1}$ (OH), 1724 cm $^{-1}$ (-CO_2-), 1524 and 1343 cm^{-1} (-NO_2).

5-Nitro-26-methyloxy-25,28-bisbenzoyloxy-27-hydroxycalix[4]arene 2f. Following the procedure described for **2a** with 0.30 g of **1f**, 0.26 g (60%) of **2f** was obtained after recrystallization from $CHCl_3$-MeOH. mp 275-277 °C dec. ^{1}H NMR ($CDCl_3$) δ 7.81-6.33 (m, 22H, ArH and OH), 4.10-3.35 (four pairs of d, 8H, $ArCH_2Ar$, J=12.99 Hz, 16.35 Hz, 13.95 Hz, and 13.11 Hz). ^{13}C NMR ($CDCl_3$) δ 164.34, 162.93 (-CO_2-), 159.00, 152.55, 147.90, 146.78, 143.75, 134.58, 134.20, 133.26, 133.18, 133.11, 133.05, 132.00, 130.98, 130.66, 130.41, 129.50, 129.42, 129.26, 129.18, 128.52, 128.44, 128.31, 127.99, 127.39, 125.87, 125.16, and 120.08 (Ar), 61.13 (-OCH_3), 37.86, 37.66, 31.65, and 31.56 ($ArCH_2Ar$). IR (KBr) 3384 cm $^{-1}$ (OH), 1724 cm $^{-1}$ (-CO_2-), 1522 and 1343 cm $^{-1}$ (-NO_2).

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References

1. Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.
2. Vicens, J.; Asfari, Z.; Harrowfield, J. M. *Calixarenes Fiftieth Anniversary*; Kluwer: Dordrecht, 1995.
3. Böhmer, V. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713.
4. Zhang,. L.; Godinez, L. A.; Lu, T.; Gokel, G. W.; Kaifer, A. E. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 235.
5. Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.
6. Hofmeister, G. E.; Hahn, F. E.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 2318.
7. Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom.* **1994**, *19*, 17.
8. Böhmer, V.; Kraft, D.; Vogt, W. *Supramol. Chem.* **1994**, *3*, 229.
9. Casablanca, H.; Royer, J.; Satrallah, A.; Taty-C, A.; Vicens, J. *Tetrahedron Lett.* **1987**, *28*, 6595.
10. Iwamoto, K.; Shimizu, H.; Araki, K.; Shinkai, S. *J. Am. Chem. Soc.* **1993**, *115*, 3997.
11. Otsuka, H.; Shinkai, S. *J. Am. Chem. Soc.* **1996**, *118*, 4271.
12. Pappalardo, S.; Parisi, M. F. *Tetrahedron Lett.* **1996**, *37*, 1493.
13. Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633.
14. Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379.
15. Nam, K. C.; Kim, J. M.; Kim, D. S. *Bull. Korean Chem. Soc.* **1995**, *16*, 186.
16. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
17. Jaime, C.; Mendoza, J. D.; Paradox, P.; Nicest, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
18. Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *Chem. Commun.* **1997**, 107.