

Synthesis and Properties of a New Member of the Calixnaphthalene Family: A *C*₂-Symmetrical *endo*-Calix[4]naphthalene

Sultan Chowdhury and Paris E. Georghiou*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador A1B 3X7, Canada

parisg@mun.ca

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Abstract: The synthesis of a new *endo*-calix[4]naphthalene is described. The reaction sequence involves the cyclocondensation of a key bisnaphthylmethane intermediate (8) with formaldehyde. This key intermediate (8) is formed using a modified Suzuki-Miyaura Pd-catalyzed crosscoupling reaction between bromomethylnaphthyl (6) and naphthylboronic acid (7), both of which can be derived from 2-hydroxynaphthoic acid.

Calix[*n*]arenes constitute an important class of compounds that have been widely used as "molecular baskets" in supramolecular complexation studies and in a variety of other applications.^{1,2} In general, the depth of the basket or cavity in a *cone* conformer of an unsubstituted calix[4]arene as measured from the phenolic oxygen atom to the distal hydrogen atom on the para hydrogen atom is approximately 5.3 Å. In an analogous unsubstituted *endo*-calix[4]naphthalene such as **1**, however, the comparable distance is 7.5 Å (Figure 1).³ Calix[4]naphthalenes such as **1** can therefore be thought of as deeper and electron-richer "molecular baskets" than the corresponding calix[4]arenes. Such calixnaphthalenes have been shown to be capable of complexing⁴ with C₆₀ and also of forming a dimer in the solid state.⁵

To date, there have only been a few calix[*n*]naphthalenes that have been reported.^{5–7} In this paper, we report the synthesis of the newest member of the calix[4]-naphthalene family, the C_2 -symmetrical *endo*-calix[4]-naphthalene **2** and its alkoxy derivatives. The synthetic

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FIGURE 1. *Cone* conformer of *endo*-calix[4]naphthalene (1) as determined by molecular modeling.

route includes the use of directed ortho metalation conditions and a modified⁸ Suzuki–Miyaura⁹ Pd-catalyzed cross-coupling reaction to produce key intermediates.

A simple retrosynthetic approach can be envisioned for a convergent synthesis of **2** (or its derivatives) via a "2 + 2" cross-coupling of synthons such as **3** (or **3a**) with **4** and/or **4a** (Scheme 1) using different metal-assisted or catalyzed carbon–carbon bond-forming methodologies, in particular, the modified Suzuki-Miyaura coupling reaction.^{8,9} We have previously demonstrated that it is possible to achieve Pd-catalyzed cross-coupling between phenyl- or naphthylboronic acids and benzyl bromides, iodides, or bromomethylnaphthalenes to form methylenebridged products in synthetically useful yields.⁸ However, until now, this methodology had not been tested for the "2 + 2" cross-coupling reactions between diboronic acids such as **3** (or **3a**), with **4** and/or **4a**, as envisioned, for example, in Scheme 1.

Both synthons 3 (or 3a) and 4 (or 4a) can be derived from the common intermediates bis(2-methoxy-3-naphthyl)methane (5) or its *O*-methoxymethyl analogue, 5a. These latter intermediates, in turn, could be synthesized in 89% and 79% yields, respectively, using the modified Suzuki-Miyaura Pd-catalyzed reaction between 3-bromomethyl-2-methoxynaphthalene (6)⁵ and naphthylboronic acids 7 or 7a. To efficiently produce the corresponding diboronic acid synthon **3** or **3a**, however, the alkoxy groups in 5 or 5a, respectively, needed to first be removed (Scheme 2). This was achieved using BBr₃ in CH₂Cl₂ to afford **8** in 95% yield. Bromination with Br_2 in acetic acid formed 9, which was then converted to the MOMprotected compound 9a, both steps affording nearquantitative yields. Double ortho-lithiation using n-BuLi (2.2 equiv) in THF at -78 °C followed by the *in situ* addition of trimethyl borate and subsequent hydrolysis furnished the desired diboronic acid synthon 3a. The second required synthon, 4, was synthesized from 5 by reaction with aqueous formaldehyde in HBr-acetic acid solution in 77% yield.

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During the course of this study, all of our attempts to effect cross-coupling between synthons **3** (or **3a**) and **4** or **4a** as envisioned in Scheme 1 using the modified Suzuki–Miyaura conditions under various conditions including using different halides, solvent, reaction times, and temperatures failed to produce the desired target product(s). The use of the Neighishi,¹⁰ or Stille,¹¹ procedure also failed to produce the desired products. It was concluded that the di-ortho-substituted and bulkier bisnaphthylmethyl substrates might not have been able to adequately form an essential Pd-catalytic intermediate required for the cross-coupling, resulting instead in competitive deboronation.

SCHEME 2^a



^{*a*} Reagents and conditions: (i) BBr₃, CH₂Cl₂, rt; (ii) Br₂, AcOH, rt; NaH, dry THF, MOMCl; (iv) *n*-BuLi (2.2 equiv), dry THF, -78 °C, B(OCH₃)₃, H₃O⁺; (v) aq 30% (CH₂O)_{*n*}, HBr, AcOH, rt.

A modified version of Scheme 1 was evaluated using 3-methoxy-2-naphthylboronic acid (7) or 3-O-methoxy-methyl-2-naphthylboronic acid (7a), both of which could be formed in high yields, using a modification of a procedure employed by Biehl.¹² Coupling of 7 (or 7a) with the bisnaphthyl compound 10^{6a} using our Suzuki–Miyaura conditions formed the tetranaphthyl products

SCHEME 3

3).



11 or 11a in 58% and 43% yields, respectively. These are

relatively lower yields than those observed for other

products obtained using this method.⁸ Attempts at ef-

fecting a cyclocondensation with formaldehyde at the free

1- and 1'-positions in 11 or 11a (Scheme 3); however,

failed to produce the desired calix[4]naphthalenes 2a or

2b in any appreciable amounts, affording only resinous products. Similarly, in an another attempt at effecting a

cyclocondensation with formaldehyde, the tetranaphthyl

product 12 obtained in 23% yield from reaction between

4 and 2-methoxy-1-naphthaleneboronic acid 13, also

failed to produce cyclized calix[4]naphthalene 2a (Scheme

Despite the failure of the attempts described above, calix[4]naphthalene **2** was synthesized using the bisnaphthylmethane intermediate **8** in a different approach (Scheme 4). The reaction of **8** using aqueous 37% form-

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⁽¹¹⁾ Stille, J. K.; Lau, K. S. Y. Acc. Chem. Res. 1977, 10, 434.
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SCHEME 4



aldehvde in ethanol-dioxane and concentrated HCl afforded a brown, sparingly soluble, solid crude product in 81% yield. This product could not be easily purified since it was found to be insoluble in all but DMF, pyridine, or DMSO. Two singlets at δ 4.61 and 5.19 in its ¹H NMR (pyridine- d_5) were indicative of the presence of two methylene groups in a cyclized product, however, and a (+)-FAB MS showed the presence of the expected molecular ion peak at m/z = 624. Initial experiments aimed at purifying this product involved conversion to the chromatographically separable alkoxy ethers (Scheme 4). The low yields of the alkoxy products that could be isolated and characterized as described below indicated that 2 was only present in minor amounts in the acidmediated formaldehyde cyclocondensation crude product. However, after these alkylation reactions were conducted and established unequivocally that 2 was indeed formed and could be characterized, pure 2 was obtained as a brown solid, in 54% yield, from the base-induced condensation reaction of 8 with 2 molar equiv of aqueous 37% formaldehyde solution in boiling DMF for 48 h. A stoichiometric amount of Cs₂CO₃ was employed as the base (Scheme 4). The ¹H NMR spectrum of **2** in pyridine d_5 showed the same two signals at δ 4.61 and 5.19, which were seen in the crude product derived earlier using the acidic conditions. HETCOR NMR clearly revealed signals at δ 23.3 and 34.4 that correspond to the methylene carbons and are correlated with the proton signals at δ 4.61 and 5.19, respectively. The molecular mass of the assigned structure 2 was also confirmed by CI MS analysis showing the expected molecular ion peak M⁺ + 1 at m/z = 625.

Alkylation of the crude calix[4]naphthalene **2**, described above ("crude product"), with various 1-alkyl halides under basic conditions afforded products that could now be chromatographically purified. With 1-bromobutane, the linear hexanaphthyl-formaldehyde condensation product **14** was isolated in 18% yield. The only other component that could be isolated was 1,3-di-*O*-*n*-butyloxycalix[4]naphthalene **14a** in 3% yield. (+)-FAB MS showed the expected molecular ion peak at m/z = 736, and its ¹H NMR spectrum clearly indicates it to be conformationally fixed. The four sets of doublets centered at δ 3.67, 4.50, 4.73, and 4.90 having geminal coupling



FIGURE 2. ¹H NMR spectrum of **14a** showing the splitting patterns of the methylene bridge protons linking the four naphthalene units and also of the diastereotopic methylene protons of the butyloxy groups, which are α to the ether oxygen atoms.

constants of J = 12.9, 15.2, 12.9, and 15.2 Hz, respectively (and correlated by COSY), are due to the protons of the methylene bridges linking the four naphthalene units. Two sets of overlapped multiplets appear at δ 4.03–4.07 and 4.11–4.16 ppm, revealing the diastereotopicity of the methylene protons of the *n*-butyl groups α to the oxygen atoms (Figure 2).

NOED measurements on **14a** also confirmed that the molecule is in a "*pinched*" or "*flattened*" cone (see Figure 3): saturation of the methylene signals at δ 3.67 enhanced the signals at δ 4.73, 7.08, and 7.36 by 14%, 3%, and 7%, respectively, and saturation of the signal at δ 4.90 enhanced the signals at δ 4.50 and 8.48 by 18% and 12%, respectively. The ¹³C NMR spectrum is in good agreement with the structure proposed; in particular, the two signals at δ 21.9 and 32.2 due to the two groups of equivalent methylene bridge carbons confirm that the butyl groups are *distal* to each other.

Di-*n*-propyl and diisopropyl ethers **14b** and **14c**, respectively, were obtained in a similar manner from the crude product (crude calix[4]naphthalene 2): 1,3-di-Opropylcalix[4]naphthalene 14b was obtained in 4% yield with 1-iodopropane, and 1,3-di-O-isopropylcalix[4]naphthalene **14c** was obtained in 6% yield with 2-iodopropane. The structures of 14b and 14c were confirmed on the basis of their ¹H NMR spectra, which are similar to that of 14a, also demonstrating similar diastereotopicity of the protons on the alkoxy group carbon atoms, which are α to the oxygen atoms. Similarly, 1,3-di-O-ethyl ether 14d was also obtained in 8% yield from the crude calix[4]naphthalene 2 with 1-iodoethane. Its ¹H NMR spectrum in CDCl₃ was similar to those of the other ethers; however, with 14d, suitable crystals for X-ray crystallography were obtained. The X-ray crystal structure (Figure 3) clearly showed that the two naphthalene units bearing the ethyl groups are nearly parallel to each other, while the other two naphthalene units are pushed outward to give a "pinched cone" (or flattened cone) conformation, predicted by the ¹H NMR analysis. Furthermore, the crystal structure also reveals the presence

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FIGURE 3. Stereoview of single-crystal X-ray structure of clathrate of **14d** showing a "*pinched cone*" conformation with two molecules of toluene in the cavity.

of two toluene molecules situated within the cavity and is therefore a 1:2 host–guest clathrate having C_2 symmetry.¹³ The methyl groups of each of the two toluene guest molecules suggest the presence of π -CH₃ interactions with the *distal* naphthalene units on which the ethoxy groups are located. Formation of a clathrate with *two* molecules of toluene appears to be unique to this *endo*-calix[4]naphthalene system. In one of the earliest X-ray structures determined of calix[4]arene, a single toluene molecule only was contained within the cavity of the calixarene,¹⁴ and in general, solvent moleculecontaining clathrates formed from various derivatives of *tert*-butylcalix[4]arene are usually 1:1 complexes.

Although "2 + 2" cross-coupling of **3** (or **3a**) with **4** and/ or **4a** using the modified Suzuki–Miyaura coupling reaction conditions failed to produce **2** or **2a**, the important intermediates **5** and **5a** were synthesized in high yields using this procedure. The C_2 -symmetrical *endo*calix[4]naphthalene (**2**) and was synthesized using **8**, which was derived from **5** and **5a**. The alkoxy derivatives **14a**-**d** were synthesized from **2**, and their structures were confirmed by NMR studies. X-ray crystallography of **14d** confirmed its conformation in the solid state, which was consistent also with its conformation in solution.

Experimental Section

6H,14H,22H,30H-5,31:7,13:15,21:23,29-Tetramethenotetrabenzo[*a,f,m,r*]cyclotetracosene-33,34,35,36-tetrol (*endo*-Calix[4]naphthalene) (2). (a) Acidic Conditions. To a solution of bis(2-hydroxy-3-naphthyl)methane (8) (0.86 g, 2.86 mmol) in dioxane/ethanol(1:2, 60 mL) was added aqueous 37% formaldehyde solution (0.79 mL, 28.6 mmol) followed by concentrated HCl (0.72 mL, 8.6 mmol) at rt under argon. The brown solution was stirred at rt for 24 h, during which time a brown precipitate formed. The solid was filtered off, washed several times with water and finally with dioxane to remove any unreacted starting material, and dried under vacuum to afford a brown solid "crude product **2**" (0.73 g, 81%). The solid could not be purified due to its poor solubility and was used directly for the alkylation reactions described in Scheme 4.

(b) Basic Conditions. To a solution of bis(2-hydroxy-3naphthyl)
methane (8) (0.48 g, 1.6 mmol) in an
hydrous DMF (50 $\,$ mL) were added aqueous 37% formaldehyde (0.080 mL, 2.8 mmol) and Cs_2CO_3 (0.52 g, 1.6 mmol) in H_2O (1.0 mL). The yellow solution was heated at reflux for 48 h and cooled to rt, and the solvent was evaporated under reduced pressure. The residue was redissolved in CH₂Cl₂, washed with aqueous 10% HCl, and dried over MgSO₄. After the solvent was evaporated, the product (0.45 g) was purified by flash column chromatography over silica gel, eluting with ethyl acetate-hexane 20:80 to recover 30 mg of the pure product. After further the column was further eluted with $CHCl_3$, a light brown solid (0.32 g) was obtained that showed the presence of two spots on TLC. The solid was washed several times with CHCl₃ to afford 2 as a colorless solid (0.276 g, 54%): mp >360 °C; ¹H NMR (500 MHz, pyridine- d_5) δ 4.61 (s, 4H), 5.19 (s, 4H), 7.04 (t, J = 7.4 Hz, 4H), 7.26 (t, J = 7.4 Hz, 4H), 7.47 (d, J = 7.9 Hz, 4H), 7.71 (s, 4H), 8.45 (br, 4H, OH), 8.49 (d, J = 8.6 Hz, 4H); ¹³C (125 MHz, pyridine-*d*₅) δ 23.3, 34.3, 120.2, 122.7, 126.0, 129.0, 129.7, 133.2, 133.9, 135.5, 136.3, 155.0; MS m/z 625 (M⁺ + 1, 8), 624 (M⁺, 17), 606 (10), 588 (5), 437 (4), 325 (35), 312 (M/2, 100), 300 (23), 281 (8); HRMS M⁺ 624.2352, calcd for C₄₄H₃₂O₄ 624.2300.

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Supporting Information Available: Experimental conditions for the synthesis of compounds **4–14a–d** and the ¹H and ¹³C NMR spectra of all of the new compounds reported herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹³⁾ Atomic coordinates for **14d** have been deposited with the Cambridge Crystallographic Centre. The coordinates can be obtained from the Director, Cambridge Crystallographic Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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