SIMPLE SYNTHETIC STRATEGY TO INHERENTLY CHIRAL CALIX[4]ARENE BY AN ASYMMETRIC CALIX[4]QUINONE AS A KEY INTERMEDIATE†

Saeed Taghvaei-Ganjali*, Mehdi Shafai, Morteza Khosravi
Department of Chemistry, Islamic azad University North Tehran Branch, Tehran, Iran, P.O. Box: 19585/936, Fax: +98-21-2944678, *e-mail: taghvaei@hotmail.com*

†This paper is dedicated to Prof. Dr. Junes Ipaktschi on occasion of his 62th birthday

Received 29-12-2001

Abstract

A simple procedure is developed to synthesize the cone shaped asymmetrically substituted calix[4]arene **5**. The resulting chiral calix[4]arene **5** with two hydroxy groups could be used to build up the chiral calix[4]arene hosts.

Introduction

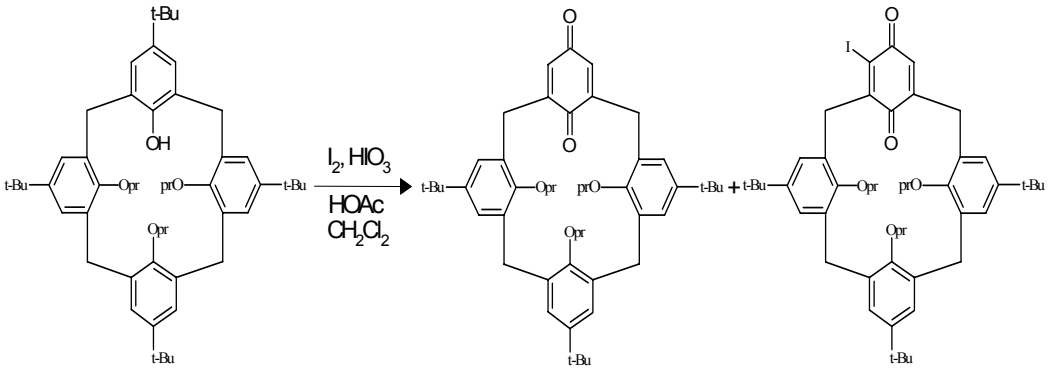
Calix[4]arenes are receptor molecules useful as enzyme mimics.[1-3] However, to mimic the enantioselective behavior of enzymes, it is necessary to use receptors having chiral cavities.[4] Although chiral calix[4]arene derivatives can be obtained by attaching chiral residues at the upper or lower rim[5-8] of the calixarene skeleton, recent interest[9-11] has been focused on the possibility of synthesizing inherently chiral calix[4]arenes, built up of nonchiral subunits still chiral due to the fact that the calixarene molecule is not planar.

Three strategies have been used for the preparation of inherently chiral calix[4]arenes: a) The fragment condensation. b) Asymmetrical arrangement of different substituents at the lower or upper rim. c) Direct introduction of a substituted at the meta position. The first one is based on stepwise synthesis of asymmetric calixarenes having three or four different phenolic units. In most cases this methodology have serious synthetic problems. The second strategy is based on the regio and stereoselective functionalization of convential calixarenes at the lower or upper rim and molecular asymmetry is introduced after the macrolization step. Meta substituted calixarene have been obtained by shinkai in tricarbonylchromium calixarene. Gutsche reported the 1,4-

conjugate addition reaction in calix[4]monoquinones to give asymmetrically meta-substituted calix[4]arene.

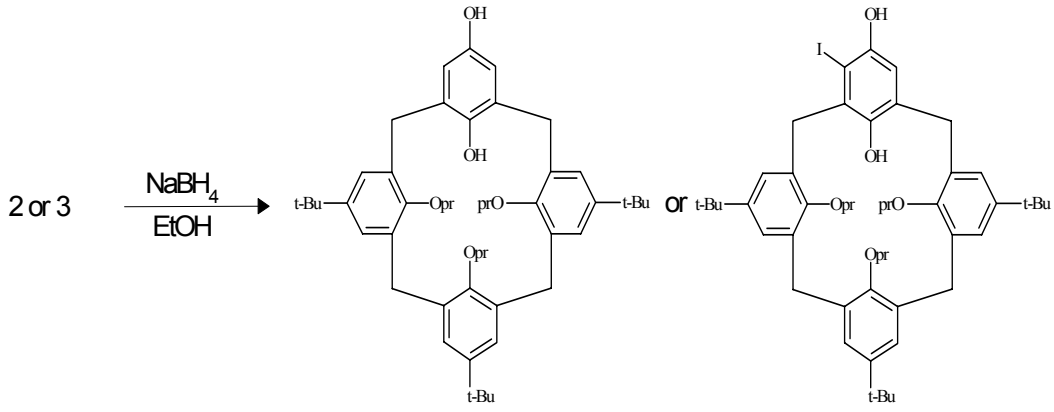
Results and discussion

In the present communication we describe a very simple method for the preparation of asymmetrically, meta-substituted calixarene by direct introduction of a iodine atom at the meta position of one aryl unit.



1 2 3

The synthesis was done by oxidation of rigidly cone conformation of calix[4]arene triether **1**[12].Oxidation of **1** by HIO_3/I_2 affords a mixture of quinone **2** and its iodo substituted **3** (in 3:1 ratio). Reduction of **3** produce **5** in quantitative yeild. ^{1}H-NMR spectroscopy of **5** shows the bridge methylene protons (Ar-C**H**$_2$-Ar) as four doublet of doublet. Also the ^{13}C-NMR spectrum exhibits a set of 24 peaks for aromatic region indicating the asymmetric structure of **5**.



4 5

Experimental

Melting points are taken on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM-400MHz in $CDCl_3$ with

Me_4Si as an internal standard. Elemental analyses were carried out on Carlo-Erba-Analysor Model 1104. IR spectra were recorded on Bruker IFS 25 spectrophotometer.

Procedure for the preparation of 2 and 3: To solution of 10 mmol of compound 1 in 50 ml acetic acid and 75 ml CH_2Cl_2 was added concentrated sulfuric acid (2ml), iodine (5gr 19.6mmol) and HIO_3 (2.5gr, 14.2mmol). Then reaction mixture was stirred vigorously at room temperature for 8 h. The resulting dark brown solution was decolorized with $Na_2S_2O_5$ (100ml of a 10% solution) The organic layer was separated, washed three times with water, dried over Na_2SO_4 and evaporated to dryness. Crystallization of the crude material from ethanol gave yellow crystals of 2 in 63% yield.

Compound **3** was obtained by column chromatography of the remained liquor after crystallization of using CH_2Cl_2/n-hexane (1:3) as eluent in 32% yield.

5,11,17-Tri-*tert*-butyl-26,27,28-tris(propoxy)-calix[4]-25-quinone(2), mp. 214-217 °C; δH (400 MHz; $CDCl_3$) 0.62[3H, t, CH_3], 0.86[6H, t, CH_3], 0.87[18H, s, $C(CH_3)_3$], 1.18[9H, s, $C(CH_3)_3$], 1.66 [4H, m, CH_2], 1.75[2H, m, CH_2], 2.94, 3.99[4H, d of d, J=12.7 Hz, $ArCH_2Ar$], 3.35[4H, s, $ArCH_2Ar$], 3.41[4H, t, OCH_2], 3.52[2H, t, OCH_2], 6.41[2H, d, J=2.4, ArH], 6.44[2H, s, ArH], 6.68[2H, d, J=2.4, ArH], 6.94[2H, s, ArH]; δC(100MHz) 9.18, 10.70, 22.16, 23.64, 30.86, 31.34, 31.65, 33.78, 34.02, 35.22, 76.09, 76.35, 77.62, 125.63, 126.36, 127.43, 132.77, 133.47, 135.68, 144.97, 145.61, 146.94, 148.25, 148.88, 149.52, 153.86, 154.12, 186.28, 189.18; M/Z(FD) 733(m^+,100%). Anal. calcd for $C_{49}H_{64}O_5$:C, 80.29%; H, 8.80%; found C, 80.14%; H, 9.21%.

5,11,17-Tri-*tert*-butyl-24-iodo-26,27,28-tris(propoxy)-calix[4]-25-quinone (3), mp. 177-179 °C; δH (400 MHz; $CDCl_3$) 0.74[3H, t, CH_3], 0.84[3H, t, CH_3], 0.89[9H, s, $C(CH_3)_3$], 0.91[9H, s, $C(CH_3)_3$], 0.94[3H, t, CH_3], 1.26[9H, s, $C(CH_3)_3$], 1.76[2H, m, CH_2], 1.88-1.92[4H, m, CH_2], 3.04, 4.10[4H, d of d, J=12.8, $ArCH_2Ar$], 3.32, 4.22[2H, d of d, J=13.6, $ArCH_2Ar$], 3.58, 4.22[2H, d of

d, J=13.7, $ArCH_2Ar$], 3.30-3.86[6H, m, OCH_2], 6.49[1H, d, J=2.4, ArH], 6.53[1H, d, J=2.4, ArH], 6.68[1H, d, J=2.4, ArH], 6.78[1H, s, ArH], 6.83[1H, d, J=2.4, ArH], 7.00[1H, d, J=2.4 ArH], 7.02[1H, d, J=2.4, ArH]; δC(100 MHz) 9.33, 10.21, 10.69, 21.94, 23.52, 23.57, 31.03, 31.12, 31.33, 31.65, 31.72, 33.79, 33.99, 40.79, 75.61, 76.54, 77.24, 125.19, 125.23 125.50, 126.22, 126.28 126.63, 127.02, 127.29, 131.50, 132.69, 133.02, 135.63, 135.72, 144.97, 144.99, 147.28, 153.87, 153.92, 155.25, 181.29, 183.56; M/Z(FD) 859(m^+,100%). Anal. calcd for $C_{49}H_{63}O_5I$:C, 68.51%; H, 7.39; found C, 69.10%; H, 7.54%.

*Procedure for the preparation of **4** and **5***: To solution of 1.36 mmol of **2** or **3** in 25 ml ethanol, sodium borohydride was added (0.12gr, 3.2 mmol). The reaction mixture was stirred at room temperature until the yellowish solution turned colorless. HCl (10ml, 0.2 N) and 50 ml CH_2Cl_2 was added. The organic layer was separated, washed with water and $NaHCO_3$ (10% solution), dried over Na_2SO_4 and evaporated to dryness. The product thus obtained was enough pure for subsequent reactions and could be further purified by crystallization in CH_2Cl_2/MeOH.

5,11,17-Tri-*tert*-butyl-23,25-dihydroxy-26,27,28-tris(propoxy)-calix[4]aren (4), mp 205-208 °C; δH(400 MHz; $CDCl_3$) 0.86[18H, s, $C(CH_3)_3$], 0.93[3H, t, CH_3], 1.08 [6H, t, CH_3], 1.33[9H, s, $C(CH_3)_3$], 1.89 [4H, m, CH_2], 2.31[2H, m, CH_2], 3.16, 4.33[4H, d of d, J=13.3, $ArCH_2Ar$], 3.18, 4.37[4H, d of d, J=12.6, $ArCH_2Ar$], 3.72[4H, t, OCH_2], 3.84[2H, t, OCH_2], 4.22[1H, s, OH], 4.90[1H, s, OH], 6.52[2H, d, J=2.3, ArH], 6.56[2H, d, J=2.3, ArH], 6.58[2H, s, ArH], 7.12[2H, s, ArH]; δC(100 MHz) 9.49, 10.66, 10.74, 22.34, 23.30, 23.36, 39.63, 31.02, 31.06, 31.08, 31.28, 31.63 34.09, 34.50, 69.47, 76.31, 77.62, 77.91 113.62 123.31, 124.39, 125.07, 125.21, 125.60, 125.67, 130.37, 130.94, 132.07, 132.15, 132.43, 134.41, 135.84, 136.16, 145.11, 145.53, 145.61, 145.73, 146.77,

147.83, 151.51, 152.07, 153.78; M/Z(FD) 735(m^+,100%). Anal. calcd for $C_{49}H_{66}O_5$:C, 80.07%; H, 9.05%; found C, 80.19%; H, 9.09%.

5,11,17-Tri-*tert*-butyl-24-iodo-23,25-dihydroxy-26,27,28-tris(propoxy)-calix[4]aren (5), mp 165 °C ; δH (400 MHz; $CDCl_3$) 0.81[9H, s, $C(CH_3)_3$], 0.86[9H, s, $C(CH_3)_3$], 0.94[3H, t, CH_3], 1.09 [3H, t, CH_3], 1.26[3H, t, CH_3], 1.35[9H, s, $C(CH_3)_3$], 1.82-1.94 [4H, m, CH_2], 2.36[2H, m, CH_2], 3.18, 4.29[2H, d of d, J=13.3, $ArCH_2Ar$], 3.21, 4.35[2H, d of d, J=12.3, $ArCH_2Ar$], 3.21, 4.38[2H, d of d, J=12.5, $ArCH_2Ar$], 3.81, 4.53[2H, d of d, J=13.8, $ArCH_2Ar$], 3.67-3.76[4H, m, OCH_2], 3.84[2H, m, OCH_2], 5.05[1H, s, OH], 5.09[1H, s, OH], 6.51[1H, d, J=2.8, ArH], 6.52[1H, d, J=2.8, ArH], 6.58[1H, d, J=2.3, ArH], 6.65[1H, d, J=2.3, ArH], 6.84[1H, s, ArH], 7.15[2H, s, ArH]; δC(100 MHz) 9.49, 10.66, 10.74, 22.34, 23.30, 23.36, 39.63, 31.02, 31.06, 31.08, 31.28, 31.63, 34.09, 34.50, 69.47, 76.31, 77.62, 77.91, 113.62, 123.31, 124.39, 125.07, 125.21, 125.60, 125.67, 130.37, 130.94, 132.07, 132.15, 132.43, 134.41, 135.84, 136.16, 145.11, 145.53, 145.61, 145.73, 146.77, 147.83, 151.51, 152.07, 153.78; M/Z(FD) 861(m^+,100%). Anal. calcd for $C_{49}H_{65}O_5I$:C, 68.36%; H, 7.61; found C, 68.37%; H,7.82%.

Acknowledgements

Saeed Taghvaei-Ganjali is grateful to the Research Council of Islamic azad University. Generous support from Prof. Dr. J. Ipaktschi, Institute of Organic Chemistry, Giessen University is highly acknowledged.

References and Notes

1. S. Shinkai, *Pure & Appl. Chem*. **1986**, *58*, 1523.
2. V. Bohmer*, Angew. Chem*. **1995,** *107*, 785.
3. M. Gardiner and C. Raston, *Coord. Chem. Rev*. **1997**, *166*, 1.
4. W. Saenger, *Angew.Chem. Int. Ed*. **1980**, *19*, 344.
5. K. Iwamoto, K. Araki and S. Shinkai, *J. Org. Chem*. **1991**, *113* , 2385.
6. C. D. Gutsche and K. C. Nam, *J. Am. Chem. Soc*. **1988**, *110*, 6153.
7. R. Muthukrishnan and C. D. Gutsche, *J. Org. Chem*. **1979**, *44*, 3962.
8. S. Shinkai, Arimura, T. Arimura and H. Satoh, *J. Chem. Soc.; Chem. Commun*. **1987**,1495.
9. V. Bohmer, A. Volff, W. Vogt; *J. Chem. Soc, Chem. Commun*. **1990**, 968.
10. V. Bohmer, A. Volff, W. Vogt; *J. Org. Chem*. **1990**, *55*, 5665.
11. G. Andreetti, V. Bohmer, M. Tabatabai*; J. Org. Chem*. **1993**, *58*, 4023.
12. K. Iwamoto; K. Araki and S. Shinkai, *Tetrahedron* **1991**, *25* , 4325.

Povzetek

Razvili smo preprosto metodo za sintezo asimetrično substituiranega kaliks[4]arena **5**, ki lahko služi za sintezo kiralnih kaliks[4]arenskih gostiteljev.