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Synthesis of chiral calix[*n*]arenes. Part 2: Synthesis of new chiral calix[*n*]arenes based on (*p*-hydroxy-phenyl)-menthone

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Abstract

The synthesis of new chiral calix[*n*]arenes, related to Corey's phenyl-menthol, is described. Starting from enantiomerically pure (*R*)-(+)-pulegone, calix[*n*]arenes with different ring sizes could be obtained in reasonable yield. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Calix[*n*]arenes are a well known class of macrocyclic compounds[1] in supramolecular chemistry. The introduction of chirality into calix[*n*]arenes offers the possibility to study chiral recognition phenomena in host–guest interactions. Therefore our interest focused on new methods to synthesize enantiomerically pure calix[*n*]arenes.[2] Here, we wish to report a new method which makes enantiomerically pure calix[*n*]arenes with different ring sizes readily accessible.

Inspired by Corey's work on phenyl-menthol[3] as a chiral auxiliary, we planned to synthesize enantiomerically pure (*p*-hydroxy-phenyl)-menthone **6** and to convert this chiral phenol under appropriate conditions into the corresponding calix[*n*]arenes. The synthesis of **6** is outlined in Scheme 1. Starting from *p*-bromophenol **1**, we first protected the phenolic hydroxyl as *tert*-butyl ether **2** under standard conditions[4] in 95% yield. Next we converted **2** into the Grignard reagent which was coupled under CuBr catalysis to (*R*)-(+)-pulegone **3** (ee >99.8%; determined by GC on γ-CHIRASIL-DEX,[5] 2 m, 250 μm id, 50°C, 0.5 bar H_2, t_R=2.5 min) in a Michael addition.[3] We obtained in 59% yield, a mixture of two diastereomers, **4** and **5**, in a ratio of 60:40, which were readily separated by flash chromatography

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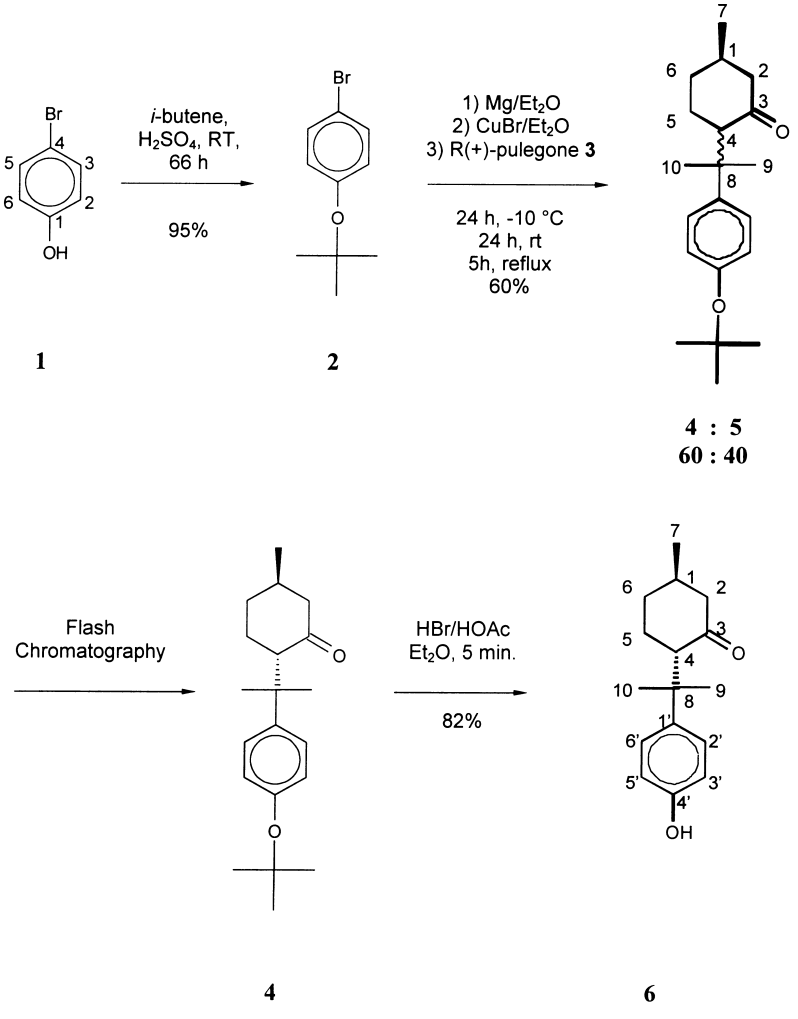
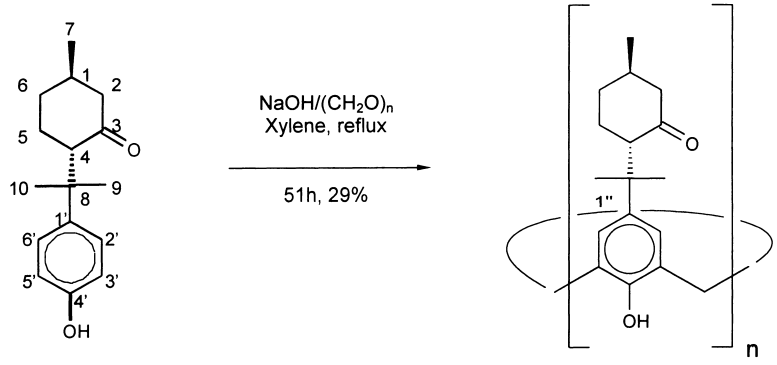
using 5% diethyl ether in *n*-hexane as eluting solvent. Finally, treatment of the *tert*-butyl ether **4** with concentrated hydrobromic acid in acetic acid for 5 min gave the enantiomerically pure phenol **6** (82%). Under these conditions, epimerization during cleavage of **4** occurred to an extent of less than 3%.[6]



Scheme 1. Synthesis of enantiomerically pure phenol **6**

With **6** at our disposal, we studied the conversion to enantiomerically pure calix[*n*]arenes using the one-pot procedure described by Gutsche and coworkers[7] (Scheme 2). The reaction was very sluggish and it was necessary to add paraformaldehyde and NaOH four times to drive the reaction to completion. The total yield of calix[*n*]arenes was 29%.

From the mixture we were able to isolate the calix[5]arene **7** (8.3%), calix[6]arene **8** (8.3%) and calix[8]arene **9** (12.4%) as white powders. The calix[*n*]arenes were characterized by FD mass spectrometry. For **7**, the FD mass spectrum showed $(M+Na)^+$, M^+, $(M+Na-112)^+$ and $(M-112)^+$. The signals indicating loss of 112 mass units can be explained through McLafferty rearrangement leading to the cleavage of one methyl cyclohexanone moiety. The FD mass spectrum of **9** contains signals which arise from repeated fragmentation through McLafferty rearrangement. Surprisingly, **8** did not ionize under FD conditions. In that case, after addition of CsI we could obtain an ESI mass spectrum which showed signals for $(M+Cs)^+$ and $(M+2Cs)^{2+}$.



6

7 (n = 5)
8 (n = 6)
9 (n = 8)

Scheme 2. Synthesis of enantiomerically (at C1) pure and epimeric (at C4) calix[*n*]arenes

The observed HRMS data measured by the use of an FT-ICR mass spectrometer (resolution 70 000) gave differences from the calculated values between Δ=3 ppm and Δ=10 ppm. From the ^{1}H and ^{13}C spectra (see experimental) we deduced that prior to or after calixarene formation, epimerization at C4 of the menthone moiety occurred, because the spectra obtained were very similar to the spectra from a mixture of **6** and epi-**6**.[6]

To prove the optical activity of the calixarenes we measured the CD spectra. For calix[5]arene **7** we obtained a positive Cotton effect, clearly indicating the optical activity of the calixarenes. The CD spectra were also very similar to the CD spectrum from a mixture of **6** and epi-**6**,[6] as mentioned already for the NMR spectra. This also indicates that epimerization occurred during calixarene synthesis. To circumvent this epimerization we currently study the use of (*p*-hydroxy-phenyl)-menthol as well as other terphenyl phenols.

2. Experimental

2.1. General

All reactions were performed under nitrogen in oven-dried glassware. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 NMR spectrometer at 250 MHz and 62.9 MHz, respectively. EI and FD mass spectra were recorded on a Finnigan TSQ 70 mass spectrometer. ESI mass spectra were recorded on a SCIEX API III TAGA 6000 E spectrometer. High resolution mass spectra were measured on a Bruker APEX II FT-ICR mass spectrometer. IR spectra were obtained on a Bruker FT-IR IFS 48 IR spectrometer. 4-Bromophenol was purchased from Aldrich, Steinheim, Germany. (*R*)-(+)-pulegone was obtained from Haarmann & Reimer GmbH, Holzminden, Germany. Isobutene was purchased from Messer Griesheim GmbH, Frankfurt, Germany. Diethyl ether was dried with sodium/benzophenone. All other reagents were technical grade.

2.2. *4-Bromophenol*-tert-*butyl ether* ***2***

In an autoclave was placed a solution of 34.6 g of 4-bromophenol (0.2 mol) in 300 ml of dichloromethane. After cooling to −40°C, 450 ml of isobutene and 2 ml of concd sulfuric acid were added. After closing the autoclave, the reaction mixture was stirred for 66 h at room temperature. The autoclave was recooled to −10°C and a solution of 5 g of sodium hydroxide in 10 ml of water was added carefully with stirring to remove unreacted 4-bromophenol and to neutralize remaining sulfuric acid.[8] After transferring the contents of the autoclave to a precooled flask, the isobutene was removed (distillation into a cold trap, cooled to −60°C) and the dichloromethane phase was separated from the NaOH phase. The organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated. The product was purified by flash chromatography on silica gel which was deactivated with 5% of its weight of triethyl amine using 20% diethyl ether in *n*-hexane as eluent. Yield: 43.5 g (95%). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 7.36 (d, ^{3}J=8.8 Hz, 2H, H_{aromat}); 6.86 (d, ^{3}J=8.8 Hz, 2H, H_{aromat}); 1.25 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 63.3 MHz, ppm): 154.6 (s, C1′); 125.4 (d, C2′/C6′); 131.9 (d, C3′/C5′); 116.2 (s, C4′); 78.9 (s, *C*$(CH_3)_3$); 28.8 (q, CH_3). MS (EI, 70 eV): 230 (M^+(^{81}Br), 5%); 228 (M^+(^{79}Br), 5%); 174 (M(^{81}Br)−C_4H_8, 99%); 172 (M(^{79}Br)−C_4H_8, 88%); 57 ($C_4H_9^+$, 100%).

2.3. *(1*R,*4*S*)-8-(4′*-tert-*Butyloxy-phenyl)-menthone* ***4***

In a three necked round bottom flask with dropping funnel and reflux condenser, the Grignard reagent of **2** was prepared from 3.96 g of magnesium turnings (0.16 mol), 20 ml of diethyl ether and 36.60 g of compound **2** (0.16 mol) in 36 ml of diethyl ether. In a second flask, 1.58 g of CuBr was suspended in 25 ml of diethyl ether under nitrogen and the suspension was cooled to −20°C. The Grignard solution was transferred to the second flask via a double ended needle. To this suspension was added dropwise a solution of 14.40 g of (*R*)-(+)-pulegone (0.09 mol) in 20 ml of diethyl ether at −10°C during 2 h. The reaction mixture was stirred at −10°C for 24 h, at room temperature for another 24 h and at reflux temperature for 5 h. After removing the solvent, the crude product was purified by flash chromatography using 5% diethyl ether in *n*-hexane as eluent. The fractions were analyzed by TLC and GC and combined to give 9.70 g of pure **4** with d.e.=95.2%, 2.15 g of a mixture with d.e.=36.8% of **5** and 5.17 g of **5** with d.e.=79.2%. Total yield: 17.02 g (60.0%). MS (EI, 70 eV, m/z): 302 (M^+, 1%); 246 (M^+−C_4H_8, 5%); 135 (M^+−C_4H_8−$C_7H_{11}O$, 100%).

2.4. *(1*R,*4*S*)-8-(4′-Hydroxy-phenyl)-menthone* ***6***

5.20 g of **4** (17.2 mmol) was dissolved in 15 ml of diethyl ether. To this solution was added, at once, a mixture of 8.70 ml of 47% aqueous HBr and 17.30 ml of acetic acid with vigorous stirring. After 5 min, the reaction mixture was poured onto ice and the phases were separated. The aqueous layer was extracted twice with 50 ml diethyl ether and the combined organic layers were washed with satd $NaHCO_3$ solution until all acid was removed from the ethereal layer (CAUTION! strong CO_2 evolution), with brine, and dried with $MgSO_4$. Flash chromatography with 30% diethyl ether in hexanes yielded 2.3 g of **6** with d.e.=95% ($[\alpha]_D^{25}$ −40.9 (c=11, $CHCl_3$)) and 1.2 g of **6** with d.e.=84%. Total yield: 82.6%. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 7.05 (d, ^{3}J=8.3 Hz, 2H, H_{aromat}); 6.63 (d, ^{3}J=8.3 Hz, 2H, H_{aromat}); 6.81 (br s, 1H, OH); 2.53 (dd, $^3J_{axax}$=13 Hz, $^3J_{axeq}$=4.4 Hz, 1H, H4); 2.01 (m, 1H, $H2_{eq}$); 1.90 (t, ^{3}J=12 Hz, 1H, $H2_{ax}$); 1.71 (m, 3H, $H5_{eq}$, $H6_{eq}$, $H1_{eq}$); 1.44 (s, 3H, CH_3 9, together with $H5_{ax}$); 1.36 (s, 3H, CH_3 10, together with $H6_{ax}$); 0.82 (d, ^{3}J=6.3 Hz, 3H, CH_3 7). ^{13}C NMR ($CDCl_3$, 63.3 MHz, ppm): 212.8 (s, C3); 153.5 (s, C4′); 141.6 (s, C1′); 126.7 (d, C2′, C6′); 114.8 (d, C3′, C5′); 59.9 (d, C4); 52.3 (t, C2); 38.4 (s,

C8); 36.5 (d, C1); 34.7 (t, C6); 29.2 (t, C5); 26.4 (q, C10/C9); 24.7 (q, C9/C10); 22.2 (q, C7). MS (EI, 70 eV): 246 (M^+, 4%); 135 ($M^+-C_7H_{11}O$, 100%).

2.5. *(1*R,*4*RS*)-Menthonyl-calix[*n*]arenes

2.30 g of **6** (9.3 mmol), 488 mg of paraformaldehyde (16.3 mmol), 28 μl of 10 N NaOH (1.1 mmol) and 16 ml of xylene were refluxed using a Dean–Stark trap filled with activated molecular sieves, 4 Å, or a small dropping funnel filled with molecular sieves to remove the reaction water. After 9.5 h, 26.5 h and 33.5 h, 25 μl of 10 N NaOH (1.0 mmol) and 400 mg of paraformaldehyde (13.3 mmol) were added, and after 51.5 h the reaction mixture was cooled to room temperature and 1.3 ml of 1 N HCl and 100 ml of diethyl ether were added. This mixture was washed with 50 ml of 1 N HCl and three times with 50 ml water and dried with $MgSO_4$. After removing the solvent, the crude mixture was separated by flash chromatography using 30% acetone in *n*-hexane into the following calix[*n*]arenes:

2.5.1. *(1*R,*4*RS*)-Menthonyl-calix[5]arene **7***

200 mg (8.3%); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 8.76 (br s, 1H, OH); 7.19 (br s, 2H, H_{aromat}); 4.14 and 3.50 (two br s, 2H, AB system from Ar–CH_2–Ar); 2.5 (br m, 1H, H4); 2.1–2.3 (br m, 1H, H2); 1.9–2.0 (br m, 1H, H2); 1.6–1.8 (br m, 3H, H1, H5, H6); 1.41 (br s, 3H, CH_3 9); 1.36 (br s, 3H, CH_3 10); 0.89 (br s, 3H, CH_3 7). ^{13}C NMR ($CDCl_3$, 63 MHz, ppm): 211.3 (s, C3); 147.7 (s, C4′); 142.5 (s, C1′); 126.4 (d, C2′, C6′, C3′, C5′); 59.9 (d, C4); 52.5, 50.4 (t, C2); 38.4, 38.5, 38.9 (s, C8); 36.3, 32.3 (d, C1); 34.8, 25.0 (t, C6); 31.6 (t, Ar–CH_2–Ar); 29.1, 31.2 (t, C5); 27.9, 27.6 (q, C10 or C9); 23.6, 23.1 (q, C9 or C10); 22.3, 19.4 (q, C7). FAB-MS: 1313 ($[M+Na]^+$); 1290 ($[M-H]^+$); 1201 ($[M+Na-C_7H_{12}O]^+$); 731 ($[M-5(C_7H_{12}O)]^+$). HRMS (electrospray ion-source, neg. charged ions): calculated for $C_{85}H_{110}O_{10}$: 1290.8099; found: 1290.8121.

2.5.2. *(1*R,*4*RS*)-Menthonyl-calix[6]arene **8***

200 mg (8.3%); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 10.4 (br s, 1H, OH); 7.09 (br s, 2H, H_{aromat}); 4.2 and 3.5 (two vbr s, 2H, AB system from Ar–CH_2–Ar); 2.56–0.83 (signals from menthyl substructure). ^{13}C NMR ($CDCl_3$, 63 MHz, ppm): 211.2 (s, C3); 147.7 (s, C4′); 142.6 (s, C1′); 128.4 (d, C2′, C6′); 127.0 (s, C3′, C5′); 59.9 (d, C4); 52.5, 50.3 (t, C2); 38.6, 39.1 (s, C8); 36.3, 32.3 (d, C1); 34.9, 24.9 (t, C6); 33.1 (t, Ar–CH_2–Ar); 29.1, 31.2 (t, C5); 27.7, 27.2 (q, C9 or C10); 23.3, 23.8 (q, C10 or C9); 22.2, 19.5 (q, C7). ESI-MS: 1683.1 ($[M+Cs]^+$); 907.5 ($[M+2Cs]^+$). FAB-MS: 1571.4 ($M+Na^+$); 876.8 ($[M-6(C_7H_{12}O)]^+$). HRMS (electrospray ion-source, neg. charged ions): calculated for $C_{102}H_{132}O_{12}$: 1548.9663; found: 1548.9718.

2.5.3. *(1*R,*4*RS*)-Menthonyl-calix[8]arene **9***

300 mg (12.4%); ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 6.94 (s, 2H, H_{aromat}); 3.2–4.3 (very broad signal, 2H, AB system from Ar–CH_2–Ar); 2.5–0.8 (signals from the menthyl substructure). ^{13}C NMR ($CDCl_3$, 63 MHz, ppm); 211.4 (s, C3); 147.1 (s, C4′); 142.7 (s, C1′); 127.4 (d, C2′, C6′); 126.9 (s, C3′, C5′); 59.8 (d, C4); 52.5, 50.4 (t, C2); 38.6, 39.1 (s, C8); 36.3, 32.3 (d, C1); 34.9, 25.0 (t, C6); 33.0 (t, Ar–CH_2–Ar); 29.1, 31.3 (t, C5); 27.7 (q, C9 or C10); 23.4 (q, C10 or C9); 22.3, 19.5 (q, C7). FAB-MS: 2088.4 ($M+Na^+$); 1168.9 ($[M-8(C_7H_{12}O)]^+$). HRMS (electrospray ion-source, neg. charged ions): calculated for $C_{136}H_{176}O_{16}$: 2065.2958; found 2065.2777.

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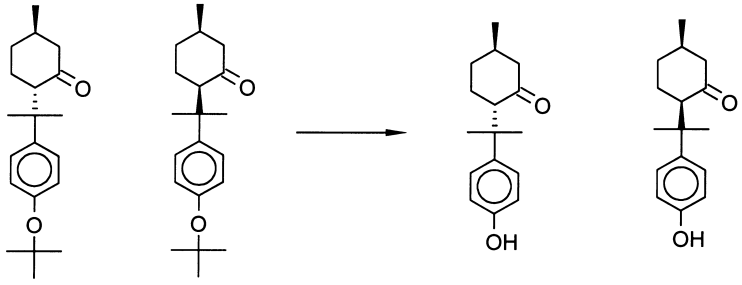
6. Kinetic studies starting from a mixture of **4** and **5** (20:80) showed that after 1 h, the epimeric ratio of the products **6** and epi-**6** has equilibrated to 78:22. **6** and epi-**6** were separated by flash chromatography with 30% diethyl ether in *n*-hexane.



4		**5**		**6**		epi-**6**
20	:	80		78	:	22

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8. If a solid precipitate forms, the mixture has to be warmed until the precipitate dissolves again. Otherwise neutralization is incomplete which results in decreased yields since the *tert*-butyl group is partially removed under these acidic conditions.