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Synthesis of an enantiomerically pure resorcinarene with pendant L-valine residues and its attachment to a polysiloxane (Chirasil-Calix)

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Abstract—The synthesis of a new enantiomerically pure resorcinarene by reaction of all resorcinic groups with *N*-bromoacetyl-L-valine-*tert*-butyl-amide is described. The chiral macrocyclic product was chemically bonded to a poly(hydro)dimethylsiloxane by hydrosilylation using a platinum catalyst. The resulting chiral polysiloxane Chirasil-Calix can be used as chiral stationary phase (CSP) in capillary gas chromatography.[1] © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Resorcinarenes are cyclic oligomers in which four resorcinic units are linked via alkylmethylene bridges in the *ortho*-position to each resorcinic hydroxyl group. Their structure resembles that of calixarenes and renders them of interest as host compounds in many contemporary fields of supramolecular chemistry.[2] Self-assembled monolayers (SAMs) of resorcinarene derivatives on gold surfaces provide an important starting point for fabricating and operating nanoscale devices for advanced information technologies.[3–5]

Resorcinarene derivatives have been used as stationary phase in achiral capillary gas chromatography for the separation of positional isomers of substituted benzenes.[6,7] Also mixed stationary phases with cyclodextrins are described.[8]

Recently, we have reported the first use of an enantiomerically pure resorcinarene as a chiral stationary phase (CSP) in enantioselective capillary gas chromatography.[1] Herein we wish to report a synthetic pathway toward the chiral polysiloxane Chirasil-Calix containing an enantiomerically pure resorcinarene with pendant L-valine residues chemically attached to a dimethylpolysiloxane matrix.

In resorcinarenes, chirality can be introduced either indirectly by cyclisation of monomers containing chiral moieties[9,10] or directly by synthesis of macrocycles possessing a C_n-type symmetry defined as inherent chirality.[11,12] A third option is the modification of preformed resorcinarenes by the introduction of chiral headgroups, e.g. by Mannich reaction[13] or alternatively by derivatization of the hydroxyl groups.

2. Results and discussion

Adopting a recent approach by Reinhoudt et al.,[14] we developed a convergent synthetic pathway toward a novel chiral macrocycle (Scheme 1). The hydroxyl groups of resorcinarene **1** derived from the ω-unsaturated aldehyde undec-10-enal and resorcinol[14] were quantitatively reacted with *N*-bromoacetyl-L-valine-*tert*-butylamide **4** via alkylation under basic conditions. This amino acid derivative was obtained in a three-step synthesis starting from enantiomerically pure (Boc)-L-valine, which was firstly converted into the corresponding *tert*-butyl amide **2** following a standard procedure. After cleavage of the protecting Boc group with trifluoroacetic acid (TFA), the free amino group of the amide **3** was functionalized with 2-bromoacetic acid. A 1.2 molar excess of the amino acid derivative **4** per equivalent of the resorcinic groups was sufficient for complete aryl–alkyl–ether formation. Quantitative conversion of the hydroxyl groups was established by ESI-MS and HRMS. It should be pointed out that racemisation of the L-valine selectors was absent within

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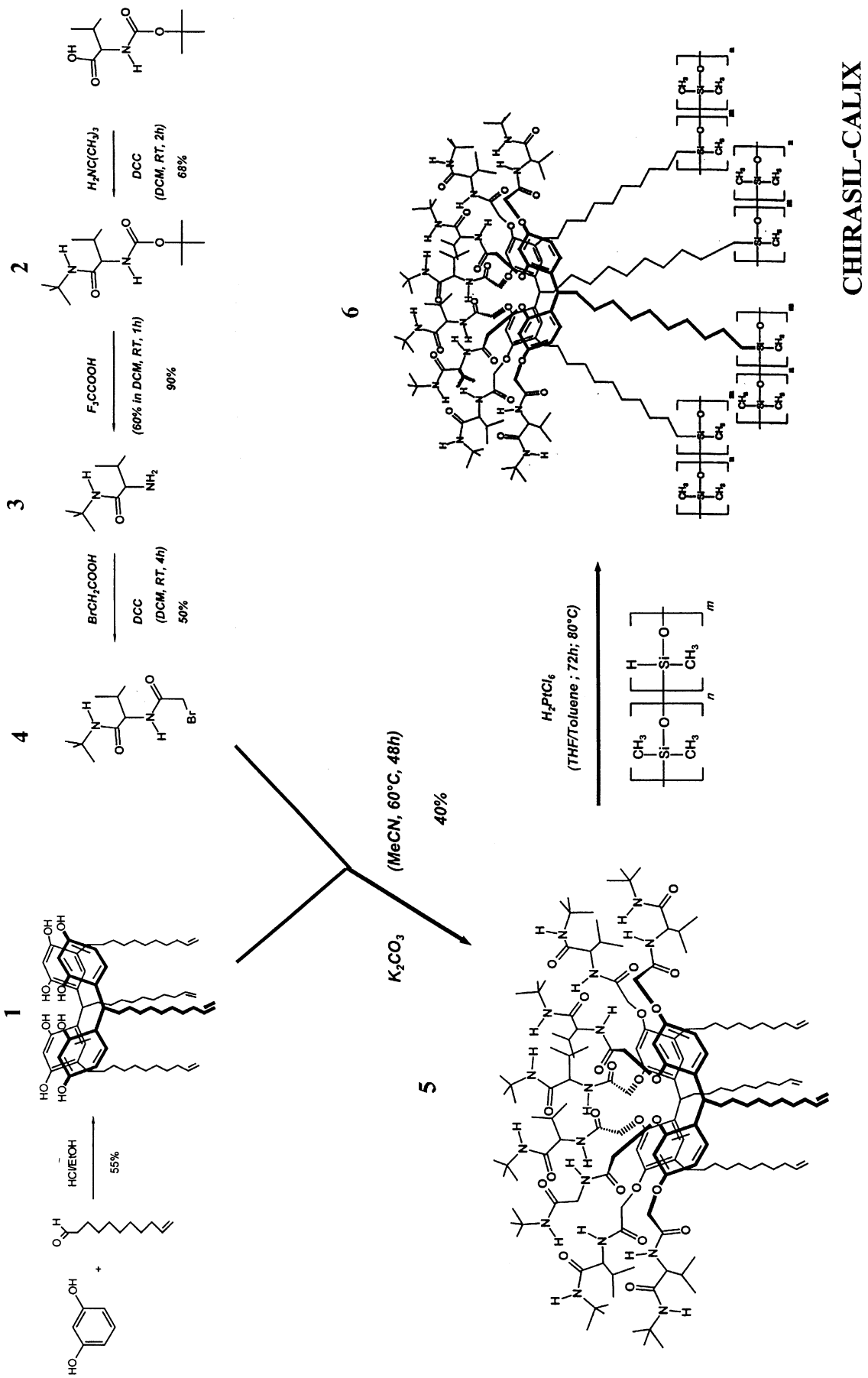

Scheme 1. Synthesis of Chirasil-Calix.

experimental error. Thus, cleavage of the derivatized resorcinarene and enantioselective analysis of the liberated L-valine as *N*-TFA *iso*-propyl esters by GC–MS on Chirasil-Val[15] proved that the amount of D-enantiomer was below 0.5%, thus virtually excluding racemisation during the synthesis.

The ω-unsaturated functions of the long alkyl chains allowed the attachment of the chiral resorcinarene **5** to a polysiloxane containing hydro(methyl)silyl groups via hydrosilylation using hexachloroplatinic acid as catalyst to give Chirasil-Calix **6**.[1] In contrast to a former report,[16] the amount of catalyst could be reduced to a molar ratio of 1:1000 (catalyst to chiral resorcinarene). However, due to the presence of the more polar headgroups of the resorcinarene, THF had to be added as co-solvent to increase the solubility of the resorcinarene in the reaction mixture. Furthermore, the reaction time had to be extended from 48 to 72 h. The quantitative hydrosilylation was established by ^{1}H NMR spectra which indicated the complete disappearance of the olefinic functions. The amount of resorcinarene attached to the polysiloxane was calculated by integration of the corresponding ^{1}H NMR signals of the various silyl units in the polymer. Absence of racemisation of the L-valine selector in this step was again proved, as described above by GC–MS on Chirasil-Val.[15] The amount of D-valine was determined as still less than 0.5%.

In Fig. 1 the CD spectra of the L-valine selector **4** and the chiral derivatized resorcinarene **5** are compared. The spectra were measured at a wavelength range from 450 to 180 nm. For the L-valine selector **4** a negative Cotton effect was observed at 235 nm, whereas the chiral derivatized resorcinarene exhibited a positive Cotton effect at the same wavelength and an additional positive Cotton effect at 280 nm.

The thermal stability of Chirasil-Calix was evaluated by thermogravimetric analysis (TGA).[17] According to Fig. 2, the polymer began to decompose slightly at 220°C and dramatically over 260°C. The onset point was determined at 300°C. These results corroborate the observed behaviour of Chirasil-Calix as a CSP in GC. Thus, the new chiral stationary phase is thermostable below 200°C and can even be used up to 240°C for short periods of time in enantioselective GC.[1]

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 NMR spectrometer at 250 and 62.9 MHz, respectively, or on a Bruker WM 400 at 400 and 100 MHz, respectively. IR spectra were obtained on a Bruker FT-IR IFS 48 IR spectrometer. FD and EI mass spectra were recorded on a Finnigan MAT TSQ 70 mass spectrometer. ESI mass spectra were measured on an API-III-TAGA 6000 E spectrometer with triple-quadrupole focusing. Samples were dissolved in methanol (conc. 1 mg/mL, additive: sodium, potassium or ammonium acetate). HRMS spectra were obtained using a Bruker APEX II FT-IRC mass spectrometer (sample dissolved in methanol/water, 95:5 additive 1% acetic acid). Melting points are uncorrected. Optical rotations were measured at the sodium D line on a Perkin–Elmer polarimeter 241. The CD spectra were obtained with an ASCO spectral polarimeter J 720. The elemental composition was determined with a Carlo Erba elemental analyser 1104. Boc-L-valine, *tert*-butylamine, trifluoroacetic acid and bromoacetic acid were

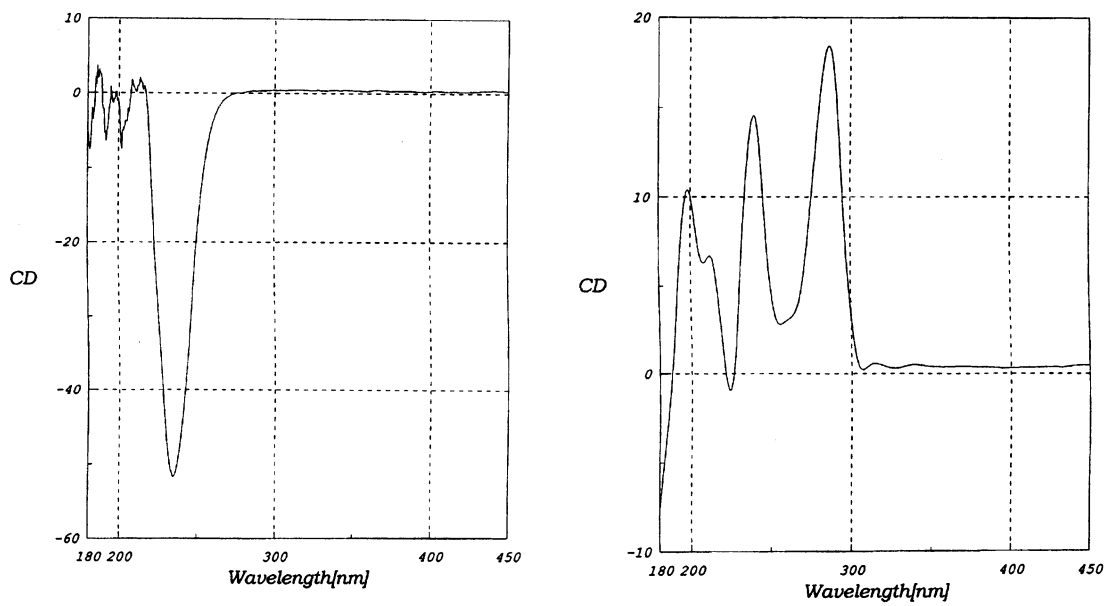

Figure 1. CD spectra of **4** (right side) and **5** (left side) (c = 1 mmol/mL, THF).

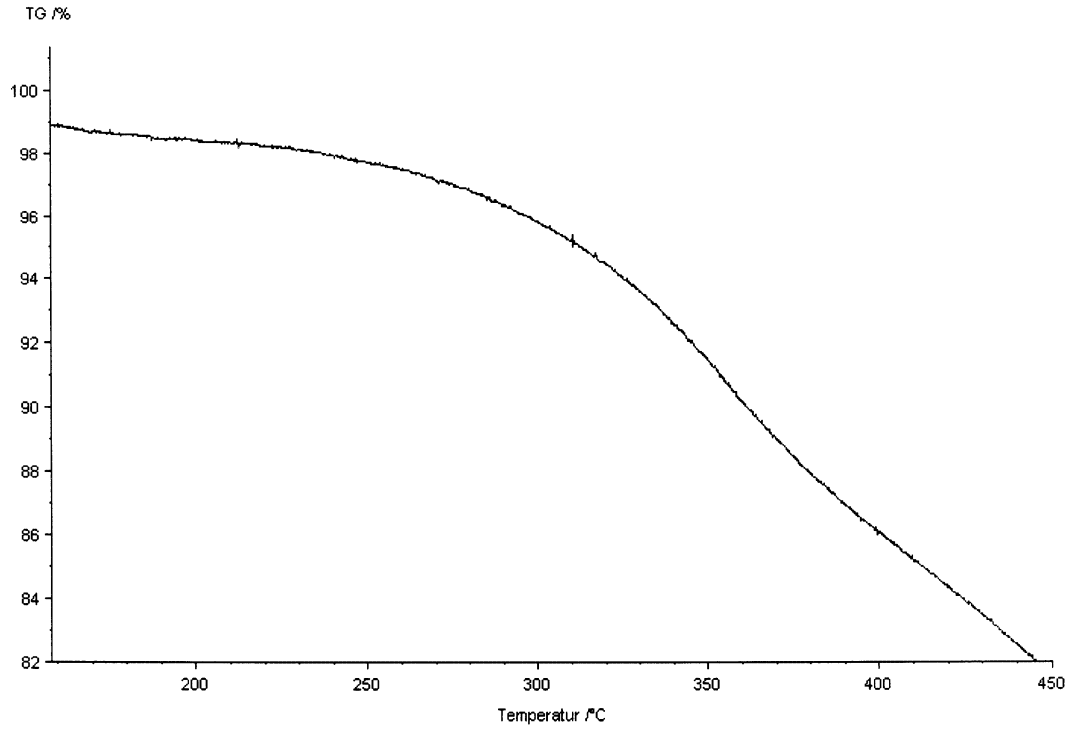

Figure 2. TGA of Chirasil-Calix.

purchased from Fluka AG, Buchs, Switzerland. Undec-10-enal was purchased from Sigma-Aldrich, Steinheim, Germany and hexachloroplatinic acid from Degussa, Mannheim, Germany. Dichloromethane was dried over $CaCl_2$ and filtered over basic Al_2O_3. All other reagents were of technical grade.

3.2. *C*-Dec-1-enylresorcinarene 1

C-Dec-1-enylresorcinarene was derived from the ω-unsaturated aldehyde undec-10-enal and resorcinol, according to the published method.[14] The crude product was recrystallized from acetonitrile. Yield: 19.2 g (42%). Mp 290°C. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 9.63–9.4 (br s, 8H, OH); 7.21 (s, 4H, H_{aromat}); 6.12 (s, 4H, H_{aromat}); 5.89–5.73 (m, 4H, -C*H*=CH_2); 5.02–4.91 (dd, 8H, -CH=CH_2); 4.31 (t, 4H, Ar-C*H*R-Ar); 2.17 (s, 8H); 2.08–2.00 (m, 8H); 1.29 (s, 32 H). ^{13}C NMR ($CDCl_3$, 62.9 MHz, ppm): 150.6, 139.2, 124.8, 123.8, 114.1, 102.7, 33.8, 33.2, 33.0, 30.9, 29.7, 29.5, 29.1, 29.0, 28.0. MS(FD): 1043.0.

3.3. Boc-L-valine-*tert*-butylamide 2

Boc-L-valine (21.73 g, 0.1 mol) was dissolved with stirring in dry dichloromethane (150 mL) in a 250 mL round bottom flask equipped with a dropping funnel. The solution was cooled to 5°C and dicyclohexylcarbodiimide (DCC, 20.63 g, 0.1 mol) was added slowly in small portions. *tert*-Butylamine (12.14 mL, 0.115 mol) was added dropwise to the reaction mixture. After stirring for 4 h at room temperature the solution was diluted to double its volume with dichloromethane. Urea formed was separated by filtration. The solvent was removed. In order to remove further amounts of urea the residue was dissolved in 50 mL of ethylacetate and heated to 50°C. The remaining urea was filtered off. This procedure was repeated until no more urea was formed. *n*-Pentane (100 mL) was added to the solution. The solution was maintained at −5°C and the precipitated **2** was collected by filtration and dried for 24 h at 0.01 mbar/room temperature. Yield: 23.7 g (87%), colourless needles. Mp 192–194°C. $[\alpha]_D^{20}$ −14.2 (*c* 1, MeOH). Anal. calcd for $C_{14}H_{28}N_2O_3$: C, 61.72; H, 10.37; N, 10.29. Found: C, 62.26; H, 9.34; N, 10.54%. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 7.65 (br d, -CON*H*), 5.2 (br d, -OCON*H*), 4.09 (dd, 1H, -C*H*NH), 2.00 (m, 1H, C*H*$(CH_3)_2$), 1.40 (s, 9H, -OC$(CH_3)_3$), 1.27 (s, 9H, -NHC$(CH_3)_3$), 0.85 (d, 6H, CH$(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 63 MHz, ppm): 171.2 (C(O)NHR), 153.6 (OC(O)NH), 80.1 (O*C*$(CH_3)_3$), 59.1 (C*), 50.2 (-NH-*C*$(CH_3)_3$), 31.3 (-*C*H$(CH_3)_2$), 28.3 (-NHC-$(CH_3)_2$), 27.5 (-OC$(CH_3)_3$), 19.3 (-CH$(CH_3)_2$). MS (EI, 70 eV): 274 (M+1, 4%), 273 (M, 26%), 217 (M+1–C_4H_9, 43%), 173 (M–C_4H_9OCO, 19%), 116 (M–C_4H_9OCO, M–C_4H_9, respectively, 54%), 72 ($C_4H_{10}N$, 100%), 57 (C_4H_9, 91%).

3.4. L-Valine-*tert*-butylamide 3

Amide **2** (20 g, 73.2 mmol) was dissolved in dry dichloromethane (25 mL) in a 100 mL round bottom flask equipped with a dropping funnel. The solution was cooled to 0°C. Trifluoroacetic acid (35 mL, 0.46 mol) was added dropwise to the stirred mixture. The solution was stirred at room temperature for a further hour. The solvent and the unreacted acid were removed

in vacuo using a rotary evaporator. The resulting viscous residue was dissolved in diethyl ether (50 mL) and stored overnight at −10°C. The precipitate was separated by filtration and washed with saturated sodium hydrogen carbonate solution (25 mL) to remove the remaining trifluoroacetic acid. This procedure was repeated until the product did not show any acidic reaction in a solution with methanol (pH* 6–7). The product was dried for 24 h at 60°C under reduced pressure (0.01 mbar). Yield: 12.2 g (97%), colourless needles. Mp 172–174°C. $[\alpha]_D^{20}$ +32.0 (*c* 1, MeOH). Anal. calcd for $C_9H_{20}ON_2$: C, 62.73; H, 11.71; N, 16.27. Found: C, 61.86; H, 10.93; N, 15.84%. ^{1}H NMR (DMSO-d_6, 250 MHz, ppm): 8.07 (br d, -NH_2), 3.50 (d, 1H, -CHNH$_2$), 3.36 (s, 1H, CONH), 2.00 (m, 1H, CH(CH$_3$)$_2$), 1.27 (s, 9H, C(CH$_3$)$_3$), 0.90 (d, 6H, CH(CH_3)$_2$). MS (EI, 70 eV): 173 (m, 13%), 72 (C_4H_9, 100%).

3.5. *N*-Bromoacetyl-L-valine-*tert*-butylamide 4

Bromoacetic acid (9.96 g, 70 mmol) was dissolved in dry dichloromethane (100 mL) in a 250 mL three-necked round-bottomed flask. The solution was cooled to −5°C. A solution of dicyclohexylcarbodiimide (DCC, 15.88 g, 77 mmol) in dry dichloromethane (10 mL) was added dropwise to the cooled solution followed by small portions of **3** (total: 12 g, 69.8 mmol). After stirring the mixture for 6 h at room temperature the solution was diluted to double its volume with dichloromethane. The precipitated urea was removed by filtration. The solvent was removed in vacuo. In order to remove further amounts of urea the residue was dissolved in ethyl acetate (50 mL) and heated to 50°C. The remaining urea was filtered off. This procedure was repeated until no more urea was formed. Subsequently *n*-pentane (100 mL) was added to the solution. The solution was maintained at −5°C and the precipitated **4** was collected by filtration and dried for 24 h at room temperature/0.01 mbar. Yield: 10.5 g (51%) of a colourless powder. Mp 182–184°C. $[\alpha]_D^{20}$ −24.3 (*c* 1, MeOH). Anal. calcd for $C_{11}H_{21}O_2N_2Br$: C, 45.19; H, 7.25; N, 9.59; Br, 27.02. Found: C, 44.63; H, 6.97; N, 9.72; Br, 25.09%. IR (KBr, cm^{-1}): 3273, 3076, 2967, 1641, 1553, 1222, 656. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 7.30 (d, 1H, -NH-), 6.0 (d, 1H, -NH-), 4.15 (dd, 1H, C*), 3.85 (s, 2H, Br-CH_2-), 2.04 (dq, 1H, -CH(CH$_3$)$_2$), 1.33 (s, 9H, -C(CH$_3$)$_3$), 0.93 (dd, 6H, -CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 69.9 MHz, ppm): 169.7, 165.9, 59.4, 51.7, 34.0, 28.7, 19.1, 18.3. MS (EI, 70 eV): 295.2, 293.2 (M, 23%, respectively), 114.2 (M−C_4H_9, 100%), 72.13 ([$C_4H_{10}N$]$^+$, 84%).

3.6. Octakis-*O*-(acetyl-L-valine-*tert*-butylamide)-*C*-decenyl-resorcinarene 5

Amide **4** (1.46 g, 5 mmol) was added in small portions to a suspension of **1** (0.44 g, 0.42 mmol) and potassium carbonate (0.61 g, 4.42 mmol) in dry acetonitrile (20 mL). The reaction mixture was stirred for 24 h at 60°C. Afterwards additional **4** (0.73 g, 2.5 mmol) was added. The mixture was allowed to stir for a further 12 h at 60°C. After cooling, the solvent was evaporated and the brown residue was dissolved in diethyl ether (50 mL). The precipitated salts were separated by filtration. The organic phase was washed with water (2×20 mL). After drying over magnesium sulfate the solvent was removed. The resulting brown oil was purified by flash chromatography using ethylacetate/*n*-hexane (3:1) as eluent. The separated product was recrystallized from *n*-hexane/diisopropylether and dried for 24 h at 0.01 mbar. Yield: (0.6 g, 68%), colourless crystals. Mp 155–157. $[\alpha]_D^{20}$ −7.3 (*c* 1, MeOH). Anal. calcd for $C_{156}H_{256}N_{16}O_{24}$: C, 68.39; H, 9.42; N, 8.18. Found: C, 67.45; H, 9.68; N, 8.13%. IR (KBr, cm^{-1}): 3324, 3074, 2963, 2926, 2854, 1613, 1546, 1455, 1391, 1364, 1286, 1252, 1225, 1186, 1108, 1060, 909. ^{1}H NMR (MeOD, 400 MHz, ppm):[18] 7.75, 7.69 (4H, H_g) 6.83 (s, 4H, H_A), 6.42 (s, 4H, H_B), 5.83–5.69 (m, 4H, H_L), 5.03 (d, 4H, $H_{M(trans)}$, J=18 Hz), 4.97 (d, 4H, $H_{M(cis)}$, J=10 Hz), 4.73 (t, 4H, H_C), 4.42 (br s, 16H, H_e) 4.26 (m, 8H, H_d), 2.07 (m, 16H, H_c/H_K), 1.94 (m, 8H, H_D), 1.41–1.35 (m, 108H, $H_{E\text{-}J}$/H_a), 0.98 (m, 48H, H_b). ^{13}C NMR (MeOD, 100 MHz, ppm): 172.6, 172.3, 171.0, 170.6, 156.0, 140.0, 127.8, 114.4, 101.7, 70.5, 68.9, 60.3, 59.7, 52.3, 52.2, 37.5, 35.0, 32.9, 32.6, 31.4, 30.4, 30.2, 29.3, 20.0, 19.9, 19.2, 18.2. MS (FD, positive charged ions): calcd for $C_{156}H_{256}N_{16}O_{24}$: 2739.7. Found: 2739.3 ([M]$^+$), 2599.4 ([M−$C_{10}H_{19}$]$^+$). MS (FD, negative charged ions): calcd for $C_{156}H_{256}N_{16}O_{24}$: 2739.7. Found: 2739.9 ([M]$^+$), 2525.8 ([M−$C_{11}H_{21}N_2O_2$]$^+$), 2312.9 ([M−2($C_{11}H_{21}N_2O_2$)]$^+$). ESI-MS: 1392.0 ([M+2Na]$^{2+}$), 1390.0 ([M+H+K]$^{2+}$), 1381.0 ([M+H+Na]$^{2+}$), 1369.5 ([M+2H]$^{2+}$). HRMS: calcd: 1369.2481 ([M+2H]$^{2+}$). Found: 1369.2483.

3.7. Chirasil-Calix 6

Resorcinarene **5** (50 mg, 0.0182 mmol) and poly(90.7% dimethyl- 9.3% hydromethyl)-siloxan (283 mg) were dissolved in a mixture of dry tetrahydrofuran (5 mL) and dry toluene (5 mL) under an inert atmosphere. A solution of hexachloroplatinic acid (1 mg) in dry tetrahydrofuran (1 mL) was prepared separately and 100 μL thereof were added to the reaction mixture. After stirring the mixture under reflux for 72 h at 80°C, the solution was allowed to cool to room temperature. The solvent was removed and the residue was dissolved in dry dichloromethane (5 mL). After adding 20 mL of diethyl ether the mixture was kept at 5°C for 1 h. The residual unreacted particles were separated by filtration (pore 0.45 μm). Evaporation of the solvent afforded Chirasil-Calix **6** (239 mg, 72%). To avoid cross-linking of the polymer, the product was stored as a solution in dry dichloromethane with exclusion of light. $[\alpha]_D^{20}$ −9.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): 7.78, 6.77, 4.54, 4.31, 4.00, 2.15, 1.64, 1.28, 0.88, 0.06.

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17. The TGA and DTA were measured on a Netzsch-Gerätebau STA 409C thermobalance. The sample (62.2 mg) was heated under a nitrogen atmosphere. The heating rate was 5 K/min starting from room temperature to 450°C.
18. The abbreviations used for the ^{1}H NMR spectra of compound **5** are as follows.