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A novel method for the upper rim alkoxy-substitution of calix[4]arene via a bis(spirodienone) route

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ABSTRACT

A mild and efficient one-step procedure for the upper rim modification of calix[4]arene via a bis(spirodienone) is described. The bis(spirodienone) on reaction with alcohols in the presence of *p*-TSA affords mono- and 1,3-disubstituted alkoxy derivatives in moderate to good yields.

Calix[4]bis(spirodienones) are versatile molecular skeletons derived from *p-tert*-butyl-calix[4]arene.[1] The rather fortuitous discovery of bis(spirodienones) comprising three isomers (either stereo or positional), dates back to 1992 and resulted from a mild oxidative cyclization reaction[2] of *p-tert*-butyl-calix[4]arene. Despite having a macrocyclic 14-membered cavity bordered with two sets of carbonyl and ether linkages in a non-alternate/alternate fashion, bis(spirodienones) are not suitable candidates as ionophores. This may be attributed to the orientation of the two carbonyl groups and ether linkages in opposite directions thereby creating a non-congenial environment for co-ordination of metal ions. However, bis(spirodienones) have been utilized successfully by Biali et al. for effecting transformations of *p-tert*-butyl-calix[4]arene into various analogues which are otherwise difficult to synthesize. Derivatization of the bridging methylene groups,[3] selective aminodehydroxylation[4] and replacement of the lower rim hydroxyls with methyl groups[5] are some of the functionalizations that have been reported on bis(spirodienones). There have also been reports on synthesis of extraannular-substituted calix[4]arenes possessing one or two fluorosubstituted dehydroxylated rings by reaction of bis(spirodienol) with DAST (Et_2NSF_3).[6]

Selective introduction of functional groups at the upper rim of calix[*n*]arenes is synthetically more challenging due to the involvement of two or more preliminary steps prior to functionalization. These involve selective protection of the phenolic hydroxyls followed by selective removal of the *tert*-butyl groups positioned at the upper rim. Reactions reported under this category are halogenation,[7] nitration,[8] sulfonation,[9] chloromethylation,[10] acylation,[11] formylation,[12] etc. Both exhaustive and selective *ipso*-substitutions such as sulfonation,[13] chlorosulfonation,[14] nitration[15] and formylation[16] of calixarenes requiring prior protection of the narrow rim hydroxyls have also been reported. A few scattered reports[17] have appeared on the indirect upper rim alkoxy-substitution of calix[*n*]arenes which involved multi-step conversions. Thus, the development of a simple and more versatile approach for the direct and selective upper rim alkoxylation of calixarene would be very useful for the synthesis of complex molecular receptors. In this context, the new methodology to selectively functionalize the upper rim of the calix moiety described in this Letter assumes importance. The acid-mediated reaction of bis(spirodienones), in the presence of primary alcohols affords, in single step, upper rim substituted mono- and 1,3-dialkoxy-calix[4]arenes in the cone conformation which are stabilized by a circular array of hydrogen bonds at the lower rim.

We came across this unprecedented reaction during our studies on the reactivity of the dienone carbonyls towards acetal formation. When we reacted the most stable bis(spirodienone) isomer **1** with 1,2-ethylene glycol in the presence of *p*-TSA, in addition to the expected cyclic acetal, a calix[4]arene with alkoxy-substitution at the upper rim was also obtained. Subsequently, we reacted **1** with dry methanol in anhydrous toluene under reflux in the presence of *p*-TSA (0.6 equiv) for 6 h (Scheme 1).[18] The reaction mixture after work up followed by column chromatography afforded a mixture of four products **3–6**.

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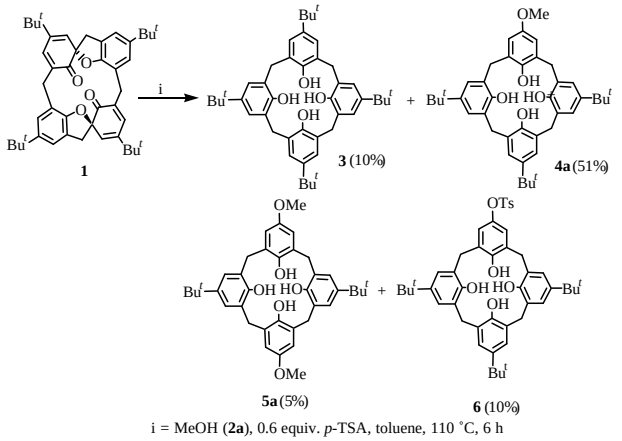
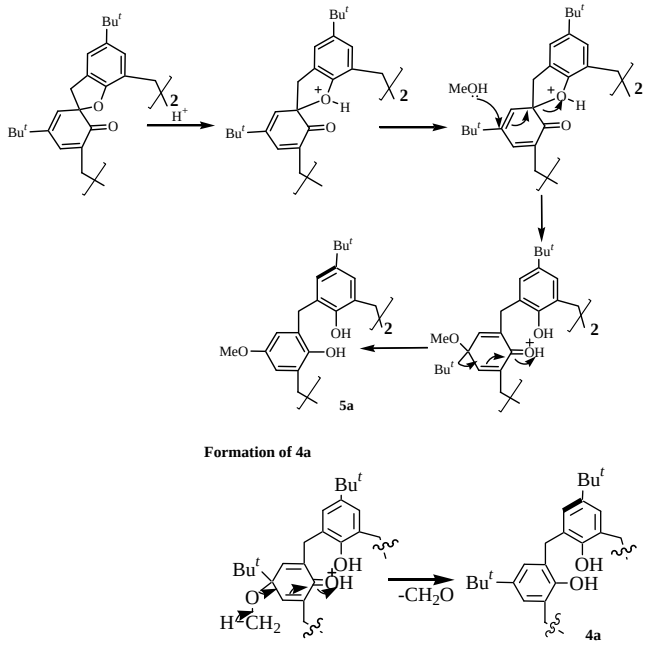


Scheme 1. *p*-TSA-mediated reaction of calix[4]bis(spirodienone) **1** with methanol.

The ^{1}H NMR spectrum of **3** revealed it to be *p*-*tert*-butyl-calix[4]arene. In the ^{1}H NMR spectrum of **4a**, the OH protons resonated at δ 10.20 and the OCH_3 protons occurred at 3.64 ppm as a sharp singlet. The *tert*-butyl groups appeared as two singlets at δ 1.22 and δ 1.19 in a 2:1 ratio. In the ^{13}C NMR spectrum, a peak at δ 55.3 corresponding to methoxy carbon was observed. The cone conformation was confirmed by the ^{13}C NMR spectrum which showed the methylene bridge carbons at δ 31.6 and δ 29.8.[19] The structures of the other products **5a** and **6** were established on the basis of spectral analyses (see Supplementary data).

The mechanism outlined in Scheme 2 is suggested to rationalize the formation of products **4a** and **5a**. Protonation of the spiro oxygen followed by the nucleophilic attack of methanol at one of the carbon atoms bearing a *tert*-butyl group results in the cleavage of the spiro bond and formation of a protonated cross-dienone. The aromaticity of cross-dienone can be achieved by the removal of the *tert*-butyl group resulting in the formation of the disubstituted product **5a**. The formation of the monosubstituted product **4a** can be explained by the oxidative removal of a molecule of formaldehyde at reflux temperature of toluene as indicated in Scheme 2.

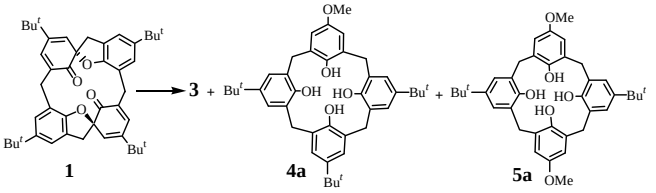


Scheme 2. A general mechanism for the reaction of **1** in the presence of MeOH and *p*-TSA.

Next, we investigated the effects of various Lewis acids on this reaction and the results are shown in Table 1.

A superior result was obtained employing $BF_3{\cdot}OEt_2$ (entry 3) but at the reflux temperature of toluene, mild etching of glassware was observed due to release of hydrogen fluoride vapours. The use of 5 equiv of *p*-TSA gave both mono- and dimethoxy calixarenes in

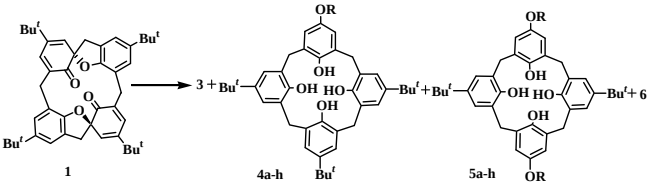
Table 1
Reaction of calix[4]bis(spirodienone) **1** and methanol using different catalysts



Entry	Lewis acid[a]	Yield (%)			
		3	**4a**	**5a**	**6**
1	*p*-TSA (0.6 equiv)	16	51	5	10
2	*p*-TSA (5 equiv)	11	32	45	13
3	$BF_3{\cdot}OEt_2$	6	56	22	—
4	Anhydrous $ZnCl_2$		No reaction		
5	Montmorillonite K-10		No reaction		
6	$Sc(OTf)_3$	17	50	—	—
7	$Cu(OTf)_2$	58	2	—	—
8	AgOTf	8	54	11	—
9	$Sn(OTf)_2$	26	(50:50)[b]	—	—
10	$La(OTf)_3$		No reaction		
11	$Yb(OTf)_3$		No reaction		
12	Camphor sulfonic acid		No reaction		

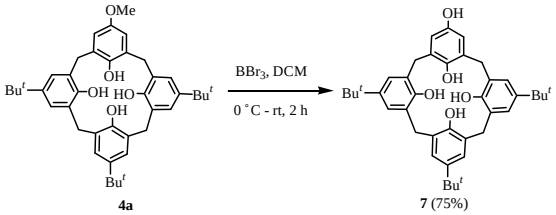
Reaction conditions: MeOH, toluene, 110 °C, 6 h.
[a] Unless otherwise stated, 0.6 equiv of Lewis acid was used.
[b] Obtained as an inseparable mixture of **4a** and **1**.

Table 2
Reaction of calix[4]bis(spirodienone) **1** with various alcohols



Entry	Lewis acid	Yield (%)			
		3	**4**	**5**	**6**
1	CH_3OH (**2a**)	11	**4a**/32	**5a**/45	15
2	OH (**2b**)	17	**4b**/49	—	20
3	OH (**2c**)	20	**4c**/37	—	26
4	OH (**2d**)	22	**4d**/35	—	28
5	OH (**2e**)	18	**4e**/30	—	31
6	OH (**2f**)	12	**4f**/33	**5f**/38	17
7	OH (**2g**)	16	**4g**/28	—	18
8	OH (**2h**)	20	**4h**/22	—	34

Reaction conditions: **2**, 5 equiv *p*-TSA, toluene, 110 °C, 6 h.
For entries 6–8, the reaction time is 10 min.



Scheme 3. Reaction of **4a** with BBr_3.

32% and 45% yields, respectively. Considering the cost effectiveness and ease of handling of the various catalysts used, 5 equiv of *p*-TSA in toluene was selected as the optimal acid concentration for upper rim modifications.

With the optimal conditions in hand, we next examined the reactivities of a variety of primary alcohols towards bis(spirodienones). The reaction was found to be general with both saturated and unsaturated alcohols yielding monosubstituted products **4** and **6** in all the cases investigated except for entries 1 and 6. Unsaturated alcohols (entries 6–8) were found to react faster and the reactions were complete within 10 min (Table 2).

The reaction of **4a** with BBr_3 in dichloromethane at 0 °C afforded 5-hydroxycalix[4]arene **7** in 75% yield (Scheme 3).[20] Although there has been a report on the synthesis of detertiarybutylated 5-hydroxy calix[4]arene,[21] to the best of our knowledge, this is the first synthesis of 7,11,23-tri-*p*-*tert*-butylcalix[4]arene with a hydroxyl group on the upper rim.

In conclusion, a direct and efficient acid-mediated protocol for the upper rim *ipso*-alkoxy substitution of calix[4]arene via bis(spirodienone) **1** has been described in this letter. The transformation is distinguished by mild reaction conditions, experimental simplicity and considerable generality. Studies to transform the upper rim-substituted products to highly functionalized macrocycles are underway and a detailed study of the reactivity of bis(spirodienones) with nucleophiles such as amines and thiols is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.118.

References and notes

1. For reviews on calixarenes see: (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989; (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713; (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; (d)*Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001.
2. Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, *57*, 1945.
3. (a) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flamig, G. *Macromol. Chem.* **1990**, *191*, 81; (b) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667; (c) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495; (d) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136; (e) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 95.
4. (a) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 1994; (b) Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645.
5. Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511.
6. (a) Agbaria, K.; Wohnert, J.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 7059; For a review on spirodienone calixarene derivatives, see: (b) Biali, S. E. *Synlett* **2003**, 1.
7. Arduini, A.; Pochini, A.; Sicuri, A. R.; Secchi, A.; Ungaro, R. *Gazz. Chim. Ital.* **1994**, *124*, 129.
8. (a) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313; (b) Kelderman, E.; Derhaeg, L.; Heesnik, G. J. T.; Verboom, W.; Engbersen, J. F. J.; van Hulst, N. F.; Persoons, A.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1057.
9. Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G. G. *Tetrahedron* **1993**, *49*, 9815.
10. Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177.
11. (a) Shinkai, S.; Nagasaki, T.; Iwamoto, K.; Ikeda, A.; Matsuda, T.; Iwamoto, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 381; (b) Conner, M.; Janout, V.; Regen, S. L. *J. Org. Chem.* **1992**, *57*, 3744.
12. Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936.
13. Atwood, J. L.; Bott, S. G. *Water Soluble Calixarene Salts. A Class of Compounds with Solid State Structures Resembling Those of Clays*, in Ref. 2, p 199.
14. Coquiere, D.; Cadeau, H.; Rondelez, Y.; Giorgi, M.; Reinaud, O. *J. Org. Chem.* **2006**, *71*, 4059.
15. Redon, S.; Li, Y.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 7004.
16. Arora, V.; Chawla, H. M.; Santra, A. *Tetrahedron* **2002**, *58*, 5591.
17. (a) Morita, Y.; Agawa, T. *J. Org. Chem.* **1992**, *57*, 3659; (b) Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361; (c) Arduini, A.; Mirone, L.; Peganuzzi, D.; Pinalli, A.; Pochini, A.; Secchi, A.; Ungaro, R. *Tetrahedron* **1996**, *52*, 6011.
18. *Typical experimental procedure*: A mixture of bis(spirodienone) **1** (50 mg, 0.08 mmol), methanol (4 equiv) and *p*-TSA (60 mol %) in toluene was stirred at reflux (110 °C). Refluxing was continued until the reaction was complete as shown by TLC (~12 h). The solvent was removed under reduced pressure. The reaction mixture was worked-up using dichloromethane–water mixture and the solid mass obtained was purified by column chromatography. With unsaturated alcohols, the reaction was complete within 10 min as indicated by thin layer chromatography. Spectral characterization of products **4a**: Yield: 32% as a white solid. R_f: 0.90, mp: Decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2960, 2858, 1800, 1259, 1053 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.20 (s, OH, 4H), 7.02 (m, ArH, 6H), 6.55 (s, ArH, 2H), 4.24 (d, J = 12.0 Hz, $ArCH_2Ar$, 4H), 3.64 (s, OMe, 3H), 3.46 (br s, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (C–OH), 146.9, 146.3, 144.4, 144.3, 142.6, 129.4, 127.9, 127.7, 127.3, 126.0, 125.9, 125.6, 113.9 (Ar–C), 55.3 (O–CH_3), 34.1, 32.6, 31.6, 31.5, 29.8 ($ArCH_2Ar$, –OCH_3, *t*-Bu). MS (FAB): calcd for $C_{41}H_{50}O_5$, M$^+$: 622.37; found: 622.85. Compound **5a**: Yield: 45% as a white solid. R_f: 0.83. Mp: Decomposed >240 °C. IR (KBr) ν_{max}: 3173, 2963, 1259, 1051 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.04 (s, OH, 4H), 7.04 (s, ArH, 4H), 6.52 (s, ArH, 4H), 4.23 (d, J = 13.2 Hz, $ArCH_2Ar$, 4H,), 3.62 (s, OMe, 6H), 3.43 (d, J = 14.7 Hz, $ArCH_2Ar$, 4H,), 1.24 (s, *t*-Bu, 18H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 147.1, 144.7, 144.4, 142.2, 132.4, 130.8, 129.8, 129.2, 128.8, 128.3, 128.1, 127.3, 125.7, 113.9, 55.9, 55.2 (–OCH_3), 34.0, 32.4, 31.5, 30.6, 29.7, 27.7, 21.6, 19.2. MS (FAB): calcd for $C_{38}H_{44}O_6$, M$^+$: 596.31; found: 596.23. Compound **6**: Yield: 15% as a brown semi-solid. R_f: 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.25 (s, OH, 4H), 7.70 (d, J = 8.3 Hz, ArH tolyl, 2H), 7.32 (m, ArH tolyl, 2H), 7.05 (m, ArH, 4H), 6.91 (s, ArH, 2H), 6.68 (m, ArH, 2H), 4.20 (br s, $ArCH_2Ar$, 4H), 3.44 (br s, $ArCH_2Ar$, 4H), 2.46 (s, CH_3, 3H), 1.20 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 148.2, 146.8, 146.2, 144.5, 142.7, 134.2, 129.6, 127.9, 127.6, 127.5, 127.1, 126.1, 125.9, 125.6, 123.3, 115.5, 56.0, 34.4, 34.0, 32.5, 32.3, 31.9, 31.5, 31.3, 31.1, 30.7, 29.7, 29.4, 26.9, 22.7, 14.1. MS (FAB): calcd for $C_{47}H_{54}O_7S$, M$^+$: 762.36; found: 762.77.
19. Jaime, C.; de Mendoza, J.; Prados, P.; Neito, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372.
20. *Procedure for the synthesis of 5-hydroxycalix[4]arene* (**7**): 7,11,23-Tri-*tert*-butyl-5-methoxycalix[4]arene, **4a** (50 mg, 0.08 mmol) was dissolved in 10 mL of dry dichloromethane and cooled in an ice-salt mixture. BBr_3 (30 mg, 0.12 mmol) was added over a period of 0.5 h and the reaction mixture was allowed to stir under argon for 3 h (0 °C). The extent of reaction was tested by TLC. The reaction mixture was worked-up using dichloromethane–water mixture and the product was obtained using column chromatography [petroleum ether–ethyl acetate (90:10)] as a colourless semi solid **7** (36 mg, 75%). R_f: 0.65. IR (KBr) ν_{max}: 3173, 2960, 2858, 1786, 1060 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.20 (s, OH, 4H), 7.04 (m, ArH, 6H), 6.53 (s, ArH, 2H), 4.10 (br s, $ArCH_2Ar$, 4H), 3.32 (br s, $ArCH_2Ar$, 4H), 1.22 (s, *t*-Bu, 18H), 1.19 (s, *t*-Bu, 9H), one of the OH protons could not be detected. ^{13}C NMR (75 MHz, $CDCl_3$): 153.9 (C–OH), 146.9, 146.3, 144.4, 144.3, 142.6, 129.4, 127.9, 127.7, 127.3, 126.0, 125.9, 125.6, 113.9 (Ar–C), 34.1, 32.6, 31.6, 31.5, 29.8 ($ArCH_2Ar$, *t*-Bu). MS (FAB): calcd for $C_{40}H_{48}O_5$, [M+1]$^+$: 609.81; found: 609.92.
21. Lee, M.-D.; Yang, K.-M.; Tsoo, C.-Y.; Shu, C.-M.; Lin, L.-G. *Tetrahedron* **2001**, *57*, 8095.