Notes

Calix[4]arenes with Two Differently Substituted Phenolic Units

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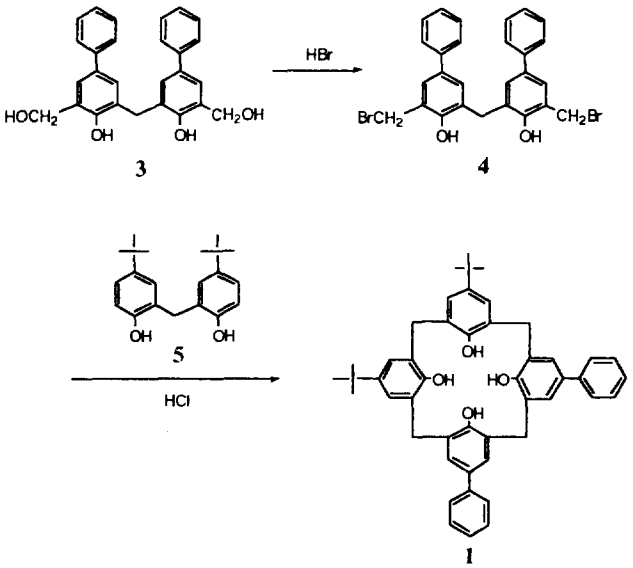
Calix[4]arenes of differently substituted phenolic units are attractive with respect to the long term goal of calixarene research, *viz.* the construction of a new type of enzyme mimics[1,2]. In principle, calix[4]arenes with different phenolic units in a definite sequence can be obtained by a stepwise procedure, the last step being the cyclization of a monohydroxymethylated linear tetramer[3,4]. A shorter way that consists of the stepwise synthesis of suitable di- or tri-nuclear compounds from which the calixarenes are formed in the final step by condensation was published by Bohmer[5,6]. Here a suitable bisbromomethylated compound is treated with the appropriate oligomer having two reactive ortho-positions.

The 4'-position of the biphenyl unit is directly amenable to functionalization, and the 4-position of *p-tert*-butylphenyl unit can be functionalized after removal of the *tert*-butyl group by the de-*tert*-butylation. Mixed calix[4]arenes, containing two nuclei of *p*-phenylphenol and two nuclei of *p-tert*-butylphenol, are attractive starting material for the syntheses of functionalized calix[4]arenes. Calix[4]arene **1** that consists of two different phenolic units in the order of AABB, is also used as starting material for the synthesis of chiral calixarene as reported by No and Gutsche[7] and Bohmer[8].

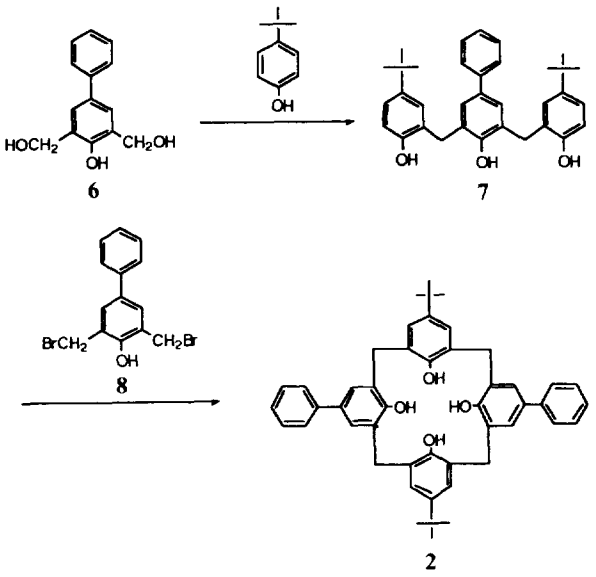
Calix[4]arene **1** was first synthesized by No and Gutsche[7], in which a *p*-phenylphenol was treated with formaldehyde under carefully controlled conditions to produce the bis-hydroxymethyl dimer **3**. Acid catalyzed arylation of **3** with two equivalents of *p-tert*-butylphenol yielded tetramer which was selectively hydroxymethylated to form monohydroxymethyl tetramer. Acid-catalyzed cyclization using the standard Hayes and Hunter conditions[9] then produces the mixed calix[4]arene **1**. The principal drawback in the published method is the separation of monohydroxymethylated tetramer from non-hydroxymethylated and bis-hydroxymethylated tetramer, which lowered the total yield to only *ca.* 10%. Therefore in this paper we deal with the improved synthesis of the *p*-phenyl-*p-tert*-butylcalix[4]arene **1** and also report the synthesis of isomeric calix[4]arene **2** as shown on Scheme 1 and 2 respectively.

Bis-hydroxymethyl dimer **3** was prepared using the published procedure[7]. When the mixture of *p*-phenylphenol, 37% formaldehyde and KOH was stirred for 4 days at 40℃, the mixture of compound **3** and **6** was resulted as white solid from which compound **3** and **6** can be separated from one another by the fact that the compound **3** is sparingly soluble in boiling chloroform. After the product mixture was boiled with chloroform, the insoluble material was collected by filtration while it was hot. A recrystallization of chloroform insoluble material from methanol afforded **3** in 55% yield, making this material easily preperable in large quantity. Compound **3** was refluxed with conc HBr[10] to produce the bis bromomethyl dimer **4** in 75% yield. Compound **5**, the other part of this convergent synthesis, was prepared by acid-catalyzed condensation of *p-tert*-butylphenol and paraformaldehyde. After the mixture of *p-tert*-butylphenol, paraformaldehyde and conc HCl in *p*-xylene was heated at 70℃ for 15 hr, the unreacted *p-tert*-butylphenol and solvent were removed by steam distillation. The residue was dissolved in chloroform, washed with water several times, dried over $MgSO_4$ and then evaporated to give a yellow oil, which was recrystallized from hexane to yield compound **5** in 92% yield (based on consumed *p-tert*-butylphenol). Reactions carried out under more strenuous conditions contain higher oligomers. The compound **1** was prepared by the '2+2' convergent method developed by Bohmer and coworkers[6]. A solution of compounds **4** and **5** in dioxane was added dropwise to the refluxing solution of $TiCl_4$ in dioxane. After reflux under nitrogen, the dark red solution was evaporated, the residue was dissolved in chloroform, and, after the addition of silica gel, the resultant mixture was evaporated again. The silica gel was extracted with hexane in a Soxhlet apparatus to remove unwanted by products and the titanium complex. The crude product was recrystallized from chloroform and hexane to give the pure product **1** in 20% yield. The physical and spectral data of this compound were identical with those reported in the literature[7]. The overall yield (*ca.* 9%) is comparable with the published method, however, the handling procedures are much simpler. The high yield and easy purification of compound **3** and **5** make this new convergent route attractive.



Scheme 1.

In the preparation of **3**, bis-(hydroxymethyl)monomer **6** was also isolated in moderate yield (35%), thus **6** becomes



Scheme 2.

a readily available starting material for the synthesis of another mixed calix[4]arene **2**. Therefore calix[4]arene **2** of ABAB pattern was prepared by the '3+1' coupling as shown on Scheme 2.

The chloroform solution, which was obtained after removal of hot chloroform insoluble material, was concentrated and then treated with hexane. The resulting precipitate, the mixture of **3** and **6**, was recrystallized from water to afford **6** in 35% yield. When the reaction was carried out under milder condition, the yield of **6** was increased up to 50% with concomitant decrease of that of compound **3**. Compound **6** was treated with HBr to produce bis-(bromomethyl) monomer **8** in 67% yield. The conversion of **6** to the linear trimer **7** by *p*-toluenesulfonic acid catalyzed reaction with *p-tert*-butylphenol was straightforward, and when a large excess of *p-tert*-butylphenol was used, it afforded **7** in 94% yield. The excess *p-tert*-butylphenol could be easily removed by steam distillation. The calix[4]arene **2** was synthesized in 25% yield by '3+1' coupling method. The mixed solution of **6** and **7** in dioxane was added dropwise to the solution of $TiCl_4$ in dioxane. The routine work-up, same as that of calix [4]arene **1**, and recrystallization of the crude product from chloroform and methanol gave pure product **2** in 25% yield.

Experimental

Melting points of all compounds were taken in a sealed and evacuated capillary tube on a Syblon themolyne apparatus with polarizing microscope and were not corrected. IR spectra were determined on a Shimadzu IR-435 spectrometer. ^{1}H-NMR spectra were recorded on Varian EM-360A (60 MHz) or Varian Gemini 300 (300 MHz) instrument and ^{13}C-NMR spectra on the Varian Gemini 300 (75 MHz) spectrometer. Chemical shifts are reported as δ values in parts per million relative to TMS (δ 0.0) as an internal standard. TLC analyses were carried out on silica gel plates (absorbent thickness 250 μm). Flash chromatography[11] was carried out with E. Merck silica gel (230-400 mesh ASTM). Elution rate were 2 in./min.

3-(3-Hydroxymethyl-5-phenylsalicyl)-5-phenyl-2-hydroxybenzyl alcohol 3. A mixture of 15.3 g (90 mmole) of *p*-phenylphenol and 75 mL of 37% formaldehyde was cooled in an ice bath, treated slowly with 10.2 g of KOH, and then stirred for 4 d at 40℃. The resulting yellow paste was suspended in ice-cold water, acidified with 10% HCl, and the precipitate was collected by filtration. The crude product, which showed two major components by TLC, was heated with 100 mL of boiling chloroform, and the insoluble fraction was collected by filtration, washed twice with 20 mL of chloroform, and once with 50 mL of hexane, and recrystallized from methanol to yield 10.12 g (55%) of **4** as a powder; mp. 128-129℃ (lit[7] 127-128℃); IR (KBr) 3340 (OH), 880 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^{1}H-NMR (acetone-d_6) δ 7.55-7.20 (m, 14, ArH), 4.89 (s, 4, CH_2O), 4.11 (s, 2, CH_2), 3.48 (s, 3, OH).

2-(3-Bromomethyl-5-phenylsalicyl)-4-phenyl-6-hydroxymethylphenol 4. A solution of 6.0 g (14 mmol) of compound **3** in 50 mL of benzene was added 7 mL of conc HBr and refluxed for 19 h, while water was removed using Dean-Stark trap. After quenching the reaction by adding 25 mL of 6 N NaOH, the organic layer was separated, washed in succession with 10% HCl, brine and water, dried over $MgSO_4$, and then evaporated to dryness. The resulting residue was recrystallized from chloroform and hexane to yield 5.65 g (75%) of compound **4** as a colorless powder; mp. 158-159℃; IR (KBr) 3400 cm^{-1} (br, OH); ^{1}H-NMR (Aceton d_6) δ 6.9-7.6 (m, 16, ArH & OH), 4.8 (s, 4, CH_2O), 4.2 (s, 2, CH_2).

2-(5-tert-Butylsalicyl)-4-*tert*-butylphenol 5. A solution of 22.5 g (250 mmol) of *p-tert*-butylphenol and 19.5 g of paraformaldehyde in 190 mL of xylene was added 8 mL of conc HCl. After the mixture was heated at 50℃ during 24 h, unreacted *p-tert*-butylphenol was removed by steam distillation. The resulting solid was dissolved in chloroform and the chloroform solution was washed with water, dried over $MgSO_4$, evaporated to dryness, and then triturated with a small amount of hexane. The precipitate was filtered and recrystallized from chloroform and hexane to give 17.6 g (75% based on staring *p-tert*-butyphenol, 92% based on consumed *p-tert*-butylphenol) of the desired product as colorless powder; mp. 157-158℃; IR (KBr) 3210 (OH), 820 cm^{-1} (1,2,4-trisubstituted Ar); ^{1}H-NMR ($CDCl_3$) δ 7.60-6.80 (m, 8, ArH and OH), 3.90 (s, 2, CH_2), 1.21 (s, 18, t-Bu).

5,11-Diphenyl-17,23-di-*tert*-butyl-25,26,27,28-terahydroxycalix[4]arene 1. In a 1 L three neck flask equipped with condenser, dropping funnel and stirrer, a mixture of 150 mL of dry dioxane and 1.7 mL (15.5 mmole) of $TiCl_4$ was refluxed under nitrogen. A solution of 2.00 g (3.5 mmole) of **4** and 1.20 g (3.8 mmole) of **5** in 200 mL of dried dioxane was added during 6 h. After refluxing was continued for 53 h, the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform, and after addition of 20 g of silica gel, the solvent was evaporated again. The silica gel was extracted for 1.5 d with hexane in a Soxhlet apparatus. After removal of solvent, the residue was recrystallized from chloroform and hexane to give 0.53 g (20%) of a colorless crystalline solid; mp. 332-333℃ (lit[4] 332-333℃); IR (KBr) 3160 (OH), 875 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^{1}H-NMR ($CDCl_3$) δ 10.31 (s, 4, OH), 7.35 (m, 10, ArH), 7.27 (s, 4, ArH), 7.07 (s, 4, ArH), 3.95 (br, 8, CH_2); ^{13}C-NMR ($CDCl_3$)

δ 134.4 (Ar), 132.5 (Ar), 123.7 (Ar), 119.0 (Ar), 118.6 (Ar), 118.3 (Ar), 117.8 (Ar), 117.6 (Ar), 116.9 (Ar), 116.8 (Ar), 116.3 (Ar), 116.1 (Ar), 42.6 (C of tBu), 41.3 (CH_2), 40.5 (CH_3 of t-Bu).

2,6-Bishydroxymethyl-4-phenylphenol 6. This compound was isolated from chloroform solution after removal of **3** as a chloroform-insoluble material from the reaction product mixture. The chloroform solution was concentrated to 100 mL, added 50 mL of hexane, and then stood overnight at room temperature. The precipitate was collected by filtration, washed with hexane and dried over $MgSO_4$. Recrystallization from water afforded 7.29 g (35%) of the desired product as needles; mp. 116-117℃ ; IR (KBr) 3360 (OH), 873 cm^{-1} (1,2,3,5-tetrasubstituted Ar); ^{1}H-NMR (acetone-d_6) δ 7.78-7.18 (m, 7, ArH), 4.80 (s, 4 CH_2), 4.10 (br, 3, OH).

2-[3-(5-*tert*-Butylsalicyl)-5-phenylsalicyl]-4-*tert*-butylphenol 7. A solution of 60.0 g (400 mmole) of *p*-*tert*-butylphenol and 130 mg of *p*-TsOH in 200 mL of benzene was refluxed. A total of 10.0 g (43.5 mmole) of **6** was added in portions over a period of 8 h, and the reflux was extended overnight. After removing the excess *p*-*tert*-butylphenol by steam distillation, the residue was collected by filtration, washed with water and dried over $MgSO_4$. Recrystallization of the crude product from hexane afforded 20.2 g (94%) of a colorless crystalline **7**; mp. 204-206℃ ; IR (KBr) 3290 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ 8.66 (br, 3, OH), 7.47-6.76 (m, 13, ArH), 4.00 (s, 4, CH_2), 1.30 (s, 18, tBu).

2,6-Bis bromopmethyl-4-phenylphenol 8. A solution of 3.20 g (14 mmole) of **6** and 7 mL of conc HBr in 100 mL of benzene was refluxed for 19 h with removing the water by Dean Stark trap. The reaction was quenched with 6 N NaOH and the organic layer was separated, washed successively with 10% HCl, water and brine, and dried over $MgSO_4$. The residue obtained by evaporation of solvent was recrystallized twice from chloroform and hexane to yield 3.35 g (67%) of **8** as a colorless powder; mp. 125-127℃ ; IR (KBr) 3400 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ 7.70-7.50 (m, 7, ArH), 5.70 (s, 1, OH), 4.60 (s, 4, CH_2).

5,17-Di-*tert*-butyl-11,23-diphenyl-25,26,27,28-tetrahydroxycalix[4]arene 2. In a 1-L three neck round-bottomed flask equipped with condenser, dropping funnel and stirrer a mixture of 150 mL of dried dioxane and 1.7 mL (15.5 mmole) of $TiCl_4$ was refluxed under nitrogen. A solution of 1.20 g (3.5 mmole) of **8** and 1.87 g (3.7 mmole) of **7** in 300 mL of dioxane was added during 6 h. After refluxing was continued for 53 h, the reaction mixture was worked up as the same method as compound **1** and afforded 0.60 g (25%) of colorless crystalline **2**; mp; >360℃ ; IR (KBr) 3200 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) δ 10.38 (s, 4, OH), 7.38-7.24 (m, 18, ArH), 4.30 (d, 4, CH_2), 3.60 (d, 4, CH_2), 1.22 (s, 18, t-Bu); ^{13}C-NMR ($CDCl_3$) δ 149.00 (Ar), 147.23 (Ar), 145.39 (Ar), 141.60 (Ar), 136.02 (Ar), 129.09 (Ar), 129.03 (Ar), 128.38 (Ar), 127.99 (Ar), 127.39 (Ar), 127.09 (Ar), 126.49 (Ar), 34.25 (CH_2), 32.52 (C of tBu), 31.63 (CH_3 of tBu).

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A Convenient Synthesis of 2-methyl-8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo [4,3-a] pyrazines

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As part of an investigation on the synthesis of cephalosporin antibiotics[1,2], we needed various heterocyclic thiols, in particular, of bridgehead-nitrogen heterocycles containing the 1,2,4-triazole moiety, and we recently reported[3] the novel synthesis of 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazines. We now describe a general method for the preparation of hitherto unknown 2-methyl derivatives **6** based on the simple annulation of the pyrazinone ring onto the triazole ring precursor **5** followed by the previously reported method[3].

The reaction of methyl *N*-(2,2-dimethoxyethyl)dithiocarbamate (**1**) with methylhydrazine was carried out in ethanol at reflux temperature and gave a regioselective product, 4-(2,2-dimethoxyethyl)-2-methylthiosemicarbazide (**2**) in good yield (88%). The reaction of 2-methylthiosemicarbazide **2** with ethyl oxalyl chloride in the presence of triethylamine in tetrahydrofuran afforded 1-ethoxyoxalyl-2-methylthiosemicarbazide **3**, which was used in the next step without purification. Interestingly the reaction of **3** with excess ammonia or primary amines in water at room temperature gave cycli-