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Reductive deoxygenation of *ortho*-hydroxyaromatic aldehydes to 1,2-bis(hydroxyaryl)ethanes: application to the synthesis of ethylene bridged calixarene-analogous metacyclophanes

Suchitra Bhatt, Sandip K. Nayak *

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India

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ABSTRACT

A novel and convenient protocol for the synthesis of hexahydroxy[2.1.2.1.2.1]- and octahydroxy[2.1.2.1.2.1.2.1]metacyclophanes from 4-substituted phenol in four steps has been developed. The synthetic route involved the preparation of the key intermediate 1,2-bis(5-substituted-2-hydroxyphenyl)ethanes in good yields via (i) formylation of 4-substituted phenol, (ii) reductive deoxygenation of 5-substituted 2-hydroxy aromatic aldehydes with low-valent titanium reagent and (iii) catalytic hydrogenation. The metacyclophanes were prepared by base-catalyzed macrocyclization of the above intermediates with formaldehyde in refluxing xylene in high yields.

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Calix[*n*]arenes (*n* = 4–20), which are phenolic [1$_n$] metacyclophanes and have a basket-like shape,[1] have attracted great attention in the recent years. This is due to their ability to include other entities such as metal ions,[2] anions,[3] and neutral molecules[4] within their cavities. They have also been used as potential enzyme mimics in host–guest chemistry.[1] In calixarenes, the aromatic rings are connected by methylene units and the phenolic hydroxyl groups are ordered in a well-shaped cyclic array due to strong intramolecular hydrogen bonding. The cavity size of calixarenes can be changed by varying the number of phenolic units. A large number of calixarene derivatives containing pendant ether, amide, ketone, and ester groups have been examined for selective recognition, sensing and separation of various alkali, alkaline earth, and transition metal ions. Calixarenes synthesized with bridges other than methylene groups (homocalixarenes) are likely to have a bigger cavity size, and characterization of their hydrogen bonding network and ionophoric properties with larger guests remains an important area in supramolecular chemistry.

In contrast to calixarenes, very few reports are available for the synthesis of homocalixarenes with a bigger cavity size.[5] Literature reports on the synthesis of homocalixarenes are usually low yielding and too long for large scale synthesis and therefore it remained difficult to obtain a sufficient amount of homocalixarenes to investigate their chemical behavior. We report herein a short route for the synthesis of [(2.1)$_n$](*n* = 3,4)-metacyclophanes in reasonably good yields via low-valent titanium (LVT) reagent-mediated reductive deoxygenation of *ortho*-hydroxy aromatic aldehydes as the key step.

So far there has been only one report on the synthesis of hexahydroxy[2.1.2.1.2.1.]- and octahydroxy[2.1.2.1.2.1.2.1]metacyclophanes by Yamato et al.[6] using anisole as the starting material. The synthetic strategy involved the preparation of the key intermediate, 1,2-bis(5-*tert*-butyl-2-hydroxyphenyl)ethane (**3a**) in four steps which remains too long to be practical for large scale synthesis of metacyclophanes. In continuation of our work on supramolecular chemistry of calixarenes,[7] it was of interest to develop a simple and shorter route for the large scale synthesis of [(2.1)$_n$]-metacyclophanes without the use of sophisticated reagents.

Synthesis of **3a**, in principle, can be accomplished via the metathesis reaction of 4-*tert*-butyl-2-vinylphenol with Grubb's catalyst to 1,2-bis(5-*tert*-butyl-2-hydroxyphenyl)ethylene (**2a**) followed by catalytic reduction of the double bond. However, synthesis of 5-*tert*-butyl-2-vinylphenol from commercially available 4-*tert*-butylphenol itself involves several synthetic steps including Wittig olefination. As an alternative, we felt that LVTreagent-mediated reductive deoxygenation of 5-*tert*-butyl-2-hydroxybenzaldehyde (**1a**) may be a convenient route for the synthesis of **3a**. Classically, LVT reagent-mediated reductive deoxygenation of benzaldehyde leads to the formation of (*E*)-stilbenes (McMurry coupling). However, we have observed earlier that reductive

* Corresponding author. Tel: +91 22 25592410; fax: +91 22 25505151.
E-mail address: sknayak@barc.gov.in (S.K. Nayak).

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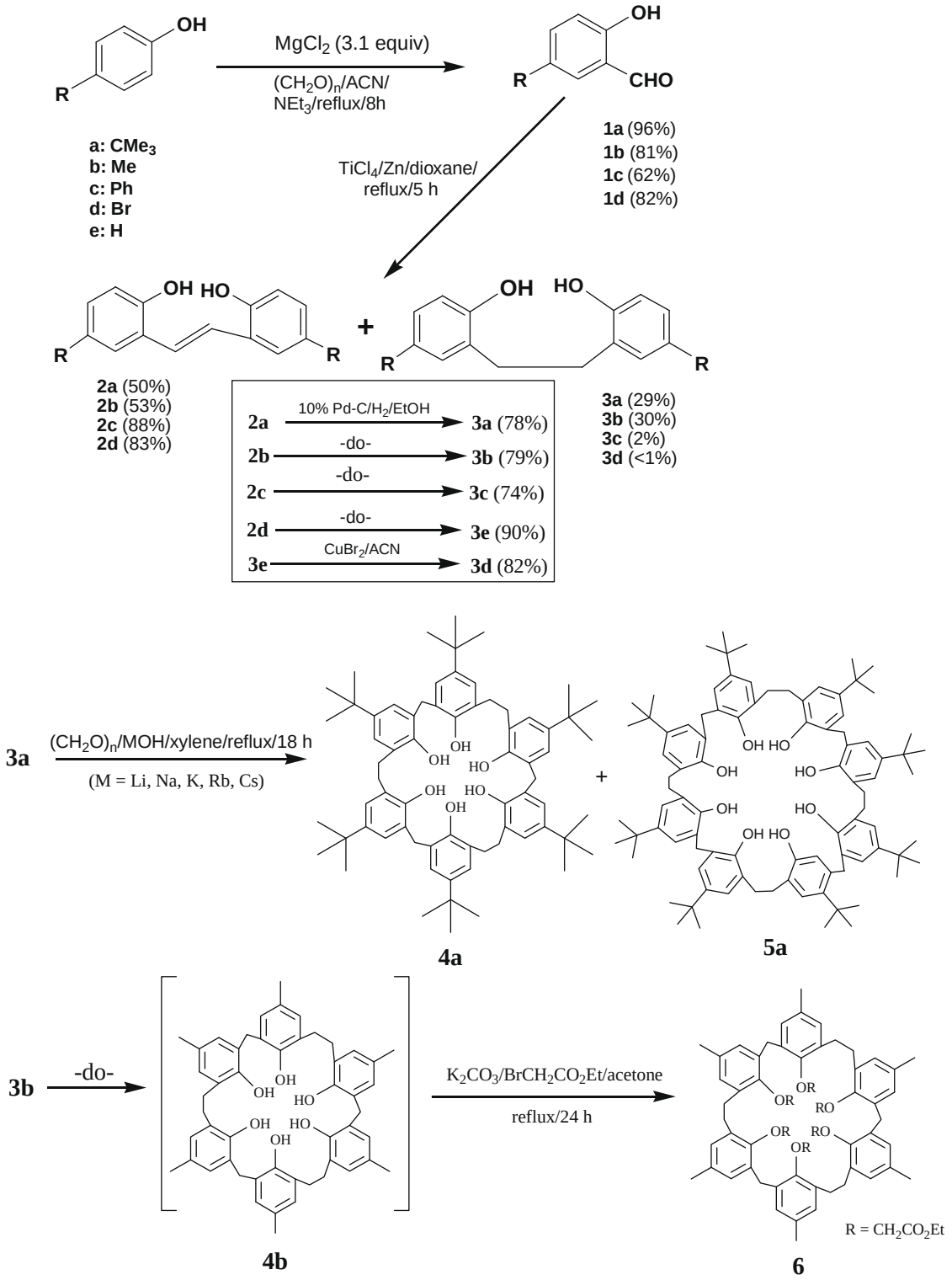
deoxgenation of 2-hydroxybenzaldehyde with LVT leads to the formation of 1,2-bis(2-hydroxyphenyl)ethane (reduced stilbene) as a sole product instead of the expected 1,2-bis(2-hydroxyphenyl)ethylene.[8] Under identical reaction conditions, however, 3-hydroxybenzaldehyde and 4-hydroxybenzaldehyde yielded 1,2-bis(3-hydroxyphenyl)ethylene and 1,2-bis(4-hydroxyphenyl)ethylene, respectively, as the sole products without the formation of their reduced products.

Keeping this in view, we envisaged that 1,2-bis(5-substituted-2-hydroxyphenyl)ethanes, which are key intermediates in the synthesis of $[(2.1)_n]$-metacyclophanes, can be achieved by the reductive deoxygenation of 5-substituted-2-hydroxybenzaldehydes



Scheme 1.

with LVT reagent. Thus, formylation of 4-*tert*-butylphenol with $MgCl_2/(HCHO)_n$[9a] afforded 5-*tert*-butyl-2-hydroxybenzaldehyde[9b] (**1a**) in 96% yield.[10] Reductive deoxygenation of **1a** with LVT reagent (prepared from $TiCl_4$/Zn/dioxane) furnished a mixture of (*E*)-**2a**[11] and **3a**[6] in 50% and 29% yields, respectively, which were separated by column chromatography (Scheme 1). The reaction was carried out on 0.1 M scale without any appreciable change in the yield and composition of the products. Compound **2a** was smoothly converted to **3a** in 78% yield by catalytic hydrogenation. Thus, synthesis of **3a** from 4-*tert*-butylphenol was accomplished in three steps with 65% overall yield. It is important to mention that the overall yield in the reported synthesis of **3a** from anisole was only 38%.[6]

Condensation of **3a** with paraformaldehyde and aqueous NaOH in xylene, following the procedure for the synthesis of calix[6]arene by Gutsche et al.,[12] yielded a mixture of hexa-*tert*-butyl-hexahydroxy[2.1.2.1.2.1]metacyclophane (**4a**, 32%) and octa-*tert*-butyloctahydroxy[2.1.2.1.2.1.2.1]metacyclophane (**5a**, 40%), which were separated by column chromatography.[13]

The template effect of different alkaline metal ions in the macrocyclization reaction of **3a** with formaldehyde was also investigated. As outlined in Table 1, use of bases with larger alkali metal ions such as KOH, RbOH, and CsOH afforded smaller cavity macrocycle **4a** as the major product, while LiOH and NaOH afforded larger cavity metacyclophane **5a** as the predominant product. Among the different bases used, CsOH afforded the highest total yield of the metacyclophanes. Thus the synthesis of metacyclophanes **4a** and **5a** was accomplished from 4-*tert*-butylphenol in four steps in overall yields of 40% and 14%, respectively, using CsOH in the macrocyclization step.

To see the scope and generality of the above protocol, 2-hydroxy-5-methyl-benzaldehyde[14] (**1b**) (prepared from 4-methylphenol) was subjected to LVT-induced reductive deoxygenation to yield a mixture of (*E*)-1,2-bis(2-hydroxy-5-methylphenyl)ethylene[15] (**2b**) and 1,2-bis(2-hydroxy-5-methylphenyl)ethane (**3b**).[11] As before, the compound **2b** on catalytic hydrogenation yielded **3b** which was subjected to NaOH-induced macrocyclization with formaldehyde. However, inspite of several attempts the metacyclophane formed could not be purified because of its poor solubility in commonly used organic solvents. To overcome this, the phenolic OH groups were alkylated with K_2CO_3/ethyl bromoacetate to afford hexa-methyl-hexakis [(ethoxycarbonyl)methoxy][2.1.2.1.2.1]metacyclophane **6** as the sole product.[16] This indirectly shows the formation of hexamer **4b** as the sole product in the macrocyclization reaction of **3b**.

As in the case of **3a**, different alkali metal bases were screened to optimize the yields and composition in the macrocyclization reaction of **3b**. In all cases hexamer **6** was obtained as the sole product (Table 2) and no octamer was detected. The best yield of **6** was achieved using CsOH as base followed by alkylation.

The difference in product composition from the reactions of **3a** and **3b** with HCHO/alkali prompted us to explore the role of substituents *para*- to phenolic-OH group in the macrocyclization reaction of **3**. Thus phenols with electron-withdrawing *para*-substituent such as 2-hydroxy-5-phenylbenzaldehyde[17] (**1c**) were converted to 1,2-bis(5-phenyl-2-hydroxyphenyl)ethane[11] (**3c**) by a similar sequence of reactions as mentioned earlier for **3a** and **3b**. However, all attempts to macrocyclize **3c** with formaldehyde and base remained unsuccessful. This is possibly due to the electron-withdrawing effect of the phenyl group *para* to phenol, thus deactivating the aromatic ring for electrophilic reaction. Similarly, reductive deoxygenation of 5-bromo-2-hydroxybenzaldehyde[18] (**1d**) yielded (*E*)-1,2-bis(5-bromo-2-hydroxyphenyl)ethylene[19] **(2d)** as the sole product with a trace amount of 1,2-bis(5-bromo-2-hydroxyphenyl)ethane[11] **(3d)**. Interestingly, catalytic hydrogenation of **2d** led to the reduction of stilbene double bond with concomitant aromatic debromination to afford 1,2-bis(2-hydroxyphenyl)ethane[8] (**3e**) in 90% yield. Compound **3e** was further brominated exclusively at the *para*-position of the phenolic group using the protocol ($CuBr_2/CH_3CN$) developed earlier in our laboratory[20] to yield **3d** in 82% yield. However, like **3c**, all attempts to base-induce macrocyclization of **3d** with formaldehyde remained unsuccessful, and the starting material was quantitatively recovered. All the compounds were crystallized and characterized by their spectral (IR, ^1H NMR, ^{13}C NMR, and MS) and analytical data.

In conclusion, we have developed an easy and convenient route for the synthesis of $[(2.1)_n]$ ($n = 3$, 4)-metacyclophanes. The only report[6] so far on the synthesis of this class of macrocycles involved the preparation of the key intermediate **3a** from anisole in four steps in 38% overall yield while in the present methodology, **3a** was prepared from commercially available 4-*tert*-butyl phenol in three steps with much higher yield (65%). The studies on the ionophoric properties of synthesized metacyclophanes are currently underway.

Table 1
Condensation of **3a** with paraformaldehye in the presence of different alkali metal hydroxides

Metal hydroxide	**4a**[a] (yield %)	**5a**[a] (yield %)
LiOH	19	43
NaOH	32	40
KOH	50	29
RbOH	54	24
CsOH	61	22

[a] Isolated yield after column chromatography.

Table 2
Condensation of **3b** with paraformaldehye in the presence of different alkali metal hydroxides followed by alkylation with ethyl bromoacetate

Metal hydroxide	**6**[a,b] (yield %)
LiOH	29
NaOH	34
KOH	42
RbOH	57
CsOH	73

[a] Isolated yield after column chromatography.
[b] Due to its insolubility, the intermediate **4b** was alkylated to **6**. Thus, the yield of **6** refers to the overall yield in two steps.

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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.2009.07.156.

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10. *Typical procedure for the synthesis of 5-tert-butyl-2-hydroxybenzaldehyde* (**1a**) *from 4-tert-butylphenol*: dry paraformaldehyde (3.5 g) was added in portions to a mixture of 4-*tert*-butylphenol (5.0 g, 33.3 mmol), triethylamine (13 mL, 93.3 mmol), and anhydrous $MgCl_2$ (9.8 g, 103 mmol) in acetonitrile (300 mL). The mixture was refluxed for 8 h, cooled to room temperature, acidified with aqueous 3 N HCl solution, and extracted with ether. The ether layer was washed with water, and brine, and dried ($MgSO_4$). Removal of solvent yielded a crude material which was purified by column chromatography (SiO_2) to yield **1a** (5.69 g, 96% yield); oil; IR (neat): ν 3418, 2964, 1660, 1486, 1265 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 9H), 6.93 (d, 1H, J = 10 Hz), 7.51 (d, 1H, J = 2 Hz), 7.58 (dd, 1H, J = 2, 10 Hz), 9.88 (s, 1H, OH), 10.86 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.1, 34.0, 117.1, 119.9, 129.6, 134.6, 142.6, 159.4, 196.7; EIMS: m/z = 178.
11. *Typical procedure for the synthesis of (E)-1,2-bis-(5-tert-butyl-2-hydroxyphenyl)ethene (**2a**) and 1,2-bis-(5-tert-butyl-2-hydroxyphenyl)ethane (**3a**)*: a dry argon-filled three-necked round-bottomed flask was charged with dry dioxane (350 mL), titanium(IV) chloride (10.5 mL, 96 mmol), and zinc dust (12.6 g, 192 mmol), and the mixture was refluxed for 3 h. The black slurry thus obtained was cooled to 0 °C and then a solution of **1a** (5.69 g, 32 mmol) in dioxane (20 mL) was added to it. The mixture was further refluxed for 2 h and cooled to room temperature, diluted with diethyl ether, quenched with 10% aqueous K_2CO_3 solution (5 mL), and passed through a small bed of Celite. The Celite bed was thoroughly washed with ether and the filtrate was dried ($MgSO_4$). Removal of the solvent and subsequent column chromatography over silica gel yielded **2a** (2.59 g, 50% yield) and **3a** (1.51 g, 29% yield), respectively. Catalytic hydrogenation [Pd–C(10%)–EtOH] of **2a** afforded **3a** in 78% yield. Compounds **3b**, **3c,** and **3e** were synthesized following a similar procedure used for **3a**. Spectral data for selected compounds: **2a**: solid; mp 210–211 °C; IR (KBr): ν 3424, 2950, 1642 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 18H), 6.84 (d, 2H, J = 8.4 Hz), 7.13 (m, 2H), 7.60 (m, 4H), 8.38 (s, 2H, OH); ^{13}C NMR (50 MHz, acetone-d_6): δ 30.9, 33.6, 115.2, 122.9, 123.6, 124.3, 125.0, 141.9, 152.3; EIMS: m/z = 324. Compound **3b**: solid; mp 133–134 °C; IR (KBr): ν = 3252, 2920, 1614, 1505 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.29 (s, 6H), 2.80 (s, 4H), 6.71 (br s, 2H, OH), 6.80 (d, 2H, J = 7.8 Hz), 6.96 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.4, 32.0, 115.3, 127.7, 128.1, 130.1, 130.6, 151.3; EIMS: m/z = 242. Compound **2c**: solid; mp 265–267 °C; IR (KBr): ν 3331, 3020, 1603 cm^{-1}; ^1H NMR (200 MHz, C_5D_5N): δ 7.28–7.58 (m, 10H), 7.71 (d, 4H, J = 7.4 Hz), 8.30 (s, 2H), 8.46 (s, 2H), 12.2 (br s, 2H, OH); ^{13}C NMR (50 MHz, C_5D_5N): δ 117.1, 124.7, 125.6, 126.7, 126.8, 126.9, 127.5, 129.2, 132.8, 141.6, 156.4; EIMS: m/z = 364. Compound **3c**: solid; mp 165–166 °C; IR (KBr): ν 3313, 3019, 2399, 2363 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6): δ 3.08 (s, 4H), 6.98 (d, 2H, J = 8.2 Hz), 7.18–7.54 (m, 14H), 8.60 (s, 2H, OH); ^{13}C NMR (50 MHz, acetone-d_6): δ 30.5, 115.5, 125.5, 126.3, 126.4, 128.7, 128.9, 132.4, 141.3, 155.0; EIMS: m/z = 366. **3d**: solid mp 168–170 °C; IR (KBr): ν 3392, 3019 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6): δ 2.87(s, 4H), 6.80 (d, 2H, J = 8.4 Hz), 7.18 (m, 4H), 8.78 (s, 2H, OH); ^{13}C NMR (50 MHz, acetone-d_6): δ 29.4, 110.5 116.5, 129.2, 130.5, 132.0, 154.0; EIMS: m/z = 374.
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