Asymmetrically-substituted Calix(4)arenes

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Asymmetric calix(4)arenes (**5**) consisting of three different phenolic units were obtained by fragment condensation either of a trinuclear compound (**1**) with a 2,6-bis(bromomethyl)phenol (**2**) or a dinuclear compound (**3**) with a bisbromomethylated dimer (**4**) in a dioxane–$TiCl_4$ system.

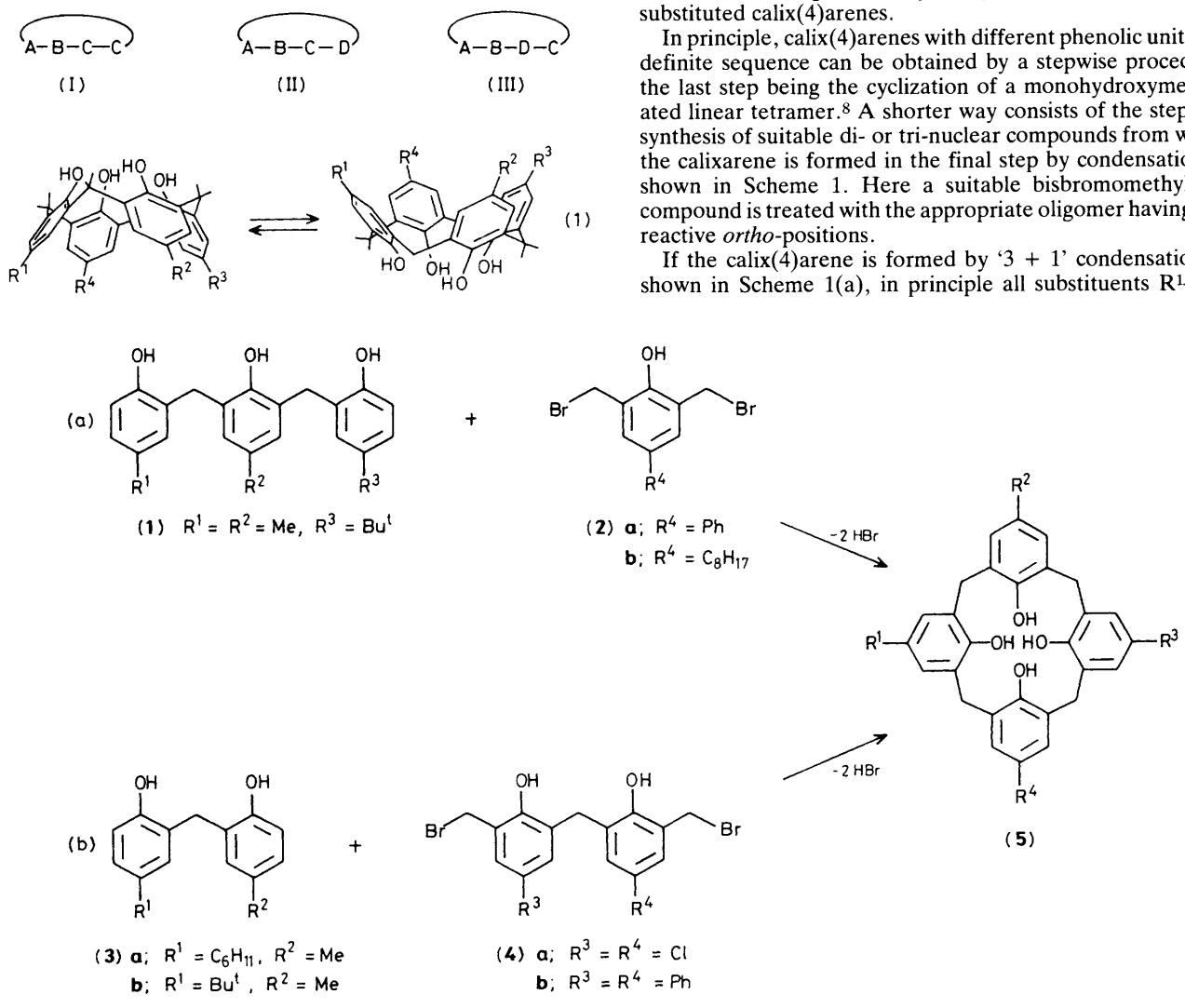
Calixarenes have attracted appreciable interest during the last decade.[1] They represent a class of host molecules which may be varied in numerous ways to fit the special requirements of different guests. For instance, they have been used as ion carrier molecules for the proton-driven cation transport through liquid membranes[2] and suitable derivatives were found to be highly selective complexing agents for several cations.[3] Their cup-like structure (potentially) enables them to include other molecules[4] and to act as enzyme mimics.[5]

One of the striking features of enzymes is their ability for enantioselective catalysis. Therefore, an important step in imitating their properties consists of chiral recognition. Calix(4)arene molecules are not planar (normally they exist in the cone conformation), and thus, calix(4)arenes consisting of four different phenolic units or three different units in the order given in structure (I) are chiral. By introduction of bulky substituents R at the hydroxy groups, which cannot penetrate through the annulus, the racemization process shown in equation (1) cannot take place, and the separation into enantiomeric host molecules should be possible.

Many of those derivatives with a fixed cone conformation are known already from symmetrical compounds[3,6] [*e.g.* from t-butylcalix(4)arene]. However, only one example of an asymmetrical calix(4)arene, which was obtained more or less accidentally,[7] has been reported up to now. We describe here for the first time general ways to synthesize asymmetrically-substituted calix(4)arenes.

In principle, calix(4)arenes with different phenolic units in a definite sequence can be obtained by a stepwise procedure, the last step being the cyclization of a monohydroxymethylated linear tetramer.[8] A shorter way consists of the stepwise synthesis of suitable di- or tri-nuclear compounds from which the calixarene is formed in the final step by condensation as shown in Scheme 1. Here a suitable bisbromomethylated compound is treated with the appropriate oligomer having two reactive *ortho*-positions.

If the calix(4)arene is formed by '3 + 1' condensation as shown in Scheme 1(a), in principle all substituents R^1—R^4



Scheme 1

Table 1. Asymmetrically-substituted calix(4)arenes, prepared according to Scheme 1: (a) compounds (**5a**,**b**) and (b), compounds (**5c**—**f**).*[a]

	R^1	R^2	R^3	R^4	% Yield	M.p./°C
(**5a**)	Me	Me	Bu^t	Ph	19.5	343—345
(**5b**)	Me	Me	Bu^t	C_8H_{17}	17.5	99—102
(**5c**)	C_6H_{11}	Me	Cl	Cl	15	308—310
(**5d**)	Bu^t	Me	Cl	Cl	20	322—324
(**5e**)	C_6H_{11}	Me	Ph	Ph	9.5	307—309
(**5f**)	Bu^t	Me	Ph	Ph	21	325

[a] Satisfactory elemental analyses were obtained for all compounds. Their structures were further confirmed by ^1H n.m.r. and mass spectra.

may be different (and of course two adjacent phenolic units may be equal as in the examples reported here). If the condensation is '2 + 2' as shown in Scheme 1(b), two isomers (II) and (III) would be formed simultaneously. To obtain a definite product, a necessary condition in this case is $R^1 = R^2$ or $R^3 = R^4$.

The condensation is carried out in dioxane, using $TiCl_4$ as a catalyst and possibly also as a template molecule, since high dilution conditions are not necessary. In a typical experiment 1.19 g (4.4 mmol) (**3b**) and 2.0 g (4.4 mmol) (**4a**) were added to 5.0 g (26.4 mmol) $TiCl_4$ in 250 ml dioxane. The mixture was refluxed for 90 h under argon and evaporated to dryness after addition of 50 g silica gel. Extraction with CH_2Cl_2 (Soxhlet apparatus) and subsequent flash chromatography (silica gel, $CHCl_3$ respectively CCl_4) finally gave 0.5 g (0.88 mmol, 20%) of the calixarene (**5d**). These reaction conditions, which have been used also for the synthesis of bridged calixarenes,[9] usually give better results than the condensation in acetic acid.[10]

Table 1 summarizes the compounds synthesized in this way. The yield of pure products usually is in the range of 15—20%, which is reasonable considering the simple synthetic procedure. There is no obvious advantage of one or other of the two synthetic pathways. Therefore the '2 + 2' condensation seems preferable in those cases where a simple or short way exists to prepare one of the educts (**3**) or (**4**). [(**4a**) for instance is obtained by direct bromomethylation of the commercially available dinuclear compound and (**4b**) is easily prepared in two steps starting with *p*-phenylphenol *via* the bishydroxymethylated dimer.[7]]

We have demonstrated by these examples that asymmetrically-substituted calix(4)arenes are readily available by fragment condensation. Experiments are underway to fix the cone conformation by suitable derivatization and to separate the derivatives into the pure enantiomers.

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