Nonsteroidal Bivalent Estrogen Ligands - An Application of the Bivalent Concept to the Estrogen Receptor

Supporting Information

Min Shan,[†] Kathryn E. Carlson,[‡] Alexander Bujotzek,[§] Anja Wellner,[□] Ronald Gust,[□] Marcus Weber,[§] John A. Katzenellenbogen,[‡] Rainer Haag[*,†]

[†]Institut für Chemie und Biochemie, Freie Universität Berlin, Takustrasse 3, 14195 Berlin, Germany

[‡]Department of Chemistry, University of Illinois at Urbana-Champaign, 600 S. Mathews Ave., Urbana, IL 61801, United States

[§]Zuse Institut Berlin, Takustrasse 7, 14195 Berlin, Germany

[□]Institute of Pharmacy, Department of Pharmaceutical Chemistry, University of Innsbruck, Innrain 80/82, A-6020 Innsbruck, Austria

* Correspondence should be addressed to haag@chemie.fu-berlin.de; Tel.: +49-30-838-52633; Fax: +49-30-838-53357.

Table of contents:

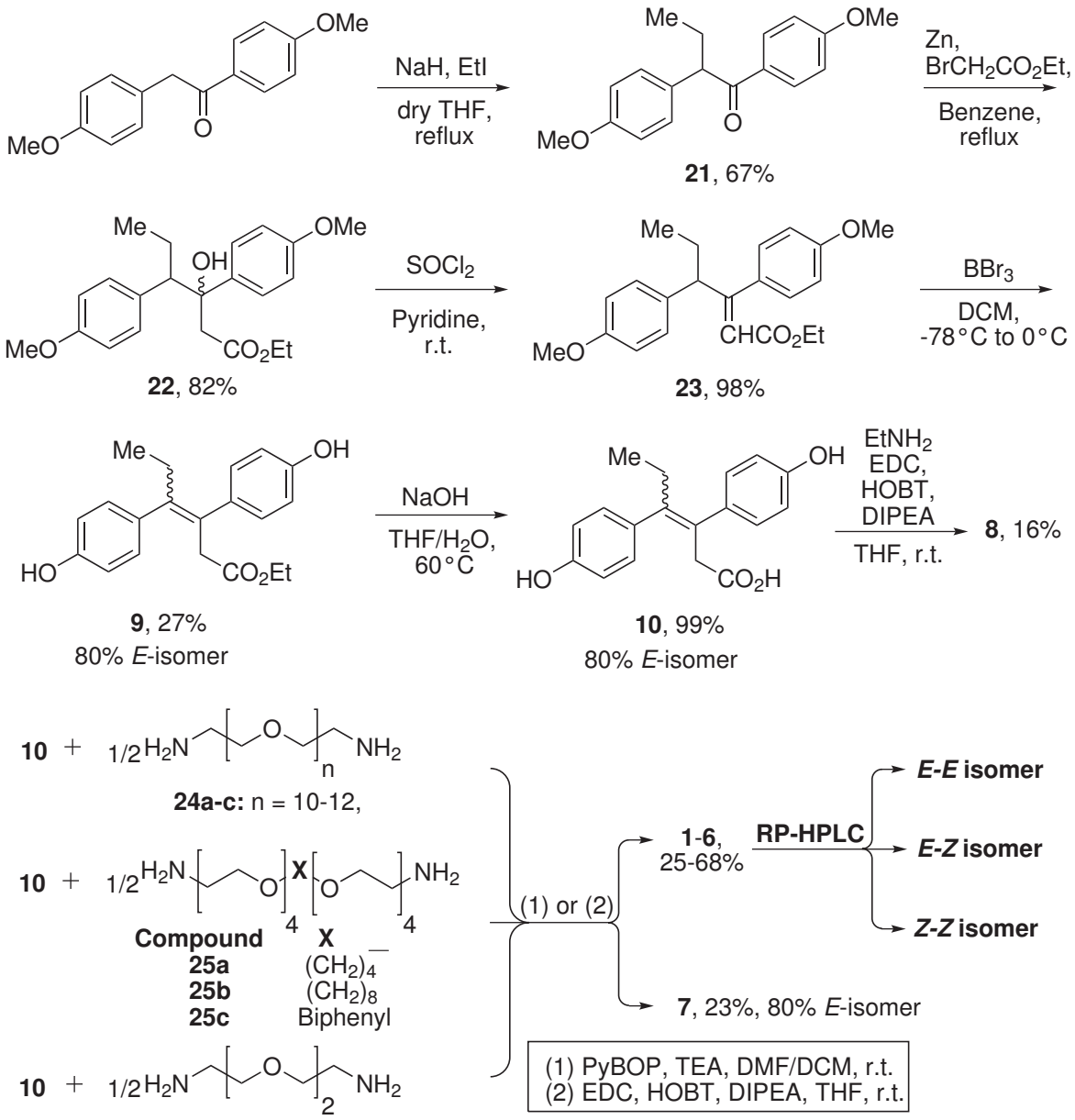
1. General information of chemical methods

All chemical were purchased from Sigma-Aldrich, Arcos, and AlfaAesar, and were used without further purification. Anhydrous solvents were obtained from an anhydrous solvent purification system. For all anhydrous reactions, glassware was oven-dried overnight and cooled under vacuum, then purged with argon; all such reactions were conducted under argon. ^{1}H, ^{13}C, COSY, HMBC, HMQC, NOE, and NOESY NMR spectra were recorded either on a Bruker AC250 spectrometer or a Joel EXC400 spectrometer or a Joel ECP500 spectrometer or a Bruker Avance III 700 spectrometer with probe temperatures of 25°C. ^{1}H NMR chemical shifts are reported in ppm relative to the residual proton signal of the NMR solvent and coupling constants (*J*) are given in hertz (Hz). ^{13}C chemical shifts are reported in ppm relative to the carbon signal of the NMR solvent. Thin layer chromatography (TLC) plates (Merck F254 silica gel on aluminum plates) were visualized by using 1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH in 200 mL water and UV light (254 nm). High resolution mass spectra were obtained on an Agilent 6210 ESI-TOF spectrometer. The analytic geometrical investigation was performed by an analytic HPLC (Nucleosil 50-5, 4×250 mm). The geometrical separation of *E*- and *Z*-isomers was performed either by a HPLC (Nucleosil 50-5, 32×238 mm) or by a RP-HPLC (Gemini 5µ C18 110 Å, 250×21.20 mm, 5 micron).

2. General synthetic route of mono- and bivalent ligands **1**–**20**

2.1. DES-based ligand **1**–**10**

According to the previously reported procedure,[1] a mixture of *E*- and *Z*-isomers of the unsaturated ester **23** was obtained in three steps, an alkylation, a Reformatsky reaction, and an elimination, all of which proceeded in satisfactory yields (Scheme S1). During the deprotection of the methyl ether of **23** with boron tribromide, migration of the double bond occurred spontaneously to form the stilbene ester **9** in 27% yield, as a *E*:*Z* = 4:1 isomer mixture, determined by HPLC (2% MeOH/DCM) and a NOESY experiment. Subsequently, hydrolysis of the stilbene ester isomer mixture **12** with aqueous sodium hydroxide gave the desired carboxylic acid **10** in quantitative yield, as a *E*:*Z* = 4:1 mixture of isomers. Meanwhile, the OEG spacer diols of varying lengths were prepared, based on an ABA or AB pattern,[27] and subsequent conversion of the OEG diols to OEG diamine derivatives **24** and **25** was readily achieved in satisfactory yields (see the Supporting Information). Finally, formation of the amide linker was carried out and gave mono- and bivalent DES ligands **1**–**7** in up to 70% yield. Afterwards, separation of geometric isomers by RP-HPLC (70% MeOH/H_2O) was performed to obtain the desired *E*-*E* isomer of each bivalent DES ligand (Pure *E*-*E* isomer of **1**–**6**, 60% *E*-*E* isomer of **7**, and 80% *E*-isomer of **8**–**10**) for biological evaluation.



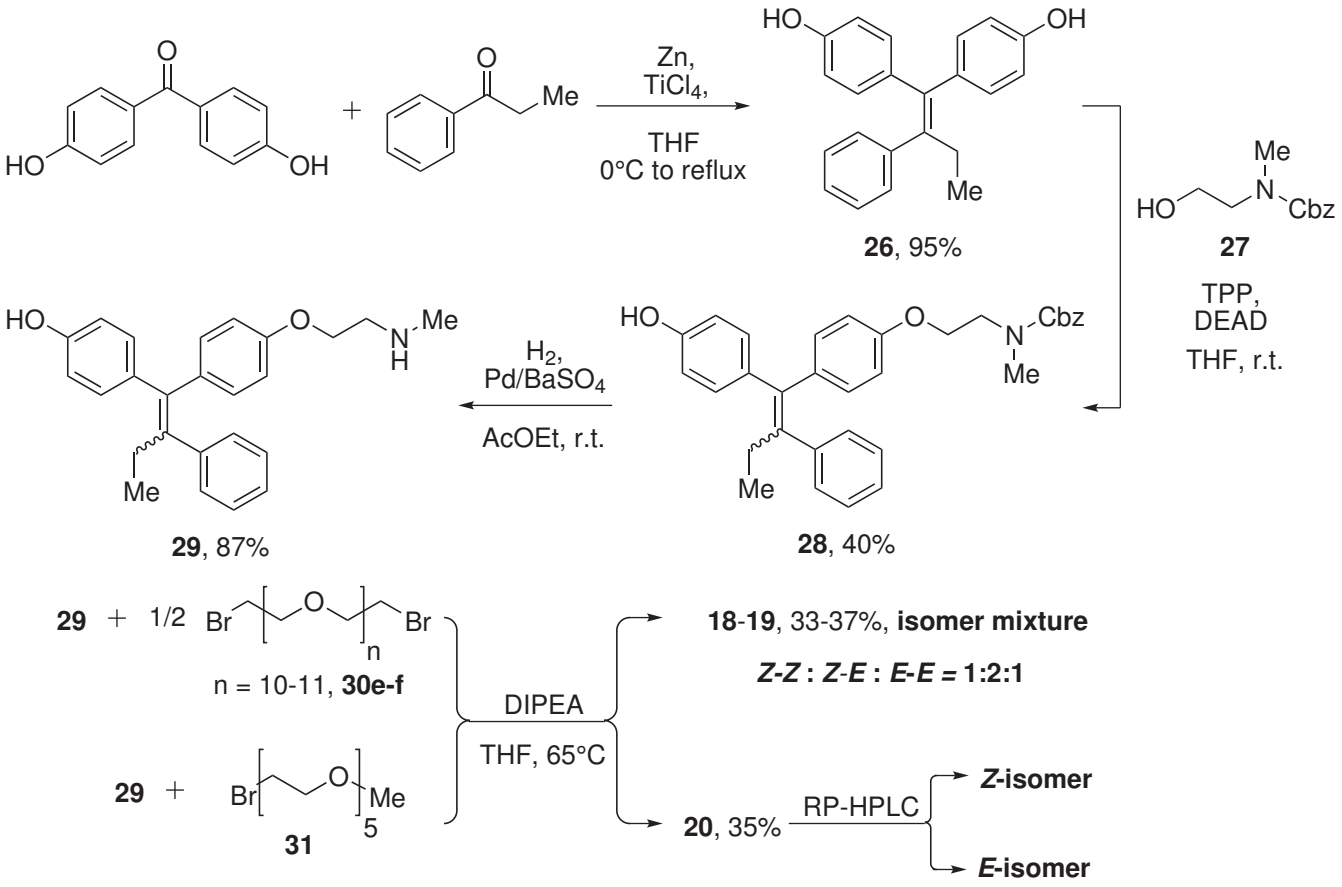
Scheme S1. The synthesis of chemical precursor **10** (top), mono- and bivalent DES ligands **1**–**8** (bottom).

2.2. OHT-based ligand **11**–**20**

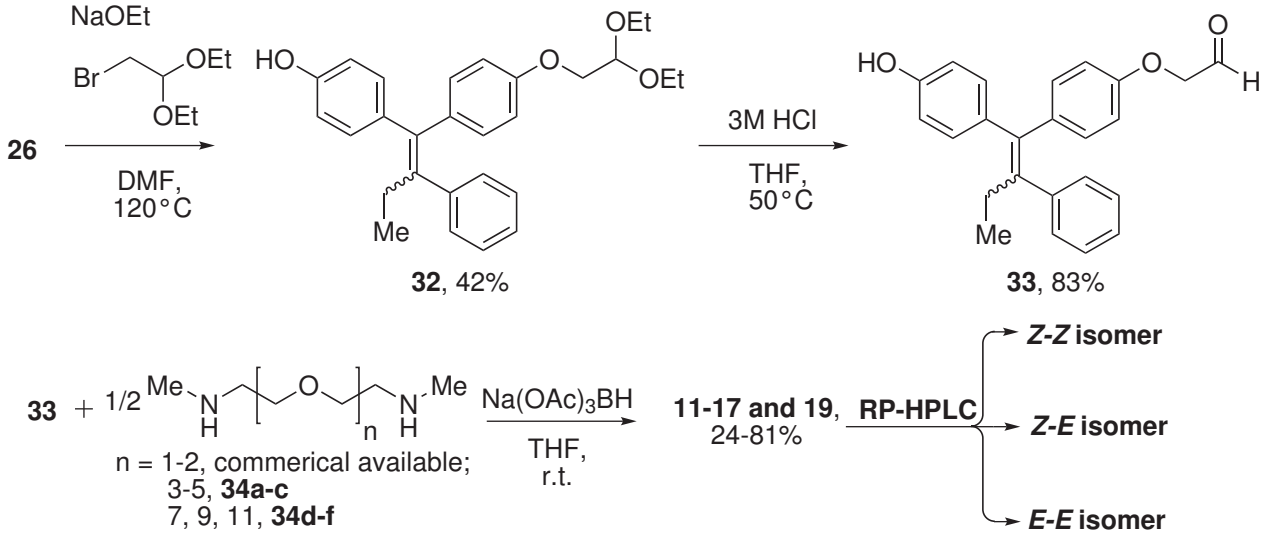
The triarylethylene structure of **26** can be obtained in a straightforward manner by the McMurry reaction between 4,4'-dihydroxybenzophenone and propiophenone with low-valent titanium in 95% yield.[2-4] Subsequently, a Mitsunobu reaction between one phenol group of **26** and benzyl carbamate-protected 2-(methylamino) ethanol **27** in the presence of triphenylphosphine and diethyl azodicarboxylate gave benzyl carbamate-protected endoxifen **28** as a mixture of *E*:*Z* = 1:1 isomers in 40% yield.[5] Under mild hydrogenation conditions, endoxifen **29** was obtained as a mixture of *E*:*Z* = 1:1 isomers with a yield of 82% (Scheme S2). Meanwhile, a modification of OEG diols to OEG dibromide derivatives **30** proceeded in satisfactory yields (see the Supporting Information). Additionally, although the geometrical isomers of **29** could be separated by a RP-HPLC (75% MeOH/H_2O + 0.05% TFA),[6] the isomerization of *Z*-isomer of **29** to *E*-isomer took place spontaneously during the subsequent nucleophilic substitution. Therefore, bivalent ligands **18** and **19** were prepared based on both isomers of **29** in yields of 33 and 37%, respectively.[7] Furthermore, a similar synthetic pathway was carried out to obtain the monovalent ligand **20** as a mixture of *E*:*Z* = 1:1 isomers 35% yield. Initially, an isomer separation by RP-HPLC (75% MeOH/H_2O + 50mM NH_4OH) was not successful for bivalent ligands **18** and **19**, but succeeded with monovalent ligand **20**.

In order to obtain sufficient material for the ER-binding assays, a novel synthetic pathway was developed (Scheme S3) in which a nucleophilic substitution between dihydroxy triarylethylene **26** and bromoacetaldehyde diethyl acetal was performed to give the diethyl acetal **32** 42% yield, as a mixture of *E*:*Z* = 1:1 isomers according to geometrical isomer analysis by RP-HPLC (85%MeOH/H_2O) and an NOE experiment. After acid-catalyzed hydrolysis, the aldehyde **33** was obtained in 83% yield. Meanwhile, OEG dibromide derivatives **30** were converted into bis(N-methylamine) OEG spacers **34**. Finally, both isomers of **33** were subjected to reductive amination with **34** to obtain bivalent OHT ligands **16**-**22** and **24** in 40–80% yields.[8] Fortunately, geometrical isomer separations with RP-HPLC (82% MeOH/H_2O + 0.4% diethylamine) were successful and gave *Z*-*Z*, *Z*-*E*, and *E*-*E* isomers for each bivalent ligand. To ensure the purity of these isomers, reexamination by analytic RP-HPLC was

performed for *Z*-*Z* isomers after 48 hours in the aqueous solution at room temperature, and it was found that only less than 3% the *Z*-*Z* isomer undergoes conversion to the *Z*-*E* isomer, with no *E*-*E* isomer being observed. In addition, the stereochemistry of these OHT ligands was characterized by ^{1}H-NMR experiments and was consistent with previous reports on the chemical shift of the triarylethylene structure.[2-4]



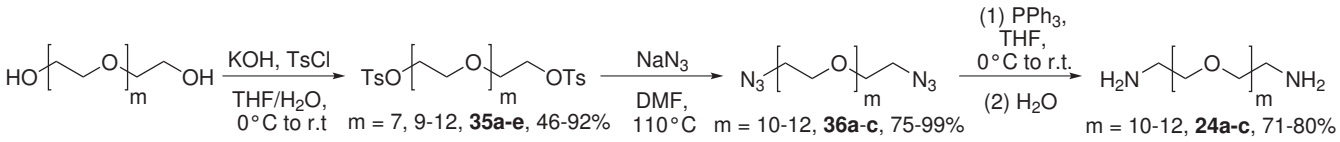
Scheme S2. The chemical preparation of endoxifen **29** (top) and mono- and bivalent OHT ligands **18**, **19**, and **20** via a nucleophilic substitution (bottom).



Scheme S3. The chemical preparation of the aldehyde **33** and bivalent OHT ligands (**11**–**17** and **19**) via a reductive amination.

3. Chemical preparation oligoethylene glycol (OEG) spacer **24**, **25**, **30**, **31**, and **34**

3.1. Chemical preparation of OGE diamine **24a-c**



Scheme S4. Chemical preparation of **24a-c**.

3.1.1. General procedure for chemical preparations of ditosylate **35**, **37**, **40**, and **45**

To a solution of the diol (1.0 equivalent) in THF, 4-methylbenzene sulfonyl chloride (3.0 equivalents) was added at room temperature and then cooled to 0°C. To this mixture, potassium hydroxide (6.6 equivalents) in H_2O (0.9 g/mL) was added dropwise over 1 h. Then the reaction mixture was kept at 0°C for 30 min and some white precipitation appeared. Afterwards this mixture was further stirred at room temperature until TLC analysis indicated complete consumption of the diol. The reaction mixture was neutralized with a saturated ammonium chloride solution and concentrated in vacuo. The residue was absorbed on the silica gel and further purified by column chromatography to obtain the pure ditosylate.

3.1.2. Chemical preparation of **35a**

Octaethylene glycol[9] (217 mg, 0.590 mmol), 4-methylbenzene sulfonyl chloride (339 mg, 1.76 mmol), potassium hydroxide (217 mg, 3.87 mmol), 5 mL THF, and 0.20 mL H_2O were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the ditosylate **35a** as a light yellow oil (184 mg, 46%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.4 Hz, Ar-*H*), 7.34 (4H, d, J = 8.0 Hz, Ar-*H*), 4.17-4.14 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.66 (4H, m, $OCH_2CH_2OSO_2$), 3.65-3.60 (16H, m, OCH_2CH_2O), 3.58 (8H, br s, OCH_2CH_2O), 2.45 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 70.9, 70.7, 70.6, 69.4, 68.8, 21.8.

HRMS (ESI-TOF, positive): $[C_{30}H_{46}O_{13}S_2Na]^+$ cal. 701.2272, found 701.2250; $[C_{30}H_{46}O_{13}S_2K]^+$ cal. 717.2011, found 717.1992.

3.1.3. Chemical preparation of **35b**

Decaethylene glycol[9] (175 mg, 0.380 mmol), 4-methylbenzene sulfonyl chloride (221 mg, 1.15 mmol), potassium hydroxide (142 mg, 2.52 mmol), 5 mL THF, and 0.14 mL H_2O were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the ditosylate **35b** as a light yellow oil (211 mg, 73%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.3 Hz, Ar-*H*), 7.34 (4H, d, J = 8.0 Hz, Ar-*H*), 4.17-4.14 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.66 (4H, m, $OCH_2CH_2OSO_2$), 3.66-3.60 (24H, m, OCH_2CH_2O), 3.58 (8H, br s, OCH_2CH_2O), 2.45 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 71.1, 71.0, 70.9, 69.6, 69.1, 22.0.

HRMS (ESI-TOF, positive): $[C_{34}H_{54}O_{15}S_2Na]^+$ cal. 789.2796, found 789.2772; $[C_{34}H_{54}O_{15}S_2K]^+$ cal. 805.2536, found 805.2511.

3.1.4. Chemical preparation of **35c**

Undecaethylene glycol[9] (246 mg, 0.490 mmol), 4-methylbenzene sulfonyl chloride (278 mg, 1.45 mmol), potassium hydroxide (179 mg, 3.19 mmol), 10 mL THF, and 0.20 mL H_2O were used and the crude product was purified by column chromatography (DCM : MeOH = 10 : 1) to give the ditosylate **35c** as a light yellow oil (380 mg, 98%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.4 Hz, Ar-*H*), 7.34 (4H, d, J = 8.1 Hz, Ar-*H*), 4.17-4.15 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.67 (4H, m, $OCH_2CH_2OSO_2$), 3.65-3.61 (28H, m, OCH_2CH_2O), 3.58 (8H, br s, OCH_2CH_2O), 2.45 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 70.9, 70.8, 70.7, 69.4, 68.9, 21.8.

3.1.5. Chemical preparation of **35d**

Dodecaethylene glycol[9] (302 mg, 0.552 mmol), 4-methylbenzene sulfonyl chloride (319 mg, 1.66 mmol), potassium hydroxide (205 mg, 3.65 mmol), 13 mL THF, and 0.23 mL H_2O were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1 to 15 : 1) to give the ditosylate **35d** as a light yellow oil (434 mg, 92%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.2 Hz, Ar-*H*), 7.34 (4H, d, J = 8.0 Hz, Ar-*H*), 4.17-4.15 (4H, m, $OCH_2CH_2OSO_2$), 3.72-3.55 (44H, m, $OCH_2CH_2OSO_2$ and OCH_2CH_2), 2.45 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 70.9, 70.7, 69.4, 68.9, 21.8.

HRMS (ESI-TOF, positive): $[C_{38}H_{62}S_2O_{17}Na]^+$ cal. 877.3321, found 877.3277; $[C_{38}H_{62}S_2O_{17}K]^+$ cal. 893.3060, found 893.3016.

3.1.6. Chemical preparation of **35e**

Tridecaethylene glycol[9] (1.29 g, 2.19 mmol), 4-methylbenzene sulfonyl chloride (0.92 g, 4.82 mmol), potassium hydroxide (490 mg, 8.76 mmol), 15 mL THF, and 1.0 mL H_2O were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1) to give the ditosylate **35e** as a light yellow oil (1.76 g, 90%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.4 Hz, Ar-*H*), 7.34 (4H, d, J = 8.0 Hz, Ar-*H*), 4.17-4.15 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.57 (48H, m, $OCH_2CH_2OSO_2$ and OCH_2CH_2), 2.45 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 71.0, 70.8, 69.5, 68.9, 21.9.

3.1.7. General procedure for chemical preparations of diazide **36**, **41**, and **46**

To a solution of the ditosylate (1.0 equivalent) in anhydrous DMF, sodium azide (3.0 equivalents) was added at room temperature and then this mixture was stirred and heated up to 110°C for 12 h until TLC analysis indicated complete consumption of the ditosylate. The solvent was removed in vacuo and the residue was absorbed on the silica gel and further purified by column chromatography to obtain the pure diazide.

Chemical preparation of **36a**

Ditosylate **35c** (177 mg, 0.218 mmol), sodium azide (43.0 mg, 0.654 mmol), and 10 mL anhydrous DMF were used and the crude product was purified by column chromatography (DCM : MeOH = 10 : 1) to give the diazide **36a** as a light yellow oil (122 mg, 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.72-3.60 (40H, m, OCH_2CH_2O), 3.39 (4H, t, J = 5.1 Hz, N_3OCH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 70.9, 70.8, 70.7, 70.2, 50.8.

3.1.8. Chemical preparation of **36b**

Ditosylate **35d** (195 mg, 0.228 mmol), sodium azide (45.0 mg, 0.685 mmol), and 6 mL anhydrous DMF were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1) to give the diazide **36b** as a light yellow oil (103 mg, 75%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.70-3.61 (44H, m, OCH_2CH_2O), 3.39 (4H, t, J = 5.2 Hz, N_3OCH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 70.9, 70.8, 70.3, 50.9.

3.1.9. Chemical preparation of **36c**

Ditosylate **35e** (500 mg, 0.556 mmol), sodium azide (108 mg, 1.67 mmol), and 10 mL anhydrous DMF were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1) to give the diazide **36c** as a light yellow oil (352 mg, 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.68-3.61 (48H, m, OCH_2CH_2O), 3.36 (4H, t, J = 5.2 Hz, N_3OCH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 70.9, 70.8, 70.7, 70.2, 50.9.

3.1.10. General procedure for chemical preparations of diamine OEG **14** and **15**

To a solution of diazide (1.0 equivalent) in anhydrous THF, triphenylphosphine (2.1 equivalents) was added at 0°C and then the reaction mixture was stirred at room temperature for 10 h. Afterwards 0.05 mL water was added to hydrolyze the iminophosphoranes and the mixture was stirred at room temperature until TLC analysis indicated complete consumption of the diazide. The solvent was removed and the residue was absorbed on the silica gel and further purified by column chromatography to obtain the pure diamine.

3.1.11. Chemical preparation of **24a**:

Diazide **36a** (121 mg, 0.219 mmol), triphenylphosphine (122 mg, 0.459 mmol), and 10 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the diamine **24a** as a light yellow oil (78.6 mg, 71%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.67-3.60 (36H, m, OCH_2CH_2O), 3.52 (4H, t, J = 5.1 Hz, H_2NOCH$_2$CH_2), 2.87 (4H, br s, H_2NOCH_2CH$_2$), 1.67 (4H, br s, H_2NOCH$_2$CH$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 73.5, 70.7, 70.5, 42.0.

HRMS (ESI-TOF, positive): $[C_{22}H_{49}N_2O_{10}]^+$ cal. 501.3382, found 501.3398.

3.1.12. Chemical preparation of **24b**:

Diazide **36b** (97.8 mg, 0.164 mmol), triphenylphosphine (95.5 mg, 0.361 mmol), and 20 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the diamine **24b** as a light yellow oil (62.5 mg, 72%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.68-3.61 (40H, m, OCH_2CH_2O), 3.53 (4H, t, J = 5.2 Hz, H_2NOCH$_2$CH_2), 2.89 (4H, t, J = 5.0 Hz, H_2NOCH_2CH$_2$), 1.99 (4H, br s, H_2NOCH$_2$CH$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 73.3, 70.7, 70.5, 41.9.

HRMS (ESI-TOF, positive): $[C_{24}H_{53}N_2O_{11}]^+$ cal. 545.3644, found 545.3629.

3.1.13. Chemical preparation of **24c**:

Diazide **36c** (199 mg, 0.311 mmol), triphenylphosphine (180 mg, 0.685 mmol), and 20 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the diamine **24c** as a light yellow oil (146 mg, 80%).

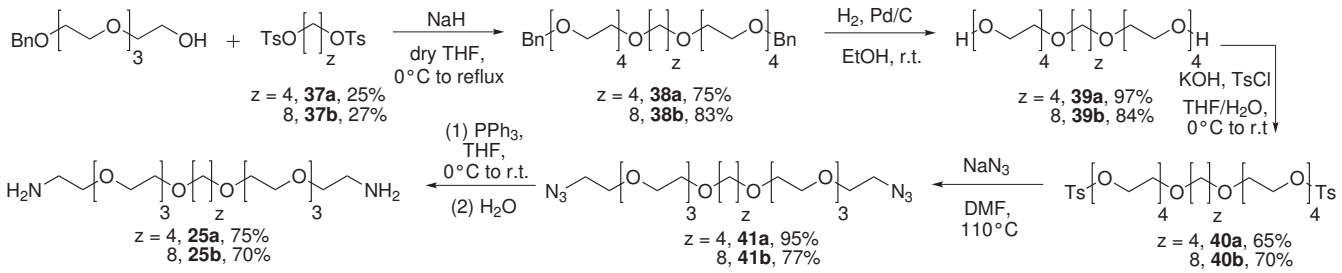
^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.70-3.61 (44H, m, OCH_2CH_2O), 3.52 (4H, t, J = 5.2 Hz, H_2NOCH$_2$CH_2), 2.87 (4H, t, J = 5.0 Hz, H_2NOCH_2CH$_2$), 1.72 (4H, br s, H_2NOCH$_2$CH$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 73.5, 70.8, 70.5, 42.0.

HRMS (ESI-TOF, positive): $[C_{26}H_{57}N_2O_{12}]^+$ cal. 589.3906, found 589.3954.

3.2. Chemical preparation of hybrid OEG **25**

3.2.1. Chemical preparation of hybrid OEG **25a-b**



Scheme S5. Chemical preparation of **25a** and **25b**.

3.2.1.1. Chemical preparation of **37a**

1,4-butandiol (5.00 mL, 55.2 mmol), 4-methylbenzene sulfonyl chloride (31.9 g, 165 mol), potassium hydroxide (20.4 g, 364 mmol), 70 mL THF, and 20 mL H_2O were used and the crude product was purified two times recrystallization in $CHCl_3$ to give the ditosylate **37a** as a light crystal (5.47 g, 25%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.75 (4H, d, J = 8.1 Hz, Ar-*H*), 7.35 (4H, d, J = 8.5 Hz, Ar-*H*), 3.99 (4H, t, J = 5.0 Hz, OC*H*$_2$CH$_2$), 2.46 (6H, s, C*H*$_3$), 1.70 (4H, p, J = 2.3 Hz, OCH$_2$C*H*$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 69.6, 25.2, 21.9.

3.2.1.2. Chemical preparation of **37b**

1,8-octanediol (7.08 g, 48.4 mmol), 4-methylbenzene sulfonyl chloride (28.0 g, 145 mol), potassium hydroxide (16.3 g, 291 mmol), 120 mL THF, and 16 mL H_2O were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the ditosylate **37b** as a light crystal (5.73 g, 27%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.78 (4H, d, J = 8.2 Hz, Ar-*H*), 7.35 (4H, d, J = 8.1 Hz, Ar-*H*), 4.00 (4H, t, J = 6.4 Hz, OC*H*$_2$CH$_2$), 2.45 (6H, s, C*H*$_3$), 1.61 (4H, p, J = 6.6 Hz, OCH$_2$C*H*$_2$CH$_2$), 1.30-1.17 (8H, m, C*H*$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 70.7, 28.8, 25.4, 21.8.

3.2.1.3. General procedure for preparation of dibenzylate **38a-b**

To a solution of 1-phenyl-2,5,8,11-tetraoxatridecan-13-ol[1] (2.05 equivalents) in anhydrous THF at 0°C, sodium hydride (2.5 equivalents) was added portionwise at 0°C and the reaction mixture was stirred for an additional 30 min. Afterwards the mixture was heated up to reflux for 1 h and then cooled to 0°C again. To this mixture, the ditosylate **37** (1.0 equivalent) in anhydrous THF was added dropwise though

a dropping funnel over 30 min. Then the mixture was heated up to reflux for 20 h. The mixture was cooled to 0°C and neutralized with a saturated ammonium chloride solution and concentrated in vacuo. The residue was absorbed on the silica gel and further purified by column chromatography to obtain the pure dibenzylate.

3.2.1.4. Chemical preparation of **38a**

1-phenyl-2,5,8,11-tetraoxatridecan-13-ol[9] (2.39 g, 8.39 mmol), sodium hydride (409 mg, 10.2 mmol), the ditosylate **37a** (1.63 g, 4.09 mmol), and 40 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the dibenzylate hybrid OEG **38a** as a colorless oil (1.91 g, 75%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.34-7.31 (8H, m, Ar-*H*), 7.29-7.26 (2H, m, Ar-*H*), 4.56 (4H, s, BnCH_2O), 3.72-3.55 (32H, m, OCH_2CH_2O), 3.45 (4H, m, CH_2), 1.63 (4H, m, CH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 138, 128, 73.3, 72.6, 71.2, 70.7, 70.4, 70.2, 69.5, 61.8, 26.4.

3.2.1.5. Chemical preparation of **38b**

1-phenyl-2,5,8,11-tetraoxatridecan-13-ol[9] (1.97 g, 6.92 mmol), sodium hydride (338 mg, 8.44 mmol), the ditosylate **37b** (1.54 g, 3.38 mmol), and 40 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the dibenzylate hybrid OEG **38b** as a colorless oil (1.91 g, 83%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.34-7.26 (2H, m, Ar-*H*), 4.56 (4H, s, BnCH_2O), 3.68- 3.54 (32H, m, OCH_2CH_2O), 3.43 (4H, t, J = 6.8 Hz, CH_2), 1.56 (4H, p, J = 6.7 Hz, CH_2), 1.35- 1.25 (8H, m, CH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 138, 128, 73.2, 71.5, 70.7, 70.6, 70.1, 69.4, 29.6, 29.4, 26.0.

3.2.1.6. General procedure for preparation of hybrid OEG **39a**-**b**:

To a solution of the dibenzylated **38** (1.0 equivalent) in EtOH, palladium on carbon (0.1 equivalent) was added and the reaction mixture was hydrogenated under 1.0 bar H_2 and stirred at room temperature until TLC analysis indicated complete consumption of the dibenzylate. Afterwards the mixture was filtered

over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the pure diol **39** was obtained without any further purification.

3.2.1.7. Chemical preparation of **39a**

The dibenzylated **38a** (1.86 g, 2.98 mmol), palladium on carbon (317 mg, 0.298 mmol), and 20 mL EtOH were used and the diol **39a** as a colorless oil (1.27 g, 97%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.71-3.58 (32H, m, OCH_2CH_2), 3.47 (4H, br s, HOCH_2CH_2), 2.97 (2H, br s, OH), 1.64 (4H, br s, $OCH_2CH_2CH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 73.1, 72.7, 71.3, 70.7, 70.5, 70.2, 70.1, 61.8, 61.7, 26.4.

3.2.1.8. Chemical preparation of **39b**

The dibenzylated **38b** (1.88 g, 2.77 mmol), palladium on carbon (295 mg, 0.277 mmol), and 20 mL EtOH were used and the diol **39b** as a colorless oil (1.15 g, 84%).

^{1}H-NMR (DMSO-d6, 400 MHz) δ (ppm) = 4.58-4.56 (2H, t, J = 5.3 Hz, OH), 3.51-3.34 (36H, m, OCH_2CH_2), 1.47 (4H, t, J = 6.4 Hz, $OCH_2CH_2CH_2CH_2$), 1.26 (8H, br s, $OCH_2CH_2CH_2CH_2$).

^{13}C-NMR (DMSO-d6, 100 MHz) δ (ppm) = 72.3, 70.3, 69.8, 69.5, 60.2, 29.2, 28.8, 25.6.

3.2.1.9. Chemical preparation of **40a**

Diol **39a** (656 mg, 1.48 mmol), 4-methylbenzene sulfonyl chloride (856 mg, 4.45 mmol), potassium hydroxide (549 mg, 9.78 mmol), 20 mL THF, and 0.5 mL H_2O were used and the crude product was purified by column chromatography (DCM : MeOH = 40 : 1) to give the ditosylate **40a** as a light yellow oil (718 mg, 65%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.2 Hz, Ar-H), 7.34 (4H, d, J = 8.0 Hz, Ar-H), 4.17-4.15 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.67 (4H, m, OCH_2CH_2OSO$_2$), 3.64-3.61 (12H, m, OCH_2CH_2), 3.59-5.54 (12H, m, OCH_2CH_2), 3.46 (4H, t, J = 5.3 Hz, OCH_2CH_2CH_2CH_2O), 2.45 (6H, s, CH_3), 1.63 (4H, p, J = 3.4 Hz, $OCH_2CH_2CH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 71.3, 70.9, 70.8, 70.7, 70.3, 69.4, 68.9, 26.5, 21.9.

3.2.1.10. Chemical preparation of **40b**

Diol **39b** (1.13 g, 2.27 mmol), 4-methylbenzene sulfonyl chloride (1.31 g, 6.82 mmol), potassium hydroxide (842 mg, 15.0 mmol), 10 mL THF, and 0.8 mL H_2O were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the ditosylate **40b** as a light yellow oil (1.29 g, 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.79 (4H, d, J = 8.2 Hz, Ar-*H*), 7.34 (4H, d, J = 8.1 Hz, Ar-*H*), 4.17-4.15 (4H, m, $OCH_2CH_2OSO_2$), 3.70-3.67 (4H, m, $OCH_2CH_2OSO_2$), 3.64-3.61 (12H, m, OCH_2CH_2), 3.58-5.55 (12H, m, OCH_2CH_2), 3.43 (4H, t, J = 6.7 Hz, $OCH_2CH_2CH_2CH_2$) 2.45 (6H, s, CH_3), 1.58-1.52 (4H, m, $OCH_2CH_2CH_2CH_2$), 1.29 (8H, br s, $OCH_2CH_2CH_2CH_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 71.7, 70.9, 70.8, 70.7, 70.2, 69.4, 68.9, 29.8, 29.6, 26.2, 21.8.

3.2.1.11. Chemical preparation of **41a**

Ditosylate **40a** (341 mg, 0.450 mmol), sodium azide (89.5 mg, 1.36 mmol), and 10 mL anhydrous DMF were used and the crude product was purified by column chromatography (DCM : MeOH = 40 : 1) to give the diazide **41a** as a light yellow oil (211 mg, 95%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.70-3.62 (24H, m, OCH_2CH_2O), 3.58-3.56 (4H, m, $N_3OCH_2CH_2$), 3.47 (4H, t, J = 5.3 Hz, $OCH_2CH_2CH_2CH_2O$), 3.39 (4H, t, J = 5.2, $N_3OCH_2CH_2$), 1.64 (4H, p, J = 2.6 Hz, $OCH_2CH_2CH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.3, 70.9, 70.8, 70.2, 50.9, 26.5.

3.2.1.12. Chemical preparation of **41b**

Ditosylate **40b** (367 mg, 0.450 mmol), sodium azide (89.5 mg, 1.36 mmol), and 15 mL anhydrous DMF were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the diazide **41b** as a light yellow oil (190 mg, 77%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.70-3.63 (24H, m, OCH_2CH_2O), 3.59-3.57 (4H, m, $N_3OCH_2CH_2$), 3.44 (4H, t, J = 6.8 Hz, $OCH_2CH_2CH_2CH_2$), 3.39 (4H, t, J = 5.1, $N_3OCH_2CH_2$), 1.57 (4H, t, J = 6.7 Hz, $OCH_2CH_2CH_2CH_2$), 1.30 (8H, s, $OCH_2CH_2CH_2CH_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.7, 70.9, 70.3, 50.9, 29.8, 29.7, 26.3.

3.2.1.13. Chemical preparation of **25a**

Diazide **41a** (206 mg, 0.419 mmol), triphenylphosphine (244 mg, 0.922 mmol), and 15 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the diamine **25a** as a light yellow oil (140 mg, 75%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.61-3.52 (24H, m, OCH_2CH_2O), 3.46-3.43 (8H, m, $OCH_2CH_2CH_2CH_2O$ and $H_2NCH_2CH_2O$), 2.80 (4H, t, J = 5.2 Hz, $H_2NOCH_2CH_2$), 1.61 (4H, t, J = 2.9 Hz, $OCH_2CH_2CH_2CH_2O$), 1.49 (4H, br s, $H_2NOCH_2CH_2$).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 73.9, 71.3, 70.9, 70.6, 70.4, 42.2, 26.8.

HRMS (ESI-TOF, positive): $[C_{20}H_{45}N_2O_8]^+$ cal. 441.3170, found 441.3198; $[C_{20}H_{46}N_2O_8]^{2+}$ cal. 221.1622, found 221.1625.

3.2.1.14. Chemical preparation of **25b**

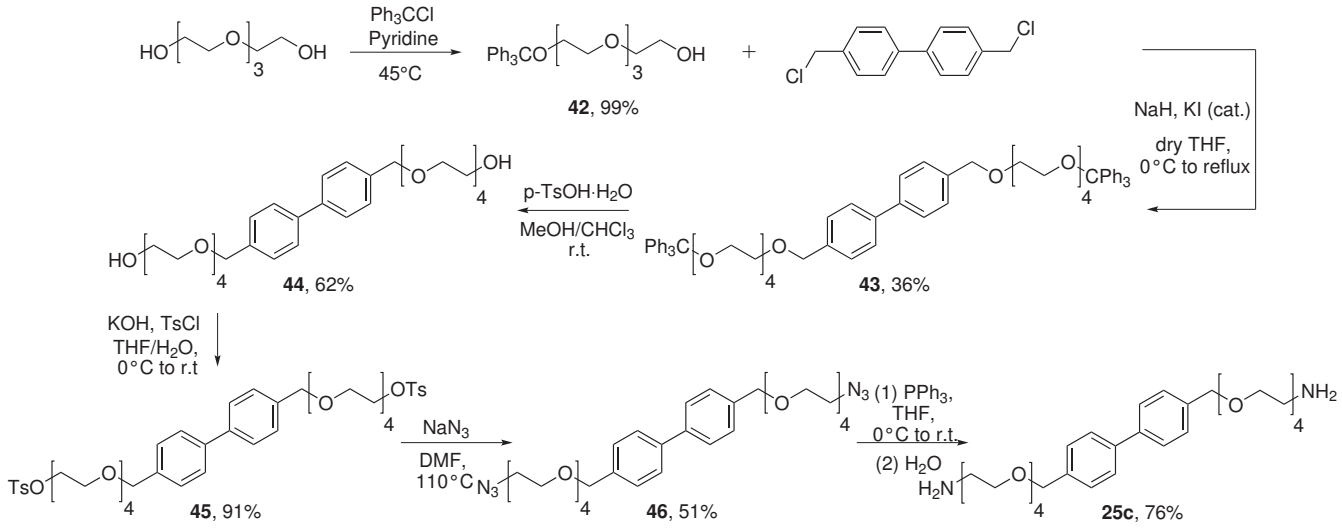
Diazide **41b** (102 mg, 0.186 mmol), triphenylphosphine (103 mg, 0.390 mmol), and 10 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the diamine **25b** as a light yellow oil (64.5 mg, 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.69-3.61 (20H, m, OCH_2CH_2O), 3.59-3.56 (4H, m, OCH_2CH_2O), 3.53 (4H, t, J = 5.0 Hz, $H_2NCH_2CH_2O$), 3.44 (4H, t, J = 6.8 Hz, $OCH_2CH_2CH_2CH_2$), 2.88 (4H, br s, $H_2NOCH_2CH_2$), 2.04 (4H, br s, $H_2NCH_2CH_2O$), 1.57 (4H, p, J = 6.6 Hz, $OCH_2CH_2CH_2CH_2$), 1.30 (8H, br s, $OCH_2CH_2CH_2CH_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 73.2, 71.7, 70.7, 70.4, 70.2, 41.8, 29.8, 29.6, 26.2.

HRMS (ESI-TOF, positive): $[C_{24}H_{53}N_2O_8]^+$ cal. 497.3796, found 497.3805.

3.2.2. Chemical preparation of hybrid OEG **25c**



Scheme S6. Chemical preparation of **25c**.

3.2.2.1. Chemical preparation of **42**

To a mixture of tetraethylene glycol (20.0 mL, 0.115 mol) and pyridine (1.39 mL, 17.0 mmol), powdered trityl chloride (3.26 g, 11.0 mmol) were added portionwise at 45°C and this reaction mixture was further stirred at 45°C for 16 h. This reaction suspension was first separated and the solid was removed. The residue was dissolved in toluene and washed with water for three times to remove the excess of tetraethylene glycol. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to obtain monotritylate **42** as a light yellow liquid (4.99 g, 99%).

^{1}H-NMR (Acetone-d6, 250 MHz) δ (ppm) = 7.52-7.48 (5H, m, Ar-*H*), 7.36-7.24 (10H, m, Ar-*H*), 3.68-3.51 (14H, m, OCH_2CH_2), 3.18 (2H, t, J = 5.2 Hz, CH_2OH), 2.08 (1H, s, O*H*).

^{13}C-NMR (Acetone-d6, 62.5 MHz) δ (ppm) = 145, 130, 129, 128, 73.6, 71.6, 71.4, 71.2, 64.4, 62.1.

3.2.2.2. Chemical preparation of **43**

To a mixture of **42** (4.36 g, 10.0 mmol) in anhydrous THF, sodium hydride (460 mg, 11.4 mmol) was added portionwise at 0°C. The mixture was first stirred at room temperature for 30 min and then heated up to reflux for 1 h. To this cooled reaction mixture, potassium iodide (160 mg, 0.952 mmol) and 4,4'-bis(chloromethyl)-1,1'-biphenyl (1.26 g, 4.76 mmol) was added at room temperature. The mixture was heated up to reflux for 18 h. The reaction was controlled until TLC analysis indicated complete consumption of 4,4'-bis(chloromethyl)-1,1'-biphenyl. The mixture was quenched with water and

extracted with ether and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by 2 times column chromatography (chloroform : AcOEt = 40:1 to 10:1) to obtain **43** as a light yellow oil (1.81 g, 36%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.53 (4H, d, J = 8.4 Hz, Ar-*H*), 7.45 (12H, m, Ar-*H*), 7.38 (4H, d, J = 8.4 Hz, Ar-H), 7.27 (12H, m, Ar-*H*), 7.21 (6H, m, Ar-*H*), 4.58 (4H, s, ArCH_2O), 3.68 (28H, m, OCH_2CH_2), 3.22 (4H, t, J = 5.2 Hz, ArCH$_2$OCH_2CH$_2$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 144, 140, 138, 129, 128, 127, 73.2, 71.0, 70.9, 69.7, 63.5.

3.2.2.3. Chemical preparation of **44**

To a solution of ditriylate hybrid OEG **43** (2.65 g, 2.53 mmol) in a mixture of MeOH (12 ml) and chloroform (8 ml), catalytic amount of para-toluene-4-sulfonic acid monohydrate (30.0 mg, 0.127 mmol) and 2 drops water were added and then the reaction mixture was stirred at room temperature for 24 h. The reaction was controlled until TLC analysis indicated complete consumption of ditriylate **10**. Afterwards, a solution sodium carbonate (30.0 mg, 0.250 mmol) was added. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue purified by column chromatography (DCM : MeOH = 20:1) to obtain **44** as a yellow oil (890 mg, 62%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.55 (4H, d, J = 8.0 Hz, Ar-*H*), 7.40 (4H, d, J = 8.0 Hz, Ar-*H*), 4.59 (4H, s, ArCH_2O), 3.65 (28H, m, OCH_2CH_2), 3.58 (4H, t, J = 4.4 Hz, CH_2OH), 3.45 (2H, s, O*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 141, 138, 129, 127, 73.2, 72.7, 70.8, 70.5, 69.7, 62.0.

3.2.2.4. Chemical preparation of **45**

Diol **44** (97.0 mg, 0.171 mmol), 4-methylbenzene sulfonyl chloride (72.0 mg, 0.376 mmol), potassium hydroxide (38.0 mg, 0.684 mmol), 10 mL THF, and 0.4 mL H_2O were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the ditosylate **45** as a light yellow oil (136 mg, 91%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.76 (4H, d, J = 8.2 Hz, Ar-*H*), 7.34 (4H, d, J = 8.2 Hz, Ar-*H*), 7.38 (4H, d, J = 8.1 Hz, Ar-*H*), 7.30 (4H, d, J = 8.0 Hz, Ar-*H*), 4.58 (4H, s, ArCH_2O), 4.14-4.11 (4H, m, OCH_2CH$_2$OSO$_2$), 3.67-3.56 (28H, m, OCH_2CH$_2$OSO$_2$ and OCH_2CH_2O), 2.41 (6H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 140, 138, 133, 130, 128, 127, 73.2, 71.0, 70.9, 70.8, 70.7, 69.7, 69.4, 68.9, 21.8.

3.2.2.5. Chemical preparation of **46**

Ditosylate **45** (501 mg, 0.570 mmol), sodium azide (113 mg, 1.72 mmol), and 10 mL anhydrous DMF were used and the crude product was purified by 2 times column chromatography (DCM : MeOH = 40 :1 and chloroform : MeOH = 40 : 1) to give the ditosylate **46** as a light yellow oil (179 mg, 51%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.56 (4H, d, J = 8.1 Hz, Ar-*H*), 7.34 (4H, d, J = 8.1 Hz, Ar-*H*), 4.61 (4H, s, ArCH_2O), 3.71-3.62 (28H, m, OCH_2CH_2O), 3.37 (4H, t, J = 5.2 Hz, N_3OCH_2CH_2).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 140, 138, 128, 127, 73.2, 70.9, 70.2, 69.7, 50.9.

3.2.2.6. Chemical preparation of **25c**

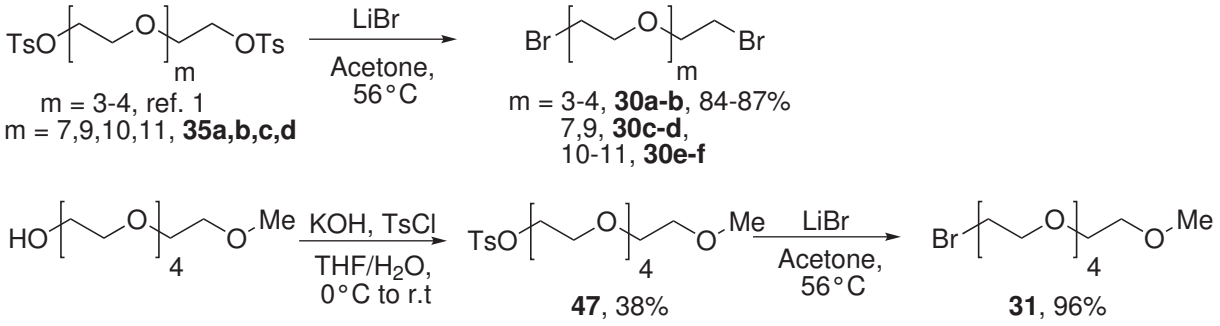
Diazide **46** (171 mg, 0.278 mmol), triphenylphosphine (170 mg, 0.611 mmol), and 15 mL anhydrous THF were used and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the ditosylate **25c** as a light yellow oil (120 mg, 76%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 7.59 (4H, d, J = 8.2 Hz, Ar-*H*), 7.42 (4H, d, J = 8.2 Hz, Ar-*H*), 4.58 (4H, s, ArCH_2O), 3.65-3.56 (24H, m, OCH_2CH_2O), 3.44 (4H, t, J = 5.2 Hz, H_2NCH_2CH_2O), 2.79 (4H, t, J = 5.3 Hz, H_2NOCH_2CH_2), 1.46 (4H, br s, H_2NCH_2CH_2O).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 140, 138, 129, 127, 74.0, 73.1, 70.9, 70.6, 70.1, 42.2.

HRMS (ESI-TOF, positive): $[C_{30}H_{49}N_2O_8]^+$ cal. 565.3483, found 565.3472; $[C_{30}H_{50}N_2O_8]^{2+}$ cal. 283.1778, found 283.1773.

3.3. Chemical preparation of OEG **30** and **31**



Scheme S7. Chemical preparation of **30** (top) and **31** (bottom).

3.3.1. General procedure for preparation of dibromide **30**

To a solution of ditosylate (1.0 equivalent) in acetone, lithium bromide (4.0 equivalents) was added at room temperature and the reaction mixture was stirred and heated up to reflux until TLC analysis indicated complete consumption of the ditosylate. The reaction mixture was concentrated in vacuo and the crude product was absorbed on the silica gel and further purified by column chromatography to obtain the pure dibromide.

3.3.2. Chemical preparation of **30a**

Tetraethylene glycol ditosylate[1] (342 mg, 0.680 mmol), lithium bromide (179 mg, 2.04 mmol) and 20 mL acetone were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the dibromide **30a** as a light yellow oil (188 mg, 87%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.82 (4H, t, J = 6.2 Hz, $BrCH_2CH_2O$), 3.68 (8H, s, OCH_2CH_2O), 3.48 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.9, 70.8, 30.6.

HRMS (ESI-TOF, positive): $[C_8H_{16}Br_2O_3Na]^+$ cal. 340.9358, 342.9338, 344.9318, found 340.9354, 342.9335, 344.9315.

3.3.3. Chemical preparation of **30b**

Pentaethylene glycol ditosylate[1] (464 mg, 0.850 mmol), lithium bromide (224 mg, 2.54 mmol) and 20 mL acetone were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the dibromide **30b** as a light yellow oil (261 mg, 84%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.81 (4H, t, J = 6.4 Hz, $BrCH_2CH_2O$), 3.71-3.65 (12H, m, OCH_2CH_2O), 3.47 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.9, 70.8, 30.5.

HRMS (ESI-TOF, positive): $[C_{10}H_{20}Br_2O_4Na]^+$ cal. 384.9621, 386.9600, 388.9580, found 384.9644, 386.9624, 388.9602.

3.3.4. Chemical preparation of **30c**

Ditosylate **35a** (165 mg, 0.242 mmol), lithium bromide (84.2 mg, 0.969 mmol) and 10 mL acetone were used and the crude product was purified by column chromatography (chloroform : MeOH = 40 : 1) to give the dibromide **30c** as a light yellow oil (110 mg, 92%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.79 (4H, t, J = 6.4 Hz, $BrCH_2CH_2O$), 3.68-3.60 (24H, m, OCH_2CH_2O), 3.45 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.9, 70.8, 30.6.

HRMS (ESI-TOF, positive): $[C_{16}H_{32}Br_2O_7Na]^+$ cal. 517.0407, 519.0387, 521.0369, found 517.0815, 519.0367, 521.0348.

3.3.5. Chemical preparation of **30d**

Ditosylate **35b** (108 mg, 0.141 mmol), lithium bromide (49.6 mg, 0.565 mmol) and 5 mL acetone were used and the crude product was purified by column chromatography (chloroform : MeOH = 20 : 1) to give the dibromide **30d** as a light yellow oil (82.3 mg, 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.79 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$), 3.71-3.52 (32H, m, OCH_2CH_2O), 3.46 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.9, 70.8, 30.6.

HRMS (ESI-TOF, positive): $[C_{20}H_{40}Br_2O_9Na]^+$ cal. 605.0931, 607.0912, 609.0894, found 605.0862, 607.0830, 609.0815; $[C_{20}H_{40}Br_2O_9K]^+$ cal. 621.0671, 623.0651, 625.0634, found 621.0588, 623.0568, 625.0552.

3.3.6. Chemical preparation of **30e**

The ditosylate OEG **35c** (146 mg, 0.180 mmol), lithium bromide (63.3 mg, 0.722 mmol) and 5 mL acetone were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1) to give the dibromide **30e** as a light yellow oil (116 mg, 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.81 (4H, t, J = 6.4 Hz, $BrCH_2CH_2O$), 3.72-3.61 (36H, m, OCH_2CH_2O), 3.47 (4H, t, J = 6.4 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.9, 70.8, 70.7, 30.5.

MS (FAB, positive): $[C_{22}H_{45}Br_2O_{10}]^+$ cal. 629.14 found 629.2; $[C_{22}H_{44}Br_2O_{10}Na]^+$ cal. 651.12 found 651.3.

3.3.7. Chemical preparation of **30f**

The ditosylate **35d** (191 mg, 0.222 mmol), lithium bromide (78.2 mg, 0.891 mmol) and 5 mL acetone were used and the crude product was purified by column chromatography (DCM : MeOH = 20 : 1) to give the dibromide **30f** as a light yellow oil (139 mg, 94%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.79 (4H, t, J = 6.4 Hz, $BrCH_2CH_2O$), 3.69-3.54 (40H, m, OCH_2CH_2O), 3.45 (4H, t, J = 6.3 Hz, $BrCH_2CH_2O$).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 71.4, 70.7, 70.5, 70.4, 30.5.

HRMS (ESI-TOF, positive): $[C_{24}H_{48}Br_2O_{11}Na]^+$ cal. 693.1456, 695.1437, 697.1421, found 693.1487, 695.1457, 697.1440; $[C_{24}H_{48}Br_2O_{11}K]^+$ cal. 709.1195, 711.1176, 713.1160, found 709.1213, 711.1196, 713.1180.

3.3.8. Chemical preparation of **47**

To a solution of 2,5,8,11,14-pentaoxahexadecan-16-ol (318 mg, 1.26 mmol) in 20 mL THF, 4-methylbenzene sulfonyl chloride (364 mg, 1.89 mmol) was added at room temperature and the solution was then cooled to 0°C. To this mixture, potassium hydroxide (234 mg, 4.16 mmol) in H_2O (0.9 g/mL) was added dropwise over 15 min. Then the reaction mixture was stirred at 0°C for 30 min and some white precipitation appeared. Afterwards this mixture was further stirred at room temperature until TLC analysis indicated complete consumption of the OEG alcohol. The reaction mixture was neutralized with a saturated ammonium chloride solution and concentrated in vacuo. The residue was absorbed on the silica gel and further purified by flash column chromatography (DCM : MeOH = 20:1) to obtain the pure monotosylate OEG monomethyl ether **47** as a colorless solid (194 mg, 38%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.80 (2H, d, J = 8.3 Hz, Ar-*H*), 7.34 (2H, d, J = 8.1 Hz, Ar-*H*), 4.18-4.14 (2H, m, $OCH_2CH_2OSO_2$), 3.70-3.67 (2H, m, $OCH_2CH_2OSO_2$), 3.66-3.53 (20H, m, OCH_2CH_2O), 3.38 (3H, s, $CH_3OCH_2CH_2$), 2.45 (3H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 145, 133, 130, 128, 72.1, 70.9, 70.8, 70.7, 69.4, 68.9, 59.2, 21.8.

3.3.9. Chemical preparation of **31**

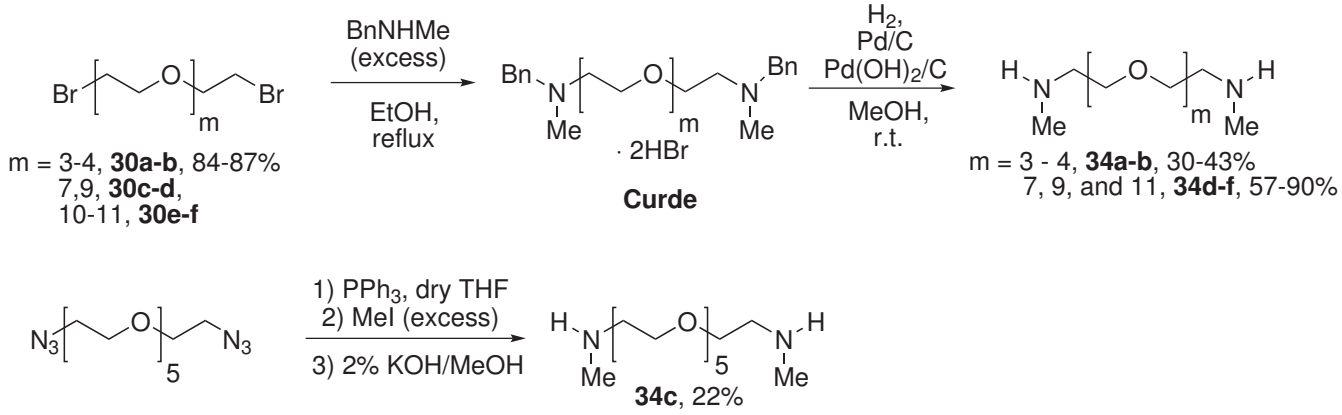
To a solution of monotosylate OEG monomethyl ether **47** (177 mg, 0.436 mmol) in 10 mL acetone, lithium bromide (153 mg, 1.74 mmol) was added at room temperature and the reaction mixture was stirred and heated up to reflux until TLC analysis indicated complete consumption of the monotosylate. The reaction mixture was concentrated in vacuo and the crude product was absorbed on the silica gel and further purified by column chromatography (chloroform : MeOH = 20:1) to obtain the pure bromide **31** (132 mg, 96%) as a light yellow oil.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 3.81 (2H, t, J = 6.4 Hz, $BrCH_2CH_2O$), 3.69-3.63 (14H, m, OCH_2CH_2O), 3.57-3.53 (2H, m, $CH_3OCH_2CH_2$), 3.48 (2H, t, J = 6.3 Hz, $BrCH_2CH_2O$), 3.38 (3H, s, CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 72.1, 71.4, 70.9, 70.8, 70.7, 59.2, 30.5, 27.6.

HRMS (ESI-TOF, positive): $[C_{11}H_{24}BrO_5]^+$ cal. 315.0802, 317.0781, found 315.0727, 317.0688; $[C_{11}H_{23}BrO_5Na]^+$ cal. 337.0621, 339.0601, found 337.0624, 339.0605; $[C_{11}H_{23}BrO_5K]^+$ cal. 353.0360, 355.0340, found 353.0356, 355.0341.

3.4. Chemical preparation of *N*-methyl diamine OEG **34**



Scheme S8. Chemical preparation of **34**.

3.4.1. Chemical preparation of **34a**

To a solution of the dibromide **30a** (101 mg, 0.314 mmol) in EtOH (10 mL), *N*-benzyl methylamine (125 µL, 0.942 mmol) was added and the reaction mixture was heated up to reflux for 24 h until TLC and ESI-TOF analysis indicated complete consumption of the dibromide. The solvent was removed in vacuo. Afterwards the residue was dissolved in MeOH (10 mL) followed by hydrogenation with 10% palladium hydroxide on carbon (21.8 mg, 0.155 mmol) and 1M HCl (3.1 mL) under 15 bar hydrogen pressure for 10 h. Then the mixture was filtered over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1 to 5:1) to give the bis-*N*-methylamine **34a** as a yellow solid (29.6 mg, 43%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.61-3.56 (12H, m, OC*H*$_2$C*H*$_2$O and $CH_3HNCH_2CH_2O$), 3.00 (4H, br s, $CH_3HNCH_2CH_2O$), 2.77 (2H, br s, $CH_3HNCH_2CH_2O$), 2.43 (6H, s, CH_3NHCH_2).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.7, 70.5, 69.7, 51.1, 35.7.

HRMS (ESI-TOF, positive): $[C_{10}H_{25}N_2O_3]^+$ cal. 221.1860, found 221.1866.

3.4.2. Chemical preparation of **34b**

To a solution of the ditosylate **30b** (196 mg, 0.358 mmol) in EtOH (10 mL), *N*-benzyl methylamine (143 µL, 1.07 mmol) was added and the reaction mixture was heated up to reflux for 48 h until TLC analysis indicated complete consumption of the ditosylate. The solvent was removed in vacuo. Afterwards the residue was dissolved in MeOH (10 mL) followed by hydrogenation with 10% palladium hydroxide on carbon (26.3 mg, 0.0374 mmol) and 1M HCl (0.96 mL) under 15 bar hydrogen pressure for 20 h. Then the mixture was filtered over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the crude product was washed with triethylamine to give the bis-*N*-methylamine **34b** as colorless oil (28.5 mg, 30%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.89 (4H, t, J = 4.6 Hz, $CH_3HNCH_2CH_2O$), 3.72-3.59 (14H, m, OC*H*$_2$C*H*$_2$O and $CH_3HNCH_2CH_2O$), 3.15 (4H, t, J = 4.6 Hz, $CH_3HNCH_2CH_2O$), 2.71 (6H, s, CH_3NHCH_2).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.2, 70.1, 70.0, 66.1, 48.7, 33.7.

HRMS (ESI-TOF, positive): $[C_{12}H_{28}N_2O_4Na]^+$ cal. 287.1941, found 287.1947.

3.4.3. Chemical preparation of **34c**

To a solution of hexaethylene glycol 1,20-diazide[10] (170 mg, 0.511 mmol) in anhydrous THF, triphenylphosphine (295 mg, 1.13 mmol) was added at room temperature and the reaction mixture was stirred at room temperature until TLC and ESI-TOF analysis indicated complete consumption of the azide. To this iminophosphorane intermediate, iodomethane (70.7 µL, 1.13 mmol) were added and a white participation appeared. After 24 h, ESI-TOF analysis indicated the complete consumption of this intermediate and the solvent including the excess of iodomethane was removed in vacuum. Afterward, 1% KOH in MeOH (5.7 mL) was added to hydrolyze aminophosphonium salt. The solvent was removed in vacuo and the residue was absorbed on the silica gel and further purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1 to 5:1) to obtain the pure bis-*N*-methylamine OEG **34c** as a colorless oil (34.4 mg, 22%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.64-3.44 (24H, m, OCH_2CH_2O and $CH_3HNCH_2CH_2O$), 2.70 (4H, br s, $CH_3HNCH_2CH_2O$), 2.39 (6H, s, CH_3NHCH_2), 1.75 (2H, br s, $CH_3HNCH_2CH_2O$).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.9, 70.7, 70.6, 51.7, 36.4.

HRMS (ESI-TOF, positive): $[C_{14}H_{32}N_2O_5Na]^+$ cal. 331.2203, found 331.2207.

3.4.4. Chemical preparation of **34d**

To a solution of the dibromide **30c** (109 mg, 0.219 mmol) in EtOH (2 mL), *N*-benzyl methylamine (175 µL, 1.32 mmol) was added and the reaction mixture was heated up to 78°C for 20 h until TLC and ESI-TOF analysis indicated complete consumption of the dibromide. The solvent was removed in vacuo. Afterwards the residue was dissolved in MeOH (2.5 mL) followed by hydrogenation with 10% palladium hydroxide on carbon (30.8 mg, 0.0438 mmol) and palladium on carbon (46.7 mg, 0.0438 mmol) under 15 bar hydrogen pressure for 20 h. Then the mixture was filtered over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the bis-*N*-methylamine dibromide salt **34d** as a colorless solid (110 mg, 90%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.94 (4H, t, J = 5.0 Hz, $CH_3HNCH_2CH_2O$), 3.74-3.62 (26H, m, OCH_2CH_2O and $CH_3HNCH_2CH_2O$), 3.41 (2H, s, $CH_3HNCH_2CH_2O$), 3.22 (4H, t, J = 5.1 Hz, $CH_3HNCH_2CH_2O$), 2.74 (6H, s, CH_3NHCH_2).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.7, 70.5, 70.3, 70.2, 66.2, 50.7, 49.0, 33.9.

HRMS (ESI-TOF, positive): $[C_{18}H_{41}N_2O_7]^+$ cal. 397.2908, found 397.2897; $[C_{18}H_{42}N_2O_9]^{2+}$ cal. 199.1491, found 199.1481; $[C_{18}H_{40}N_2O_7Na]^+$ cal. 419.2728, found 419.2715.

3.4.5. Chemical preparation of **34e**

To a solution of the dibromide **30d** (81.8 mg, 0.140 mmol) in EtOH (2 mL), *N*-benzyl methylamine (112 µL, 0.840 mmol) was added and the reaction mixture was heated up to 78°C for 20 h until TLC and ESI-TOF analysis indicated complete consumption of the dibromide. The solvent was removed in vacuo. Afterwards the residue was dissolved in MeOH (2.0 mL) followed by hydrogenation with 10% palladium hydroxide on carbon (19.7 mg, 0.0280 mmol) and palladium on carbon (29.8 mg, 0.0280 mmol) under 15 bar hydrogen pressure for 20 h. Then the mixture was filtered over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give the bis-*N*-methylamine dibromide salt **34e** as a colorless solid (80.7 mg, 89%).

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.92 (4H, t, J = 5.0 Hz, $CH_3HNCH_2CH_2O$), 3.74-3.58 (32H, m, OCH_2CH_2O), 3.41 (4H, s, $CH_3HNCH_2CH_2O$), 3.20 (4H, t, J = 5.2 Hz, $CH_3HNCH_2CH_2O$), 2.72 (6H, s, CH_3NHCH_2).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.7, 70.6, 70.5, 70.4, 70.2, 66.2, 50.7, 49.0, 33.8.

HRMS (ESI-TOF, positive): $[C_{22}H_{49}N_2O_9]^+$ cal. 485.3433, found 485.3596; $[C_{22}H_{50}N_2O_9]^{2+}$ cal. 243.1753, found 243.1851; $[C_{22}H_{48}N_2O_9Na]^+$ cal. 507.3252, found 507.3420.

3.4.6. Chemical preparation of **34f**

To a solution of the dibromide **30f** (80.0 mg, 0.118 mmol) in EtOH (3 mL), *N*-benzyl methylamine (47.5 µL, 0.357 mmol) was added and the reaction mixture was heated up to 78°C for 20 h until TLC and ESI-TOF analysis indicated complete consumption of the dibromide. The solvent was removed in vacuo.

Afterwards the residue was dissolved in MeOH (2.0 mL) followed by hydrogenation with 10% palladium hydroxide on carbon (16.8 mg, 0.0238 mmol) and 1M HCl (1.18 mL) under 15 bar hydrogen pressure for 20 h. Then the mixture was filtered over Celite and the filter cake was washed with MeOH three times. This solution was concentrated in vacuo and the crude product was purified by column chromatography (MeOH : NH_4OH [25% in water] = 9 : 1) to give to give the bis-*N*-methylamine **34f** as a colorless oil (39.2 mg, 57%)

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 3.61-3.51 (44H, m, $CH_3HNCH_2CH_2O$, OCH_2CH_2O, and $CH_3HNCH_2CH_2O$), 2.70 (4H, t, J = 5.2 Hz, $CH_3HNCH_2CH_2O$), 2.39 (6H, s, CH_3NHCH_2).

^{13}C-NMR (DCM-d2, 100 MHz) δ (ppm) = 70.9, 70.6, 51.7, 36.4.

HRMS (ESI-TOF, positive): $[C_{26}H_{57}N_2O_{11}]^+$ cal. 573.3957, found 573.4009; $[C_{26}H_{58}N_2O_{11}]^{2+}$ cal. 287.2015, found 287.2003; $[C_{26}H_{56}N_2O_{11}Na]^+$ cal. 595.3776, found 595.3752.

4. Chemical preparation of diethylstilbestrol (DES) ligands **1-10**

4.1. Chemical preparation of DES precursors

4.1.1. Chemical preparation of (d,l)-1,2-bis-(4-methoxyphenyl)-l-butane **21**

To a solution of sodium hydride (2.47 g, 61.8 mmol) in anhydrous THF (50 mL), a solution of desoxyanisoin (10.6 g, 41.2 mmol) in anhydrous THF (80 mL) was added dropwise at 0 °C, then the reaction mixture was allowed to warm up to room temperature and stirred for 1 h. This mixture was added slowly to a solution of iodoethane (3.36 mL, 41.2 mmol) in anhydrous THF (20 mL) at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h. Afterwards the reaction was quenched with water at 0°C. The solvent was removed in vacuo and the residue was washed with DCM, brine, and dried over $MgSO_4$. The organic solvent was evaporated in vacuo and the residue was purified by column chromatography (hexane: AcOEt = 5:1) to obtain (d,l)-α-ethyl deoxyanisoin **21** as a yellow oil (7.87 g, 67%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.95 (2H, d, J = 8.9 Hz, Ar-*H*), 7.21 (2H, d, J = 8.7 Hz, Ar-*H*), 6.86 (2H, d, J = 9.0 Hz, Ar-*H*), 6.81 (2H, d, J = 8.8 Hz, Ar-*H*), 4.34 (1H, t, J = 7.3 Hz, *H*CC=O), 3.81 (3H, s, C*H*$_3$OAr), 3.74 (3H, s, C*H*$_3$OAr), 2.15 (1H, septet, J = 7.3 Hz, H_3CH_2CHC), 1.81 (1H, septet, J = 7.5 Hz, H_3CH_2CHC), 0.88 (3H, t, J = 7.4 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 199, 163, 159, 132, 131, 130, 129, 114, 55.6, 55.4, 54.3, 27.3, 12.5.

HRMS (ESI-TOF, positive): $[C_{18}H_{20}O_3Na]^+$ cal. 307.1305, found 307.1325; $[C_{18}H_{20}O_3K]^+$ cal. 323.1044, found 323.1065.

4.1.2. Chemical preparation of ethyl 3-hydroxy-3,4-bis-(4-methoxyphenyl)hexanoate **22**

Zinc powder (10 μm) was washed with dilute hydrochloric acid, twice with water, and once each with ethanol and diethyl ether and finally dried in vacuum. To this washed zinc (3.37 g, 50.6 mmol), 50% of a solution of d,l-α-ethyldeoxyanisoin **21** (3.42 g, 12.0 mmol) and ethyl bromoacetate (5.72 mL, 50.6 mmol) in dry benzene (20 mL) was added and the reaction mixture was heated briefly to reflux, initiating the reaction. The remainder of the reagent solution was then added dropwise, and the mixture

was heated to reflux for 2 h. The organozinc intermediate was hydrolyzed by the gradual addition of 5% aqueous sulfuric acid, and this mixture was washed with ether, water, 5% sodium hydrogen carbonate, and again with water, dried over $MgSO_4$. The organic solution was filtered over silica gel and concentrated in vacuo. The residue, i.e., a mixture of diastereomers of ethyl 3-hydroxy-3,4-bis-(4-methoxyphenyl)hexanoate, was purifed with HPLC (DCM, 20 mL/min) to obtain three factions: (1) Starting materials **21** and ethyl bromoacetate; (2) More mobile diastereomer of **10** and (3) less mobile diastereomer of **22** as a colorless oil (3.68 g, 82%).

More mobile diastereomer of **22** (R_t = 3.5 min):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.33 (2H, d, J = 8.7 Hz, Ar-*H*), 7.22 (2H, d, J = 7.9 Hz, Ar-*H*), 6.89-6.81 (4H, m, Ar-*H*), 4.35 (1H, br s, *H*O), 3.87-3.78 (8H, q and s, J = 7.2 Hz, H_3CH_2COC=O and H_3COAr), 2.75 (1H, d, J = 16 Hz, CH_2CC=O), 2.56 (1H, dd, J = 2.1 Hz, 12 Hz, H_3CH_2CHC), 2.36 (1H, d, J = 16 Hz, CH_2CC=O), 1.78-1.65 (1H, m, H_3CH_2CHC), 1.51-1.41 (1H, m, H_3CH_2CHC), 0.96 (3H, t, J = 7.2 Hz, H_3CH_2COC=O), 0.52 (3H, t, J = 7.3 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 174, 159, 158, 138, 133, 131, 127, 114, 113, 104, 60.7, 58.8, 55.4, 45.1, 22.2, 14.1, 12.8.

Less mobile diastereomer of **22** (R_t = 3.7 min):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.09 (2H, d, J = 8.8 Hz, Ar-*H*), 6.80-6.72 (6H, m, Ar-*H*), 4.52 (1H, br s, *H*O), 3.97 (2H, q, J = 6.7 Hz, H_3CH_2COC=O) 3.79 and 3.78 (6H, s, H_3COAr), 2.92 (1H, d, J = 16 Hz, CH_2CC=O), 2.78-2.72 (2H, dd and d, J = 3.1 Hz, 12 Hz, and 16 Hz, H_3CH_2CHC and CH_2CC=O), 2.08-1.98 (1H, m, H_3CH_2CHC), 1.42-1.28 (1H, m, H_3CH_2CHC), 1.07 (3H, t, J = 7.2 Hz, H_3CH_2COC=O), 0.62 (3H, t, J = 7.3 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 174, 159, 158, 136, 132, 131, 128, 113, 104, 77.2, 60.8, 58.5, 55.3, 43.5, 21.8, 14.2, 12.5.

4.1.3. Chemical preparation of (*E*,*Z*)-ethyl 3,4-bis-(4-methoxyphenyl)-2-hexenoate **23**

To a solution of both diastereomers of ethyl 3-hydroxy-3,4-bis(4-methoxyphenyl)hexanoate **22** (3.26 g, 8.76 mmol) in dry pyridine (20 mL), thionyl chloride (1.27 mL, 17.5 mmol) were added dropwise at

room temperature and then the reaction mixture was stirred at room temperature for 3 h. Benzene (10 mL) was added to precipitate the pyridine hydrochloride, and the solvent was removed in vacuo. The residue was dissolved in ether, washed with two times water, dried over $MgSO_4$. The black crude product was purified by column chromatography (hexane : AcOEt = 10:1) to obtain *Z*- and *E*- isomers of ethyl 3,4-bis-(4-methoxyphenyl)-2-hexenoate **23** as a yellow oil (3.03 g, 98%).

Z-isomer of **23** (the first fraction):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.18 (2H, d, J = 8.4 Hz, Ar-*H*), 6.82 (2H, d, J = 8.7 Hz, Ar-*H*), 6.79 (2H, d, J = 8.9 Hz, Ar-*H*), 6.69 (2H, d, J = 8.8 Hz, Ar-*H*), 5.91 (1H, s, C=C*H*C=O), 5.36 (1H, dd, J = 6.1 Hz, 9.2 Hz, H_3CH_2CHCC), 4.25 (2H, q, J = 7.1 Hz, H_3CH_2COC=O) 3.80 (3H, s, H_3COAr), 3.76 (3H, s, H_3COAr), 1.88 (1H, septet, J = 7.3 Hz, H_3CH_2CHC), 1.72-1.61 (1H, m, H_3CH_2CHC), 1.33 (3H, t, J = 7.2 Hz, H_3CH_2COC=O), 0.92 (3H, t, J = 7.3 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 167, 163, 160, 158, 134, 133, 130, 129, 120, 114, 113, 60.2, 55.4, 45.0, 24.4, 14.5, 12.3.

E-isomer of **23** (the second fraction):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 6.99 (2H, d, J = 8.7 Hz, Ar-*H*), 6.82-6.73 (6H, m, Ar-*H*), 5.91 (1H, d, J = 0.68 Hz, C=C*H*C=O), 3.97 (2H, q, J = 7.1 Hz, H_3CH_2COC=O), 3.78 (3H, s, H_3COAr), 3.77 (3H, s, H_3COAr), 3.42 (1H, t, J = 7.8 Hz, H_3CH_2CHCC), 1.93-1.68 (2H, m, H_3CH_2CHC), 1.07 (3H, t, J = 7.2 Hz, H_3CH_2COC=O), 0.89 (3H, t, J = 7.2 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 167, 162, 159, 158, 133, 132, 130, 129, 117, 114, 113, 60.0, 56.4, 55.4, 55.3, 26.5, 14.2, 12.7.

4.1.4. Chemical preparation of (*E*,*Z*)-ethyl 3,4-bis-(4-hydroxyphenyl)-3-hexenoate **9**

To a solution of (*E*,*Z*)-ethyl 3,4-bis-(4-methoxyphenyl)-2-hexenoate **9** (160 mg, 0.450 mmol) in anhydrous DCM (8 mL) which was cooled in a dry ice/2-propanol bath, boron tribromide (170 μL, 1.80 mmol) were added dropwise and this reaction mixture was further stirred under the cooling for 1 h. Afterwards, the reaction mixture was warmed up to 0°C and stirred for 4 h. The reaction mixture was again cooled to -78°C followed by the addition of absolute EtOH (2 mL) to quench the reaction. The

solvent was removed under a stream of dry argon and the residue was absorbed on the silica gel and further purified by column chromatography (chloroform : MeOH = 20:1) to obtain a mixture of *Z*- and *E*- isomers (*E*-isomer: 84%) of ethyl 3,4-bis- (4-hydroxyphenyl)-3-hexenoate **9** as a red oil (38.9 mg, 27%) and a styrene byproduct (105 mg, 72%). Since the facile isomerization of the stilbene structure takes place in organic solvent of low dielectric constant, both stereoisomers were applied for the next step without any further separation. A geometrical isomer separation by analytic HPLC (2% MeOH/DCM, 2 mL/min) was only performed for the characterization of *E*-isomer of **9**. The chemical shift of *E*-isomer of **9** was further characterized by NOESY spectra and consistent with previous report.[11]

E-isomer of **9** (the first fraction, R_t = 2.3 min):

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.08-7.03 (4H, m, Ar-*H*), 6.78-6.72 (4H, m, Ar-*H*), 3.94 (2H, q, *J* = 7.1 Hz, $H_3C\mathit{H}_2COC{=}O$), 3.14 (2H, s, $\mathit{H}_2CC{=}O$), 2.19 (2H, q, *J* = 7.4 Hz, $H_3C\mathit{H}_2CHC$), 1.08 (3H, t, *J* = 7.2 Hz, $\mathit{H}_3CH_2COC{=}O$), 0.78 (3H, t, *J* = 7.4 Hz, H_3CH_2CHC).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 173, 156, 144, 133, 130, 129, 115, 114, 50.7, 40.9, 28.1, 12.2.

^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm) = 7.14 (2H, d, *J* = 8.0 Hz, Ar-*H*), 7.12 (2H, d, *J* = 8.0 Hz, Ar-*H*), 6.85 (2H, d, *J* = 8.2 Hz, Ar-*H*), 6.83 (2H, *J* = 8.2 Hz, Ar-*H*), 3.94 (2H, q, *J* = 7.1 Hz, $H_3C\mathit{H}_2COC{=}O$), 3.16 (2H, s, $\mathit{H}_2CC{=}O$), 2.22 (2H, q, *J* = 7.6 Hz, $H_3C\mathit{H}_2CHC$), 1.09 (3H, t, *J* = 7.1 Hz, $\mathit{H}_3CH_2COC{=}O$), 0.80 (3H, t, *J* = 7.6 Hz, H_3CH_2CHC).

HRMS (ESI-TOF, positive): $[C_{20}H_{22}O_4Na]^+$ cal. 349.1410, found 349.1402; $[C_{40}H_{44}O_8Na]^+$ cal. 675.2928, found 675.2888.

Z-isomer of **9** (the second fraction, R_t = 3.4 min)

4.1.5. Chemical preparation of (*E*,*Z*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10**

To a solution of (*E*,*Z*)-ethyl 3,4-bis- (4-hydroxyphenyl)-3-hexenoate **9** (354 mg, 1.09 mmol) in THF (10 mL), 2.5 mL of 5 N NaOH solution was added. This mixture was heated up to reflux for 2 h. To this cold reaction mixture, 0.5 mL 1 N NaOH solution was added and the aqueous layer was washed with ether and concentrated in vacuo. The aqueous layer was acidified with 6 N HCl, and the precipitate was

collected. The crude product was purified by column chromatography (chloroform : MeOH = 10:1) to obtain a mixture of *Z*- and *E*- isomers (*E*-isomer: 85%) of 3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** as a colorless solid (408 mg, 99%).

E-isomer of **10**:

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.08-7.03 (4H, d, J = 8.6 Hz, Ar-*H*), 6.81-6.75 (4H, m, Ar-*H*), 3.15 (2H, s, H_2CC=O), 2.22 (2H, q, J = 7.4 Hz, H_3CH_2CHC), 0.80 (3H, t, J = 7.4 Hz, H_3CH$_2$CHC).

^{13}C-NMR (MeOD, 100 MHz) δ (ppm) = 176, 157, 145, 135, 134, 132, 131, 116, 115, 62.1, 42.6, 29.6, 13.7.

HRMS (ESI-TOF, positive): $[C_{18}H_{18}O_4Na]^+$ cal. 321.1097, found 321.1103; $[C_{36}H_{36}O_8Na]^+$ cal. 619.2302, found 619.2312.

4.2. Chemical preparation of DES ligands **1**-**8**

4.2.1. General procedure for chemical preparations of bivalent DES ligands **1**-**4** and **6**

To a solution of (*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 2.1 equivalents), diamine **24** or **25** (1.0 equivalent), and triethylamine (2.2 equivalents) in anhydrous DMF at 0°C, a solution of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP, 2.2 equivalents) in anhydrous DCM was added. The reaction mixture was further stirred at 0°C for 30 min and then at room temperature for 24 h. The organic solvent was evaporated in vacuo and the residue was purified by column chromatography to obtain the bivalent DES ligand. A separation with RP-HPLC (Gemini 5µ C18 110 Å, 250×21.20 mm, 5 micron) was performed to separate the bivalent DES ligand into *Z*-*Z*, *Z*-*E*, and *E*-*E* isomers.

4.2.2. Chemical preparation of **1**

(*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 42.0 mg, 0.141 mmol), diamine **24a** (33.6 mg, 0.0671 mmol), triethylamine (20.7 µL, 0.148 mmol), PyBOP (76.8 mg, 0.148 mmol), anhydrous DMF (4 mL), and anhydrous DCM (4 mL) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 5:1) to obtain bivalent DES ligand **1** as a colorless oil (45.1 mg, 63%). *Z*-*Z* (5%), *Z*-*E* (34%), and *E*-*E* (61%) isomers were separated by RP-

HPLC (70% MeOH/H_2O, 10 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-Z isomer of **1** (the first fraction, R_t = 13.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 6.90-6.83 (8H, d and d, J = 8.7 Hz, 8.6 Hz, Ar-*H*), 6.60 (4H, d, J = 8.6 Hz, Ar-*H*), 6.56 (4H, d, J = 8.6 Hz, Ar-*H*), 3.60-3.54 (32H, m, OH_2CH_2CO), 3.53-3.49 (4H, m, OH_2CH_2CO), 3.46-3.39 (8H, s and t, J = 5.4 Hz, HNH_2CH_2CO, and H_2CC=O), 3.31 (4H, t, J = 5.3 Hz, HNH_2CH_2CO), 2.58 (4H, q, J = 7.6 Hz, H_3CH_2C), 0.94 (6H, t, J = 7.6 Hz, H_3CH_2C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 156, 143, 135, 132, 131, 115, 71.1, 45.0, 42.8, 39.8, 28.7, 13.2.

Z-E isomer of **1** (the second fraction, R_t = 15.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (2H, d, J = 8.4 Hz, (*E*)-Ar-*H*), 7.14 (2H, d, J = 8.5 Hz, (*Z*)-Ar-*H*), 6.90-6.81 (8H, m, (*E*,*Z*)-Ar-*H*), 6.59 (2H, d, J = 8.6 Hz, (*Z*)-Ar-H), 6.55 (2H, d, J = 8.6 Hz, (*Z*)-Ar-*H*), 3.61-3.46 (32H, m, OH_2CH_2CO), 3.46-3.40 (4H, s and t, J = 5.3 Hz, H_2CC=O and OH_2CH_2CO), 3.37-3.29 (6H, t and m, J = 5.6 Hz, OH_2CH_2CO, HNH_2CH_2CO, and H_2CC=O), 3.21 (2H, t, J = 5.2 Hz, HNH_2CH_2CO), 2.58 (2H, q, J = 7.6 Hz, (*Z*)-H_3CH_2C), 2.24 (2H, q, J = 7.4 Hz, (*E*)-H_3CH_2C), 0.94 (3H, t, J = 7.4 Hz, (*Z*)-H_3CH_2C), 0.80 (3H, t, J = 7.4 Hz, (*E*)-H_3CH_2C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 170, 156, 155, 143, 134, 133, 131, 130, 115, 70.4, 70.2, 69.7, 43.1, 42.0, 39.1, 28.0, 12.9, 12.4, 11.1.

E-E isomer of **1** (the third fraction, R_t = 17.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (4H, d, J = 8.5 Hz, Ar-*H*), 7.14 (4H, d, J = 8.4 Hz, Ar-*H*), 6.85 (8H, m, Ar-*H*), 3.58-3.52 (32H, m, OH_2CH_2CO), 3.50-3.46 (4H, m, OH_2CH_2CO), 3.35 (4H, t, J = 5.7 Hz, HNH_2CH_2CO), 3.22 (4H, t, J = 5.4 Hz, HNH_2CH_2CO), 3.11 (4H, s, H_2CC=O), 2.24 (4H, q, J = 7.4 Hz, H_3CH_2C), 0.80 (6H, t, J = 7.4 Hz, H_3CH_2C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 157, 144, 134, 132, 131, 116, 71.2, 71.0, 70.4, 49.6, 43.9, 39.8, 13.7, 11.9.

HRMS (ESI-TOF, positive): $[C_{58}H_{80}N_2O_{16}Na]^+$ cal. 1083.5400, found 1083.5420; $[C_{58}H_{80}N_2O_{16}K]^+$ cal. 1099.5139, found 1099.5162.

4.2.3. Chemical preparation of **2**

(*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 32.0 mg, 0.107 mmol), diamine **24b** (27.8 mg, 0.0510 mmol), triethylamine (16.0 μL, 0.112 mmol), PyBOP (58.4 mg, 0.112 mmol), anhydrous DMF (5 mL), and anhydrous DCM (5 mL) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1) to obtain bivalent DES ligand **2** as a colorless oil (27.4 mg, 49%). *Z*-*Z* (4%), *Z*-*E* (31%), and *E*-*E* (65%) isomers were separated by RP-HPLC (70% MeOH/H_2O, 10 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-*Z* isomer of **2** (the first fraction, R_t = 13.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 6.90-6.84 (8H, d and d, J = 8.7 Hz, 8.7 Hz, Ar-*H*), 6.60 (4H, d, J = 8.7 Hz, Ar-*H*), 6.56 (4H, d, J = 8.7 Hz, Ar-*H*), 3.62-3.54 (36H, m, OH_2CH_2CO), 3.53-3.49 (4H, m, OH_2CH_2CO), 3.45-3.40 (8H, s and t, J = 5.3 Hz, HNH_2CH_2CO, and H_2CC=O), 3.37-3.29 (4H, m, HNH_2CH_2CO), 2.58 (4H, q, J = 7.6 Hz, H$_3$CH_2C), 0.94 (6H, t, J = 7.4 Hz, H_3CH_2C).

Z-*E* isomer of **2** (the second fraction, R_t = 15.2 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (2H, d, J = 8.6 Hz, (*E*)-Ar-*H*), 7.14 (2H, d, J = 8.7 Hz, (*Z*)-Ar-*H*), 6.90-6.82 (8H, m, (*E*,*Z*)-Ar-*H*), 6.60 (2H, d, J = 8.7 Hz, (*Z*)-Ar-H), 6.55 (2H, d, J = 8.7 Hz, (*Z*)-Ar-*H*), 3.60-3.46 (40H, m, OH_2CH_2CO), 3.45-3.40 (4H, s and t, J = 5.4 Hz, H_2CC=O and OH_2CH_2CO), 3.38-3.29 (4H, m, OH_2CH_2CO, HNH_2CH_2CO, and H_2CC=O), 3.25-3.20 (2H, m, HNH_2CH_2CO), 2.58 (2H, q, J = 7.4 Hz, (*Z*)-H$_3$CH_2C), 2.24 (2H, q, J = 7.5 Hz, (*E*)-H$_3$CH_2C), 0.94 (3H, t, J = 7.4 Hz, (*Z*)-H_3CH_2C), 0.80 (3H, t, J = 7.4 Hz, (*E*)-H_3CH_2C).

E-*E* isomer of **2** (the third fraction, R_t = 17.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (4H, d, J = 8.6 Hz, Ar-*H*), 7.14 (4H, d, J = 8.6 Hz, Ar-*H*), 6.86-6.81 (8H, m, Ar-*H*), 3.60-3.52 (40H, m, OH_2CH_2CO), 3.50-3.46 (4H, m, OH_2CH_2CO), 3.36

(4H, t, J = 5.6 Hz, HNH$_2$CH_2CO), 3.22 (4H, q, J = 5.6 Hz, HNH_2CH$_2$CO), 3.11 (4H, s, H_2CC=O), 2.25 (4H, q, J = 7.6 Hz, H$_3$CH_2C), 0.80 (6H, t, J = 7.4 Hz, H_3CH$_2$C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171,157, 144, 134, 132, 131, 116, 115, 71.1, 71.0, 70.5, 44.0, 39.9, 29.2, 13.7.

HRMS (ESI-TOF, positive): $[C_{58}H_{80}N_2O_{16}Na]^+$ cal. 1083.5400, found 1083.5420; $[C_{58}H_{80}N_2O_{16}K]^+$ cal. 1099.5139, found 1099.5162.

4.2.4. Chemical preparation of **3**

(*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 36.9 mg, 0.124 mmol), diamine OEG **24c** (34.7 mg, 0.0590 mmol), triethylamine (18.2 μL, 0.130 mmol), PyBOP (67.5 mg, 0.130 mmol), anhydrous DMF (5 mL), and anhydrous DCM (5 mL) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1) to obtain bivalent DES ligand **3** as a colorless oil (39.5 mg, 58%). *Z*-*Z* (4%), *Z*-*E* (33%), and *E*-*E* (62%) isomers were separated by RP-HPLC (70% MeOH/H_2O, 10 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-*Z* isomer of **3** (the first fraction, R_t = 14.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 6.90-6.84 (8H, d and d, J = 8.7 Hz, 8.6 Hz, Ar-*H*), 6.60 (4H, d, J = 8.7 Hz, Ar-*H*), 6.56 (4H, d, J = 8.7 Hz, Ar-*H*), 3.62-3.54 (40H, m, OH_2CH_2CO), 3.54-3.50 (4H, m, OH_2CH$_2$CO), 3.46-3.40 (8H, s and t, J = 5.3 Hz, HNH$_2$CH_2CO, and H_2CC=O), 3.35-3.29 (4H, m, HNH_2CH$_2$CO), 2.58 (4H, q, J = 7.6 Hz, H$_3$CH_2C), 0.94 (6H, t, J = 7.4 Hz, H_3CH$_2$C).

Z-*E* isomer of **3** (the second fraction, R_t = 16.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (2H, d, J = 8.6 Hz, (*E*)-Ar-*H*), 7.14 (2H, d, J = 8.6 Hz, (*Z*)-Ar-*H*), 6.90-6.82 (8H, m, (*E*,*Z*)-Ar-*H*), 6.59 (2H, d, J = 8.6 Hz, (*Z*)-Ar-H), 6.55 (2H, d, J = 8.7 Hz, (*Z*)-Ar-*H*), 3.60-3.47 (44H, m, OH_2CH_2CO), 3.45-3.40 (4H, s and t, J = 5.3 Hz, H_2CC=O and OH_2CH$_2$CO), 3.38-3.28 (4H, m, OH_2CH$_2$CO, HNH$_2$CH_2CO, and H_2CC=O), 3.25-3.19 (2H, m, HNH_2CH$_2$CO), 2.58 (2H, q, J = 7.4 Hz, (*Z*)-H$_3$CH_2C), 2.24 (2H, q, J = 7.4 Hz, (*E*)-H$_3$CH_2C), 0.94 (3H, t, J = 7.4 Hz, (*Z*)-H_3CH$_2$C), 0.80 (3H, t, J = 7.4 Hz, (*E*)-H_3CH$_2$C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 170, 156, 155, 143, 134, 133, 131, 130, 115, 114, 70.3, 70.1, 69.6, 50.7, 50.4, 43.1, 42.0, 40.7, 39.1, 28.2, 27.9, 12.9, 12.3.

E-E isomer of **3** (the third fraction, R_t = 19.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (4H, d, J = 8.6 Hz, Ar-*H*), 7.14 (4H, d, J = 8.6 Hz, Ar-*H*), 6.86-6.81 (8H, m, Ar-*H*), 3.60-3.51 (40H, m, OH_2CH_2CO), 3.50-3.46 (4H, m, OH_2CH$_2$CO), 3.36 (4H, t, J = 5.6 Hz, HNH$_2$CH_2CO), 3.22 (4H, q, J = 5.5 Hz, HNH_2CH$_2$CO), 3.11 (4H, s, H_2CC=O), 2.25 (4H, q, J = 7.4 Hz, H$_3$CH_2C), 0.80 (6H, t, J = 7.4 Hz, H_3CH$_2$C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 157, 144, 134, 132, 131, 116, 71.2, 70.9, 70.4, 43.9, 39.9, 29.1, 13.6, 11.8.

HRMS (ESI-TOF, positive): $[C_{62}H_{89}N_2O_{18}]^+$ cal. 1149.6105, found 1149.6143; $[C_{62}H_{88}N_2O_{18}Na]^+$ cal. 1171.5924, found 1171.5961; $[C_{62}H_{88}N_2O_{18}K]^+$ cal. 1187.5664, found 1187.5701.

4.2.5. Chemical preparation of **4**

(*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 43.7 mg, 0.146 mmol), diamine **25a** (30.7 mg, 0.0695 mmol), triethylamine (22.0 μL, 0.153 mmol), PyBOP (77.0 mg, 0.153 mmol), anhydrous DMF (5 mL), and anhydrous DCM (5 mL) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1) to obtain bivalent DES ligand **4** as a colorless oil (35.4 mg, 51%). *Z-Z* (2%), *Z-E* (23%), and *E-E* (75%) isomers were separated by RP-HPLC (75% MeOH/H_2O, 20 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-Z isomer of **4** (the first fraction, R_t = 5.4 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 6.91-6.83 (8H, m, Ar-*H*), 6.59 (4H, d, J = 8.6 Hz, Ar-*H*), 6.55 (4H, d, J = 8.6 Hz, Ar-*H*), 3.59-3.49 (24H, m, OH_2CH_2CO), 3.46-3.39 (12H, m, HNH$_2$CH_2CO, H_2CC=O, and OCH_2CH$_2$), 3.34-3.27 (4H, q, J = 5.4 Hz, HNH_2CH$_2$CO), 2.57 (4H, q, J = 7.6 Hz, H$_3$CH_2C), 1.59 (4H, p, J = 3.3 Hz, OCH$_2$CH_2), 0.94 (6H, t, J = 7.4 Hz, H_3CH$_2$C).

Z-E isomer of **4** (the second fraction, R_t = 6.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (2H, d, J = 8.6 Hz, (*E*)-Ar-*H*), 7.13 (2H, d, J = 8.5 Hz, (*Z*)-Ar-*H*), 6.91-6.81 (8H, m, (*E*,*Z*)-Ar-*H*), 6.59 (2H, d, J = 8.6 Hz, (*Z*)-Ar-H), 6.55 (2H, d, J = 8.6 Hz, (*Z*)-Ar-*H*), 3.60-3.46 (22H, m, OH_2CH_2CO), 3.46-3.39 (8H, m, OH_2CH_2CO, H_2CC=O and OCH_2CH_2), 3.38-3.28 (8H, m, HNH_2CH_2CO and HNH_2CH_2CO), 3.10 (2H, s, H_2CC=O), 2.58 (2H, q, J = 7.6 Hz, (*Z*)-H_3CH_2C), 2.24 (2H, q, J = 7.6 Hz, (*E*)-H_3CH_2C), 1.58 (4H, p, J = 3.3 Hz, OCH_2CH_2), 0.94 (3H, t, J = 7.4 Hz, (*Z*)-H_3CH_2C), 0.80 (3H, t, J = 7.4 Hz, (*E*)-H_3CH_2C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 157, 156, 144, 143, 135, 134, 132, 131, 116, 115, 71.5, 71.2, 71.0, 70.8, 70.4, 39.9, 28.7, 27.2, 13.7, 13.2, 11.9.

E-*E* isomer of **4** (the third fraction, R_t =6.7 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (4H, d, J = 8.6 Hz, Ar-*H*), 7.14 (4H, d, J = 8.6 Hz, Ar-*H*), 6.88-6.80 (8H, m, Ar-*H*), 3.58-3.46 (22H, m, OH_2CH_2CO), 3.45-3.39 (4H, m, OH_2CH_2CO), 3.38-3.28 (9H, t and m, J = 5.6 Hz, HNH_2CH_2CO), 3.22 (4H, q, J = 5.4 Hz, HNH_2CH_2CO), 3.11 (4H, s, H_2CC=O), 2.25 (4H, q, J = 7.4 Hz, H_3CH_2C), 1.57 (4H, p, J = 3.2 Hz, OCH_2CH_2), 0.80 (6H, t, J = 7.4 Hz, H_3CH_2C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 157, 144, 134, 132, 131, 116, 71.5, 71.3, 71.2, 71.0, 70.8, 70.4, 47.0, 44.0, 39.9, 27.2, 13.7, 11.9.

HRMS (ESI-TOF, positive): $[C_{56}H_{77}N_2O_{14}]^+$ cal. 1001.5369, found 1001.5390; $[C_{56}H_{76}N_2O_{14}Na]^+$ cal. 1023.5189, found 1023.5212; $[C_{56}H_{76}N_2O_{14}K]^+$ cal. 1039.4928, found 1039.4955.

4.2.6. Chemical preparation of **5**

To a solution of (*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 43.1 mg, 0.144 mmol), 1H-benzotriazole (HOBT·H2O, 24.2 mg, 0.179 mmol), 1-(3-dimethylaminopropyl) -3-ethylcarbodimide hydrocholorid (EDCl, 34.3 mg, 0.179 mmol), and diisopropyl amine (51.0 μL, 0.289 mmol) in THF (5 mL), diamine OEG **25b** (34.2 mg, 0.0688 mmol) in THF (1 mL) was added at room temperature and the reaction mixture was stirred at 56°C for 24 h. The reaction mixture was adjusted to pH = 7~8 with 5% $NaHCO_3$ and washed with ether, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (chloroform : MeOH = 10:1) to obtain bivalent

DES ligand **5** as a colorless oil (18.1 mg, 25%). *Z-Z* (2%), *Z-E* (34%), and *E-E* (64%) isomers were separated by RP-HPLC (75% MeOH/H_2O, 20 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-Z isomer of **5** (the first fraction, R_t = 10.6 min)

Z-E isomer of **5** (the second fraction, R_t = 12.2 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.24 (2H, d, *J* = 8.4 Hz, (*E*)-Ar-*H*), 7.14 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.90-6.81 (8H, m, (*E*,*Z*)-Ar-*H*), 6.60 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-H), 6.55 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 3.59-3.46 (24H, m, O*H*$_2$C*H*$_2$CO), 3.45-3.39 (8H, m, OC*H*$_2$CH$_2$ and HNH$_2$C*H*$_2$CO), 3.37-3.28 (4H, m, HN*H*$_2$CH$_2$CO and *H*$_2$CC=O), 3.21 (2H, q, *J* = 5.2, HN*H*$_2$CH$_2$CO), 3.10 (2H, s, *H*$_2$CC=O), 2.58 (2H, q, *J* = 7.5 Hz, (*Z*)-H$_3$C*H*$_2$C), 2.24 (2H, q, *J* = 7.6 Hz, (*E*)-H$_3$C*H*$_2$C), 1.58-1.45 (4H, m, OCH$_2$C*H*$_2$ CH$_2$CH$_2$), 1.33-1.27 (8H, m, OCH$_2$CH$_2$ C*H*$_2$C*H*$_2$), 0.94 (3H, t, *J* = 7.4 Hz, (*Z*)-*H*$_3$CH$_2$C), 0.80 (3H, t, *J* = 7.4 Hz, (*E*)-*H*$_3$CH$_2$C).

E-E isomer of **5** (the third fraction, R_t = 13.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.23 (4H, d, *J* = 8.5 Hz, Ar-*H*), 7.14 (4H, d, *J* = 8.4 Hz, Ar-*H*), 6.87-6.81 (8H, m, Ar-*H*), 3.59-3.44 (24H, m, O*H*$_2$C*H*$_2$CO), 3.41 (4H, t, *J* = 6.6 Hz, O*H*$_2$CH$_2$CH$_2$CH$_2$), 3.35 (4H, t, *J* = 5.6 Hz, HNH$_2$C*H*$_2$CO), 3.22 (4H, q, *J* = 4.9 Hz, HN*H*$_2$CH$_2$CO), 3.10 (4H, s, *H*$_2$CC=O), 2.25 (4H, q, *J* = 7.5 Hz, H$_3$C*H*$_2$C), 1.50 (4H, p, *J* = 6.8 Hz, OCH$_2$C*H*$_2$CH$_2$CH$_2$), 1.37-1.26 (8H, m, OCH$_2$CH$_2$C*H*$_2$C*H*$_2$), 0.80 (6H, t, *J* = 7.4 Hz, *H*$_3$CH$_2$C).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 171, 157, 144, 134, 132, 131, 116, 115, 71.7, 71.2, 71.0, 70.8, 70.5, 44.0, 39.9, 30.5, 30.2, 26.9, 13.7, 11.9.

HRMS (ESI-TOF, positive): $[C_{60}H_{84}N_2O_{14}Na]^+$ cal. 1079.5815, found 1079.5729; $[C_{60}H_{84}N_2O_{14}Na_2]^{2+}$ cal. 551.2854, found 551.2805.

4.2.7. Chemical preparation of **6**

(*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 39.6 mg, 0.133 mmol), diamine **25c** (35.7 mg, 0.0633 mmol), triethylamine (19.5 μL, 0.139 mmol), PyBOP (72.4 mg, 0.139 mmol), anhydrous DMF (5 mL), and anhydrous DCM (5 mL) were used and the crude product was purified by

column chromatography (chloroform : MeOH = 20:1 to 10:1) to obtain bivalent DES ligand **6** as a colorless oil (48.4 mg, 68%). *Z*-*Z* (6%), *Z*-*E* (31%), and *E*-*E* (63%) isomers were separated by RP-HPLC (75% MeOH/H_2O, 20 mL/min) and characterized with ^{1}H-NMR according to the chemical shift of **9**.

Z-*Z* isomer of **6** (the first fraction, R_t = 10.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.63 (4H, d, *J* = 8.2 Hz, biphenyl-*H*), 7.44 (4H, d, *J* = 8.1 Hz, biphenyl-*H*), 6.89-6.83 (8H, m, Ar-*H*), 6.59 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.55 (4H, d, *J* = 8.6 Hz, Ar-*H*), 4.60 (4H, s, OCH_2Ar), 3.67-3.55 (20H, m, OH_2CH_2CO), 3.53-3.49 (4H, m, OH_2CH_2CO) 3.44-3.38 (8H, s and t, *J* = 5.5 Hz, H_2CC=O and HNH$_2$CH_2CO), 3.29 (4H, q, *J* = 5.7 Hz, HNH_2CH$_2$CO), 2.56 (4H, q, *J* = 7.5 Hz, H$_3$CH_2C), 0.92 (6H, t, *J* = 7.6 Hz, H_3CH$_2$C).

Z-*E* isomer of **6** (the second fraction, R_t = 12.3 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.63 (4H, d, *J* = 8.1 Hz, biphenyl-*H*), 7.44 (4H, dd, *J* = 3.5 Hz, 8.2 Hz, biphenyl-*H*), 7.23 (2H, d, *J* = 8.6 Hz, (*E*)-Ar-*H*), 7.13 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.89-6.81 (8H, m, (*E*,*Z*)-Ar-*H*), 6.59 (2H, d, *J* = 8.7 Hz, (*Z*)-Ar-H), 6.55 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 4.59-4.58 (4H, s and s, OCH_2Ar), 3.67-3.53 (22H, m, OH_2CH_2CO), 3.53-3.46 (4H, m, OH_2CH$_2$CO) 3.44-3.39 (4H, s and t, *J* = 5.4 Hz, CH_2C=O and HNH$_2$CH_2CO), 3.36-3.32 (2H, m, HNH_2CH$_2$CO), 3.22-3.16 (2H, q, *J* = 5.4 Hz, HNH_2CH$_2$CO), 3.09 (2H, s, CH_2C=O) 2.56 (2H, q, *J* = 7.5 Hz, (*Z*)-H$_3$CH_2C), 2.23 (2H, q, *J* = 7.6 Hz, (*E*)-H$_3$CH_2C), 0.92 (3H, t, *J* = 7.6 Hz, (*Z*)-H_3CH$_2$C), 0.79 (3H, t, *J* = 7.4 Hz, (*E*)-H_3CH$_2$C).

E-*E* isomer of **6** (the third fraction, R_t = 13.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.62 (4H, d, *J* = 8.2 Hz, biphenyl-*H*), 7.44 (4H, d, *J* = 8.1 Hz, biphenyl-*H*), 7.22 (4H, d, *J* = 8.6 Hz, Ar-*H*), 7.13 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.87-6.80 (8H, m, Ar-*H*), 4.58 (4H, s, OCH_2Ar), 3.67-3.53 (20H, m, OH_2CH_2CO), 3.50-3.46 (4H, m, OH_2CH$_2$CO), 3.34 (4H, t, *J* = 5.4 Hz, HNH$_2$CH_2CO), 3.19 (4H, q, *J* = 5.5 Hz, HNH_2CH$_2$CO), 3.09 (4H, s, H_2CC=O), 2.23 (4H, q, *J* = 7.4 Hz, H$_3$CH_2C), 0.79 (6H, t, *J* = 7.4 Hz, H_3CH$_2$C).

HRMS (ESI-TOF, positive): $[C_{66}H_{81}N_2O_{14}]^+$ cal. 1125.5682, found 1125.5694; $[C_{66}H_{80}N_2O_{14}Na]^+$ cal. 1147.5502, found 1147.5514; $[C_{66}H_{80}N_2O_{14}K]^+$ cal. 1163.5241, found 1163.5261.

4.2.8. Chemical preparation of **7**

To a solution of (*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 105 mg, 0.353 mmol), 1H-benzotriazole ($HOBT \cdot H_2O$, 59.0 mg, 0.437 mmol), 1-(3-dimethylaminopropyl) -3-ethylcarbodimide hydrocholorid (EDCl, 83.7 mg, 0.437 mmol), and diisopropyl amine (124 μL, 0.706 mmol) in THF (15 mL), 2,2'-(ethylenedioxy)-bis-(ethylamine) (25.1 μL, 0.168 mmol) was added at room temperature and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was adjusted to pH = 7~8 with 5% $NaHCO_3$ and washed with ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (chloroform : MeOH = 10:1) to obtain a mixture of *Z*- and *E*- isomers (*E*-isomer: 80%, according to ^{1}H-NMR) of bivalent DES ligand **7** as a colorless oil (27.2 mg, 23%). *E*-isomer was characterized with ^{1}H-NMR according to the chemical shift of **9**.

E-isomer of **7**:

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.21 (2H, d, J = 8.5 Hz, Ar-*H*), 6.08 (2H, d, J = 8.6 Hz, Ar-*H*), 6.85-6.80 (4H, m, Ar-*H*), 3.45-3.42 (4H, m, OCH_2CH_2O) 3.33 (4H, q, J = 5.7 Hz, $HNCH_2CH_2O$), 2.22 (4H, q, J = 5.4 Hz, $HNCH_2CH_2O$), 3.14 (2H, s, $H_2CC{=}O$), 2.25 (4H, q, J = 7.4 Hz, H_3CH_2C), 0.80 (6H, t, J = 7.4 Hz, H_3CH_2CHC).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 172, 157, 144, 135, 134, 132, 131, 116, 115, 71.0, 70.4, 44.1, 40.0, 39.9, 13.7.

HRMS (ESI-TOF, positive): $[C_{42}H_{48}N_2O_8Na]^+$ cal. 731.3303, found 731.3294.

4.2.9. Chemical preparation of **8**

To a solution of (*E*)-3,4-bis-(4-hydroxyphenyl)-3-hexenoic acid **10** (85% of *E*-isomer, 109 mg, 0.367 mmol), 1H-benzotriazole ($HOBT \cdot H_2O$, 59.5 mg, 0.440 mmol), 1-(3-dimethylaminopropyl) -3-ethylcarbodimide hydrocholorid (EDCl, 84.4 mg, 0.440 mmol), and diisopropyl amine (128 μL, 0.733 mmol) in THF (15 mL), 2.0 M ethylamine in THF (367 μL, 0.733 mmol) was added at room

temperature and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was adjusted to pH = 7~8 with 1 M HCl and washed with ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (chloroform : MeOH = 10:1) to obtain a mixture of *Z*- and *E*- isomers (*E*-isomer: 80%, according to ^{1}H-NMR) of **8** as a white solid (19.7 mg, 16%). *E*-isomer was characterized with ^{1}H-NMR according to the chemical shift of **9**.

E-isomer of **8**:

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.15 (2H, d, J = 8.6 Hz, Ar-*H*), 6.08 (2H, d, J = 8.6 Hz, Ar-*H*), 6.80-6.74 (4H, m, Ar-*H*), 3.06 (2H, s, H_2CC=O), 3.01 (2H, q, J = 7.2 Hz, HNCH_2CH$_3$), 2.23 (2H, q, J = 7.4 Hz, H$_3$CH_2C), 0.91 (3H, t, J = 7.2 Hz, HNCH$_2$CH_3), 0.79 (3H, t, J = 7.4 Hz, H_3CH$_2$CHC).

^{13}C-NMR (MeOD, 100 MHz) δ (ppm) = 157, 134, 132, 131, 116, 115, 44.1, 35.3, 29.7, 14.9, 13.7.

HRMS (ESI-TOF, positive): $[C_{20}H_{24}NO_3]^+$ cal. 326.1751, found 326.1761; $[C_{20}H_{23}NO_3Na]^+$ cal. 348.1570, found 348.1586; $[C_{40}H_{46}N_2O_6Na]^+$ cal. 673.3248, found 673.3272.

5. Chemical preparation of 4-hydroxytamoxifen (OHT) ligands **11**–**20**

5.1. Chemical preparation of 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene **26**

To a stirred suspension of zinc powder (6.40 g, 98.0 mmol) in anhydrous THF (20 mL), titanium tetrachloride (4.88 mL, 44.2 mol) was added dropwise under argon at 0°C. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. To the cooled dark suspension of the titanium reagent, a solution of 4,4'-hydroxybenzophenone (1.60 g, 7.25 mmol) and propiophenone (3.14 g, 23.2 mmol) in anhydrous THF (40 mL) was added dropwise at 0°C, and the mixture was refluxed in the dark for 2 h. After being cooled to room temperature, the reaction mixture was quenched with 10% aqueous potassium carbonate (30 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The rosy residue was dissolved in the *n*-hexane and the insoluble solid was filtered. The rosy crude product was purified by column chromatography ($CHCl_3$: AcOEt = 5:1) to obtain 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene **26** as a white solid (2.27 g, 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.17-7.11 (2H, m, Ar-*H*), 7.10-7.05 (3H, m, Ar-*H*), 7.04-6.99 (2H, d, J = 8.6 Hz, Ar-*H*), 6.76 (2H, d, J = 8.7 Hz, Ar-*H*), 6.65 (2H, d, J = 8.7 Hz, Ar-*H*), 6.39 (2H, d, J = 8.7 Hz, Ar-*H*), 2.47 (2H, d, J = 7.4 Hz, CCH_2CH$_3$), 0.90 (3H, t, J = 7.3 Hz, CCH$_2$CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 157, 156, 144, 142, 140, 137, 136, 133, 131, 129, 127, 116, 115, 30.0, 14.1.

HRMS (ESI-TOF, negative): $[C_{22}H_{19}O_2]^-$ cal. 315.1391, found 315.1418; $[C_{44}H_{39}O_4]^-$ cal. 631.2854, found 631.2893.

5.2. Chemical preparation of 2-[(*N*-benzyloxycarbonyl)methylamino]ethanol **27**

To a solution of 2-(methylamino) ethanol (2.95 g, 39.3 mmol) and triethyl amine (7.11 mL, 51.1 mmol) in anhydrous DCM (100 mL), benzyl chloroformate (6.13 mL, 41.3 mmol) in anhydrous DCM (40 mL) was added dropwise at 0°C over 30 min and the reaction mixture was further stirred at room temperature for 24 h. The reaction mixture was washed with 10% citric acid (120 mL), 10% $KHCO_3$, water, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography

(hexane : AcOEt = 3:2) to obtain 2-[(*N*-benzyloxycarbonyl) methylamino] ethanol **27** as colorless oil (5.78 g, 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.39-7.28 (5H, m, Ar-*H*), 5.12 (2H, s, ArCH_2O), 3.75 (2H, br s, CH_2CH_2OH), 3.44 (2H, t, J = 4.5 Hz, CH_2CH_2OH), 2.99 (3H, s, NCH_3), 2.60 (1H, s, O*H*).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 158, 137, 129, 128, 67.4, 61.3, 61.1, 52.1, 51.2, 35.5.

5.3. Chemical preparation of (*E*,*Z*)-benzyl 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl) phenoxy)ethyl(methyl)carbamate **28**

To a solution of 2-[(*N*-benzyloxycarbonyl)methylamino]ethanol **27** (206 mg, 0.983 mmol), triphenylphosphine (391 mg, 1.47 mmol), and 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene **26** (311 mg, 0.983 mmol) in anhydrous THF (10 mL), a solution of diethyl azodicarbonylate (DEAD, 236 μL, 1.47 mmol) in anhydrous THF (10 mL) was added at 0°C over 30 min. This reaction mixture was further stirred at room temperature for 24 h. The solvent was removed in vacuo and the residue was dissolved in diethyl ether, washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was further purified by two times column chromatography (chloroform : MeOH = 20:1, hexane : AcOEt = 3:2) to obtain a mixutrue of *Z*- and *E*- isomers (*Z* : *E* = 1:1) of benzyl 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl) phenoxy)ethyl(methyl)carbamate **28** as a light yellow solid (200 mg, 40%). Due to the facile isomerization of the triarylethylene structure, a geometrical isomer separation was not performed for **28**.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm) = 7.38-7.28 (10H, m, Ar-*H*), 7.18-7.06 (14H, m, Ar-*H*), 6.88-6.78 (4H, m, Ar-*H*), 6.73-6.69 (4H, m, Ar-*H*), 6.54-6.43 (4H, m, Ar-*H*), 5.15 (2H, s, ArCH_2O), 5.11 (2H, s, ArCH_2O), 4.14 (1H, t, J = 4.8 Hz, OCH_2CH$_2$N), 4.08 (1H, t, J = 5.0 Hz, OCH_2CH$_2$N), 3.98 (1H, t, J = 5.0 Hz, OCH_2CH$_2$N), 3.92 (1H, t, J = 5.2 Hz, OCH_2CH$_2$N), 3.72-3.64 (2H, m, OCH$_2$CH_2N), 3.61-3.54 (2H, m, OCH$_2$CH_2N), 3.09 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 2.52-2.43 (4H, 2 × d, J = 7.4 Hz, 7.4 Hz, CCH_2CH$_3$), 0.92 (6H, t, J = 7.4 Hz, CCH$_2$CH_3).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm) = 155, 154, 143, 141, 138, 137, 136, 132, 131, 130, 129, 128, 126, 115, 114, 113, 67.6, 67.5, 49.5, 49.2, 36.3, 29.3, 29.2, 13.8.

5.4. Chemical preparation of (*E*,*Z*)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut- 1-enyl)phenol **29**

To a solution of (*E*,*Z*)-benzyl 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy)ethyl (methyl)carbamate **28** (352 mg, 0.694 mmol) in ethyl acetate (50 mL), palladium on barium sulfate (5%, 148 mg, 0.0694 mmol) was added and the mixture was hydrogenated for 96 h until TLC analysis indicated complete consumption of **28**. The mixture was filtered over Celite and the filter cake was washed with ethyl acetate. The crude product was concentrated in vacuo and further purified by column chromatography (chloroform : MeOH = 10:1, + 3% triethylamine) to obtain a mixutrue of *Z*- and *E*-isomers (*Z* : *E* = 1:1) of 4-(1-(4-(2-(methylamino) ethoxy)phenyl)-2-phenylbut- 1-enyl)phenol **29** as a colorless oil (224 mg, 87%). *Z*- and *E*- isomers were separated by RP-HPLC (75% MeOH/H_2O + 0.05% TFA, 20 mL/min) and characterized with ^{1}H-NMR according to the previous report.[6]

Z-isomer of **29** (the first fraction, R_t = 3.8 min):

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.17-7.05 (7H, m, Ar-*H*), 6.93 (2H, d, *J* = 8.8 Hz, Ar-*H*), 6.64 (2H, d, *J* = 8.8 Hz, Ar-*H*), 6.39 (2H, d, *J* = 8.7 Hz, Ar-*H*), 4.11 (2H, t, *J* = 5.2 Hz, OCH_2CH_2N), 2.96 (2H, t, *J* = 5.2 Hz, OCH_2CH_2N), 2.47 (5H, s and q, *J* = 7.4 Hz, NCH_3 and CCH_2CH_3), 0.90 (3H, t, *J* = 7.4 Hz, CCH_2CH_3).

E-isomer of **29** (the second fraction, R_t = 4.1 min):

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.18-7.04 (5H, m, Ar-*H*), 7.01 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.93 (4H, 2 × d, *J* = 8.6 Hz, 8.7 Hz, Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, Ar-*H*), 3.95 (2H, t, *J* = 5.1 Hz, OCH_2CH_2N), 2.87 (2H, t, *J* = 5.3 Hz, OCH_2CH_2N), 2.48 (2H, q, *J* = 7.4 Hz, CCH_2CH_3), 2.41 (3H, s, NCH_3), 0.90 (3H, t, *J* = 7.4 Hz, CCH_2CH_3).

HRMS (ESI-TOF, positive): $[C_{25}H_{28}NO_2]^+$ cal. 374.2115, found 374.2142; $[C_{25}H_{27}NO_2Na]^+$ cal. 396.1934, found 396.1866.

5.5. Chemical preparation of (*E*,*Z*)-4-(1-(4-(2,2-diethoxyethoxy)phenyl)-2-phenylbut-1-enyl)phenol **32**

To a solution of 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene **26** (1.07 g, 3.39 mmol) in anhydrous DMF (20 mL), a solution of sodium ethoxide (21% in EtOH, 1.27 mL, 3.39 mmol) in anhydrous DMF (10 mL) was added dropwise over 30 min at 70°C and the reaction mixture was stirred and heated up to 120°C for 30 min. After the mixture was cooled to room temperature, a solution of bromoacetal diethylacetal (526 μL, 3.39 mmol) in anhydrous DMF (20 mL) was added dropwise and the mixture was stirred at 120°C for 3 h. The solvent was removed in vacuo. The residue was washed with ethyl acetate, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was further purified by 2 times column chromatography (chloroform : MeOH = 40:1, hexane : AcOEt = 5:1) to a mixture of *Z*- and *E*-isomers of 4-(1-(4-(2,2- diethoxyethoxy)phenyl)-2-phenylbut-1-enyl)phenol **32** as a yellow oil (627 mg, 43%). Due to the facile isomerization of the triarylethylene structure, a geometrical isomer separation by RP-HPLC (85%MeOH/H_2O, 21.2 mL/min) was only performed for the characterization of *Z*- and *E*-isomers of **32** with the NOE spectra method.

Z-isomer of **32** (the first fraction, R_t = 30.0 min):

^{1}H-NMR (Acetone-d6, 250 MHz) δ (ppm) = 8.38 (1H, s, Ar-O*H*), 7.24-7.02 (7H, m, Ar-*H*), 6.90-6.74 (4H, 2 × d, *J* = 8.8 Hz, 8.8 Hz, Ar-*H*), 6.59 (2H, d, *J* = 8.1 Hz, Ar-*H*), 4.74 (1H, t, *J* = 5.2 Hz, OCH_2CH), 3.84 (2H, d, *J* = 5.9 Hz, OCH_2CH), 3.77-3.48 (4H, m, OCH_2CH_3), 2.50 (2H, q, *J* = 7.4 Hz, CCH_2CH_3), 1.14 (6H, t, *J* = 6.6 Hz, OCH_2CH_3), 0.91 (3H, t, *J* = 7.4 Hz, CCH_2CH_3).

^{13}C-NMR (Acetone-d6, 62.5 MHz) δ (ppm) =157, 143, 141, 139, 137, 136, 133, 131, 130, 129, 127, 116, 114, 101, 69.1, 62.8, 29.5, 15.7, 13.8.

E-isomer of **32** (the second fraction, R_t = 32.0 min):

^{1}H-NMR (Acetone-d6, 250 MHz) δ (ppm) = 8.13 (1H, s, Ar-O*H*), 7.23-7.07 (7H, m, Ar-*H*), 6.96 (2H, d, *J* = 8.1 Hz, Ar-*H*), 6.70 (2H, d, *J* = 8.8 Hz, Ar-*H*), 6.49 (2H, d, *J* = 8.8 Hz, Ar-*H*), 4.85 (1H, t, *J* = 5.1 Hz, OCH_2CH), 4.00 (2H, d, *J* = 5.2 Hz, OCH_2CH), 3.80-3.58 (4H, m, OCH_2CH_3), 2.48 (2H, q, *J* = 7.4 Hz, CCH_2CH_3), 1.19 (6H, t, *J* = 7.4 Hz, OCH_2CH_3), 0.91 (3H, t, *J* = 7.4 Hz, CCH_2CH_3).

^{13}C-NMR (Acetone-d6, 62.5 MHz) δ (ppm) = 158, 156, 144, 141, 139, 137, 133, 131, 129, 127, 116, 115, 114, 101, 69.4, 69.2, 62.9, 29.5, 15.7, 13.9.

HRMS (ESI-TOF, positive): $[C_{28}H_{32}O_4Na]^+$ cal. 455.2193, found 455.2170; $[C_{28}H_{32}O_4K]^+$ cal. 471.1932, found 471.1908; $[C_{56}H_{64}O_8Na]^+$ cal. 887.4493, found 887.4453.

5.6. Chemical preparation of (*E*,*Z*)-2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl)phenoxy) acetaldehyde **33**

To a solution of (*E*,*Z*)-4-(1-(4-(2,2-diethoxyethoxy)phenyl)-2-phenylbut- 1-enyl)phenol **32** (467 mg, 1.08 mmol) in THF (4.7 mL), 3 M HCl (4.7 mL) was added and the reaction mixture was stirred at 50°C for 20 h until TLC analysis indicated complete consumption of **32**. The organic solvent was removed in vacuo and the residue was neutralized with saturated $NaHCO_3$, washed with diethyl ether, brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was further purified by column chromatography (hexane : AcOEt = 5:1 to 1:1) to obtain a mixture of *Z*- and *E*-isomers (*Z* : *E* = 1:1) of 2-(4-(1-(4-hydroxyphenyl)-2-phenylbut-1-enyl) phenoxy)acetaldehyde **33** as a white solid (318 mg, 82%). Since the aldehyde forms a stabile hemiacetal with alcohol, a geometrical isomer separation by HPLC was not performed and the product was characterized according to the chemical shift of **32**.

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 9.83 (1H, s, aldehyde-*H*), 9.72 (1H, s, aldehyde-*H*), 8.37 (1H, s, Ar-O*H* of *Z*-isomer), 8.13 (1H, s, Ar-O*H* of *E*-isomer), 7.20-7.06 (14H, m, Ar-*H*), 7.07 (4H, d, *J* = 8.6 Hz, Ar-H of *Z*-isomer), 6.96 (2H, d, *J* = 8.8 Hz, Ar-*H* of *E*-isomer), 6.84 (2H, d, *J* = 8.7 Hz, Ar-H of *Z*-isomer), 6.81 (2H, d, *J* = 8.9 Hz, Ar-*H* of *Z*-isomer), 6.70 (2H, d, *J* = 8.7 Hz, Ar-*H* of *E*-isomer), 6.60 (2H, d, *J* = 9.0 Hz, Ar-H of *Z*-isomer), 6.49 (2H, d, *J* = 8.7 Hz, Ar-*H* of *E*-isomer), 4.80 (2H, s, OCH_2C=O), 4.61 (2H, s, OCH_2C=O), 2.53-2.43 (4H, 2 × q, *J* = 7.5 Hz, 7.4 Hz, CCH_2CH$_3$), 0.90 (3H, t, *J* = 7.4 Hz, CCH$_2$CH_3).

^{13}C-NMR (Acetone-d6, 100 MHz) δ (ppm) = 199, 158, 157, 156, 144, 142, 139, 138, 136, 135, 133, 131, 129, 127, 116, 115, 114, 73.7, 73.4, 13.9.

HRMS (ESI-TOF, negative): $[C_{24}H_{21}O_3]^-$ cal. 357.1496, found 357.1505; $[C_{48}H_{43}O_6]^-$ cal. 715.3065, found 715.3075.

5.7. Chemical preparation of bivalent 4-hydroxytamoxifen ligands **11-19**

5.7.1. General procedure for chemical preparations of bivalent 4-hydroxytamoxifen ligands **11-17** and **19**

To a solution of bis(N-methylamine) OEG spacer **34** (1.0 equivalent) and sodium triacetoxyborohydride (3.0 equivalents) in anhydrous THF, **33** (2.2 equivalents) were added at room temperature and the reaction mixture was stirred at room temperature until TLC analysis indicated complete consumption of **33**. The reaction mixture was neutralized with a saturated $NaHCO_3$ solution and concentrated in vacuo. The residue was absorbed on the silica gel and further purified by column chromatography to obtain the pure product. Three pure isomers was obtained by a separation with RP-HPLC and characterized by ^{1}H-NMR according to the chemical shift of **32**.

5.7.2. Chemical preparation of **11**

1,5-bis(methylamino)-3-oxapentane (6.00 mg, 0.0445 mmol), (*E*, *Z*)-isomer of **33** (40.7 mg, 0.111 mmol), sodium triacetoxyborohydride (28.9 mg, 0.133 mmol) and 10 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 10:1 to 5:1 + 3% triethylamine) and by RP-HPLC (85% MeOH/H_2O + 0.4% diethylamine, 30 mL/min) to obtain **11** (33.1 mg, 81%) as three pure isomers: *Z*-*Z* (29%), *Z*-*E* (47%), and *E*-*E* (24%) isomer.

Z-*Z* isomer of **11** (the first fraction, R_t= 8.9 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.19-7.11 (8H, m, Ar-*H*), 7.11-7.04 (6H, m, Ar-*H*), 6.84 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.77 (4H, d, *J* = 8.8 Hz, Ar-*H*), 6.55 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.92 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.49 (8H, t, *J* = 5.9 Hz, C*H*$_2$OC*H*$_2$), 2.74 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.60 (4H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$O), 2.49 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.29 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

Z-*E* isomer of **11** (the second fraction, R_t= 9.9 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.03 (14H, m, Ar-*H*), 6.92 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.7 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.8 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.09 (2H, t, *J* = 5.9 Hz, (*E*)-ArOC*H*$_2$CH$_2$N), 3.94 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOC*H*$_2$CH$_2$N), 3.57-3.51 (4H, m, C*H*$_2$OC*H*$_2$), 2.84 (2H, t,

J = 6.0 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.76 (2H, t, *J* = 5.9 Hz, (*E*)-NC*H*$_2$CH$_2$O), 2.66 (2H, t, *J* = 5.8 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.63 (2H, t, *J* = 5.8 Hz, (*E*)-ArOCH$_2$C*H*$_2$N), 2.51-2.44 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, C*H*$_2$CH$_3$), 2.36 (3H, s, (*Z*)-NC*H*$_3$), 2.31 (3H, s, (*E*)-NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

E-*E* isomer of **11** (the third fraction, R_t = 11.2 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.05 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.69 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.48 (4H, d, *J* = 8.7 Hz, Ar-*H*), 4.14 (4H, t, *J* = 5.9 Hz, ArOC*H*$_2$CH$_2$N), 3.61 (4H, *J* = 5.7 Hz, C*H*$_2$OC*H*$_2$), 2.92 (4H, t, *J* = 5.7 Hz, ArOCH$_2$C*H*$_2$N), 2.75 (4H, t, *J* = 5.6 Hz, ArOCH$_2$C*H*$_2$N), 2.47 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.42 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

HRMS (ESI-TOF, positive): $[C_{54}H_{62}O_5N_2]^{2+}$ cal. 409.2324, found 409.2333; $[C_{54}H_{61}O_5N_2]^{+}$ cal. 817.4575, found 817.4581; $[C_{54}H_{60}O_5N_2Na]^{+}$ cal. 839.4394, found 839.4406.

5.7.3. Chemical preparation of **12**

1,8-bis(methylamino)-3,6-dioxaoctane (10.0 mg, 0.0556 mmol), (*E*, *Z*)-isomer of **33** (46.8 mg, 0.128 mmol), sodium triacetoxyborohydride (37.2 mg, 0.167 mmol) and 15 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (85% MeOH/H_2O + 0.4% diethylamine, 30 mL/min) to obtain **2** (27.5 mg, 53%) as three pure isomers: *Z*-*Z* (31%), *Z*-*E* (47%), and *E*-*E* (22%) isomer.

Z-*Z* isomer of **12** (the first fraction, R_t = 16.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.11 (8H, m, Ar-*H*), 7.10-7.05 (6H, m, Ar-*H*), 6.84 (4H, d, *J* = 8.5 Hz, Ar-*H*), 6.77 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.56 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.91 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.53-3.47 (8H, m, C*H*$_2$OC*H*$_2$), 2.72 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.58 (4H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$O), 2.48 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.28 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

Z-*E* isomer of **12** (the second fraction, R_t = 17.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.12 (10H, m, Ar-*H*), 7.10-7.05 (4H, m, Ar-*H*), 6.92 (2H, d, *J* = 8.8 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.7 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*),

6.69 (2H, d, J = 8.7 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, J = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, J = 8.7 Hz, (*E*)-Ar-*H*), 4.08 (2H, t, J = 6.0 Hz, (*E*)-ArOCH_2CH$_2$N), 3.93 (2H, t, J = 6.0 Hz, (*Z*)-ArOCH_2CH$_2$N), 3.59-3.48 (8H, m, CH_2OCH_2), 2.83 (2H, t, J = 6.0 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.74 (2H, t, J = 6.0 Hz, (*E*)-NCH_2CH$_2$O), 2.65 (2H, t, J = 5.9 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.60 (2H, t, J = 6.0 Hz, (*E*)-ArOCH$_2$CH_2N), 2.53-2.43 (4H, 2×q, J = 7.4 Hz, 7.4 Hz, CH_2CH$_3$), 2.35 (3H, s, (*Z*)-NCH_3), 2.29 (3H, s, (*E*)-NCH_3), 0.90 (6H, t, J = 7.4 Hz, CH$_2$CH_3).

E-*E* isomer of **12** (the third fraction, R_t = 18.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.07 (14H, m, Ar-*H*), 6.93 (4H, d, J = 8.8 Hz, Ar-*H*), 6.69 (4H, d, J = 8.7 Hz, Ar-*H*), 6.48 (4H, d, J = 8.7 Hz, Ar-*H*), 4.10 (4H, t, J = 6.0 Hz, ArOCH_2CH$_2$N), 3.61-3.51 (8H, m, CH_2OCH_2), 2.85 (4H, t, J = 6.0 Hz, ArOCH$_2$CH_2N), 2.67 (4H, t, J = 5.9 Hz, ArOCH$_2$CH_2N), 2.47 (4H, q, J = 7.4 Hz, CH_2CH$_3$), 2.36 (6H, s, NCH_3), 0.90 (6H, t, J = 7.3 Hz, CH$_2$CH_3).

HRMS (ESI-TOF, positive): $[C_{56}H_{66}O_6N_2]^{2+}$ cal. 431.2455, found 431.2470; $[C_{56}H_{65}O_6N_2]^{+}$ cal. 861.4837, found 861.4854; $[C_{56}H_{64}O_6N_2Na]^{+}$ cal. 883.4657, found 883.4676.

5.7.4. Chemical preparation of **13**

The bis(N-methylamino) OEG spacer **34a** (12.0 mg, 0.0545 mmol), (*E*, *Z*)-isomer of **33** (44.9 mg, 0.125 mmol), sodium triacetoxyborohydride (35.7 mg, 0.163 mmol) and 5 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (80% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **18** (13.3 mg, 29%) as three pure isomers: *Z*-*Z* (26%), *Z*-*E* (49%), and *E*-*E* (25%) isomer.

Z-*Z* isomer of **13** (the first fraction, R_t = 21.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.12 (8H, m, Ar-*H*), 7.11-7.05 (6H, m, Ar-*H*), 6.84 (4H, d, J = 8.6 Hz, Ar-*H*), 6.77 (4H, d, J = 8.8 Hz, Ar-*H*), 6.57 (4H, d, J = 8.8 Hz, Ar-*H*), 3.93 (4H, t, J = 6.0 Hz, ArOCH_2CH$_2$N), 3.54-3.48 (12H, m, CH_2OCH_2), 2.74 (4H, t, J = 6.0 Hz, ArOCH$_2$CH_2N), 2.60 (4H, t, J = 5.9 Hz, NCH_2CH$_2$O), 2.48 (4H, q, J = 7.4 Hz, CH_2CH$_3$), 2.29 (6H, s, NCH_3), 0.90 (6H, t, J = 7.3 Hz, CH$_2$CH_3).

Z-E isomer of **13** (the second fraction, R_t = 23.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.10 (10H, m, Ar-*H*), 7.10-7.05 (4H, m, Ar-*H*), 6.93 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.4 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.7 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.11 (2H, t, *J* = 5.9 Hz, (*E*)-ArOCH_2CH$_2$N), 3.95 (2H, t, *J* = 5.9 Hz, (*Z*)-ArOCH_2CH$_2$N), 3.59-3.51 (12H, m, CH_2OCH_2), 2.87 (2H, t, *J* = 5.8 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.77 (2H, t, *J* = 5.9 Hz, (*E*)-NCH_2CH$_2$O), 2.69 (2H, t, *J* = 5.8 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.63 (2H, t, *J* = 5.7 Hz, (*E*)-ArOCH$_2$CH_2N), 2.53-2.44 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, CH_2CH$_3$), 2.38 (3H, s, (*Z*)-NCH_3), 2.32 (3H, s, (*E*)-NCH_3), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$CH_3).

E-E isomer of **13** (the third fraction, R_t = 27.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.06 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.69 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.49 (4H, d, *J* = 8.6 Hz, Ar-*H*), 4.11 (4H, t, *J* = 5.9 Hz, ArOCH_2CH$_2$N), 3.60-3.54 (12H, m, CH_2OCH_2), 2.86 (4H, t, *J* = 5.8 Hz, ArOCH$_2$CH_2N), 2.68 (4H, t, *J* = 5.8 Hz, ArOCH$_2$CH_2N), 2.47 (4H, q, *J* = 7.4 Hz, CH_2CH$_3$), 2.38 (6H, s, NCH_3), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$CH_3). HRMS (ESI-TOF, positive): $[C_{58}H_{70}O_7N_2]^{2+}$ cal. 453.2586, found 453.2583; $[C_{58}H_{69}O_7N_2]^+$ cal. 905.5099, found 905.5093; $[C_{58}H_{68}O_7N_2Na]^+$ cal. 927.4919, found 927.4913.

5.7.5. Chemical preparation of **14**

The bis(N-methylamino) OEG spacer **34b** (12.6 mg, 0.0477 mmol), (*E*, *Z*)-isomer of **33** (39.3 mg, 0.110 mmol), sodium triacetoxyborohydride (31.2 mg, 0.143 mmol) and 5 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (82% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **14** (18.4 mg, 39%) as three pure isomers: *Z-Z* (27%), *Z-E* (49%), and *E-E* (24%) isomer.

Z-Z isomer of **14** (the first fraction, R_t = 14.4 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.11 (8H, m, Ar-*H*), 7.10-7.04 (6H, m, Ar-*H*), 6.84 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.77 (4H, d, *J* = 9.0 Hz, Ar-*H*), 6.57 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.93 (4H, t, *J* = 6.0 Hz, ArOCH_2CH$_2$N), 3.61-3.52 (16H, m, CH_2OCH_2), 2.74 (4H, t, *J* = 6.0 Hz, ArOCH$_2$CH_2N), 2.60

(4H, t, J = 5.9 Hz, NCH_2CH$_2$O), 2.48 (4H, q, J = 7.4 Hz, CH_2CH$_3$), 2.30 (6H, s, NCH_3), 0.90 (6H, t, J = 7.4 Hz, CH$_2$CH_3).

Z-*E* isomer of **14** (the second fraction, R_t = 16.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.12 (10H, m, Ar-*H*), 7.10-7.05 (4H, m, Ar-*H*), 6.93 (2H, d, J = 8.8 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, J = 8.7 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, J = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, J = 8.8 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, J = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, J = 8.8 Hz, (*E*)-Ar-*H*), 4.10 (2H, t, J = 5.9 Hz, (*E*)-ArOCH_2CH$_2$N), 3.93 (2H, t, J = 6.0 Hz, (*Z*)-ArOCH_2CH$_2$N), 3.59-3.50 (16H, m, CH_2OCH_2), 2.84 (2H, t, J = 6.0 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.74 (2H, t, J = 6.0 Hz, (*E*)-NCH_2CH$_2$O), 2.67 (2H, t, J = 5.9 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.60 (2H, t, J = 5.9 Hz, (*E*)-ArOCH$_2$CH_2N), 2.52-2.44 (4H, 2×q, J = 7.4 Hz, 7.4 Hz, CH_2CH$_3$), 2.36 (3H, s, (*Z*)-NCH_3), 2.30 (3H, s, (*E*)-NCH_3), 0.90 (6H, t, J = 7.4 Hz, CH$_2$CH_3).

E-*E* isomer of **14** (the third fraction, R_t = 18.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.06 (14H, m, Ar-*H*), 6.94 (4H, d, J = 8.8 Hz, Ar-*H*), 6.69 (4H, d, J = 8.7 Hz, Ar-*H*), 6.48 (4H, d, J = 8.7 Hz, Ar-*H*), 4.10 (4H, t, J = 6.0 Hz, ArOCH_2CH$_2$N), 3.60-3.53 (16H, m, CH_2OCH_2), 2.85 (4H, t, J = 6.0 Hz, ArOCH$_2$CH_2N), 2.67 (4H, t, J = 5.9 Hz, ArOCH$_2$CH_2N), 2.47 (4H, q, J = 7.3 Hz, CH_2CH$_3$), 2.37 (6H, s, NCH_3), 0.90 (6H, t, J = 7.4 Hz, CH$_2$CH_3).

HRMS (ESI-TOF, positive): $[C_{60}H_{74}O_8N_2]^{2+}$ cal. 475.2717, found 475.2721; $[C_{60}H_{73}O_8N_2]^{+}$ cal. 949.5361, found 949.5367; $[C_{60}H_{72}O_8N_2Na]^{+}$ cal. 971.5181, found 971.5187.

5.7.6. Chemical preparation of **15**

The bis(N-methylamino) OEG spacer **34c** (15.5 mg, 0.0503 mmol), (*E*, *Z*)-isomer of **33** (39.6 mg, 0.111 mmol), sodium triacetoxyborohydride (32.9 mg, 0.151 mmol) and 10 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (82% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **15** (32.6 mg, 66%) as three pure isomers: *Z*-*Z* (28%), *Z*-*E* (48%), and *E*-*E* (24%) isomer.

Z-*Z* isomer of **15** (the first fraction, R_t = 16.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.12 (8H, m, Ar-*H*), 7.12-7.05 (6H, m, Ar-*H*), 6.84 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.78 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.58 (4H, d, *J* = 8.8 Hz, Ar-*H*), 4.00 (4H, t, *J* = 5.8 Hz, ArOCH_2CH_2N), 3.61-3.52 (20H, t and m, *J* = 5.8 Hz, CH_2OCH_2), 2.90 (4H, t, *J* = 5.6 Hz, ArOCH$_2$CH_2N), 2.75 (4H, t, *J* = 5.6 Hz, NCH_2CH$_2$O), 2.48 (4H, q, *J* = 7.3 Hz, CH_2CH$_3$), 2.42 (6H, s, NCH_3), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$CH_3).

Z-*E* isomer of **15** (the second fraction, R_t = 18.2 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.19-7.11 (10H, m, Ar-*H*), 7.10-7.05 (4H, m, Ar-*H*), 6.94 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.6 Hz, (*E*)-Ar-*H*), 6.58 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.14 (2H, t, *J* = 5.9 Hz, (*E*)-ArOCH_2CH$_2$N), 3.97 (2H, t, *J* = 5.8 Hz, (*Z*)-ArOCH_2CH$_2$N), 3.64-3.52 (20H, t and m, *J* = 5.8 Hz, CH_2OCH_2), 2.93 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.83 (2H, t, *J* = 5.8 Hz, (*E*)-NCH_2CH$_2$O), 2.75 (2H, t, *J* = 5.8 Hz, (*Z*)-ArOCH$_2$CH_2N), 2.69 (2H, t, *J* = 5.8 Hz, (*E*)-ArOCH$_2$CH_2N), 2.51-2.45 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, CH_2CH$_3$), 2.43 (3H, s, (*Z*)-NCH_3), 2.37 (3H, s, (*E*)-NCH_3), 0.90 (6H, t, *J* = 7.3 Hz, CH$_2$CH_3).

E-*E* isomer of **15** (the third fraction, R_t = 20.2 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.05 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.69 (4H, d, *J* = 8.8 Hz, Ar-*H*), 6.49 (4H, d, *J* = 8.7 Hz, Ar-*H*), 4.15 (4H, t, *J* = 5.8 Hz, ArOCH_2CH$_2$N), 3.65-3.54 (20H, t and m, *J* = 5.8 Hz, CH_2OCH_2), 2.94 (4H, t, *J* = 5.9 Hz, ArOCH$_2$CH_2N), 2.76 (4H, t, *J* = 5.8 Hz, ArOCH$_2$CH_2N), 2.52-2.41 (10H, q and s, *J* = 7.5 Hz, CH_2CH$_3$ and NCH_3), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$CH_3).

HRMS (ESI-TOF, positive): $[C_{62}H_{78}O_9N_2]^{2+}$ cal. 497.2848, found 497.2839; $[C_{62}H_{77}O_9N_2]^+$ cal. 993.5624, found 993.5627; $[C_{62}H_{76}O_9N_2Na]^+$ cal. 1015.5443, found 1015.5442; $[C_{62}H_{76}O_9N_2K]^+$ cal. 1031.5182, found 1031.5192.

5.7.7. Chemical preparation of **16**

The bis(N-methylamino) OEG spacer **34d** (21.8 mg, 0.0390 mmol), (*E*, *Z*)-isomer of **33** (30.8 mg, 0.0859 mmol), sodium triacetoxyborohydride (25.6 mg, 0.117 mmol) and 5 mL anhydrous THF/DCM

(3:2) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (82% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **16** (12.0 mg, 28%) as three pure isomers: *Z-Z* (28%), *Z-E* (48%), and *E-E* (24%) isomer.

Z-Z isomer of **16** (the first fraction, R_t = 15.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.11 (8H, m, Ar-*H*), 7.10-7.04 (6H, m, Ar-*H*), 6.84 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.78 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.57 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.94 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.57-3.49 (28H, m, C*H*$_2$OC*H*$_2$), 2.74 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.61 (4H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$O), 2.49 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.30 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

Z-E isomer of **16** (the second fraction, R_t = 18.5 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.12 (10H, m, Ar-*H*), 7.12-7.05 (4H, m, Ar-*H*), 6.94 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.6 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.10 (2H, t, *J* = 6.0 Hz, (*E*)-ArOC*H*$_2$CH$_2$N), 3.94 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOC*H*$_2$CH$_2$N), 3.62-3.45 (28H, m, C*H*$_2$OC*H*$_2$), 2.85 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.74 (2H, t, *J* = 6.0 Hz, (*E*)-NC*H*$_2$CH$_2$O), 2.67 (2H, t, *J* = 5.9 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.61 (2H, t, *J* = 5.9 Hz, (*E*)-ArOCH$_2$C*H*$_2$N), 2.53-2.44 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, C*H*$_2$CH$_3$), 2.37 (3H, s, (*Z*)-NC*H*$_3$), 2.30 (3H, s, (*E*)-NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

E-E isomer of **16** (the third fraction, R_t = 19.4 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.05 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.70 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.48 (4H, d, *J* = 8.7 Hz, Ar-*H*), 4.11 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.61-3.52 (28H, m, C*H*$_2$OC*H*$_2$), 2.85 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.67 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.47 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.37 (6H, s, NC*H*$_3$), 0.91 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$). HRMS (ESI-TOF, positive): $[C_{66}H_{86}O_{11}N_2]^{2+}$ cal. 541.3110, found 541.3070; $[C_{66}H_{85}O_{11}N_2]^{+}$ cal. 1081.6148, found 1081.6095; $[C_{66}H_{84}O_{11}N_2Na]^{+}$ cal. 1103.5967, found 1103.5915; $[C_{66}H_{84}O_{11}N_2K]^{+}$ cal. 1119.5707, found 1119.5663.

5.7.8. Chemical preparation of **17**

The bis(N-methylamino) OEG spacer **34e** (21.7 mg, 0.0336 mmol), (*E*, *Z*)-isomer of **33** (36.1 mg, 0.101 mmol), sodium triacetoxyborohydride (29.3 mg, 0.134 mmol) and 4 mL anhydrous THF/DCM (1:1) were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (80% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **17** (9.30 mg, 24%) as three pure isomers: *Z-Z* (30%), *Z-E* (45%), and *E-E* (25%) isomer.

Z-Z isomer of **17** (the first fraction, R_t = 15.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.19-7.11 (8H, m, Ar-*H*), 7.10-7.04 (6H, m, Ar-*H*), 6.85 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.78 (4H, d, *J* = 8.8 Hz, Ar-*H*), 6.58 (4H, d, *J* = 8.8 Hz, Ar-*H*), 3.94 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.58-3.49 (36H, m, C*H*$_2$OC*H*$_2$), 2.75 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.61 (4H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$O), 2.48 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.31 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

Z-E isomer of **17** (the second fraction, R_t = 18.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.11 (10H, m, Ar-*H*), 7.10-7.05 (4H, m, Ar-*H*), 6.94 (2H, d, *J* = 8.8 Hz, (*E*)-Ar-*H*), 6.84 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.48 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.11 (2H, t, *J* = 6.0 Hz, (*E*)-ArOC*H*$_2$CH$_2$N), 3.94 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOC*H*$_2$CH$_2$N), 3.60-3.44 (36H, m, C*H*$_2$OC*H*$_2$), 2.85 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.74 (2H, t, *J* = 6.0 Hz, (*E*)-NC*H*$_2$CH$_2$O), 2.67 (2H, t, *J* = 5.9 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.61 (2H, t, *J* = 5.9 Hz, (*E*)-ArOCH$_2$C*H*$_2$N), 2.53-2.44 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, C*H*$_2$CH$_3$), 2.37 (3H, s, (*Z*)-NC*H*$_3$), 2.30 (3H, s, (*E*)-NC*H*$_3$), 0.90 (6H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$).

E-E isomer of **17** (the third fraction, R_t = 22.0 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.06 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.70 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.48 (4H, d, *J* = 8.7 Hz, Ar-*H*), 4.11 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.61-3.52 (36H, m, C*H*$_2$OC*H*$_2$), 2.85 (4H, t, *J* = 5.8 Hz, ArOCH$_2$C*H*$_2$N), 2.68 (4H, t, *J* = 5.9 Hz,

ArOCH$_2$C*H*$_2$N), 2.47 (4H, q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 2.37 (6H, s, NC*H*$_3$), 0.91 (6H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$).

HRMS (ESI-TOF, positive): $[C_{70}H_{94}O_{13}N_2]^{2+}$ cal. 585.3373, found 585.3386; $[C_{70}H_{93}O_{13}N_2]^{+}$ cal. 1169.6672, found 1169.6694.

5.7.9. Chemical preparation of **19**

The bis(N-methylamino) OEG spacer **34f** (23.9 mg, 0.0417 mmol), (*E*, *Z*)-isomer of **33** (32.9 mg, 0.0918 mmol), sodium triacetoxyborohydride (27.4 mg, 0.125 mmol) and 5 mL anhydrous THF were used and the crude product was purified by column chromatography (chloroform : MeOH = 20:1 to 10:1 + 3% triethylamine) and by RP-HPLC (82% MeOH/H_2O + 0.4% diethylamine, 25 mL/min) to obtain **19** (30.9 mg, 61%) as three pure isomers: *Z*-*Z* (28%), *Z*-*E* (48%), and *E*-*E* (24%) isomer.

Z-*Z* isomer of **19** (the first fraction, 14.8 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.12 (8H, m, Ar-*H*), 7.12-7.04 (6H, m, Ar-*H*), 6.85 (4H, d, *J* = 8.6 Hz, Ar-*H*), 6.78 (4H, d, *J* = 8.8 Hz, Ar-*H*), 6.58 (4H, d, *J* = 9.0 Hz, Ar-*H*), 3.94 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.59-3.51 (44H, m, C*H*$_2$OC*H*$_2$), 2.75 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.61 (4H, t, *J* = 5.9 Hz, NC*H*$_2$CH$_2$O), 2.49 (4H, q, *J* = 7.4 Hz, C*H*$_2$CH$_3$), 2.30 (6H, s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$).

Z-*E* isomer of **19** (the second fraction, R_t = 16.4 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.20-7.12 (10H, m, Ar-*H*), 7.11-7.05 (4H, m, Ar-*H*), 6.94 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.85 (2H, d, *J* = 8.6 Hz, (*Z*)-Ar-*H*), 6.78 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.69 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 6.57 (2H, d, *J* = 8.8 Hz, (*Z*)-Ar-*H*), 6.49 (2H, d, *J* = 8.7 Hz, (*E*)-Ar-*H*), 4.11 (2H, t, *J* = 6.0 Hz, (*E*)-ArOC*H*$_2$CH$_2$N), 3.94 (2H, t, *J* = 6.0 Hz, (*Z*)-ArOC*H*$_2$CH$_2$N), 3.62-3.47 (44H, m, C*H*$_2$OC*H*$_2$), 2.85 (2H, t, *J* = 5.9 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.75 (2H, t, *J* = 6.0 Hz, (*E*)-NC*H*$_2$CH$_2$O), 2.68 (2H, t, *J* = 5.9 Hz, (*Z*)-ArOCH$_2$C*H*$_2$N), 2.61 (2H, t, *J* = 5.9 Hz, (*E*)-ArOCH$_2$C*H*$_2$N), 2.53-2.44 (4H, 2×q, *J* = 7.4 Hz, 7.4 Hz, C*H*$_2$CH$_3$), 2.37 (3H, s, (*Z*)-NC*H*$_3$), 2.30 (3H, s, (*E*)-NC*H*$_3$), 0.91 (6H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$).

E-*E* isomer of **19** (the third fraction, R_t = 18.6 min):

^{1}H-NMR (Acetone-d6, 400 MHz) δ (ppm) = 7.18-7.06 (14H, m, Ar-*H*), 6.94 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.70 (4H, d, *J* = 8.7 Hz, Ar-*H*), 6.49 (4H, d, *J* = 8.6 Hz, Ar-*H*), 4.11 (4H, t, *J* = 6.0 Hz, ArOC*H*$_2$CH$_2$N), 3.61-3.53 (44H, m, C*H*$_2$OC*H*$_2$), 2.85 (4H, t, *J* = 6.0 Hz, ArOCH$_2$C*H*$_2$N), 2.67 (4H, t, *J* = 5.9 Hz, ArOCH$_2$C*H*$_2$N), 2.47 (4H, q, *J* = 7.6 Hz, C*H*$_2$CH$_3$), 2.37 (6H, s, NC*H*$_3$), 0.91 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

HRMS (ESI-TOF, positive): $[C_{74}H_{102}O_{15}N_2]^{2+}$ cal. 629.3635, found 629.3608; $[C_{74}H_{101}O_{15}N_2]^{+}$ cal. 1257.7197, found 1257.7149; $[C_{74}H_{100}O_{15}N_2Na]^{+}$ cal. 1279.7016, found 1279.6968; $[C_{74}H_{100}O_{15}N_2K]^{+}$ cal. 1295.6755, found 1295.6736.

5.7.10. Chemical preparation of **18**

The dibromide OEG spacer **30a** (26.2 mg, 0.0417 mmol), the endoxifen **29** (34.2 mg, 0.0917 mmol), diisopropylethylamine (22.0 µL, 0.125 mmol), and 3 mL anhydrous THF were used. The crude product was purified by column chromatography (Chloroform : MeOH = 10:1 to 10:1 + 3% triethylamine) to give **18** (18.0 mg, 37%) as a mixture of *Z*-*Z*, *Z*-*E*, and *E*-*E* isomers.

^{1}H-NMR (DCM-d2, 400 MHz) δ (ppm) = 7.20-7.02 (14H, m, Ar-*H*), 6.84-6.66 (8H, m, Ar-*H*), 6.49-6.42 (4H, m, Ar-*H*), 4.11-4.03 (2H, m, ArOC*H*$_2$CH$_2$N), 3.95-6.87 (2H, m, ArOC*H*$_2$CH$_2$N), 3.61-3.49 (40H, m, C*H*$_2$OC*H*$_2$), 2.90-2.84 (2H, m, ArOCH$_2$C*H*$_2$N), 2.80-2.74 (2H, m, NC*H*$_2$CH$_2$O), 2.74-2.68 (2H, m, ArOCH$_2$C*H*$_2$N), 2.68-2.62 (2H, m, ArOCH$_2$C*H*$_2$N), 2.50-2.42 (4H, m, C*H*$_2$CH$_3$), 2.39, 2.37, 2.32, and 2.30 (6H, 4×s, NC*H*$_3$), 0.90 (6H, t, *J* = 7.4 Hz, CH$_2$C*H*$_3$).

HRMS (ESI-TOF, positive): $[C_{72}H_{98}O_{14}N_2]^{2+}$ cal. 607.3504, found 607.3511; $[C_{72}H_{97}O_{14}N_2]^{+}$ cal. 1213.6934, found 1213.6772; $[C_{72}H_{96}O_{14}N_2Na]^{+}$ cal. 1235.6754, found 1235.6892; $[C_{72}H_{96}O_{14}N_2K]^{+}$ cal. 1251.6493, found 1251.6490.

5.7.11. Chemical preparation of monovalent 4-hydroxytamoxifen ligands **20**

The monomethyl bromide OEG ether **31** (17.5 mg, 0.0555 mmol), the endoxifen **29** (21.8 mg, 0.583 mmol), diisopropylethylamine (38.9 µL, 0.222 mmol), and 3 mL anhydrous THF were used. The crude product was purified by column chromatography (DCM : MeOH = 10:1 to 5:1 to 100% MeOH) and RP-

HPLC (75%MeOH/H_2O + 50mM NH_4OH, 20 mL/min) to give **20** (11.9 mg, 35%) as two pure isomers: *Z*-isomer (34%) and *E*-isomer (66%).

Z-isomer of **20** (the first fraction, R_t = 17.0 min):

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.17-7.12 (2H, m, Ar-*H*), 7.11-7.05 (3H, m, Ar-*H*), 7.01 (2H, d, *J* = 8.6 Hz, Ar-*H*), 6.78-6.83 (4H, m, Ar-*H*), 6.56 (2H, d, *J* = 8.8 Hz, Ar-*H*), 3.97 (2H, t, *J* = 5.6 Hz, ArOCH_2CH_2N), 3.62-3.54 (14H, m, CH_2OCH_2), 3.53-3.49 (2H, m, NCH_2CH_2O), 3.34 (3H, s, OCH_3), 2.82 (2H, t, *J* = 5.6 Hz, ArOCH_2CH_2N), 2.69 (2H, t, *J* = 5.6 Hz, NCH_2CH_2O), 2.48 (2H, q, *J* = 7.4 Hz, CH_2CH_3), 2.35 (3H, s, NCH_3), 0.91 (3H, t, *J* = 7.4 Hz, CH_2CH_3).

E-isomer of **20** (the second fraction, R_t = 18.7 min):

^{1}H-NMR (MeOD, 400 MHz) δ (ppm) = 7.16-7.12 (2H, m, Ar-*H*), 7.12-7.05 (5H, m, Ar-*H*), 6.92 (2H, d, *J* = 8.7 Hz, Ar-*H*), 6.64 (2H, d, *J* = 8.7 Hz, Ar-*H*), 6.39 (2H, d, *J* = 8.6 Hz, Ar-*H*), 4.14 (2H, t, *J* = 5.4 Hz, ArOCH_2CH_2N), 3.67-3.57 (14H, m, CH_2OCH_2), 3.53-3.50 (2H, m, NCH_2CH_2O), 3.34 (3H, s, OCH_3), 2.93 (2H, t, *J* = 5.6 Hz, ArOCH_2CH_2N), 2.76 (2H, t, *J* = 5.7 Hz, NCH_2CH_2O), 2.51-2.39 (5H, q and s, *J* = 7.3 Hz, CH_2CH_3 and NCH_3), 0.91 (3H, t, *J* = 7.4 Hz, CH_2CH_3).

HRMS (ESI-TOF, positive): $[C_{36}H_{50}O_7N]^+$ cal. 608.3582, found 608.3575; $[C_{36}H_{49}O_7NNa]^+$ cal. 630.3401, found 630.3392.

6. [1]H, COSY, HMQC, HMBC, and NOESY spectra of diethylstilbestrol ligand **9**

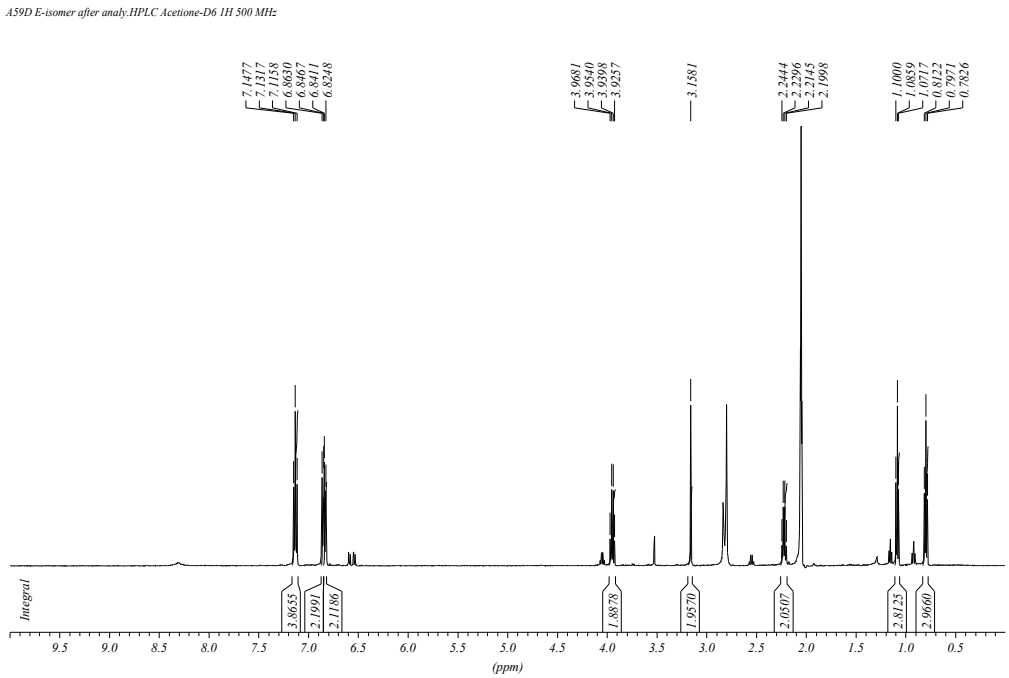


Figure S1. [1]H NMR spectra of *E*-isomer **9** after an analytic HPLC separation.

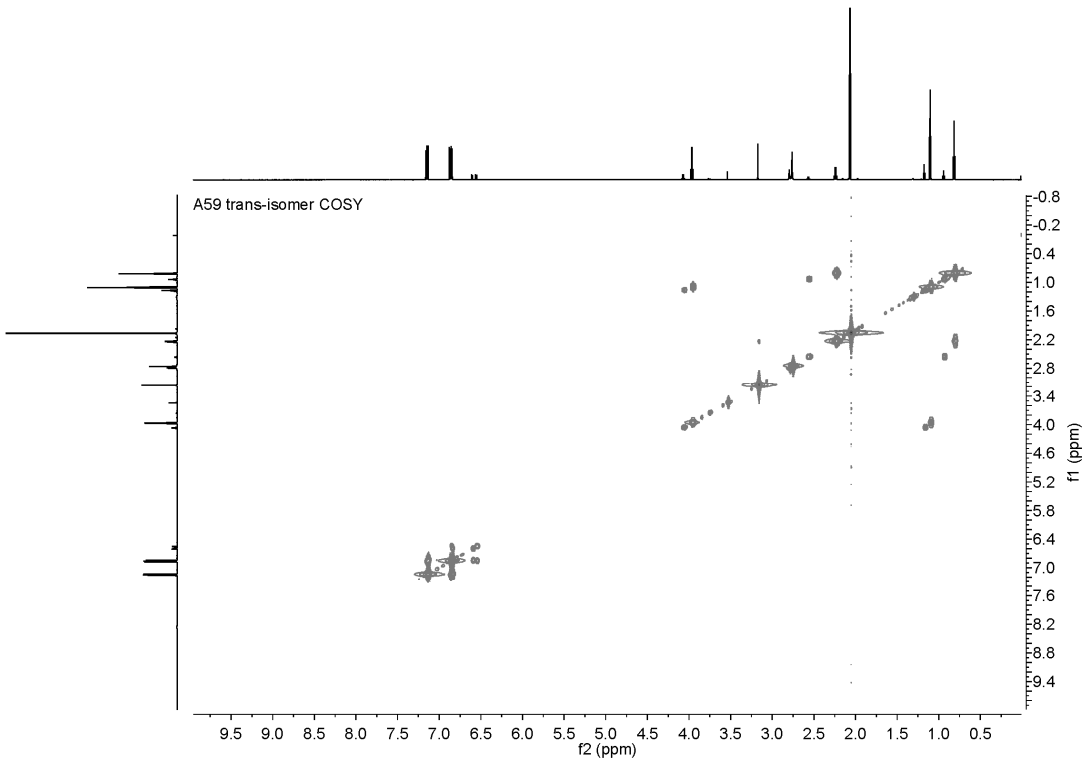


Figure S2. COSY spectra of *E*-isomer **9**.

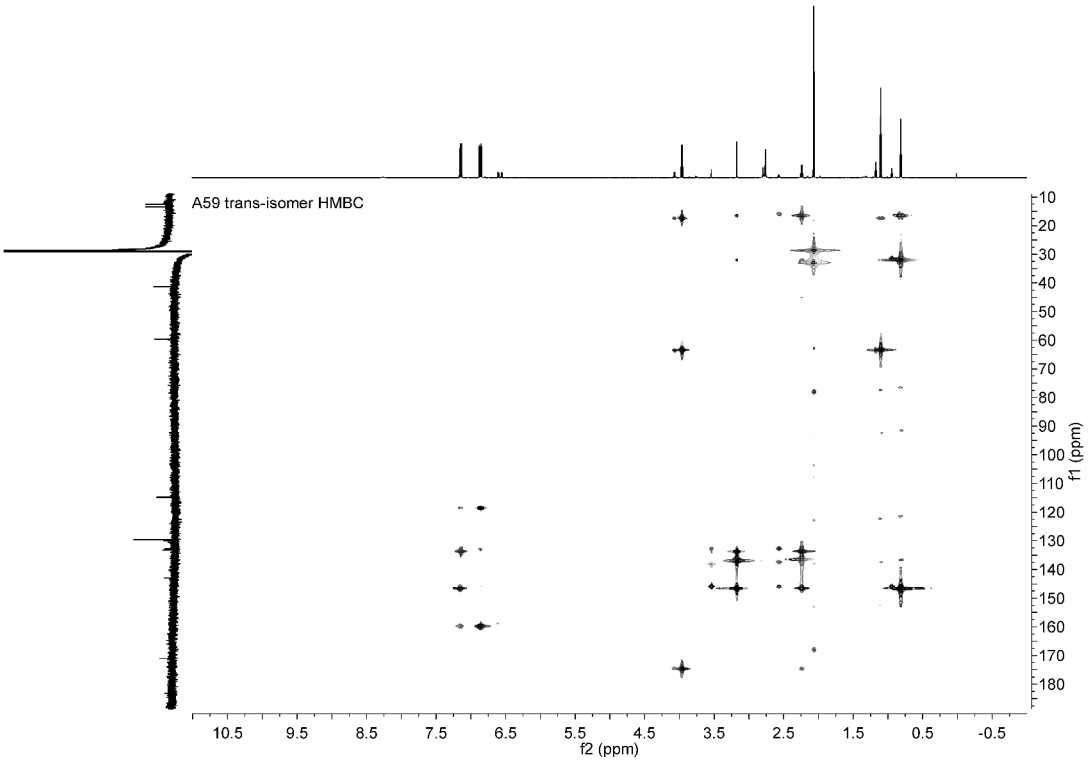


Figure S3. HMBC spectra of *E*-isomer **9**.

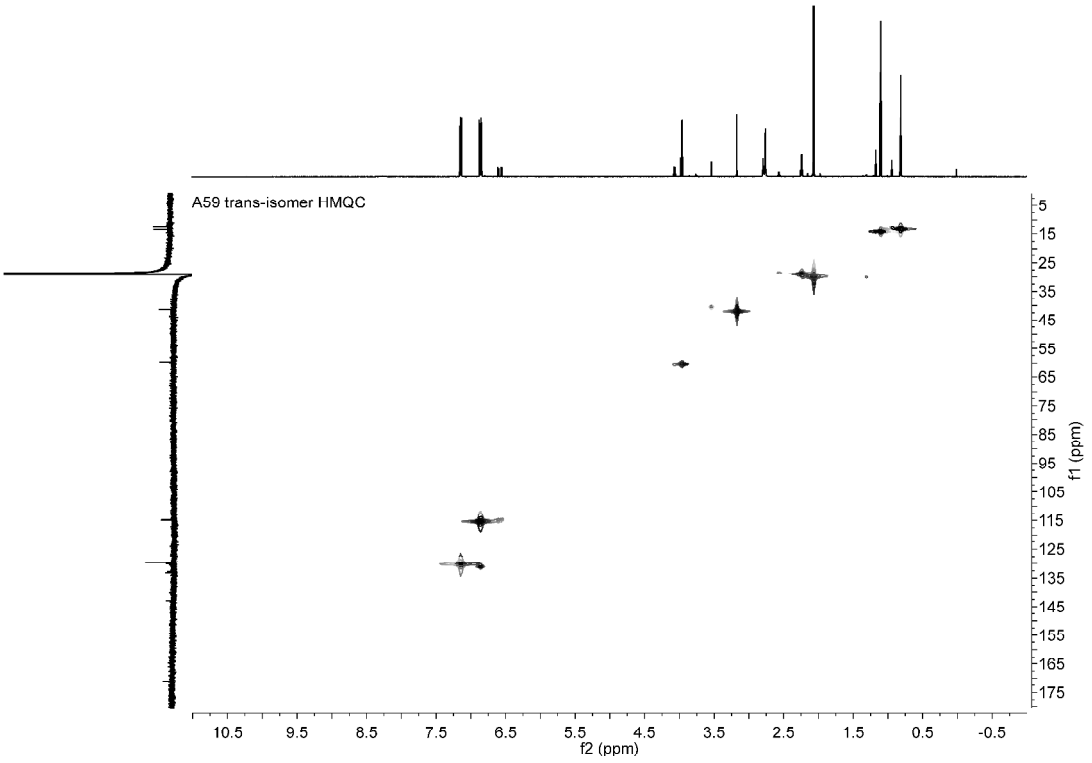


Figure S4. HMQC spectra of *E*-isomer **9**.

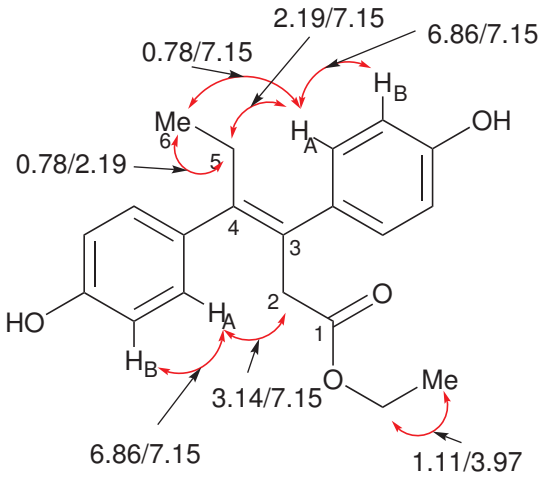


Figure S5. NOE relationship of *E*-isomer **9** (according to the NOESY spectra in Figure S6).

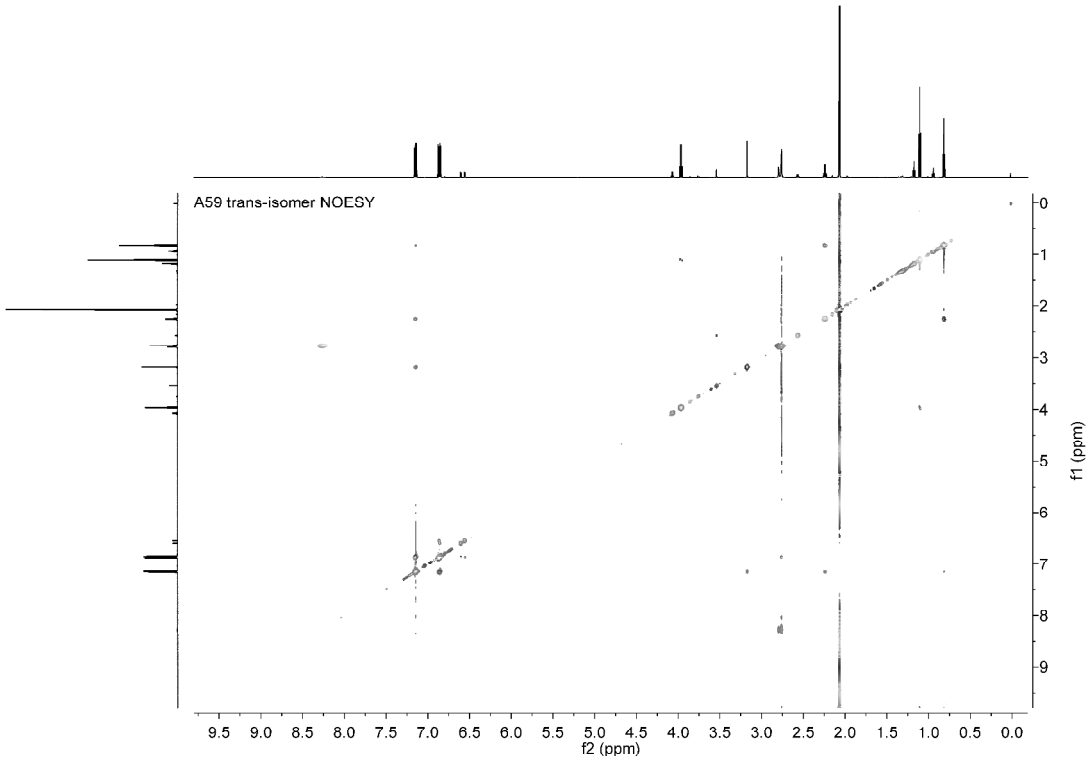


Figure S6. NOESY spectra of *E*-isomer **9**.

7. [1]H, COSY, and NOE spectra of 4-hydroxytamoxifen (OHT) ligand **32**

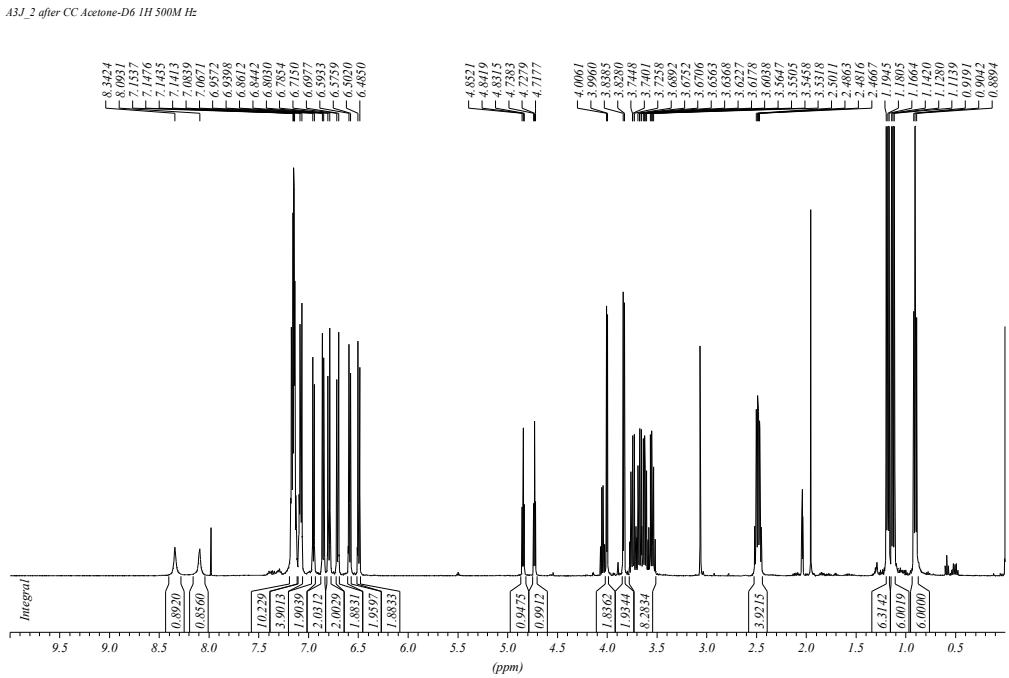


Figure S7. [1]H NMR spectra of *Z*- and *E*-isomer **32** before a RP-HPLC separation.

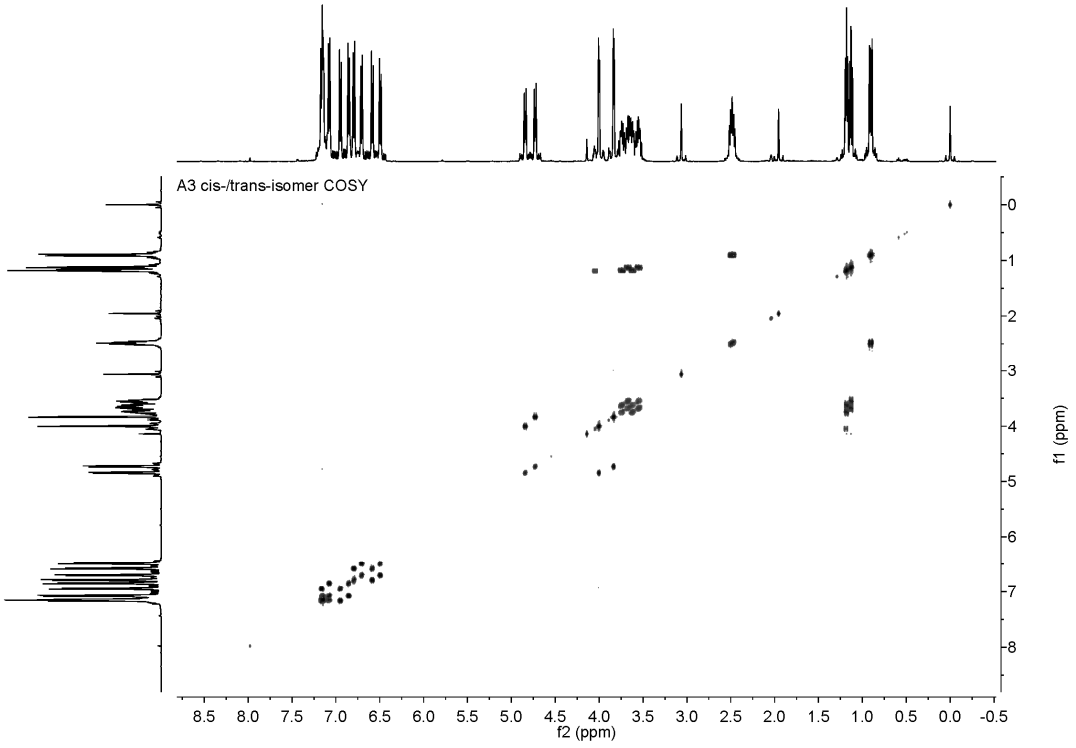


Figure S8. COSY spectra of *Z*- and *E*-isomer **32** before a RP-HPLC separation.

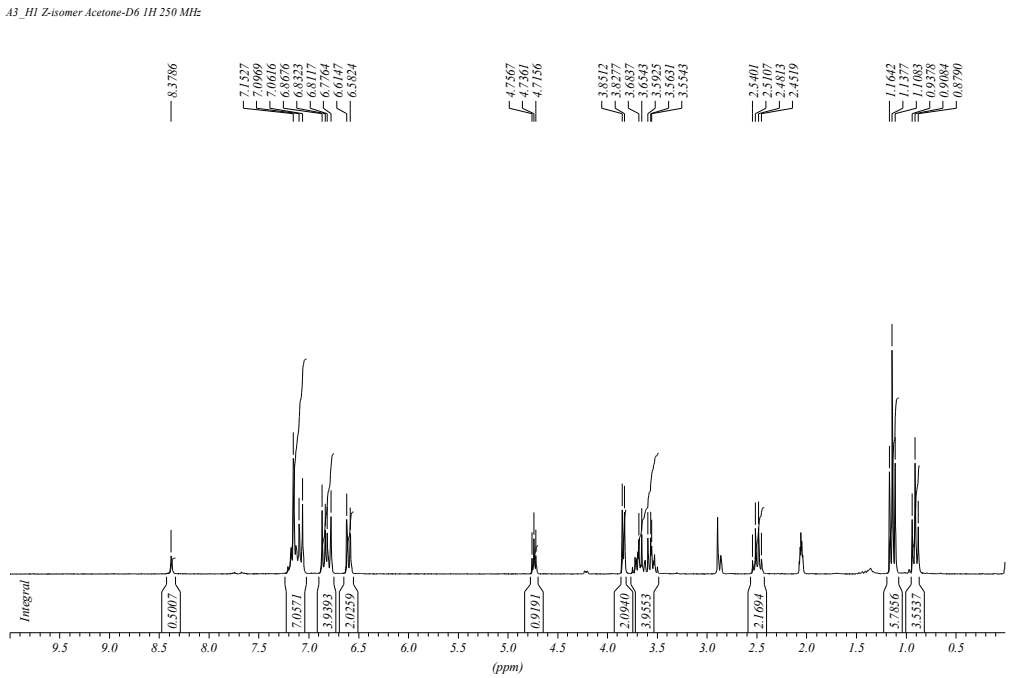


Figure S9. ^{1}H NMR spectra of *Z*-isomer **32** after a RP-HPLC separation.

Table S1. NOE spectra analysis of *Z*-isomer **32** (the assignment of proton chemical shifts according to ^{1}H and COSY spectra in Figure S8 and S9 and the integration of each positive NOE signal according to Figure S11-S18).

Multiplet	br s	m	d	d	d	d	t	d	m	m	q	t	t
δ (ppm)	8.38	7.15	7.08	6.84	6.79	6.59	4.74	3.83	3.65	3.56	2.49	1.14	0.91
	OH	Ph	$H_{A''}$	$H_{B''}$	$H_{A'}$	$H_{B'}$	9'-CH	8'-CH_2	11'-CH_2	11'-CH_2	3-CH_2	12'-CH_3	4-CH_3
Fig. S11	-100			17.3									
Fig. S12	0.9		-100	8.7							1.1		1.8
Fig. S13	3.6		13.8	-100									
Fig. S14					-100	9.2							
Fig. S15					14	-100		4.0					
Fig. S16						13.7	5.8	-100				0.8	
Fig. S17	0.8	14.6	8.2		0.7				0.5		-100		5.1
Fig. S18	0.5	1.9	3.4						0.5		2.8		-100

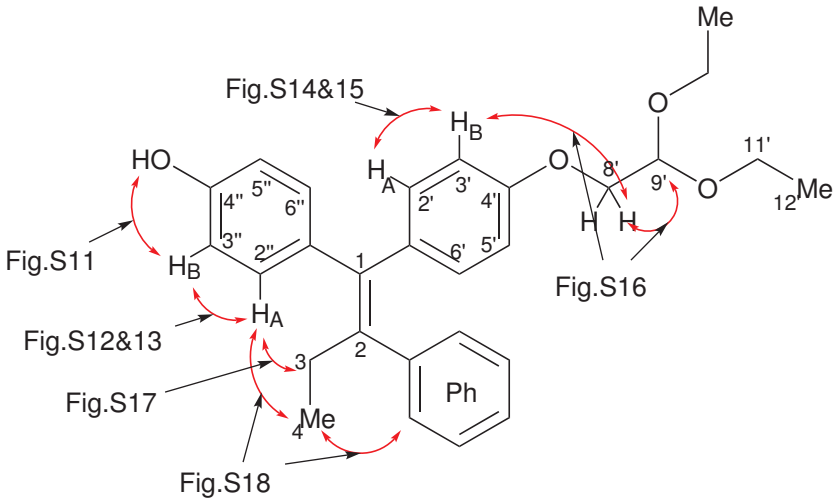


Figure S10. NOE relationship of *Z*-isomer **32** according to Table S1.

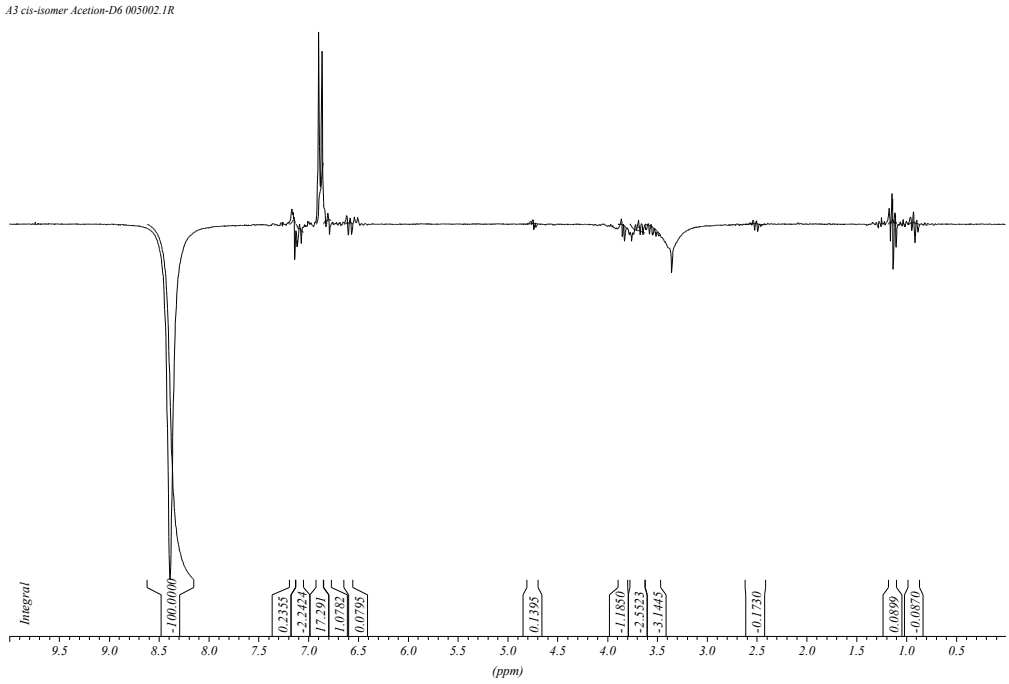


Figure S11. NOE spectra of *Z*-isomer **32**.

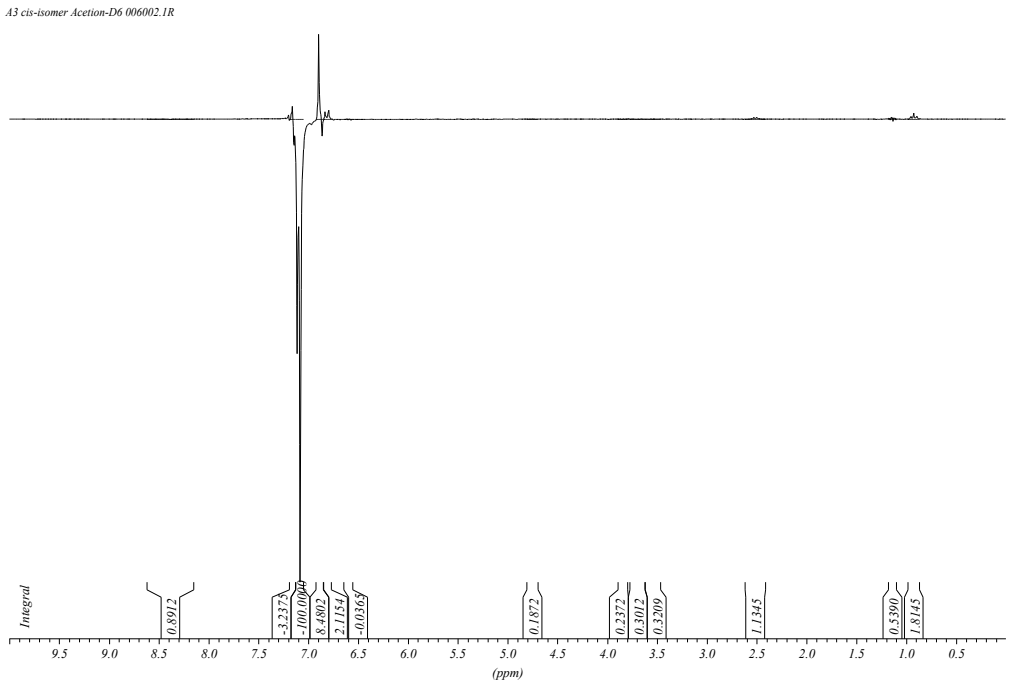


Figure S12. NOE spectra of *Z*-isomer **32**.

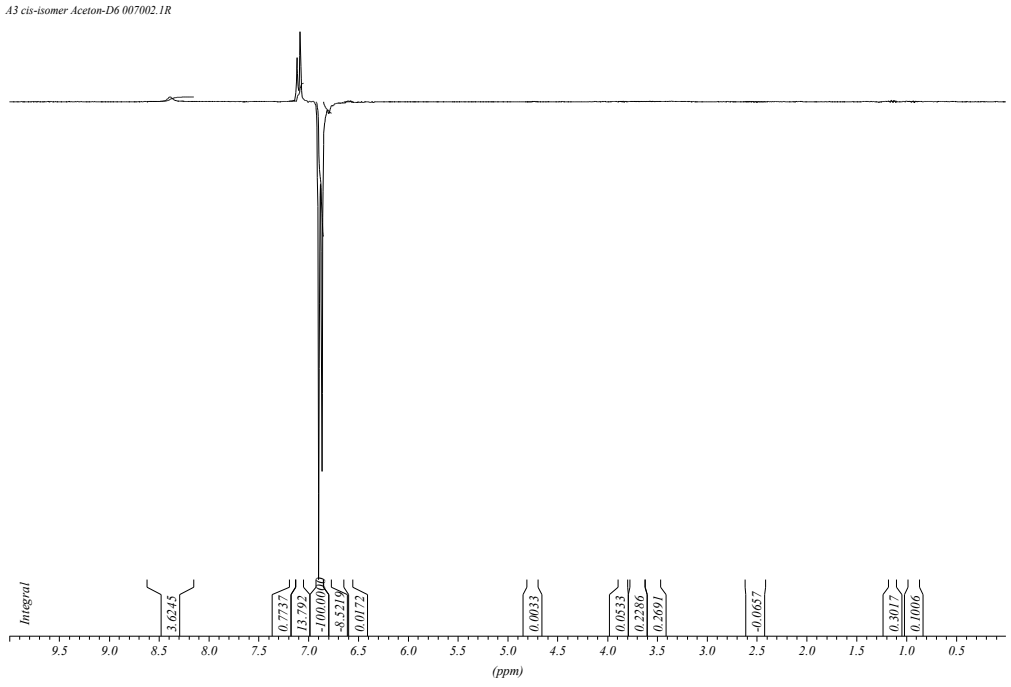


Figure S13. NOE spectra of *Z*-isomer **32**.

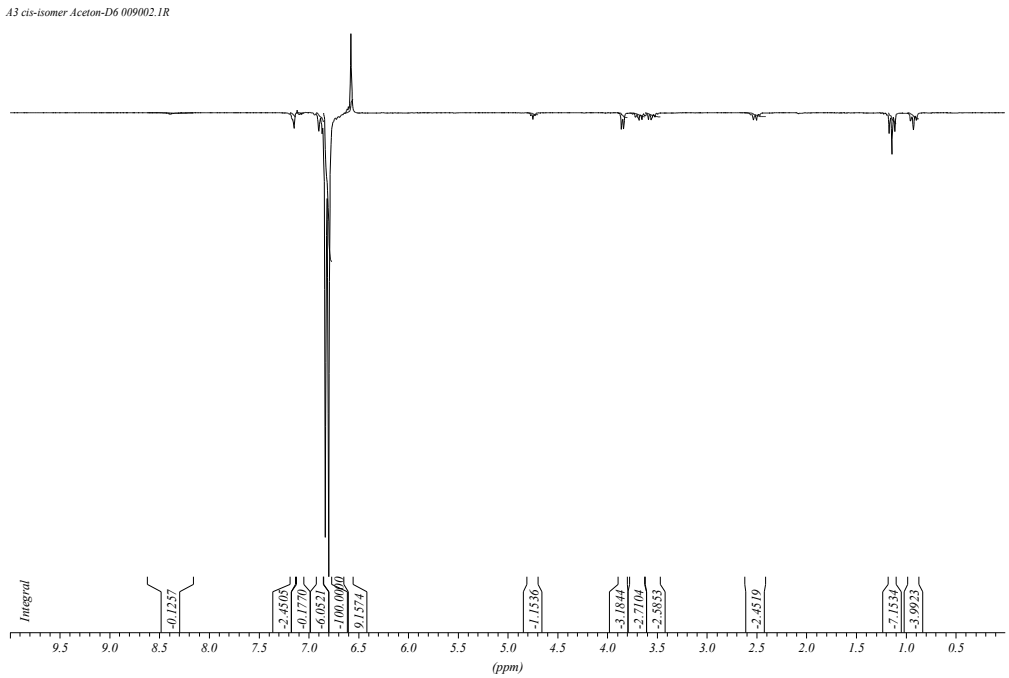


Figure S14. NOE spectra of *Z*-isomer **32**.

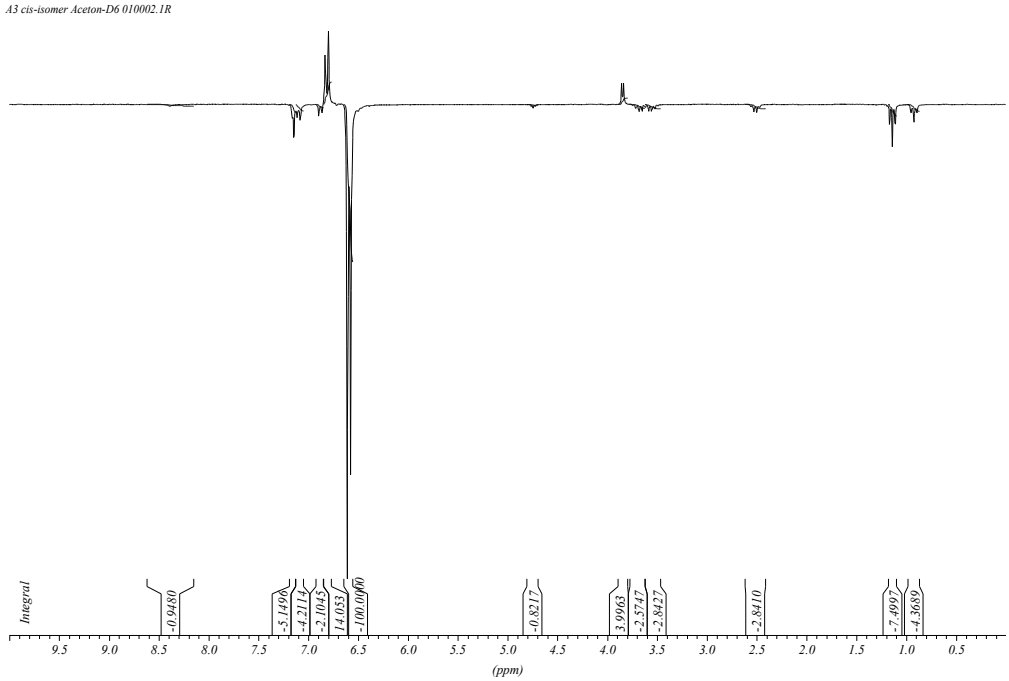


Figure S15. NOE spectra of *Z*-isomer **32**.

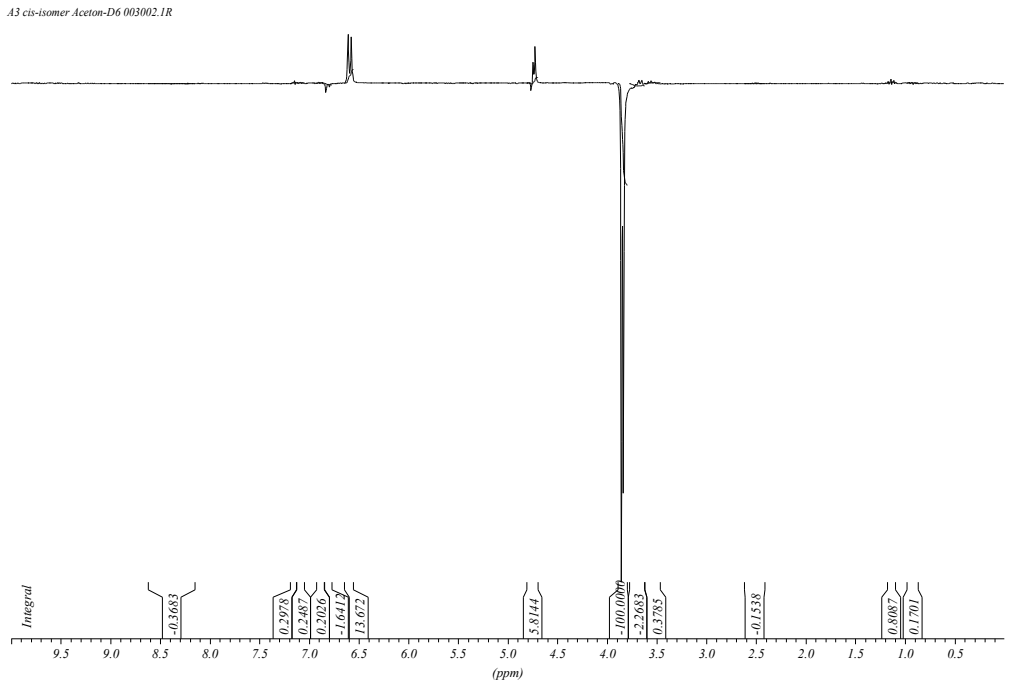


Figure S16. NOE spectra of *Z*-isomer **32**.

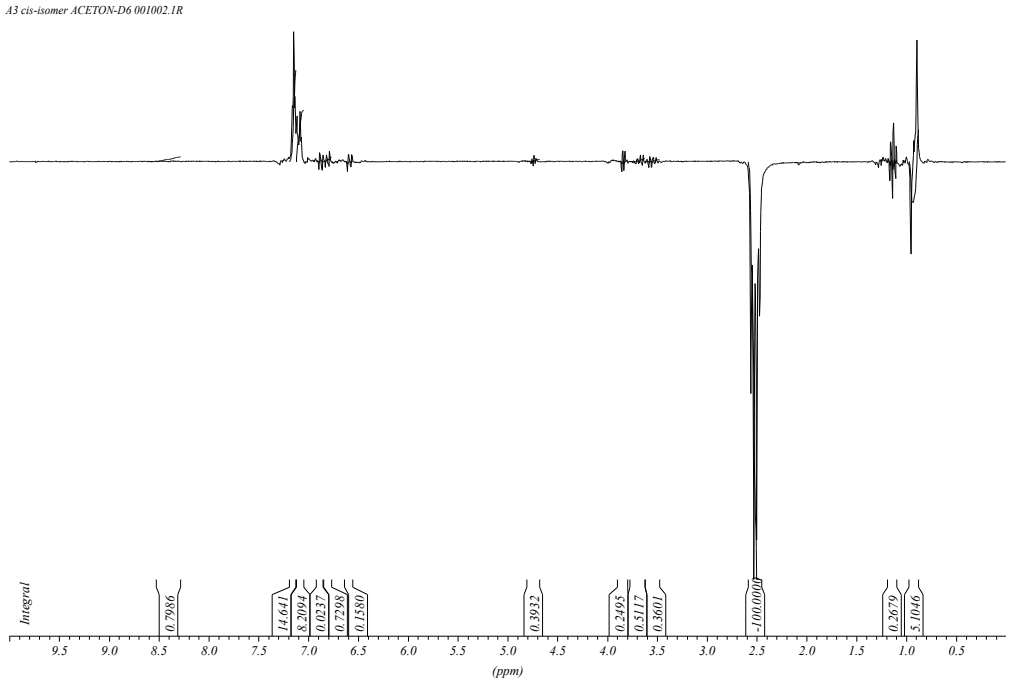


Figure S17. NOE spectra of *Z*-isomer **32**.

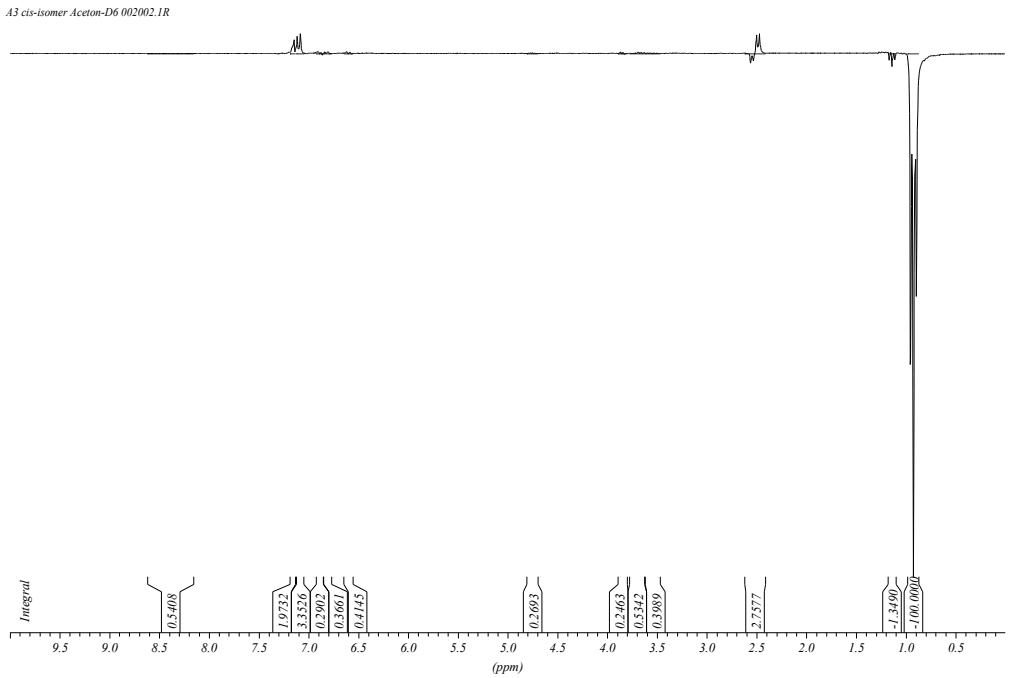


Figure S18. NOE spectra of *Z*-isomer **32**.

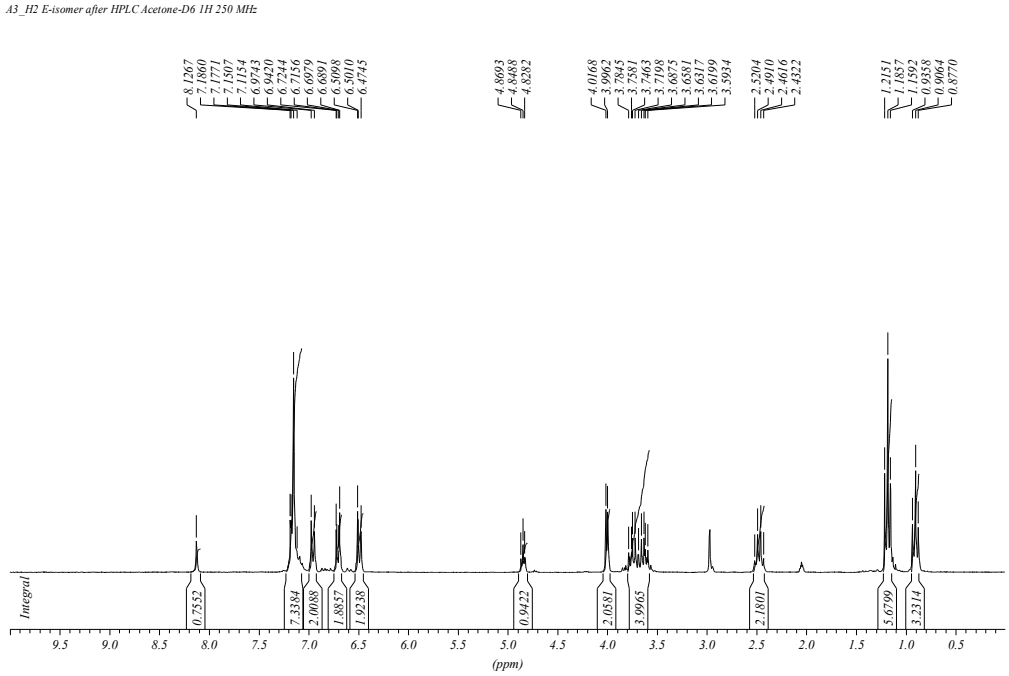


Figure S19. ^{1}H NMR of *E*-isomer **32** after a RP-HPLC separation.

8. ^{1}H NMR spectra of *Z-Z*, *E-Z*, and *E-E* isomer **2**

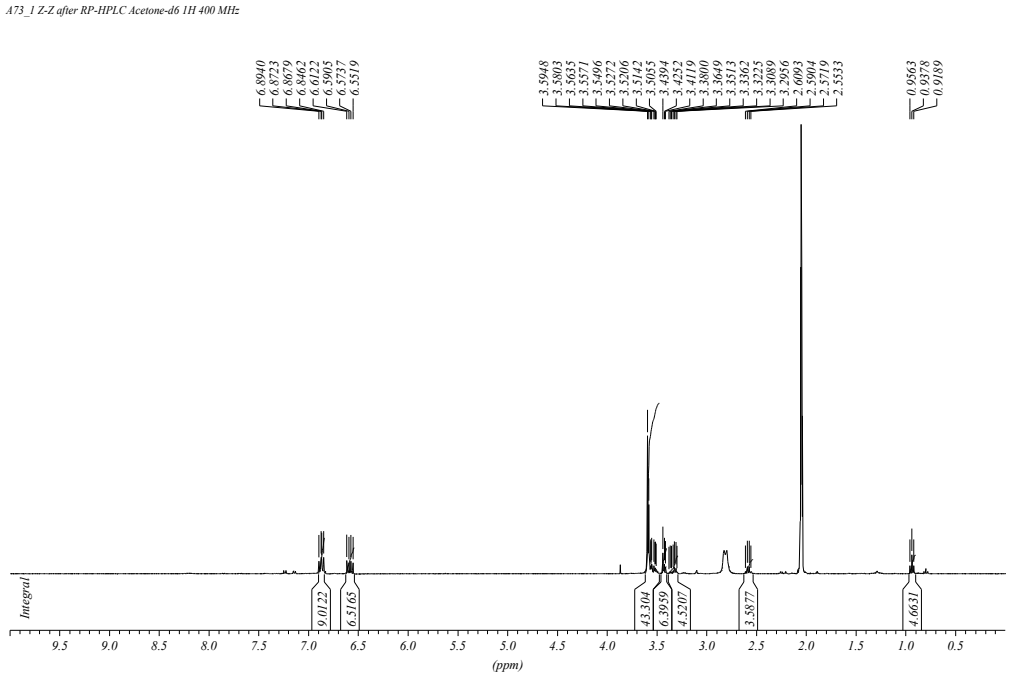


Figure S20. ^{1}H NMR spectra of *Z-Z* isomer **2**.

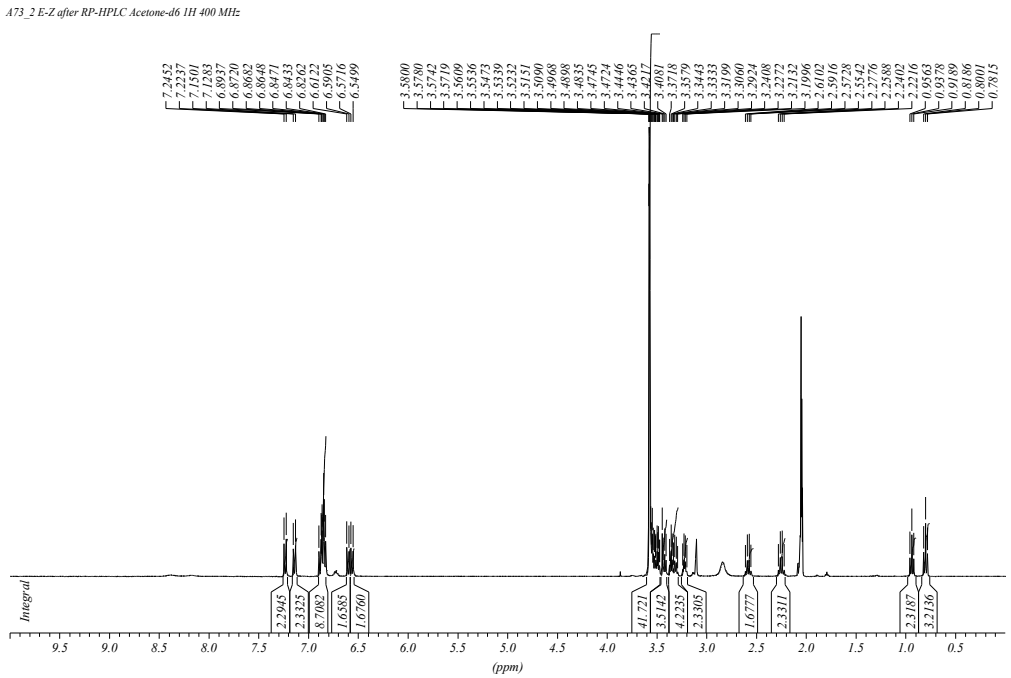


Figure S21. ^{1}H NMR spectra of *Z-E* isomer **2**.

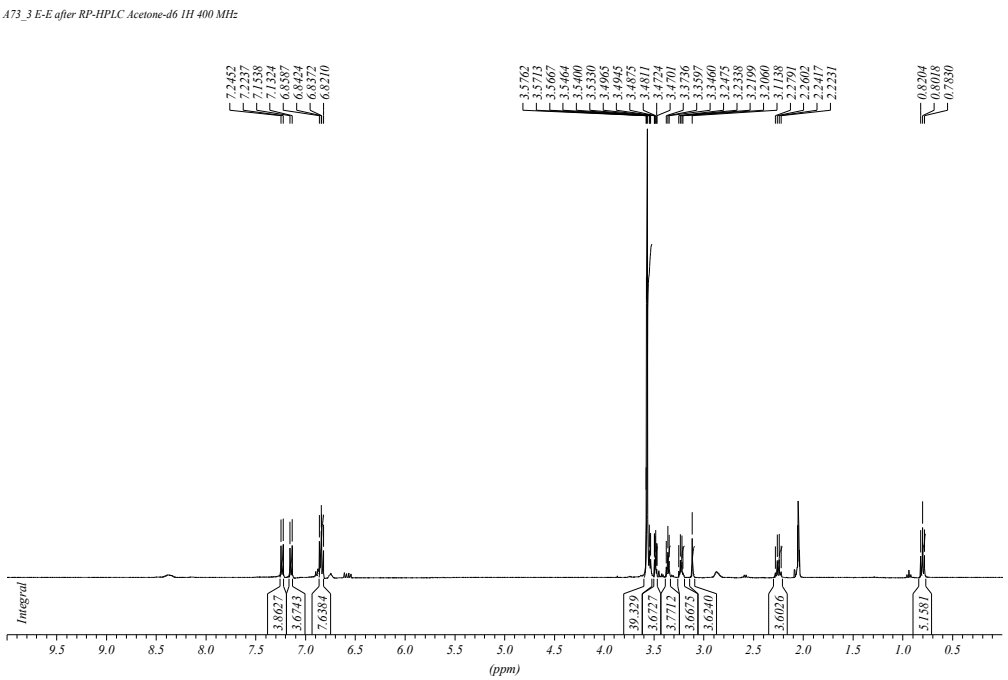


Figure S22. ^{1}H NMR spectra of *E-E* isomer **2**.

9. [1]H NMR spectra of *Z-Z*, *Z-E*, and *E-E* isomer **13**

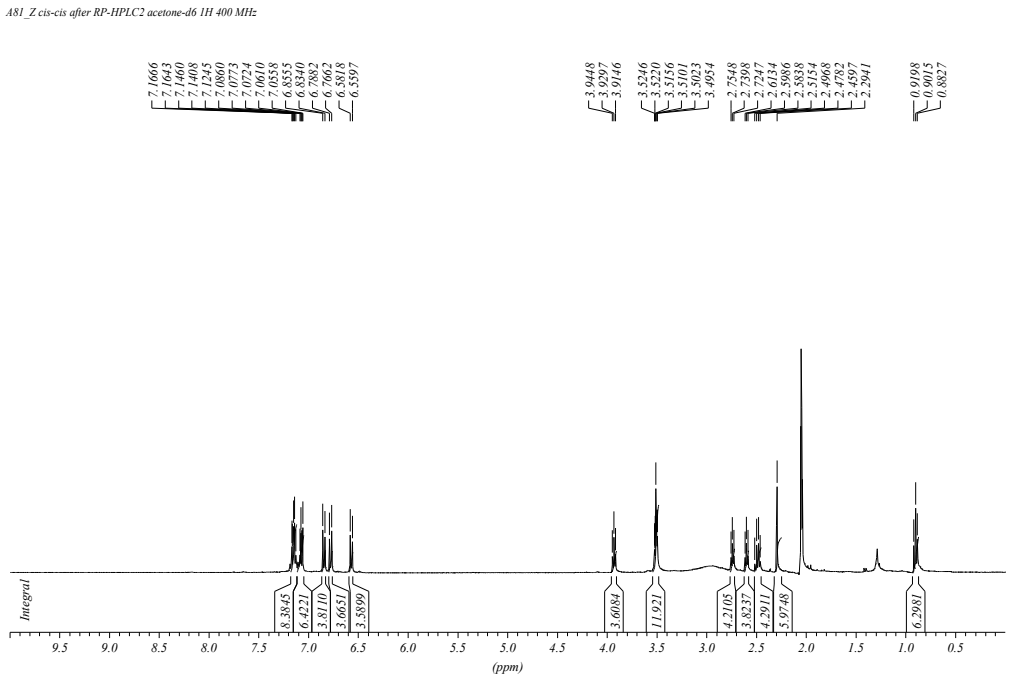


Figure S23. [1]H NMR spectra of *Z-Z* isomer **13**.

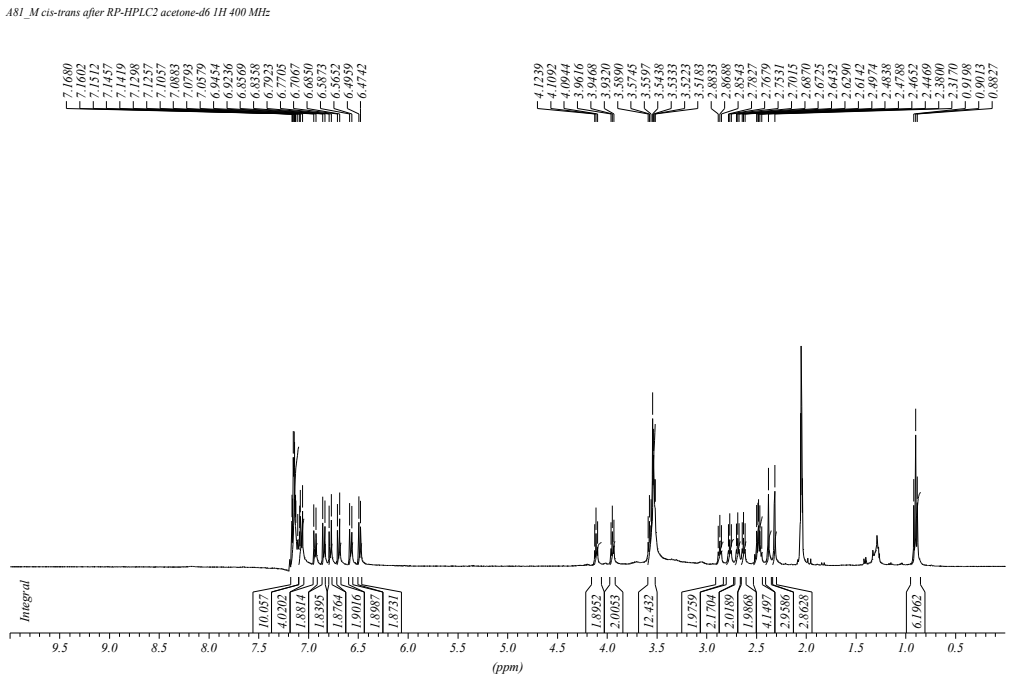


Figure S24. [1]H NMR spectra of *Z-E* isomer **13**.

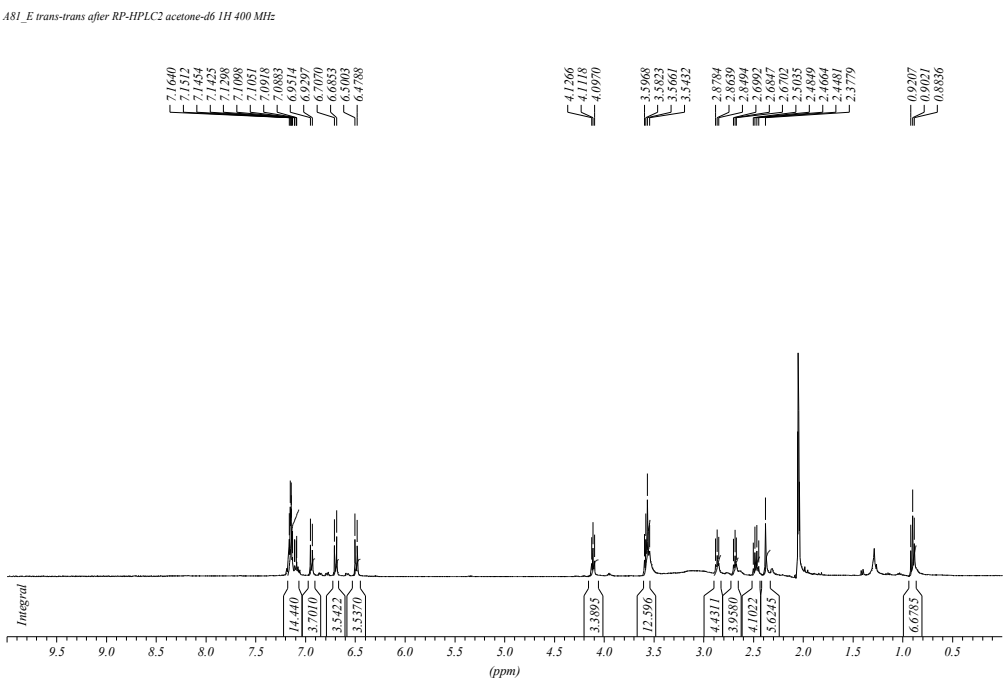


Figure S25. ^{1}H NMR spectra of *E-E* isomer **13**.

10. ^{1}H NMR spectra of *Z-Z*, *Z-E*, and *E-E* isomer **16**

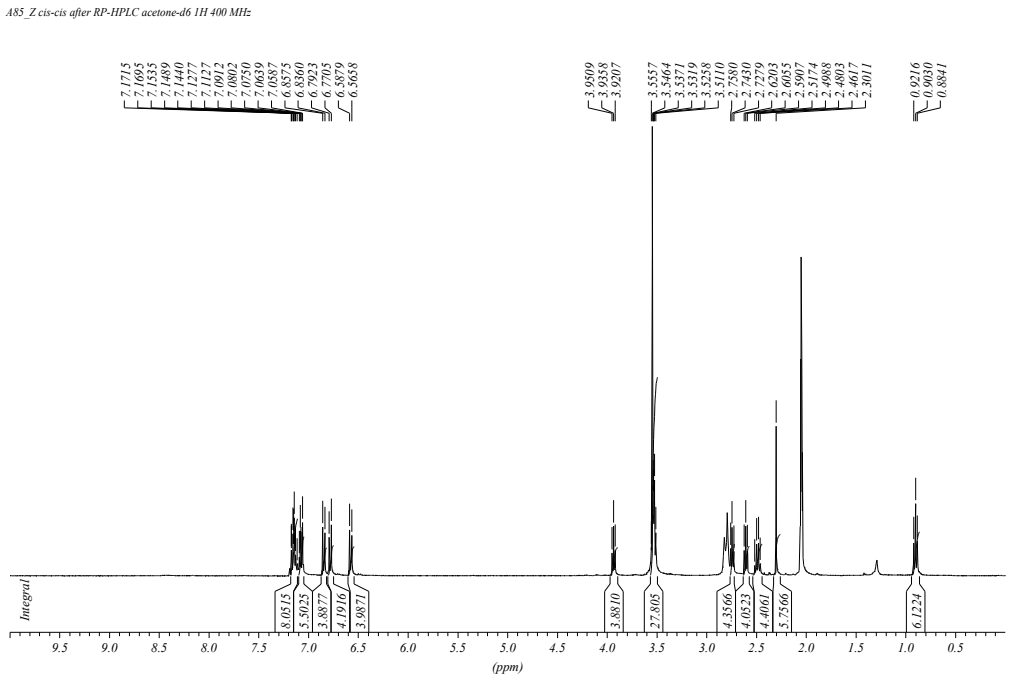


Figure S26. ^{1}H NMR spectra of *Z-Z* isomer **16**.

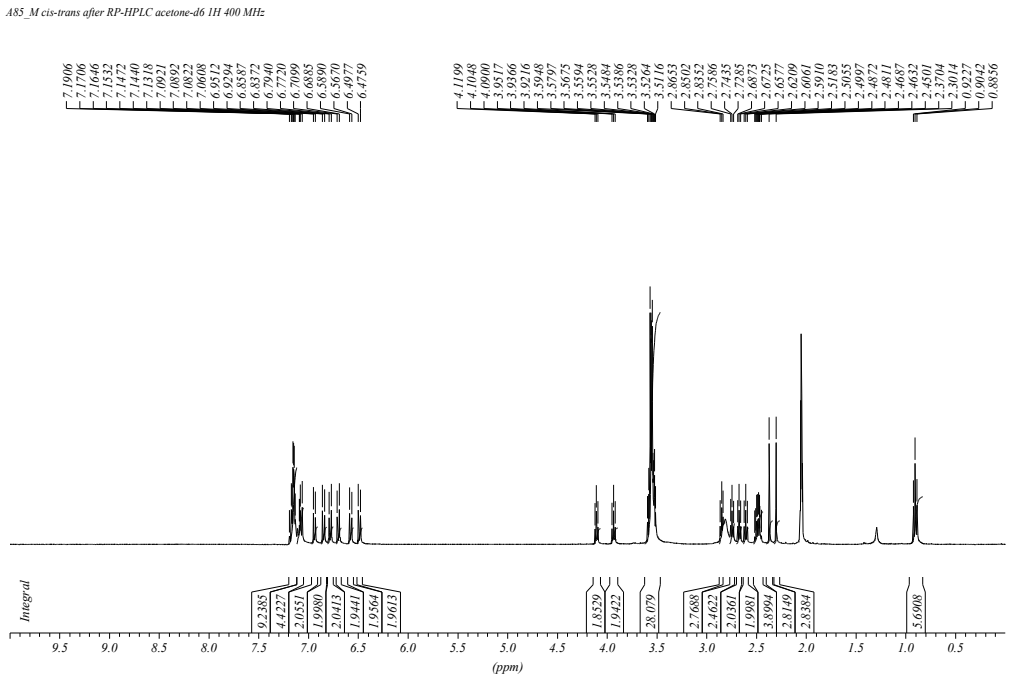


Figure S27. ^{1}H NMR spectra of *Z-E* isomer **16**.

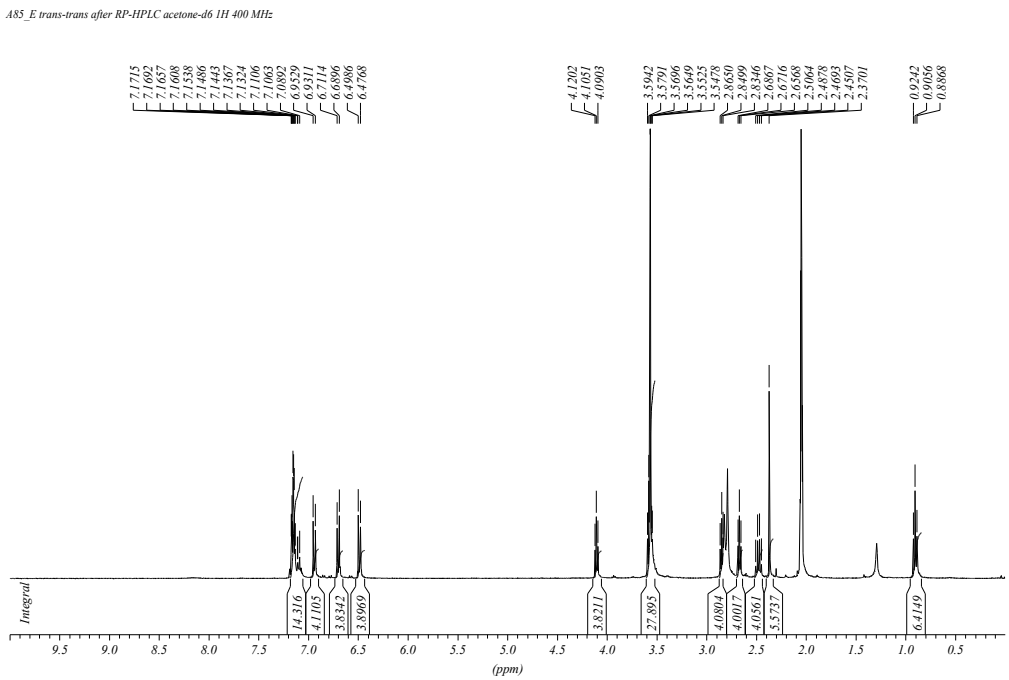


Figure S28. ^{1}H NMR spectra of *E-E* isomer **16**.

11. ^{1}H NMR spectra of *Z*- and *E*-isomer **20**

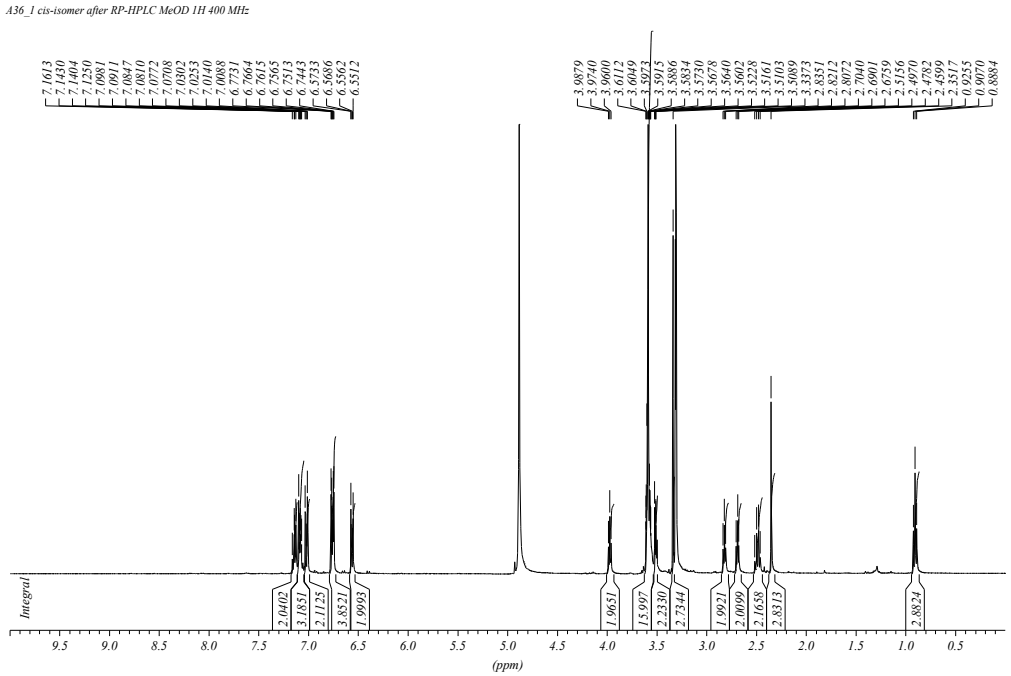


Figure S29. ^{1}H NMR spectra of *Z*-isomer **20**.

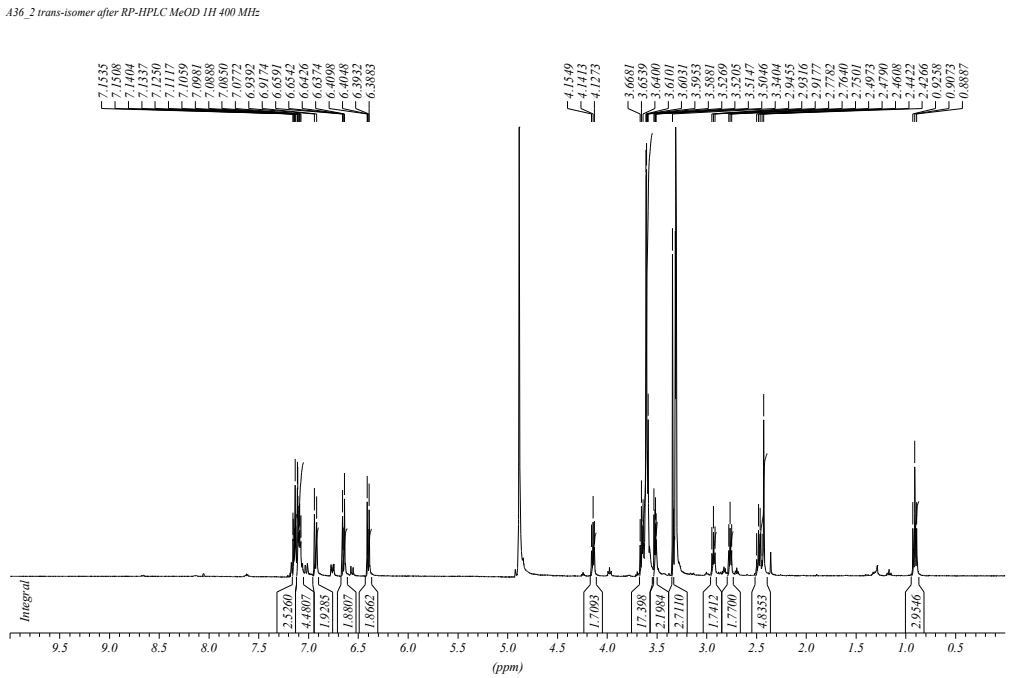


Figure S30. ^{1}H NMR spectra of *E*-isomer **20**.

12. Estrogen receptor binding assays

Relative binding affinities were determined by competitive radiometric binding assays with 2 nM [^{3}H]E_2 as tracer ([2,4,6,7-^{3}H]estra-1,3,5,(10)-triene-3,17β-diol, 70-120Ci/mmol, GE Healthcare, Piscataway, NJ), as a modification of methods previously described.[12,13] The source of ER was purified full-length human ERα and ERβ purchased from Pan Vera/Invitrogen (Carlsbad, CA). Incubations were done at 0°C for 18-24 h, and hydroxyapatite (Bio-Rad, Hercules, CA) was used to absorb the purified ER-ligand complexes.[6] The binding affinities are expressed as RBA values, where the RBA of estradiol is 100%; under these conditions, the K_d of E_2 for ERα and ERβ is 0.2 and 0.5 nM, respectively. The determination of these RBA values is reproducible in separate experiments with a CV of 0.3, and the values shown represent the average ± range or SD of 2 or more separate determinations.

13. Computer modeling

Structures of the bivalent ligands were created using the visualization software Amira.[14] The starting conformation of the OHT moieties was adapted from crystal structures with PDB ID 3ERT and 2FSZ. The complexed structures were prepared by aligning a pre-minimized conformation of the bivalent ligand with the OHT ligands in the respective crystal structure, and then performing additional energy minimization (MMFF94 force field[15]) in order to relax the spacer. For the unknown binding modes (in particular OHT binding to the Coactivator-binding site on ERα), the docking algorithm FADO[16] was used to predict the most likely binding mode of the outside OHT moiety. Where possible, incomplete or missing amino acids in the crystal structures were remodeled. The resulting protein-ligand complexes were put into rhombic dodecahedron solvent boxes of 10.5 nm (ERα) and 9.3 nm (ERβ) side length each. Positions of water molecules contained in the crystal structures were conserved. The overall charge of the simulation boxes was neutralized using the adequate amount of counter ions. The energy of the systems was minimized with the steepest descent algorithm, and afterwards 200 ps simulations were performed during which the position of all ligand and protein (non-hydrogen) heavy atoms was restrained in order to settle the solvent molecules. The resulting configurations were used as starting point for a molecular dynamics (MD) run of 10 ns length each. We used the Amber-99SB force field[17] with the TIP4P-Ew water model.[18] The novel bivalent ligand structures were parameterized using the software Antechamber from AmberTools 1.2,[19-21] with charges calculated by the AM1-BCC method.[22,23] To maintain a constant temperature of 300 K and a pressure of 1 bar, velocity rescaling[24] and Berendsen weak coupling[25] were applied. A twin range cut-off of 1.0/1.4 nm for van der Waals interactions was applied and the smooth particle mesh Ewald algorithm[26] was used for Coulomb interactions, with a switching distance of 1.0 nm. Bond lengths were constrained using the LINCS algorithm,[27] allowing for an integration step of 2 fs. All simulations were performed using the GROMACS 4 software[28] and the according port of the Amber force fields, ffamber.[29,30] As the OHT conformation known from the crystal structure was not overly well reproduced by the MD simulation, we performed another modeling and

minimization step with the MMFF94 force field in order to arrive at the final geometries that were used for our structural evaluations.

14. References

(1) Goswami, R., Harsy, S. G., Heiman, D. F., and Katzenellenbogen, J. A. (1980) Estrogen-Receptor Based Imaging Agents. 2. Synthesis and Receptor-Binding Affinity of Side-Chain Halogenated Hexestrol Derivatives, *J. Med. Chem. 23*, 1002–1008.

(2) Gauthier, S., Mailhot, J., and Labrie, F. (1996) New highly stereoselective synthesis of (Z)-4-Hydroxytamoxifen and (Z)-4-hydroxytoremifene via McMurry reaction, *J. Org. Chem. 61*, 3890–3893.

(3) Detsi, A., Koufaki, M., and Calogeropoulou, T. (2002) Synthesis of (Z)-4-hydroxytamoxifen and (Z)-2-[4-[1-(p-hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic acid, *J. Org. Chem. 67*, 4608–4611.

(4) Yu, D. D., and Forman, B. M. (2003) Simple and efficient production of (Z)-4-hydroxytamoxifen, a potent estrogen receptor modulator, *J. Org. Chem. 68*, 9489–9491.

(5) Mohler, D. L., and Shen, G. (2006) The synthesis of tethered ligand dimers for PPAR gamma-RXR protein heterodimers, *Org. Biomol. Chem. 4*, 2082–2087.

(6) Ogawa, K., Matsushita, Y., Yamawaki, I., Kaneda, M., Shibata, J., Toko, T., and Asao, T. (1991) Synthesis and Antiestrogenic Activity of the Compounds Related to the Metabolites of (Z)-4-[1-[4-[2-(Dimethylamino)Ethoxy]Phenyl]-2-(4-Isopropylphenyl)-1-Butenyl]Phenyl Monophosphate (Tat-59), *Chem. Pharm. Bull. 39*, 911–916.

(7) Burke, P. J., and Koch, T. H. (2004) Design, synthesis, and biological evaluation of doxorubicin - Formaldehyde conjugates targeted to breast cancer cells, *J. Med. Chem. 47*, 1193–1206.

(8) Abdel-Magid, A. F., Carson, K. G., Harris, B. D., Maryanoff, C. A., and Shah, R. D. (1996) Reductive amination of aldehydes and ketones with sodium triacetoxyborohydride. Studies on direct and indirect reductive amination procedures, *J. Org. Chem. 61*, 3849–3862.

(9) Shan, M., Bujotzek, A., Abendroth, F., Wellner, A., Gust, R., Seitz, O., Weber, M., and Haag, R. (2011) Conformational Analysis of Bivalent Estrogen Receptor Ligands: From Intramolecular to Intermolecular Binding. *ChemBioChem 12*, 2587–2598.

(10) LaFrate, A. L., Carlson, K. E., and Katzenellenbogen, J. A. (2009) Steroidal bivalent ligands for the estrogen receptor: Design, synthesis, characterization and binding affinities. *Bioorg. Med. Chem. 17*, 3528–3535.

(11) Hill, K.A., and Peterson, D. M. (1981) Synthesis of metabolic intermediates of diethylstilbestrol. *Steroids 37*, 327–343.

(12) Katzenellenbogen, J. A., Johnson, H. J., and Myers, H. N. (1973) Photoaffinity Labels for Estrogen Binding Proteins of Rat Uterus, *Biochemistry 12*, 4085–4092.

(13) Carlson, K. E., Choi, I., Gee, A., Katzenellenbogen, B. S., and Katzenellenbogen, J. A. (1997) Altered ligand binding properties and enhanced stability of a constitutively active estrogen receptor: Evidence that an open pocket conformation is required for ligand interaction, *Biochemistry 36*, 14897–14905.

(14) Stalling, D., Westerhoff, M., and Hege, H. C. (2005) In *The Visualization Handbook*, (Hansen, C. D., Johnson, C. R., Ed.), pp 749–767, Elsevier, Burlington.

(15) Halgren, T. A. (1996) Merck molecular force field. 1. Basis, form, scope, parameterization, and performance of MMFF94, *J. Comput. Chem. 17*, 490–519.

(16) Guerler, A., Moll, S., Weber, A., Meyer, H., and Cordes, F. (2008) Selection and flexible optimization of binding modes from conformation ensembles, *Biosystems 92*, 42–48.

(17) Hornak, V., Abel, R., Okur, A., Strockbine, B., Roitberg, A., and Simmerling, C. (2006) Comparison of multiple amber force fields and development of improved protein backbone parameters, *Proteins 65*, 712–725.

(18) Horn, H. W., Swope, W. C., Pitera, J. W., Madura, J. D., Dick, T. J., Hura, G. L., and Head-Gordon, T. (2004) Development of an improved four-site water model for biomolecular simulations: TIP4P-Ew, *J. Chem. Phys. 120*, 9665–9678.

(19) Case, D. A., Cheatham, T. E., Darden, T., Gohlke, H., Luo, R., Merz, K. M., Onufriev, A., Simmerling, C., Wang, B., and Woods, R. J. (2005) The Amber biomolecular simulation programs, *J. Comput. Chem. 26*, 1668–1688.

(20) Wang, J. M., Wolf, R. M., Caldwell, J. W., Kollman, P. A., and Case, D. A. (2004) Development and testing of a general amber force field, *J. Comput. Chem. 25*, 1157–1174.

(21) Wang, J. M., Wang, W., Kollman, P. A., and Case, D. A. (2006) Automatic atom type and bond type perception in molecular mechanical calculations, *J. Mol. Graph. Model 25*, 247–260.

(22) Jakalian, A., Bush, B. L., Jack, D. B., and Bayly, C. I. (2000) Fast, efficient generation of high-quality atomic Charges. AM1-BCC model: I. Method, *J. Comput. Chem. 21*, 132–146.

(23) Jakalian, A., Jack, D. B., and Bayly, C. I. (2002) Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation, *J. Comput. Chem. 23*, 1623–1641.

(24) Bussi, G., Donadio, D., and Parrinello, M. (2007) Canonical sampling through velocity rescaling, *J. Chem. Phys. 126*, 14101–14107.

(25) Berendsen, H. J. C., Postma, J. P. M., Vangunsteren, W. F., Dinola, A., and Haak, J. R. (1984) Molecular-Dynamics with Coupling to an External Bath, *J. Chem. Phys. 81*, 3684–3690.

(26) Essmann, U., Perera, L., Berkowitz, M. L., Darden, T., Lee, H., and Pedersen, L. G. (1995) A Smooth Particle Mesh Ewald Method, *J. Chem. Phys. 103*, 8577–8593.

(27) Hess, B., Bekker, H., Berendsen, H. J. C., and Fraaije, J. G. E. M. (1997) LINCS: A linear constraint solver for molecular simulations, *J. Comput. Chem. 18*, 1463–1472.

(28) Hess, B., Kutzner, C., van der Spoel, D., and Lindahl, E. (2008) GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation, *J. Chem. Theory Comput. 4*, 435–447.

(29) Sorin, E. J., and Pande, V. S. (2005) Exploring the helix-coil transition via all-atom equilibrium ensemble simulations, *Biophys. J. 88*, 2472–2493.

(30) DePaul, A. J., Thompson, E. J., Patel, S. S., Haldeman, K., and Sorin, E. J. (2010) Equilibrium conformational dynamics in an RNA tetraloop from massively parallel molecular dynamics, *Nucleic Acids Res. 38*, 4856–4867.