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Effect of stereochemistry of Δlac-acetogenins on the inhibition of mitochondrial complex I (NADH-ubiquinone oxidoreductase)

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Abstract—Δlac-Acetogenins are a new type of inhibitors of bovine heart mitochondrial complex I (NADH-ubiquinone oxidoreductase). We synthesized a series of Δlac-acetogenins in which the stereochemistry around the hydroxylated tetrahydrofuran (THF) ring moiety was systematically modified, and examined their inhibitory effect on complex I. The present results revealed that the inhibitory effects of the bis-THF ring analogs are much more potent than those of the mono-THF ring analogs and that the stereochemistry around the bis-THF ring moiety significantly influences the inhibitory effect. The profiles of the structure–activity relationship observed for Δlac-acetogenins were entirely different from those for natural-type acetogenins.

1. Introduction

Acetogenins isolated from the plant family Annonaceae have potent and diverse biological effects such as antitumor, antimalarial, and insecticidal activities.[1,2] Their inhibitory effect on mitochondrial NADH-ubiquinone oxidoreductase (complex I) is of particular importance since the diverse biological activities of acetogenins are thought to be attributable to this effect.[1] Their unique structural features and multiple chiral centers, especially the four or more in the tetrahydrofuran (THF) portion, make acetogenins challenging synthetic targets.[3] On the other hand, structural simplification while maintaining all the essential functionalities of acetogenins may facilitate the task of synthesizing a variety of acetogenin mimics, which may be used not only as possible chemotherapeutic agents, but also as molecular probes to investigate the functional features of mitochondrial complex I,[4–6] one of the largest known membrane protein complexes.

In the course of the synthesizing simplified acetogenin mimics, we deleted a α,β-unsaturated γ-methylbutyrolactone ring, which is a structural feature common to a large number of natural acetogenins,[1,2] from the mother skeleton of the natural products and named the resultant compounds 'Δlac-acetogenins'. Unexpectedly, some Δlac-acetogenins (e.g., compound **1** in Fig. 1) exhibited a strong inhibitory effect on bovine heart mitochondrial complex I at the nanomolar level.[7] Several lines of evidence, e.g., competition tests using a fluorescent ligand and the effect on superoxide production from complex I, revealed that the site of inhibition by Δlac-acetogenins is different from that by natural acetogenins as well as ordinary complex I inhibitors such as rotenone and piericidin A.[8,9] Thus Δlac-acetogenins were shown to be a new type of inhibitors acting at the terminal electron transfer step in complex I. Accordingly, a detailed analysis of their inhibitory action would provide valuable insights into the functional features of complex I.

To elucidate the mode of inhibitory action of Δlac-acetogenins, identification of the crucial structural factors required for the inhibition is needed. A previous structure–activity study concerning Δlac-acetogenins indicated that the number of carbon atoms (i.e., hydrophobicity) of the alkyl side chains remarkably affects the inhibitory potency.[7] In addition, the balance of the hydrophobicity of the two chains attached to the C_2-symmetric bis-THF portion was also an important structural factor of these inhibitors.[10] This is probably because the side chains decide the precise location of the hydrophilic THF moiety at or close to the membrane interface. On the other hand, information about the effect of both the number of THF rings and the stereochemistry around the THF ring including flanking OH groups is limited since we have examined solely bis-THF analogs having *R*-configurations at all chiral centers like compound **1**. To examine these subjects, we here synthesized a series of Δlac-acetogenins in which the stereochemistry around the hydroxylated THF moiety was systematically modified (Fig. 1), and examined their inhibitory effect on bovine mitochondrial complex I.

Keywords: Stereoselective synthesis; Acetogenin; Respiratory inhibitor; Mitochondrial complex I.
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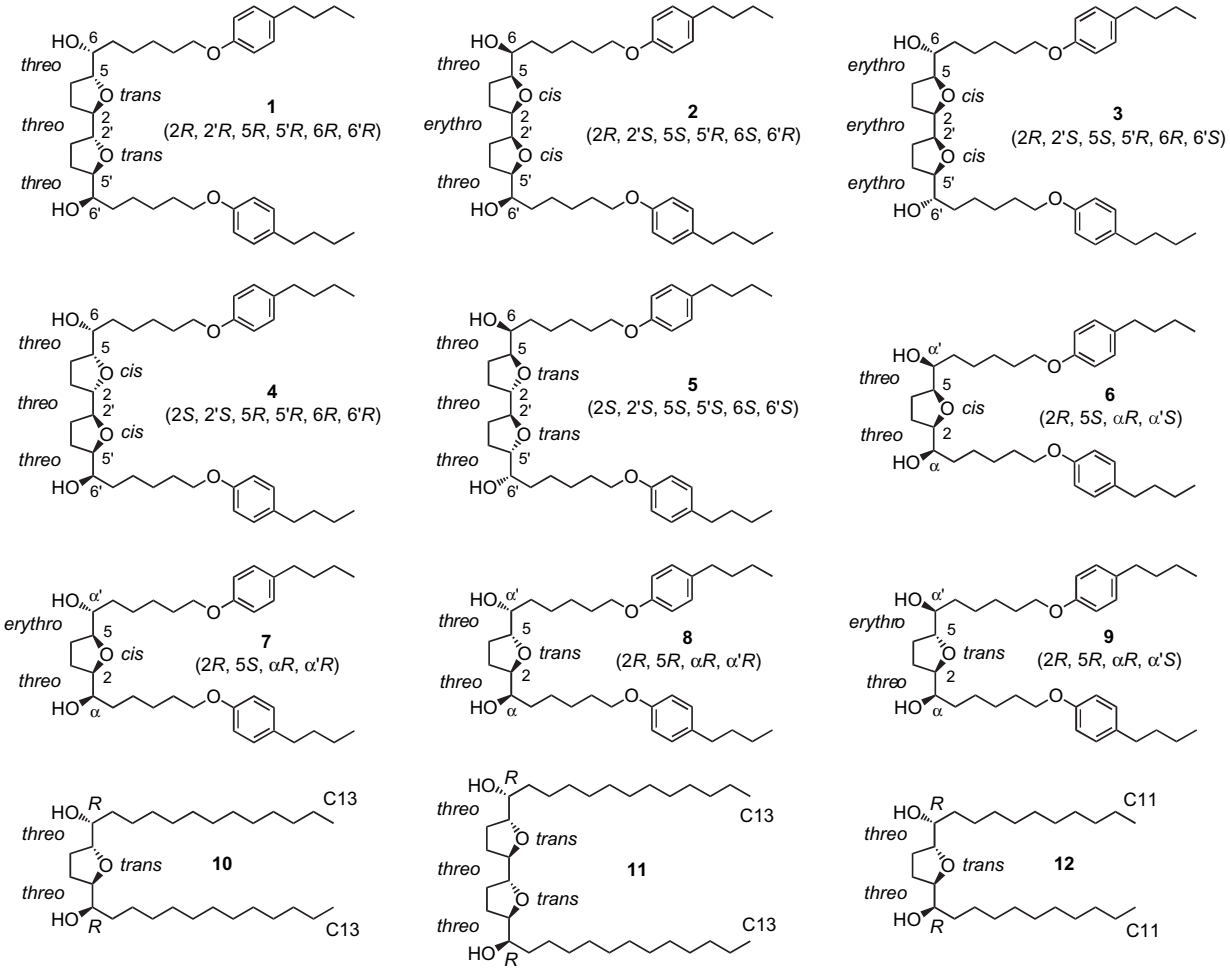


Figure 1. Structures of Δlac-acetogenins studied in the present study. Compounds **1**, **10** and **11** are the same samples as used previously.[8]

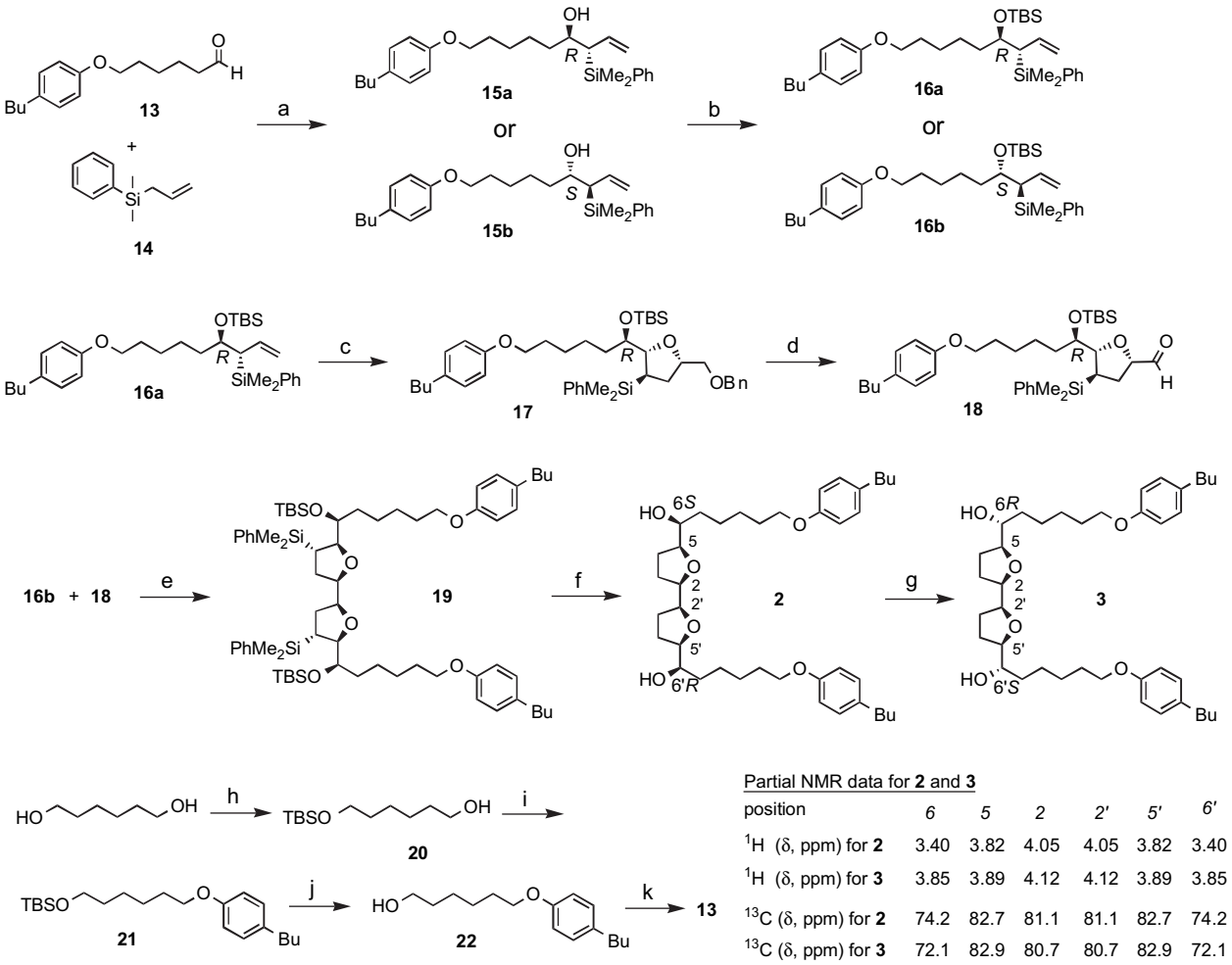
2. Results and discussion

2.1. Synthesis of diastereomeric Δlac-acetogenins

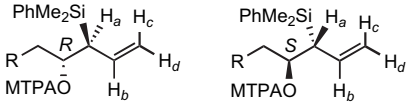
To synthesize small libraries of stereochemically diverse bis-THF systems, Roush and colleagues recently reported double asymmetric [3+2]-annulation reaction of chiral β-silyloxyallylsilanes with chiral 2-tetrahydrofuranyl carbaldehydes, leading to the stereocontrolled synthesis of diastereomeric bis-THF structures.[11–13] This excellent strategy is a highly useful way to synthesize diastereomeric Δlac-acetogenins to elucidate the effect of the stereochemistry of the hydroxylated bis-THF moiety on the inhibitory action. We therefore synthesized the following test compounds, except compound **5**, largely according to their procedures. The side chains of all test compounds were fixed as identical to that of compound **1** since this inhibitor is the most potent Δlac-acetogenin to be synthesized in our laboratory.[7,8]

For the synthesis of compounds **2–4**, we prepared chiral allylsilanes **16a** and **16b** through the reaction of aldehyde **13** with (*E*)-γ-[(dimethylphenysilyl)allyl]diisopinocampheylbornane, which was derived from allyldimethylphenylsilane **14** and (−)-Ipc$_2$BOMe (for **16a**) or (+)-Ipc$_2$BOMe (for **16b**), respectively (Scheme 1).[11–13] Aldehyde **13** was synthesized by four reaction steps from a commercially available 1,6-hexanediol, as shown in the bottom of Scheme 1. Allyldimethylphenylsilane **14** was synthesized by the Grignard reaction of a commercially available chlorodimethylphenylsilane with allylmagnesium chloride. The absolute configurations and enantiopurity of **16a** and its enantiomer **16b** were determined through a Mosher ester analysis of the corresponding secondary alcohols **15a** (*R* configuration, 96% ee) and **15b** (*S* configuration, 96% ee), as shown in Figure 2.[11,14]

A $BF_3\cdot Et_2O$-catalyzed [3+2]-annulation reaction between **16a** and α-(benzyloxy)acetoaldehyde gave the 2,5-*cis*-THF **17** in 56% yield with 17:1 ds. The relative stereochemistry at the C2 and C5 positions in **17** was assigned using a ^{1}H NOE analysis (Fig. 3).[11] As closely studied by Roush's group,[11–13] the relative configuration about the C2–Cα bond in **17** was assigned as *threo* on the basis of the finding that the *threo* relationship at this position results from [3+2]-annulation reactions of β-silyloxyallylsilanes with *anti* relative stereochemistry, such as **16a** and **16b**. The 2,5-*cis*-THF **17** was converted to the aldehyde **18** in 72% yield by $Pd(OH)_2$/C-catalyzed debenzylation and subsequent Swern oxidation. The $BF_3\cdot Et_2O$-catalyzed [3+2]-annulation reaction of **16b** with **18** afforded the *cis–threo–cis* bis-THF structure **19** as 16:1 ds. Subsequent treatment with TBAF gave the compound **2** in 63% yield (two steps). The stereochemistry



Scheme 1. Reagents and conditions: (a) *t*-BuOK, *n*-BuLi, $BF_3{\cdot}Et_2O$, (−)-Ipc_2BOMe for **15a**, (+)-Ipc_2BOMe for **15b**, THF, −78 °C, 4 h, 51% for **15a**, 55% for **15b**; (b) TBSCl, imidazole, DMF, 50 °C, 48 h, 98% for **16a**, 94% for **16b**; (c) α-(benzyloxy)acetaldehyde, $BF_3{\cdot}Et_2O$, 4 Å MS, CH_2Cl_2, −78 to −45 °C, 22 h, 56%; (d) (i) 20% $Pd(OH)_2$/C, H_2, THF, rt, 2 h, 86%, (ii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 84%; (e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 4 Å MS, −78 °C, 1 h; (f) TBAF, DMF, 90 °C, 6.5 h, 63% (two steps); (g) (i) 4-nitrobenzoic acid, PPh_3, DIAD, toluene, 100 °C, 2 h, (ii) K_2CO_3, MeOH, 35 °C, 1.5 h, 23%; (h) NaH, TBSCl, THF, 0 °C, 2 h, 58%; (i) 4-butylphenol, PPh_3, DIAD, THF, 0 °C to rt, 3 h; (j) TBAF, THF, 0 °C to rt, 3.5 h, 82% (two steps); (k) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 84%.



position	*a*	*b*	*c*	*d*
Δδ (ppm) for **15a**	-0.11	-0.02	-0.07	-0.06
	(2.14-2.25)	(5.71-5.73)	(4.79-4.86)	(4.93-4.99)
Δδ (ppm) for **15b**	+0.09	+0.02	+0.07	+0.06
	(2.22-2.13)	(5.73-5.71)	(4.86-4.79)	(4.99-4.93)

Figure 2. Determination of the absolute configurations of **15a** and **15b**. Differences in chemical shifts [Δ_{S-R} values in δ (400 MHz, $CDCl_3$)] between (*S*)- and (*R*)-MTPA esters of **15a** and **15b** are shown.

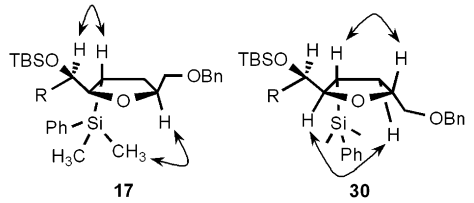
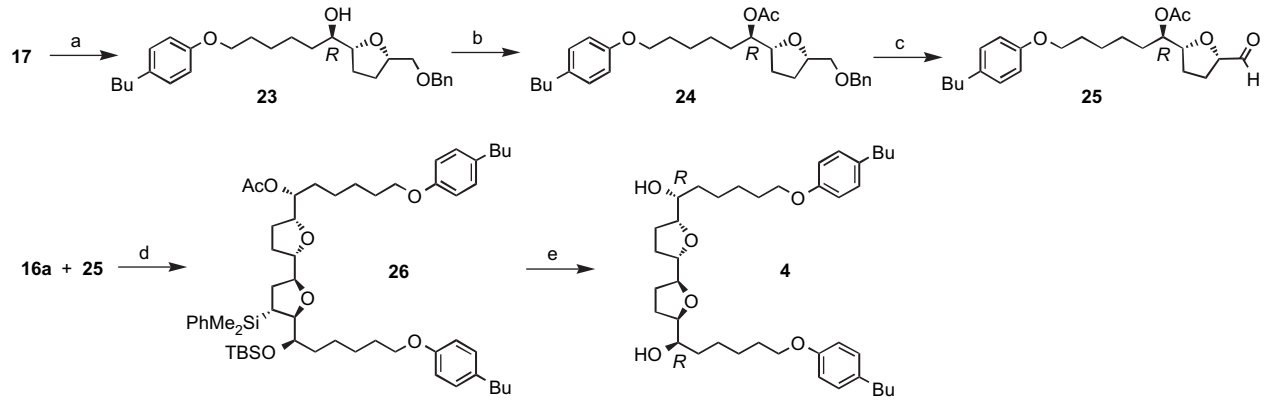


Figure 3. NOEs observed for **17** and **30**.

of **2** was assigned through inspection of its ^1H and ^{13}C NMR spectral data, which exhibit only three nonequivalent methine resonances, indicating that **2** has a C_2-symmetric structure. The *R* absolute configuration of C6′ in **2** is known from the stereochemistry of the parent allylsilane **16a**. Likewise, the *S* configuration of C6 is known from allylsilane **16b**. We also know that one THF ring in **2** possesses the 2′,5′-*cis* stereochemistry present in aldehyde **18**, and a *threo* relationship exists between the C5′ and C6′ substituents. Thus, there is no symmetric structure other than the *threo–cis–erythro–cis–threo* structure that can be assigned for **2**.

Compound **3**, in which the relative configurations about C5–C6 and C5′–C6′ bonds are the *erythro* relationship, cannot be obtained by Roush's procedures since the *threo* relationship at these positions selectively results from [3+2]-annulation reactions of β-silyloxyallylsilanes.[11–13] Therefore compound **3** was synthesized from **2** through Mitsunobu inversion (Scheme 1). The relative configuration was determined by the application of Born's rule to ^1H and ^{13}C NMR spectral data of **3**.[15,16] The spectral data still exhibit

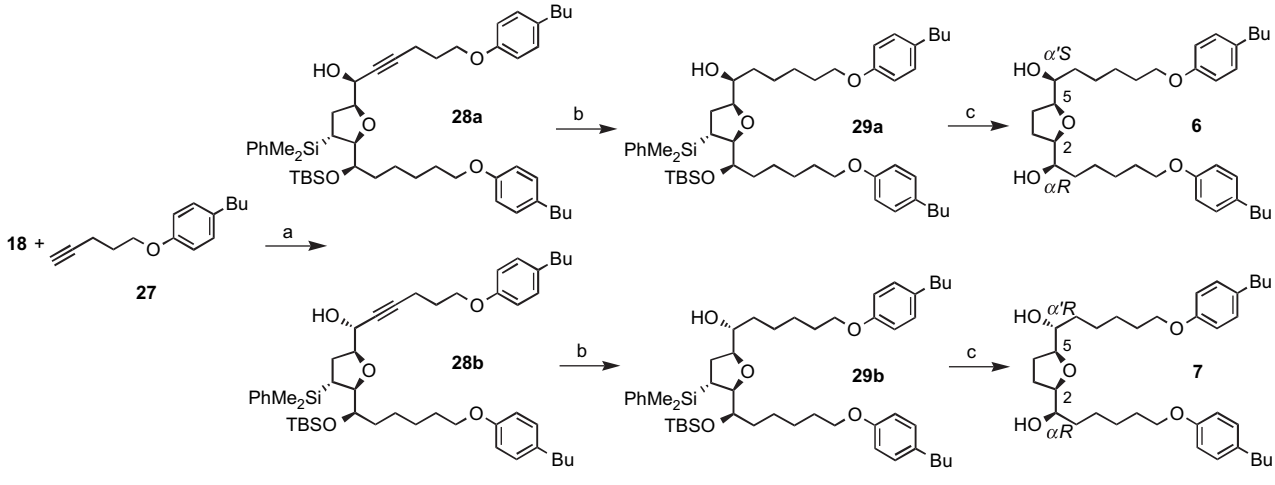


Scheme 2. Reagents and conditions: (a) TBAF, DMF, 90 °C, 5.5 h, 96%; (b) AcCl, DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 92%; (c) (i) 20% $Pd(OH)_2$/C, H_2, THF, rt, 2 h, 92%, (ii) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 89%; (d) $SnCl_4$, 4 Å MS, CH_2Cl_2, −78 °C, 6 h, 67%; (e) (i) K_2CO_3, MeOH, 35 °C, 1.5 h, (ii) TBAF, DMF, 90 °C, 3.5 h, 54%.

only three nonequivalent methine resonances, indicating that there is no symmetric structure other than the *erythro–cis–erythro–cis–erythro* structure that can be assigned for **3**.

The $SnCl_4$-catalyzed [3+2]-annulation reaction between allylsilane **16a** and aldehyde **25** was successful (6.5:1 ds, 67% yield) for construction of a bis-THF skeleton in **26**, which was the key reaction step in the synthesis of compound **4** (Scheme 2). The diastereomers (**26** and its epimer) were separated by chromatography on silica gel. Aldehyde **25** was synthesized from **17** through protiodesilylation with TBAF, protection of alcohol **23** by an acetate group, $Pd(OH)_2$/C-catalyzed debenzylation, and subsequent Swern oxidation in 72% yield (four steps). The acetate protecting group adjacent to the tetrahydrofuran ring of **25**, rather than a TBS group, is likely favorable for construction of the *cis–threo–cis* stereochemistry of **26**.[11] The *cis–threo–cis* stereochemistry of **26** was established upon hydrolysis with K_2CO_3/MeOH and protiodesilylation with TBAF to afford **4**, a bis-THF with ^1H and ^{13}C NMR spectral data indicating a symmetric product. The *R* configuration at the C6 and C6′ positions in **4** is known from allylsilane **16a**, and one 2,5-*cis*-tetrahydrofuran ring must be present in the structure. There are no other possible symmetric stereochemical assignments for **4** other than the *cis–threo–cis* structure.

The synthesis of mono-THF ring analogs (**6–9**) was accomplished by alkyne addition to chiral 2-tetrahydrofuranyl carbaldehydes (Schemes 3 and 4). The reaction of aldehyde **18** with the lithium acetylide derived from **27** in the presence of anhydrous $CeCl_3$[17] gave alkynyl compounds **28a** and **28b** as a 1:2.2 mixture (Scheme 3), which could be separated by chromatography on silica gel. Hydrogenation of **28a** and **28b** with catalytic 10% Pd/C and subsequent protiodesilylation with TBAF provided **6** and **7**. The stereochemistry of **6** was assigned through inspection of its ^1H and ^{13}C NMR spectral data, which exhibit only two nonequivalent methine resonances, indicating that **6** has a C_2-symmetric structure.



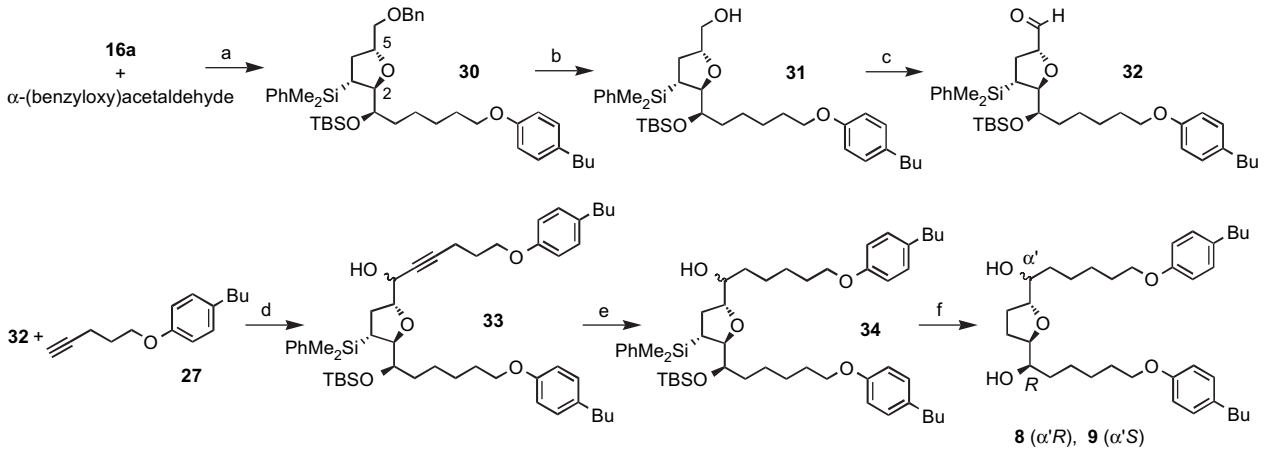
Partial NMR data for **6**

position	α	2	5	α′
^1H (δ, ppm)	3.44	3.82	3.82	3.44
^{13}C (δ, ppm)	74.3	82.6	82.6	74.3

Partial NMR data for **7**

position	α	2	5	α′
^1H (δ, ppm)	3.44	3.82	3.90	3.85
^{13}C (δ, ppm)	74.3	82.6	82.2	72.2

Scheme 3. Reagents and conditions: (a) *n*-BuLi, $CeCl_3$, THF, −78 to −23 °C, 5 h, 18% for **28a**, 40% for **28b**; (b) 10% Pd/C, H_2, EtOH, rt, 3 h, 87% for **29a**, 91% for **29b**; (c) TBAF, DMF, 90 °C, 4 h, 44% for **6**, 28% for **7**.



Scheme 4. Reagents and conditions: (a) $SnCl_4$, 4 Å MS, CH_2Cl_2, −45 °C, 20 h, 81%; (b) 20% $Pd(OH)_2$/C, H_2, THF, rt, 2 h, 92%; (c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h, 88%; (d) *n*-BuLi, $CeCl_3$, THF, −78 to −23 °C, 5 h, 74%; (e) 10% Pd/C, H_2, EtOH, rt, 12 h, 91%; (f) (i)TBAF, DMF, 90 °C, 6 h, 57%, (ii) AcCl, DMAP, CH_2Cl_2, 0 °C, 2 h, (iii) K_2CO_3, MeOH, 24% for **8**, 50% for **9**.

The *R* absolute configuration of Cα in **6** is known from the stereochemistry of the parent allylsilane **16a**. We also know that the THF ring in **6** possesses the 2,5-*cis* stereochemistry present in aldehyde **18** and a *threo* relationship exists between the C2 and Cα substituents. Thus, there is no symmetric structure other than the *threo–cis–threo* one that can be assigned for **6**. The ^1H and ^{13}C NMR spectral data of **7** exhibit four different methine resonances, indicating that **7** has an asymmetric structure. We know that the THF ring in **7** possesses the 2,5-*cis* stereochemistry present in aldehyde **18** and a *threo* relationship also exists between the C2 and Cα substituents. Thus, there is no asymmetric structure other than the *erythro–cis–threo* one that can be assigned for **7**.

To synthesize compounds **8** and **9**, the 2,5-*trans* THF structure was constructed for compound **30** through a $SnCl_4$-catalyzed [3+2]-annulation reaction between allylsilane **16a** and α-(benzyloxy)acetaldehyde with complete diastereoselectivity in 81% yield (Scheme 4). The relative stereochemistry at the C2 and C5 positions in **30** was assigned using a ^1H NOE analysis (Fig. 3).[11] The relative configuration about the C2–Cα bond in **30** was assigned as *threo*, as described above. Debenzylation of **30** catalyzed by 10% $Pd(OH)_2$/C and subsequent Swern oxidation gave the aldehyde **32**, which was coupled with the alkyne **27** to afford the alkynyl compound **33** as a 4:5 mixture of diastereoisomers. Although the mixture was hydrogenated and protiodesilylated only to give a mixture of **8** and **9** without any success in separation by chromatography on silica gel, we found that the diacetate derivatives could be separated by chromatography on silica gel. Hydrolysis of the resultant diacetate provided **8** (and **9**). The stereochemistry of **8** and **9** was assigned through the application of Born's rule to their ^1H and ^{13}C NMR spectral data,[15,16] indicating that the *threo-trans-threo* and *erythro-trans-threo* structures can be assigned for **8** and **9**, respectively.

In previous studies,[18,19] the six stereogenic centers in compound **1** were constructed by sequential double Sharpless asymmetric epoxidation and dihydroxylation (AD) using (+)-diethyl tartrate (DET) and AD-mix-β, respectively. Compound **5**, an enantiomer of **1**, was synthesized following the procedure used for the synthesis of **1**, but using (−)-DET and AD-mix-α in place of (+)-DET and AD-mix-β, respectively. The ^1H and ^{13}C NMR spectral data of **5** were identical to those of **1**. Optical rotations ($[\alpha]_D$) of **1** and **5** were +17 (*c* 0.41, EtOH) and −19 (*c* 0.21, EtOH) at 16 °C, respectively.

The total synthesis of stereoisomer library of bis- and mono-THF acetogenins has been disclosed in Refs. 11 and 20, respectively. The ^1H and ^{13}C NMR spectral data of the bis-THF portion of **1–5** and mono-THF portion of **6–9** matched the data published in these papers.

2.2. Biological activity

The inhibition of complex I in bovine heart submitochondrial particles was investigated by NADH oxidase assay. The inhibitory potencies of the test compounds, in terms of IC_{50} values, are listed in Table 1, taking bullatacin and piericidin A as references. Compound **1** was the most potent inhibitor among the Δlac-acetogenins synthesized so far in our laboratory.[8,10] All modifications of the stereochemistry around the THF moiety of **1** (i.e., all *R* isomer) significantly reduced the inhibitory potency, but none resulted in drastic changes such as a 10^3–10^4 fold loss in activity. The *threo* stereochemistry about the C2–C2′ bond seems to be slightly better for the activity than the *erythro* stereochemistry.

With respect to the mono-THF analogs, it was revealed that their inhibitory effects are much weaker than those of

Table 1. Summary of the inhibitory potencies (IC_{50}) of the test compounds[a]

Compound no.	IC_{50} (nM)	Compound no.	IC_{50} (nM)
1	0.90 (±0.05)	**8**	47 (±2)
2	16 (±1)	**9**	38 (±2)
3	9.0 (±1.4)	**10**	>25,000[b]
4	5.2 (±0.5)	**11**	9.0 (±0.7)[b]
5	3.8 (±0.3)	**12**	308 (±13)
6	39 (±8)	Piericidin A	1.3 (±0.05)[b]
7	41 (±3)	Bullatacin	0.85 (±0.03)[b]

[a] The IC_{50} value is the molar concentration needed to reduce the control NADH oxidase activity (0.60–0.65 μmol NADH/min/mg of protein) in submitochondrial particles by half. Values are means±SD of three independent experiments.
[b] From Ref. 8.

compound **1** and that the changes among them due to the modification of stereochemistry are negligibly small. We previously showed that a mono-THF derivative possessing two tridecyl groups in the side chain portion (compound **10**, IC_{50}>25,000 nM) drastically lost inhibitory activity compared to the corresponding bis-THF analog (compound **11**, IC_{50}=9.0 nM).[7,8] No such drastic loss in activity was observed for the present set of mono-THF analogs, indicating that the physicochemical properties of the side chains markedly affect the molecular interaction of the polar hydroxylated mono-THF with the enzyme. In particular, the drastic reduction in the activity of **10** may be due to an excessive increase in hydrophobicity of the alkyl tails, which results in some sort of trapping in the hydrophobic lipid bilayer of mitochondrial membrane. This phenomenon is generally observed for largely hydrophobic inhibitors.[7] To address this possibility, we newly synthesized compound **12** possessing two undecyl groups in place of tridecyl groups and examined its inhibitory effect. Expectedly, **12** (IC_{50}=308±13 nM) significantly recovered the inhibitory effect compared to **10**, but still much weaker than the corresponding bis-THF analog (compound **3** in Ref. 7: IC_{50}=1.6±0.2 nM) as well as **11**. Taken together, it is obvious that the mono-THF skeleton is much less favorable for the inhibition than bis-THF.

The structure–activity studies for natural-type acetogenins including mono- and bis-THF acetogenins showed that the stereochemistry around the THF moiety including flanking OH groups does not significantly affect the inhibitory activity and that mono-THF analogs are just about 2-fold less potent than bis-THF analogs if other structural factors, such as the length of the alkyl spacer linking γ-lactone and THF moieties, are identical among them.[21–24] Thus, the structural factors governing the inhibitory effect are appreciably different between Δlac-acetogenins and natural acetogenins. This result also supports our previous view derived from various biochemical experiments; namely, that the site of inhibition by Δlac-acetogenins in complex I is different from that by natural acetogenins.

3. Experimental

3.1. General procedures

^{1}H NMR spectra were recorded at 500 or 400 MHz with a Bruker ARX500 or Bruker AVANCE400 spectrometer using tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded at 100 MHz. The ESI-MS and HR ESI-MS spectra were recorded with a Perkin–Elmer Sciex API165 and Shimadzu LCMS-IT-TOF, respectively. Optical rotations were measured with a JASCO P-1010 polarimeter. Column chromatography was performed on Wako silica gel (C-200, 75–150 μm) or YMC silica gel (SIL-60-S75, 42–105 μm). Dry solvents were either used as purchased or freshly distilled using common practices where appropriate.

3.2. Synthesis of compound 2

3.2.1. 6-(4-Butylphenyloxy)-1-hexanal (13). To a cooled solution of oxalyl chloride (2.6 mL, 30 mmol) in anhydrous CH_2Cl_2 (60 mL) at −78 °C was added dropwise DMSO (4.0 mL, 56 mmol) and the mixture was stirred for 15 min at the same temperature. A CH_2Cl_2 solution (50 mL) of alcohol **22** (4.9 g, 20 mmol) was added slowly. After stirring for 30 min, the mixture was quenched with Et_3N (14 mL) at −78 °C. The reaction mixture was slowly warmed to 0 °C over 1 h and then saturated aqueous NH_4Cl was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by Wako silica gel chromatography (10% EtOAc/hexane) to give aldehyde **13** (4.1 g, 17 mmol, 84%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, J=1.7 Hz, 1H), 7.07 (d, J=8.6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 3.93 (t, J=6.3 Hz, 2H), 2.54 (t, J=7.6 Hz, 2H), 2.46 (dt, J=7.4, 1.7 Hz, 2H), 1.79 (tt, J=7.1, 6.3 Hz, 2H), 1.70 (quint, J=7.7 Hz, 2H), 1.56–1.51 (m, 4H), 1.34 (tq, J=7.5, 7.3 Hz, 2H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.53, 157.08, 134.84, 129.19 (2C), 114.25 (2C), 67.77, 34.72, 34.31, 33.91, 29.21, 25.87, 23.30, 13.96; ESI-HRMS (m/z) calcd for $C_{16}H_{25}O_2$ $[M+H]^+$ 249.1848, observed 249.1844.

3.2.2. Allyldimethylphenylsilane (14). To a solution of chlorodimethylphenylsilane (5.0 g, 29.3 mmol) in anhydrous Et_2O (40 mL) was added allylmagnesium chloride (14.6 mL of a 2.0 M solution in THF, 29.3 mmol) slowly over 20 min and the resulting mixture was refluxed at 60 °C for 18.5 h. The mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl, and partitioned between H_2O and Et_2O. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5% $CHCl_3$/hexane) to give **14** (4.4 g, 25 mmol, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.49 (m, 2H), 7.36–7.33 (m, 3H), 5.77 (ddt, J=16.8, 10.1, 8.0 Hz, 1H), 4.86 (dd, J=16.8, 2.6 Hz, 1H), 4.83 (dd, J=10.1, 2.6 Hz, 1H), 1.75 (d, J=8.0 Hz, 2H), 0.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.67, 134.63, 133.61 (2C), 129.00, 127.74 (2C), 113.38, 23.67, −3.48 (2C); ESI-MS (m/z) 177.2 $[M+H]^+$.

3.2.3. (3*S*,4*R*)-9-(4-Butylphenyloxy)-3-dimethylphenylsilyl-4-hydroxy-1-nonene (15a). To a solution of *t*-BuOK (0.86 g, 7.7 mmol) in THF (15 mL) at −78 °C was added **14** (1.5 g, 8.5 mmol). The mixture was stirred for 5 min, then *n*-BuLi (1.57 M in hexane, 4.9 mL, 7.7 mmol) was added slowly via a syringe over 5 min. The mixture was stirred at −78 °C for 10 min and then warmed to −45 °C and stirred for 1 h. The mixture was recooled to −78 °C and (−)-Ipc$_2$BOMe (2.4 g, 7.7 mmol) was added as a solution in THF (9 mL) slowly over 5 min. The mixture was stirred for 30 min and then $BF_3\cdot Et_2O$ (1.5 g, 10.2 mmol) was added in one portion. After 5 min, aldehyde **13** (2.32 g, 9.4 mmol) was added as a solution in THF (15 mL) slowly over 5 min. The mixture was stirred at −78 °C for 4 h and then diluted with KOH/KH_2PO_4 buffer (1.0 M solution of KH_2PO_4, adjusted to pH 6.0 with KOH, 7.5 mL) and warmed to room temperature. H_2O_2 (30%, 1.4 mL) was added and then the two-phase mixture was stirred at ambient temperature for 16 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. The organic layer was dried over anhydrous $MgSO_4$, and concentrated, and the residue was dissolved in MeOH

(20 mL) for subsequent reduction of the excess aldehyde **13**. This reduction step enabled the product **15a** to be isolated as a pure form on purification by silica gel chromatography. $NaBH_4$ (0.13 g, 3.4 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was poured into 15 mL of saturated aqueous NH_4Cl, and the resulting suspension was extracted with Et_2O, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (10% EtOAc/hexane) to give allylsilane **15a** (1.7 g, 3.9 mmol, 51%) as a colorless oil: $[\alpha]_D^{21}$ +2.3 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H), 7.35–7.34 (m, 3H), 7.07 (d, *J*=8.6 Hz, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 5.82 (ddd, *J*=17.0, 10.4, 10.4 Hz, 1H), 5.05 (dd, *J*=10.4, 2.0 Hz, 1H), 4.91 (dd, *J*=17.0, 2.0 Hz, 1H), 3.87 (t, *J*=6.5 Hz, 2H), 3.75–3.69 (m, 1H), 2.53 (t, *J*=7.7 Hz, 2H), 1.91 (dd, *J*=10.4, 4.5 Hz, 1H), 1.75–1.67 (m, 2H), 1.57–1.53 (m, 2H), 1.56 (br s, 1H), 1.40–1.30 (m, 9H), 0.91 (t, *J*=7.3 Hz, 3H), 0.35 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 137.9, 135.1, 134.8, 134.0 (2C), 129.1 (2C), 129.0, 127.7 (2C), 115.6, 114.2 (2C), 71.34, 67.80, 42.12, 37.03, 34.72, 33.91, 29.22, 25.93, 25.46, 22.30, 13.97, −3.37, −3.97; ESI-HRMS (*m*/*z*) calcd for $C_{27}H_{40}SiO_2Na$ $[M+Na]^+$ 447.2685, observed 447.2690.

3.2.4. (3*R*,4*S*)-9-(4-Butylphenyloxy)-3-dimethylphenylsilyl-4-hydroxy-1-nonene (15b). Compound **15b** was synthesized by the same procedure used for the synthesis of **15a**, except that (+)-Ipc_2BOMe was used in place of (−)-Ipc_2BOMe, in a 55% yield as a colorless oil: $[\alpha]_D^{21}$ −2.3 (*c* 0.17, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H), 7.35–7.34 (m, 3H), 7.06 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 5.82 (ddd, *J*=17.0, 10.4, 10.4 Hz, 1H), 5.05 (dd, *J*=10.4, 2.0 Hz, 1H), 4.91 (dd, *J*=17.0, 2.0 Hz, 1H), 3.87 (t, *J*=6.5 Hz, 2H), 3.74–3.70 (m, 1H), 2.53 (t, *J*=7.7 Hz, 2H), 1.90 (dd, *J*=10.4, 4.5 Hz, 1H), 1.75–1.67 (m, 2H), 1.57–1.53 (m, 2H), 1.56 (br s, 1H), 1.40–1.30 (m, 9H), 0.91 (t, *J*=7.3 Hz, 3H), 0.35 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 137.9, 135.1, 134.8, 134.0 (2C), 129.1 (2C), 129.0, 127.7 (2C), 115.6, 114.2 (2C), 71.34, 67.79, 42.12, 37.02, 34.72, 33.91, 29.22, 25.93, 25.46, 22.30, 13.96, −3.37, −3.98; ESI-HRMS (*m*/*z*) calcd for $C_{27}H_{40}SiO_2Na$ $[M+Na]^+$ 447.2685, observed 447.2685.

3.2.5. (3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-9-(4-butylphenyloxy)-3-dimethylphenylsilyl-1-nonene (16a). To a solution of allylsilane **15a** (0.77 g, 1.81 mmol) in DMF (3 mL) was added TBSCl (0.55 g, 3.62 mmol) and imidazole (0.25 g, 3.62 mmol) at room temperature. The reaction flask was flushed with N_2, sealed with a septum, and heated to 50 °C for 48 h. The mixture was cooled to room temperature and partitioned between H_2O and Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5% EtOAc/hexane) to give allylsilane **16a** (0.96 g, 1.8 mmol, 98%) as a colorless oil: $[\alpha]_D^{21}$ +1.3 (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.33–7.31 (m, 3H), 7.07 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 5.83 (ddd, *J*=17.2, 10.4, 10.2 Hz, 1H), 4.94 (dd, *J*=10.2, 2.2 Hz, 1H), 4.74 (dd, *J*=17.2, 2.2 Hz, 1H), 3.87 (t, *J*=6.5 Hz, 2H), 3.85–3.82 (m, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.00 (dd, *J*=10.4, 3.4 Hz, 1H), 1.75–1.67 (m, 2H), 1.56–1.54 (m, 2H), 1.45–1.31 (m, 8H), 0.91 (t, *J*=7.3 Hz, 3H), 0.86 (s, 9H), 0.34 (s, 3H), 0.29 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.10, 138.79, 136.01, 134.84, 134.07 (2C), 129.20 (2C), 128.74, 127.52 (2C), 114.44, 114.25 (2C), 73.29, 67.85, 40.68, 36.79, 34.73, 33.92, 29.29, 26.13 (3C), 25.70, 25.21, 22.31, 18.23, 13.97, −3.01, −3.66, −3.74, −3.87; ESI-HRMS (*m*/*z*) calcd for $C_{33}H_{54}Si_2O_2Na$ $[M+Na]^+$ 561.3546, observed 561.3545.

3.2.6. (3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-9-(4-butylphenyloxy)-3-dimethylphenylsilyl-1-nonene (16b). Compound **16b** was synthesized by the same procedure used for the synthesis of **16a** in a 94% yield as a colorless oil: $[\alpha]_D^{22}$ −1.4 (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.33–7.31 (m, 3H), 7.07 (d, *J*=8.6 Hz, 2H), 6.78 (d, *J*=8.6 Hz, 2H), 5.83 (ddd, *J*=17.2, 10.4, 10.2 Hz, 1H), 4.94 (dd, *J*=10.2, 2.2 Hz, 1H), 4.74 (dd, *J*=17.2, 2.2 Hz, 1H), 3.87 (t, *J*=6.5 Hz, 2H), 3.85–3.82 (m, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.00 (dd, *J*=10.4, 3.4 Hz, 1H), 1.75–1.67 (m, 2H), 1.56–1.54 (m, 2H), 1.45–1.31 (m, 8H), 0.91 (t, *J*=7.3 Hz, 3H), 0.86 (s, 9H), 0.34 (s, 3H), 0.29 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.10, 138.79, 136.01, 134.84, 134.07 (2C), 129.20 (2C), 128.74, 127.52 (2C), 114.44, 114.25 (2C), 73.29, 67.85, 40.68, 36.79, 34.73, 33.92, 29.29, 26.13 (3C), 25.70, 25.21, 22.31, 18.23, 13.97, −3.01, −3.66, −3.74, −3.87; ESI-HRMS (*m*/*z*) calcd for $C_{33}H_{54}Si_2O_2Na$ $[M+Na]^+$ 561.3546, observed 561.3546.

3.2.7. (2*S*,3*R*,5*S*)-5-Benzyloxymethyl-2-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-3-dimethylphenylsilyltetrahydrofuran (17). To a −78 °C mixture of allylsilane **16a** (0.50 g, 0.93 mmol), α-(benzyloxy)acetaldehyde (0.13 mL, 0.93 mmol), CH_2Cl_2 (2.0 mL), and oven-dried powdered 4 Å molecular sieves (130 °C, 12 h, 8.6 mg) was added $BF_3\cdot Et_2O$ (59 μL, 0.47 mmol) dropwise from a syringe. The resulting mixture was stirred for 22 h, warming slowly from −78 to −45 °C. The reaction mixture was quenched through addition of Et_3N (0.3 mL) and warmed to room temperature. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5% EtOAc/hexane) to give tetrahydrofuran **17** (0.36 g, 0.52 mmol, 56%) as a colorless oil containing a 17:1 mixture of diastereomers (favoring **17**) as determined by ^1H NMR analysis: $[\alpha]_D^{23}$ −15 (*c* 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2H), 7.35–7.33 (m, 3H), 7.31–7.30 (m, 4H), 7.27–7.23 (m, 1H), 7.07 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 4.55 (d, *J*=12.2 Hz, 1H), 4.47 (d, *J*=12.2 Hz, 1H), 4.04–3.99 (m, 1H), 3.91 (m, 1H), 3.90 (t, *J*=6.4 Hz, 2H), 3.41 (dd, *J*=9.6, 5.6 Hz, 1H), 3.36–3.32 (dd, *J*=9.6, 6.6 Hz, 1H), 3.35–3.33 (m, 1H), 2.54 (t, *J*=7.7 Hz, 2H), 1.89–1.86 (m, 2H), 1.75–1.70 (m, 2H), 1.70–1.61 (m, 2H), 1.60–1.52 (m, 2H), 1.40–1.30 (m, 7H), 0.91 (t, *J*=7.3 Hz, 3H), 0.85 (s, 9H), 0.33 (s, 3H), 0.33 (s, 3H), −0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.5, 137.7, 134.8, 133.9 (2C), 129.2 (3C), 128.3 (2C), 127.8 (2C), 127.6 (2C), 127.4, 114.2 (2C), 83.32, 73.29, 73.18, 72.87,

67.84, 34.72, 34.55, 33.92, 32.15, 29.36, 26.32, 26.09 (3C), 25.69, 24.46, 22.30, 18.22, 13.97, −3.84, −4.06, −4.24, −4.33; ESI-HRMS (*m/z*) calcd for $C_{42}H_{64}Si_2O_4Na$ $[M+Na]^+$ 711.4224, observed 711.4253.

3.2.8. (2*S*,4*R*,5*S*)-5-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-4-dimethylphenylsilyltetrahydrofuran-2-carbaldehyde (18). A mixture of **17** (150 mg, 0.22 mmol), THF (13 mL), and 20% $Pd(OH)_2$ on carbon (37 mg) was stirred at room temperature under a hydrogen gas atmosphere for 2 h. The reaction mixture was then filtered through a Celite layer. The Celite layer was washed with 10 mL of EtOAc. The combined filtrates were concentrated and purified by YMC silica gel chromatography (10% EtOAc/hexane) to give 113 mg of alcohol as a colorless oil. Then, to a cooled solution of oxalyl chloride (22 μL, 0.25 mmol) in anhydrous CH_2Cl_2 (0.50 mL) at −78 °C was added dropwise DMSO (34 μL, 0.47 mmol) and the mixture was stirred for 5 min at the same temperature. A CH_2Cl_2 solution (1.2 mL) of the alcohol (0.10 g, 0.17 mmol) was added slowly. After stirring for 15 min, the mixture was quenched with Et_3N (0.12 mL) at −78 °C. The reaction mixture was slowly warmed to 0 °C over 1 h and then saturated aqueous NH_4Cl (2 mL) was added. The mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by Wako silica gel chromatography (10% EtOAc/hexane) to give aldehyde **18** (85 mg, 0.14 mmol, 84%, two steps) as a pale yellow oil: $[\alpha]_D^{21}$ −35 (*c* 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.47–7.44 (m, 2H), 7.37–7.33 (m, 3H), 7.07 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 4.11–4.07 (m, 2H), 3.92 (t, *J*=6.4 Hz, 2H), 3.26 (dd, *J*=8.9, 4.5 Hz, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.36 (ddd, *J*=12.7, 8.9, 2.4 Hz, 1H), 1.93 (m, 1H), 1.90–1.82 (m, 1H), 1.76–1.72 (m, 2H), 1.57–1.31 (m, 8H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H), 0.84 (s, 9H), 0.35 (s, 3H), 0.34 (s, 3H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.50, 157.08, 136.73, 134.90, 133.84 (2C), 129.51, 129.23 (2C), 128.03 (2C), 114.24 (2C), 83.97, 83.02, 73.36, 67.78, 35.26, 34.73, 33.92, 31.78, 29.36, 26.35, 25.98 (3C), 25.57, 25.43, 22.30, 18.15, 13.96, −4.20, −4.25, −4.37, −4.57; ESI-HRMS (*m/z*) calcd for $C_{35}H_{56}Si_2O_4Na$ $[M+Na]^+$ 619.3600, observed 619.3605.

3.2.9. (2*R*,2′*S*,4*S*,4′*R*,5*R*,5′*S*)-5-[(1*S*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5′-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-4,4′-bis-dimethylphenylsilyloctahydro-2,2′-bifuran (19). A solution of allylsilane **16b** (0.11 g, 0.20 mmol), aldehyde **18** (70 mg, 0.12 mmol), and oven-dried powdered 4 Å molecular sieves (130 °C, 12 h, 16 mg) in anhydrous CH_2Cl_2 (2.0 mL) was cooled to −78 °C. $BF_3\cdot Et_2O$ (18 μL, 0.14 mmol) was added slowly dropwise to the cold solution and the reaction mixture was stirred at −78 °C for 1 h. The mixture was quenched cold by dropwise addition of Et_3N (0.8 mL) and the resulting mixture was warmed to room temperature. A 1:1 EtOAc/hexane solution (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to form a cloudy white suspension, which was stirred at room temperature for 12 h. The suspension was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5% EtOAc/hexane) twice to give **19** (175 mg) as a colorless oil still containing the excess allylsilane **16b**, which was brought to the next reaction step without further purification. The product was a 16:1 mixture of diastereomers (favoring **19**) as determined through ^1H NMR analysis: $[\alpha]_D^{22}$ −5.2 (*c* 0.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 4H), 7.32–7.30 (m, 6H), 7.07 (d, *J*=8.6 Hz, 4H), 6.81 (d, *J*=8.6 Hz, 4H), 3.89 (t, *J*=6.5 Hz, 4H), 3.77 (dd, *J*=9.6, 2.0 Hz, 2H), 3.62 (m, 2H), 3.29 (m, 2H), 2.54 (t, *J*=7.6 Hz, 4H), 2.04 (m, 2H), 1.84–1.81 (m, 2H), 1.78–1.70 (m, 4H), 1.60–1.54 (m, 8H), 1.36–1.26 (m, 10H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H), 0.84 (s, 18H), 0.31 (s, 6H), 0.30 (s, 6H), −0.04 (s, 6H), −0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.13 (2C), 137.94 (2C), 134.82 (2C), 133.95 (4C), 129.21 (4C), 129.07 (2C), 127.78 (4C), 114.24 (4C), 83.51 (2C), 79.45 (2C), 73.17 (2C), 67.88 (2C), 34.74 (4C), 33.93 (2C), 32.01 (2C), 29.41 (2C), 26.33 (2C), 26.10 (6C), 25.67 (2C), 24.20 (2C), 22.31 (2C), 18.22 (2C), 13.97 (2C), −3.89 (2C), −3.93 (2C), −3.98 (2C), −4.44 (2C); ESI-HRMS (*m/z*) calcd for $C_{68}H_{110}Si_4O_6Na$ $[M+Na]^+$ 1157.7248, observed 1157.7262.

3.2.10. (2*R*,2′*S*,5*S*,5′*R*)-5-[(1*S*)-6-(4-Butylphenyloxy)-1-hydroxyhexyl]-5′-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]octahydro-2,2′-bifuran (2). To a solution of crude bis-tetrahydrofuran **19** (131 mg) in DMF (1.0 mL) was added TBAF (0.20 mL of a 1.0 M solution in THF, 0.20 mmol). The resulting solution was stirred at 90 °C for 6.5 h. The mixture was cooled to room temperature and diluted with EtOAc. The resulting solution was washed with 1.0 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (30–70% EtOAc/hexane) to give **2** (34 mg, 53 μmol, 63%, two steps from **18**) as a white solid: $[\alpha]_D^{25}$ +6.7 (*c* 0.12, EtOH); mp 83–84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 4.05 (m, 2H), 3.91 (t, *J*=6.5 Hz, 4H), 3.82 (m, 2H), 3.40 (m, 2H), 2.78 (br s, 2H), 2.53 (t, *J*=7.6 Hz, 4H), 1.99–1.95 (m, 4H), 1.79–1.75 (m, 8H), 1.57–1.51 (m, 16H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.09 (2C), 134.79 (2C), 129.19 (4C), 114.23 (4C), 82.76 (2C), 81.18 (2C), 74.23 (2C), 67.85 (2C), 34.27 (2C), 34.15 (2C), 33.91 (2C), 29.32 (2C), 28.04 (2C), 27.04 (2C), 26.13 (2C), 25.55 (2C), 22.30 (2C), 13.97 (2C); ESI-HRMS (*m/z*) calcd for $C_{40}H_{62}O_6Na$ $[M+Na]^+$ 661.4428, observed 661.4400.

3.3. Synthesis of compound 3

3.3.1. (2*R*,2′*S*,5*S*,5′*R*)-5-[(1*R*)-6-(4-Butylphenyloxy)-1-hydroxyhexyl]-5′-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]octahydro-2,2′-bifuran (3). A solution of **2** (30 mg, 47 μmol), PPh_3 (123 mg, 0.47 mmol), 4-nitrobenzoic acid (79 mg, 0.47 mmol) and DIAD (91 μL, 0.47 mmol) in toluene (0.2 mL) was stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and directly subjected to silica gel chromatography (30% EtOAc/hexane) to give a crude product. To a MeOH (3 mL) solution of the product was added K_2CO_3 (39 mg, 0.28 mmol) and then the resulting mixture was stirred at 35 °C for 1.5 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with

EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (30–70% EtOAc/hexane) to give **3** (7 mg, 11 μmol, 23%) as a colorless oil: $[\alpha]_D^{25}$ +44 (*c* 0.18, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 4.12 (m, 2H), 3.91 (t, *J*=6.5 Hz, 4H), 3.89 (m, 2H), 3.85 (m, 2H), 2.53 (t, *J*=7.6 Hz, 4H), 2.50 (br s, 2H), 1.99–1.95 (m, 4H), 1.80–1.75 (m, 8H), 1.57–1.46 (m, 16H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.08 (2C), 134.83 (2C), 129.20 (4C), 114.24 (4C), 82.94 (2C), 80.73 (2C), 72.19 (2C), 67.84 (2C), 34.72 (2C), 33.91 (2C), 32.74 (2C), 29.26 (2C), 26.54 (2C), 26.14 (2C), 25.84 (2C), 23.96 (2C), 22.31 (2C), 13.97 (2C); ESI-HRMS (*m*/*z*) calcd for $C_{40}H_{62}O_6Na$ $[M+Na]^+$ 661.4428, observed 661.4404.

3.4. Synthesis of compound 4

3.4.1. (2*R*,5*S*)-5-Benzyloxymethyl-2-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]tetrahydrofuran (23). Compound **23** was synthesized by protiodesilylation of **17** according to the procedure used for the synthesis of **2** in a 96% yield as a colorless oil: $[\alpha]_D^{20}$ +1.7 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 4H), 7.30–7.28 (m, 1H), 7.07 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.58 (d, *J*=12.2 Hz, 1H), 4.55 (d, *J*=12.2 Hz, 1H), 4.15 (m, 1H), 3.92 (t, *J*=6.5 Hz, 2H), 3.84 (ddd, *J*=6.5, 5.3, 5.3 Hz, 1H), 3.58 (dd, *J*=10.0, 3.8 Hz, 1H), 3.45 (dd, *J*=10.0, 4.7 Hz, 1H), 3.38 (m, 1H), 2.67 (br s, 1H), 2.53 (t, *J*=7.6 Hz, 2H), 1.94–1.76 (m, 6H), 1.56–1.43 (m, 8H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.11, 138.00, 134.82, 129.20 (3C), 128.43 (2C), 127.74 (2C), 114.26 (2C), 82.80, 78.46, 74.29, 74.38, 72.43, 67.88, 34.73, 34.25, 33.92, 29.34, 28.13, 28.05, 26.15, 25.59, 22.31, 13.97; ESI-HRMS (*m*/*z*) calcd for $C_{28}H_{40}O_4Na$ $[M+Na]^+$ 463.2814, observed 463.2813.

3.4.2. (2*R*,5*S*)-2-[(1*R*)-1-Acetyloxy-6-(4-butylphenyloxy)-hexyl]-5-benzyloxymethyltetrahydrofuran (24). A solution of **23** (100 mg, 0.22 mmol) and DMAP (107 mg, 0.88 mmol) in anhydrous CH_2Cl_2 (3.0 mL) was cooled to 0 °C. AcCl (39 μL, 0.55 mmol) was added slowly dropwise to the solution and the resulting mixture was warmed to 35 °C. After stirring for 1 h, the mixture was recooled to 0 °C and quenched with H_2O. The resulting mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (20% EtOAc/hexane) to give **24** (98 mg, 0.20 mmol, 92%) as a colorless oil: $[\alpha]_D^{20}$ +1.8 (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.33 (m, 4H), 7.28–7.27 (m, 1H), 7.07 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.90 (ddd, *J*=6.9, 5.6, 5.6 Hz, 1H), 4.59 (d, *J*=12.2 Hz, 1H), 4.55 (d, *J*=12.2 Hz, 1H), 4.12 (dddd, *J*=6.6, 6.0, 5.7, 5.1 Hz, 1H), 3.98 (ddd, *J*=6.9, 6.9, 5.3 Hz, 1H), 3.90 (t, *J*=6.5 Hz, 2H), 3.51 (dd, *J*=9.9, 5.7 Hz, 1H), 3.44 (dd, *J*=9.9, 5.1 Hz, 1H), 2.53 (t, *J*=7.6 Hz, 2H), 2.03 (s, 3H), 1.99–1.91 (m, 2H), 1.76–1.53 (m, 8H), 1.46–1.34 (m, 4H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.88, 157.07, 138.48, 134.87, 129.21 (2C), 128.34 (2C), 127.66 (2C), 127.52, 114.25 (2C), 80.13, 78.54, 75.38, 73.34, 72.77, 67.76, 34.73, 33.91, 30.99, 29.21, 28.41, 27.42, 26.03, 25.22, 22.30, 21.16, 13.96; ESI-HRMS (*m*/*z*) calcd for $C_{30}H_{42}O_5Na$ $[M+Na]^+$ 505.2919, observed 505.2937.

3.4.3. (2*S*,5*R*)-5-[(1*R*)-1-Acetyloxy-6-(4-butylphenyloxy)-hexyl]tetrahydrofuran-2-carbaldehyde (25). Compound **25** was synthesized by the same procedure used for the synthesis of **18** in a 82% yield as a pale yellow oil: $[\alpha]_D^{20}$ −8.3 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J*=1.3 Hz, 1H), 7.07 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.92 (ddd, *J*=8.0, 4.8, 4.8 Hz, 1H), 4.25 (ddd, *J*=6.7, 6.7, 1.3 Hz, 1H), 4.18 (ddd, *J*=7.0, 7.0, 4.8 Hz, 1H), 3.92 (t, *J*=6.4 Hz, 2H), 2.53 (t, *J*=7.6 Hz, 2H), 2.12–2.10 (m, 2H), 2.09 (s, 3H), 2.07–1.99 (m, 1H), 1.78–1.75 (m, 2H), 1.72–1.66 (m, 2H), 1.57–1.39 (m, 7H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.78, 170.74, 157.04, 134.92, 129.22 (2C), 114.24 (2C), 83.40, 81.34, 75.11, 67.70, 34.72, 33.91, 31.34, 29.18, 27.76, 27.66, 26.01, 25.16, 22.30, 21.12, 13.96; ESI-HRMS (*m*/*z*) calcd for $C_{23}H_{34}O_5Na$ $[M+Na]^+$ 413.2295, observed 413.2313.

3.4.4. (2*S*,2′*S*,4′*R*,5*R*,5′*S*)-5-[(1*R*)-1-Acetyloxy-6-(4-butylphenyloxy)hexyl]-5′-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-4′-dimethylphenylsilyloctahydro-2,2′-bifuran (26). A solution of aldehyde **25** (57 mg, 0.15 mmol) and oven-dried powdered 4 Å molecular sieves (130 °C, 12 h, 4 mg) in anhydrous CH_2Cl_2 (0.8 mL) was cooled to −78 °C. $SnCl_4$ (0.15 mL of 1.0 M solution in CH_2Cl_2, 0.15 mmol) was added dropwise to the cold solution and the reaction mixture was stirred at −78 °C for 20 min. A solution of allylsilane **16a** (79 mg, 0.15 mmol) in 0.4 mL of CH_2Cl_2 was added slowly dropwise to the reaction mixture and stirring at −78 °C proceeded for 6 h. The reaction mixture was quenched at −78 °C by the dropwise addition of Et_3N (0.1 mL) and the resulting mixture was warmed to room temperature. EtOAc (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added to form a cloudy white suspension, which was stirred at room temperature overnight. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (10% EtOAc/hexane) to give a mixture of **26** and its epimer (91 mg, 98 μmol, 67%). The product was a 6.5:1 mixture of diastereomers (favoring **26**) as determined through ^{1}H NMR analysis. Chromatography was repeated under the same conditions to give pure **26** as a colorless oil: $[\alpha]_D^{21}$ +4.4 (*c* 0.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.48 (m, 2H), 7.35–7.33 (m, 3H), 7.07 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.88 (ddd, *J*=8.0, 4.8, 4.8 Hz, 1H), 3.95 (m, 1H), 3.92 (m, 1H), 3.90 (t, *J*=6.5 Hz, 4H), 3.80 (ddd, *J*=8.7, 6.7, 6.7 Hz, 1H), 3.67 (ddd, *J*=7.1, 7.1, 7.1 Hz, 1H), 3.48 (m, 1H), 2.53 (t, *J*=7.6 Hz, 4H), 2.01 (s, 3H), 1.88–1.68 (m, 8H), 1.62–1.53 (m, 9H), 1.36–1.30 (m, 10H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H), 0.87 (s, 9H), 0.34 (s, 3H), 0.33 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.84, 157.13, 157.09, 138.04, 134.84, 133.90 (2C), 133.04, 129.66, 129.20 (2C), 129.13 (2C), 127.92 (2C), 127.85 (2C), 114.25 (2C),

83.80, 82.15, 81.19, 79.51, 75.21, 74.14, 67.90, 67.80, 34.73 (2C), 33.92 (2C), 33.57, 31.22, 30.56, 29.38, 29.25, 27.58, 27.46, 26.34, 26.13 (3C), 26.04, 25.91, 25.32, 25.15, 22.31 (2C), 21.17, 18.27, 13.97 (2C), −3.34, −3.92, −4.30, −4.41; ESI-HRMS (*m/z*) calcd for $C_{56}H_{88}Si_2O_7Na$ $[M+Na]^+$ 951.5943, observed 951.5955.

3.4.5. (2*S*,2′*S*,5*R*,5′*R*)-5,5′-Bis-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]octahydro-2,2′-bifuran (4). To a solution of **26** (90 mg, 97 μmol) in MeOH (1 mL) and THF (2 mL) was added K_2CO_3 (40 mg, 0.29 mmol) and the resulting mixture was stirred at 35 °C for 3 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (10% EtOAc/hexane) to give 67 mg of colorless oil, which was dissolved in DMF (1 mL). To this solution was added TBAF (0.29 mL of a 1.0 M solution in THF, 0.29 mmol) and the resulting mixture was stirred at 90 °C for 3.5 h. The mixture was cooled to room temperature and diluted with EtOAc. The resulting solution was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (50–70% EtOAc/hexane) to give **4** (33 mg, 52 μmol, 54%, two steps) as a colorless oil: $[\alpha]_D^{25}$ +26 (*c* 0.14, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 3.91 (t, *J*=6.5 Hz, 4H), 3.89 (m, 2H), 3.83 (m, 2H), 3.41 (m, 2H), 2.89 (br s, 2H), 2.53 (t, *J*=7.6 Hz, 4H), 1.99–1.96 (m, 4H), 1.79–1.75 (m, 8H), 1.57–1.46 (m, 16H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.10 (2C), 134.79 (2C), 129.19 (4C), 114.24 (4C), 82.71 (2C), 81.07 (2C), 73.89 (2C), 67.86 (2C), 34.73 (2C), 34.25 (2C), 33.92 (2C), 29.33 (2C), 28.34 (2C), 27.96 (2C), 26.14 (2C), 25.60 (2C), 22.31 (2C), 13.97 (2C); ESI-HRMS (*m/z*) calcd for $C_{40}H_{62}O_6Na$ $[M+Na]^+$ 661.4428, observed 661.4417.

3.5. Synthesis of compound 5

3.5.1. (2*S*,2′*S*,5*S*,5′*S*)-5,5′-Bis-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]octahydro-2,2′-bifuran (5). Compound **5** was synthesized following the procedure used for the synthesis of **1**, but using (−)-DET and AD-mix-α in place of (+)-DET and AD-mix-β, respectively:[8] $[\alpha]_D^{16}$ −19 (*c* 0.21, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 3.92 (t, *J*=6.5 Hz, 4H), 3.87–3.81 (m, 4H), 3.39 (m, 2H), 2.53 (t, *J*=7.6 Hz, 4H), 2.48 (br s, 2H), 1.99–1.96 (m, 4H), 1.80–1.75 (m, 4H), 1.69–1.43 (m, 20H), 1.33 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.09 (2C), 134.82 (2C), 129.20 (4C), 114.24 (4C), 83.14 (2C), 81.80 (2C), 73.94 (2C), 67.84 (2C), 34.72 (2C), 33.92 (2C), 33.36 (2C), 29.31 (2C), 28.98 (2C), 28.35 (2C), 26.15 (2C), 25.44 (2C), 22.30 (2C), 13.97 (2C); ESI-HRMS (*m/z*) calcd for $C_{40}H_{62}O_6Na$ $[M+Na]^+$ 661.4428, observed 661.4411.

3.6. Synthesis of compound 6

3.6.1. 5-(4-Butylphenyloxy)-1-pentyne (27). To a 0 °C solution of 4-pentyne-1-ol (0.5 g, 5.9 mmol), PPh_3 (3.1 g, 12 mmol), and 4-butylphenol (1.3 g, 8.8 mmol) in THF (9.0 mL) was added DIAD (2.3 mL, 12 mmol) dropwise from a syringe over 5 min. The mixture was stirred at room temperature for 1 h and concentrated. The crude product was purified by silica gel chromatography (5% EtOAc/hexane) twice to give **27** (1.2 g, 5.6 mmol, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.5 Hz, 2H), 4.04 (t, *J*=6.1 Hz, 2H), 2.54 (t, *J*=7.6 Hz, 2H), 2.40 (dt, *J*=7.0, 2.6 Hz, 2H), 2.00 (tt, *J*=7.0, 6.1 Hz, 2H), 1.96 (t, *J*=2.6 Hz, 1H), 1.55 (tt, *J*=7.6, 7.5 Hz, 2H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.89, 135.11, 129.25 (2C), 114.30 (2C), 83.61, 68.76, 66.14, 34.73, 33.91, 28.28, 22.30, 15.21, 13.96; ESI-HRMS (*m/z*) calcd for $C_{15}H_{20}ONa$ $[M+Na]^+$ 239.1407, observed 239.1472.

3.6.2. (2*S*,3*R*,5*S*)-2-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxy-2-hexynyl]-3-dimethylphenylsilyltetrahydrofuran (28a) and (2*S*,3*R*,5*S*)-2-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxy-2-hexynyl]-3-dimethylphenylsilyltetrahydrofuran (28b). To a stirred solution of alkyne **27** (30 mg, 173 μmol) in THF (1.4 mL) was added dropwise *n*-BuLi (1.57 M in hexane, 0.10 mL, 163 μmol) at −78 °C and stirred for 1 h. To the resulting solution was added anhydrous cerium chloride (40 mg, 163 μmol) and stirring was continued for 1 h at −78 °C. A solution of aldehyde **18** (61 mg, 102 μmol) in THF (0.6 mL) was added dropwise at −78 °C and the mixture was stirred at −78 °C for 2 h and warmed to −23 °C over 3 h with stirring. After being quenched with saturated aqueous NH_4Cl, the resulting suspension was warmed to room temperature and extracted with Et_2O, washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5–30% EtOAc/hexane) to give **28a** (14 mg, 18 μmol, 18%) and **28b** (31 mg, 41 μmol, 40%) as a colorless oil. **28a**: $[\alpha]_D^{22}$ −17 (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.44 (m, 2H), 7.36–7.33 (m, 3H), 7.08 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 4.03 (m, 2H), 4.00 (t, *J*=6.1 Hz, 2H), 3.98 (m, 1H), 3.93 (m, 1H), 3.91 (t, *J*=6.5 Hz, 2H), 3.36 (br s, 1H), 3.20 (dd, *J*=9.4, 3.6 Hz, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.53 (t, *J*=7.6 Hz, 2H), 2.40 (dt, *J*=7.0, 1.7 Hz, 2H), 2.01–1.89 (m, 4H), 1.80–1.67 (m, 4H), 1.56–1.53 (m, 4H), 1.38–1.31 (m, 4H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H), 0.87 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), −0.02 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.07, 156.92, 136.97, 134.97, 134.88, 133.89 (2C), 129.47, 129.21 (4C), 128.02 (2C), 114.29 (2C), 114.24 (2C), 84.56, 82.94, 81.53, 79.62, 73.06, 67.77, 66.35, 65.19, 35.58, 34.73 (2C), 33.91 (2C), 31.95, 29.38, 28.39, 26.30, 26.02 (3C), 25.31, 25.28, 22.30 (2C), 18.19, 15.61, 13.96 (2C), −3.93, −4.11, −4.66, −4.72; ESI-HRMS (*m/z*) calcd for $C_{50}H_{76}Si_2O_5Na$ $[M+Na]^+$ 835.5109, observed 835.5129. **28b**: $[\alpha]_D^{22}$ −36 (*c* 1.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.35–7.33 (m, 3H), 7.08 (d, *J*=8.6 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 4.54 (m,

2H), 4.00 (m, 1H), 3.99 (t, J=6.4 Hz, 2H), 3.97 (m, 1H), 3.91 (t, J=6.4 Hz, 2H), 3.86 (br s, 1H), 3.27 (dd, J=9.9, 3.7 Hz, 1H), 2.54 (t, J=7.6 Hz, 2H), 2.53 (t, J=7.6 Hz, 2H), 2.41 (m, 1H), 2.40 (dt, J=7.0, 1.7 Hz, 2H), 1.95 (quint, J=6.6 Hz, 2H), 1.94–1.74 (m, 5H), 1.56 (tt, J=7.6, 7.5 Hz, 4H), 1.40–1.32 (m, 4H), 1.34 (tq, J=7.5, 7.3 Hz, 4H), 1.18 (m, 1H), 0.91 (t, J=7.3 Hz, 6H), 0.87 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), 0.00 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.06, 156.91, 137.12, 135.00, 134.89, 133.97 (2C), 129.40, 129.23 (4C), 127.99 (2C), 114.26 (2C), 114.23 (2C), 85.32, 82.77, 81.26, 78.78, 73.02, 67.76, 66.36, 66.00, 35.46, 34.73 (2C), 33.91, 33.90, 29.75, 29.37, 28.30, 26.64, 26.30, 26.10 (3C), 25.33, 22.30 (2C), 18.21, 15.68, 13.96 (2C), −3.78, −3.87, −4.86, −5.10; ESI-HRMS (m/z) calcd for $C_{50}H_{76}Si_2O_5Na$ $[M+Na]^+$ 835.5109, observed 835.5127.

3.6.3. (2*S*,3*R*,5*S*)-2-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]-3-dimethylphenylsilyltetrahydrofuran (29a). A mixture of **28a** (14 mg, 18 μmol), EtOH (2 mL), and catalytic 10% Pd on carbon was stirred at room temperature under a hydrogen gas atmosphere for 3 h. The reaction mixture was then filtered through a Celite layer. The Celite layer was washed with 5 mL of EtOAc. The combined filtrates were concentrated and purified by YMC silica gel chromatography (5% EtOAc/hexane) to give **29a** (12 mg, 16 μmol, 87%) as a colorless oil: $[\alpha]_D^{22}$ −11 (c 0.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.35–7.33 (m, 3H), 7.08 (d, J=8.6 Hz, 2H), 7.06 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 3.93 (m, 1H), 3.90 (t, J=6.6 Hz, 4H), 3.74 (m, 1H), 3.27 (br s, 1H), 3.25 (m, 1H), 3.24 (m, 1H), 2.54 (t, J=7.6 Hz, 2H), 2.53 (t, J=7.6 Hz, 2H), 1.93 (m, 2H), 1.83–1.75 (m, 6H), 1.58–1.53 (m, 6H), 1.43–1.32 (m, 10H), 1.34 (tq, J=7.5, 7.3 Hz, 4H), 1.20 (m, 1H), 0.91 (t, J=7.3 Hz, 6H), 0.87 (s, 9H), 0.34 (s, 3H), 0.32 (s, 3H), 0.00 (s, 3H), −0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.13, 157.08, 137.28, 134.88, 134.76, 133.90 (2C), 129.38, 129.22 (2C), 129.17 (2C), 127.98 (2C), 114.24 (4C), 82.25, 81.09, 74.16, 73.64, 67.93, 67.80, 35.62, 34.73 (2C), 34.59, 33.92 (2C), 32.45, 29.39, 29.36, 26.33, 26.20, 26.00 (3C), 25.74, 25.67, 25.35, 22.30 (2C), 18.18, 13.96 (2C), −3.98, −4.08, −4.58, −4.76; ESI-HRMS (m/z) calcd for $C_{50}H_{80}Si_2O_5Na$ $[M+Na]^+$ 839.5421, observed 839.5420.

3.6.4. (2*R*,5*S*)-2-[(1*R*)-6-(4-Butylphenyloxy)-1-hydroxyhexyl]-5-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]-tetrahydrofuran (6). Compound **6** was synthesized by protiodesilylation of **29a** according to the procedure used for the synthesis of **2** in a 44% yield as a waxy oil: $[\alpha]_D^{25}$ −1.4 (c 0.14, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J=8.6 Hz, 4H), 6.80 (d, J=8.6 Hz, 4H), 3.93 (t, J=6.5 Hz, 4H), 3.82 (m, 2H), 3.44 (m, 2H), 2.53 (t, J=7.6 Hz, 4H), 2.33 (br s, 2H), 1.99–1.93 (m, 2H), 1.80–1.70 (m, 6H), 1.57–1.45 (m, 16H), 1.34 (tq, J=7.5, 7.3 Hz, 4H), 0.91 (t, J=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.08 (2C), 134.86 (2C), 129.21 (4C), 114.24 (4C), 82.66 (2C), 74.27 (2C), 67.83 (2C), 34.73 (2C), 34.03 (2C), 33.92 (2C), 29.31 (2C), 28.12 (2C), 26.14 (2C), 25.49 (2C), 22.31 (2C), 13.97 (2C); ESI-HRMS (m/z) calcd for $C_{36}H_{56}O_5Na$ $[M+Na]^+$ 591.4011, observed 591.3992.

3.7. Synthesis of compound 7

3.7.1. (2*S*,3*R*,5*S*)-2-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]-3-dimethylphenylsilyltetrahydrofuran (29b). Compound **29b** was synthesized from **28b** by the same procedure used for the synthesis of **29a** in a 91% yield as a colorless oil: $[\alpha]_D^{22}$ −14 (c 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.35–7.33 (m, 3H), 7.08 (d, J=8.6 Hz, 2H), 7.06 (d, J=8.6 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 3.92 (m, 1H), 3.91 (t, J=6.5 Hz, 2H), 3.90 (t, J=6.4 Hz, 2H), 3.79 (m, 2H), 3.29 (dd, J=9.1, 4.0 Hz, 1H), 3.25 (br s, 1H), 2.54 (t, J=7.6 Hz, 2H), 2.53 (t, J=7.6 Hz, 2H), 2.13 (m, 1H), 1.81–1.68 (m, 7H), 1.56–1.53 (m, 6H), 1.38–1.16 (m, 11H), 1.34 (tq, J=7.5, 7.3 Hz, 4H), 0.91 (t, J=7.3 Hz, 6H), 0.87 (s, 9H), 0.33 (s, 3H), 0.32 (s, 3H), 0.00 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.10, 157.08, 137.35, 134.87, 134.78, 133.92 (2C), 129.33, 129.22 (2C), 129.18 (2C), 127.96 (2C), 114.25 (2C), 114.24 (2C), 81.74, 81.65, 73.94, 73.23, 67.88, 67.78, 35.32, 34.73 (2C), 33.92 (2C), 32.74, 29.38, 29.26, 27.60, 26.62, 26.30, 26.21, 26.05 (3C), 25.79, 25.42, 22.30 (2C), 18.26, 13.97 (2C), −4.00, −4.05, −4.55, −4.65; ESI-HRMS (m/z) calcd for $C_{50}H_{80}Si_2O_5Na$ $[M+Na]^+$ 839.5421, observed 839.5434.

3.7.2. (2*R*,5*S*)-2,5-Bis-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]tetrahydrofuran (7). Compound **7** was synthesized by protiodesilylation of **29b** according to the procedure used for the synthesis of **2** in a 28% yield as a waxy oil: $[\alpha]_D^{25}$ +2.5 (c 0.24, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J=8.6 Hz, 4H), 6.80 (d, J=8.6 Hz, 4H), 3.92 (t, J=6.5 Hz, 4H), 3.90 (m, 1H), 3.85 (m, 1H), 3.82 (m, 1H), 3.44 (m, 1H), 2.53 (t, J=7.6 Hz, 4H), 2.39 (br s, 2H), 1.99–1.91 (m, 2H), 1.79–1.72 (m, 6H), 1.59–1.49 (m, 16H), 1.34 (tq, J=7.5, 7.3 Hz, 4H), 0.91 (t, J=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.07 (2C), 134.87 (2C), 129.21 (4C), 114.24 (4C), 82.67, 82.22, 74.34, 72.27, 67.80 (2C), 34.72 (2C), 34.11, 33.91 (2C), 32.99, 29.26 (2C), 28.39, 26.13 (2C), 25.74, 25.50, 24.39, 22.30, 13.97 (2C); ESI-HRMS (m/z) calcd for $C_{36}H_{56}O_5Na$ $[M+Na]^+$ 591.4011, observed 591.3985.

3.8. Synthesis of compounds 8 and 9

3.8.1. (2*S*,3*R*,5*R*)-5-Benzyloxymethyl-2-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-3-dimethylphenylsilyltetrahydrofuran (30). To a −45 °C solution of allylsilane **16a** (0.3 g, 0.56 mmol), α-(benzyloxy)acetaldehyde (126 mg, 0.84 mmol), and oven-dried powdered 4 Å molecular sieves (130 °C, 12 h, 150 mg) in CH_2Cl_2 (1.3 mL) was added $SnCl_4$ (0.28 mL of a 1.0 M solution of CH_2Cl_2, 0.28 mmol) dropwise from a syringe over 2 min. The reaction mixture was stirred at −45 °C for 20 h and then quenched with Et_3N (0.3 mL) and warmed to room temperature. The mixture was diluted with Et_2O (3 mL) and saturated aqueous $NaHCO_3$ (3 mL), and then stirred for 24 h. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers

were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (5% EtOAc/hexane) to give tetrahydrofuran **30** (0.31 g, 0.45 mmol, 81%) as a colorless oil: $[\alpha]_D^{21}$ +2.6 (*c* 1.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.35–7.31 (m, 7H), 7.25 (m, 1H), 7.07 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 4.56 (d, *J*=12.2 Hz, 1H), 4.52 (d, *J*=12.2 Hz, 1H), 4.05 (dddd, *J*=10.0, 5.0, 5.0, 5.0 Hz, 1H), 3.93 (dd, *J*=8.7, 1.7 Hz, 1H), 3.89 (t, *J*=6.5 Hz, 2H), 3.51 (dd, *J*=10.1, 5.4 Hz, 1H), 3.43 (dd, *J*=10.1, 4.7 Hz, 1H), 3.25 (m, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.02 (m, 1H), 1.73–1.69 (m, 4H), 1.57–1.47 (m, 3H), 1.37–1.30 (m, 5H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H), 0.87 (s, 9H), 0.32 (s, 3H), 0.31 (s, 3H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.22, 138.68, 137.87, 134.80, 133.89 (2C), 129.27, 129.23 (2C), 128.32 (2C), 127.92 (2C), 127.69 (2C), 127.48, 114.31 (2C), 82.84, 78.58, 74.74, 73.22, 72.67, 67.87, 34.78, 34.67, 34.01, 33.20, 29.40, 26.55, 26.33, 26.10 (3C), 25.69, 22.34, 18.25, 13.99, −3.93, −4.20, −4.28, −4.32; ESI-HRMS (*m*/*z*) calcd for $C_{42}H_{64}Si_2O_4Na$ $[M+Na]^+$ 711.4224, observed 711.4242.

3.8.2. (2*R*,4*R*,5*S*)-5-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-4-dimethylphenylsilyl-2-carbaldehyde (32). Compound **32** was synthesized via alcohol **31** by the same procedure used for the synthesis of **18** in a 81% yield as a pale yellow oil: $[\alpha]_D^{21}$ +13 (*c* 0.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J*=2.6 Hz, 1H), 7.48–7.45 (m, 2H), 7.36–7.33 (m, 3H), 7.08 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 4.20 (m, 1H), 4.06 (dd, *J*=8.9, 1.4 Hz, 1H), 3.91 (t, *J*=6.5 Hz, 2H), 3.25 (m, 1H), 2.54 (t, *J*=7.6 Hz, 2H), 2.20 (m, 1H), 1.82–1.51 (m, 6H), 1.44–1.21 (m, 6H), 1.34 (tq, *J*=7.5, 7.3 Hz, 2H), 0.91 (t, *J*=7.3 Hz, 3H), 0.87 (s, 9H), 0.34 (s, 6H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.56, 157.09, 136.86, 134.90, 133.77 (2C), 129.51, 129.23 (2C), 128.03 (2C), 114.24 (2C), 84.11, 83.63, 74.20, 67.80, 34.74 (2C), 33.93, 31.86, 29.33, 26.54, 26.28, 25.98 (3C), 25.52, 22.31, 18.14, 13.97, −3.85, −4.34, −4.44 (2C); ESI-HRMS (*m*/*z*) calcd for $C_{35}H_{56}Si_2O_4Na$ $[M+Na]^+$ 619.3600, observed 619.3619.

3.8.3. (2*S*,3*R*,5*R*)-2-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[6-(4-butylphenyloxy)-1-hydroxy-2-hexynyl]-3-dimethylphenylsilyltetrahydrofuran (33). Compound **33** was synthesized by the same procedure used for the synthesis of **28a** and **28b**, except that **32** was used in place of **18**, in a 74% yield as a colorless oil, which was an unseparable 4:5 mixture of alcohols: ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.34–7.33 (m, 3H), 7.08 (d, *J*=8.6 Hz, 2H), 7.07 (d, *J*=8.6 Hz, 2H), 6.80 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 4.50 (m, 0.56H), 4.11 (m, 0.44H), 3.99 (t, *J*=6.1 Hz, 2H), 3.96 (m, 2H), 3.89 (t, *J*=6.5 Hz, 2H), 3.24 (m, 0.44H), 3.20 (m, 0.56H), 2.54 (t, *J*=7.6 Hz, 4H), 2.39 (t, *J*=7.1 Hz, 2H), 2.32 (br s, 0.44H), 2.22 (br s, 0.56H), 1.95–1.82 (m, 3H), 1.73–1.70 (m, 3H), 1.57–1.47 (m, 7H), 1.36–1.24 (m, 4H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H), 0.87 (s, 9H), 0.32 (s, 6H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.10, 156.89, 137.70, 135.05, 134.87, 133.82 (2C), 129.24 (4C), 129.22 (2C), 127.88, 114.27 (2C), 114.24 (2C), 85.44 (0.44C), 83.66, 83.37 (0.56C), 82.46 (0.44C), 81.59, 78.37 (0.56C), 74.44 (0.56C), 74.32 (0.44C), 67.83 (1.44C), 66.28 (0.56C), 65.93 (0.44C), 63.28 (0.56C), 34.74 (2C), 34.60 (0.56C), 34.53 (0.44C), 33.92 (2C), 29.67 (0.44C), 29.34 (1.56C), 28.41, 26.66 (0.44C), 26.49 (0.56C), 26.26, 26.03 (3C), 25.60, 22.31 (2C), 18.19, 15.59, 13.97 (2C), −3.90, −4.30, −4.33, −4.43; ESI-HRMS (*m*/*z*) calcd for $C_{50}H_{76}Si_2O_5Na$ $[M+Na]^+$ 835.5109, observed 835.5120.

3.8.4. (2*S*,3*R*,5*R*)-2-[(1*R*)-1-(*tert*-Butyldimethylsilyloxy)-6-(4-butylphenyloxy)hexyl]-5-[6-(4-butylphenyloxy)-1-hydroxyhexyl]-3-dimethylphenylsilyltetrahydrofuran (34). Compound **34** was synthesized by the same procedure used for the synthesis of **29a** in a 91% yield as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.35–7.33 (m, 3H), 7.08 (d, *J*=8.6 Hz, 2H), 7.06 (d, *J*=8.6 Hz, 2H), 6.81 (d, *J*=8.6 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 3.91 (t, *J*=6.5 Hz, 4H), 3.90 (m, 1H), 3.87 (m, 0.56H), 3.86 (m, 0.44H), 3.73 (m, 0.56H), 3.33 (m, 1H), 3.21 (m, 0.44H), 3.18 (br s, 0.44H), 2.54 (t, *J*=7.6 Hz, 2H), 2.53 (t, *J*=7.6 Hz, 2H), 2.24 (br s, 0.56H), 1.93 (m, 0.56H), 1.79–1.61 (m, 5.44H), 1.57–1.51 (m, 8H), 1.47–1.23 (m, 15H), 0.91 (t, *J*=7.3 Hz, 6H), 0.87 (s, 9H), 0.32 (s, 6H), 0.00 (s, 6H).

3.8.5. (2*R*,5*R*)-2,5-Bis-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]tetrahydrofuran (8) and (2*R*,5*R*)-2-[(1*R*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]-5-[(1*S*)-6-(4-butylphenyloxy)-1-hydroxyhexyl]tetrahydrofuran (9). A mixture of **8** and **9** was synthesized by protiodesilylation of **34** according to the procedure used for the synthesis of **2** in a 57% yield (a 5:4 mixture of **8** and **9**) as a colorless oil, 26 mg (41 μmol) of which was dissolved in anhydrous CH_2Cl_2 (0.5 mL). DMAP (75 mg, 0.61 mmol) was added and the mixture was cooled to 0 °C. To this solution was added AcCl (30 μL, 0.41 mmol) and the resulting mixture was stirred at room temperature for 2 h. The mixture was then quenched with H_2O and extracted with Et_2O, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography twice (20% EtOAc/hexane and then 10% EtOAc/hexane) to give a diacetate derivative of **8** (10 mg, 15 μmol, 37%) and **9** (15 mg, 23 μmol, 56%) as a colorless oil. Then, to a solution of the diacetate derivative of **8** (7 mg, 11 μmol) in MeOH (1 mL) was added K_2CO_3 (4 mg, 30 μmol) and the resulting mixture was stirred at 35 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by YMC silica gel chromatography (50% EtOAc/hexane) to give **8** (4 mg, 7 μmol, 64%) as a waxy oil: $[\alpha]_D^{25}$ +14 (*c* 0.18, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 3.93 (t, *J*=6.5 Hz, 4H), 3.79 (m, 2H), 3.42 (m, 2H), 2.53 (t, *J*=7.6 Hz, 4H), 2.34 (br s, 2H), 1.99–1.93 (m, 2H), 1.80–1.72 (m, 4H), 1.70–1.63 (m, 2H), 1.57–1.44 (m, 16H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.06 (2C), 134.85 (2C), 129.20 (4C), 114.22 (4C), 82.62 (2C), 73.92 (2C), 67.80 (2C), 34.72 (2C), 33.91 (2C), 33.38 (2C), 29.29 (2C), 28.73 (2C), 26.14 (2C), 25.38 (2C), 22.30 (2C), 13.97 (2C); ESI-HRMS (*m*/*z*) calcd for $C_{36}H_{56}O_5Na$ $[M+Na]^+$ 591.4011, observed 591.4006.

Compound **9** was prepared from the diacetate derivative of **9** by the same procedure used for the synthesis of **8** in a 90% yield as a waxy oil: $[\alpha]_D^{25}$ +4.7 (*c* 0.30, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J*=8.6 Hz, 4H), 6.80 (d, *J*=8.6 Hz, 4H), 3.92 (t, *J*=6.5 Hz, 4H), 3.87 (ddd, *J*=9.4, 6.0, 3.4 Hz, 1H), 3.82 (m, 2H), 3.40 (m, 1H), 2.53 (t, *J*=7.6 Hz, 4H), 2.37 (br s, 1H), 2.06 (br s, 1H), 1.99–1.93 (m, 1H), 1.90–1.85 (m, 1H), 1.83–1.72 (m, 4H), 1.58–1.46 (m, 18H), 1.34 (tq, *J*=7.5, 7.3 Hz, 4H), 0.91 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.06 (2C), 134.85 (2C), 129.20 (4C), 114.22 (4C), 83.22, 82.13, 74.23, 71.45, 67.80 (2C), 34.72 (2C), 33.91 (2C), 33.13, 32.46, 29.29, 29.26, 28.57, 26.15 (2C), 25.79, 25.36, 25.28, 22.30 (2C), 13.97 (2C); ESI-HRMS (*m*/*z*) calcd for $C_{36}H_{56}O_5Na$ $[M+Na]^+$ 591.4011, observed 591.3990.

3.9. Synthesis of compound 12

3.9.1. (2*R*,5*R*)-2,5-Bis-[(1*R*)-1-hydroxyundecyl]tetrahydrofuran (12). Compound **12** was synthesized by the same procedure used for the synthesis of **8** as a waxy oil: $[\alpha]_D^{26}$ +22 (*c* 0.10, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82–3.87 (m, 2H), 3.42–3.38 (m, 2H), 2.32 (br s, 2H), 1.99–1.93 (m, 2H), 1.71–1.65 (m, 2H), 1.52–1.49 (m, 2H), 1.43–1.41 (m, 4H), 1.35–1.26 (m, 30H), 0.87 (t, *J*=6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.62 (2C), 74.04 (2C), 33.51 (2C), 31.91 (2C), 29.72 (2C), 29.62 (2C), 29.60 (2C), 29.34 (2C), 28.74 (2C), 28.60 (2C), 25.61 (2C), 22.69 (2C), 14.12 (2C); ESI-HRMS (*m*/*z*) calcd for $C_{26}H_{52}O_3Na$ $[M+Na]^+$ 435.3801, observed 435.3814.

3.10. Measurement of complex I activity

Bovine heart submitochondrial particles were prepared by the method of Matsuno-Yagi and Hatefi[25] using a sonication medium containing 0.25 M sucrose, 1 mM succinate, 1.5 mM ATP, 10 mM $MgCl_2$, 10 mM $MnCl_2$, and 10 mM Tris–HCl (pH 7.4), and stored in a buffer containing 0.25 M sucrose and 10 mM Tris–HCl (pH 7.4) at −84 °C. The NADH oxidase activity in submitochondrial particles was followed spectrometrically with a Shimadzu UV-3000 (340 nm, ε=6.2 mM^{-1} cm^{-1}) at 30 °C. The reaction medium (2.5 mL) contained 0.25 M sucrose, 1 mM $MgCl_2$, and 50 mM phosphate buffer (pH 7.4). The final mitochondrial protein concentration was 30 μg of protein/mL. The reaction was started by adding 50 μM NADH after the equilibration of SMP with an inhibitor for 4 min.

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