Determination of the Absolute Configuration of Inherently Chiral Resorc[4]arenes

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The absolute configuration of twelve inherently chiral resorcarenes was determined using a combination of the X-ray structure of (–)-**3a** and optical rotation as well as NMR techniques. Starting from a racemic mixture of **1** both diastereomers (–)-**3a** and (+)-**3b** can be obtained in high yields in two steps and the absolute configuration of these diastereomers could be determined by X-ray analysis. Using enantiomerically pure (–)-**1** for the same reactions, however, (+)-**3b** is formed. The alkylation of (–)-**1** with (*S*)-2-methylbutyl tosylate and the methylation of (–)-**5a** lead to the same resorcarene (–)-**4a**, while the alkylation of (+)-**1** and the methylation of (+)-**5b** yield in resorcarene (+)-**4b**.

Introduction

Synthesis of inherently chiral calix[4]resorcarenes[1] includes the reaction of achiral resorcarenes with camphorsulphonic chloride,[2] hydrophosphorylderivatives,[3] trimethylsilyl isocyanates,[4] 1,3-oxazine formation[5,6] or introduction of the chiral axis during cyclization process.[7–9] However, not in all cases the enantiomers were separated and the absolute configuration of the pure enantiomers is often unknown. To understand complexation processes and to verify observed data from optical rotation or CD spectra, it is necessary to know the absolute configuration of these molecules.

The formation of crystals suitable for X-ray analysis is a goal which cannot always be achieved due to ring opening and oxidation reactions of the resorcarenes upon standing in solution.[10] For this reason a combination of different analytical techniques is often necessary to deduce the stereochemistry of various compounds on the basis of the crystals obtained.

The reaction of 2-bromomethyl acetate with deprotonated resorc[4]arenes was often performed to extend the cavity size or to provide a carboxy group at the upper rim of the macrocycle.[11] At that point the methyl ester can e.g. be saponificated, reduced or transformed to an amide via aminolysis.[12] We chose this preparation route to introduce a chiral moiety using (–)-1-phenylethylamine for the aminolysis reaction yielding the diastereomers (–)-**3a** and (+)-**3b** which could be separated by column chromatography (Figure 1). Since (–)-**3a** could be crystallized from ethyl acetate while crystallization of other inherently chiral resorcarenes failed we decided to deduce the absolute configuration of these macrocycles by NMR on the basis of the known configuration of the amides (–)-**3a** and (+)-**3b**.

Results and Discussion

Deprotonation of racemic **1** with K_2CO_3 in acetonitrile and reaction with 2-bromomethyl acetate leads to the corresponding methyl ester **2** in high yields. This racemate was purified by recrystallization from ethanol. The ^{1}H NMR shows a single set of bridging methin protons indicating a C_4 symmetry, while the crystal structure shows that this compound forms an extreme boat conformation in the solid state. Aminolysis of methyl esters is often performed in solution using an equimolar mixture of ester and amine. We have chosen more drastic reaction conditions to prevent only partially converted resorcarenes.

The aminolysis of this resorc[4]arene using (–)-1-phenylethylamine as solvent at 160 °C leads to the tetraamides (–)-**3a** and (+)-**3b** (Figure 1). In fact, by heating just to 100 °C only up to three methyl ester moieties were transformed. The diastereomers were separated by silica gel column chromatography with ethyl acetate/cyclohexane (3:1) as eluent and obtained with an overall yield of 83 %. As expected both diastereomers were formed in equal amounts, which was derived from the ^{1}H NMR of the diastereomeric mixture. The R_f values are 0.50 for (–)-**3a** and 0.28 for (+)-**3b**, respectively. Due to the huge difference in R_f values the separation is almost quantitative.

Since the diastereomers can be separated without HPLC these enantiomerically pure resorc[4]arenes are interesting

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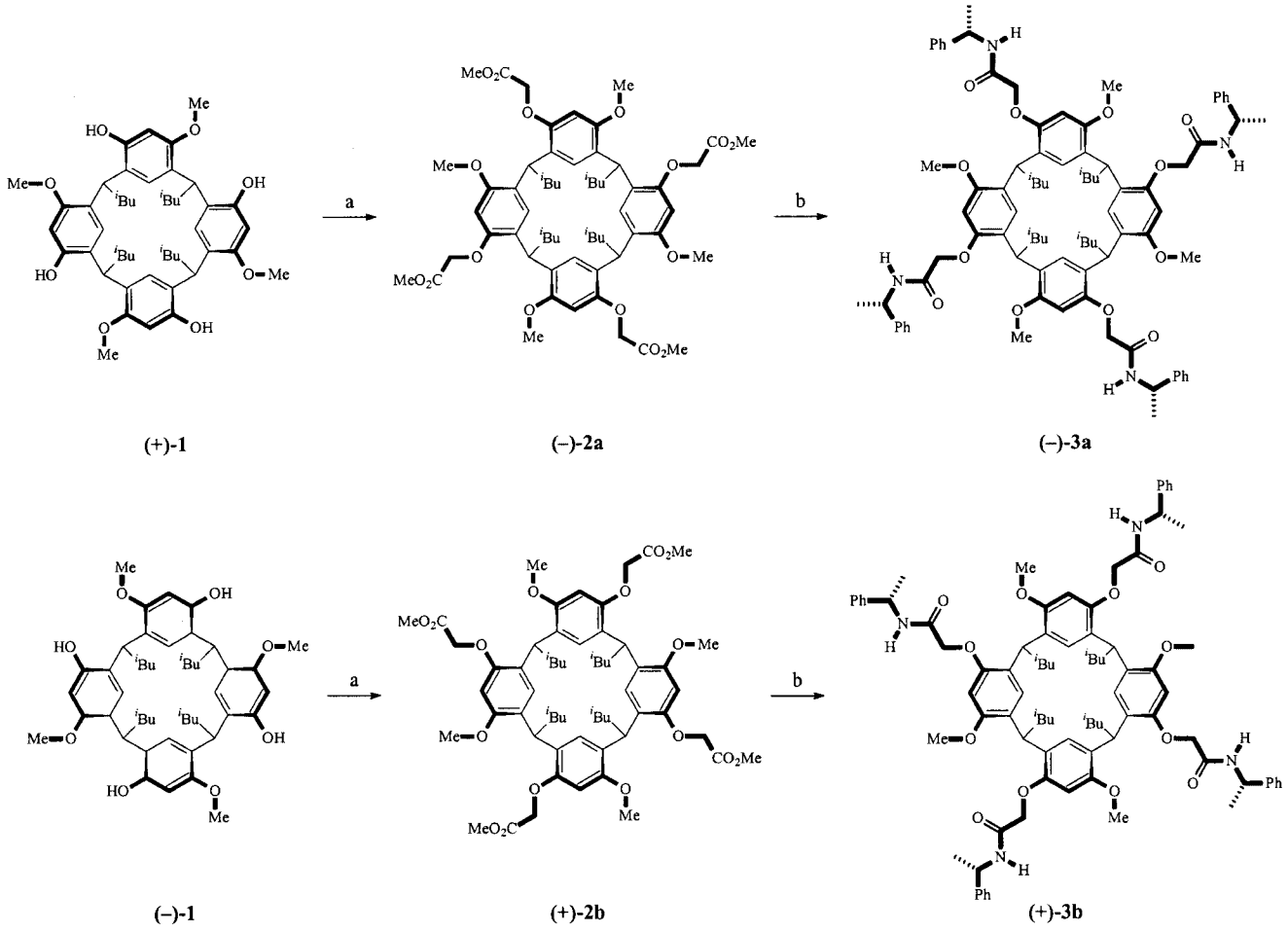

Figure 1. Alkylation of tetramethylresorc[4]arenenes **1** and aminolysis of the resulting methyl esters yield the diastereomeric amides **3a/b**.

synthons for further syntheses. In addition, this synthetic route is the best way to obtain enantiomerically pure inherently chiral resorc[4]arens in high yields and in a half gram scale, so far.

By the introduction of a chiral center during the aminolysis reaction with (*S*)-1-phenylethylamine we were able to determine the absolute configuration of the amide (–)-**3a** (Figure 2). This molecule exhibits eight stereo centers, four at the introduced chiral moiety, which possesses *S* configuration, and four due to the inherent chirality. In this case all stereo centers of the methine bridges are *S*-configured.[13]

Since we are interested in the absolute configuration of the tetra methylated resorcarenes **1** we followed the same reaction pathway with pure (–)-**1** as starting material instead of racemic **1** and compared the ^{1}H NMR spectra with the spectra of the diastereomeric amides obtained before. Especially the chemical shifts at δ = 3.416 ppm for the methoxy group and δ = 6.200 ppm assigned to the aromatic proton at C-2 show that (+)-**3b** was formed in this reaction. This means that (–)-**1** is the *all-S* enantiomer and (+)-**1** can be assigned to the *all-R* enantiomer.[7,14]

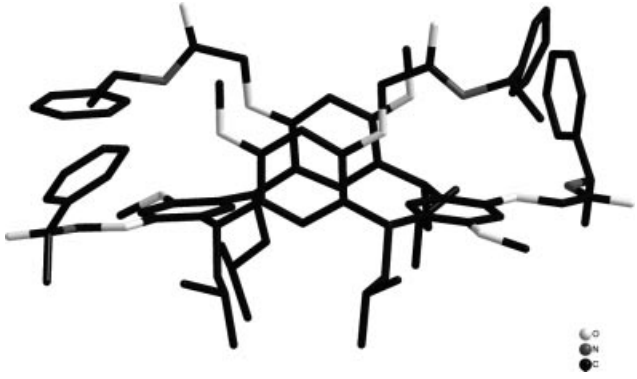

Figure 2. X-ray structure of the amide (–)-**3a**, protons are omitted for clarity.

Knowing the absolute configuration of the tetra-*O*-methylresorc[4]arenes **1** we decided to alkylate a racemic mixture of **1** with (*S*)-(–)-2-methylbutyl tosylate. The reaction affords two diastereomers in an overall yield of 61 %, which can be separated by HPLC using silica gel with chlo-

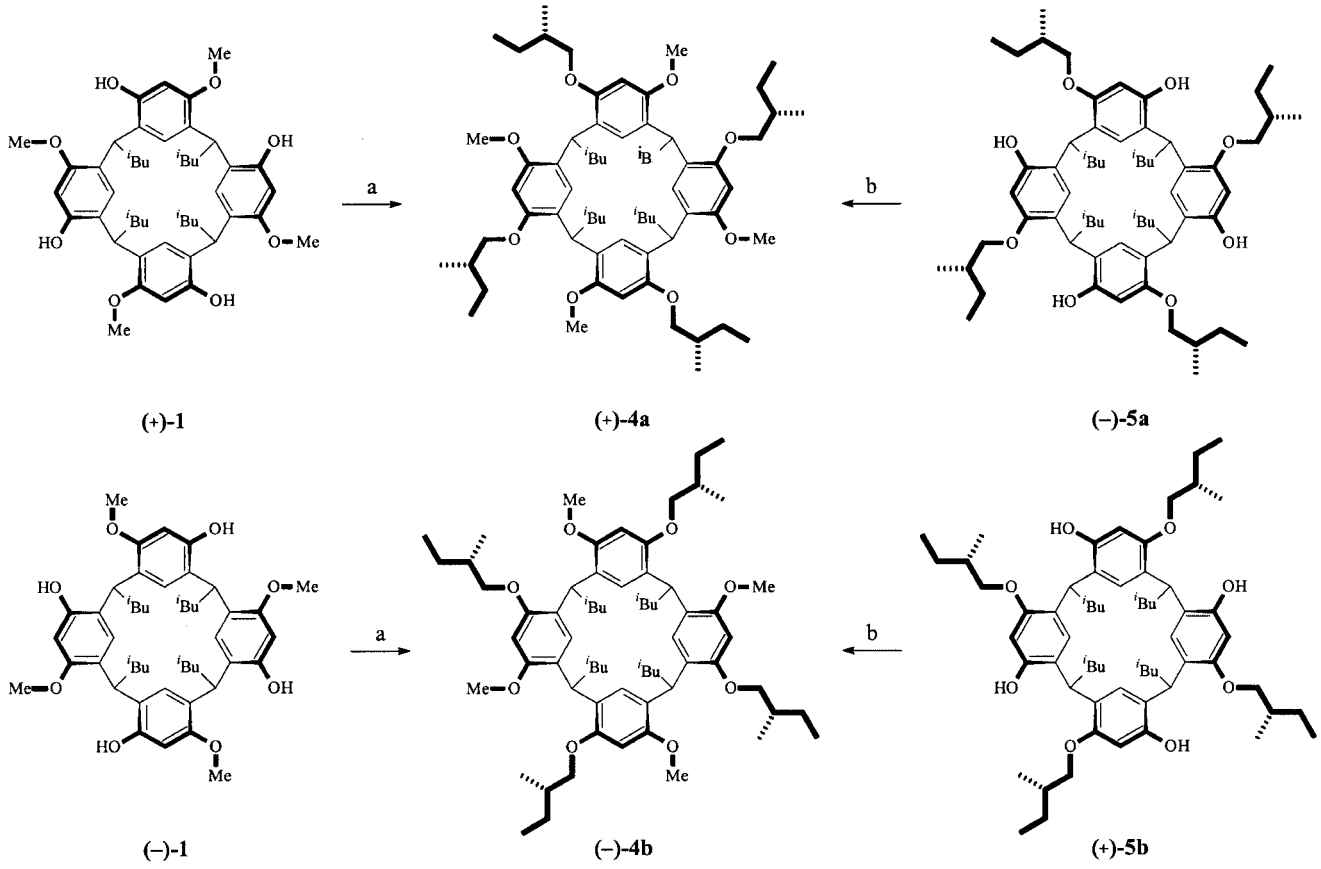

Figure 3. Synthesis of octaalkylated resorc[4]arenes **4a/b** to determine the configuration of **5a/b**.

roform/cyclohexane (6:4) as eluent. This diastereomeric mixture **4a/b** shows two sets of chemical shifts for the bridging methin protons and the methoxy groups in CD_2Cl_2, respectively.[15] These chemical shifts can be used to determine the absolute configuration of **5a/b** according to Figure 3. In addition, enantiomerically pure (–)-**1** was alkylated in the same way, while (–)-**5a** was methylated with K_2CO_3 and MeI in acetonitrile.[16] For these reactions only small amounts were used due to the extensive synthesis of the starting materials. In general it is difficult to permethylate **5a/b** due to steric hindrance, causing longer reaction times and sometimes only semi-methylated products.

Figure 4 shows a part of the ^{1}H NMR of (–)-**4a** and (+)-**4b**. The octaalkylated resorcarene (–)-**4b** was obtained by methylation of (–)-**1** and is therefore the *all-R* enantiomer, while (+)-**4a** is the *all-S* enantiomer (the stereochemistry of the side chain is ignored).

Finally, the stereochemistry of the tetra-*O*-alkyl-resorcarenes **5a/b** can be deduced from the ^{1}H NMR shown in Figure 4. The alkylation of (–)-**5a** leads to (+)-**4a**, so that (–)-**5a** is the *all-S* enantiomer and (+)-**5b** is the *all-R* enantiomer.[17]

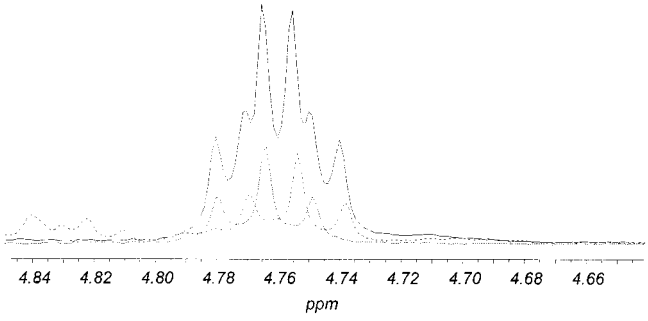

Figure 4. ^{1}H NMR of (–)-**4a** and (+)-**4b** solid line: diastereomeric mixture, dotted line: (+)-**4a** synthesized by methylation of (–)-**5a**, dashed line: (–)-**4b** obtained by alkylation of (–)-**1**.

Conclusions

In this work we have presented the crystal structure of an enantiomerically pure inherently chiral resorc[4]arene. Knowing the absolute configuration of the two amides **3a/b** we were able to deduce the absolute configuration of ten inherently chiral resorc[4]arenes by comparison of NMR spectra, which were recently synthesized by us.

Further investigations concerning complexation of chiral ammonium ions and CD spectroscopy of these macrocycles are currently in progress. Knowing the stereochemistry of the host molecule may help to explain observed phenomena.

Experimental Section

General Remarks: All solvents were used in p.A. grade or were distilled prior to use. Melting points were recorded on a Büchi B-540 and are uncorrected, specific rotations were measured on a Perkin–Elmer 341 polarimeter. HRMS were performed using a Fourier Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer APEX III with a 7.0 T, 160 mm bore superconducting magnet (Bruker Analytik GmbH – Magnetics, Karlsruhe, Germany), infinity cell, and interfaced to an external (nano)ESI or MALDI ion source. NMR spectra were recorded on a Bruker DRX 500 (^{1}H NMR: δ = 500.13 MHz. ^{13}C NMR: δ = 125.77 MHz).

Compound 2: A mixture of racemic **1** (2.92 g, 3.78 mmol) and K_2CO_3 (10.46 g, 75.7 mmol) in acetonitrile (190 mL) was heated for 20 min at 80 °C. Bromomethyl acetate (9 mL, 94.7 mmol) was added to the solution via a syringe and the reaction mixture was stirred for 18 hours. The solvent was evaporated and the residue was treated with ether and dist. water. The water phase was extracted with diethyl ether (4×50 mL) and the combined organic layers were washed with dist. water and brine and dried over $MgSO_4$. After evaporation of the solvent the product was recrystallized from ethanol to yield **2** (3.76 g, 3.56 mmol, 94 %) as colorless crystals. M.p. 172.1 °C. HRMS ESI [M + Na^+: $C_{60}H_{80}O_{16}Na^+$]: calcd. 1079.5339; found 1079.5346; declination 0.7 mmu/0.6 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.918 [d, ^3J = 6.7 Hz, 12 H, CHCH_3], 0.925 [d, ^3J = 6.4 Hz, 12 H, CHCH_3], 1.522–1.575 [m, 8 H, Me_2CH), 1.663–1.737 [m, 8 H, CHCH_2CH], 3.625 [s, 12 H, ArOCH_3], 3.769 [s, 12 H, CO_2CH_3], 4.063 [d, ^2J = 16.2 Hz, 4 H, OCH_2), 4.226 [d, ^2J = 16.2 Hz, 4 H, OCH_2], 4.674 [dd, ^3J = 7.5, ^3J = 7.5 Hz, 4 H, ArCHAr), 6.308 [s, 4 H, CH *ortho* to OMe], 6.605 [s, 4 H, CH *meta* to OMe). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 22.85 [(CH$_3$)$_2$CH], 22.87 [(CH$_3$)$_2$CH], 25.81 [Me_2CH], 33.25 [ArCHAr], 43.96 [CHCH$_2$CH], 51.89 [CO_2CH$_3$], 55.56 [ArOCH_3], 68.21 [OCH_2], 99.54 [CH *ortho* to C-O], 126.40 [CH *ortho* to C-O], 127.33 and 128.11 [2 × C_q*ortho* to C-O], 154.84 [C-OCH_2], 155.57 [C-OMe], 170.04 [CO_2Me].

Compounds (–)-3a and (+)-3b: 2 (0.50 g, 0.47 mmol) was heated with (–)-1-phenylethylamine (2.5 mL, 19.4 mmol) at 160 °C for 5 h. The reaction mixture was allowed to cool to room temp. and Et_2O was added. This solution was acidified with 5 % HCl. After separation of the organic phase the water phase was extracted with Et_2O (3×50 mL). The organic layers were combined, washed with dist. water and brine and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by column chromatography (silica gel, ethyl acetate/cyclohexane, 3:1) to afford (–)-**3a** (0.28 g, 0.20 mmol, 42 %) and (+)-**3b** (0.27 g, 0.19 mmol, 41 %). Suitable crystals of (–)-**3a** were obtained from ethyl acetate.

Compound (–)-3a: M.p. 194.6 °C, $[\alpha]_D^{25}$ = –6.9 (c = 1.00 in $CHCl_3$). HRMS ESI [M + Na^+: $C_{88}H_{108}O_{12}Na^+$]: calcd. 1435.7856; found 1435.7870; declination 1.4 mmu/1.0 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.929 [d, ^3J = 6.3 Hz, 24 H, (CH$_3$)$_2$CH], 1.406 [d, ^3J = 6.9 Hz, 12 H, CH_3CH], 1.451 [m, 4 H, Me_2CH], 1.770 [t, ^3J = 7.4 Hz, 8 H, CHCH_2CH], 3.248 [s, 12 H, OCH_3], 4.111 [d, ^2J = 14.4 Hz, 4 H, OCH_2], 4.333 [d, ^2J = 14.4 Hz, 4 H, OCH_2], 4.754 [t, ^3J = 7.8 Hz, 4 H, ArCHAr], 5.195 [dq, ^3J = 8.7, ^3J = 6.9 Hz, 4 H, ArCH(CH_3)NH], 5.957 [s, 4 H, CH *ortho* to C-OMe], 6.897 [d, ^3J = 8.8 Hz, 4 H, NH], 6.956 [s, 4 H, CH *meta* to C-OMe], 7.005–7.120 [m, 5 H, $H_{arom.}$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.58 [CH_3CH], 22.94 [(CH_3)$_2$CH], 23.04 [(CH_3)$_2$CH], 25.81 [Me_2CH], 31.98 [ArCHAr], 45.10 [CHCH$_2$CH], 47.91 [CHNH], 56.16 [OCH_3], 67.68 [OCH_2], 97.32 [CH *ortho* to C-O], 125.71 [$C_{q,arom.}$*ortho* to C-O], 125.96 [CH_{ortho}], 126.30 [CH *meta* to C-O], 126.52 [$C_{q,arom.}$*ortho* to C-O], 127.22 [CH_{para}], 128.49 [CH_{meta}], 142.67 [NHCH(CH_3)C], 153.21 [C-OCH_2] 155.52 [C-OMe], 167.51 [C=O].

Crystal Data: $C_{88}H_{108}N_4O_{12}$ + 2.5 $C_4H_8O_2$, M = 1634.04, colorless needles, crystal size: 0.26 × 0.16 × 0.08 mm^3, crystal system, space group: monoclinic, P21, unit cell dimensions; a = 15.9370(2), b = 38.6180(5), c = 16.0870(2) Å, β = 111.8650(5)°, volume: 9188.6(2) Å^3, Z = 4, T = 100 K, μ(Mo-$K\alpha$) = 0.080 mm^{-1}, λ = 0.71073 Å, 82628 reflections measured, 31053 unique (R_{int} = 0.069). The data were collected on a Bruker Nonius–KappaCCD (θ range = 3–25°). The structure was solved by direct methods and refined with full-matrix-block least-squares on F^2 (SHELXS/SHELXL-97). Final R_F, wR_{F2} values on all data: 0.1056, 0.1600, R_F, wR_{F2} for 21577 reflections with $I > 2\sigma(I)$: 0.0643, 0.1398; largest diff. peak and hole 0.600 and –0.437 e·Å^{-3}. The absolute structure configuration could not determined reliably by Flack parameter of –0.1(7) but follows the known one of the starting material. CCDC-245101 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound (+)-3b: M.p. 182.5 °C, $[\alpha]_D^{25}$ = +4.3 (c = 1.00 in $CHCl_3$). HRMS ESI [M + Na^+: $C_{88}H_{108}O_{12}Na^+$]: calcd. 1435.7856; found 1435.7859; declination 0.3 mmu/0.2 ppm. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.863 [d, ^3J = 6.3 Hz, 12 H, (CH$_3$)$_2$CH], 0.898 [d, ^3J = 6.9 Hz, 12 H, (CH$_3$)$_2$CH], 1.450 [m, 4 H, Me_2CH], 1.478 [d, ^3J = 6.9 Hz, 12 H, CH_3CH], 1.707 [t, ^3J = 6.9, ^3J = 7.5 Hz, 8 H, CHCH_2CH], 3.416 [s, 12 H, OCH_3], 4.232 [d, ^2J = 15.1 Hz, 4 H, OCH_2], 4.321 [d, ^2J = 15.1 Hz, 4 H, OCH_2], 4.698 [t, ^3J = 7.8 Hz, 4 H, ArCHAr], 5.213 [dq, ^3J = 8.2, ^3J = 7.1 Hz, 4 H, ArCH(CH_3) NH], 6.200 [s, 4 H, CH *ortho* to C-OMe], 6.822 [s, 4 H, CH *meta* to C-OMe], 7.021 [d, ^3J = 8.2 Hz, 4 H, NH], 7.190–7.330 [m, 5 H, $H_{arom.}$]. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.61 [CH_3CH], 22.86 [(CH_3)$_2$CH], 22.96 [(CH$_3$)$_2$CH], 25.78 [Me_2CH], 32.36 [ArCHAr], 44.93 [CHCH$_2$CH], 48.01 [CHNH], 56.50 [OCH_3], 68.32 [OCH_2], 98.25 [CH *ortho* to C-O], 126.02 [CH_{ortho}], 126.14 [$C_{q,arom.}$*ortho* to C-O], 126.41 [CH *meta* to C-O], 127.11 [$C_{q,arom.}$*ortho* to C-O], 127.31 [CH_{para}], 128.61 [CH_{meta}], 142.67 [NHCH(CH_3)C], 153.43 [C-OCH_2] 155.60 [C-OMe], 167.67 [C=O].

Compounds (–)-4a and (+)-4b. General Procedure: The resorcarene was dissolved in dry acetonitrile and treated with K_2CO_3 at reflux for 30 min. Subsequently excess of alkylation reagent (either methyl iodide or 2-methylbutyl tosylate) was added via syringe. The reaction mixture was heated for 96 h to ensure complete conversion, acidified and extracted with diethyl ether. The combined organic layers were washed with dist. water and brine and dried over $MgSO_4$. After evaporation of the solvent the colorless solid was either recrystallized from EtOH or analyzed without further purification.

Compound (–)-4a: $[\alpha]_D^{25}$ = –11.3 (c = 0.33 in $CHCl_3$). ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 0.863 [d, ^3J = 6.5 Hz, 24 H, (CH$_3$)$_2$CH], 0.903 [t, ^3J = 7.2 Hz, 12 H, CH_3CH$_2$], 0.988 [d, ^3J = 6.8 Hz, 12 H, CH_3CH(CH_2)$_2$], 1.213 [ddq, ^2J = 13.5, ^3J = 7.7, ^3J = 7.6 Hz, 4 H, CH_3CH$_2$], 1.446 [m, 4 H, Me_2CH], 1.533 [m, 4

H, CH_3CH_2], 1.644 [m, 8 H, $CHCH_2CH$], 1.744 [m, 4 H, CH_3CH_2CH], 3.602–3.688 [m, 8 H, OCH_2], 3.643 [s, 12 H, OCH_3], 4.765 [t, ^3J = 7.5 Hz, 4 H, ArCHAr], 6.277 [s, 4 H, CH *ortho* to OMe], 6.755 [s, 4 H, CH *meta* to OMe]. ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 11.63 [CH_3CH_2], 16.73 [$CH_3CH(CH_2)_2$], 22.79 and 23.01 [2 × $(CH_3)_2CH$], 26.24 and 26.41 [Me_2CH and CH_3CH_2], 32.40 [Ar*C*HAr], 35.54 [CH_2CHCH_2], 45.22 [$CHCH_2CH$], 55.84 [OCH_3], 73.56 [OCH_2], 96.72 [CH *ortho* to OMe], 125.17 and 125.64 [C_q*ortho* to C-O], 126.68 [CH *meta* to C-O], 155.50 and 155.89 [2 × C-O].

Compound (+)-4b: $[\alpha]_D^{25}$ = +16.0 (*c* = 0.36 in $CHCl_3$). ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 0.861 [d, ^3J = 6.5 Hz, 24 H, $(CH_3)_2CH$], 0.907 [t, ^3J = 7.5 Hz, 12 H, CH_3CH_2], 0.961 [d, ^3J = 6.8 Hz, 12 H, $CH_3CH(CH_2)_2$], 1.220 [ddq, ^2J = 13.4, ^3J = 7.6, ^3J = 7.6 Hz, 4 H, CH_3CH_2], 1.447 [m, 4 H, Me_2CH], 1.569 [ddq, ^2J = 13.1, ^3J = 7.6, ^3J = 5.5 Hz, 4 H, CH_3CH_2], 1.641 [m, 8 H, $CHCH_2CH$], 1.756 [m, 4 H, CH_3CH_2CH], 3.560 [dd, ^2J = 8.7, ^3J = 6.2 Hz, 4 H, OCH_2], 3.637 [s, 12 H, OCH_3], 3.726 [dd, ^2J = 8,6, ^3J = 6.2 Hz, 4 H, OCH_2], 4.755 [t, ^3J = 7.8 Hz, 4 H, ArCHAr], 6.279 [s, 4 H, CH *ortho* to OMe], 6.743 [s, 4 H, CH *meta* to OMe]. ^{13}C NMR (125 MHz, CD_2Cl_2, 25 °C): δ = 11.56 [CH_3CH_2], 16.58 [$CH_3CH(CH_2)_2$], 22.81 and 23.00 [2 × $(CH_3)_2CH$], 26.24 and 26.40 [Me_2CH and CH_3CH_2], 32.47 [Ar*C*HAr], 35.49 [CH_2CHCH_2], 45.19 [$CHCH_2CH$], 55.90 [OCH_3], 73.55 [OCH_2] 96.77 [CH *ortho* to OMe], 125.29 and 125.58 [C_q*ortho* to C-O], 126.68 [CH *meta* to C-O], 155.53 and 155.90 [2 × C-O].

Acknowledgments

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[13] The complete name of (–)-**3a** is (–)-*rccc*-(2*S*,8*S*,14*S*,20*S*)-tetraisobutyl-6,12,18,24-tetra-*O*-methyl-4,10,16,22-tetra-*O*-[*N*-((*S*)-1-phenylethyl)carbamoyl]methyl)resorc[4]arene.
[14] The tetramethylresorcarenes **1** were synthesized via cleavage of the mono-functionalized camphor-10-sulfonic acid esters. Therefore the absolute configuration of the esters can be deduced as well.
[15] The ^{1}H NMR spectra of the diastereomeric mixture in $CDCl_3$ looked like the one of a single compound due to only marginal differences in the chemical shifts.
[16] It is very important to use dry base and solvent for this reaction, otherwise only partly methylated products are formed.
[17] The complete name of (–)-**4a** is (–)-*rccc*-(2*S*,8*S*,14*S*,20*S*)-tetraisobutyl-4,10,16,22-tetra-*O*-[(*S*)-2-methylbutyl]resorc[4]arene.

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