Selective Formylation of Calix[4]arenes at the 'Upper Rim' and Synthesis of New Cavitands[1]

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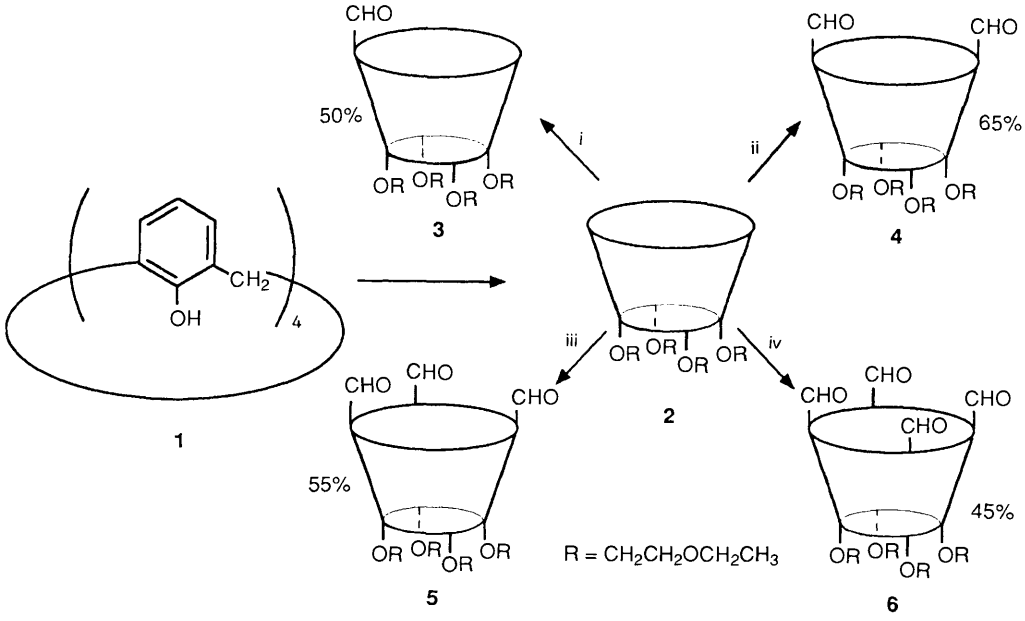
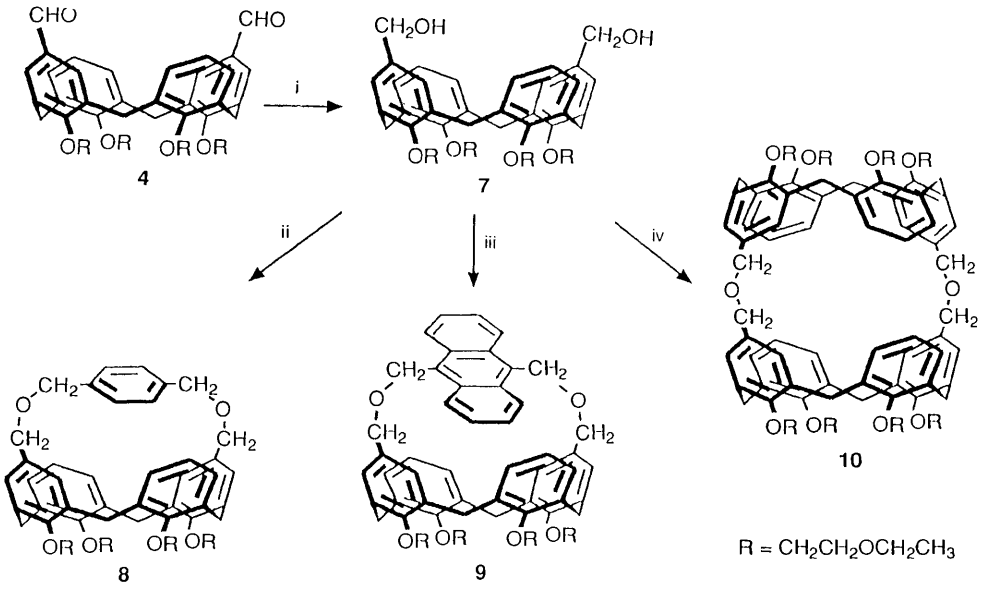
The direct selective upper rim 1,3-formylation of conformationally rigid calix[4]arenes is achieved for the first time; the diametrical bis(formyl)calix[4]arene **4** is used as a key intermediate for the synthesis of new cavitands.

The ability of calix[4]arenes[2,3] to form *intra*cavity inclusion complexes with organic neutral molecules in the solid state[4] and in aqueous solution[5] is well documented.

However, despite the efforts of several laboratories, little evidence has been obtained so far for complex formation in organic media. This could be due to the very low stability constant of such complexes which, in turn, depends on the extensive solvation of the calix[4]arene hosts, on their conformational flexibility[2,3] and on the nature of the host–guest interaction involved, which is rather weak. Since complexes of uncharged guests with uncharged hosts, interacting *via* van der Waals dispersion forces, have been observed in



Scheme 1 *Reagents and conditions*: i, 14 equiv. $CHCl_2OMe{\cdot}SnCl_4$, $CHCl_3$, −10 °C, 30 min; ii, 18 equiv. $CHCl_2OMe{\cdot}SnCl_4$, $CHCl_3$, −10 °C, 30 min; iii, 50 equiv. $CHCl_2OMe$, 40 equiv. $TiCl_4$, $CHCl_3$, room temp., 90 min; iv, 50 equiv. $CHCl_2OMe$, 25 equiv. $TiCl_4$, $CHCl_3$, 40 °C, 30 min



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, EtOH, room temp., 2 h; ii, α,α′-dibromoxylene, NaH, 1,2-dimethoxyethane (DME), room temp., 48 h; iii, α,α′-dibromo-9,10-dimethylanthracene, NaH, DME, room temp., 15 h; iv, 1 equiv. TsCl, NaH, Toluene–DME, 60 °C, 48 h

organic media only with highly preorganized receptors such as cryptophanes,[6] cavitands[7] and carcerands,[8] we have designed the synthesis of such molecules from calix[4]arenes.

The conformationally mobile calix[4]arene **1** was first transformed into the cavitand **2**,[9] which is fixed in the cone conformation.†

The Gross formylation of aromatic compounds[10] (Cl_2CHOMe–Lewis acid) as applied to cavitand **2** (Scheme 1) results in a quite selective functionalization of calix[4]arene ethers at the upper rim (aromatic nuclei).

By a careful choice of catalyst, solvent, temperature and molar ratio of substrate to reagent it has been possible to obtain a good regioselectivity.

Mono- **3** and diformyl derivatives **4** have been isolated in 50 and 65% yield respectively by using $SnCl_4$ as the catalyst whereas tri- **5** and tetraformylated calix[4]arenes **6** have been obtained in 55 and 45% yield respectively with $TiCl_4$.

This is the first direct method for the selective functionalization of calix[4]arene derivatives having four equivalent positions at the upper rim, since other reported methodologies[11] take advantage of the different reactivity of aromatic nuclei induced by the selective functionalization at the phenolic OH groups at the lower rim. Particularly interesting is the regioselectivity observed in the bis-formylation in which the 1,3-diformyl derivative is the major product, with less than 5% of the 1,2-isomer.

Reduction ($NaBH_4$, EtOH) of the diformyl derivative **4** gives quantitatively the corresponding dimethylol **7** whose disodium salt reacts with α,α′-dibromo-*p*-xylene and α,α′-dibromo-9-10-dimethylanthracene under high dilution conditions to give the two upper rim bridged cavitands **8** and **9** in 30% yield. A similar reaction of dimethylol **7** with its *in situ* prepared ditosylate gives the double calixarene **10** in 25% yield (Scheme 2).[12]

Variable temperature ^1H NMR experiments show that compounds **8–10** are not completely rigid and that 'portals' are available for guest molecules of suitable size to enter the apolar cavity. We are currently investigating the inclusion abilities of the new host synthesized toward organic neutral molecules.

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† All compounds synthesized **2–10** give satisfactory elemental analyses and show molecular ion on DCI mass spectra. ^1H NMR spectra ($CDCl_3$ 200 MHz) **4**: 9.59 (2H, CHO, s), 7.18 (4H, ArH, s), 6.59 (6H, ArH, s), 4.55 and 3.22 (8H, $ArCH_2Ar$, 2d), 3.7–4.3 (16H, OCH_2CH_2O, 2m), 3.53 and 3.50 (8H, OCH_2CH_3, 2q), 1.19 and 1.16 (12H, OCH_2CH_3, 2t). For **10**: (218 K) 7.10 (8H, ArH, d), 6.91 (4H, ArH, t), 5.93 and 5.54 (8H, ArH, 2s), 4.53 and 3.46 (8H, $ArCH_2OCH_2Ar$, 2d), 4.38 (8H, $ArCH_2Ar$, d), 3.09 and 3.05 (8H, $ArCH_2Ar$, 2d), 3.3–4.2 (48H, $OCH_2CH_2OCH_2$, m), 1.10 and 1.21 (24H, OCH_2CH_3, 2t).

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