An Efficient Synthetic Approach to Substituted Trisphenols (Phloroglucide Analogues) Using Tungstosilicic Acid in Water

Reza Fareghi-Alamdari,*[a] Ali Khalafi-Nezhad,[b] Negar Zekri[a]

[a] Faculty of Chemistry & Chemical Engineering, Malek-Ashtar University of Technology, Tehran, Iran
Fax +98(21)22970195; E-mail: reza_fareghi@yahoo.com

[b] College of Science, Department of Chemistry, Shiraz University, Shiraz, Iran

Received: 17.11.2013; Accepted after revision: 08.01.2014

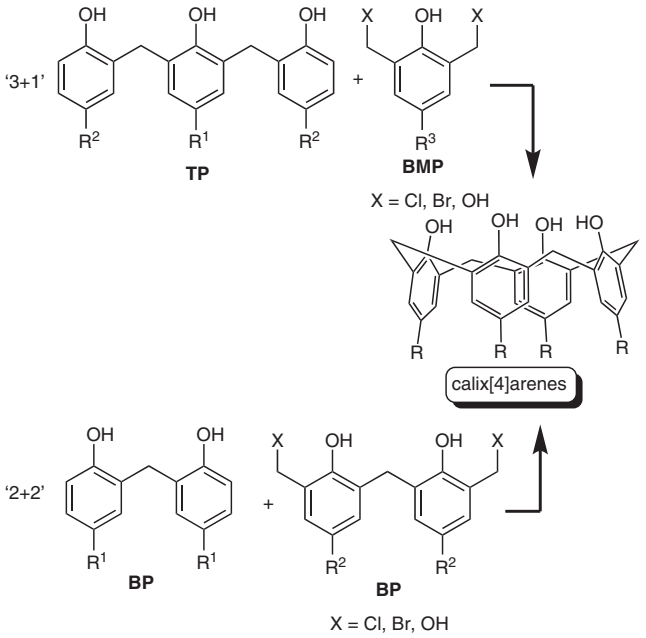
Abstract: Tungstosilicic acid was found to be an efficient catalyst for the synthesis of trisphenols using the reaction of 2,6-bis(hydroxymethyl)phenols with phenols in an aqueous medium. The catalytic reactivity of tungstosilicic acid in boiling water was examined with a series of substrates, demonstrating that this catalyst is reactive in the presence of a variety of functionalities.

Key words: tungstosilicic acid, trisphenols, phenols, 2,6-bis(hydroxymethyl)phenols, synthesis

There are many natural products, pharmaceuticals, catalysts and advanced materials with phenolic structural units.[1] The presence of hydroxy groups in the structure of these materials results in special activity.[2] Some important and biologically active phenol-based compounds have been isolated from nature.[3] Also, a large number of complex molecules have been synthesized in a single or multistep process by the use of phenols as reagents in organic reactions.[4] One of the most important classes of phenolic compounds is comprised of polyhydroxy aromatic (PHA) compounds. Members of this category of materials show versatile biological activities and have been used as drugs in the treatment of many diseases.[5] In addition to being potent pharmaceuticals in their own right, they play a versatile role in organic synthesis, especially for the preparation of calixarenes and macrocyclic crown ethers.[6]

Calixarenes have seen widespread use as receptors for cations, anions and neutral molecules, and can be used as sensitive sensors for the detection of special molecules.[7] Owing to the wide applications and significance of calixarenes, there is considerable interest in the synthesis of these compounds.[8] It is noteworthy that in most of the reported methods for the multistep synthesis of calixarenes, PHA compounds are the main starting material.

The convergent stepwise synthesis (fragment condensation procedure) of calixarenes has been extensively studied by Böhmer and co-workers, with two different strategies based on the use of PHA compounds in '3+1' and '2+2' procedures in which trisphenols (TP) and bisphenols (BP) are the main starting materials (Scheme 1).[9]



Scheme 1 The '3+1' and '2+2' convergent stepwise synthesis of calix[4]arenes

The choice between the '3+1' and '2+2' procedures often depends on the relative ease of construction of the component parts; however, the diversity of the obtained calix[4]arenes via method '3+1' is greater than that via method '2+2'. For example, employment of a trisphenol which carries two different substituents R^1 and R^2 on the structure leads to a calix[4]arene with three differently substituted phenyl rings.[10]

On the other hand, in procedure '3+1' the key step is the synthesis of the starting trisphenols, and there are few methods for the preparation of these compounds. Although each of the methods has its benefits, they often suffer from one or more disadvantages. Low yield, the use of only reactive substrates, the production of analogues containing three similar phenolic rings, the use of a large excess of phenolic compounds, tedious workup processes, oxidation of the phenolic hydroxy groups, alkyl isomerization and hazardous reaction conditions are the most important deficiencies associated with these methods.[5f,g,11–14]

Owing to the importance of the described compounds, and in continuation of our previous studies on the preparation of polyhydroxy aromatic compounds,[15] herein, we present tungstosilicic acid (TSA) as a novel catalyst for the prep-

SYNTHESIS 2014, 46, 0887–0892
Advanced online publication: 11.02.2014
DOI: 10.1055/s-0033-1340681; Art ID: SS-2013-N0484-OP

aration of trisphenols from 2,6-bis(hydroxymethyl)phenols [2,6-bis(methylol)phenols, BMP] and various substituted phenols in an aqueous medium.

We first synthesized BMP **1a–d** based on literature procedures.[16] Then, the reaction between 4-chloro-2,6-bis(hydroxymethyl)phenol (**1c**) and 4-chlorophenol (**2a**) was chosen as a model to establish optimized conditions for the preparation of 4-chloro-2,6-bis(5-chloro-2-hydroxybenzyl)phenol (**3a**). The results of the optimization study are summarized in Table 1.

When the reaction was carried out in the absence of catalyst, no product was observed, even after 24 hours (Table 1, entry 1). To obtain the desired product **3a**, we tested various Brønsted and Lewis acids in the model reaction (Table 1, entries 2–12). The use of silica sulfuric acid (SSA)[13] in water solvent led to none of the desired product, even after 12 hours, while this catalyst showed good reactivity in 1,4-dioxane solvent (Table 1, entries 2 and 3). Aluminum methanesulfonic acid (AMA)[17] was the next catalyst tested for this reaction: a trace amount of product was observed after 12 hours in water, and 35% yield of **3a** was obtained in methanol solvent (Table 1, entries 4 and 5).

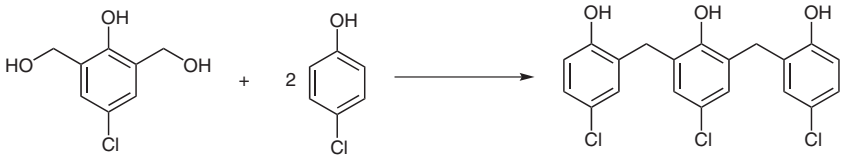
Then, tungstophosphoric acid (TPA)[18] and molybdatophosphoric acid (MPA),[19] as two important members of Keggin-type heteropolyacids, were tested; no significant improvement in the reaction yield was observed (Table 1, entries 6 and 7). Interestingly, TSA showed a good reactivity and was the best catalyst tested. In the presence of 4 mol% of TSA, compound **3a** was isolated in 86% yield after only 5 hours in water as a 'green' solvent (Table 1, entry 8). The advantages in using heteropolyacid catalysts are as follows: high catalytic performance, strong acidity, recycling capability, selectivity to a particular reaction product by selective stabilization of the reaction intermediate, safety, lower waste, and ease of separation.[20] Performing the reaction in the presence of $ZnCl_2$, TiO_2 or

Table 2 Effect of Temperature on the Reaction of BMP **1c** with 4-Chlorophenol (**2a**) in the Presence of TSA Catalyst in Water[a]

Entry	Temp (°C)	Time (h)	Yield[b] (%)
1	r.t.	24	trace
2	50	24	23
3	80	12	61
4	reflux	5	86

[a] Reaction conditions: **1c** (1 mmol), **2a** (3 mmol), TSA (0.04 g), H_2O (5 mL).
[b] Isolated yield.

Table 1 Optimization of the Reaction between BMP **1c** and 4-Chlorophenol (**2a**)[a]



1c **2a** **3a**

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	–	H_2O	24	0
2	SSA	H_2O	12	0
3	SSA	1,4-dioxane	2	78
4	AMA	H_2O	12	trace
5	AMA	MeOH	5	35
6	TPA	H_2O	5	51
7	MPA	H_2O	5	39
8	TSA	H_2O	5	86
9	$ZnCl_2$[c]	H_2O	12	0
10	TiO_2[c]	H_2O	12	trace
11	LiCl[c]	H_2O	12	0
12	PTSA[d]	H_2O	12	trace

[a] Reaction conditions: **1c** (1 mmol), **2a** (3 mmol), catalyst (0.04 g), solvent (5 mL), reflux.
[b] Isolated yield.
[c] 20 mol% of catalyst was used.
[d] 50 mol% of catalyst was used.

Table 3 Optimization of the TSA Catalyst Loading in the Reaction of BMP **1c** with 4-Chlorophenol (**2a**) in Water[a]

Entry	Amount of catalyst	Time (h)	Yield[b] (%)
1	4 mol% H^+	5	86
2	2 mol% H^+	12	71
3	3 mol% H^+	12	78
4	5 mol% H^+	5	89
5	6 mol% H^+	5	85

[a] Reaction conditions: **1c** (1 mmol), **2a** (3 mmol), TSA, H_2O (5 mL), reflux.
[b] Isolated yield.

Table 4 Effect of the Amount of 4-Chlorophenol (**2a**) in the Model Reaction with BMP **1c**[a]

Entry	Ratio **2a**/**1c**	Time (h)	Yield[b] (%)
1	3:1	5	89
2	4:1	5	86
3	2:1	12	78
4	2.5:1	12	84

[a] Reaction conditions: **1c**, **2a**, TSA (0.05 g), H_2O (5 mL), reflux.
[b] Isolated yield.

LiCl as Lewis acid in water resulted in the production of **3a** in trace amounts (Table 1, entries 9–11). *p*-Toluenesulfonic acid (PTSA) showed no reactivity for this reaction in water (Table 1, entry 12).

The effect of temperature on the progress of the model reaction was investigated next, and the results are summarized in Table 2; the best yield was obtained under reflux conditions (entry 4).

In optimization studies of the TSA catalyst loading, it was established that 5 mol% of catalyst is sufficient to obtain maximum product in a relatively short reaction time (Table 3).

To determine the best stoichiometric ratio of phenol to BMP, we performed the model reaction with **1c** in the presence of different amounts of 4-chlorophenol (**2a**) (Table 4); the best yield was obtained with a ratio of 3 mmol of phenol per 1 mmol of BMP (entry 1).

Thus, under the optimized reaction conditions (refluxing water, 5 mol% catalyst loading, ratio phenol/BMP 3:1), a series of trisphenols **3b**–**r** were synthesized (Table 5).

It is clear from Table 5 that the TSA catalyst is effective for the synthesis of trisphenols using the reaction of phenols with BMP. Although the catalytic activity of TSA is dependent on the type of phenol, all of the phenols were converted into the corresponding products in excellent yields. The wide scope capability of this protocol was highlighted by the application of both phenols with electron-withdrawing groups and phenols with electron-donating groups under the same reaction conditions. In all cases, the reactions were accomplished in relatively short reaction times (see Table 5). The functional group compatibility of this reaction was highlighted by the use of 4-allyl-2-methoxyphenol as an acid-sensitive substrate (Table 5, entries 14 and 15).

In general, the synthesis of trisphenols using TSA as a catalyst in an aqueous medium has some advantages, including the following: 1) the reaction is carried out in water as a 'green' solvent; 2) this protocol avoids the use of corrosive and toxic acidic catalysts; 3) a catalytic amount of TSA and a minimum amount of phenol are required.

In summary, trisphenols were synthesized using tungstosilicic acid as a catalyst under mild conditions. The tungstosilicic acid catalyst efficiently promoted the reaction between phenols and 2,6-bis(hydroxymethyl)phenols in water to produce the target products **3a**–**r** in excellent isolated yields.

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies, and were used without further purification. Compounds **1a**–**d** were prepared according to previously reported procedures.[16] The known products were characterized by comparison of their spectroscopic and physical data with literature data. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution with TMS as an internal standard on a Bruker Avance 250 MHz spectrometer. Chemical shifts are given in the δ scale in parts per million (ppm) and the couplings are assigned as singlet (s), doublet (d), triplet (t) and multiplet (m). FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed for compound characterization. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. Reaction monitoring was accomplished by TLC on silica gel Polygram SILG/UV254 plates.

Substituted 2,6-Bis(2-hydroxybenzyl)phenols 3; General Procedure

Into a conical flask containing a 2,6-bis(hydroxymethyl)phenol **1a**–**d** (1 mmol), a substituted phenol (3 mmol) and H_2O (5 mL), was added a catalytic amount of TSA (0.14 g, 5 mol%), and the reaction mixture was refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction (see Table 5 for reaction time), the mixture was cooled to r.t. and then extracted with EtOAc (2 × 20 mL). The combined organic extract was dried over Na_2SO_4, filtered and concentrated, and the product was purified by column chromatography (hexane–EtOAc).

4-Chloro-2,6-bis(5-chloro-2-hydroxybenzyl)phenol (3a)[12]

Yield: 0.36 g (89%); yellow solid; mp 233–235 °C.

IR (KBr): 3150, 3010, 2980, 1610, 1220 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.82 (s, 4 H), 6.67–7.09 (m, 8 H), 8.82 (br s, 1 H), 9.82 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.6, 116.4, 122.4, 122.8, 126.9, 127.2, 128.4, 129.4, 129.5, 151.4, 153.9.

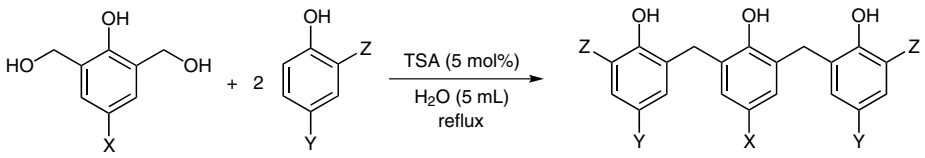
Anal. Calcd for $C_{20}H_{15}Cl_3O_3$: C, 58.63; H, 3.69. Found: C, 58.61; H, 3.70.

4-Chloro-2,6-bis(2-hydroxy-5-methylbenzyl)phenol (3b)[12]

Yield: 0.30 g (82%); white solid; mp 137–139 °C.

IR (KBr): 3208, 3018, 2876, 1605, 1448, 810 cm^{-1}.

Table 5 Synthesis of Trisphenols **3** by the Reaction of Phenols with 2,6-Bis(hydroxymethyl)phenols Using TSA in Refluxing Water



1 mmol 3 mmol **3a–m**

1a: X = Me, **1b**: X = F
1c: X = Cl, **1d**: X = Br

Entry	X	Y	Z	Time (h)	Product	Yield[a] (%)
1	Cl	Cl	H	5	**3a**	89
2	Cl	Me	H	4	**3b**	82
3	Cl	F	H	5	**3c**	81
4	Br	Br	H	5	**3d**	81
5	Cl	Br	H	6	**3e**	85
6	Br	Cl	H	6	**3f**	84
7	F	F	H	5	**3g**	89
8	Me	Cl	H	5	**3h**	87
9	Cl	OH	H	3	**3i**	86
10	Cl	NO_2	H	6	**3j**	80
11	Cl	Ph	H	6	**3k**	82
12	Br	F	H	5	**3l**	83
13	Me	Me	H	5	**3m**	80
14	Cl	$CH_2CH{=}CH_2$	OMe	6	**3n**	81
15	Br	$CH_2CH{=}CH_2$	OMe	6	**3o**	80
16	F	F	Ac	8	**3p**	79
17	Cl	F	Ac	8	**3q**	79
18	Cl	Me	*t*-Bu	5	**3r**	85

[a] Isolated yields.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.13 (s, 6 H), 3.77 (s, 4 H), 6.68–6.83 (m, 8 H), 8.69 (br s, 1 H), 9.34 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 20.1, 29.6, 114.8, 122.6, 125.6, 126.7, 127.5, 127.6, 130.1, 130.9, 151.1, 152.4.

Anal. Calcd for $C_{22}H_{21}ClO_3$: C, 71.64; H, 5.74. Found: C, 71.73; H, 5.81.

4-Chloro-2,6-bis(5-fluoro-2-hydroxybenzyl)phenol (3c)[13]
Yield: 0.32 (81%); white solid; mp 223–224 °C.

IR (KBr): 3190, 1600, 1495, 1445, 1235, 1190 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.80 (s, 4 H), 6.77–6.89 (m, 8 H), 8.75 (s, 1 H), 9.57 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.7, 113.1, 113.4, 115.5, 116.1, 122.9, 127.1, 127.6, 129.5, 151.3, 153.5, 157.2.

Anal. Calcd for $C_{20}H_{15}ClF_2O_3$: C, 63.75; H, 4.01. Found: C, 63.67; H, 3.92.

4-Bromo-2,6-bis(5-bromo-2-hydroxybenzyl)phenol (3d)[12]
Yield: 0.44 g (81%); yellow solid; mp 237–238 °C.

IR (KBr): 3200, 3090, 2950, 1600, 1250 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.81 (s, 4 H), 6.76–7.20 (m, 8 H), 8.8 (s, 1 H), 9.89 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.4, 110.0, 110.7, 117.0, 128.9, 129.8, 129.9, 130.0, 132.3, 151.8, 154.3.

Anal. Calcd for $C_{20}H_{15}Br_3O_3$: C, 44.23; H, 2.78. Found: C, 44.23; H, 2.83.

2,6-Bis(5-bromo-2-hydroxybenzyl)-4-chlorophenol (3e)[13]
Yield: 0.42 g (85%); white solid; mp 251–253 °C.

IR (KBr): 3150, 3020, 2990, 1600, 1220 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 3.84 (s, 4 H), 6.78–7.21 (m, 8 H), 9.68 (br s, 3 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.6, 110.1, 117.0, 122.9, 127.2, 128.9, 129.4, 129.8, 132.4, 151.4, 154.3.

Anal. Calcd for $C_{20}H_{15}Br_2ClO_3$: C, 48.18; H, 3.03. Found: C, 48.27; H, 3.09.

4-Bromo-2,6-bis(5-chloro-2-hydroxybenzyl)phenol (3f)[13]
Yield: 0.38 g (84%); pale-yellow solid; mp 235–236 °C.

IR (KBr): 3150, 3050, 2950, 1600, 1220 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.82 (s, 4 H), 6.74–7.18 (m, 8 H), 8.8 (br s, 1 H), 9.86 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.5, 110.7, 116.4, 122.4, 126.9, 128.3, 129.0, 129.5, 130.0, 151.9, 153.8.

Anal. Calcd for $C_{20}H_{15}BrCl_2O_3$: C, 52.89; H, 3.33. Found: C, 52.95; H, 3.36.

4-Fluoro-2,6-bis(5-fluoro-2-hydroxybenzyl)phenol (3g)[21]
Yield: 0.32 g (89%); white solid; mp 239–240 °C.

IR (KBr): 3150, 3050, 2950, 1600, 1220 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.82 (s, 4 H), 6.58–6.84 (m, 8 H), 8.5 (br s, 1 H), 9.56 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 15.8, 123.8, 124.0, 125.4, 126.6, 127.2, 128.5, 132.8, 134.2, 151.5.

Anal. Calcd for $C_{20}H_{15}F_3O_3$: C, 66.67; H, 4.20. Found: C, 66.71; H, 4.24.

2,6-Bis(5-chloro-2-hydroxybenzyl)-4-methylphenol (3h)[14]
Yield: 0.34 g (87%); white solid; mp 235–236 °C.

IR (KBr): 3135, 3030, 2930, 1600, 1485, 1420, 1390 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.06 (s, 3 H), 3.80 (s, 4 H), 6.63–7.19 (m, 8 H), 8.32 (br s, 1 H), 9.8 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 20.3, 29.6, 116.2, 122.3, 126.4, 126.7, 127.7, 128.0, 129.2, 129.5, 144.9, 153.7.

Anal. Calcd for $C_{21}H_{18}Cl_2O_3$: C, 64.79; H, 4.66. Found: C, 64.83; H, 4.69.

2,2′-[(5-Chloro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(benzene-1,4-diol) (3i)[12]
Yield: 0.32 g (86%); light-brown crystals; mp 179–180 °C.

IR (KBr): 3200, 3020, 2990, 1610, 1600, 1500, 1450, 1250, 850 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.89 (s, 4 H), 6.49–6.83 (m, 8 H), 8.65 (s, 2 H), 8.77 (br s, 1 H), 9.00 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.7, 113.6, 115.5, 116.8, 122.7, 126.7, 126.8, 130.0, 147.0, 149.7, 151.2.

Anal. Calcd for $C_{20}H_{17}ClO_5$: C, 64.44; H, 4.60. Found: C, 64.42; H, 4.67.

4-Chloro-2,6-bis(2-hydroxy-5-nitrobenzyl)phenol (3j)[13]
Yield: 0.34 g (80%); yellow solid; mp 221–223 °C.

IR (KBr): 3400, 3090, 2920, 1630, 1590, 1500, 1300 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.86 (s, 4 H), 6.87–7.06 (m, 4 H), 7.89–8.22 (m, 4 H), 8.86 (br s, 1 H), 11.15 (br s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.6, 114.9, 122.9, 124.0, 125.7, 127.6, 128.8, 129.4, 139.5, 151.6, 161.8.

Anal. Calcd for $C_{20}H_{15}ClN_2O_7$: C, 55.76; H, 3.51. Found: C, 55.85; H, 3.46.

3,3′-[(5-Chloro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(1,1′-biphenyl-4-ol) (3k)[13]
Yield: 0.40 g (82%); white solid; mp 144–145 °C.

IR (KBr): 3200, 3030, 2910, 1610, 1600, 1520, 1490, 1220 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.87 (s, 4 H), 6.7–7.61 (m, 18 H), 8.82 (s, 1 H), 9.79 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 33.4, 115.7, 117.3, 125.2, 125.8, 125.9, 126.7, 128.3, 128.6, 129.7, 129.8, 130.9, 140.6, 157.2, 159.7.

Anal. Calcd for $C_{32}H_{25}ClO_3$: C, 77.96; H, 5.11. Found: C, 78.11; H, 5.16.

4-Bromo-2,6-bis(5-fluoro-2-hydroxybenzyl)phenol (3l)[16]
Yield: 0.35 g (83%); white solid; mp 231–232 °C.

IR (KBr): 3190, 2935, 1612, 1501, 1241, 1019 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.81 (s, 4 H), 6.74–7.03 (m, 8 H), 9.36 (br s, 3 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.7, 110.6, 113.0, 113.4, 115.6, 116.5, 127.6, 130.0, 151.0, 151.9.

Anal. Calcd for $C_{20}H_{15}BrF_2O_3$: C, 57.03; H, 3.59. Found: C, 57.10; H, 3.64.

2,6-Bis(2-hydroxy-5-methylbenzyl)-4-methylphenol (3m)[14]
Yield: 0.28 g (80%); white solid; mp 214–215.5 °C.

IR (KBr): 3440, 3291, 3001, 1580, 1430, 1345, 1231 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.06 (s, 3 H), 2.14 (s, 6 H), 3.82 (s, 4 H), 6.64–6.82 (m, 8 H), 9.25 (s, 3 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 20.2, 20.3, 29.6, 114.7, 126.7, 127.2, 127.3, 127.4, 127.5, 128.2, 130.6, 149.8, 152.1.

Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.35; H, 6.99.

6,6′-[(5-Chloro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(4-allyl-2-methoxyphenol) (3n)[13]
Yield: 0.39 g (81%); pale-yellow solid; mp 55–57 °C.

IR (KBr): 3450, 3090, 2985, 2950, 1600, 1510, 1450 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.16 (d, J = 6.6 Hz, 4 H), 3.63 (s, 4 H), 3.72 (s, 6 H), 4.83 (dd, J = 16.5, 10.3 Hz, 4 H), 5.21 (br s, 3 H), 5.71–5.73 (m, 2 H), 6.89–7.31 (m, 6 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 30.1, 40.0, 56.4, 111.3, 115.4, 117.5, 122.7, 124.4, 125.9, 128.7, 134.0, 138.8, 141.7, 143.0, 156.3.

Anal. Calcd for $C_{28}H_{29}ClO_5$: C, 69.92; H, 6.08. Found: C, 70.01; H, 6.15.

6,6′-[(5-Bromo-2-hydroxy-1,3-phenylene)bis(methylene)]bis(4-allyl-2-methoxyphenol) (3o)[13]
Yield: 0.42 g (80%); light-brown solid; mp 59–60 °C.

IR (KBr): 3450, 3087, 2982, 2953, 1659, 1516, 1432, 1198 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 3.36 (d, J = 6.4 Hz, 4 H), 3.86 (s, 4 H), 4.39 (s, 6 H), 5.03 (dd, J = 16.8, 10.3 Hz, 4 H), 5.15 (br s, 3 H), 5.95–5.97 (m, 2 H), 6.47–7.33 (m, 6 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 29.6, 40.4, 56.5, 111.4, 115.3, 117.7, 122.7, 124.4, 125.8, 128.7, 134.5, 138.3, 141.3, 143.2, 154.4.

Anal. Calcd for $C_{28}H_{29}BrO_5$: C, 64.01; H, 5.56. Found: C, 64.09; H, 5.61.

1,1′-{[(5-Fluoro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(5-fluoro-2-hydroxy-3,1-phenylene)}bis(ethan-1-one) (3p)
Yield: 0.35 g (79%); light-yellow solid; mp 145–147 °C.

IR (KBr): 3460, 3085, 2980, 1600, 1450, 1211, 1095, 1005, 950 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.64 (s, 6 H), 3.92 (s, 4 H), 6.63 (d, J = 9.2 Hz, 1 H), 6.83 (s, 1 H), 7.10–7.20 (m, 2 H), 7.67 (dd, J = 8.6, 2.2 Hz, 2 H), 8.56 (s, 1 H), 8.89 (s, 1 H), 12.41 (s, 1 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.1, 29.1, 114.0, 114.7, 118.7, 123.6, 124.0, 127.5, 128.5, 130.6, 151.9, 155.7, 205.3.

Anal. Calcd for $C_{24}H_{19}F_3O_5$: C, 64.86; H, 4.31. Found: C, 64.79; H, 4.26.

1,1′-{[(5-Chloro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(5-fluoro-2-hydroxy-3,1-phenylene)}bis(ethan-1-one) (3q)
Yield: 0.37 g (79%); pale-yellow solid; mp 149–151 °C.

IR (KBr): 3390, 3061, 2985, 1593, 1448, 1201, 1090, 1025, 890 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 2.64 (s, 6 H), 3.91 (s, 4 H), 6.83 (s, 2 H), 7.14–7.19 (m, 2 H), 7.64–7.69 (m, 2 H), 8.89 (s, 1 H), 12.41 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 27.1, 29.1, 114.4, 114.7, 118.7, 123.0, 123.6, 124.0, 127.5, 128.8, 130.5, 130.6, 151.7, 151.9, 155.7, 205.2, 205.3.

Anal. Calcd for $C_{24}H_{19}ClF_2O_5$: C, 62.55; H, 4.16. Found: C, 62.49; H, 4.11.

6,6′-[(5-Chloro-2-hydroxy-1,3-phenylene)bis(methylene)]bis(2-*tert*-butyl-4-methylphenol) (3r)
Yield: 0.41 g (85%); white solid; mp 191–193 °C.

IR (KBr): 3552, 3510, 2995, 2915, 1445, 1170, 1090, 1020, 870 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 1.38 (s, 18 H), 2.11 (s, 6 H), 3.95 (s, 4 H), 6.61–6.97 (m, 6 H), 7.45 (s, 1 H), 8.12 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 20.9, 29.6, 32.2, 35.1, 126.0, 127.5, 127.8, 128.5, 131.6, 131.8, 135.0, 137.9, 147.2, 151.1.

Anal. Calcd for $C_{30}H_{37}ClO_3$: C, 74.90; H, 7.75. Found: C, 74.99; H, 7.81.

Acknowledgment

We acknowledge the financial support from the Malek-Ashtar University of Technology.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Stockley, C.; Teissedre, P. L.; Boban, M.; Lorenzo, C. D.; Restani, P. *Food Funct.* **2012**, *3*, 995. (b) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29. (c) Guo, Y. J.; Deng, G. F.; Xu, X. R.; Wu, S.; Li, S.; Xia, E. Q.; Li, F.; Chen, F.; Ling, W. H.; Li, H. B. *Food Funct.* **2012**, *3*, 1195. (d) Hasegawa, I.; Nakamura, T.; Motojima, S.; Kajiwara, M. *J. Mater. Chem.* **1995**, *5*, 193.
(2) (a) Weinger, J. S.; Strobel, S. A. *Biochemistry* **2006**, *45*, 5939. (b) He, K.; Shi, G.; Zhao, G. X.; Zeng, L.; Ye, Q.; Schwedler, J. T.; Wood, K. V.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, *59*, 1029. (c) Parker, S. F. *Chem. Commun.* **2011**, *47*, 1988. (d) Niu, F.; Liu, C. C.; Cui, Z. M.; Zhai, J.; Jiang, L.; Song, W. G. *Chem. Commun.* **2008**, 2803.
(3) (a) Huang, H.; Sun, H. D.; Wang, M. S.; Zhao, S. X. *J. Nat. Prod.* **1996**, *59*, 1079. (b) Song, M. C.; Nigussie, F.; Jeong, T. S.; Lee, C. Y.; Regassa, F.; Markos, T.; Baek, N. I. *J. Nat. Prod.* **2006**, *69*, 853. (c) Nomura, T.; Hano, Y. *Nat. Prod. Rep.* **1994**, *11*, 205. (d) Whiting, D. A. *Nat. Prod. Rep.* **2001**, *18*, 583.
(4) (a) Money, T. *Chem. Rev.* **1970**, *70*, 553. (b) Kametani, T.; Fukumoto, K.; Yagi, H.; Satoh, F. *Chem. Commun.* **1967**, 878.
(5) (a) Widén, C.-J.; Fraser-Jenkins, C. R.; Lounasmaa, M.; Euw, J.v.; Reichstein, T. *Helv. Chim. Acta* **1973**, *56*, 831. (b) Appendino, G.; Ottino, M.; Marquez, N.; Bianchi, F.; Giana, A.; Ballero, M.; Sterner, O.; Fiebich, B. L.; Munoz, E. *J. Nat. Prod.* **2007**, *70*, 608. (c) Closse, A.; Sigg, H. P. *Helv. Chim. Acta* **1973**, *56*, 619. (d) Albert, A. *Nature* **1953**, *172*, 201. (e) Fu, G. M.; Yu, B. Y.; Zhu, D. N. *J. Asian Nat. Prod. Res.* **2006**, *8*, 149. (f) Hakimelahi, G. H.; Moshfegh, A. A. *Helv. Chim. Acta* **1981**, *64*, 599. (g) Moshfegh, A. A.; Mazandarani, B.; Nahid, A.; Hakimelahi, G. H. *Helv. Chim. Acta* **1982**, *65*, 1229.
(6) (a) Böhmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200. (b) Kraft, D.; Cacciapaglia, R.; Böhmer, V.; El-Fadl, A. A.; Harkema, S.; Mandolini, L.; Reinhoudt, D. N.; Verboom, W.; Vogt, W. *J. Org. Chem.* **1992**, *57*, 826.
(7) Sharma, K.; Cragg, P. J. *Chem. Sens.* **2011**, *1*, 1.
(8) (a) Gutsche, C. D. *Calixarenes: An Introduction*, 2nd ed.; RSC Publishing: Cambridge, **2008**. (b) *Calixarenes*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J.; Saadioui, M., Eds.; Kluwer Academic Publishers: Dordrecht, **2001**.
(9) (a) Böhmer, V.; Chhim, P.; Kammerer, H. *Makromol. Chem.* **1979**, *180*, 2503. (b) Böhmer, V.; Merkel, L.; Kunz, U. *J. Chem. Soc., Chem. Commun.* **1987**, 896. (c) Böhmer, V.; Vogt, W. *Pure Appl. Chem.* **1993**, *65*, 403. (d) Pappalardo, S.; Ferguson, G.; Gallagher, J. F. *J. Org. Chem.* **1992**, *57*, 7102. (e) Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267.
(10) Gopalsamuthiram, V.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 13936.
(11) Rodia, J. S. *J. Org. Chem.* **1961**, *26*, 2966.
(12) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Hakimelahi, G. H. *Helv. Chim. Acta* **2003**, *86*, 2396.
(13) Khalafi-Nezhad, A.; Parhami, A.; Bargebid, R.; Molazade, S.; Zare, A.; Foroughi, H. *Mol. Diversity* **2011**, *15*, 373.
(14) Foster, H. M.; Hein, D. W. *J. Org. Chem.* **1961**, *26*, 2539.
(15) (a) Fareghi-Alamdari, R.; Hosseinabadi, Z.; Farhadi-Khouzani, M. *J. Chem. Sci.* **2012**, *124*, 827. (b) Fareghi-Alamdari, R.; Golestanzadeh, M.; Agend, F.; Zekri, N. *C. R. Chim.* **2013**, *16*, 878. (c) Fareghi-Alamdari, R.; Golestanzadeh, M.; Agend, F.; Zekri, N. *J. Chem. Sci.* **2013**, *125*, 1185. (d) Fareghi-Alamdari, R.; Golestanzadeh, M.; Agend, F.; Zekri, N. *Can. J. Chem.* **2013**, *91*, 982.
(16) McGarry, E. J.; Forsyth, B. A. US Patent 4282390, **1981**.
(17) Sharghi, H.; Jokar, M. *Synth. Commun.* **2009**, *39*, 958.
(18) Firouzabadi, H.; Jafari, A. A. *J. Iran. Chem. Soc.* **2005**, *2*, 85.
(19) Heydari, A.; Khaksar, S.; Sheykhan, M.; Tajbakhsh, M. *J. Mol. Catal. A: Chem.* **2008**, *287*, 5.
(20) (a) Yang, L.; Xu, L. W.; Xia, C. G. *Tetrahedron Lett.* **2008**, *49*, 2882. (b) Timofeeva, M. N. *Appl. Catal., A* **2003**, *256*, 19.
(21) Forsyth, B. A.; McGarry, E. J. US Patent 4163801, **1979**.

