# First Synthesis of Lower-Rim-Substituted Aryl Ethers of *p-tert*-Butylcalix[4]arene

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With the use of $S_NAr$ or Ullmann reactions, the synthesis of the first lower-rim aryl ether derivatives of *tert*-butylcalix[4]arene is reported, as are some of their conformational properties, $^1$H NMR spectra, and X-ray crystal structures. The lower-rim aryl pendants reported herein provide for new scaffolds upon which a host of other new molecular architectures can be constructed, thus extending the capability of the versatile calix[4]arenes even further.

## Introduction

In recent years, much attention has been devoted to the synthesis and study of the properties of functionalized calix[4]arenes because of their potential utility as supramolecular hosts for neutral guest molecules such as [60]fullerene and as selective ionophores for various cations or anions.[1] Calix[4]arenes, **1** (see Chart 1), can be readily functionalized at either their lower or their upper rim or both. Functional groups such as amides, esters, poly(ethylene glycol) units, alkyl ethers, and benzyl ethers are most often introduced at the lower rims of the calix[4]arene scaffold. However, no lower-rim aryl ether derivatives of calix[4]arenes, such as **2** and **3**, have been reported although such derivatives could be useful lower-rim cavitands[2] in which the aryl pendant groups define an additional hydrophobic cavity. Furthermore, because the pendant aryl groups themselves can easily be modified, such calix[4]arene aryl ethers can provide additional scaffolds for constructing desirable molecular architectures.

While lower-rim O-alkylated and lower-rim O-benzylated calix[4]arenes are easily formed via simple Williamson-type nucleophilic substitution reactions of the corresponding calixarenes with alkyl or benzyl halides, the synthesis of O-aryl ether analogues has not been reported. A single publication by Gutsche[3] exists which describes the mono-, di-, and hexa-2,4-dinitrophenyl ether derivatives of the larger and conformationally more flexible *tert*-butylcalix[8]arenes. To the best of our knowledge, this is the only published report of any lower-rim aryl ether derivatives of a calixarene. As part of our studies on developing methods to functionalize the lower rim of calix[4]arenes[4] and calix[4]naphthalenes[5] to create new target molecules, we report herein the first syntheses of lower-rim-substituted aryl ethers of *p-tert*-butylcalix[4]arene (**4**).

## Results and Discussion

The endeavors required for the synthesis and study of the vancomycin group of antibiotics have necessitated development of mild methods for macrocyclization of 16-membered ring systems in which, essentially, a diaryl ether is formed.[6] Recently, Chan[7] and Evans[8] reported methods for relatively mild Cu(II) acetate-promoted arylation of phenols with arylboronic acids. However, the use of their methodology with **4** and phenylboronic acid in our hands failed to produce any of the corresponding phenyl ethers, affording only unreacted starting materials. Normal Ullmann conditions also failed with simple aryl halides and **4**. In this regard, these findings were consistent with our earlier observations that the lower-rim Suzuki−Miyaura coupling reactions with phenylboronic acids and *p-tert*-butylcalix[4]arene triflates were unsuccessful, presumably because of steric crowding of the intermediates that lead to product formation.[4]

On the other hand, when a nucleophilic aromatic substitution ($S_NAr$)-based reaction was employed using 2 equiv of the readily available 4-fluoro-3-nitrobenzaldehyde (**5**) with **4** in the presence of $K_2CO_3$/DMF (Table 1, entry 1), the monoaryl ether **3a** was formed in 58% isolated yield. The $^1$H NMR spectrum in acetone-$d_6$ revealed it to be exclusively in a cone conformation, although when the solvent was changed to $CDCl_3$ or $C_6D_6$ the presence of another conformer was observed. VT-$^1$H NMR experiments on **3a** over the range of 223−323 K revealed only that the relative concentration of the minor component increased with increasing temperature, but we were unable to isolate and unequivocally assign a structure to it. The closely related corresponding hydroxymethyl compound **6** (vide infra) however did not

(1) Gutsche, C. D. *Calixarenes Revisited*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, U.K., 1998 and references therein.

(2) For a recent overview of cavitands, see: Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Org. Chem.* **1999**, *64*, 4555 and references therein.

(3) Muthukrishnan, R.; Gutsche, C. D. *J. Org. Chem.* **1979**, *44*, 3962.

(4) Chowdhury, S.; Bridson, J. N.; Georghiou, P. E. *J. Org. Chem.* **2000**, *65*, 3299.

(5) Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819.

(6) For a recent review of these macrocyclization reactions directed toward the synthesis of vancomycin, see: Nicolaou, K. C.; Boddy, C. N.; Bräse, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096 and references therein.

(7) Chan, D. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933.

(8) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

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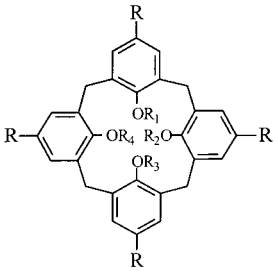
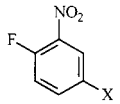
**Chart 1**



**1** R = $R_1$ = $R_2$ = $R_3$ = $R_4$ : *all* H or H *and/or* alkyl, ester, etc.
**2** R = H *or* Alkyl; $R_1$ *and/or* $R_2$ *and/or* $R_3$ *and/or* $R_4$ = Aryl
**3** R = *tert*-Butyl; $R_1$ = Aryl; $R_2$ = $R_3$ = $R_4$ = H *and/or* Aryl
**3a** R = *tert*-Butyl; $R_1$ = $C_7H_4NO_3$; $R_2$ = $R_3$ = $R_4$ = H
**3b** R = *tert*-Butyl; $R_1$ = $R_3$ = $C_7H_4NO_3$; $R_2$ = $R_4$ = H
**3c** R = *tert*-Butyl; $R_1$ = $R_2$ = $R_3$ = $C_7H_4NO_3$; $R_4$ = H
**3d** R = *tert*-Butyl; $R_1$ = $R_2$ = $R_3$ = $R_4$ = $C_7H_4NO_3$
**3e** R = *tert*-Butyl; $R_1$ = $R_2$ = $C_7H_4NO_3$; $R_3$ = $R_4$ = H
**4** R = *tert*-Butyl; $R_1$ = $R_2$ = $R_3$ = $R_4$ = H
**6** R = *tert*-Butyl; $R_1$ = $C_7H_6NO_3$; $R_2$ = $R_3$ = $R_4$ = H
**7** R = *tert*-Butyl; $R_1$ = $R_3$ = benzyl; $R_2$ = $R_4$ = H
**8** R = *tert*-Butyl; $R_1$ = $R_3$ = benzyl; $R_2$ = $R_4$ = $C_7H_4NO_3$
**9a** R = *tert*-Butyl; $R_1$ = $C_9H_8NO_4$; $R_2$ = $R_3$ = $R_4$ = H
**9b** R = *tert*-Butyl; $R_1$ = $R_3$ = $C_9H_8NO_4$; $R_2$ = $R_4$ = H



**5** X = CHO
**5a** X = $CH_2OH$
**5b** X = $CO_2C_2H_5$

**Table 1. Reaction of Various Aryl Halides with 4 and 7**

| entry | substrates | conditions | product(s) |
|---|---|---|---|
| 1 | 4-fluoro-3-nitrobenzaldehyde | $K_2CO_3$/DMF or $K_2CO_3$/CuO/pyridine | **3a**−**c** |
| 2 | 1,3-dinitro-2-fluorobenzene | $K_2CO_3$/DMF | no reaction |
| 3 | 4-fluorobenzaldehyde | $K_2CO_3$/DMF | no reaction |
| 4 | 4-fluoro-3-nitrobenzaldehyde | NaH/DMF | **8** |
| 5 | 3-fluorobenzaldehyde | $K_2CO_3$/DMF | no reaction |
| 6 | ethyl 4-fluoro-3-nitrobenzoate | $K_2CO_3$/CuO/pyridine | **9a** and **9b** |
| 7 | 4-fluoro-1-nitrobenzene | $K_2CO_3$/CuO/pyridine | **10** and **11** |

show similar behavior in the different solvents. The pattern of the methylene proton signals observed for **3a** is consistent with those typically found in lower-rim-substituted *tert*-butylcalix[4]arenes existing in a cone conformation. Further confirmation for the assignment of **3a** was obtained by NOED experiments in both $C_6D_6$ and in acetone-$d_6$. A single-crystal X-ray structure of **3a** crystallized from benzene solution clearly reveals its cone conformation in the solid state[9] and reveals that it is a clathrate with three molecules of benzene contained in the lattice. One of the benzene molecules is situated within the cavity (or basket) of **3a**, and the other two are situated outside the cavity.

Reaction of **4** with larger amounts of **5** produced mixtures of the di- and triaryl ethers **3b** and **3c** which could not be separated, although (+) FAB MS indicated the presence of **3c** but not of the corresponding tetraaryl ether **3d**. Table 1 lists several other aryl halides, which contain electron-withdrawing substituents and which were evaluated for their reactivities with **4**. The aryl halides listed in entries 2, 3, and 5 of Table 1 failed to produce the corresponding aryl ethers with **4**. To determine whether steric crowding due to the presence of four aryl groups on the lower rim of the calixarene might have been a factor inhibiting the formation of tri- or tetraaryl ethers, the 1,3-di-O-benzylated *tert*-butylcalixarene **7**[10] was treated with **5** using NaH in DMF (Table 1, entry 4) to successfully afford in 53% yield the di-*O*-benzyl-di-*O*-aryl ether **8**, which was determined by NMR to be in a cone conformation. It is thus possible to functionalize the lower rim of **4** with two aryl ether and two benzyl ether pendants using $S_NAr$-type reaction conditions, and therefore, steric crowding should not be a factor inhibiting potential tetraarylation.

The $^1H$ NMR spectrum of **8** shows that there is a large upfield shift for the axial and equatorial protons of the methylene bridges in the calixarene ring, from $\delta$ 3.20 and 4.22 ppm in the parent calixarene **7** to $\delta$ 2.86 and 3.98 ppm in compound **8** for the axial and equatorial protons, respectively (correlated with the $^{13}C$ NMR signal at $\delta$ 31.3 ppm). This can be explained by assuming that the observed shielding effect occurs as a result of the presence of the aryl ether group in close proximity to the methylene protons. NOED experiments on **8** confirmed this hypothesis; irradiation of the signal centered at $\delta$ 2.86 ppm (equatorial methylene proton) enhances the signals at $\delta$ 3.98 ppm, 6.39 ppm (proton meta to the nitro group in the aryl substituent), and $\delta$ 6.97 ppm (proton ortho to the benzyl methylene) by 19%, 3%, and 4%, respectively, while the signal centered at $\delta$ 3.98 ppm (axial methylene proton) enhanced the signal at $\delta$ 2.86 ppm, 5.47 ppm (benzyl methylene protons), and $\delta$ 6.99 ppm (calixarene aromatic protons) by 14%, 4%, and 1%, respectively. The downfield shift for the benzylic protons from $\delta$ 5.00 (in **7**) to 5.46 ppm (in **8**) can be explained by assuming that the deshielding effect is likely due to the anisotropic effects of the neighboring nitro-aryl ring. The 1,3-alternate structure would not likely have resulted in this observed downfield shift. Furthermore, the single $^{13}C$ signal at $\delta$ 31.3 ppm due to the methylene bridges ("de Mendoza rule"[1,11]) supports the assignment of a cone conformation.

(9) Atomic coordinates of the structures of **3a** and **3e** have been deposited with the Cambridge Crystallographic Data Centre. These are available on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EK, U.K.

(10) Ikeda, A.; Shinkai, S.; *Tetrahedron* **1991**, *47*, 4325.

(11) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. D.; Sànchez, C. *J. Org. Chem.* **1991**, *56*, 3372.

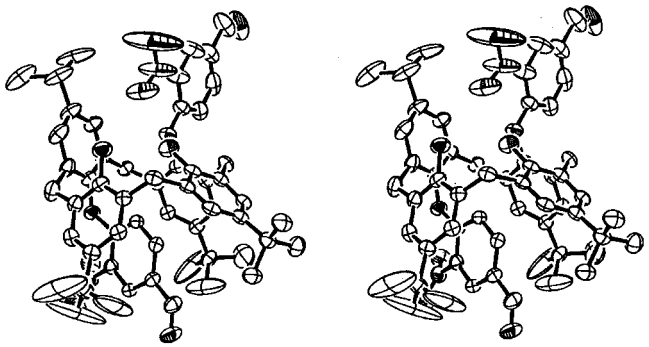


**Figure 1.** Stereoview of **3e** in a partial cone conformation. One of the aryl ether pendants is sandwiched between two adjacent *tert*-butyl-bearing phenyl rings within the calix[4]-arene cavity.

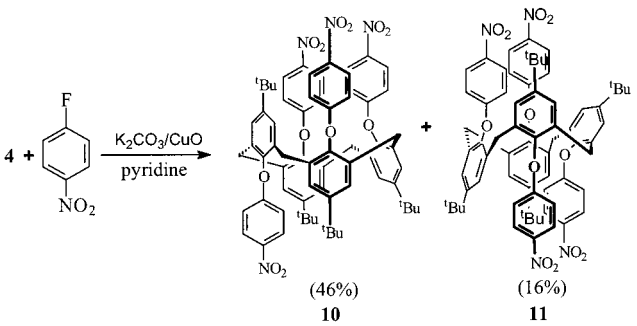
The use of Ullmann ether conditions ($K_2CO_3$/CuO/pyridine, reflux)[12] with **5** and other aryl halides that were previously found to be reactive was then evaluated, and in general, workup was found to be more convenient. With the use of 3 equiv of **5**, both monoaryl ether **3a** and the distal diaryl ether **3b** were formed in 38% yield each (Table 1, entry 1) and could be easily separated by chromatography. The $^1$H NMR spectrum of **3b** revealed two AB systems centered at $\delta$ 3.22 and 4.00 ppm (geminal coupling constant of $J$ = 13.6 Hz) due to the methylene bridge protons of the calixarene ring. The corresponding $^{13}$C methylene carbons were at $\delta$ 31.0 and 31.5 ppm, respectively, a feature which, according to the de Mendoza rule, is typical for 1,3-substituted calix[4]arenes in the cone conformation.

It was surprising therefore to see that the X-ray structure of a single crystal obtained from what was presumed to be entirely **3b** showed it to be proximally (i.e., 1,2-) disubstituted and in a partial cone conformation (Figure 1).[9] The two aryl groups are trans to each other, with one being "sandwiched" between two adjacent *tert*-butyl-bearing phenyl rings within the calixarene cavity. The other aryl pendant is twisted outside of the cavity. The most likely explanation for the X-ray crystal structure, which is not in accord with the NMR assignments, is that it is due to a minor contaminant, **3e**, formed alongside **3b** which was not detected in the NMR spectra.

With 2 equiv of ethyl-4-fluoro-3-nitrobenzoate (**5b**), the corresponding mono- and diaryl ethers, **9a** and **9b**, were obtained in 37% and 24% yields, respectively (Table 1, entry 6). With 4 equiv, again only **9a** and **9b** could be isolated, although this time in 73% and 21% yields, respectively, with no evidence of any of the tri- or tetrasubstituted aryl ethers having been formed. Analysis of both the $^1$H and $^{13}$C NMR spectra is in agreement with the proposed structures for each of **9a** and **9b** being in cone conformations.

To obtain tetraaryl ethers of **4**, the efficacy of both Ullmann and $S_NAr$ conditions was evaluated using 4 equiv of 4-fluoro-1-nitrobenzene. As depicted in Scheme 1 (Table 1, entry 7), **10** was obtained as the major product (46%) and **11** as a minor product (16%). Compound **10** was unambiguously confirmed by NMR analysis and mass spectrometry to be the expected tetraaryl ether derivative of **4** in a partial cone conformation. The $^1$H

**Scheme 1**



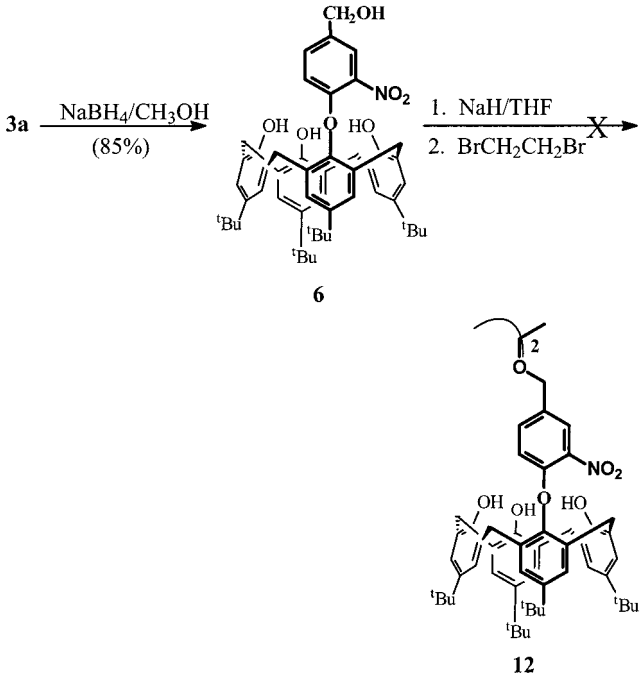

NMR spectrum of **10** in $CD_2Cl_2$ shows the presence of three signals at $\delta$ 1.14, 1.44, and 1.63 ppm in a 1:2:1 ratio, which are assigned to the three different *tert*-butyl groups. Two AB quartets due to the methylene bridge protons are centered at $\delta$ 3.25 and 3.34 ppm with geminal coupling constants of $J$ = 13 and 15 Hz, respectively. The $^{13}$C NMR spectrum shows a pattern that is consistent for a partial cone conformation and shows eight upfield resonances due to the quaternary carbons ($\delta$ 34.7, 35.1, and 35.4 ppm), the methyl carbons of the *tert*-butyl groups ($\delta$ 31.7, 31.9, and 32.5 ppm), and the methylene carbons ($\delta$ 31.0 and 37.4 ppm). The methylene carbon signals at $\delta$ 31.0 and 37.4 ppm deviate only slightly from the positions typically found at $\delta$ 31.1 and 37.0 ppm as described by de Mendoza for calix[4]arenes in partial cone conformations. The downfield resonances consisting of 22 signals arising from the aromatic carbons are in agreement with the predicted structure. Additional support for the assigned structure was obtained by CI MS analysis, which showed a molecular ion peak at the expected value of $m/z$ = 1132.

The minor product **11** is also a tetraaryl ether derivative of **4** that exists in the 1,2-alternate conformation in solution. Its structure was determined by NMR analysis, and its molecular mass was confirmed by CI MS. The $^1$H NMR spectrum of **11** in $CD_2Cl_2$ was very simple, showing a singlet at $\delta$ 1.25 ppm due to the *tert*-butyl protons, a pair of doublets centered at $\delta$ 3.20 and 3.57 ppm ($J$ = 12.5 Hz), and a singlet at $\delta$ 3.40 ppm for the methylene protons indicating that **11** has $C_{2h}$ symmetry and is in a 1,2-alternate conformation. The doublet at $\delta$ 5.98 ppm ($J$ = 9 Hz) is due to the aromatic protons ortho to the oxygen atoms on the aryl ether groups, and it is coupled with the doublet at $\delta$ 7.83 ppm. A proton ortho to a strongly electron-withdrawing group, such as the nitro group, would be expected to appear further downfield than $\delta$ 7.83 ppm. In the case of **11** however, these protons are shielded by the aromatic units of the calixarene and therefore appear upfield. The $^{13}$C NMR spectrum exhibits signals at $\delta$ 30.4 and 38.5 ppm due to the methylene carbons, while the signals at $\delta$ 31.9 and 34.9 ppm are due to the methyl and quaternary carbons of the *tert*-butyl groups, respectively. The chemical shifts of the methylene carbons are consistent for calix[4]arenes having a 1,2-alternate conformation.[11]

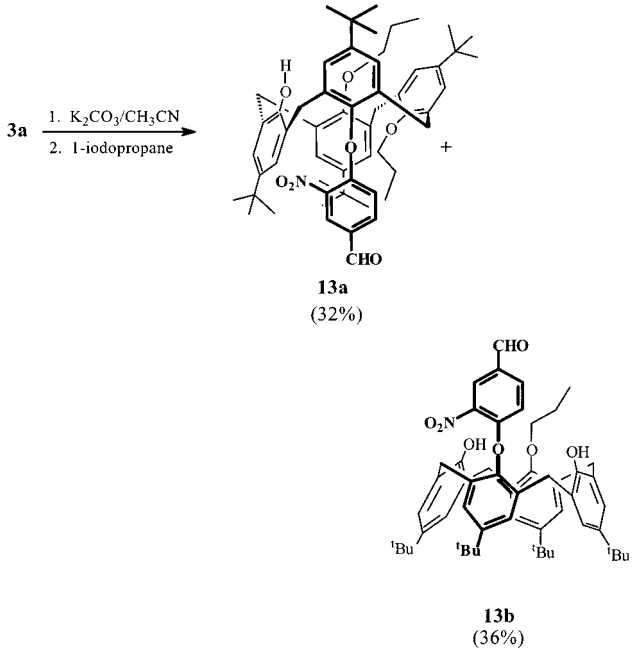
With these lower-rim aryl ethers in hand, experiments aimed at the coupling of two such arylated calix[4]arene molecules via a spacer molecule such as 1,2-dibromoethane were conducted. Reduction of **3a** with $NaBH_4$ afforded, in 85% yield, the corresponding alcohol **6** which could serve as a direct precursor toward **12** as outlined in Scheme 2. The structure of **6** was determined in the usual manner to be in a cone conformation, and as

(12) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. (b) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211.

**Scheme 2**




**Scheme 3**




referred to previously, none of the complex behavior seen with **3a** in the different deuterated solvents was observed for **6**. Reaction of **6** with 1,2-dibromoethane in the presence of NaH in THF, however, has thus far failed to unambiguously afford the expected double calix[4]arene product **12**. The NMR analysis of the product obtained did not provide any conclusive evidence to allow for the determination of its structure. It was therefore thought necessary to first protect the free phenolic groups in **3a** before attempting the coupling reaction. Through the use of excess 1-iodopropane in the presence of $K_2CO_3$ in acetonitrile with **3a**, the mono-*O*-aryl-*O*-dipropoxy-*tert*-butylcalix[4]arene **13a** and the mono-*O*-aryl-*O*-propoxy-*tert*-butylcalix[4]arene **13b** were obtained in 36% and 32% yields, respectively (Scheme 3). The structures of **13a** and **13b** were determined in the usual manner.

The spectra of **13b** are relatively straightforward; however, the $^1$H NMR spectrum of **13a** is more complex and revealing. The eight methylene bridge protons of the calixarene scaffold appear as a set of six one-proton doublets due to three clearly defined AB systems and a two-proton apparent broad singlet at $\delta$ 3.94 ppm. Each of the doublets is centered at $\delta$ 2.99, 3.36, 3.53, 3.86, and 3.97 ppm (the latter consisting of a pair of overlapping doublets) having typical geminal coupling constants ($J \approx 13-15.5$ Hz). The signal at $\delta$ 3.94 ppm is due to the methylene protons, which bridge the pair of propoxy-bearing aromatic rings of the calixarene, which are trans to each other. These protons would therefore be pseudoaxial and pseudoequatorial and thus would have relatively small chemical shift differences. Thus, the compound is proximally dipropoxy-substituted and exists in a 1,2-alternate conformation. There are four signals at $\delta$ 31.3, 32.9, 39.1, and 39.6 ppm that can be assigned to the methylene bridges, their positions being consistent with the $^{13}$C NMR signal patterns for 1,2-alternate conformations of calix[4]arenes,[9] the signals at $\delta$ 39.1 and 39.6 ppm being more deshielded than the value of $\delta$ 38.2 ppm generally reported. The $^1$H NMR spectrum also reveals a strong upfield shift for the methyl protons of one of the propoxy groups. The triplet centered at the exceptionally high field position of $\delta$ 0.04 ppm ($J = 7.3$ Hz) coupled to the multiplet at $\delta$ 0.92 ppm ($J = 7.3$ Hz) is assigned to the methyl and to the vicinal methylene protons of the propoxy group. There are a total of four sets of quartets centered at $\delta$ 2.39, 2.55, 3.60, and 4.11 ppm that all have the same geminal coupling constant ($J = 9$ Hz). These clearly indicate that the protons on each of these methylene groups are diastereotopic because of the different magnetic environments experienced by these protons when the molecule is in a 1,2-alternate conformation. The unusual upfield shifts experienced by one propoxy group, and to a lesser extent by the second propoxy group (triplet at $\delta$ 1.02 ppm, multiplet at $\delta$ 1.90 ppm, and the two sets of AB quartets centered at $\delta$ 2.39 and 2.55 ppm), indicate that one of the propoxy groups is strongly shielded by the neighboring calixarene aromatic ring which bears the aryl ether pendant, as shown in the structure depicted in Scheme 3. Such diastereotopicity for the protons of simple propoxy-bearing calix[4]arenes has not been noted by others but has been observed with the propyl and other alkyl ether derivatives of *tert*-butylcalix[4]naphthalenes and calix[4]naphthalenes.[13]

In conclusion, either $S_NAr$ or Ullmann ether conditions can be used to functionalize the lower rim of *tert*-butylcalix[4]arene (**4**) in synthetically useful yields. It has been shown that all four free hydroxyl groups of **4** can be derivatized with several readily available aryl fluorides containing electron-withdrawing groups, which, once coupled to the calix[4]arenes, can be further modified. Particularly interesting structural features were revealed in the $^1$H NMR spectrum of **13a**, which shows a very strong upfield signal at $\delta$ 0.04 ppm for the methyl group of one of the propoxy ether groups, indicating that the molecule is in a partial cone conformation. In addition, diastereotopicity of the propoxy protons can be clearly seen. Overall, because compounds such as **10** and

(13) Chowdhury, S. Ph.D. Dissertation, Memorial University of Newfoundland, St. John's, Newfoundland, Canada, 2001.

**11** could be produced, thus showing that all the hydroxyl groups can be arylated at the lower rim, these findings may open up many new possibilities for calixarene structural modifications. Ongoing experiments are being conducted in an attempt to find the optimal conditions required for the synthesis of double calixarenes envisioned as a result of the findings which have been described herein.

## Experimental Section

All reactions were performed under argon unless otherwise indicated. Pyridine was distilled over KOH, and DMF was distilled over $MgSO_4$ under argon. Organic solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed according to the procedure of Still[14] using MERCK silica gel 230−400 mesh, 60 Å. Preparative layer chromatography (PLC) plates were made from Scientific Adsorbents Inc. silica gel (TLC standard grade 2−25 $\mu$m) with calcium sulfate as a binder. Thin-layer chromatography was performed using precoated silica gel 60 $F_{254}$ plates. Unless otherwise indicated, $^1$H NMR and $^{13}$C NMR spectra were conducted using $CDCl_3$ as solvent and were recorded at 500 and 125 MHz, respectively, using TMS as an internal standard.

**5,11,17,23-Tetra-*tert*-butyl-25-(4-formyl-2-nitrophenoxy)-calix[4]arene-26,27,28-triol (Cone Conformer) (3a).** A mixture of **4** (1.01 g, 1.57 mmol), 4-fluoro-3-nitrobenzaldehyde (0.53 g, 3.13 mmol), and powdered anhydrous $K_2CO_3$ (1.73 g, 12.5 mmol) in anhydrous DMF (15.7 mL) was stirred at room temperature for 5 days. The black mixture was diluted with EtOAc (50 mL), and the precipitate was removed by filtration. The organic layer was washed with aqueous 10% HCl and brine, dried over anhydrous $MgSO_4$, and filtered. The organic solvent was evaporated, and the residue was purified by column chromatography eluting with EtOAc/hexane 20:80 to afford **3a** (0.97 g, 58%) as a light yellow solid: mp 178−180 °C. $^1$H NMR (acetone-$d_6$): $\delta$ 1.2 (s, 9H), 1.14 (s, 9H), 1.23 (s, 18H), 3.53 (d, $J$ = 13.3 Hz, 2H), 3.59 (d, $J$ = 13.7 Hz, 2H), 4.04 (d, $J$ = 13.1 Hz, 2H), 4.25 (d, $J$ = 13.7 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 1H), 7.21 (s, 2H), 7.27 (d, $J$ = 1.9 Hz, 2H), 7.32 (d, $J$ = 1.9 Hz, 2H), 7.44 (s, 2H), 8.19 (dd, $J$ = 1.8, 8.7 Hz, 1H), 8.42 (s, 2H, $D_2O$ exchangeable), 8.74 (d, $J$ = 1.8 Hz, 1H), 10.11 (s, 1H, $D_2O$ exchangeable). $^{13}$C NMR ($C_6D_6$): $\delta$ 30.9, 31.4, 31.6, 32.0, 32.3, 32.4, 33.3, 33.9, 34.3, 34.5, 117.1, 121.0, 125.8, 126.6, 127.0, 127.8, 129.6, 131.2, 132.8, 133.6, 139.9, 143.4, 144.2, 144.9, 147.1, 150.3, 156.4, 188.2. FAB MS (*m*/*z*), relative intensity (%): 797 (100, $M^+$), 782 (20), 740 (15), 630 (72), 611 (25); calcd for $C_{51}H_{59}NO_7$, 797.4291.

**X-ray crystal data for 3a**: crystal (benzene) mp 178−180 °C, $C_{51}H_{59}NO_7 \cdot 3C_6H_6$, monoclinic, space group $P2_1/c$ (No. 14), $Z$ = 4, $a$ = 19.281(1) Å, $b$ = 15.153(1) Å, $c$ = 20.866(1) Å, $\beta$ =101.249(2)°, $V$ = 5979.0(6) Å$^3$, $D_{calcd}$ = 1.147 g cm$^{-3}$, crystal size = 0.35 × 0.24 × 0.07 mm. Intensity data were measured at 193 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo K$\alpha$ ($\lambda$ = 0.710 73 Å) radiation to $2\theta_{max}$ = 52.9°; 34 213 reflections converged to a final $R_{int}$ of 0.102 for 12 254 reflections with $I > 2.00\sigma(I)$. Final R1 and wR2 values were 0.073 and 0.210, respectively, and GOF = 0.90.[9]

**5,11,17,23-Tetra-*tert*-butyl-25,26-di(4-formyl-2-nitrophenoxy)calix[4]arene-27,28-diol (Partial Cone Conformer) (3b).** Pyridine (10 mL) was added to a mixture of **4** (324 mg, 0.50 mmol), 4-fluoro-3-nitrobenzaldehyde (169 mg, 1.0 mmol), $K_2CO_3$ (278 mg, 1.0 mmol), and CuO (158 mg, 1.0 mmol). The resultant black mixture was heated at reflux for 24 h. TLC plates showed the presence of the monoaryl ether product **3a**, so an additional equivalent of **5** was added, and the reaction was continued at reflux for a further 24 h. The mixture was cooled to room temperature, and the precipitate was removed by filtration. The organic layer was diluted with $CH_2Cl_2$ (50 mL), washed with aqueous 10% $NaHSO_4$ and then with water, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated, and the crude product was purified by column chromatography eluting with EtOAc/hexane 20:80 to afford **3a** (0.15 g, 38%) and **3b** (0.19 g, 38%): mp 252−254 °C (dec). $^1$H NMR: $\delta$ 0.92 (s, 18H), 1.31 (s, 18H), 3.22 (d, $J$ = 13.6 Hz, 4H), 4.00 (d, $J$ = 13.6 Hz, 4H), 5.90 (s, 2H), 6.79 (s, 2H), 6.87 (d, $J$ = 8.5 Hz, 2H), 7.06 (s, 4H), 7.97−7.99 (dd, $J$ = 1.9, 8.8 Hz, 2H), 8.95 (d, $J$ = 1.9 Hz, 2H), 9.99 (s, 2H). $^{13}$C NMR: $\delta$ 30.9, 31.0, 31.5, 34.8, 125.2, 126.3, 127.3, 129.0, 130.1, 131.6, 134.0, 139.9, 142.0, 144.5, 149.1, 150.1, 150.4, 156.7, 188.8. FAB MS (*m*/*z*), relative intensity (%): 946 ($M^+$, 100), 931 (28), 874 (20); calcd for $C_{58}H_{62}O_{10}N_2$, 946.4400.

**X-ray crystal data for 3e:** crystal (benzene) mp 252−254 °C, $C_{58}H_{62}O_{10}N_2 \cdot 3H_2O$, triclinic, space group $P\bar{1}$ (No. 2), $Z$ = 2, $a$ = 10.9363(7) Å, $b$ = 12.6808(8) Å, $c$ = 20.501(1) Å, $\alpha$ = 89.837(1)°, $\beta$ = 83.837(1)°, $\gamma$ = 78.003(1)°, $V$ = 2764.4(3) Å$^3$, $D_{calcd}$ = 1.203 g cm$^{-3}$, crystal size = 0.60 × 0.44 × 0.14 mm. Intensity data were measured at 193 K on a Bruker P4/CCD diffractometer with graphite monochromated Mo K$\alpha$ ($\lambda$ = 0.710 73 Å) radiation to $2\theta_{max}$ = 52.8°; 15 875 reflections converged to a final $R_{int}$ = 0.026 for 11 133 reflections with $I > 2.00\sigma(I)$. Final R1 and wR2 values were 0.098 and 0.324, respectively, with GOF = 1.05.[9]

**5,11,17,23-Tetra-*tert*-butyl-25-(4-hydroxymethyl-2-nitrophenoxy)calix[4]arene-26,27,28-triol (Cone Conformer) (6)**. To a solution of **3a** (258 mg, 0.33 mmol) in methanol (10 mL) was added in one portion $NaBH_4$ (65 mg, 0.25 equiv, based on starting material). The reaction slurry was stirred at room temperature for 2 h. The solvent was evaporated, the residue was diluted with $CH_2Cl_2$ (25 mL), and the resulting solution was washed with aqueous saturated $NH_4Cl$ (3 × 10 mL). The organic solution was dried over anhydrous $MgSO_4$ and filtered. After the solvent was evaporated, the crude yellow product was purified by column chromatography eluting with EtOAc/hexane 30:70 to afford **6** (0.23 g, 87%): mp 160−162 °C. $^1$H NMR ($C_6D_6$): $\delta$ 0.78 (s, 9H), 0.87 (s, 9H), 1.16 (br, 1H, $D_2O$ exchangeable), 1.40 (s, 18H), 3.23 (d, $J$ = 13.2 Hz, 2H), 3.32 (d, $J$ = 14.0 Hz, 2H), 4.04 (s, 2H), 4.16 (d, $J$ = 13.3 Hz, 2H), 4.52 (d, $J$ = 14.0 Hz, 2H), 6.46 (d, $J$ = 8.5 Hz, 1H), 6.82 (m, 3H), 7.17 (m, 6H), 7.71 (s, 1H), 9.11 (s, 2H, $D_2O$ exchangeable), 9.88 (s, 1H, $D_2O$ exchangeable). $^{13}$C NMR: $\delta$ 31.0, 31.5, 32.3, 32.6, 33.3, 33.9, 34.3, 34.5, 62.5, 116.5, 125.1, 125.9, 126.5, 126.8, 127.5, 127.7, 128.5, 128.8, 132.8, 133.3, 136.5, 140.0, 143.2, 144.2, 145.2, 147.2, 149.8, 150.4, 151.9. FAB MS (*m*/*z*), relative intensity (%): 799 (100, $M^+$), 798 (75), 781 (5), 764 (15), 743 (12), 708 (8); calcd for $C_{51}H_{61}NO_7$, 799.4448.

**5,11,17,23-Tetra-*tert*-butyl-25,27-di-(4-formyl-2-nitrophenoxy)-26,28-di-[(4-methylbenzyl)oxy]calix[4]arene (Cone Conformer) (8):** A mixture of **7**[10] (373 mg, 0.43 mmol), **5** (333 mg, 1.97 mmol), and NaH (60% suspension in oil, 114 mg, 2.96 mmol) in DMF (5 mL) was stirred at room temperature for 3 days. The dark reaction mixture was diluted with EtOAc, washed with two portions of water and with aqueous saturated $NH_4Cl$, dried over anhydrous $MgSO_4$, and filtered. After the solvent was evaporated, the crude product was purified by preparative TLC eluting with EtOAc/hexane 20:80 to obtain **8** (264 mg, 53%): mp 275−277 °C. $^1$H NMR: $\delta$ 0.89 (s, 18H), 1.29 (s, 18H), 2.18 (s, 6H), 2.86 (d, $J$ = 14.1 Hz, 4H), 3.98 (d, $J$ = 12.9 Hz, 4H), 5.46 (s, 4H), 6.39 (d, $J$ = 8.9 Hz, 2H), 6.53 (s, 4H), 6.81 (d, $J$ = 7.8 Hz, 4H), 6.97−6.99 (m, 8H), 7.77 (dd, $J$ = 1.8, 8.4 Hz, 2H), 8.45 (d, $J$ = 1.8 Hz, 2H), 9.95 (s, 2H). $^{13}$C NMR: $\delta$ 21.2, 31.1, 31.3, 31.7, 33.9, 34.0, 74.6, 125.6, 125.7, 127.9, 128.1, 129.4, 130.4, 131.9, 133.7, 134.3, 135.3, 137.0, 139.7, 145.2, 146.0, 147.4, 151.7, 157.6, 188.8. MS CI (*m*/*z*), relative intensity (%): 1153 ($M^+ - 1$, 30), 1099 (92), 1042 (31), 992 (15), 958 (78), 903 (45), 901 (30); calcd for $C_{74}H_{78}N_2O_{10}$, 1154.5656.

**5,11,17,23-Tetra-*tert*-butyl-25-[4-(ethylcarboxy)-2-nitrophenoxy]calix[4]arene-26,27,28-triol (Cone Conformer) (9a) and 5,11,17,23-Tetra-*tert*-butyl-25,27-di-(4-ethylformate-2-nitrophenoxy)calix[4]arene-26,28-diol (Cone Conformer) (9b)**. A flask containing **4** (0.32 g, 0.5 mmol), ethyl 4-fluoro-3-nitrobenzoate (0.21 g, 1.0 mmol), $K_2CO_3$ (0.56 g, 4.0 mmol), and CuO (0.32 g, 4.0 mmol) was flushed

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

with Ar, and then pyridine (10 mL) was added. The resulting black mixture was refluxed for 48 h. The reaction mixture was cooled to room temperature, and the solid was filtered off. The organic layer was diluted with EtOAc (25 mL), washed with aqueous 10% $NaHSO_4$ and then with water, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated, and the crude product was purified by column chromatography eluting with EtOAc/hexane 20:80 to afford **9a** (243 mg, 57%) as a colorless solid: mp 199−201 °C. $^1$H NMR: $\delta$ 1.18 (s, 9H, *tert*-butyl), 1.22 (s, 27 H, *tert*-butyl), 1.40 (t, $J$ = 7.1 Hz, 3H), 3.30 (d, $J$ = 13.3 Hz), 3.45 (d, $J$ = 13.8 Hz), 3.94 (d, $J$ = 13.3 Hz, 2H), 4.32 (d, $J$ = 13.8 Hz, 2H), 4.41 (q, $J$ = 7.1 Hz, 2H), 6.67 (d, $J$ = 8.8 Hz, 1H), 7.01 (s, 2H), 7.02 (s, 2H), 7.04 (s, 2H), 7.12 (s, 2H), 8.15 (d, $J$ = 8.7 Hz, 1H), 8.37 (s, 2H), 8.78 (s, 1H), 9.83 (s, 1H, $D_2O$ exchangeable). $^{13}$C NMR: $\delta$ 14.3, 31.1, 31.4, 31.5, 32.8, 33.9, 34.0, 34.4, 61.7, 116.4, 124.8, 125.3, 125.7, 126.1, 126.5, 126.9, 127.4, 128.2, 132.6, 135.6, 138.8, 143.0, 143.3, 147.6, 147.6, 148.6, 150.0, 155.5. Compound **9b** (101 mg, 19%) was obtained as a light yellow solid: mp 270−272 °C. $^1$H NMR: $\delta$ 0.91 (s, 18H), 1.30 (s, 18H), 1.41 (t, $J$ = 7.2 Hz, 6H), 3.20 (d, $J$ = 13.6 Hz, 4H), 4.01 (d, $J$ = 13.6 Hz, 4H), 4.39−4.43 (q, $J$ = 7.2 Hz, 4H), 5.97 (s, 2 × O*H*), 6.78 (m, 6H), 7.05 (s, 4H), 8.09−8.11 (dd, $J$ = 2.1, 8.8 Hz, 2H), 8.75 (d, $J$ = 2.0 Hz, 2H). $^{13}$C NMR: $\delta$ 14.3, 30.9, 31.3, 31.7, 33.8, 33.9, 61.6, 124.0, 125.2, 126.2, 127.4, 131.7, 135.2, 138.5, 141.7, 144.6, 150.5, 155.7, 164.5. MS CI (*m*/*z*), relative intensity (%): 1036 ($M^+$ + 4, 60), 1035 ($M^+$ + 3, 100), 1034 ($M^+$ + 2, 78), 391 (75), 279 (38); calcd for $C_{53}H_{60}N_2O_8$, 1032.4768.

**5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis-(4-nitrophenoxy)calix[4]arene (Partial Cone Conformer) (10) and 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis-(4-nitrophenoxy)calix[4]arene (1,2-Alternate Conformer) (11)**. A mixture of **4** (324 mg, 0.50 mmol), 4-fluoro-1-nitrobenzene (0.21 mL, 2.0 mmol), $K_2CO_3$ (278 mg, 2.0 mmol), and CuO (159 mg, 2.0 mmol) in pyridine was refluxed for 3 days. After the reaction mixture was cooled to room temperature, the mixture was filtered, and the organic layer was partitioned between EtOAc and aqueous 10% $Na_2HPO_4$. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated, and the crude product was purified by preparative TLC, eluting with hexane/benzene 5:95. The yellow solid obtained was purified further by preparative TLC using the same solvent mixture to afford **10** (159 mg, 46%) as the major product and **11** (90 mg, 16%) as a minor product. Data for **10**: mp >360 °C. $^1$H NMR ($CD_2Cl_2$): $\delta$ 1.14 (s, 18H), 1.44 (s, 9 H), 1.63 (s, 9 H), 3.10 (d, $J$ = 13.0 Hz, 2H), 3.30 (d, $J$ = 15.0 Hz, 2H), 3.38 (d, $J$ = 15.0 Hz, 2H), 3.40 (d, $J$ = 13.0 Hz, 2H), 6.47 (d, $J$ = 9.0 Hz, 4H), 6.53 (br, H), 6.64 (d, $J$ = 2.0 Hz, 2H), 7.02 (d, $J$ = 2.0 Hz, 2H), 7.26 (s, 2H), 7.39 (s, 2H), 8.05 (d, $J$ = 9.5 Hz, 4H), 8.19 (br, 2H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 31.0, 31.7, 31.9, 32.5, 34.7, 35.1, 35.4, 37.4, 115.2, 126.5, 126.9, 128.0, 128.1, 132.4, 132.9, 134.5, 135.4, 142.5, 142.6, 142.8, 147.1, 147.6, 148.1, 149.3, 150.4, 162.1, 163.9, 164.1. MS CI (*m*/*z*), relative intensity(%): 1133 ($M^+$ + 1, 40), 431 (28), 391 (100); calcd for $C_{68}H_{68}N_4O_{12}$, 1132.4829.

Compound **11** was obtained as a light yellow solid: mp >300 °C. $^1$H NMR ($CD_2Cl_2$): $\delta$ 1.25 (s, 36H), 3.20 (d, $J$ = 12.5 Hz, 2H), 3.40 (s, 4H), 3.57 (d, $J$ = 12.5 Hz, 2H), 5.98 (d, $J$ = 9 Hz, 8H), 6.60 (d, $J$ = 2.0 Hz, 4H), 7.74 (d, $J$ = 2.0 Hz, 4H), 7.83 (d, $J$ = 9 Hz, 8H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 30.4, 31.9, 34.9, 38.5, 126.1, 127.1, 127.4, 131.8, 134.3, 142.2, 147.6, 148.9, 163.2. MS CI (*m*/*z*), relative intensity (%): 1132 ($M^+$, 60), 391 (100); calcd for $C_{68}H_{68}N_4O_{12}$, 1132.4829.

**5,11,17,23-Tetra-*tert*-butyl-25-(4-formyl-2-nitrophenoxy)-26,27-dipropoxycalix[4]arene-28-ol (1,2-Alternate Conformer) (13a) and 5,11,17,23-Tetra-*tert*-butyl-25-(4-formyl-2-nitrophenoxy)-27-propoxycalix[4]arene-26,28-diol (Cone Conformer) (13b)**. A mixture of **3a** (459 mg, 0.576 mmol), 1-iodopropane (0.22 mL, 2.30 mmol), and $K_2CO_3$ (640 mg, 4.60 mmol) in $CH_3CN$ (25 mL) was refluxed for 28 h. The reaction mixture was cooled to room temperature and filtered, and then the solvent was evaporated. The organic layer was extracted with $CH_2Cl_2$, washed with aqueous saturated $NH_4Cl$ solution, dried over anhydrous $MgSO_4$, and filtered. After the solvent was evaporated, the crude product was purified by column chromatography using EtOAc/hexane 10:90 to afford **13a** (156 mg, 32%) and **13b** (175 mg, 36%). Compound **13a** was obtained as a light yellow solid: mp 202−204 °C. $^1$H NMR ($CD_2Cl_2$): $\delta$ 0.04 (t, $J$ = 7.3 Hz, 3H), 0.87−0.95 (m, 2H), 1.02 (t, $J$ = 7.3 Hz, 3H), 1.18 (s, 9H), 1.20 (s, 9H), 1.27 (s, 18H), 1.28 (s, 3H), 1.81−1.98 (m, 2H), 2.39 (q, $J$ = 7.3 Hz, 1H), 2.55 (q, $J$ = 7.8 Hz, 1H), 2.99 (d, $J$ = 12.3 Hz, 1H), 3.36 (d, $J$ = 13.5 Hz, 1H), 3.53 (d, $J$ = 15.4 Hz, 1H), 3.60 (q, $J$ = 9.0 Hz, 1H), 3.86 (d, $J$ = 15.5 Hz, 1H), 3.94 (s, 2H), 3.97 (d, $J$ = 13.5 Hz, 2H), 4.11 (m, 1H), 6.64 (d, $J$ = 8.5 Hz, 1H), 7.01 (d, $J$ = 2.3 Hz, 1H), 7.04 (s, 1H), 7.06 (d, $J$ = 2.3 Hz, 2H), 7.10 (d, $J$ = 3.6 Hz, 2H), 7.25 (d, $J$ = 2.2 Hz, 1H), 7.47 (s, 1H), 7.89−7.92 (dd, $J$ = 2.2, 8.7 Hz, 1H), 8.45 (s, 1H), 9.94 (s, 1H). $^{13}$C NMR ($CD_2Cl_2$): $\delta$ 9.8, 10.2, 24.2, 24.3, 31.3, 31.5, 31.6, 31.8, 32.0, 32.9, 34.3, 34.4, 34.6, 34.7, 39.1, 39.6, 125.5, 126.3, 126.8, 127.1, 128.0, 128.1, 128.2, 128.4, 128.5, 129.1, 129.9, 133.3, 133.5, 133.8, 133.9, 134.0, 134.6, 139.8, 141.9, 145.3, 147.2, 147.8, 148.4, 151.1, 151.8, 154.9, 157.3, 189.9. MS CI (*m*/*z*), relative intensity (%): 883 ($M^+$ + 1, 38), 882 ($M^+$, 75), 880 ($M^+$ − 1, 100), 879 (95), 849 (30), 838 (28), 732 (30), 647 (60); calcd for $C_{57}H_{71}NO_7$, 881.5227.

Compound **13b** was obtained as a colorless solid: mp 151−153 °C. $^1$H NMR: $\delta$ 0.84 (s, 9H), 1.00 (s, 9H), 1.29 (s, 21H), 2.12−2.24 (m, $J$ = 6.8 Hz, 2H), 3.12 (d, $J$ = 13.0 Hz, 2H), 3.40 (d, $J$ = 13.6 Hz, 2H), 4.04−4.13 (m, 6H), 6.72 (s, 2H), 6.80 (s, 1H), 6.82 (s, 2H), 6.87 (s, 2H), 7.05 (s, 2H), 7.09−7.94 (dd, $J$ = 2.0, 8.7 Hz, 1H), 8.46 (d, $J$ = 2.0 Hz, 1H), 9.95 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 10.9, 23.3, 30.8, 31.0, 31.2, 31.7, 33.8, 33.9, 34.0, 79.3, 116.6, 124.8, 125.1, 125.7, 126.2, 126.4, 127.9, 129.3, 131.9, 132.3, 133.9, 139.6, 141.5, 146.4, 147.7, 147.9, 148.5, 150.5, 157.4, 188.9. MS CI (*m*/*z*), relative intensity (%): 840 ($M^+$ + 1), 838 ($M^+$ − 2, 27), 732 (30), 647 (62); calcd for $C_{54}H_{65}NO_7$, 839.4798.

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**Supporting Information Available:** $^1$H and $^{13}$C NMR spectra of compounds **3a**, **3b**, **6**, **8**−**11**, **13a**, and **13b** and an ORTEP figure for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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