Journal of Medicinal Chemistry Article

J. Med. Chem. 2011, 54, 525–533 525
DOI: 10.1021/jm101053k

Potent Antitumor Mimetics of Annonaceous Acetogenins Embedded with an Aromatic Moiety in the Left Hydrocarbon Chain Part

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Received August 16, 2010

Annonaceous acetogenins are a large family of naturally occurring polyketides exhibiting remarkable anticancer activities. The first generation of annonaceous acetogenin mimetic (**1**, AA005) exhibits comparable activity as that of natural products and presents much higher selectivity between cancer and normal cells. In this work, we report the design, synthesis, and evaluation of a new series of compound **1** analogues in which a variety of conformation-constrained fragments were embedded in the left hydrocarbon chain part. Compound **7** bearing a biphenyl moiety was identified to exhibit more potent antiproliferative activity and preferentially target cancer cells over normal cells and thus represents a new lead for further optimization.

Introduction

During the past century, many useful drugs have been developed from natural sources[1] and more than 60% of currently available anticancer drugs are either natural compounds or their analogues.[2,3] To date, natural products and their core structures are still the focus in the search for new pharmaceutically useful compounds.[4,5] Annonaceous acetogenins, a well-established family of natural products, have been attracting worldwide attention for several decades because of their significant bioactivities, especially as growth inhibitors of certain tumor cells.[6,7] They have been shown to function by blocking oxidative pathways in complex I of mitochondria,[6,8] and there is evidence that some members of the family induce apoptosis in cancer cells.[9] These features make the annonaceous acetogenins excellent leads for development of new antitumor agents. We have been engaged in modifying the annonaceous acetogenins into the corresponding mimetics with simpler structures for several years.[10−19] In our previous studies, we invented annonaceous acetogenin mimetic (**1**, AA005) by replacement of both THF rings of natural bullatacin with an ethylene glycol ether unit.[10−12] Compound **1** not only shows potent antitumor activities against a variety of human cancer cells with IC_{50} values ranging from 50 to 100 nM but also exhibits significant selectivity between a number of human normal and cancerous cells. A further investigation showed that introduction of a (4*R*)-hydroxy group into compound **1** raises the potency by up to 15 times.[13] However, introduction of (10*R*)- or (10*S*)-hydroxy group into the skeleton of compound **1** little affects the activity.[12,17] To generate further improved analogues of **1**, a parallel fragment-assembly strategy was thus developed in a systematic fashion.[16] Subsequently, introduction of appropriate conformational constraints into the middle part can increase the potency up to 30 times against MDA-MB-468 cells. However, little has been known about the conformational contributions of the left hydrocarbon chains of **1** to the bioactivity. We assumed that the hydrophobic tail of compound **1** interacts with the hydrophobic pocket of complex **I**. In the present study, we decided to keep the middle and right parts intact and pay our attention to the left hydrophobic tail of compound **1** by replacement with more constrained parts (Figure 1).

To fully explore the potential of compound **1** analogues as selective anticancer agents and to further understand SAR of compound **1**, a synthetic approach that enables the early stage replacement of hydrophobic tail from a common precursor has also been developed. By use of this strategy, a small library was efficiently set up and applied in the corresponding biological assessment. Herein, we report the above-mentioned strategy for generation of new **1**-like compounds with the modified left part and their cytotoxicities against a number of cancer cells.

Results and Discussion

Retrosynthetic Analysis. Retrosynthetic analysis of the compounds **2**−**8** is illustrated in Figure 2. We chose a synthetic approach that allowed for generation of a variety of analogues from a common precursor **14**. By variation of the combination of different fragments **15**−**21**, seven precursors of compound **1** were obtained by parallel assembly of prefunctionalized subunits. Trimethylsilylacetylene **52** plays as a two-directional C-alkylation reagent to link epoxide intermediates **11** and **29**−**35**, constructing the whole molecular skeleton of compounds **2**−**8**. All the starting materials **13** and **51** are readily available or easy to prepare.

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Published on Web 12/20/2010

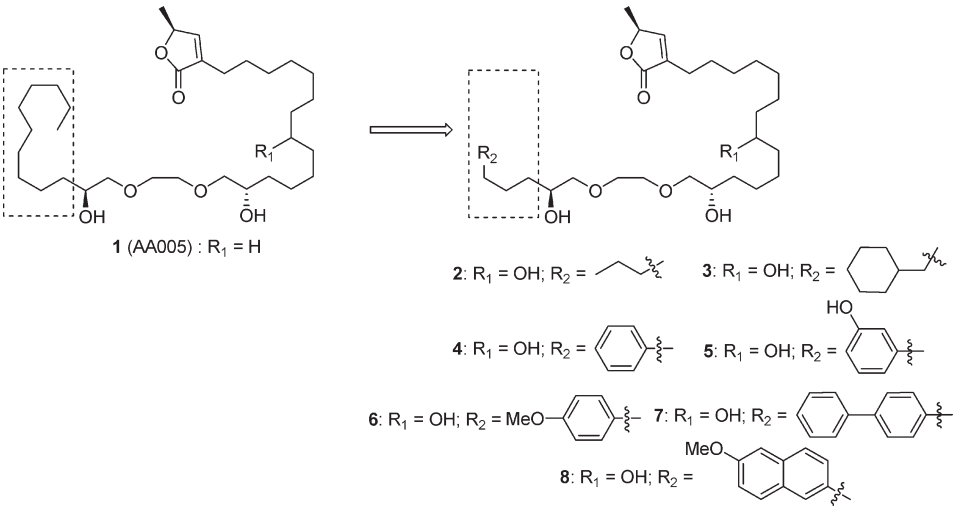


Figure 1. Design of new compound **1**-like molecules with conformation-constrained left chain.

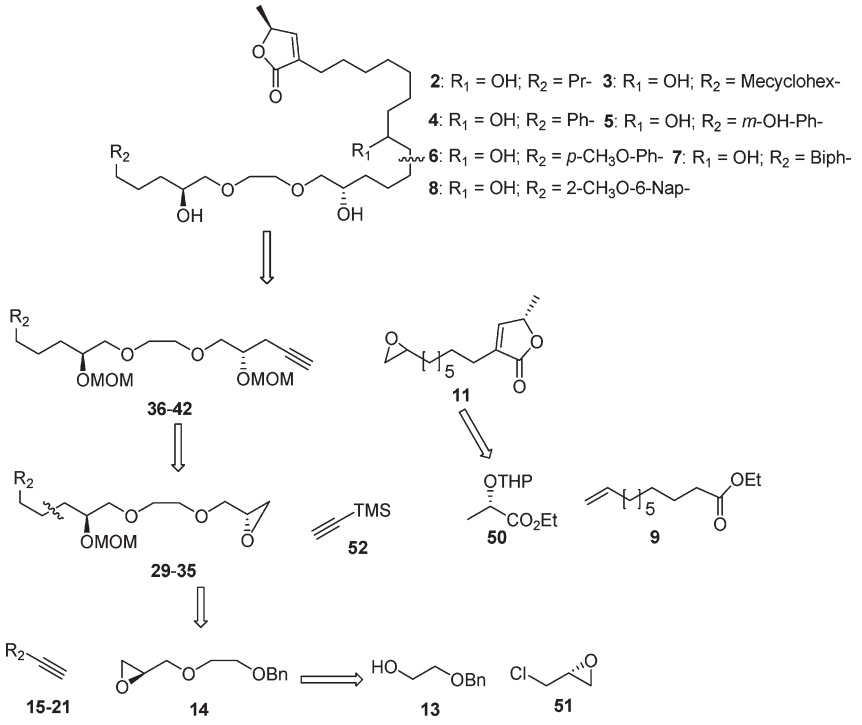


Figure 2. Retrosynthetic analysis of compounds **2**−**8**.

Chemistry. To synthesize compounds **2**−**8**, we built the suitably convergent synthetic routes. The right part of **11** was synthesized as shown in Scheme 1. Introduction of the butenolide unit to **9** involved a three-step sequence: (i) aldol reaction of **9** with (*S*)-*O*-tetrahydropyranyl lactal, (ii) acid-catalyzed THP cleavage and in situ lactonization, and (iii) α-elimination of hydroxyl in the presence of $(CF_3CO)_2O$ and Et_3N.[13,16,20,21] Regioselective epoxidation of **10** was achieved by treatment with MCPBA[a] to give **11** in 83% yield.

As shown in Scheme 2, protection of one hydroxyl group of ethylene glycol afforded the corresponding benzyl ether **13**. The remaining hydroxyl group of **13** was reacted with (−)-(*R*)-epichlorohydrin to afford the building block **14** in 83% yield. Regioselective opening of epoxide **14** by treatment with the monolithium salt of various substituted acetylenes **15**−**21** followed by protection with MOM afforded the "left-hand" segments **22**−**28** (in parallel). Reductions of the triple bonds and deprotection of benzyl protective groups were carried out by hydrogenation. O-Alkylation of the newly exposed primary hydroxyl functionality with (*R*)-epichlorohydrin gave the desired intermediates **29**−**35**. Regioselective opening of epoxides **29**−**35** by the lithium salt of trimethylsilyl acetylene in the presence of $BF_3 \cdot Et_2O$ followed by treatment with MOMCl and removal of TMS with TBAF afforded compounds **36**−**42**. Deprotonation of the terminal alkynes **36**−**42** with *n*-BuLi followed by treatment with epoxide **11** in the presence of $BF_3 \cdot Et_2O$ at −78 °C gave the whole skeleton precursors **43**−**49**.

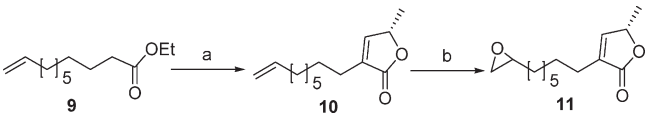
[a] Abbreviations: MCPBA, 3-chloroperbenzoic acid; TMS, trimethylsilyl; DCM, dichloromethane; DIPEA, *N*,*N*′-diisopropylethylamine; TBAF, tetrabutylammonium fluoride; MOMCl, chloromethyl methyl ether; BTEAC, benzyltriethylammonium chloride; THP, tetrahydropyran.

The triple bond of **43**−**49** was selectively reduced with in situ generated diimide. Global deprotection of the MOM ethers with a catalytic amount of concentrated HCl in MeOH provided the final products **2**−**8**.

Biological Results. Compounds **1**−**8** were evaluated with MTT assays for their activity in inhibition of cell growth against several human solid tumor cell lines, such as SGC7901, A549, MCF7, HCT-116, and HT-29, and human normal cell lines, such as HLF and Beas-2B. The results are summarized in Table 1 and showed interesting cell line selectivity. In our cell assay, compound **1** displayed good selectivity for the cancer cell lines (SGC7901, GI_{50} = 0.065 μM; A549, GI_{50} = 0.305 μM; MCF7, GI_{50} = 0.276 μM; HCT-116, GI_{50} = 0.113 μM; HT-29, GI_{50} = 0.291 μM) over the normal cell lines (HLF, GI_{50} = 20.9 μM; Beas-2B, GI_{50} = 120 μM). Compound **2**, in which the $C_{10}H_{21}$ tail was replaced by a much shorter hexane group, was designed to test the importance of the long linear hydrophobic tail of **1**. Our assay showed that compound **2** loses 20−66 times potency (by comparison of **1**) with a GI_{50} of 2.0, 10.8, 5.8, 4.2, and 19.4 μM against SGC7901, A549, MCF7, HCT-116, and HT-29 cell lines, respectively. The selectivity for cancer cells over normal cells of compound **2** slightly decreased. This suggests that a longer hydrophobic tail (decane) is needed for more potent inhibition of cancer cells growth of **1**. On the basis of this result, we thus designed and synthesized compound **3** with an *n*-butylcyclohexane side chain. Compound **3** exhibits a GI_{50} value of 0.75, 4.5 1.8, 1.6, and 5.4 μM against SGC7901, A549, MCF7, HCT-116, and HT-29 cell lines, respectively. Compound **3** is 6−18 times less potent than compound **1** in cancer cell lines and has decreased selectivity toward human cancer cells over normal cells more than 50-fold by comparison with compound **1**, further confirming the importance of the long hydrophobic tail in the mimicry.

We assumed that the long hydrophobic tail in compound **1** may interact with the hydrophobic pocket in complex **I**. Therefore, introducing a more aromatic residue in the left part of compound **1** would be able to improve van der Waals

Scheme 1. Synthesis of the right part of **11**[a]



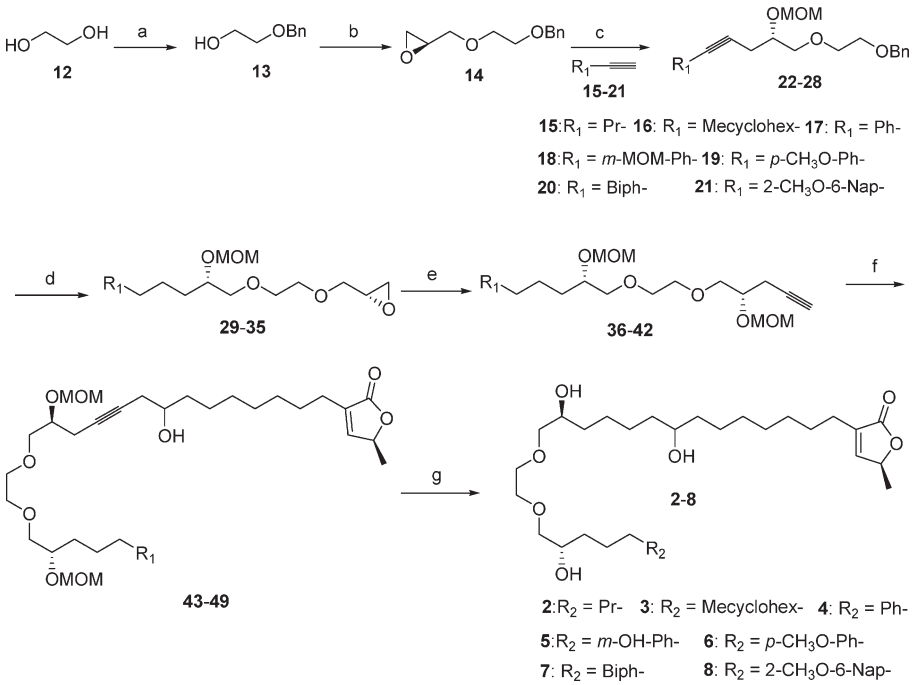
[a] Reagents and conditions: (a) (i) LDA, THF−HMPA, (*S*)-*O*-tetrahydropyranyl lactal, −78 °C; (ii) 10% H_2SO_4, THF, room temp; (iii) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 67%. (b) m-CPBA, CH_2Cl_2, 0 °C, 83%.

Table 1. Antiproliferative Activity of Compounds **1**−**8**[a]

	GI_{50} (μM)						
compd	SGC7901	A549	MCF7	HCT116	HT29	HLF	Beas-2B
1	0.065	0.305	0.276	0.113	0.291	20.9	120
2	2.0	10.8	5.8	4.2	19.4	11.1	> 100
3	0.75	4.5	1.8	1.6	5.4	5.5	61
4	0.275	0.773	0.84	0.394	1.1	7.4	> 100
5	1.0	6.0	24.5	2.8	69	> 100	> 100
6	0.198	4.5	23.3	2.3	4.3	11.3	> 100
7	0.02	0.177	0.154	0.134	0.355	> 100	> 100
8	0.082	3.7	12.6	1.1	1.1	10	> 100

[a] Compound **1** was used as a positive control. SGC7901, human gastric cancer cell line; A549, human lung cancer cell line; MCF7, human breast cancer cell line; HCT116, colorectal carcinoma cell line; HT29, human colon cancer cell line; HLF, human lung fibroblasts; Beas-2B, human bronchial epithelial cell. Inhibition of cell growth by the listed compounds in cells was determined by using a MTT assay. Standard error of the GI_{50} was generally less than 10%.

Scheme 2. Synthesis of Compounds **2**−**8**[a]



[a] Reagents and conditions: (a) NaH, THF, benzyl bromide, room temp to reflux, 81%; (b) (*R*)-epichlorohydrin **51**, BTEAC, 50% aq NaOH, room temp, 80%; (c) (i) BuLi, $BF_3 \cdot Et_2O$, **15**−**21** (in parallel), THF, −78 °C; (ii) MOMCl, DIPEA, DCM, 0 °C to room temp, 69−84% in two steps; (d) (i) 10% Pd/C, H_2, EtOH, HOAc, room temp; (ii) (*R*)-epichlorohydrin, BTEAC, 50% NaOH, room temp, 69−84% in two steps; (e) (i) trimethylsilylacetylene **52**, *n*-BuLi, $BF_3 \cdot Et_2O$, THF, −78 °C; (ii) MOMCl, DIPEA, DCM, 0 °C to room temp; (iii) TBAF, THF, 0 °C, 57−84% in three steps; (f) *n*-BuLi, $BF_3 \cdot Et_2O$, **11**, THF, −78 °C, 43−78%; (g) (i) $TsNHNH_2$, NaOAc, DME/H_2O, reflux; (ii) HCl, THF, CH_3OH, room temp, 54−94% in two steps.

interactions.[22] Considering these characteristic interactions, we thus designed and synthesized a series of new analogues by replacement of a cyclohexane subunit of compound **3** with aromatic ones, including phenyl ring, biphenyl ring, and naphthalene ring to increase the van der Waals interactions. As shown in Table 1, the potency of the modified compound **4** increases approximately 2- to 6-fold when replacing the cyclohexane moiety with phenyl ring. Compared to cyclohexane, the phenyl ring may result in favorable and well-defined van der Waals interactions. To verify this, a hydroxyl group in the meta-position on the phenyl ring was then introduced in compound **4**, aiming to decrease van der Waals interactions. Compared to compound **4**, the resulting compound **5** has almost lost the inhibitory activities against MCF7 and HT-29 cell lines and shows much less potency against other cell lines. This means that the meta-position on the phenyl ring in compound **4** is very important to achieve better anticancer activities. Compound **6**, in which a methoxyl group was introduced in the para-position on the phenyl ring of compound **4**, is 1.5 times more potent than **4** against SGC7901 cell lines, although it almost lost the activities against MCF7 cell lines. With such information, we then introduce an additional phenyl group in the para position of the phenyl ring of **4**, which is much more hydrophilic than the previous compounds. To our delight, compound **7** exhibited potent growth inhibitory activities against a variety of cancer cell lines (SGC7901, $GI_{50} = 0.02\ \mu M$; A549, $GI_{50} = 0.177\ \mu M$; MCF7, $GI_{50} = 0.154\ \mu M$; HCT-116:, $GI_{50} = 0.134\ \mu M$; HT-29, $GI_{50} = 0.355\ \mu M$). It is 14 times more potent than **4** and 3.5 times more potent than **1** against SGC7901 cell lines. Furthermore, the biphenyl compound **7** offers a much improved selectivity between cancerous and normal cell lines (HLF, $GI_{50} > 100\ \mu M$; Beas-2B, $GI_{50} > 100\ \mu M$) over that of **1**. The improved therapeutic index indicates that the newly introduced biphenyl moiety of compound **7** could be a structural factor for higher selectivity against cancer cells over normal cells. Obviously, introduction of an appropriate aromatic group in the left region of compound **1** is a useful strategy for the improvement of anticancer activity of these acetogenin mimetics. However, such protocol has to be controlled in a proper range. Overweight of the introduced hydrophobic moiety will lead to a decrease of potency under some circumstances. For instance, compound **8**, in which the decane tail of compound **1** was replaced with a naphthalene group, showed moderate potency and selectivity.

Conclusion

A series of new analogues **2**−**8** of anticancer annonaceous acetogenin mimetic **1** have been designed, synthesized, and evaluated in this work. Introduction of more hydrophobic aromatic moieties to the left part of **1** has been investigated for the first time. A flexible parallel fragment-assembly strategy has been successfully applied to the enantioselective syntheses of these analogues using acetylene−epoxide couplings as a key methodology. Biological results demonstrate that fragment variations in the left chain of **1** have various effects to the cytotoxicity and selectivity toward cancer cells over normal cells. Compound **7** bearing a biphenyl moiety was identified to show more potent inhibitory activity against a wide range of cancer cells at low to moderate nanomolar range and exhibited higher action selectivity against cancer cells than normal cells by comparison with compound **1**. These results clearly indicate that the introduction of appropriate aromatic groups into the linear compound **1** skeleton is a useful optimizing tool for this unique class of anticancer agents. Furthermore, the developed methodology will be potentially applicable to the synthesis of further analogues of this family, as well as other complex focused libraries, and may accelerate discovery of clinically useful antitumor agents.

Experimental Section

All NMR spectra were recorded at 400 MHz for ^{1}H NMR and 100 or 125 MHz for ^{13}C NMR in $CDCl_3$ solution with TMS as an internal standard, and the chemical shifts are given in δ values. Mass spectra were performed on Kompact Axima-CFR MALDI mass spectrometers. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. Anhydrous solvents were obtained as follows: THF was distilled from sodium and benzophenone, and dichloromethane was distilled from CaH_2. All other solvents were reagent grade. All moisture sensitive reactions were carried out in a flame-dried flask under nitrogen or argon atmosphere. Analytical HPLC conditions were as follows: Agilent C18 column (250 mm × 4.6 mm, 5 μm); solvent A 0.05% TFA in water; solvent B methanol. The composition of the solvents is shown in Supporting Information. Additional chromatographic parameters were as follows: flow rate, 1.0 mL/min; injection volume, 10 μL; column temperature, 30 °C; UV wavelength, 215 nm. The purity of all tested compounds was >95% using the analytical method described above unless stated otherwise.

(5*S*)-5-Methyl-3-(7-(oxiran-2-yl)heptyl)furan-2(5*H*)-one (11). Compound **11** was synthesized as the reference (see Supporting Information).[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, J = 2.8 Hz, 1H), 4.95 (dq, J = 6.8, 1.7 Hz, 1H), 2.85 (m, 1H), 2.71−2.68 (m, 1H), 2.41 (dd, J = 5.0, 2.7 Hz, 1H), 2.21 (t, J = 7.7 Hz, 2H), 1.51−1.29 (m, 12H), 1.36 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 148.9, 134.2, 77.3, 52.2, 46.9, 32.4, 29.2, 29.1, 29.0, 27.3, 25.8, 25.1, 19.1 ppm. MS (ESI, m/z): 239 ($M^+ + 1$).

(*S*)-2-((2-(Benzyloxy)ethoxy)methyl)oxirane (14). To a solution of **13** (10.7 g, 0.07 mol) was added BTEAC (1.60 g, 15%, w/w) and (*R*)-(−)-epichlorohydrin (6.6 mL, 0.084 mol). After the mixture was stirred for 3 min, a solution of 50% NaOH (55 mL) was added over 0.5 h. The reaction mixture was vigorously stirred at room temperature for additional 3.5 h until it was quenched by water (40 mL). The resulting solution was extracted by ether (40 mL × 3). The combined organic layers were washed successfully with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated. The residue was purified by silica gel chromatography to give **14** (11.7 g, 80%) as a colorless oil. $[\alpha]^{25}_D$: 6.1 (*c* 2.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.27 (m, 5H), 4.58 (s, 2H), 3.80 (dd, J = 11.6, 3.0 Hz, 1H), 3.75−3.63 (m, 4H), 3.45 (dd, J = 11.6, 5.8 Hz, 1H), 3.18−3.16 (m, 1H), 2.80−2.78 (m, 1H), 2.62 (dd, J = 5.0, 2.7 Hz, 1H) ppm. HRMS (ESI): $C_{12}H_{16}O_3$ calculated $[M + H]^+$ 209.1172, found 209.1175, $[M + Na]^+$ 231.0992, found 231.0988.

(*S*)-5-(Hex-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (22). To a solution of **15** (0.885 g, 13.0 mmol) in anhydrous THF (20 mL) was added slowly *n*-BuLi (13.0 mmol, 2.5 M in hexane) at −78 °C. The reaction mixture was stirred for 45 min at −78 °C under argon atmosphere, and $BF_3 \cdot Et_2O$ (13.0 mmol) was then added. After the mixture was stirred for an additional 30 min, a solution of **14** (1.353 g, 6.5 mmol) in anhydrous THF (5 mL) was added. The resulting reaction mixture was stirred for 3 h until it was quenched by saturated aqueous NH_4Cl (5 mL). The whole mixture was concentrated under reduced pressure. The residue was extracted with ether (15 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated. The resulting residue was used in the next step without further purification.

To the above crude product in dry DCM (20 mL) under nitrogen atmosphere was added DIPEA (9.1 mL, 52 mmol) at 0 °C. Then MOMCl (2.5 mL, 32.5 mmol) was added slowly, and the reaction mixture was stirred at ambient temperature for 20 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and DCM was then evaporated under reduced pressure. The residue was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated. Purification by silica gel chromatography afforded **22** as a yellow oil (1.50 g, 72% for two steps). $[\alpha]^{25}_D$: 10.6 (*c* 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.26 (m, 5H), 4.73 (s, 2H), 4.56 (s, 2H), 3.87−3.84 (m, 1H), 3.69−3.59 (m, 6H), 3.38 (s, 3H), 2.45 (br, 2H), 2.10 (t, J = 6.8 Hz, 2H), 1.51−1.46 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.3, 127.7, 127.6, 95.9, 81.9, 76.2, 74.8, 73.2, 72.9, 70.9, 69.5, 55.4, 22.4, 22.1, 20.8, 13.5 ppm. MS (ESI, *m*/*z*): 343 $[M + 23]^+$.

(*S*)-5-(4-Cyclohexylbut-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (23). The procedure was the same as described above for the synthesis of **22**. Compound **23** was obtained as a buff oil (0.82 g, 69% for two steps). $[\alpha]^{25}_D$: 9.6 (*c* 0.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.26 (m, 5H), 4.74 (s, 2H), 4.57 (s, 2H), 3.87−3.85 (m, 1H), 3.70−3.61 (m, 6H), 3.38 (s, 3H), 2.48−2.45 (m, 2H), 2.03 (dt, J = 6.6, 2.4 Hz, 2H), 1.79−1.68 (m, 4H), 1.45−1.36 (m, 1H), 1.28−0.91 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.3, 127.6, 127.5, 96.0, 80.8, 76.7, 75.1, 73.2, 73.0, 71.0, 69.5, 55.4, 37.5, 32.7, 26.6, 26.3, 26.1, 22.2 ppm. MS (ESI, *m*/*z*): 375 $[M + 1]^+$, 397 $[M + 23]^+$.

(*S*)-11-Phenyl-5-(3-phenylprop-2-ynyl)-2,4,7,10-tetraoxaundecane (24). The procedure was the same as described above for the synthesis of **22**. Compound **24** was obtained as a buff oil (1.51 g, 76% for two steps). $[\alpha]^{25}_D$: 11.9 (*c* 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.26 (m, 10H), 4.80 (s, 2H), 4.58 (s, 2H), 4.01−3.99 (m, 1H), 3.74−3.65 (m, 6H), 3.43 (s, 3H), 2.76−2.72 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 131.6, 128.3, 128.2, 127.7, 127.6, 127.5, 123.8, 96.1, 86.4, 82.1, 74.8, 73.3, 72.9, 71.0, 69.6, 55.5, 22.9 ppm. MS (ESI, *m*/*z*): 355 $[M + 1]^+$.

(*S*)-5-(3-(3-(Methoxymethoxy)phenyl)prop-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (25). The procedure was the same as described above for the synthesis of **22**. Compound **25** was obtained as a buff oil (0.81 g, 74% for two steps). $[\alpha]^{25}_D$: 2.8 (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.33 (m, 5H), 7.21−7.16 (m, 1H), 7.08−6.95 (m, 3H), 5.15 (s, 2H), 4.78 (s, 2H), 4.57 (s, 2H), 3.97−3.95 (m, 1H), 3.73−3.64 (m, 6H), 3.46 (s, 3H), 3.42 (s, 3H), 2.74−2.70 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.0, 138.3, 129.3, 128.3, 127.7, 127.6, 125.3, 124.7, 119.2, 116.2, 96.0, 94.4, 86.4, 81.8, 74.6, 73.2, 72.8, 71.0, 69.4, 56.0, 55.5, 22.8 ppm. MS (ESI, *m*/*z*): 415 $[M + 1]^+$.

(*S*)-5-(3-(4-Methoxyphenyl)prop-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (26). The procedure was the same as described above for the synthesis of **22**. Compound **26** was obtained as a buff oil (0.92 g, 84% for two steps). $[\alpha]^{25}_D$: 6.1 (*c* 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.26 (m, 7H), 6.82−6.79 (m, 2H), 4.78 (s, 2H), 4.57 (s, 2H), 4.00−3.97 (m, 1H), 3.79 (s, 3H), 3.73−3.64 (m, 6H), 3.42 (s, 3H), 2.77−2.67 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 138.4, 132.9, 128.3, 127.6, 127.5, 116.0, 113.9, 96.1, 84.7, 81.9, 74.9, 73.3, 72.9, 71.0, 69.6, 55.5, 55.2, 22.9 ppm. MS (ESI, *m*/*z*): 385 $[M + 1]^+$.

(*S*)-5-(3-(Biphenyl-4-yl)prop-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (27). The procedure was the same as described above for the synthesis of **22**. Compound **27** was obtained as a yellow oil (0.63 g, 70% for two steps). $[\alpha]^{25}_D$: 8.3 (*c* 0.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 7.9, 1.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.47−7.43 (m, 4H), 7.37−7.32 (m, 5H), 7.30−7.28 (m, 1H), 4.81 (s, 2H), 4.59 (s, 2H), 4.03−4.01 (m, 1H), 3.75−3.66 (m, 6H), 3.44 (s, 3H), 2.78−2.75 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 132.0, 128.8, 128.3, 127.7, 127.5, 127.0, 126.9, 122.7, 96.1, 87.1, 82.0, 74.8, 73.3, 72.9, 71.1, 69.6, 55.5, 23.0 ppm. MS (ESI, *m*/*z*): 431 $[M + 1]^+$, 453 $[M + 23]^+$.

(*S*)-5-(3-(6-Methoxynaphthalen-2-yl)prop-2-ynyl)-11-phenyl-2,4,7,10-tetraoxaundecane (28). The procedure was the same as described above for the synthesis of **22**. Compound **28** was obtained as a buff oil (0.72 g, 79% for two steps). $[\alpha]^{25}_D$: 5.1 (*c* 2.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.64 (t, J = 8.6 Hz, 2H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 7.36−7.26 (m, 5H), 7.14 (dd, J = 8.9, 2.5 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 4.81 (s, 2H), 4.58 (s, 2H), 4.04−4.00 (m, 1H), 3.92 (s, 3H), 3.77−3.64 (m, 6H), 3.43 (s, 3H), 2.82−2.71 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 138.4, 133.9, 131.0, 129.2, 129.1, 128.6, 128.3, 127.7, 127.5, 126.6, 119.2, 118.7, 105.9, 96.1, 85.9, 82.5, 74.8, 73.3, 72.9, 71.1, 69.6, 55.5, 55.3, 23.0 ppm. MS (ESI, *m*/*z*): 435 $[M + 1]^+$.

(*S*)-2-((*S*)-5-Hexyl-2,4,7,10-tetraoxaundecan-11-yl)oxirane (29). A mixture of **22** (1.36 g, 4.26 mmol), 10% palladium on charcoal (0.10 g), and EtOH (20 mL, containing 2 mL HOAc) was stirred at room temperature for 16 h under hydrogen atmosphere. After filtration, the organic phase was concentrated. The residue was used in the next step without further purification.

To the above intermediate was added BTEAC (0.17 g, 15%, w/w) and (*R*)-(−)-epichlorohydrin (0.40 mL, 5.11 mmol). After 3 min, a solution of 50% NaOH (3.5 mL) was added over 15 min. The reaction mixture was vigorously stirred at room temperature for 22 h until it was diluted with water (3 mL). The resulting solution was extracted by ether (15 mL × 3). The combined organic phases were washed successively with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated. The residue was purified by silica gel chromatography to afford **29** as a buff oil (1.033 g, 84% for two steps). $[\alpha]^{25}_D$: −3.6 (*c* 2.72, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.71 (d, J = 6.8 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 3.74 (dd, J = 11.6, 3.0 Hz, 1H), 3.68−3.35 (m, 8H), 3.33 (s, 3H), 3.11−3.09 (m, 1H), 2.75−2.72 (m, 1H), 2.56 (dd, J = 5.0, 2.7 Hz, 1H), 1.48−1.23 (m, 10H), 0.83 (t, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.0, 76.2, 74.1, 71.9, 70.7, 55.3, 50.7, 44.1, 32.0, 31.7, 29.3, 25.3, 22.5, 13.9 ppm. MS (ESI, *m*/*z*): 308 $[M + 18]^+$, 313 $[M + 23]^+$. HRMS (ESI): $C_{15}H_{30}O_5$ calculated $[M + Na]^+$ 313.1985, found 313.1989.

(*S*)-2-((*S*)-5-(4-Cyclohexylbutyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (30). The procedure was the same as described above for the synthesis of **29**. Compound **30** was obtained as pale yellow oil (0.40 g, 74% for two steps). $[\alpha]^{25}_D$: 2.6 (*c* 1.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 3.76 (dd, J = 11.6, 3.0 Hz, 1H), 3.70−3.39 (m, 8H), 3.36 (s, 3H), 3.14−3.11 (m, 1H), 2.77−2.75 (m, 1H), 2.58 (dd, J = 5.0, 2.3 Hz, 1H), 1.67−1.11 (m, 17H), 0.86−0.80 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.1, 76.3, 74.2, 71.9, 70.8, 55.4, 50.7, 44.1, 37.6, 37.4, 33.4, 32.1, 26.9, 26.7, 26.4, 25.7 ppm. MS (ESI, *m*/*z*): 345 $[M + 1]^+$. HRMS (ESI): $C_{19}H_{36}O_5$ calculated $[M + Na]^+$ 367.2455, found 367.2459.

(*S*)-2-((*S*)-5-(3-Phenylpropyl)-2,4,7,10-tetraoxaundecan-11-yl)-oxirane (31). The procedure was the same as described above for the synthesis of **29**. Compound **31** was obtained as a buff oil (0.99 g, 72% for two steps). $[\alpha]^{25}_D$: −1.8 (*c* 1.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.15 (m, 5H), 4.76 (d, J = 6.8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 3.77 (dd, J = 11.7, 2.8 Hz, 1H), 3.74−3.38 (m, 8H), 3.36 (s, 3H), 3.14−3.12 (m, 1H), 2.77 (t, J = 4.4 Hz, 1H), 2.63 (t, J = 7.4 Hz, 2H), 2.60−2.57 (m, 1H), 1.77−1.55 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 128.4, 128.3, 125.7, 96.1, 76.1, 74.1, 71.9, 70.8, 55.4, 50.8, 44.1, 35.9, 31.7, 27.1 ppm. MS (ESI, *m*/*z*): 325 $[M + 1]^+$. HRMS (ESI): $C_{18}H_{28}O_5$ calculated $[M+Na]^+$ 347.1829, found 347.1829.

(*S*)-2-((*S*)-5-(3-(3-(Methoxymethoxy)phenyl)propyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (32). The procedure was the same as described above for the synthesis of **29**. Compound **32** was obtained as a buff oil (0.54 g, 74% for two steps). $[\alpha]^{25}_D$: 3.7 (*c* 1.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.16 (m, 1H), 6.86−6.82 (m, 3H), 5.16 (s, 2H),

4.76 (d, J = 7.0 Hz, 1H), 4.65 (d, J = 7.0 Hz, 1H), 3.80−3.50 (m, 9H), 3.48 (s, 3H), 3.37 (s, 3H), 3.16−3.14 (m, 1H), 2.79−2.77 (m, 1H), 2.60 (t, J = 2.50 Hz, 2H), 1.61−1.56 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 144.1, 129.2, 122.0, 116.5, 113.6, 96.1, 94.6, 76.1, 74.1, 71.9, 70.8, 55.9, 55.5, 50.7, 44.1, 35.9, 31.7, 26.9, ppm. MS (ESI, m/z): 407 $[M + 23]^+$. HRMS (ESI): $C_{20}H_{32}O_7$ calculated $[M + Na]^+$ 407.2040, found 407.2038.

(*S*)-2-((*S*)-5-(3-(4-Methoxyphenyl)propyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (33). The procedure was the same as described above for the synthesis of **29**. Compound **33** was obtained as a buff oil (0.58 g, 69% for two steps). $[\alpha]^{25}_D$: −2.6 (c 1.15, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (dd, J = 6.7, 1.9 Hz, 2H), 6.82 (dd, J = 6.6, 2.0 Hz, 2H), 4.75 (d, J = 6. 8 Hz, 1H), 4.64 (d, J = 6.8 Hz, 1H), 3.78 (s, 3H), 3.76−3.72 (m, 1H), 3.70−3.39 (m, 8H), 3.37 (s, 3H), 3.16−3.13 (m, 1H), 2.78 (t, J = 4.6 Hz, 1H), 2.60 (t, J = 5.6 Hz, 1H), 2.57 (t, J = 8.0 Hz, 2H), 1.76−1.53 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 134.4, 129.2, 113.8, 96.1, 76.1, 74.1, 71.9, 71.0, 70.8, 55.4, 55.2, 50.8, 44.1, 35.0, 31.6, 27.3 ppm. MS (ESI, m/z): 355 $[M + 1]^+$. HRMS (ESI): $C_{19}H_{30}O_6$ calculated $[M + Na]^+$ 377.1935, found 377.1934.

(*S*)-2-((*S*)-5-(3-(Biphenyl-4-yl)propyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (34). The procedure was the same as described above for the synthesis of **29**. Compound **34** was obtained as pale yellow oil (0.44 g, 75% for two steps). $[\alpha]^{25}_D$: 3.2 (c 1.84, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 8.1, 1.3 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.45 (dd, J = 7.8, 1.8 Hz, 2H), 7.37−7.33 (m, 1H), 7.28 (dd, J = 4.1, 3.8 Hz, 2H), 4.80 (d, J = 6.8 Hz, 1H), 4.69 (d, J = 6.8 Hz, 1H), 3.81 (dd, J = 11.7, 2.9 Hz, 1H), 3.78−3.43 (m, 8H), 3.41 (s, 3H), 3.18−3.16 (m, 1H), 2.81−2.79 (m, 1H), 2.70 (t, J = 7.5 Hz, 2H), 2.62 (dd, J = 5.0, 2.7 Hz, 1H), 1.83−1.63 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 141.2, 138.8, 128.8, 128.7, 127.0, 126.9, 96.2, 76.2, 74.1, 71.9, 70.8, 55.5, 50.8, 44.1, 35.5, 31.7, 27.1 ppm. MS (ESI, m/z): 418 $[M + 18]^+$, 423 $[M + 23]^+$. HRMS (ESI): $C_{24}H_{32}O_5$ calculated $[M + Na]^+$ 423.2142, found 423.2140.

(*S*)-2-((*S*)-5-(3-(6-Methoxynaphthalen-2-yl)propyl)-2,4,7,10-tetraoxaundecan-11-yl)oxirane (35). The procedure was the same as described above for the synthesis of **29**. Compound **35** was obtained as a buff oil (0.50 g, 75% for two steps). $[\alpha]^{25}_D$: 2.3 (c 2.57, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−7.65 (m, 2H), 7.54 (s, 1H), 7.29 (dd, J = 8.4, 1.6 Hz, 1H), 7.13−7.10 (m, 2H), 4.76 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.78−3.39 (m, 9H), 3.37 (s, 3H), 3.14−3.11 (m, 1H), 2.78−2.74 (m, 3H), 2.59 (dd, J = 5.0, 2.6 Hz, 1H), 1.84−1.58 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 137.5, 133.0, 129.2, 128.9, 127.8, 126.7, 126.2, 118.6, 105.8, 96.1, 76.1, 74.1, 71.9, 70.8, 55.4, 55.3, 50.8, 44.1, 35.8, 31.8, 27.1 ppm. MS (ESI, m/z): 427 $[M + 23]^+$. HRMS (ESI): $C_{23}H_{32}O_6$ calculated $[M + Na]^+$ 427.2091, found 427.2089.

(5*S*,12*S*)-5-Hexyl-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (36). To a solution of trimethylsilylacetylene **52** (0.90 mL, 6.1 mmol) in dried THF (12 mL) was added slowly n-BuLi (6.1 mmol, 2.5 M in hexane) at −78 °C. The reaction mixture was stirred for 45 min at −78 °C under argon atmosphere, and $BF_3 \cdot Et_2O$ (6.1 mmol) was added. After the mixture was stirred for an additional 30 min, a solution of **29** (0.871 g, 3.0 mmol) in dried THF (4 mL) was added. The reaction mixture was stirred for 3 h until it was quenched by saturated aqueous NH_4Cl (3 mL). The volatiles were evaporated under reduced pressure. The residue was extracted with ether (15 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The resulting oil was used in the next step without further purification.

To the above crude product in dry DCM (12 mL) under nitrogen atmosphere was added DIPEA (4.2 mL, 24 mmol). The reaction mixture was cooled to 0 °C, and MOMCl (1.2 mL, 15 mmol) was added slowly. The mixture was stirred at ambient temperature for 20 h until it was quenched by saturated aqueous NH_4Cl (5 mL) . The volatiles were evaporated under reduced pressure. The residue was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was used directly in the subsequent step.

The above intermediate in THF (15 mL) was treated with TBAF (3.6 mmol, 1.0 M in THF) for 1 h at −10 °C. The mixture was quenched by saturated aqueous NH_4Cl (3 mL). The volatiles were evaporated under reduced pressure. The residue was extracted with ether (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography afforded **36** as a buff oil (0.62 g, 57% for three steps). $[\alpha]^{25}_D$: 3.3 (c 0.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (d, J = 6.8 Hz, 1H), 4.71 (s, 2H), 4.63 (d, J = 6.8 Hz, 1H), 3.87−3.84 (m, 1H), 3.69−3.66 (m, 1H), 3.65−3.47 (m, 8H), 3.37 (s, 3H), 3.36 (s, 3H), 2.51−2.46 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 1.50−1.26 (m, 10H), 0.86 (t, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.1, 80.7, 76.3, 74.4, 74.2, 72.5, 70.9, 70.7, 69.8, 55.5, 55.4, 32.1, 31.8, 29.3, 25.4, 22.5, 21.9, 14.0 ppm. MS (ESI, m/z): 383 $[M + 23]^+$. HRMS (ESI): $C_{19}H_{36}O_6$ calculated $[M + Na]^+$ 383.2404, found 383.2407.

(5*S*,12*S*)-5-(4-Cyclohexylbutyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (37). The procedure was the same as described above for the synthesis of **36**. Compound **37** (0.29 g, 61% for three steps) was obtained as a buff oil. $[\alpha]^{25}_D$: 1.7 (c 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (d, J = 6.8 Hz, 1H), 4.74 (s, 2H), 4.65 (d, J = 6.8 Hz, 1H), 3.90−3.85 (m, 1H), 3.72−3.68 (m, 1H), 3.66−3.47 (m, 8H), 3.39 (s, 3H), 3.38 (s, 3H), 2.57−2.44 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.69−1.11 (m, 17H), 0.89−0.81 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.0, 80.7, 76.2, 74.2, 74.1, 72.4, 70.9, 70.7, 70.0, 55.5, 55.4, 37.6, 37.5, 33.4, 32.1, 29.2, 27.4, 27.0, 26.7, 26.4, 25.9, 25.8, 21.9 ppm. MS (ESI, m/z): 437 $[M + 23]^+$. HRMS (ESI): $C_{23}H_{42}O_6$ calculated $[M + Na]^+$ 437.2874, found 437.2874.

(5*S*,12*S*)-5-(3-Phenylpropyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (38). The procedure was the same as described above for the synthesis of **36**. Compound **38** was obtained as a buff oil (0.84 g, 70% for three steps). $[\alpha]^{25}_D$: 3.2 (c 2.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.16 (m, 5H), 4.76 (d, J = 6.8 Hz, 1H), 4.74 (s, 2H), 4.65 (d, J = 6.8 Hz, 1H), 3.91−3.85 (m, 1H), 3.76−3.71 (m, 1H), 3.66−3.47 (m, 8H), 3.40 (s, 3H), 3.37 (s, 3H), 2.64 (t, J = 3.5 Hz, 2H), 2.58−2.44 (m, 2H), 2.00 (t, J = 2.0 Hz, 1H), 1.81−1.56 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 128.4, 128.2, 125.7, 96.1, 80.7, 76.2, 74.4, 74.1, 72.5, 70.9, 70.7, 69.9, 55.5, 55.4, 35.9, 31.7, 27.1, 21.9 ppm. MS (ESI, m/z): 417 $[M + 23]^+$. HRMS (ESI): $C_{22}H_{34}O_6$ calculated $[M + Na]^+$ 417.2248, found 417.2253.

(5*S*,12*S*)-5-(3-(3-(Methoxymethoxy)phenyl)propyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (39). The procedure was the same as described above for the synthesis of **36**. Compound **39** (0.51 g, 80% for three steps) was obtained as a buff oil. $[\alpha]^{25}_D$: 4.6 (c 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20−7.16 (m, 1H), 6.87−6.82 (m, 3H), 5.16 (s, 2H), 4.76−4.70 (m, 3H), 4.64 (d, J = 6.8 Hz, 1H), 3.91−3.86 (m, 1H), 3.74−3.71 (m, 1H), 3.66−3.49 (m, 8H), 3.48 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.53−2.46 (m, 2H), 1.99 (t, J = 2.0 Hz, 1H), 1.76−1.55 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 144.0, 129.2, 122.0, 116.5, 113.6, 96.1, 96.0, 94.6, 80.7, 76.1, 74.4, 74.0, 72.5, 70.9, 70.7, 69.9, 55.8, 55.4, 35.9, 31.7, 26.9, 21.9 ppm. MS (ESI, m/z): 477 $[M + 23]^+$. HRMS (ESI): $C_{24}H_{38}O_8$ calculated $[M + Na]^+$ 477.2459, found 477.2457.

(5*S*,12*S*)-5-(3-(4-Methoxyphenyl)propyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (40). The procedure was the same as described above for the synthesis of **36**. Compound **40** was obtained as a buff oil (0.48 g, 84% for three steps). $[\alpha]^{25}_D$: 1.3 (c 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, J = 6.6, 1.9 Hz, 2H), 6.82 (dd, J = 6.6, 2.0 Hz, 2H), 4.75 (d, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.88−3.86

(m, 1H), 3.78 (s, 3H), 3.73−3.70 (m, 1H), 3.65−3.47 (m, 8H), 3.39 (s, 3H), 3.37 (s, 3H), 2.57 (t, J = 7.4 Hz, 2H), 2.53−2.43 (m, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.76−1.53 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 134.5, 129.2, 113.8, 96.1, 80.7, 76.1, 74.3, 74.1, 72.5, 70.9, 70.7, 69.9, 55.5, 55.4, 55.2, 35.0, 31.6, 27.4, 21.9 ppm. MS (ESI, m/z): 447 $[M + 23]^+$. HRMS (ESI): $C_{23}H_{36}O_7$ calculated $[M + Na]^+$ 447.2353, found 447.2356.

(5*S*,12*S*)-5-(3-(Biphenyl-4-yl)propyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (41). The procedure was the same as described above for the synthesis of **36**. Compound **41** was obtained as a pale yellow oil (0.44 g, 83% for three steps). $[\alpha]^{25}_D$: 1.8 (c 0.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.42 (dd, J = 7.6, 7.5 Hz, 2H), 7.34−7.30 (m, 1H), 7.26 (dd, J = 4.0, 2.9 Hz, 2H), 4.77 (d, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.66 (d, J = 6.8 Hz, 1H), 3.89−3.86 (m, 1H), 3.76−3.70 (m, 1H), 3.66−3.49 (m, 8H), 3.39 (s, 3H), 3.38 (s, 3H), 2.68 (t, J = 7.5 Hz, 2H), 2.53−2.48 (m, 2H), 1.99 (t, J = 2.4 Hz, 1H), 1.81−1.58 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 141.2, 138.8, 128.8, 128.7, 127.0, 96.2, 96.1, 80.7, 76.2, 74.4, 74.1, 72.5, 71.0, 70.8, 69.9, 55.5, 35.6, 31.8, 27.1, 21.9 ppm. MS (ESI, m/z): 493 $[M + 23]^+$. HRMS (ESI): $C_{18}H_{38}O_6$ calculated $[M + Na]^+$ 493.2561, found 493.2560.

(5*S*,12*S*)-5-(3-(6-Methoxynaphthalen-2-yl)propyl)-12-(prop-2-ynyl)-2,4,7,10,13,15-hexaoxahexadecane (42). The procedure was the same as described above for the synthesis of **36**. Compound **42** was obtained as a buff oil (0.57 g, 84% for three steps). $[\alpha]^{25}_D$: 1.7 (c 0.88, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−7.28 (m, 2H), 7.54 (s, 1H), 7.29 (dd, J = 8.4, 1.7 Hz, 1H), 7.13−7.10 (m, 2H), 4.76 (d, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.65 (d, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.88−3.85 (m, 1H), 3.77−3.73 (m, 1H), 3.64−3.49 (m, 8H), 3.39 (s, 3H), 3.37 (s, 3H), 2.76 (t, J = 7.6 Hz, 2H), 2.52−2.47 (m, 2H), 1.98 (t, J = 2.6 Hz, 1H), 1.85−1.59 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 137.5, 133.0, 129.2, 128.9, 127.8, 126.7, 126.2, 118.6, 105.8, 96.1, 80.7, 76.2, 74.4, 74.1, 72.5, 70.9, 70.7, 69.9, 55.5, 55.4, 55.3, 35.9, 31.7, 27.1, 21.9 ppm. MS (ESI, m/z): 497 $[M + 23]^+$. HRMS (ESI): $C_{27}H_{38}O_7$ calculated $[M + Na]^+$ 497.2510, found 497.2506.

(*S*)-3-((5*S*,12*S*)-5-Hexyl-17-hydroxy-12-(methoxymethoxy)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (43). To a solution of **36** (0.37 g, 1.02 mmol) in dry THF (6 mL) was added slowly n-BuLi (1.02 mmol, 1.6 M in hexane) at −78 °C. The reaction mixture was stirred for 45 min at −78 °C under argon atmosphere until $BF_3 \cdot Et_2O$ (1.02 mmol) was added. After the mixture was stirred for 30 min, a solution of **11** (0.122 g, 0.51 mmol) in dry THF (3 mL) was added. The mixture continued to stir for 3 h, until it was quenched by saturated aqueous NH_4Cl (3 mL). The volatiles were evaporated under reduced pressure. The residue was extracted with ether (15 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography afforded **43** (0.22 g, 62%) as a colorless oil. $[\alpha]^{25}_D$: 9.4 (c 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 4.98 (dq, J = 6.7, 1.2 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.72 (s, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.85−3.82 (m, 1H), 3.70−3.48 (m, 10H), 3.38 (s, 3H), 3.37 (s, 3H), 2.49−2.27 (m, 4H), 2.25 (t, J = 7.4 Hz, 2H), 1.55−1.27 (m, 22H), 1.39 (t, J = 6.8 Hz, 3H), 0.87 (t, J = 6.2 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 148.3, 134.5, 96.2, 96.1, 79.2, 78.1, 76.5, 75.1, 74.3, 73.0, 71.0, 70.8, 70.1, 55.3, 55.2, 36.4, 32.1, 31.7, 29.3, 29.1, 29.0, 27.9, 27.4, 25.5, 25.3, 25.1, 22.4, 22.3, 19.0, 13.7 ppm. MS (ESI, m/z): 621 $[M + 23]^+$. HRMS (ESI): $C_{33}H_{58}O_9$ calculated $[M + Na]^+$ 621.3973, found 621.3974.

(*S*)-3-((5*S*,12*S*)-5-(4-Cyclohexylbutyl)-17-hydroxy-12-(methoxymethoxy)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (44). The procedure was the same as described above for the synthesis of **43**. Compound **44** was obtained as a buff oil (95.8 mg, 56%). $[\alpha]^{25}_D$: 9.9 (c 0.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 1.2 Hz, 1H), 4.97 (dq, J = 6.8, 1.5 Hz, 1H), 4.74 (d, J = 6.8 Hz, 1H), 4.71 (s, 2H), 4.63 (d, J = 6.8 Hz, 1H), 3.84−3.81 (m, 1H), 3.69−3.66 (m, 1H), 3.68−3.46 (m, 9H), 3.36 (s, 3H), 3.35 (s, 3H), 2.47−2.27 (m, 4H), 2.24 (t, J = 7.2 Hz, 2H), 1.67−1.08 (m, 29H), 1.38 (d, J = 6.8 Hz, 3H), 0.83−0.80 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 148.9, 134.2, 96.0, 95.9, 79.1, 78.2, 76.8, 76.2, 74.7, 74.1, 72.7, 70.9, 70.6, 70.0, 55.4, 37.6, 37.4, 36.2, 33.4, 32.0, 29.4, 29.2, 29.1, 27.8, 27.3, 26.9, 26.7, 26.4, 25.7, 25.6, 25.1, 22.1, 19.2 ppm. MS (ESI, m/z): 675 $[M + 23]^+$. HRMS (ESI): $C_{37}H_{64}O_9$ calculated $[M + Na]^+$ 675.4443, found 675.4442.

(*S*)-3-((5*S*,12*S*)-17-Hydroxy-12-(methoxymethoxy)-5-(3-phenylpropyl)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (45). The procedure was the same as described above for the synthesis of **43**. Compound **45** was obtained as a buff oil (0.20 g, 63%). $[\alpha]^{25}_D$: 12.9 (c 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.17 (m, 5H), 6.98 (d, J = 1.3 Hz, 1H), 4.99 (dq, J = 6.8, 1.6 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.86−3.83 (m, 1H), 3.84−3.47 (m, 10H), 3.39 (s, 3H), 3.37 (s, 3H), 2.63 (t, J = 7.5 Hz, 2H), 2.50−2.30 (m, 4H), 2.22 (t, J = 7.3 Hz, 2H), 1.77−1.32 (m, 16H), 1.40 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 148.7, 142.3, 134.3, 128.3, 128.2, 125.7, 96.1, 96.0, 79.2, 78.2, 76.7, 76.2, 74.9, 74.1, 72.8, 70.9, 70.7, 70.1, 55.4, 36.3, 35.9, 31.7, 29.4, 29.2, 29.0, 27.9, 27.4, 27.1, 25.6, 25.1, 22.2, 19.2 ppm. MS (ESI, m/z): 655 $[M + 23]^+$. HRMS (ESI): $C_{36}H_{56}O_9$ calculated $[M + Na]^+$ 655.3817, found 655.3817.

(*S*)-3-((5*S*,12*S*)-17-Hydroxy-12-(methoxymethoxy)-5-(3-(3-(methoxymethoxy)phenyl)propyl)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (46). The procedure was the same as described above for the synthesis of **43**. Compound **46** was obtained as a buff oil (78.2 mg, 74%). $[\alpha]^{25}_D$: 7.0 (c 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18−7.16 (m, 1H), 6.98 (d, J = 1.6 Hz, 1H), 6.86−6.82 (m, 3H), 5.16 (s, 2H), 4.99 (dq, J = 6.8, 1.6 Hz, 1H), 4.77−4.70 (m, 3H), 4.64 (d, J = 6.8 Hz, 1H), 3.86−3.84 (m, 1H), 3.68−3.58 (m, 10H), 3.48 (s, 3H), 3.38 (s, 3H), 3.36 (s, 3H), 2.60 (t, J = 7.4 Hz, 2H), 2.50−2.36 (m, 4H), 2.27−2.22 (m, 2H), 1.59−1.24 (m, 16H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 157.4, 148.7, 144.0, 134.4, 129.2, 122.0, 116.5, 113.6, 96.1, 96.0, 94.6, 79.2, 78.2, 76.1, 74.9, 74.1, 72.8, 70.9, 70.7, 70.1, 55.9, 55.4, 36.3, 35.9, 31.7, 29.4, 29.2, 29.1, 27.9, 27.4, 27.0, 25.6, 25.1, 22.2, 19.2 ppm. MS (ESI, m/z): 715 $[M + 23]^+$. HRMS (ESI): $C_{38}H_{60}O_{11}$ calculated $[M + Na]^+$ 715.4028, found 715.4028.

(*S*)-3-((5*S*,12*S*)-17-Hydroxy-12-(methoxymethoxy)-5-(3-(4-methoxyphenyl)propyl)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (47). The procedure was the same as described above for the synthesis of **43**. Compound **47** was obtained as a buff oil (0.14 g, 78%). $[\alpha]^{25}_D$: 10.1 (c 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 1.5 Hz, 1H), 6.82 (dd, J = 6.6, 2.0 Hz, 2H), 4.99 (dq, J = 6.8, 1.7 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.73 (s, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.87−3.82 (m, 1H), 3.78 (s, 3H), 3.73−3.71 (m, 1H), 3.63−3.41 (m, 9H), 3.39 (s, 3H), 3.37 (s, 3H), 2.57 (t, J = 7.5 Hz, 2H), 2.54−2.34 (m, 4H), 2.26 (t, J = 8.2 Hz, 2H), 1.58−1.24 (m, 16H), 1.40 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 157.7, 148.9, 134.4, 134.2, 129.2, 113.7, 96.0, 95.9, 79.1, 78.2, 76.7, 76.0, 74.7, 74.0, 72.7, 70.9, 70.7, 70.1, 55.5, 55.2, 36.3, 35.0, 31.6, 29.4, 29.2, 29.1, 27.8, 27.4, 27.3, 25.6, 25.1, 22.1, 19.2 ppm. MS (ESI, m/z): 685 $[M + 23]^+$. HRMS (ESI): $C_{37}H_{58}O_{10}$ calculated $[M + Na]^+$ 685.3922, found 685.3918.

(*S*)-3-((5*S*,12*S*)-5-(3-(Biphenyl-4-yl)propyl)-17-hydroxy-12-(methoxymethoxy)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (48). The procedure was the same as described above for the synthesis of **43**. Compound **48** was obtained as a buff oil (97 mg, 43%). $[\alpha]^{25}_D$: 13.5 (c 0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 7.6, 7.0 Hz, 2H), 7.33−7.29 (m, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 1.6 Hz, 1H), 4.97 (dq, J = 6.8, 1.6 Hz, 1H), 4.77 (d, J = 6.8 Hz,

1H), 4.72 (s, 2H), 4.65 (d, J = 6.8 Hz, 1H), 3.85−3.83 (m, 1H), 3.76−3.73 (m, 1H), 3.67−3.50 (m, 9H), 3.38 (s, 3H), 3.37 (s, 3H), 2.67 (t, J = 7.6 Hz, 2H), 2.50−2.27 (m, 4H), 2.25 (t, J = 8.5 Hz, 2H), 1.78−1.25 (m, 16H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 148.7, 141.5, 141.2, 138.7, 134.4, 128.8, 128.6, 127.0, 126.9, 96.2, 96.0, 79.2, 78.2, 76.7, 76.2, 74.9, 74.1, 72.8, 70.9, 70.7, 70.1, 55.4, 36.3, 35.5, 31.8, 29.4, 29.2, 29.1, 27.9, 27.4, 27.1, 25.6, 25.1, 22.2, 19.2 ppm. MS (ESI, m/z): 731 $[M + 23]^+$. HRMS (ESI): $C_{42}H_{60}O_9$ calculated $[M + Na]^+$ 731.4130, found 731.4127.

(*S*)-3-((5*S*,12*S*)-17-Hydroxy-12-(methoxymethoxy)-5-(3-(6-methoxynaphthalen-2-yl)propyl)-2,4,7,10-tetraoxatetracos-14-yn-24-yl)-5-methylfuran-2(5*H*)-one (49). The procedure was the same as described above for the synthesis of **43**. Compound **49** was obtained as a buff oil (60.4 mg, 54%). $[\alpha]^{25}_D$: 8.6 (c 0.55, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67−7.64 (m, 2H), 7.53 (s, 1H), 7.29 (dd, 1H, J = 8.4, 1.7 Hz, 1H), 7.12−7.10 (m, 2H), 6.96 (d, J = 1.6 Hz, 1H), 4.97 (dq, J = 6.8, 1.7 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 4.71 (s, 2H), 4.64 (d, J = 6.8 Hz, 1H), 3.90 (s, 3H), 3.84−3.82 (m, 1H), 3.76−3.73 (m, 1H), 3.67−3.40 (m, 9H), 3.38 (s, 3H), 3.36 (s, 3H), 2.75 (t, J = 7.6 Hz, 2H), 2.49−2.34 (m, 4H), 2.27−2.22 (m, 2H), 1.58−1.28 (m, 16H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 157.1, 148.9, 137.4, 134.2, 132.9, 129.1, 128.8, 127.8, 126.7, 126.2, 118.6, 105.6, 96.0, 95.9, 79.1, 78.3, 76.0, 74.7, 74.0, 72.6, 70.9, 70.6, 70.0, 55.5, 55.2, 36.3, 35.8, 31.6, 29.4, 29.2, 29.1, 27.8, 27.3, 27.1, 26.5, 25.6, 25.1, 22.1, 19.2 ppm. MS (ESI, m/z): 735 $[M + 23]^+$. HRMS (ESI): $C_{41}H_{60}O_{10}$ calculated $[M + Na]^+$ 735.4079, found 735.4077.

(*S*)-3-((13*S*)-8,13-Dihydroxy-14-(2-((*S*)-2-hydroxyoctyloxy)-ethoxy)tetradecyl)-5-methylfuran-2(5*H*)-one (2). To a stirred solution of **43** (0.192 g, 0.32 mmol) and *p*-toluenesulfonylhydrazone (3.04 g, 16 mmol) in dimethoxylethane (20 mL) was added NaOAc (2.65 g, 32 mmol) in H_2O (15 mL) dropwise within 4 h under reflux. After being stirred for an additional 10 h, the reaction mixture was then cooled to room temperature and poured into water (5 mL). The mixture was extracted with ethyl acetate (20 mL × 3), and the extracts were washed with brine, dried, and concentrated to give a crude product.

To the crude product obtained above in THF and CH_3OH (2.4 mL, v/v, 1:2) was added 6 N HCl (1.5 mL). The mixture was stirred for 1.5 h at room temperature until it was quenched by saturated aqueous $NaHCO_3$ (3 mL). The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography afforded **2** as white wax (0.16 g, 94% for two steps). $[\alpha]^{25}_D$: 13.4 (c 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, J = 1.2 Hz, 1H), 5.00 (dq, J = 6.8, 1.5 Hz, 1H), 3.79 (br, 2H), 3.71−3.62 (m, 5H), 3.58 (brs, 1H, OH), 3.55 (d, J = 2.7 Hz, 1H), 3.52 (d, J = 2.7 Hz, 1H), 3.32 (dq, J = 9.5, 2.8 Hz, 2H), 2.88 (brs, 2H, OH), 2.26 (t, J = 7.6 Hz, 2H), 1.56−1.24 (m, 30H), 1.40 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 148.7, 134.4, 77.1, 75.9, 75.8, 71.8, 71.7, 70.6, 70.3, 37.5, 37.4, 33.1, 33.0, 31.7, 29.5, 29.3, 29.2, 29.1, 27.4, 25.6, 25.5, 25.4, 25.1, 22.5, 19.2, 13.9 ppm. MS (EI, m/z): 515 $[M + 1]^+$, 537 $[M + 23]^+$. HRMS (ESI): $C_{29}H_{54}O_7$ calculated $[M + H]^+$ 515.3942, found 515.3939.

(*S*)-3-((13*S*)-14-(2-((*S*)-6-Cyclohexyl-2-hydroxyhexyloxy)-ethoxy)-8,13-dihydroxytetradecyl)-5-methylfuran-2(5*H*)-one (3). The procedure was the same as described above for the synthesis of **2**. Compound **3** was obtained as white wax (51 mg, 67% for two steps). $[\alpha]^{25}_D$: 18.9 (c 0.27, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, J = 1.4 Hz, 1H), 4.98 (dq, J = 6.8, 1.6 Hz, 1H), 3.78 (br, 2H), 3.68−3.60 (m, 5H), 3.56 (brs, 1H, OH), 3.52 (d, J = 2.4 Hz, 1H), 3.50 (d, J = 2.4 Hz, 1H), 3.31 (dq, J = 8.9, 3.6 Hz, 2H), 2.99 (brs, 2H, OH), 2.24 (t, J = 7.3 Hz, 2H), 1.67−1.09 (m, 37H), 1.39 (d, J = 6.5 Hz, 3H), 0.87−0.79 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 148.9, 134.2, 77.4, 75.9, 75.8, 71.7, 70.5, 70.4, 70.2, 70.0, 37.6, 37.4, 37.3, 33.4, 33.0, 32.8, 31.6, 29.6, 29.5, 29.2, 29.1, 27.3, 26.9, 26.7, 26.4, 25.8, 25.6, 25.5, 25.4, 25.1, 19.2 ppm. MS (EI, m/z): 569 $[M + 1]^+$, 591 $[M + 23]^+$. HRMS (ESI): $C_{33}H_{60}O_7$ calculated $[M + H]^+$ 569.4412, found 569.4416, $[M + Na]^+$ 591.4231, found 591.4234.

(*S*)-3-((13*S*)-8,13-Dihydroxy-14-(2-((*S*)-2-hydroxy-5-phenylpentyloxy)ethoxy)tetradecyl)-5-methylfuran-2(5*H*)-one (4). The procedure was the same as described above for the synthesis of **2**. Compound **4** was obtained as a white oil (94.7 mg, 54% for two steps). $[\alpha]^{25}_D$: 6.6 (c 0.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.15 (m, 5H), 6.99 (d, J = 1.4 Hz, 1H), 4.99 (dq, J = 7.5, 1.6 Hz, 1H), 3.80 (m, 2H), 3.70−3.59 (m, 5H), 3.57 (brs, 1H, OH), 3.52 (d, J = 2.8 Hz, 1H), 3.51 (d, J = 2.8 Hz, 1H), 3.31 (dq, J = 9.2, 2.4 Hz, 2H), 2.96 (br, 2H, OH), 2.63 (t, J = 7.7 Hz, 2H), 2.26 (dt, J = 11.2, 7.3 Hz, 2H), 1.84−1.25 (m, 24H), 1.40 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 148.9, 142.2, 134.2, 128.4, 128.2, 125.7, 77.4, 75.8, 71.7, 71.6, 70.4, 70.1, 70.0, 37.4, 37.3, 35.8, 32.9, 32.5, 29.5, 29.2, 29.1, 27.3, 25.6, 25.5, 25.4, 25.1, 19.2 ppm. MS (EI, m/z): 549 $[M + 1]^+$, 571 $[M + 23]^+$. HRMS (ESI): $C_{32}H_{52}O_7$ calculated $[M + H]^+$ 549.3786, found 549.3784.

(*S*)-3-((13*S*)-8,13-Dihydroxy-14-(2-((*S*)-2-hydroxy-5-(3-hydroxyphenyl)pentyloxy)ethoxy)tetradecyl)-5-methylfuran-2(5*H*)-one (5). The procedure was the same as described above for the synthesis of **2**. Compound **5** was obtained as a white wax (64.7 mg, 80% for two steps). $[\alpha]^{25}_D$: 7.0 (c 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (brs, 1H, OH), 7.10−7.06 (m, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.67−6.63 (m, 3H), 4.98 (dq, J = 6.8, 1.6 Hz, 1H), 3.78 (br, 2H), 3.66−3.30 (m, 12H), 2.55 (t, J = 7.5 Hz, 2H), 2.24 (t, J = 7.9 Hz, 2H), 1.77−1.23 (m, 24H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 156.3, 148.9, 143.9, 134.3, 129.3, 120.3, 115.4, 112.9, 76.7, 75.7, 71.8, 70.5, 70.4, 70.2, 37.4, 37.2, 35.5, 32.9, 32.5, 29.5, 29.2, 29.0, 27.4, 27.2, 26.8, 25.5, 25.4, 25.1, 19.1 ppm. MS (EI, m/z): 565 $[M + 1]^+$, 587 $[M + 23]^+$. HRMS (ESI): $C_{32}H_{52}O_8$ calculated $[M + Na]^+$ 587.3554, found 587.3555.

(*S*)-3-((13*S*)-8,13-Dihydroxy-14-(2-((*S*)-2-hydroxy-5-(4-methoxyphenyl)pentyloxy)ethoxy)tetradecyl)-5-methylfuran-2(5*H*)-one (6). The procedure was the same as described above for the synthesis of **4**. Compound **6** was obtained as a wax solid (98.5 mg, 71% for two steps). $[\alpha]^{25}_D$: 11.3 (c 0.90, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, J = 4.6 Hz, 2H), 6.98 (d, J = 1.5 Hz, 1H), 6.80 (dd, J = 6.6, 2.0 Hz, 2H), 4.98 (dq, J = 6.8, 1.6 Hz, 1H), 3.77 (s, 3H), 3.69−3.48 (m, 9H), 3.56 (br, 1H, OH), 3.33−3.28 (m, 2H), 2.97 (brs, 2H, OH), 2.56 (t, J = 7.6 Hz, 2H), 2.24 (dt, J = 7.7, 1.5 Hz, 2H), 1.64−1.24 (m, 24H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 157.8, 148.7, 134.4, 129.2, 113.8, 75.8, 71.8, 71.7, 70.6, 70.2, 55.2, 37.5, 37.3, 34.9, 33.0, 32.6, 29.5, 29.2, 29.0, 27.4, 25.6, 25.5, 25.1, 19.1 ppm. MS (EI, m/z): 579 $[M + 1]^+$, 601 $[M + 23]^+$. HRMS (ESI): $C_{33}H_{54}O_8$ calculated $[M + H]^+$ 601.3711, found 601.3712.

(*S*)-3-((13*S*)-14-(2-((*S*)-5-(Biphenyl-4-yl)-2-hydroxypentyloxy)-ethoxy)-8,13-dihydroxytetradecyl)-5-methylfuran-2(5*H*)-one (7). The procedure was the same as described above for the synthesis of **2**. Compound **7** was obtained as a white wax solid (44.8 mg, 51% for two steps). $[\alpha]^{25}_D$: 8.6 (c 0.29, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 7.1, 1.7 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 7.8, 7.6 Hz, 2H), 7.34−7.32 (m, 1H), 7.25 (dd, J = 8.2, 1.6 Hz, 2H), 6.97 (d, J = 1.5 Hz, 1H), 4.98 (dq, J = 6.8, 1.7 Hz, 1H), 3.82 (m, 2H), 3.70−3.61 (m, 5H), 3.57 (brs, 1H, OH), 3.54 (d, J = 2.6 Hz, 1H), 3.51 (d, J = 2.6 Hz, 1H), 3.33 (dq, J = 8.8, 2.6 Hz, 2H), 2.97 (br, 2H, OH), 2.68 (t, J = 7.6 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H), 1.55−1.26 (m, 24H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 148.7, 141.4, 141.2, 138.8, 134.4, 128.8, 128.6, 127.0, 126.9, 75.8, 71.8, 71.7, 70.6, 70.2, 37.5, 37.3, 35.4, 33.0, 32.7, 29.5, 29.2, 29.0, 27.4, 27.2, 25.6, 25.5, 25.1, 19.1 ppm. MS (EI, m/z): 625 $[M + 1]^+$, 647 $[M + 23]^+$. HRMS (ESI): $C_{38}H_{56}O_7$ calculated $[M + H]^+$ 625.4099, found 625.4102, $[M + Na]^+$ 647.3918, found 647.3915.

(*S*)-3-((13*S*)-8,13-Dihydroxy-14-(2-((*S*)-2-hydroxy-5-(6-methoxynaphthalen-2-yl)pentyloxy)ethoxy)tetradecyl)-5-methylfuran-2(5*H*)-one (8). The procedure was the same as described above

for the synthesis of **2**. Compound **8** was obtained as a white wax solid (36.4 mg, 62% for two steps). $[\alpha]^{25}_{D}$: 4.2 (*c* 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67−7.64 (m, 2H), 7.53 (s, 1H), 7.28 (dd, J = 8.4, 1.6 Hz, 1H), 7.12−7.10 (m, 2H), 6.97 (d, J = 1.4 Hz, 1H), 4.98 (dq, J = 6.8, 1.3 Hz, 1H), 3.90 (s, 3H), 3.80 (m, 2H), 3.68−3.59 (m, 5H), 3.57 (br, 1H, OH), 3.52 (d, J = 2.7 Hz, 1H), 3.50 (d, J = 2.7 Hz, 1H), 3.31 (dt, J = 9 Hz, 2H), 2.95 (br, 2H, OH), 2.76 (t, J = 7.6 Hz, 2H), 2.25 (dt, J = 7.3, 7.2 Hz, 2H), 1.78−1.25 (m, 24H), 1.39 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 157.2, 148.7, 137.4, 134.4, 133.0, 129.2, 128.8, 127.8, 126.7, 126.2, 118.5, 105.9, 77.2, 75.8, 71.8, 71.7, 70.6, 70.2, 55.3, 37.5, 37.3, 35.8, 33.0, 32.6, 29.5, 29.2, 29.0, 27.4, 27.2, 25.6, 25.5, 25.1, 19.1 ppm. MS (EI, m/z): 629 $[M + 1]^+$, 651 $[M + 23]^+$. HRMS (ESI): $C_{37}H_{56}O_8$ calculated $[M + H]^+$ 651.3867, found 651.3865.

Biological Assays. Cell Culture Conditions. Human cancer cells (SGC7901, A549, MCF7) and human normal cells (HLF and Beas-2B) were cultured in Dulbecco's modified Eagle's medium (DMEM), supplemented with penicillin−streptomycin, L-glutamine, and 10% FBS. Human cancer cells (HCT-116 and HT-29) were cultured in F12/DMEM, supplemented with penicillin−streptomycin, L-glutamine, and 10% FBS. All cell lines were maintained in a humidified atmosphere of 5% CO_2 at 37 °C.

Cell Viability Assay. Cells (5×10^3) were plated in flat-bottomed 96-well microplates. Background control wells lacking the cells but containing the same volume of media were included in each assay plate. Sixteen hours after seeding, new medium was added that contained increasing concentrations of tested compounds at 0.01−10 μM or vehicle control (DMSO). Cells were further incubated for 72 h and then treated with MTT (Sigma-Aldrich, 10 μL/well, 5 mg mL^{-1}) and incubated for another 4 h. Then the medium was removed and 150 μL of DMSO was added to each well, including controls and blanks. After the samples were swirled gently, the absorbance in each well at 570 nm in a microtiter plate reader was measured with a reference wavelength at 690 nm. Experiments were performed at least in replicates of four, and growth inhibition rate was calculated as follows: growth inhibition rate (%) = {1 − [ΔOD(compounds) − ΔOD(blank)]/[ΔOD(controls) − ΔOD(blank)]} × 100%. The growth inhibition (GIC_{50}) for each compound was defined as the concentration of drug leading to a 50% reduction in A570 compared with controls.

Acknowledgment. We thank the National Major Scientific and Technological Program for Drug Discovery (Grants 2009ZX09103-101, 2009ZX09501), NSFC (Grants 20802078, 20972160, 20921091), MOST (Grants 2009CB940900, 2010CB529201, 2010CB833200), Chinese Academy of Sciences (Grant KSCX2-YW-R-215), the Guangdong Natural Science Foundation (Grant 8151066302000008), and the NN-CAS Research Foundation (Grant NNCAS-2008-8) for financial support.

Supporting Information Available: Experimental procedures for synthesis of compound **11**, RP-HPLC data for compounds **2**−**8**, and NMR spectra for all listed compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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