Synthesis of bridged and oligocalix[4]arenes *via* ruthenium-catalysed ring closing metathesis

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Ruthenium-catalysed metathesis of calix[4]arenes with alkenyl substituents on the upper or lower rims leads efficiently to singly- or doubly-bridged calix[4]arenes and oligocalix[4]arenes.

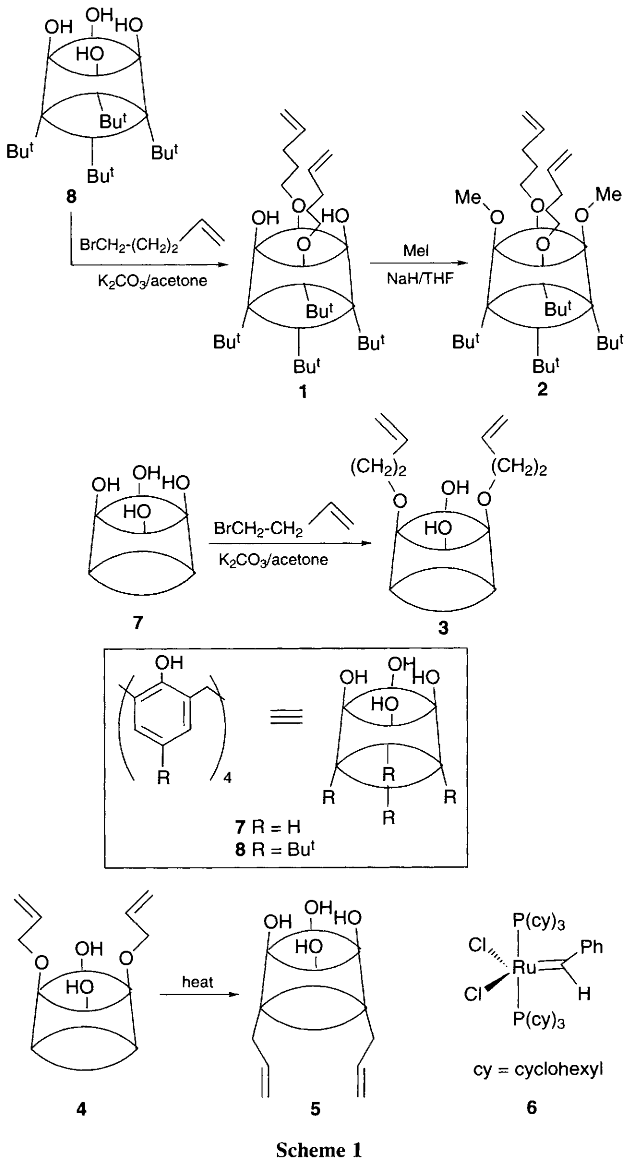
The emergence over the past few years of new robust catalysts for ring closing metathesis (RCM) has expanded the scope of this reaction to include the synthesis of many heterocycles including compounds with multiple functionality.[1] Five- to eight-membered oxygen and nitrogen heterocycles are now accessible in good yields from acyclic precursors and RCM has also been employed as the key step in the synthesis of several natural products, a notable example being the 14-membered lactam antifungal agent Sch 38516.[2]

There has been considerable recent interest in the use of calixarenes, especially calix[4]arenes, as building blocks or core structures for the construction of large multibridged assemblies with well defined macromolecular cavities or clefts and several, mostly multistep, routes have been developed.[3] It occurred to us that RCM of appropriately substituted alkenyl calix[4]arenes might provide a direct, one-step approach to an entire range of bridged and/or oligocalixarenes. Preliminary experiments were conducted with 1,3-bis(distal)calix[4]arene alkenyl ethers **1**–**3** and **5** and a recently reported alkylidene ruthenium complex **6**.[4] Lower rim alkenyl ethers **1**, **2** and **3** were readily prepared from calix[4]arene **7** and its *p-tert*-butyl derivative **8** *via* regioselective 1,3-(distal)alkylation with the appropiate alkenyl bromide in acetone containing potassium carbonate. 5-Bromopentene and **8** furnished phenolic ether **1** (77%) which was further alkylated with methyl iodide using sodium hydride in THF to afford tetraether **2** (82%). Similarly, alkylation of **7** with 4-bromobut-1-ene furnished diether **3** (75.5%). The possibility of upper rim bridging was explored using the 1,3-diallylcalix[4]arene **5**, readily accessible from diallyl ether **4** *via* Claisen rearrangement. ^{1}H NMR analysis established that compounds **1**, **3** and **5** existed in cone conformations at room temperature while the dimethoxy derivative **2** was mobile.

Reactions were conducted in dry benzene under nitrogen at room temperature.† Diphenol diether **1** furnished a single product (57%), whose ^{1}H NMR and mass spectral features were fully consistent with the bridged structure **9**. In particular, the terminal vinyl groups of **1** in the ^{1}H NMR spectrum were replaced by a single disubstituted alkene and the EI mass spectrum confirmed the loss of two methylene groups (M^+ = 756.7). Although **9** is represented here with the Z-geometry, we cannot at this stage discount the alternative *E*-geometry.‡ The remaining ^{1}H NMR features of **9** show that it retains the cone conformation of its precursor **1**. Compound **2**, the dimethyl analogue of **1**, also underwent ring closing metathesis to furnish **10** (62%). Again the spectroscopic data were in full accord with the bridged structure in **10** which, like its precursor, was conformationally mobile indicating that macrobridging of calix[4]arenes in this way does not inhibit motion of the methoxy-substituted aryl units through the calix.

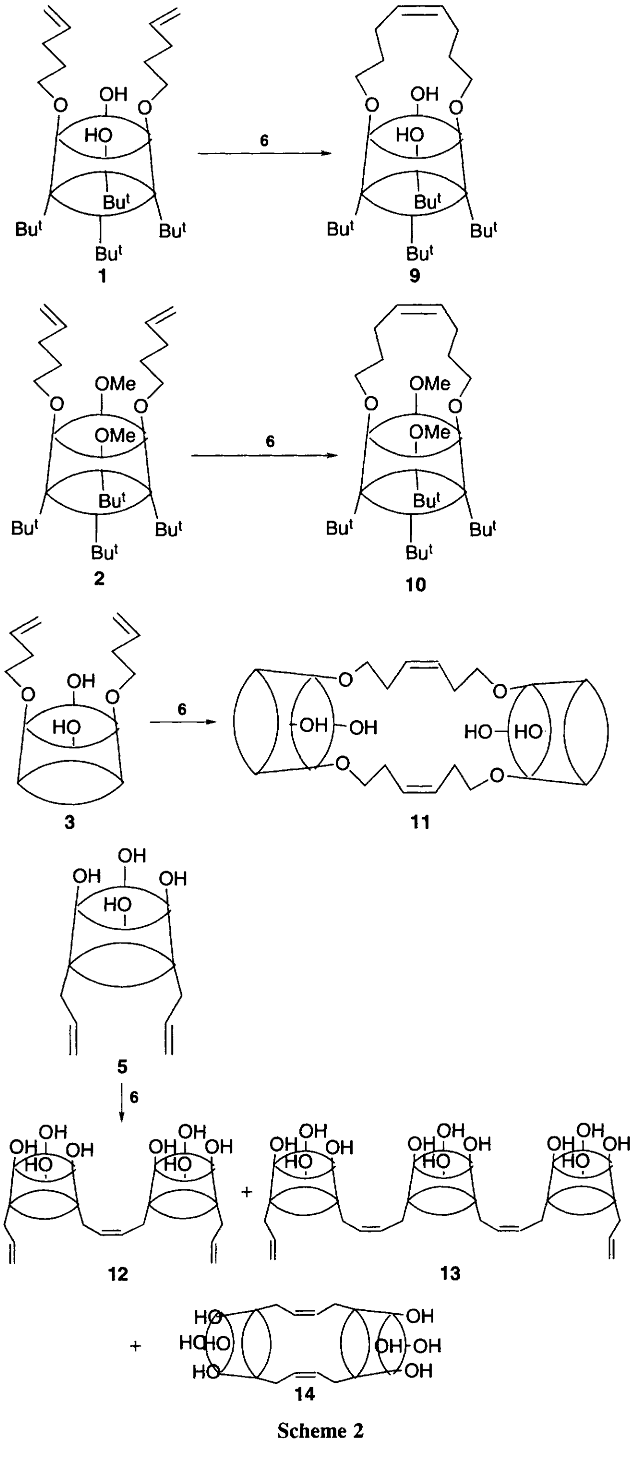
Alkenyl ether **3** has shorter methylene spacers than **2** and the question arose as to whether intermolecular metathesis might now compete with intramolecular bridging. In the event **3** produced a single product (53%), whose FAB mass spectrum (M^+ = 1009.0) confirmed that unlike **1** and **2**, this precursor had undergone an intermolecular metathesis to form the bis-calix[4]arene **11**. The preference for intermolecular reaction may simply reflect the higher angle and steric strain associated with shorter intramolecular bridges. The ^{1}H NMR spectrum of **11** was more complex than might be expected (four AB systems for the $ArCH_2Ar$ moieties as compared with two for precursor **3**) suggesting the presence of *E*,*Z*-isomers about the two alkenyl groups.

Compound **5**, with upper-rim alkenyl chains, did not show any evidence of intramolecular bridging. Rather three intermolecular reaction products were isolated, **12** (25%) and **13**



Scheme 1

(20%) representing linear oligomerisation, and **14** (5.5%) representing dimerisation. These structures are fully supported by NMR and mass spectral (FAB) measurements. The appearence of the ^1H NMR signals for the internal alkene group in **12** and **13** suggested the presence of both *E*- and *Z*-isomers.§



Scheme 2

In summary, a short general catalytic route to singly or doubly-bridged calix[4]arenes and oligocalixarenes has been developed *via* RMC. The tolerance of the reaction to free phenolic groups is particularly noteworthy with respect to further functionalisation of the reaction products for the construction of new multifunctional receptors for organic guest molecules.

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Footnotes

† *Typical experimental procedure*: Compound **1** (100 mg) was dissolved in dry benzene (8 cm^3). To the solution, 4 mol% of ruthenium catalyst was added and the homogeneous solution was stirred under nitrogen at room temperature. The reaction time was monitored by TLC. When all the starting material had reacted, the solvent was removed and the crude material was purified by column chromatography (flash silica, hexane–ethyl acetate, 95:5) and the product obtained was recrystallized from dichloromethane–methanol to afford 55 mg (57%) of compound **9**, (found $M^+ = 756.2$, $C_{52}H_{68}O_4$ requires $M^+ = 756$) as a microcrystalline white powder, mp 299-300 °C.

‡ For covenience, structures **9–13** are represented as having *Z*- geometry. *E*-Geometry is not excluded.

§ *Selected spectroscopic data* for **9**: ^1H NMR ($CDCl_3$): δ 1.18 (s, Bu^t, 18 H), 1.22 (s, Bu^t, 18 H), 2.02 (m, $C\mathit{H}_2CH=$, 4 H), 2.83 (m, $CH_2C\mathit{H}_2CH_2$, 4 H), 3.33 (d, $ArCH_2Ar$, 4 H, *J* 12.5 Hz), 4.02 (t, OCH_2, 4 H, *J* 4.5 Hz), 4.27 (d, $ArCH_2Ar$, 4 H, *J* 12.5 Hz), 5.66 (t, CH=CH, 2 H, *J* 4.4 Hz), 7.01 (s, ArH, 4 H), 7.06 (s, ArH, 4 H) and 8.99 (s, OH, 2 H). For **12** ^1H NMR ($CDCl_3$): δ 3.13 (d, $C\mathit{H}_2CHCHC\mathit{H}_2$ {*Z* or *E*}, 4 H, *J* 6.6 Hz), 3.16 (d, $C\mathit{H}_2CH=$, 4 H, *J* 8.3 Hz), 3.23 (d, $C\mathit{H}_2CHCHC\mathit{H}_2$ {*Z* or *E*}, 4 H, *J* 6.6 Hz), 3.50 (broad d, $ArCH_2Ar$, 8 H), 4.23 (broad d, $ArCH_2Ar$, 8 H), 5.01–5.05 (s + d, CH_2, 4 H), 5.50 (t, CHCH, {*Z* or *E*}, 2 H), 5.58 (t, CHCH, {*Z* or *E*}, 2 H), 5.86 (m, $CH_2C\mathit{H}$, 2 H), 6.73 (m, ArH, 4 H), 5.85 (d, ArH, 8 H), 7.03 (m, ArH, 8 H) and 10.20 (s, OH, 8 H).

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