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PROTOTYPE OF A PHOTOSWITCHABLE FOLDAMER

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General Methods. Compounds **11**[1], **12**[1], **19**[2] were prepared as described in the literature. Dibromoisocyanuric acid (DIB) was synthesized from cyanuric acid and bromine according to a reported procedure.[3] All other chemicals were commercial and used as received. THF and acetonitrile were distilled prior to use under N_2 atmosphere over sodium/benzophenone ketyl and calcium hydride, respectively. Column chromatography was carried out with 130-400 mesh silica gel. NMR spectra were recorded on Bruker AB 250 (250.1 and 62.9 MHz for ^1H and ^{13}C, respectively), Bruker DPX 300 (300 and 75 MHz for ^1H and ^{13}C, respectively), and AC 500 as well as Delta JEOL Eclipse 500 (500 and 126 MHz for ^1H and ^{13}C, respectively) spectrometers at 23 ± 2 ^oC using residual protonated solvent signal as internal standard (^1H: $\delta(CHCl_3)$ = 7.24 ppm, δ(DMSO) = 2.49, $\delta(CH_3CN)$ = 1.94 ppm and ^{13}C: $\delta(CHCl_3)$ = 77.00 ppm, δ(DMSO) = 39.70 ppm). Mass spectrometry was performed on Finnigan MAT 8200, Perkin-Elmer Varian Type MAT 771, and CH6 (EI), Finnigan MAT 95 (ESI), and Bruker Reflex with 337 nm laser excitation (MALDI-TOF) instruments. GPC measurements were performed on an Agilent 1100 series HPLC system equipped with three 300 x 8 mm SDV columns (1,000,000 Å, 100,000 Å, 1000 Å) and one 50 x 8 mm SDV column (100 Å) using both UV (230 nm and 280 nm) and RI detection. The measurements were performed in THF at 30 ^oC using a flow rate of 1 mL/min. The columns were calibrated with several narrow polydispersity polystyrene samples. Chiral GC was performed on 525,6890N Agilent instrument equipped with 30 m BGB-176/BGB-15 columns using FID detection and employing 0.6 bar of H_2 as the carrier gas.

Optical Spectroscopy. UV/visible absorption spectra were recorded in various solvents of spectroscopic grade using silylated quartz cuvettes of 1 cm path length on a Cary 50 Spectrophotometer and a Cary Eclipse Fluorescence Spectrophotometer, respectively, both equipped with Peltier thermostated cell holders (ΔT = ± 0.05 ^oC). Unless stated otherwise, all experiments were carried out at 25.00 ± 0.05 ^oC. For titration experiments, stock solutions in $CHCl_3$ and CH_3CN with optical densities OD(λ_{max}) ~ 0.8 were used to prepare samples with varying solvent composition. Circular dichroism spectra were recorded on a JASCO 700 spectrometer using quartz cuvetts of 1 cm path length at 22 ± 1 ^oC. From UV/vis spectra obtained in the titration experiments (MS Figure 2) the absorbance ratio $A_{\lambda=303nm}/A_{\lambda=288nm}$ (MS Figure 2 inset) as a function of solvent composition was used to determine the thermodynamics of folding, as described by Moore and coworkers.[1] Figure 1 shows the corresponding titration curve after normalization and the respective derivation of the helix stabilization energy in neat acetonitrile $\Delta G(CH_3CN)$.

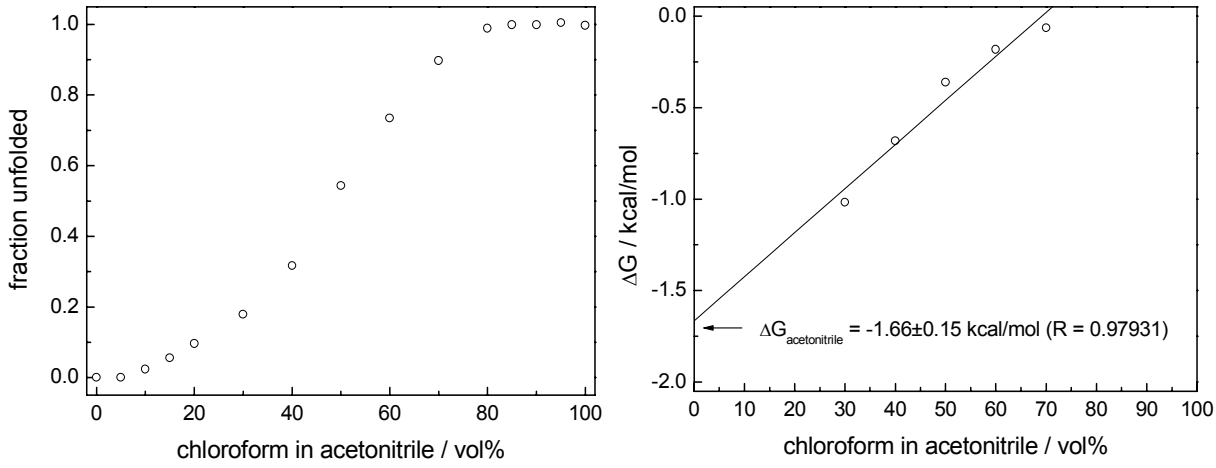

Figure 1. Normalized titration curve corresponding to UV/vis titration data shown in MS Figure 2 (left) and derivation of helix stabilization energy by linear regression of the data points in the transition region.

Irradiation experiments. Irradiation experiments were performed on degassed solutions (Ar for 5 min) of **1** in acetonitrile using a LOT-Oriel 1000 W medium-pressure xenon lamp (XBO) equipped with an interference filter ($\lambda_{max\ T}$ = 365 nm @ 10% T, FWHM = 10 nm, see Figure 2).

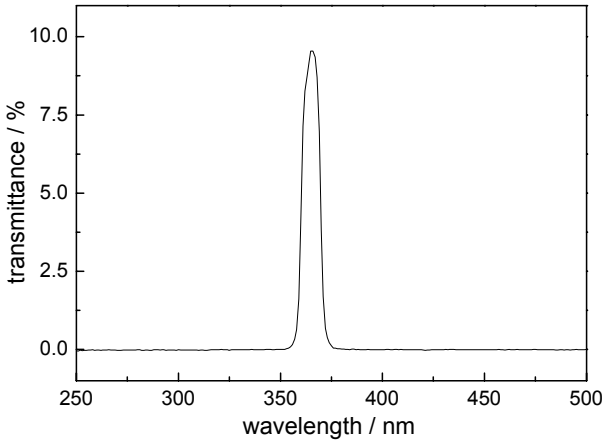

Figure 2. Interference filter ($\lambda_{max\ T}$ = 365 nm @ 10% T, FWHM = 10 nm) used for irradiation experiments.

Both photochemical *trans*→*cis* isomerization (MS Figure 4a) and thermal *cis*→*trans* isomerization were conveniently monitored by UV/vis spectroscopy. In order to investigate the thermal *cis*→*trans* isomerization by CD spectroscopy (MS Figure 3b), samples in acetonitrile were irradiated and once the photostationary state (PSS) was reached they were diluted with water (60 vol%), and CD spectra were recorded over time. This procedure was used since it allows for a more convenient detection of the PSS in pure acetonitrile as compared to aqueous acetonitrile due to the hypochromicity of foldamer **1** in polar solvent mixtures. Integration of the collected CD spectra during one thermal *cis*→*trans* isomerization was used to calculate the concentration of $\mathbf{1}_{cis}$ as a function of time. First order exponential

fitting provided the rate constant of the thermal *cis→trans* isomerization as $k_{cis \rightarrow trans} \sim 3.8 \cdot 10^{-5}\ s^{-1}$ (Figure 3).

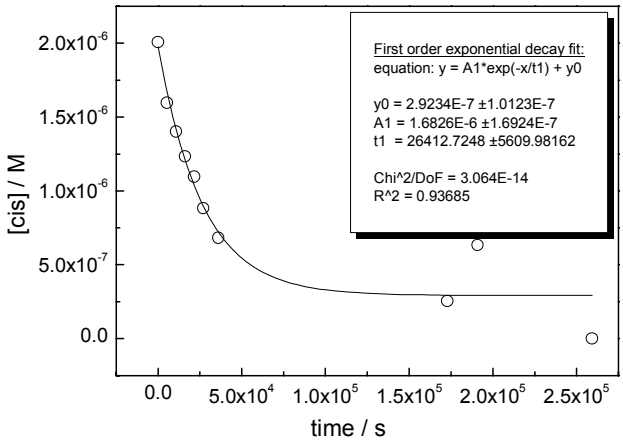

Figure 3. Thermal *cis→trans* isomerization of photogenerated $\mathbf{1}_{cis}$ as a function of time at 22 °C ($5.7 \cdot 10^{-6}$ M **1** in 60vol% H_2O/CH_3CN). Concentrations were estimated by integration of the bands ranging from 295-400 nm showing a positive Cotton-effect (see below).

The CD spectra can be correlated to the composition of the mixture, i.e. content of *cis*- and *trans*-isomers. This allows for convenient detection of the *trans*- and *cis*-content at the photostationary state as explained in Figure 4.

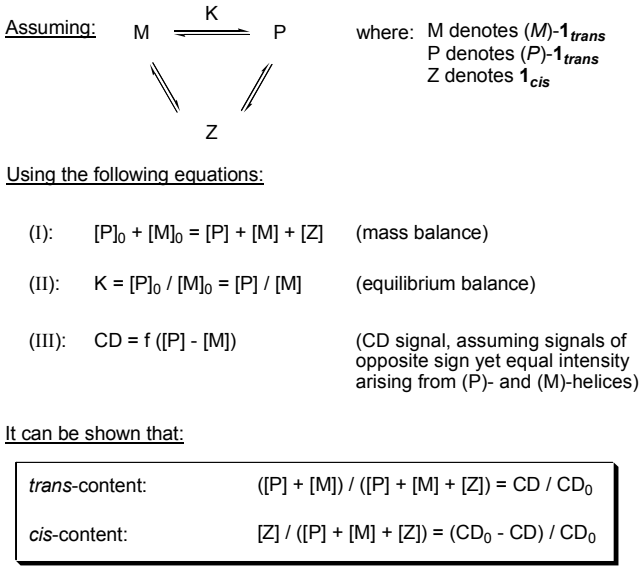

Figure 4. Relationship between CD signal intensity and composition of the mixture at the photostationary state.

Synthesis. Oligomer **1** was synthesized as outlined in Figure 5.

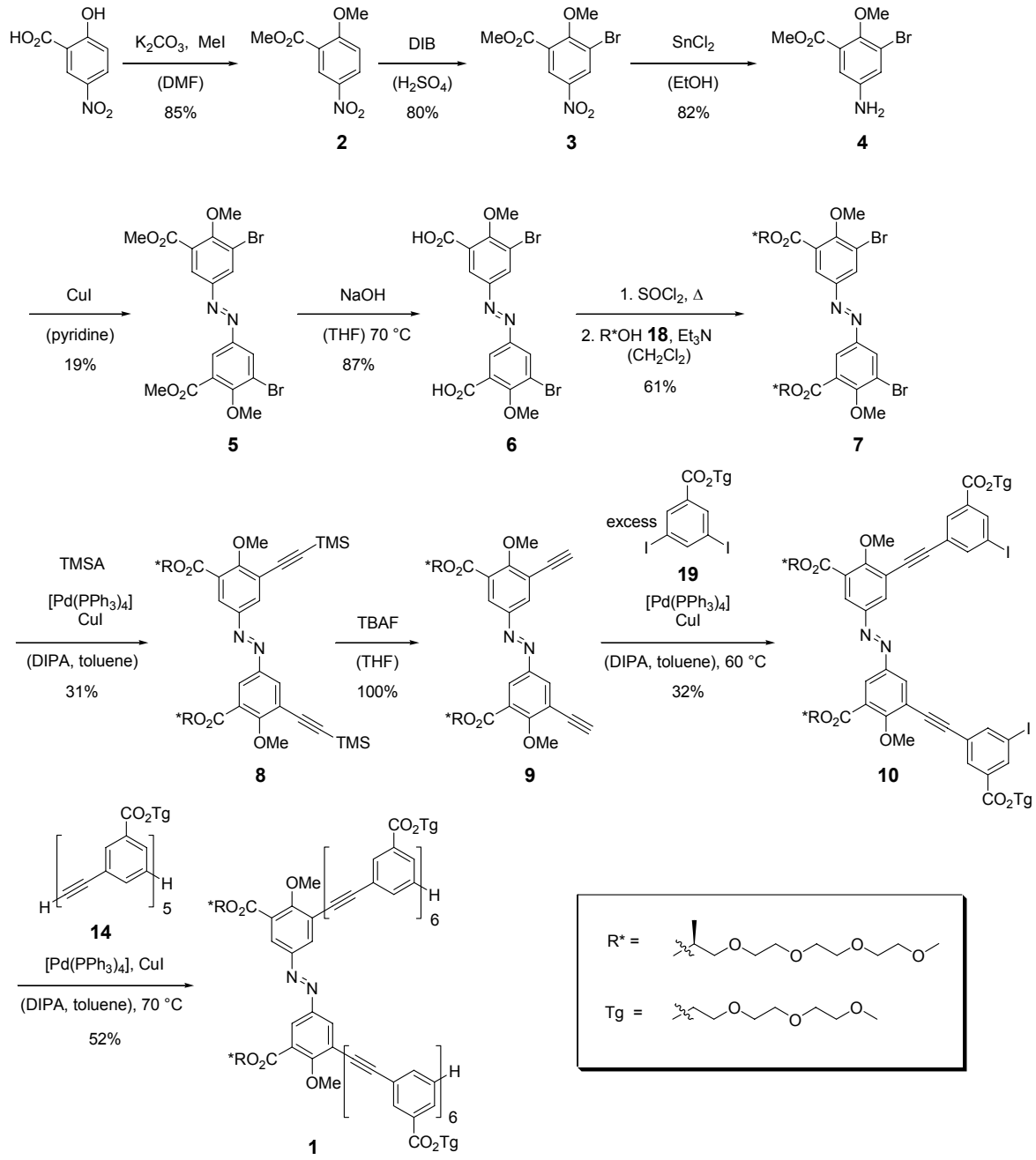

Figure 5. Synthesis of target oligomer **1** (for synthesis of **14** and **18** see Figure 11.

Methyl 2-methoxy-5-nitrobenzoate 2. 5-Nitrosalicylic acid (18.3 g, 100 mmol) was dissolved in DMF (250 mL) then K_2CO_3 (41.4 g, 300 mmol) was added in small portions followed by MeI (70 mL, 500 mmol). The reaction mixture was heated to 100 °C for 30 min then cooled down to room temperature, and poured into 1 L of water. The resulting precipitate was collected by filtration and recrystallized from ethanol giving 18 g of the product as a white solid (85% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 2.9 Hz, 1 H, Ar-H), 8.34 (dd, *J* = 9.1 and 2.9 Hz, 1 H, Ar-H), 7.04 (d, *J* = 9.1 Hz, 1 H, Ar-H), 3.99 (s, 3 H, O-

CH_3), 3.91 (s, 3 H, O-CH_3); ^{13}C- NMR (300 MHz, $CDCl_3$); δ = 164.84, 164.00, 141.05, 129.28, 128.19, 120.86, 112.38, 57.20, 52.93; EI-MS (80 eV, 60 °C): *m/z* = 211 (calcd 211.1 for $C_9H_9NO_5^+$).

Methyl 3-bromo-2-methoxy-5-nitrobenzoate 3. Methyl 2-methoxy-5-nitrobenzoate **2** (3.1 g, 15 mmol) was dissolved in conc. sulfuric acid (100 mL) at 0 °C and DIB[3] (4.3 g, 15 mmol) was added in small amounts. The reaction mixture was stirred at room temperature for 3 h and then poured on ice resulting in a yellow precipitate, which was recrystallized from ethanol furnishing 3.5 g of the product as a white solid (80% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 2.7 Hz, 1 H, Ar-H), 8.57 (d, *J* = 2.7 Hz, 1 H, Ar-H), 4.00 (s, 3 H, O-CH_3), 3.96 (s, 3 H, O-CH_3); ^{13}C- NMR (300 MHz, $CDCl_3$); δ = 163.77, 162.00, 131.85, 126.65, 126.12, 119.78, 62.73, 53.07; EI-MS (80 eV, 55 °C): *m/z* = 289 (calcd 290 for $C_9H_8NBrO_5^+$).

Methyl 3-bromo-2-methoxy-5-aminobenzoate 4. Methyl 3-bromo-2-methoxy-5-nitrobenzoate **3** (2 g, 7 mmol) was dissolved in 20 mL of ethanol, then $SnCl_2 \cdot 2H_2O$ (7.8 g, 35 mmol) was added, and the reaction mixture was heated to 80 °C for 1 h. It was then poured on ice and the solution was adjusted to pH = 8 by addition of 1 N NaOH. The aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with water and brine, and the solvent was removed under reduced pressure giving 1.5 g product as a yellow oil. (82% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.06 (s, 2 H, Ar-H), 3.88 (s, 3 H, O-CH_3), 3.81 (s, 3 H, O-CH_3); ^{13}C- NMR (300 MHz, $CDCl_3$); δ = 166.00, 158.00, 126.63, 123.53, 119.48, 116.91, 62.13, 52.42; EI-MS (80 eV, 65 °C): *m/z* = 259 (calcd 260 for $C_9H_{10}NBrO_3^+$).

Azobenzene Bis(methyl ester) 5. Methyl 3-bromo-2-methoxy-5-aminobenzoate **4** (1.3 g, 5 mmol) was dissolved in pyridine (50 mL) then CuI (4.7 g, 25 mmol) was added and the reaction mixture was stirred at room temperature for 3 d. The reaction mixture was diluted with ethyl acetate then passed through a short plug of silica gel, subsequently washed with water, brine, 1 N HCl, and again with water and brine. The organic layer was removed under reduced pressure and the remaining residue purified by column chromatography (ethyl acetate:hexanes = 1:9) giving 0.5 g of the product as an orange solid (19% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 2.5 Hz, 2 H, Ar-H), 8.26 (d, *J* = 2.5 Hz, 2 H, Ar-H), 3.98 (s, 3 H, O-CH_3), 3.96 (s, 3 H, O-CH_3); ^{13}C- NMR (300 MHz, $CDCl_3$); δ = 165.38, 159.53, 148.40, 130.26, 127.30, 120.59, 62.84, 53.08; EI-MS (80 eV, 160 °C): *m/z* = 516 (calcd 516.1 for $C_{18}H_{16}N_2Br_2O_6^+$).

Azobenzene Diacid 6. Compound **5** (0.18 g, 0.35 mmol) was dissolved in THF (2 mL), diluted with 1 N NaOH (50 mL), and then refluxed at 80 °C for 3 h. The dark red reaction mixture was neutralized with concentrated HCl. The resulting orange solid was washed with

plenty of water to give 0.15 g of the product as an orange solid (87% yield). ^{1}H-NMR (300 MHz, D_2O): δ = 8.08 (d, 2 H, Ar-H), 7.84 (d, 2 H, Ar-H), 3.92 (s, 6 H, O-CH_3); ^{13}C- NMR (300 MHz, D_2O); δ = 170.00, 155.00, 150.00, 135.00, 126.73, 123.31, 96.04, 62.36; EI-MS (80 eV, 270 °C): *m/z* = 488 (calcd 488 for $C_{16}H_{12}N_2Br_2O_6^+$).

Azobenzene Bis(Chiral Glyme Ester) 7. Compound **6** (0.43 g, 0.9 mmol) was suspended in thionyl chloride (50 mL) and refluxed for 2 h. Excess thionyl chloride was removed *in vacuo* and the remaining residue was dried on a vacuum pump for 3 h to afford the crude acid chloride as a red solid, which was subsequently added to a stirring solution of chiral alcohol **18** (0.5 mL, 2.2 mmol), triethylamine (0.45 mL, 4.5 mmol), and 4-dimethylaminopyridine (DMAP; 0.004 g, 0.04 mmol) in 15 mL of CH_2Cl_2 at 0 °C. The suspension was allowed to warm to room temperature and stirred overnight. Then the organic layer was washed with brine and sat. aq. NH_4Cl solution. The residue was purified by column chromatography (ethyl acetate:hexanes = 2:1) to yield 0.49 g of the product as an orange oil (61% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 2.4 Hz, 2 H, Ar-H), 8.23 (d, *J* = 2.4 Hz, 2 H, Ar-H), 5.4-5.35 (m, 2 H, CO_2-CH), 3.98 (s, 6 H, O-CH_3), 3.72-3.58 (m, 24 H, O-CH_2), 3.51-3.48 (m, 4 H, O-CH_2), 3.33 (s, 6 H), 1.38 (d, *J* = 6.4 Hz, 6 H); ^{13}C- NMR (300 MHz, $CDCl_3$); δ = 164.23, 158.92, 147.97, 129.06, 127.53, 127.40, 120.07, 73.56, 71.89, 70.98, 70.75, 70.62, 70.59, 70.48, 62.46, 58.98, 16.67; EI-MS (80 eV, 245 °C): *m/z* = 896 (calcd 896.6 for $C_{36}H_{52}N_2Br_2O_{14}^+$). UV/vis spectra in CH_3CN and $CHCl_3$ are shown in Figure 6.

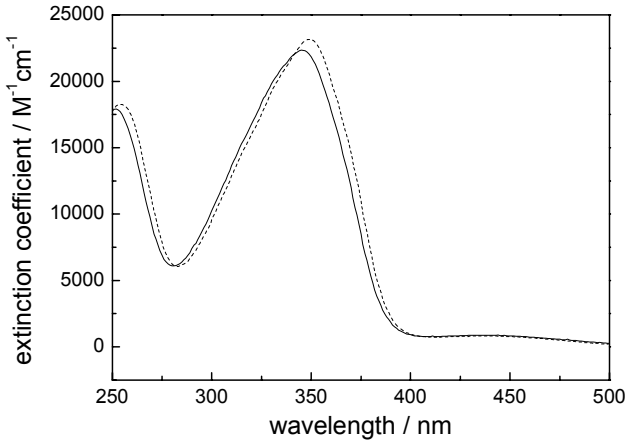

Figure 6. UV/vis absorption spectra of **7** in CH_3CN (——) and $CHCl_3$ (-----) recorded at 25 °C showing the negligible solvatochromicity of the azobenzene core chromophore.

Azobenzene Bis(TMSacetylene) 8. Dry and degassed diisopropylamine (1 mL) and toluene (0.5 mL) were added to a mixture of compound **7** (0.035 g, 0.4 mmol), trimethylsilylacetylene (TMSA; 0.4 g, 4 mmol), $Pd(PPh_3)_4$ (0.028 g, 0.02 mmol), CuI (0.008 g, 0.04 mmol), and PPh_3

(0.005 g, 0.02 mmol). The flask was sealed and heated to 60 °C for 24 h. The reaction mixture was diluted with ethylacetate, filtered, concentrated and purified by column chromatography (ethyl acetate:hexanes = 3:1) to give 0.12 g of the product as an orange oil (31% yield). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 2.4, Hz, 2 H, Ar-H), 8.08 (d, *J* = 2.4, Hz, 2 H, Ar-H), 5.37-5.31 (m, CO_2-CH, 2H), 4.15 (s, 6H, Ar-OCH_3), 3.69-3.49 (m, 24 H, O-CH_2), 3.49-3.47 (m, 4 H, O-CH_2), 3.33 (s, 6 H, O-CH_3), 1.36 (d, *J* = 6.39 Hz, 6H, C-CH_3), 0.23 (s, 18H, Si-CH_3); ^{13}C- NMR (125 MHz, $CDCl_3$); 164.79, 163.07, 147.23, 130.37, 126.83, 126.77, 119.43, 101.12, 99.68, 73.58, 71.87, 70.74, 70.61, 70.58, 70.47, 62.07, 58.99, 16.73, 0.26; ESI (pos) MS: *m/z* = 953.4 (calcd 953.4 for $C_{46}H_{70}O_{14}N_2Si_2$+$Na^+$).

Azobenzene Diiodide 10. Compound **8** (0.074 g, 0.08 mmol) was dissolved in 5 mL of THF and 1 mL of TBAF (1 M in THF) was added. The reaction mixture was stirred at room temperature for 1 min and then filtered through a short plug of silica gel using ethyl acetate as solvent. The solvent was removed under reduced pressure yielding 0.063 g of terminal bisacetylene **9** as an orange wax, which was used without further characterization. Dry and degassed diisopropylamine (6 mL) and toluene (2 mL) were then added to a mixture of bisacetylene **9** (0.063 g, 0.08 mmol), diiodide **19** (0.8 g, 1.6 mmol), $Pd(PPh_3)_4$ (0.028 g, 0.1 mmol), CuI (0.008 g, 0.04 mmol) and PPh_3 (0.01 g, 0.02 mmol). The flask was sealed and heated to 60 °C for 2 h to dissolve all the diiodide monomer then heating was turned off and the reaction was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate, filtered, concentrated, and purified by column chromatography involving a gradient (ethyl acetate:hexanes = 2:1 → methanol:ethyl acetate = 0.1:1 → 3:1) to give 0.04 g (32 % yield) of the product as orange wax. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 1.6, 1.2 Hz, 2 H, Ar-H), 8.27 (d, *J* = 2.7, Hz, 2 H, Ar-H), 8.14 (d, *J* = 2.7, Hz, 2 H, Ar-H), 8.13 (d, *J* = 1.6, 1.2 Hz, 2 H, Ar-H), 8.02 (dd, *J* = 1.6, 1.2 Hz, 2 H, Ar-H), 5.37-5.31 (m, CO_2-CH, 2H), 4.46-4.43 (m, 4 H, CO_2-CH_2), 4.08 (s, 6H, Ar-O-CH_3), 3.82-3.72 (m, 4 H, O-CH_2), 3.66-3.53 (m, 38 H, O-CH_2), 3.49-3.44 (m, 8 H, O-CH_2), 3.30 (s, 6 H, O-CH_3), 3.28 (s, 6 H, O-CH_3), 1.36 (d, *J* = 6.4 Hz, 6H, C-CH_3); ^{13}C- NMR (125 MHz, $CDCl_3$); 164.71, 164.35, 162.84, 147.44, 144.03, 138.56, 132.09, 131.93, 130.13, 127.38, 126.90, 125.04, 118.91, 93.32, 92.20, 86.65, 73.63, 71.95, 71.92, 70.84, 70.80, 70.69, 70.66, 70.62, 70.50, 69.05, 64.70, 82.58, 59.02, 58.99, 16.76; ESI (pos) MS: *m/z* = 1571.4 (calcd 1571.3 for $C_{68}H_{88}O_{24}N_2I_2^+$).

Oligomer 1. Dry and degassed diisopropylamine (0.5 mL) and toluene (0.5 mL) were added to a mixture of diiodide **10** (7 mg, 0.009 mmol), pentamer acetylene **14** (14 mg, 0.018 mmol), $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol), CuI (0.003 g, 0.01 mmol), and PPh_3 (0.005 g, 0.01 mmol).

The flask was sealed and heated to 60 °C for 12 h. The reaction mixture was then diluted with ethyl acetate, filtered, concentrated, and purified by column chromatography involving a gradient (CH_2Cl_2:acetone = 3:1 → acetone → methanol:acetone = 0.1:10) to give 10 mg of the desired product (52 % yield). For all analytical measurements, the product was further purified by prep. GPC. ^{1}H-NMR (300 MHz, $CDCl_3$, Figure 7): δ = 8.31 (d, *J* = 2.46 Hz, 2 H, Ar-H), 8.22-8.17 (m, 24 H, Ar-H), 8.05-8.01 (dt, *J* = 1.2, 7.7 Hz, 2 H, Ar-H), 7.89-7.87 (m, 10 H, Ar-H), 7.72-7.69 (dt, *J* = 1.2, 7.7 Hz, 2 H, Ar-H), 7.44 (t, *J* = 7.7 Hz 2 H, Ar-H), 5.41-5.35 (m, 2 , CO_2-CH), 4.52-4.49 (m, 24 H, CO_2-CH_2), 4.15 (s, 6 H, O-CH_3), 3.86-3.83 (m, 24 H, O-CH_2), 3.70-3.62 (m, 100 H, O-CH_2), 3.52-3.49 (m, 24 H, O-CH_2), 3.33 (s, 10 H, O-CH_3), 3.31 (s, 32 H, O-CH_3), 1.39 (d, *J* = 6.4 Hz, 6 H, C-CH_3); GPC (THF, 30 °C, Figure 8): M_w = 9500, PDI (M_w/M_n) = 1.0; ESI (pos) MS (Figure 9): *m/z* = 2134 (calcd 2134 for $C_{228}H_{270}O_{74}N_2$+2Na^{++}), 1430 (calcd 1430 for $C_{228}H_{270}O_{74}N_2$+3Na^{+++}). For a snapshot of a molecular model optimized by MM2 force field calculations see Figure 10.

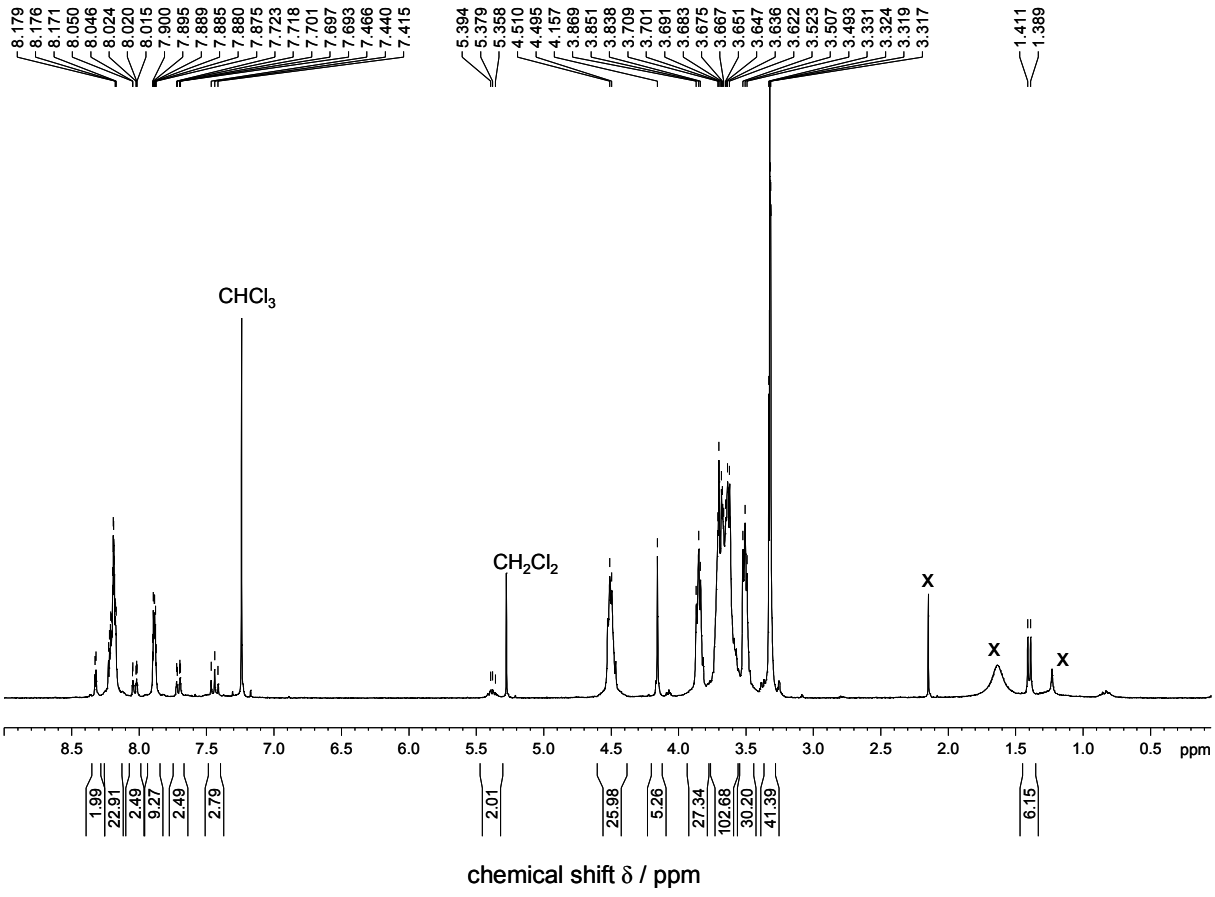

Figure 7. ^{1}H-NMR spectrum of target oligomer **1** (300 MHz, $CDCl_3$, 25 °C).

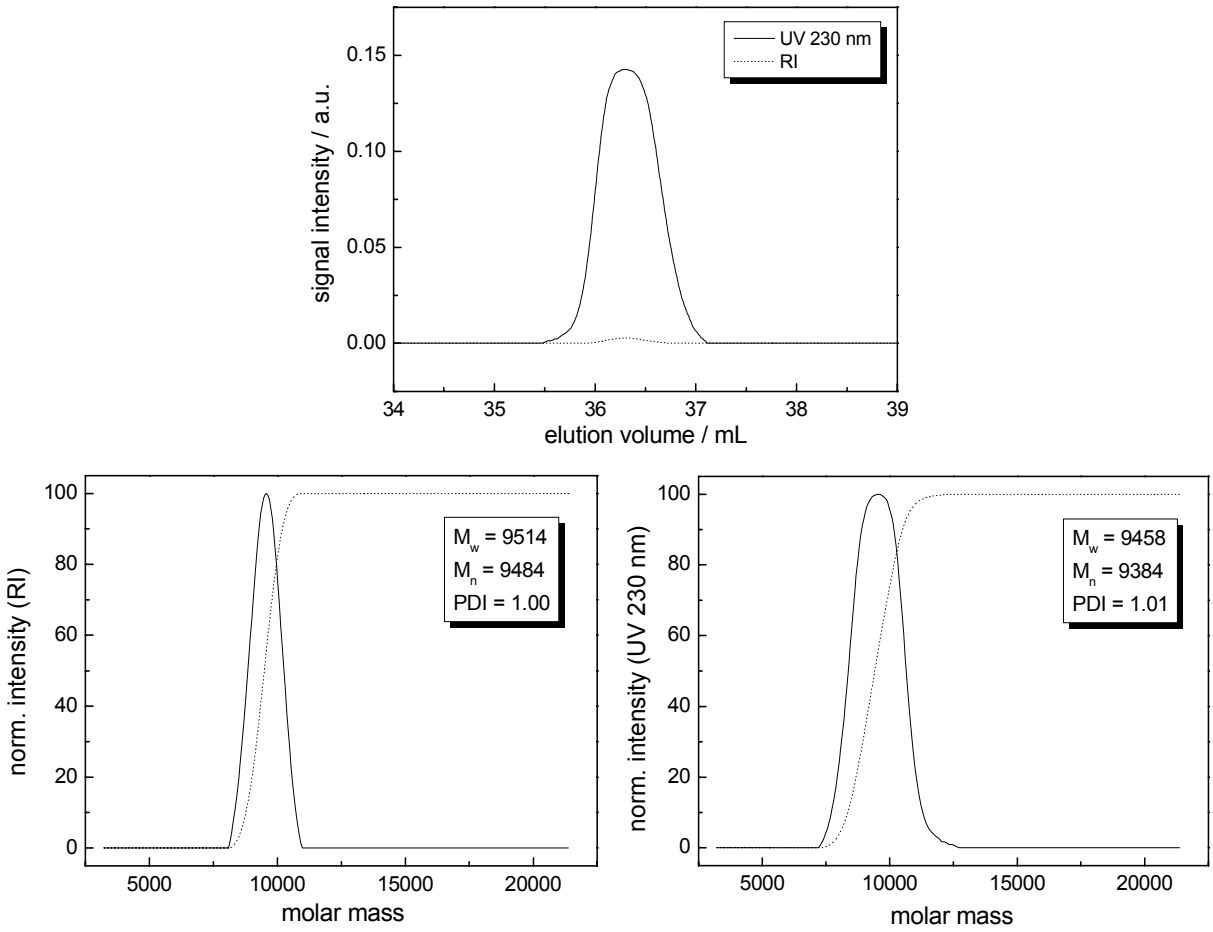

Figure 8. GPC trace (top) and molecular weight distribution using RI (bottom left) and UV detection (bottom right) of target oligomer **1** (THF, 30 ^{o}C, polystyrene calibration).

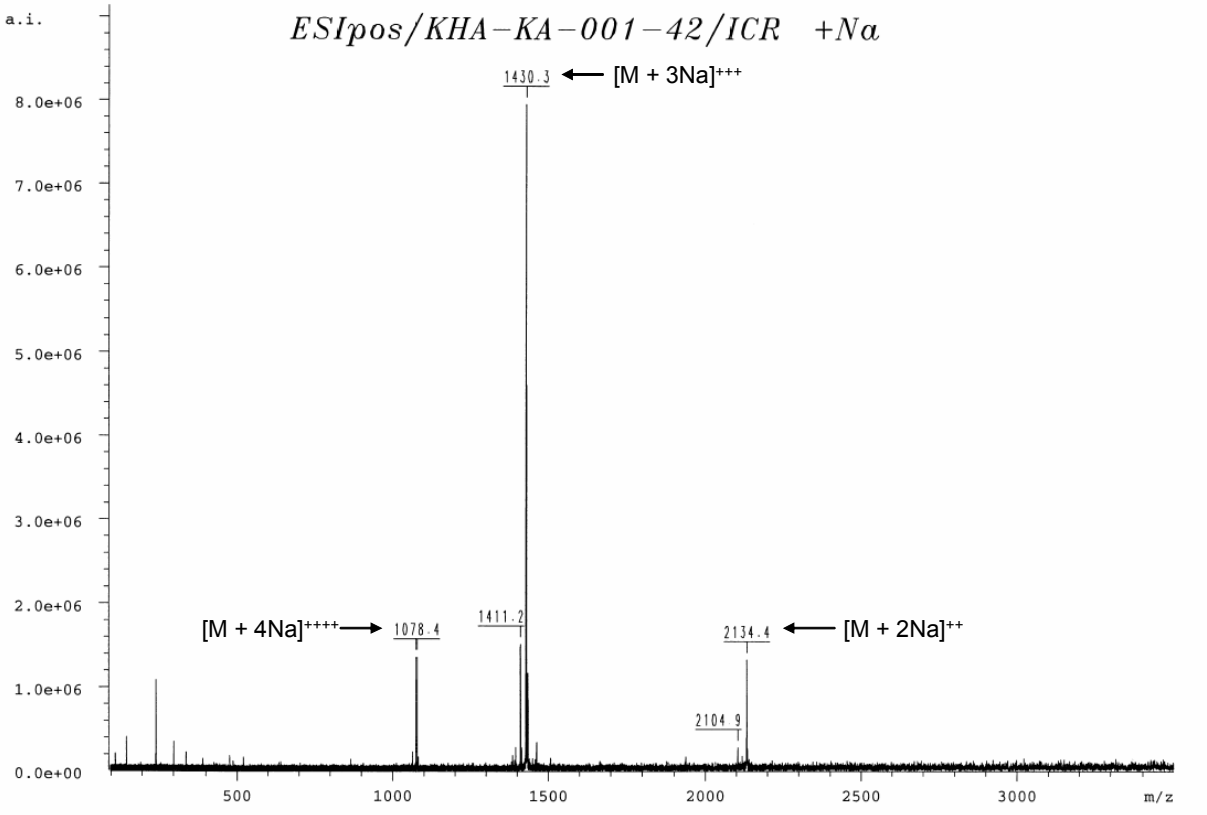

Figure 9. ESI MS spectrum (pos.) of target oligomer **1**.

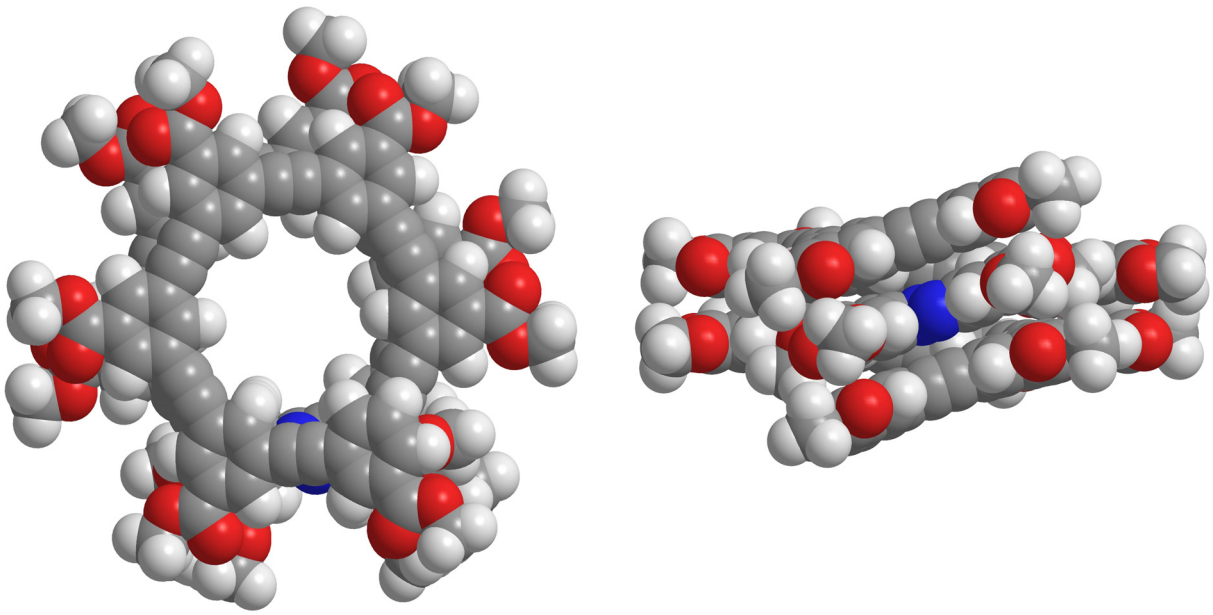

Figure 10. Snapshot of a molecular model obtained by geometry optimization using MM2 force field calculations. Top view (left) and side view (right) on the model where rudimentary methyl ester side chains have been used (O-atoms are shown in red, N-atoms in blue, C-atoms dark gray, and H-atoms in light gray).

The synthesis of pentamer acetylene **14** similar to the procedures described by Moore and coworkers[1] and chiral alcohol **18**,[4] both used in the synthesis of target oligomer **1** described above are depicted in Figure 11.

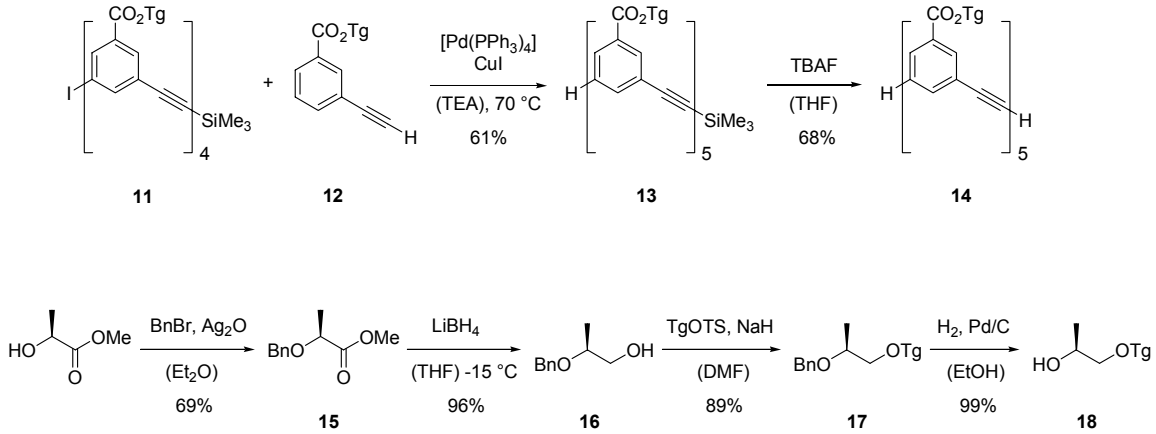

Figure 11. Synthesis of pentamer **14** and chiral alcohol **18**, used in the synthesis of **1**.

Pentamer TMSacetylene 13. Dry and degassed acetonitrile (12 mL) and triethylamine (20 mL) were added to a mixture of compound **11**[1] (4.0 g, 2.9 mmol), **12**[1] (0.81 g, 2.8 mmol), $Pd(PPh_3)_4$ (0.09 g, 0.08 mmol), CuI (0.2 g, 0.5 mmol), and PPh_3 (0.02 g, 0.05 mmol). The flask was sealed and heated to 70 °C for 16 h. The reaction mixture was diluted with ethyl acetate, filtered, concentrated, and purified by column chromatography (acetone:chloroform = 1:4) to give 2.6 g of the product as a yellow viscous oil (61% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.17-8.15 (dd, *J* = 1.7, 1.3 Hz, 1 H, Ar-H), 8.12-8.10 (m, 6 H, Ar-H), 8.08-8.07 (dd, *J* = 1.7, 1.6 Hz, 1 H, Ar-H), 8.03 (dd, *J* = 1.7, 1.6 Hz, 1 H, Ar-H), 7.98-7.96 (dt, *J* = 1.4, 7.8 Hz, 1 H, Ar-H), 7.83-7.80 (m, 3 H, Ar-H), 7.75-7.74 (t, *J* = 1.6, 1H, Ar-H), 7.66-7.64 (dt, *J* = 1.4, 7.8 Hz, 1 H, Ar-H), 7.40-7.37 (t, *J* = 7.8 Hz, 1H) 4.47-4.41 (m, 10 H, CO_2-CH_2), 3.80-3.76 (m, 10 H, O-CH_2), 3.66-3.56 (m, 30 H, O-CH_2), 3.46-3.43 (m, 10 H, O-CH_2), 3.27 (s, 3 H, O-CH_3), 3.26 (s, 9 H, O-CH_3), 3.26 (s, 3 H, O-CH_3), 0.19 (s, 9 H, Si-$(CH_3)_3$); ^{13}C NMR (500 MHz, $CDCl_3$); δ = 164.79, 164.74, 138.59, 138.19, 135.65, 132.69, 132.54, 132.34, 132.26,130.92, 130.88, 130.67, 130.42, 128.41, 123.97, 123.73, 123.47, 123.44, 123.39, 123.34, 123.11, 122.81, 102.65, 96.34, 89.83, 88.97, 88.95, 88.87, 88.85, 88.78, 88.62. 88.09, 71.73, 70.50, 70.48, 70.46, 70.45, 70.42, 70.41, 70.40, 68.94, 68.88, 64.40, 64.17, 58.78, -0.36; FAB-MS (MNBA, 3 kV) *m/z* = 1525.6 (calcd 1526. for $C_{83}H_{101}O_{25}Si^+$).

Pentamer Acetylene 14. Pentamer TMSacetylene **13** (1.9 g, 1.3 mmol) was dissolved in 40 mL of THF and 2 mL of TBAF (1 M in THF) was added. The reaction mixture was stirred for 1 min and was subsequently filtered through a short plug of silica gel. The solvent was removed and the crude mixture was purified by column chromatography (acetone:chloroform

= 1:1) to give 1.3 g of a yellow viscous oil as product (68% yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.17-8.15 (dd, *J* = 1.7, 1.3 Hz, 1 H, Ar-H), 8.12-8.10 (m, 6 H, Ar-H), 8.08-8.07 (dd, *J* = 1.7, 1.6 Hz, 1 H, Ar-H), 8.03 (dd, *J* = 1.7, 1.6 Hz, 1 H, Ar-H), 7.98-7.96 (dt, *J* = 1.4, 7.8 Hz, 1 H, Ar-H), 7.83-7.80 (m, 3 H, Ar-H), 7.75-7.74 (t, *J* = 1.6, 1H, Ar-H), 7.66-7.64 (dt, *J* = 1.4, 7.8 Hz, 1 H, Ar-H), 7.40-7.37 (t, *J* = 7.8 Hz, 1H) 4.47-4.41 (m, 10 H, CO_2-CH_2), 3.80-3.76 (m, 10 H, O-CH_2), 3.66-3.56 (m, 30 H, O-CH_2), 3.46-3.43 (m, 10 H, O-CH_2), 3.27 (s, 3 H, O-CH_3), 3.26 (s, 9 H, O-CH_3), 3.26 (s, 3 H, O-CH_3), 3.14 (s, 1H, CCH); ^{13}C NMR (500 MHz, $CDCl_3$); δ = 164.90, 164.88, 164.84, 138.81, 138.34, 138.31, 135.77, 133.10, 132.81, 132.78, 132.68, 132.47, 131.04, 130.98, 130.91, 130.53, 129.77, 128.51, 123.85, 123.56, 123.53, 123.51, 123.45, 123.39, 123.07, 122.93, 89.91, 88.97, 88.94, 88.90, 88.88, 88.86, 88.19, 81.56, 78.99, 71.85, 70.62, 70.61, 70.57, 70.57, 70.55, 70.54, 7.52, 70.52, 69.06, 68.99, 68.98, 64.52, 64.50, 64.29, 58.90, 24.76; (MALDI)-TOF MS (*trans*-indole acrylic acid matrix): *m/z* = 1475.63 (calcd 1475.59 for $C_{80}H_{92}O_{25}$+Na^+).

Methyl (2*S*)-(benzyloxy)propanoate 15.[5] Methyl (*S*)-lactate (9.1 mL, 95 mmol) and benzylbromide (17 mL, 142.5 mmol) were dissolved in 55 mL of anhydrous diethyl ether and silver oxide (22 g, 95 mmol) were added stepwise in 8 small portions. The reaction mixture was heated to reflux over night, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (hexane:ethyl acetate = 19:1) to provide 12.7 g of product as colorless liquid (69% yield). $[\alpha]_D^{23}$ = -86° (c = 1.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.26 (m, 5H, Ar-H), 4.68 (d, *J* = 11.8 Hz, 1H, Ar-CH), 4.44 (d, *J* = 11.8 Hz, 1H, Ar-CH), 4.05 (q, *J* = 6.6 Hz, 1H, C-CH), 3.73 (s, 3H, CO_2-CH_3), 1.42 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.60, 137.57, 128.35, 127.87, 127.77, 73.99, 71.97, 51.77, 18.60.

(2*S*)-(Benzyloxy)propan-1-ol 16. $LiBH_4$ (95%; 1.50 g, 61.5 mmol, 1.03 equiv.) was suspended in 100 mL of dry THF and methyl (2*S*)-(benzyloxy)propanoate (11.65 g, 60 mmol) was added slowly within 1 h at -17 °C (salt/ice cooling). After stirring at -12 °C for 2 h, the mixture was allowed to warm to room temperature and stirred over night. Ice-cold water (25 mL) was added and the aqueous layer was extracted four times with 50 mL diethyl ether. The organic phases were combined and washed twice with sat. aq. $NaHCO_3$ solution, aq. NH_4Cl solution, and brine. Drying over $MgSO_4$ and solvent removal under reduced pressure gave 9.58 g product as a light yellow liquid (96% yield). $[\alpha]_D^{23}$ = +45.0° (c = 3.02, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.35-7.25 (m, 5 H, Ar-H), 4.64 (d, *J* = 11.8 Hz, 1H, Ar-CH), 4.47 (d, *J* = 11.8 Hz, 1H, Ar-CH), 3.75-3.44 (q, 3H, C-CH_3), 2.15 (s, 1H, OH), 1.16 (d, *J* =

6.7 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.52, 128.43, 127.68, 75.54, 70.81, 66.36, 15.86.

(2*S*)-(Benzyloxy)-4,7,10,13-tetraoxatetradecane 17.[6] NaH (95%; 1.8 g, 68.6 mmol) was suspended in 45 mL of dry DMF at 0 °C and a solution of (S)-(benzyloxy)propan-1-ol (9.51 g, 57.2 mmol) in 10 mL of dry DMF was added dropwise over 20 min. The mixture was stirred at room temperature for 30 min and a solution of 3,6,9-trioxadec-1-yl tosylate (TgOTs; 20.94 g, 65.7 mmol) in 15 mL of anhydrous DMF was added within 20 min. The mixture was stirred over night at room temperature then quenched with 15 mL of aqueous ice/NH_4Cl solution. The aqueous mixture was extracted four times with 20 mL ethyl acetate. The combined organic phases were washed twice with a sat. aq. NH_4Cl solution and brine, dried over $MgSO_4$ and concentrated to give a yellow oil, which was purified by vacuum distillation (product fraction distilled at 150-160 °C). This fraction was further purified by column chromatography (hexane:ethyl acetate = 1:2) to provide 15.9 g of a colorless liquid (89% yield). $[\alpha]_D^{23}$ = +1.5° (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35-7.22 (m, 5 H, Ar-H), 4.59 (s, 2 H, Ar-CH_2), 3.74-3.68 (m, 1 H, CH), 3.66-3.59 (m, 10 H, 5 O-CH_2), 3.56-3.42 (m, 4 H, 2 O-CH_2), 3.35 (s, 3 H, OCH_3), 1.17 (d, *J* = 6.3 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.88, 128.19, 127.50, 127.30, 75.33, 73.84, 71.85, 71.00, 70.72, 70.55, 70.54, 70.43, 58.91, 17.13; MS (EI, 80eV): *m/z* = 313.2025 (calc. 313.2015 for $[C_{17}H_{29}O_5]^+$, 206.1526 (calc. 206.1518 for $[C_{10}H_{22}O_4]^+$, 206.1162 (calc. 206.1154 for $[C_9H_{18}O_5]^+$); anal. C: 63.99 H: 8.97 (calc. C: 65.36 H: 9.03); HPLC (80% MeOH / 20% H_2O, 1 mL/min): 97.37% peak area.

(2*S*)-4,7,10,13-Tetraoxatetradecan-2-ol 18. (2*S*)-(Benzyloxy)-4,7,10,13-tetraoxatetradecane **17** (13.31 g, 42.6 mmol) was dissolved in 150 mL of ethanol, Pd/C (10 wt% Pd, 1.3 g) was added under nitrogen atmosphere, and the reaction mixture was constantly shaken under a 1.5 bar hydrogen atmosphere over night. The black suspension was filtered through celite and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to give 9.4 g of the product as a colorless liquid (99% yield). $[\alpha]_D^{23}$ = +16.4° (c = 1.65, $CHCl_3$); (Mosher Ester:[7] >98% ee ^{19}F NMR, Figure 12); ^1H NMR (500 MHz, $CDCl_3$): δ = 3.93-3.91 (m, 1 H, CH), 3.65-3.59 (m, 10 H, 5 O-CH_2), 3.51-3.49 (m, 2 H, O-CH_2), 3.46 (dd, *J* = 3, 9.9 Hz, 1 H, O-CH_2), 3.34 (s, 3 H, O-CH_3), 3.23 (dd, *J* = 8.4, 9.9 Hz, 1 H, O-CH_2), 2.88 (s, 1 H, OH), 1.08 (d, *J* = 6.4 Hz, 3H, C-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 76.93, 71.86, 70.52, 70.51, 70.49, 70.48, 70.46, 70.45, 66.18, 58.93, 18.40; MS (EI, 80eV): *m/z* = 178.1221 (calc. 178.1205 for $[C_8H_{18}O_4]^+$; anal. C: 53.13 H: 9.57 (calc.

C: 54.03 H: 9.98); GC (13 m DB-Wax, G/249, t_R = 17.7 min): 98.5 % peak area. Chiral GC (t_R = ~ 26 min): >99% ee (Figure 13).

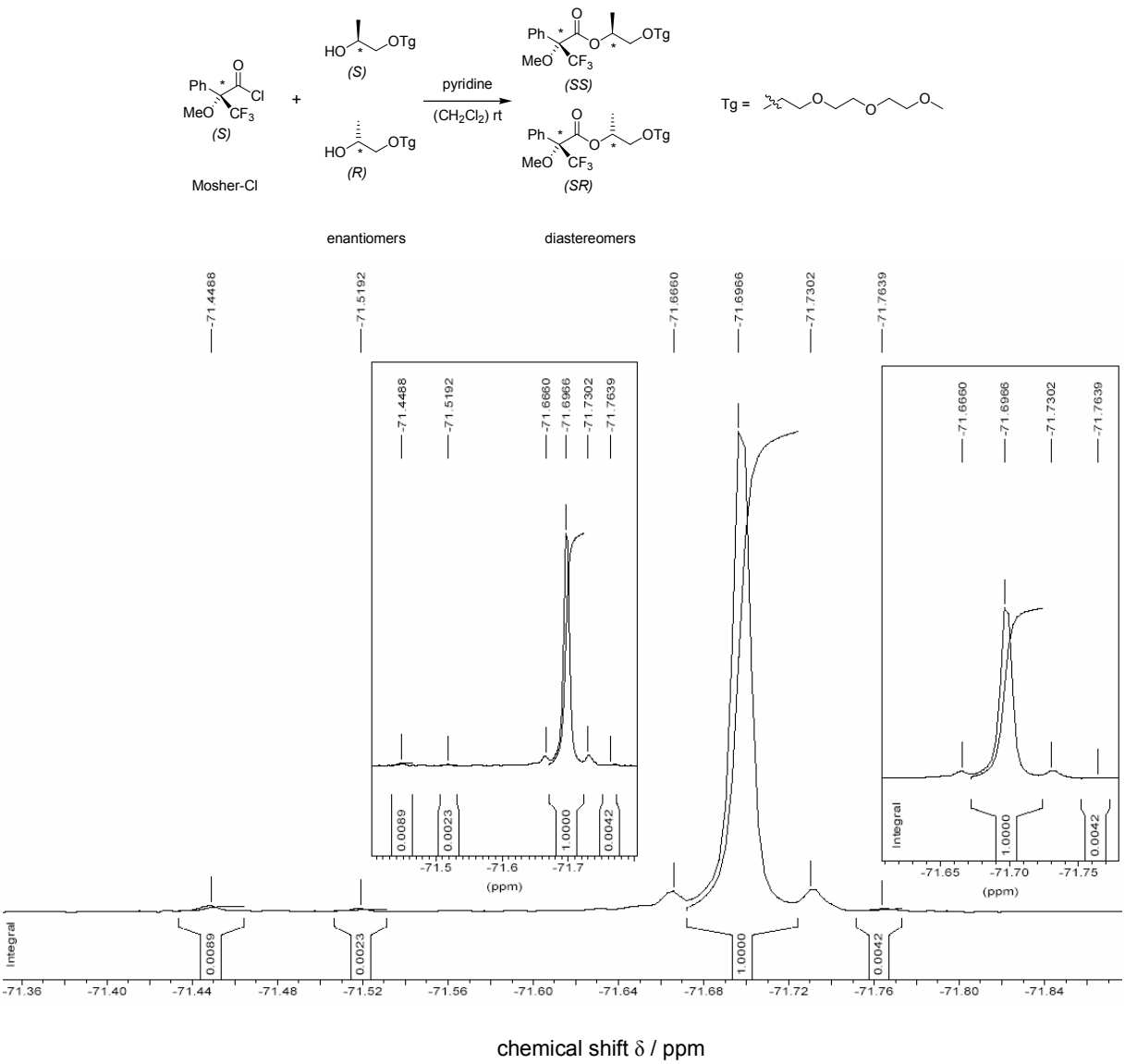

Figure 12. Synthesis of the corresponding Mosher Ester[7] of chiral alcohol **18** and ^{19}F-NMR spectrum, from which the enantiomeric purity can be deduced to be >98% ee.

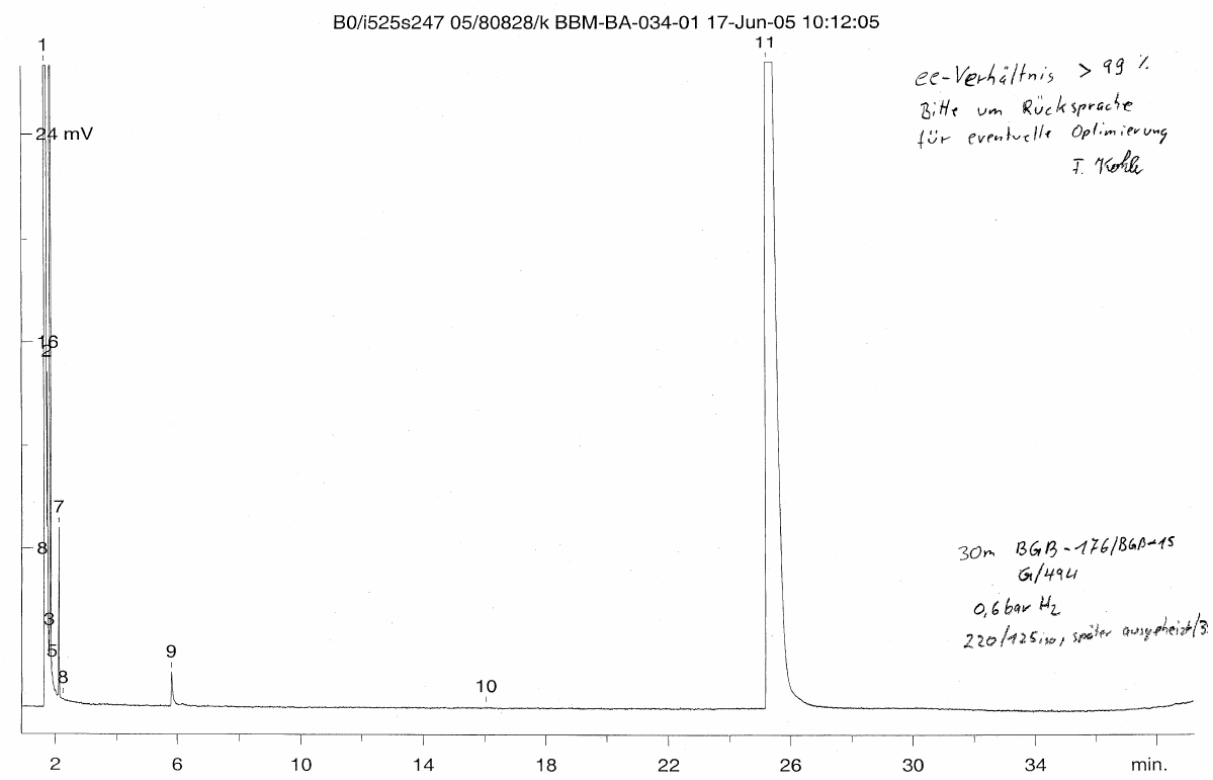

Figure 13. GC trace of chiral alcohol **18** using a chiral stationary phase provides direct method for estimating the enantiomeric purity to be >99% ee.

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