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Synthesis of chiral calix[*n*]arenes — I. A synthetic approach towards a new enantiomerically pure calix[8]arene derivative

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Abstract: The first epc-synthesis of a chiral calix[8]arene starting from (−)-menthone is described. In a three step sequence a new enantiomerically pure calix[8]arene derivative is obtained in good yield. © 1997 Published by Elsevier Science Ltd. All rights reserved.

Calix[*n*]arenes are a well known class of macrocyclic compounds,[1] capable of forming host–guest complexes with numerous classes of compounds (e.g. aromatic and heteroaromatic hydrocarbons,[1] amino acids[1] and fullerenes[2]) and forming chelate complexes with different types of metal cations.[1] Calix[*n*]arenes can be synthesized by different strategies: i) one-pot synthesis using *p*-substituted phenols, formaldehyde and NaOH,[3] ii) stepwise condensation of *p*-substituted phenols and formaldehyde with a final cyclization step,[4] and iii) fragment condensation with a final cyclization step.[5]

Enantiomerically pure calix[*n*]arenes are accessible from achiral calix[*n*]arenes by alkylation or acylation of the phenolic OH groups with enantiomerically pure reagents[6] (modification of the lower rim) or by introducing enantiomerically pure groups into the *para*-positions[7] (modification of the upper rim). The chiral calixarenes obtained in this way are not prone to racemization by ring inversion whereas inherently chiral calix[*n*]arenes,[8] synthesized by the methods ii) and iii) (see above), readily racemize if their conformation is not suitably stabilized.

Since we are interested in chiral discrimination phenomena by host–guest-complexation using chiral hosts, such as cyclodextrins,[9] we envisioned that chiral calix[*n*]arenes might be valuable candidates for our purposes. Therefore, we needed a simple method which makes enantiomerically pure calix[*n*]arenes with different ring sizes and high solubilities in nonpolar solvents readily accessible.

Here we wish to report a chiral pool synthesis of an enantiomerically pure *p*-substituted phenol, which is easily cyclized to an enantiomerically pure calix[8]arene in good yield by the one-pot procedure mentioned above.

(−)-Menthone **1** ((2*S*,5*R*)-(−)-2-isopropyl-5-methyl-cyclohexanone; Fluka, $[\alpha]_D^{20}$=26, ee=98%) undergoes smooth alkylation with methylmagnesium iodide to give predominantly one diastereomer (90%; GC; SE 30, 25 m, 250 mm id, 0.7 bar H_2, 120°C, t_R=6.3 min) of the tertiary alcohol **2**[10] in 65% yield (Scheme 1). **2** is the result of equatorial attack of the Grignard reagent at the carbonyl group[11] as could be deduced from the missing NOE between $CH_3$11 and H5 (Scheme 1).

Friedel–Crafts alkylation[12] of phenol with **2** in CS_2 in the presence of two equivalents of $TiCl_4$ afforded the enantiomerically pure *p*-substituted phenol **3**[13] in about 50% yield (based on consumed starting material) after chromatographic purification (Scheme 2). GC analysis (SE 30, 25 m, 250 mm id, 0.8 bar H_2, 200°C, t_R=11.7 min) showed that **3** consisted only of the diastereomer depicted in Scheme 2. **3** again results from an equatorial attack of phenol at the intermediate planar carbenium ion. The axial position of CH_3 11 was deduced from an observed NOE between CH_3 11 and H5.

With the enantiomerically pure phenol **3** in hand, we were able to carry out the one-pot procedure for calix[8]arenes published by Gutsche and coworkers[3,14] (Scheme 3). For small scale preparations

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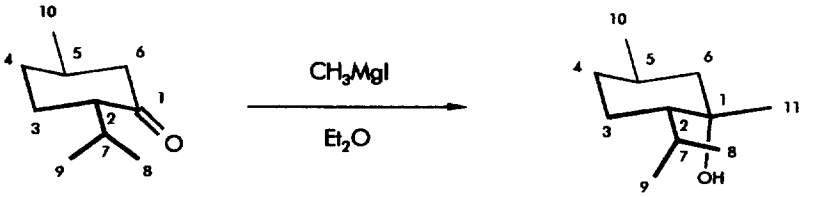
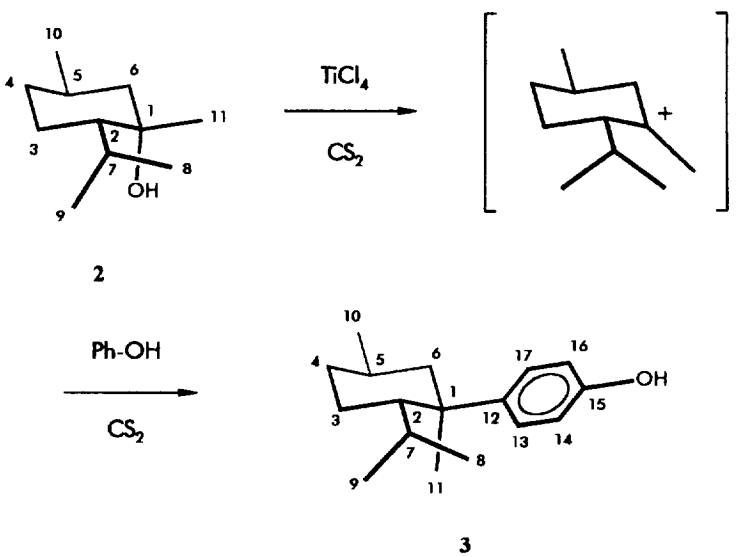


1 2

Scheme 1. Grignard reaction of (−)-menthone **1** with methylmagnesium iodide.



2 3

Scheme 2. Friedel–Crafts alkylation of phenol with **2**.

(1–10 mmol) of the calixarenes we found it convenient to use a 10 ml dropping funnel filled with activated molecular sieves (3 Å) instead of a Dean–Stark trap. We obtained calix[8]arene **4**[15] in about 30% yield after crystallization from dichloromethane/petrol ether as a white amorphous material, readily soluble in nonpolar solvents (Scheme 3). The ring size was established from FD mass spectra: $(C_{18}H_{26}O)_8$ affords M^+=2067.24; found: M^+=2068.1. In addition, $(M+Na)^+$ could be detected, which is quite common with FD mass spectra.

The application of other reaction conditions to synthesize chiral calix[*n*]arenes with other ring size and with other terpenyl phenols as well as the covalent bonding of **4** to polysiloxanes are currently under investigation and will be published in due course.

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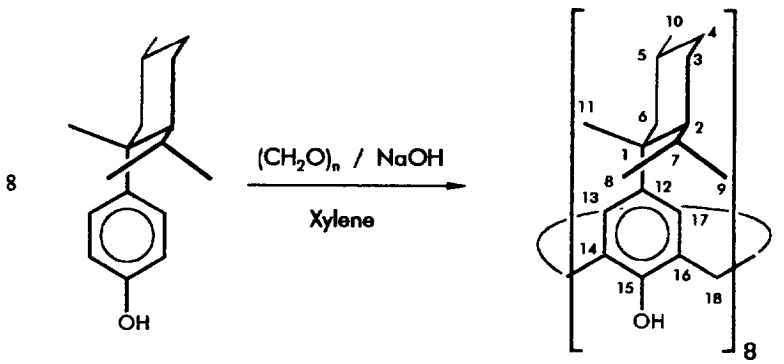

3 4

Scheme 3. One-pot synthesis of diastereomerically and enantiomerically pure **4**.

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10. ^{1}H ($CDCl_3$, 400 MHz, ppm): 2.08 (quintd, 6.4 Hz, 6.4 Hz, 1.6 Hz, H7); 1.70 (dm, 12.8 Hz, H4eq); 1.61 (m, H5ax); 1.52 (dm, 13.8 Hz, H6eq); 1.45 (dq, 12.8 Hz, 3.4 Hz, H3eq); 1.30 (qd, 12.8 Hz, 3.4 Hz, H3ax); 1.17 (s, H11); 0.98 (m, H2ax/H6ax); 0.85 (d, 6.4 Hz, H9); 0.83 (d, 6.4 Hz, H8); 0.79 (d, 6.4 Hz, H10); 0.75 (m, partially overlap with H10; H4ax). ^{13}C ($CDCl_3$, 100 MHz, ppm): 73.1 (s, C1); 50.6 (d, C2); 21.0 (t, C3); 35.3 (t, C4); 28.2 (d, C5); 50.8 (t, C6); 26.2 (d, C7); 18.3 (q, C8); 22.3 (q, C9); 23.9 (q, C10); 28.9 (q, C11).
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13. ^{1}H ($CDCl_3$, 400 MHz, ppm):7.27 (d, 8.8 Hz, H13/H17); 6.79 (d, 8.8 Hz, H14/H16); 5.04 (s, OH); 2.04 (quintd, 6.96 Hz, 6.93 Hz, 3.14 Hz, H7); 1.81 (dq, 12.6 Hz, 2.9 Hz, H4eq); 1.72 (dt, 12.8 Hz, 3.0 Hz, He6q); 1.61 (m, H5ax); 1.53 (m, H4ax); 1.52 (m, H3eq); 1.28 (brq, 13 Hz, H6ax/H3ax); 1.24 (s, H11); 0.95 (d, 6.96 Hz, H9); 0.91 (d, 6.33 Hz, H10); 0.87 (m, partially overlap with H8/H10, H2ax); 0.83 (d, 6.93 Hz, H8). ^{13}C ($CDCl_3$, 100 MHz, ppm): 36.9 (s, C1); 49.6 (d, C2); 20.5 (t, C3); 38.1 (t, C4); 30.1 (d, C5); 48.3 (t, C6); 27.0 (d, C7); 15.4 (q, C8); 21.6 (q, C9); 20.3 (q, C10); 25.1 (q, C11); 145.4 (s, C12); 126.3 (d, C13/C17); 114.9 (d, C14/C16); 153.0 (s, C15). $[\alpha]_D^{25}$ =-3.6 (c=10; $CHCl_3$).
14. According to Gutsche *et al.*[4] Phenols readily form calixarenes, if the *p*-substituent is *tert.*butyl. The methyl-menthyl group in our phenol can be regarded as a substituted *tert.*butyl group.
15. ^{1}H (CDCl3, 400 MHz, ppm):9.55 (s, OH); 7.11 (s, H13/H17); 4.30 (d, 8.0 Hz, H18); 3.43 (d, 8.0 Hz, H18); 1.94 (m, H7); 1.84–1.59 (m, H4eq/H6eq); 1.59–1.35 (m, H5ax/H3eq/H4ax); 1.35–1.13 (m, H3ax/H6ax); 1.12 (s, H11); 0.85 (d, 6.95 Hz, H9); 0.81 (d, 5.96 Hz, H10); 0.74 (d, 6.85 Hz, H8); 0.74 (m, partially overlap with H8, H2ax). ^{13}C ($CDCl_3$, 100 MHz, ppm): 146,7 (s, C15); 146,3 (s, C12); 128.8 (s, C14/C16); 125,4 (d, C13/C17); 49.7 (d, C2); 48,6 (t, C6); 38.0 (t, C4); 37.0 (s, C1); 32.6 (t, C18);30.1 (d, C5);27.0 (d, C7); 25.3 (q, C11); 21.6 (q, C9); 20.5 (t, C3); 20.4 (q, C10); 15.5 (q, C8). FD–MS: 2068.1 (M^+); 2089.5 $(M+Na)^+$. $[\alpha]_D^{20}$=-32.1 (c=4; $CHCl_3$).

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