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Selective Syntheses of Partially Etherified Derivatives of Tetrakis(2-hydroxyphenyl)ethene. An Alternative to the Calix[4]arene Ligand System

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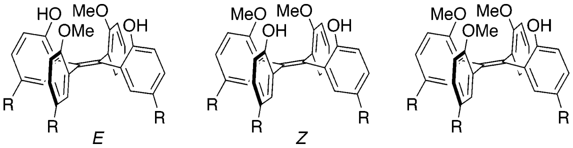
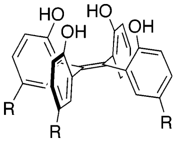
ABSTRACT



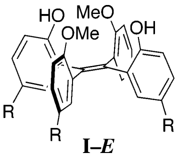
Stereoselective syntheses of (*E*)- and (*Z*)-1,2-bis(2′-hydroxyphenyl)-bis(2′-methoxyphenyl)ethene have been developed, the former by convergent coupling of an orthogonally protected 2,2′-benzophenone derivative and the latter by selective partial dealkylation of tetrakis(2-methoxyphenyl)-ethene. Selective single demethylation has also been demonstrated in the 5-*tert*-butyl series. Thus, divalent and monovalent derivatives of the preorganized tetrakis(2-hydroxyphenyl)ethene ligand system are now available for use in coordination chemistry, analogous to corresponding calix[4]arene systems.

We recently introduced a new structurally constrained multidentate ligand system based on tetrakis(2-hydroxyphenyl)ethene **1**,[1] a topologically distinct alternative to the ubiquitous calix[4]arene structural class.[2]

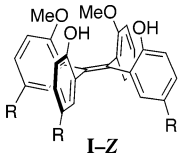


1a (R = H)
1b (R = ^{t}Bu)

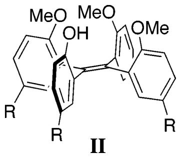
In an effort to enhance the potential utility of this new ligand template in coordination chemistry and catalysis, the development of functionally differentiated derivatives has been targeted. Among the most useful modifications accomplished in the calix[4]arene series is the selective partial etherification of the phenoxy residues, providing a malleable ligand system accommodating a range of metallic binding and valencies.[3]



I–*E*



I–*Z*



II

In this communication, we report stereoselective syntheses of the (*E*)- and (*Z*)-1,2-disubstituted bis(ether) derivatives **I** (R = H, ^{t}Bu), as well as selective generation of the tris(ether) derivative **II** (R = ^{t}Bu). The (*E*)-bis(ether) isomer

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(1) Verkerk, U.; Fujita, M.; Dzwiniel, T. L.; McDonald, R.; Stryker, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 9988−9989.

(2) (a) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001. (b) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989.

(3) Review: Thondorf, I.; Shivanyuk, A.; Böhmer, V. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, 2001; Chapter 2, pp 26−53.

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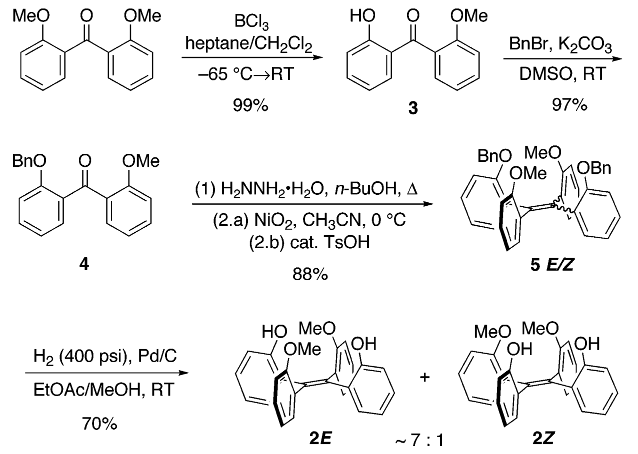
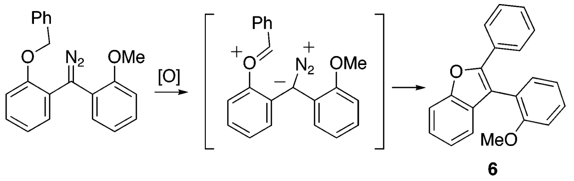
I−***E*** is accessible in reasonable selectivity by convergent synthesis; both (*Z*)-diether **I**−***Z*** and tris(ether) **II** can be prepared from symmetrically tetrasubstituted precursors directly by selective dealkylation reactions[4] starting with the readily accessible tetrakis(2-methoxyphenyl)ethene and tetrakis(5-*tert*-butyl-2-methoxyphenyl)ethene.[1]

The synthesis of isomer **2*E*** begins with 2-methoxy-2′-hydroxybenzophenone **3**,[5] prepared by the highly selective partial deprotection of 2,2′-dimethoxybenzophenone following a known procedure. Benzylation under standard conditions affords the differentially protected benzophenone **4** in near quantitative yield (Scheme 1).[6] Conversion to the tetrakis(2-alkoxyphenyl)ethene **5** then proceeds by acid-catalyzed coupling of the corresponding diazo derivative under conditions analogous to those developed by Verkerk for the synthesis of tetrakis(2-methoxyphenyl)ethene.[1,7] Thus, hydrazone formation, quantitative under standard conditions, was followed by oxidation with nickel peroxide[8] and in situ decomposition of the diazo intermediate using a catalytic amount of *p*-toluenesulfonic acid, providing an isomeric mixture of (*E*)- and (*Z*)-1,2-bis(2′-benzyloxyphenyl)-bis(2′-methoxyphenyl)ethenes **5*E*** and **5*Z*** in high yield. At this stage, the isomers are inseparable by column chromatography on silica gel and indistinguishable both by thin-layer chromatography and NMR spectroscopy.

Scheme 1



The oxidation of the hydrazone requires monitoring by thin-layer chromatography to minimize over-oxidation. Prolonged exposure to nickel peroxide leads to increasing formation of a byproduct, tentatively identified as the known diarylbenzofuran **6**[9] on the basis of NMR spectroscopy and high-resolution mass spectrometry.[6] This compound is presumed to arise from oxidation at the benzylic position, generating a transient benzyloxy carbocation, which ultimately undergoes intramolecular trapping by the diazoalkane prior to extrusion of dinitrogen (eq 1).[10]



(1)

Catalytic hydrogenolysis of **5*E/Z*** proceeds in polar medium at moderate pressure, producing a mixture of (*E*)- and (*Z*)-1,2-diols **2*E*** and **2*Z***, respectively, in good yield (Scheme 1). The ratio of stereoisomers varies from 3 to 7:1, depending on the precise reaction conditions, but always favors the formation of the (*E*)-isomer, presumably due to steric considerations. At this stage, separation of the olefin isomers can be accomplished either by selective crystallization or careful chromatography, the former abetted by the distinctly different crystal morphologies of the two isomers. This reproducibly delivers the pure (*E*)-isomer in isolated yields of about 40%, along with lesser amounts of the pure (*Z*)-isomer and mixed fractions.

Stereochemical assignment of the (*E*)- and (*Z*)-isomers of compound **2** was unambiguously established by X-ray crystallography of the more polar (*Z*)-isomer, which selectively crystallizes upon slow diffusion of hexanes into ethyl acetate (Figure 1).[6,11]

In an attempt to generate exclusively the (*E*)-isomer of **2**, tetrakis(2-hydroxyphenyl)ethene **1** was subjected to DDQ oxidation, with the expectation of "protecting" two trans-disposed arene rings as extended quinone **7** (Scheme 2). In the event, however, the oxidation proceeds exclusively to

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(4) In the calix[4]arene series, 1,2-bis(ether) derivatives (corresponding roughly to (*Z*)-isomer **I**−***Z***) and tris(ether) derivatives can be prepared by selective dealkylation of symmetrical tetrakis(ether) substrates. 1,2-Diether derivatives: (a) Arduini, A.; Casnati, A.; Dodi, L.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1990**, 968−970. (b) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, *47*, 2221−2228. Tris(ether) derivatives: (c) Iwamoto, K.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 7066−7073. (d) Ho, Z.-C.; Ku, M.-C.; Shu, C.-M.; Lin, L.-G. *Tetrahedron* **1996**, *52*, 13189−13200. The 1,3-dialkylated calix[4]arenes (corresponding to (*E*)-isomer **I**−***E***), as well as 1,2-diethers, are accessible by selective alkylation of the symmetrical parent. 1,3-Substitution: (e) van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639−5646. 1,2-Substitution: (f) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407−5409. (g) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675−2678. (h) Ferguson, G.; Gallagher, J. F.; Giunta, L.; Neri, P.; Pappalardo, S.; Parisi, M. *J. Org. Chem.* **1994**, *59*, 42−53.

(5) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Somvichien, N. *Tetrahedron Lett.* **1966**, *7*, 4153−4159.

(6) Experimental procedures and complete characterization data are provided as Supporting Information.

(7) This olefination procedure is adapted from the literature: Roberts, J. D.; Watanabe, W. *J. Am. Chem. Soc.* **1950**, *72*, 4869−4879. Bethell, D.; Callister, J. D. *J. Chem. Soc.* **1963**, 3801−3808.

(8) Nakagawa, K.; Onoue, H.; Minami, K. *J. Chem. Soc., Chem. Commun.* **1966**, 730−731.

(9) Sonoda, T.; Kobayashi, S.; Taniguchi, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2560−2566.

(10) Nickel peroxide reagent contains residual alkali; the observed over-oxidation product may arise by a less direct mechanism than suggested by eq 1.

(11) Crystal data for **2Z**: $C_{28}H_{24}O_4$, crystal size 0.25 × 0.12 × 0.04 mm^3, monoclinic, space group $P2_1/c$ (No. 14), Mo Kα ($\lambda = 0.71073$ Å), $a = 10.9757(13)$ Å, $b = 15.4466(18)$ Å, $c = 13.6421(13)$ Å, $\beta = 99.547(2)°$, $V = 2280.8(4)$ $Å^3$, $Z = 4$, $\mu = 0.082$ mm^{-1}, $\rho_{calcd} = 1.236$ g cm^{-3}, $F_{000} = 896$, $T = -80$ °C, $2\theta_{max} = 51.60°$, 12 189 total reflections, 4356 unique reflections ($R_{int} = 0.1625$), least-squares refinement on F^2, $R_1(F) = 0.0659$ (for 1167 reflections with $F_o^2 \geq 2\sigma(F_o^2)$), $wR_2(F^2) = 0.1837$, GOF(F^2) = 0.771 (for all unique data).

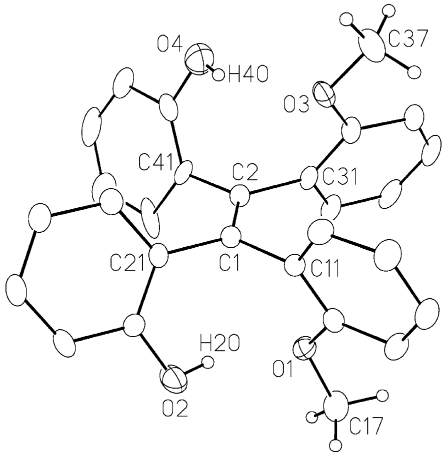
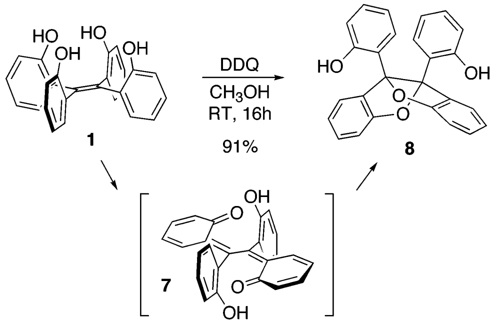


Figure 1. ORTEP diagram of compound **2Z** showing the atom labeling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydroxyl and methyl hydrogen atoms are shown with arbitrarily small thermal parameters; all other hydrogen atoms are not shown.

Scheme 2



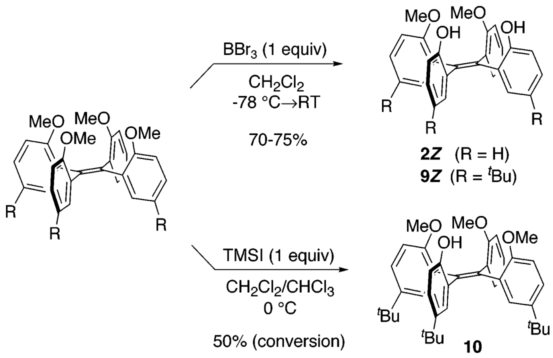
give the interesting cis-fused dihydrobenzofuro[2,3]-benzofuran **8**;[12] confirmation of the structure and stereochemistry was obtained by X-ray crystallography.[6,13]

The formation of this product is readily rationalized by assuming that conversion to the expected quinone **7** is followed by intramolecular conjugate addition of each phenolic oxygen onto the opposite *ortho*-quinomethide "enone" fragment.[14]

Methylation of the phenolic residues of **8** proceeds cleanly under standard conditions, but unfortunately, alkali metal-induced reductive fragmentation[12a] was nonselective under all conditions investigated, producing complex mixtures of isomeric **2*E*** and **2*Z***, along with other, as yet unidentified products.[15]

Selective synthesis of (*Z*)-1,2-bis(2′-hydroxyphenyl)-bis-(2′-methoxyphenyl)ethene **2*Z*** was more straightforward, proceeding directly by partial dealkylation of a symmetric precursor. Thus, treatment of tetrakis(2-methoxyphenyl)-ethene[1] with 1 equiv of boron tribromide at low temperature proceeds cleanly to the doubly deprotected (*Z*)-isomer, a reaction that proceeds equally selectively starting from tetrakis(5-*tert*-butyl-2-methoxyphenyl)ethene[1] (Scheme 3).

Scheme 3



No more than minor quantities of other isomers are observed in the crude reaction mixture, and purified products **2*Z*** and **9*Z*** are readily obtained by flash chromatography.[6] For the *tert*-butyl derivative **9*Z***, the stereochemistry was confirmed by X-ray crystallography on the corresponding monosodium salt, prepared by treatment of **9*Z*** with 1 equiv of NaH (Figure 2).[16]

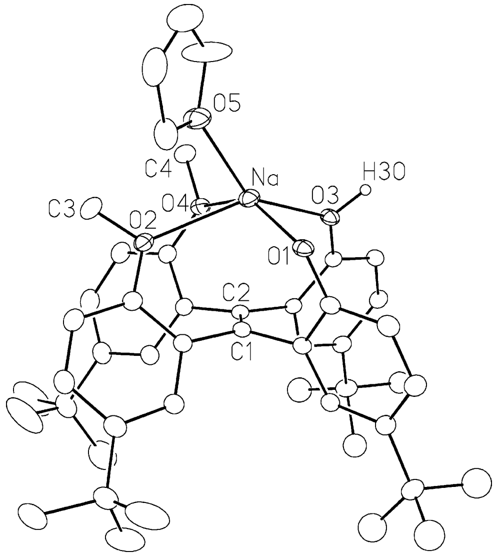


Figure 2. View of compound **Na-9Z** approximately along the C1−C2 bond. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level.

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[12] A few structurally related diaryl-substituted dihydrobenzofuro[2,3]-benzofurans have been reported, invariably formed as one product in a complex reaction mixture: (a) Rigaudy, J.; Scribe, P.; Breliere, C. *Tetrahedron* **1981**, *37*, 2593−2597. (b) Wong, R. Y.; Jurd, L. *Aust. J. Chem.* **1984**, *37*, 2585−2593.

[13] See Supporting Information for ORTEP diagrams and complete crystal data.

[14] Similar quinone-derived cyclizations are observed upon oxidation of various calix[4]arene compounds: Litwak, A. M.; Biali, S. E. *J. Org. Chem.* **1992**, *57*, 1943−1945. Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393−402. Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1994**, 2545−2546.

Finally, preliminary investigation has provided a direct synthesis of the tris(ether) derivative, (5-*tert*-butyl-2-hydroxyphenyl)-tris(5-*tert*-butyl-2-methoxyphenyl)ethene **10**, also by selective desymmetrization of tetrakis(5-*tert*-butyl-2-methoxyphenyl)ethene (Scheme 3). In this case, the reagent of choice is iodotrimethylsilane,[4b,17,18] but only the first demethylation proceeds with sufficient selectivity to be synthetically useful. Thus, the reaction of tetrakis(5-*tert*-butyl-2-methoxyphenyl)ethene with 1 equiv of TMSI proceeds to approximately 50% conversion and yields tris(ether) derivative **10** almost exclusively. Higher absolute yields of **10** can be obtained from the reaction with excess TMSI, but the progress of the reaction must be monitored by TLC analysis and terminated immediately upon complete disappearance of starting material. Under these conditions, however, the formation of tris(ether) **10** is accompanied by a complex mixture of bis(ether) and mono(ether) byproducts, each formed in relatively minor amounts. Both procedures require chromatographic purification, but the partial conversion is preferred at scale for operational simplicity and recovery of the valuable starting material.[19]

The tetrakis(2-hydroxyphenyl)ethene template offers a geometrically constrained multidentate binding platform complementary to the more familiar calix[4]arene structural class. The preparation of partially etherified tetrakis(2-hydroxyphenyl)ethene ligands significantly expands the potential contexts in which the coordination chemistry of this system may be developed. Further synthetic manipulation of the tetrakis(2-hydroxyphenyl)ethene framework remains under investigation, including the potential for selective partial alkylation of the phenolic residues.

Acknowledgment. Financial support from NOVA Chemicals Corporation and Natural Sciences and Engineering Research Council of Canada (CRD and CRO grant programs) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and complete characterization data for all new compounds; details of the X-ray crystallography for compounds **2*Z***, **8**, and the monosodium salt of **9*Z***. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Under some conditions, the major product of the reduction appears to be the one remaining isomer, 1,1-bis(2′-hydroxyphenyl)-2,2-bis(2′-methoxyphenyl)ethene, on the basis of spectroscopic analysis of impure material. A byproduct missing two methoxy residues (by mass spectrometry) was also obtained under some conditions.

(16) Colorless single crystals of the sodium salt of **9Z** were obtained in 27% yield as a nonstoichiometric THF solvate.[6] Crystal data for **Na-9Z**$\cdot{}^1/_4$ n-C_6H_{14}: $C_{49.5}H_{66.5}NaO_5$, crystal size 0.33 × 0.31 × 0.29 mm^3, triclinic, space group $P\bar{1}$ (No. 2), Mo Kα ($\lambda = 0.71073$ Å), $a = 11.2460(7)$ Å, $b = 14.8004(9)$ Å, $c = 16.0461(10)$ Å, $\alpha = 109.1463(12)°$ $\beta = 90.7286(12)°$, $\gamma = 109.0012(11)°$, $V = 2364.1(3)$ Å^3, $Z = 2$, $\mu = 0.075$ mm^{-1}, $\rho_{calcd} = 1.074$ g cm^{-3}, $F_{000} = 829$, $T = -80$ °C, $2\theta_{max} = 50.00°$, 11 433 total reflections, 8257 unique reflections ($R_{int} = 0.0235$), least-squares refinement on F^2, $R_1(F) = 0.0938$ (for 5500 reflections with $F_o{}^2 \geq 2\sigma(F_o{}^2)$), w$R_2(F^2) = 0.2980$, GOF($F^2$) = 1.029 (for all unique data).

(17) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761−3762.

(18) Use of in situ-derived TMSI reagent was not successful.

(19) Qualitatively similar results have been obtained from reactions of TMSI and the parent tetrakis(2-methoxyphenyl)ethene.