DOI: 10.1002/ejoc.201300767

Synthesis of Linear Aza and Thio Analogues of Acetogenins and Evaluation of Their Cytotoxicity

Piret Villo,*[a] Lauri Toom,[a] Elo Eriste,[a] and Lauri Vares*[a]

Keywords: Natural products / Asymmetric synthesis / Kinetic resolution / Enantioselectivity / Cytotoxicity

We report the stereoselective synthesis of thio and aza analogues of Annonaceous acetogenins. The synthetic route allows easy variation of the stereochemistry and of the thio- and aza-fragments. Kinetic resolution of terminal bis-epoxides was used to set two remote stereocentres with high enantio- and diastereoselectivities in one step. The cytotoxicity of the analogues was assessed using the HeLa cell line.

Introduction

The Annonaceous acetogenins are a very interesting class of biologically active natural products that show cytotoxic and immunosuppressive effects.[1] They include one of the most potent inhibitors of NADH-ubiquinone oxidoreductase (complex I) from the mitochondrial electron-transport system, as well as inhibitors of NADH oxidase of plasma membranes of cancer cells that interrupt the intracellular synthesis of ATP.[2] Natural acetogenins are found in species belonging to the tree family Annonaceae in the Magnoliales order, native to tropical and sub-tropical regions.[3,4] Since the first acetogenin, Uvaricin (Figure 1), was isolated,[5] acetogenins have been under increasing scientific attention, and to date, more than 400 members of this class of compounds have been isolated. The acetogenins are characterized by an unbranched fatty acid chain that is normally terminated by a butenolide moiety, and one to three THF (or THP) rings with adjacent hydroxy groups in the central region of the hydrocarbon chain.[6] Due to their potent biological activities, especially the selective cytotoxicity against tumour ells, the synthesis of acetogenins and their derivatives are the subject of increasing interest.[7] Although structure–activity relationships need to be refined, some structural features have been shown to be necessary for their biological activity. The central region with flanking OH-groups is thought to play an important role, and it has also been shown that the hydrocarbon chain that connects the central region with the butenolide moiety has an optimal length of 13 carbon atoms for a strong inhibition effect.[8] Whether or not the butenolide is necessary, or whether it can be replaced by a structurally similar moiety is under debate.[9] Continued studies of the acetogenins and their analogues will hopefully further clarify their mode of action. Based on the results of many promising in vitro assessments, and also of in vivo studies in mice[10] and insects,[11] the acetogenins are considered to be a promising group of compounds in the search for new drug leads.

It has been reported that when the acetogenin structure is simplified by replacing the THF unit with a linear moiety containing heteroatoms, the biological activities of the simplified structures are comparable with those of the natural compounds. Various linear acetogenin analogues have been synthesized in which the THF units have been substituted for polyether units,[12] hydroxy groups,[13] or amine-containing moieties.[14] For example, Zhu-Jun Yao and co-workers have reported the synthesis of analogues containing a polyether unit[15] (**I**; Figure 2), and a bis-amide unit[16] (**II**). Both

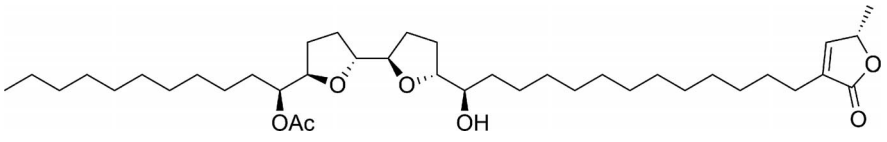


Figure 1. Uvaricin.

of these compounds have cytotoxicities comparable to known anti-cancer agents. Also, in the case of analogue **I**, the presence of the hydroxy group at C-4 clearly enhanced the biological activity compared to when it was absent.

This inspired us to explore the enantioselective synthesis of linear aza analogues **1**–**4** (Figure 3) with a hydroxy group

[a] Institute of Technology, University of Tartu, Nooruse 1, Tartu 50411, Estonia
E-mail: piret.villo@ut.ee
lauri.vares@ut.ee
http://www.tuit.ut.ee/140999

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300767.

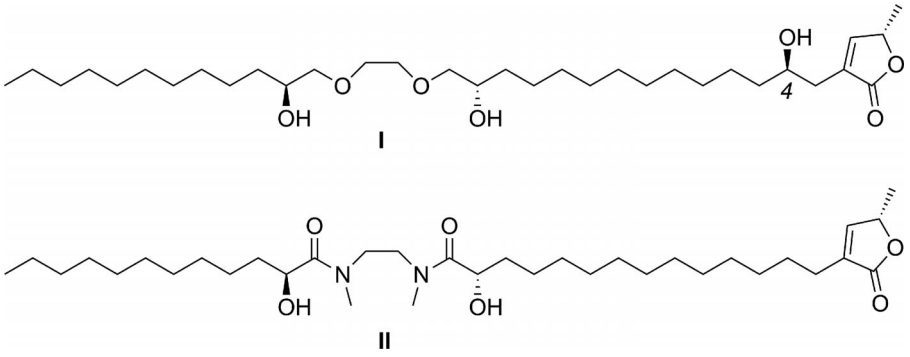


Figure 2. Examples of non-THF acetogenin analogues.

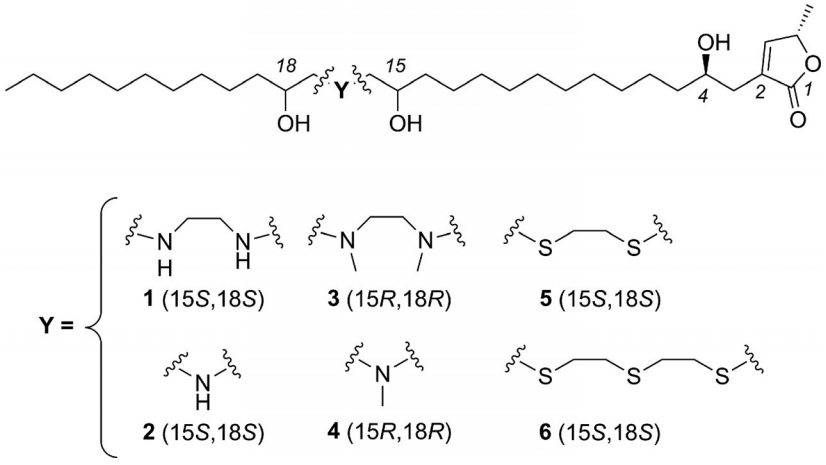


Figure 3. Synthesized aza and thio analogues **1**–**6**.

at C-4, and to assess their cytotoxicities. Thio analogues **5** and **6** were also prepared, and their cytotoxicities were compared to those of the aza analogues. Many biologically active natural compounds contain sulfur atoms,[17] but sulfur has not been reported as a component of natural acetogenin structures. Moreover, divalent sulfur can act as a hydrogen-bond donor comparable with the oxygen of an ether moiety, albeit weaker in strength.[18] And bearing in mind the importance of hydrogen bonding during binding to enzyme active sites, this could make the thio analogues of acetogenins an interesting subject along with the aza analogues.

Jacobsen's hydrolytic kinetic resolution (HKR)[19] and Sharpless asymmetric dihydroxylation (AD)[20] were both used to install the stereochemistry in the synthetic analogues. Jacobsen's kinetic resolution is a well-established method that has also been successfully used on terminal mono-epoxides with different nucleophiles.[21] Bis-epoxides, on the other hand, are more rarely used as substrates in HKR.[19a,22] Recently, we reported an efficient and highly stereoselective hydrolytic and aminolytic kinetic resolution of terminal bis-epoxides,[23] and this method has been used for the synthesis of the aza and thio analogues reported in this paper.

Results and Discussion

We envisioned two variations of the synthetic route, one based on Jacobsen's HKR, and the other on the Sharpless AD method. The retrosynthetic analysis for analogues **1**, **2**, **5**, and **6** is outlined in Figure 4a, and is based on the HKR method. According to this convergent synthetic route, there are two main fragments that must be coupled by an epoxide-opening reaction in the latter stages. These are termed the left-hand fragment, which contains the amine or thiol moieties, and the right-hand fragment **7** or **8**, an epoxide containing a terminal γ-lactone or a butenolide unit, respectively. We envisioned that the left-hand fragment could be derived from a chiral epoxide (*S*)-**9**, after epoxide opening by an amino or a thiol. The synthesis of (*S*)-**9** could be achieved by subjecting racemic epoxide **9** to HKR conditions. The racemic epoxide can be obtained from commercial sources or by oxidation of alkene **10** using *m*CPBA (*m*-chloroperbenzoic acid). The right-hand fragment **7** or **8** could be obtained by alkylation of lactone **12** with iodide **11**, which is a functionalized derivative of **13**. Epoxy-diol **13** could, in turn, be synthesized by subjecting bis-epoxide **14** to HKR conditions to install two remote stereocentres. The bis-epoxide can be obtained by oxidation of commer-

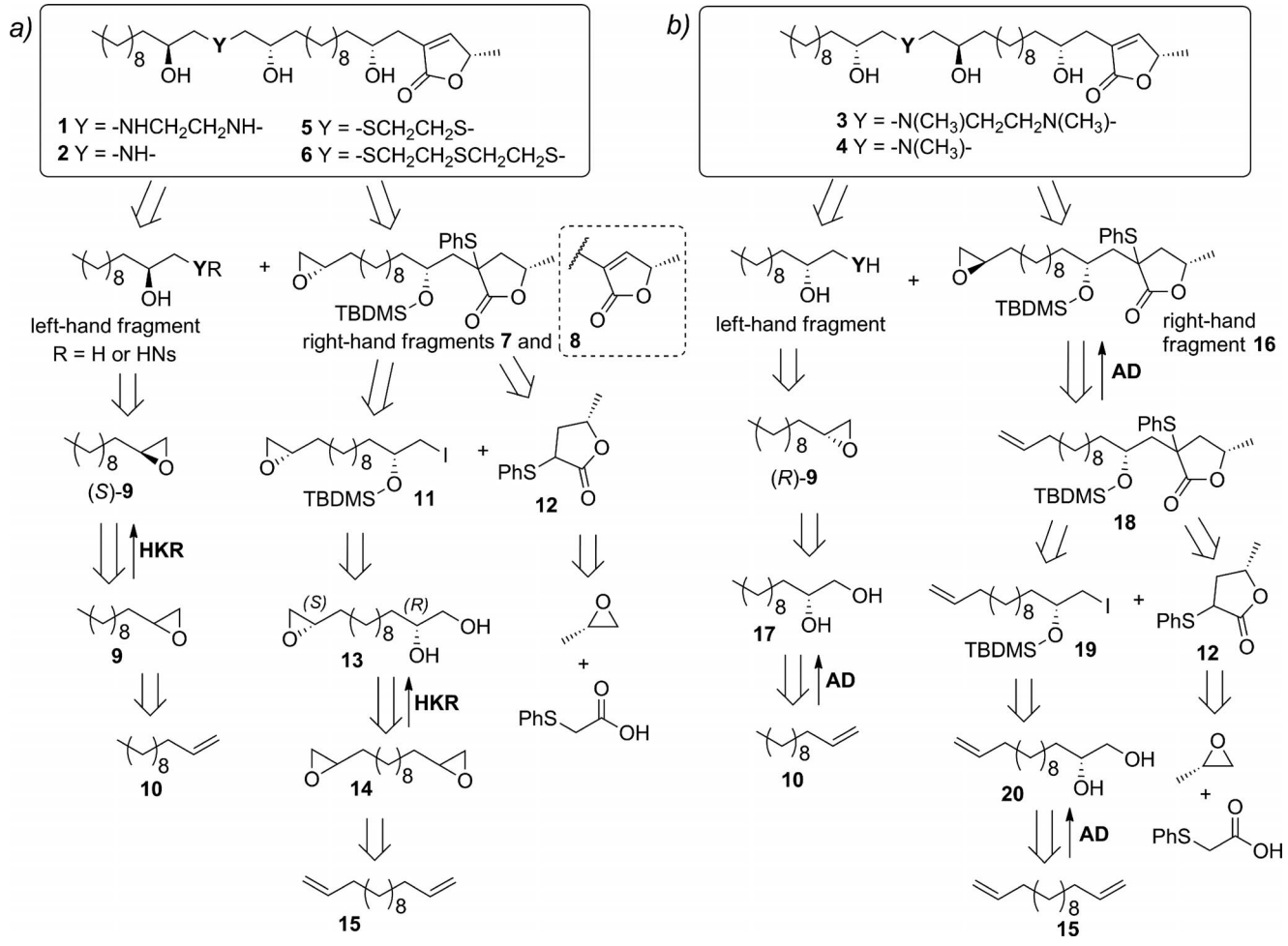
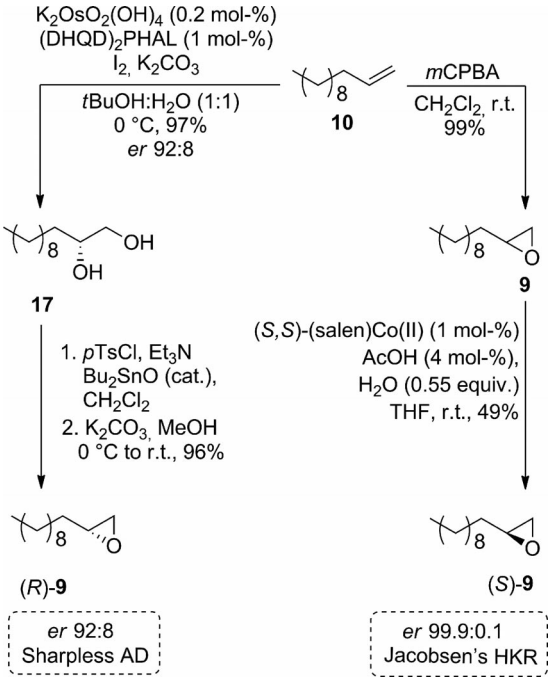


Figure 4. Retrosynthetic analysis of analogues **1**–**6** using a) Jacobsen's HKR of mono- and bis-epoxides; b) Sharpless AD of olefins.

cially available diene **15** using *m*CPBA. Lactone **12** can be synthesized from (*S*)-propylene oxide and (phenylthio)-acetic acid. Due to the possibility of epimerization of the unsaturated lactone ring under basic conditions,[24] mild reaction conditions were chosen where possible, and the insertion of the double bond into the lactone ring was planned to be one of the last steps.

For analogues **3** and **4**, a synthetic route based on the Sharpless AD method was planned (Figure 4b). This gives diastereomers that are not accessible by the HKR method, as the stereocentres are installed one at a time. The left- and right-hand fragments are to be coupled during the latter steps of the synthesis, similarly to the route in Figure 4a. But here, chiral epoxide (*R*)-**9** was to be derived from chiral diol **17**, after asymmetric dihydroxylation of alkene **10**. We planned that right-hand fragment **16** would be synthesized by subjecting alkylation product **18** to AD conditions and converting the resulting diol into the epoxide. Iodide **19** is a derivative of diol **20**, which we planned to obtain by asymmetric dihydroxylation of diene **15**.

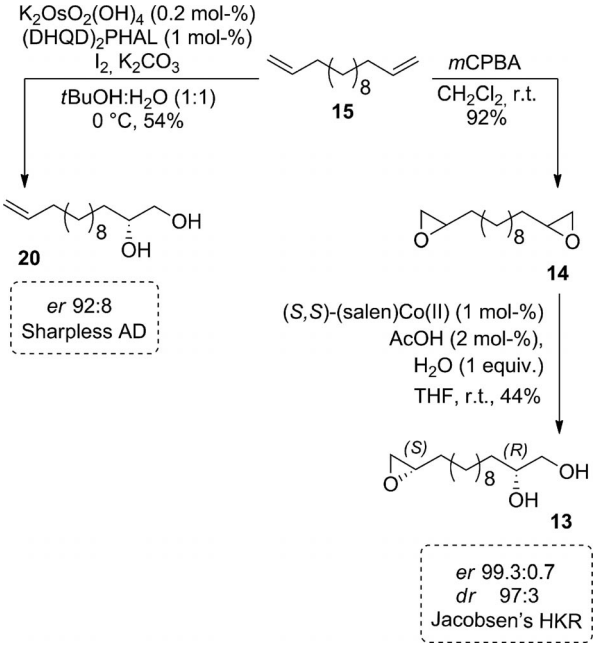
For the synthesis of the left-hand fragments, HKR and AD can both be used to give epoxides (*S*)-**9** and (*R*)-**9** (Scheme 1), but HKR gives higher enantioselectivity. When olefin **10** was subjected to osmium-catalysed asym-



Scheme 1. Synthesis of (*S*)-**9** and (*R*)-**9** by HKR and AD.

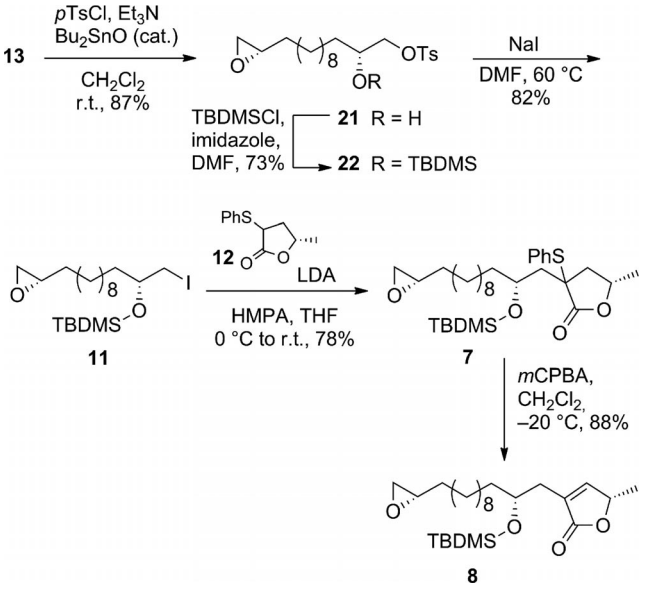
metric dihydroxylation conditions with chiral ligand $(DHQD)_2PHAL$, diol **17** was formed in excellent yield and with an enantiomeric ratio of 92:8.[25,26] On the other hand, when racemic epoxide **9** was subjected to HKR conditions, (*S*)-**9** was isolated with an excellent enantiomeric ratio of 99.9:0.1[27] and in high yield (49% from a theoretical maximum of 50%).

The importance of choosing HKR over AD becomes more relevant in the synthesis of the right-hand fragments, where two stereocentres are set. The two approaches to the right-hand fragments by AD and by HKR are shown in Scheme 2. The asymmetric dihydroxylation of diene **15** was terminated after ca. 50% conversion (monitored by TLC analysis) to give diol **20** with an *er* of 92:8.[25] To use HKR, diene **15** was first oxidized by *m*CPBA into bis-epoxide **14**, which consisted of (*R*,*R*)-**14** (25%), (*S*,*S*)-**14** (25%), and *meso* isomer (*R*,*S*)-**14** (50%). Then under HKR conditions, the *meso* derivative was converted into **13** in high yield, with an excellent *er* of 99.3:0.7 and a good *dr* of 97:3.[28] During the reaction, the aforementioned (*R*,*R*)-**14** stereoisomer was transformed into a tetrol, and the (*S*,*S*)-**14** enantiomer remained unaffected in the reaction mixture. Thus, in contrast to the AD approach, both of the olefin moieties in **15** can be functionalized simultaneously when using HKR, and also a higher enantioselectivity can be achieved.



Scheme 2. Synthesis of **20** by AD, and of **13** by HKR.

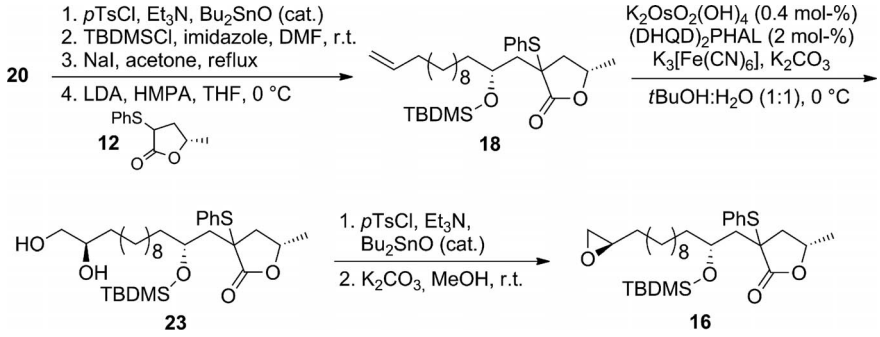
The primary hydroxy group in epoxy-diol **13** was regioselectively tosylated[29] using *p*TsCl and Bu_2SnO (cat.) to give **21** (Scheme 3). After protecting the secondary hydroxy group as a silyl ether, tosylate **22** was converted into iodide **11**. Next, alkylation of the lithium enolate derived from lactone **12**[30] with **16** was investigated. In an attempt to replace HMPA (hexamethylphosphoramide) as an additive, which has previously been used in similar alkylations,[31] DMPU (*N*,*N*′-dimethylpropyleneurea)[32] and Et_3B-promoted processes[33] were investigated, but without success. The optimal result was achieved by using LDA (lithium diisopropylamide) and HPMA (10 equiv.), and under these conditions, **7** was formed in 78% yield. Oxidation of the sulfide moiety in **7** followed by elimination gave the butenolide unit in **8**. It was noted that the elimination of the phenylsulfenic acid occurred either during the oxidation of the sulfide moiety or during the work-up without subsequent heating of the material.



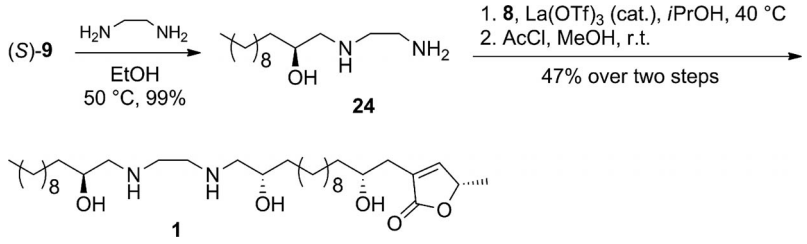
Scheme 3. Synthesis of right-hand fragments **7** and **8** by HKR.

Diol **20** was converted into compound **18** following a route similar to that used for the conversion of **13** into **7** (Scheme 4). Asymmetric dihydroxylation of **18** gave diol **23**, which was converted into epoxide **16**.

Initial efforts were directed towards the preparation of aza analogue **1**. Epoxide (*S*)-**9** was converted into amino alcohol **24** by treatment with ethylene-1,2-diamine at 50 °C (Scheme 5). When epoxide **8** was treated with amino alcohol **24** under similar conditions, no product was formed, so the second epoxide-opening reaction had to be explored more closely. Since the presence of the butenolide unit in **8** excludes the use of basic conditions and elevated temperatures, the reaction was investigated with some additional Lewis acid catalysts. Several transition metal chlorides and triflates were tested,[34,35] and it was found that at room temperature they all gave ca. 30% of the coupled product after reaction times of 2–3 d, and the unreacted starting materials were recoverable. When the reaction was heated to 40 °C, the yield doubled, but raising the temperature further resulted in the formation of unidentified by-products. Finally, epoxide **8** was opened by **24** in the presence of $La(OTf)_3$ at 40 °C to give the coupled product in 65% yield after 2 d. After removing the silyl ether, analogue **1** was formed.



Scheme 4. Synthesis of right-hand fragment **16** by AD. TBDMS = *tert*-butyldimethylsilyl.

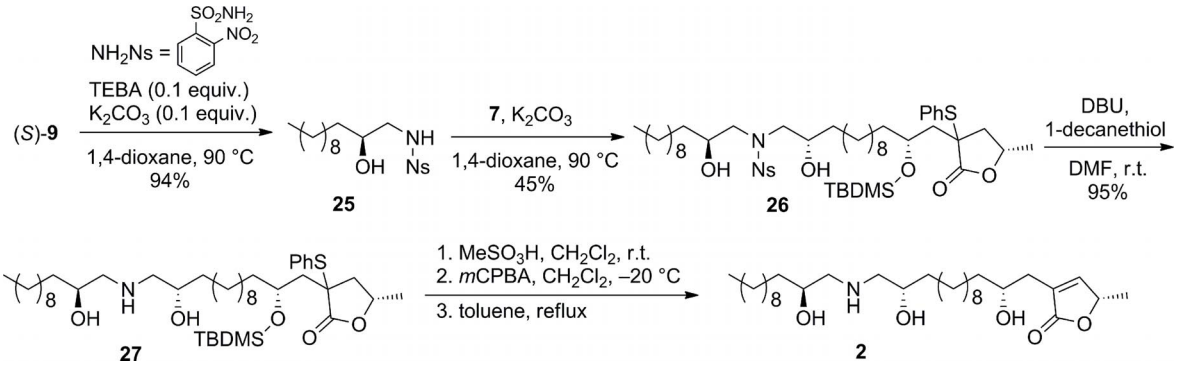


Scheme 5. Synthesis of aza analogue **1**.

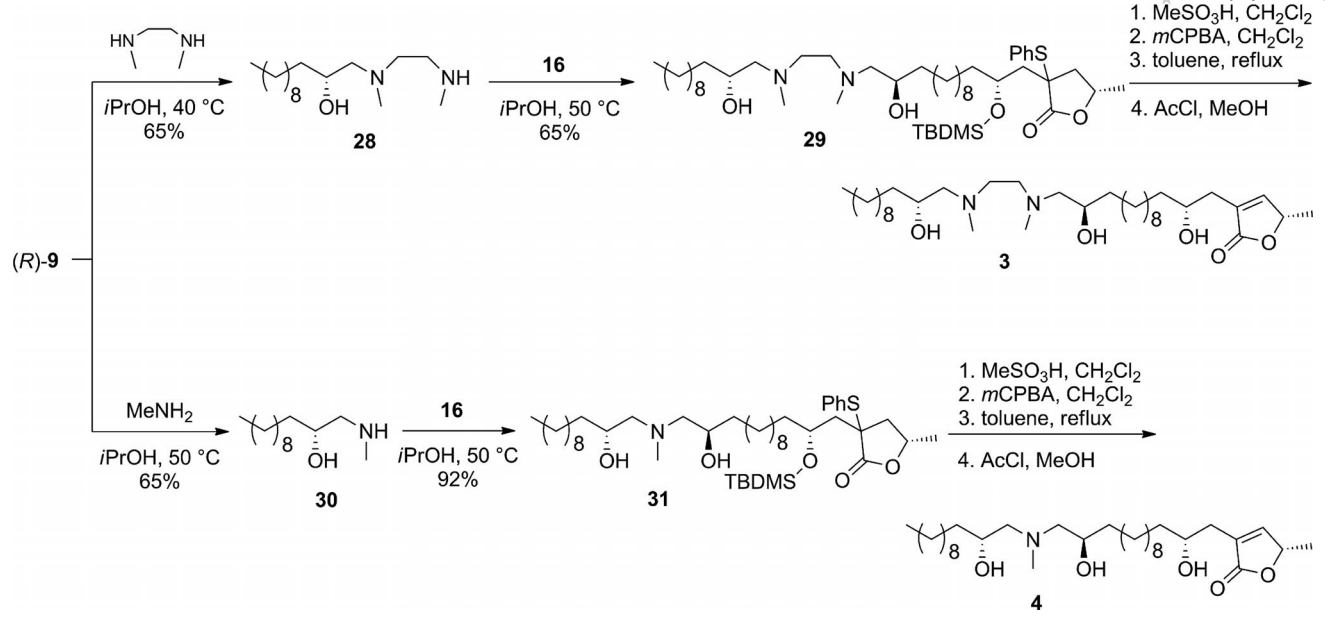
The synthesis of analogue **2** is summarized in Scheme 6. Since we have previously shown that *N*-nosyl protected amino alcohols perform well as nucleophiles in epoxide-opening reactions,[26] epoxide (*S*)-**9** was treated with 2-nitrobenzenesulfonamide (NH_2Ns) at elevated temperatures for 4 d to give amino alcohol **25** in high yield. Somewhat surprisingly, the coupling reaction between this material and epoxide **7** proceeded slowly, and 12 d were required to reach an acceptable conversion to **26**. As it is difficult to remove the *N*-nosyl group in the presence of the butenolide moiety, the protecting group had to be removed before the sulfide was oxidized. Thus, compound **26** was treated with 1-decanethiol and DBU (1,8-diazabicycloundec-7-ene)[36] to give secondary amine **27**. This was followed by quaternary ammonium salt formation with $MeSO_3H$, oxidation, and subsequent thermal elimination of the sulfoxide moiety to give analogue **2**. Gratifyingly, the silyl protecting group was also removed during the salt formation/oxidation/elimination sequence. Analogue **2** was isolated in 63% yield over three steps.

Compounds **3** and **4**, the *N*-methylated derivatives of **1** and **2**, were prepared by a synthetic route based on the Sharpless AD method (Scheme 7). Treatment of epoxide (*R*)-**9** with *N*,*N*′-dimethylethylene-1,2-diamine gave **28**, which was then coupled with right-hand fragment **16** to give **29**. Treating this material with $MeSO_3H$, followed by oxidation and elimination, gave the derivative containing the butenolide unit along with some amount of final product **3**. After hydrolysis of the silyl ether in the remaining material, analogue **3** was isolated in a combined yield of 87% over two steps. Analogue **4** was prepared following a route identical to that used for compound **3**, except that methylamine was used as the nucleophile in the first epoxide-opening reaction.

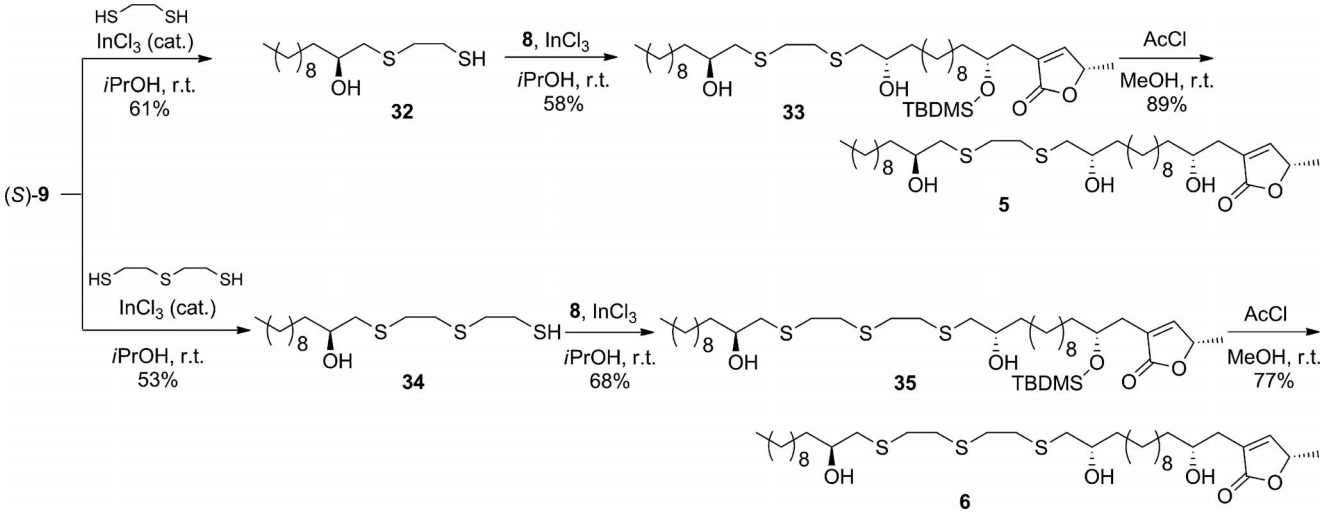
Thio analogues **5** and **6** were prepared from (*S*)-**9** following a route based on HKR (Scheme 8). Different conditions were investigated for the epoxide-opening reaction with sulfides. The best results were obtained using $InCl_3$ as a catalyst.[37] The reaction between (*S*)-**9** and 1,2-ethanedithiol in the presence of $InCl_3$ in *i*PrOH gave **32** in 61%



Scheme 6. Synthesis of aza analogue **2**. TEBA = benzyltriethylammonium chloride.



Scheme 7. Synthesis of aza analogues **3** and **4**.



Scheme 8. Synthesis of thio analogues **5** and **6**.

yield. Next, sulfide **32** was coupled with epoxide **8** to give **33**, which was deprotected to give thio analogue **5**. The final analogue, compound **6**, was prepared following an identical route but using 2,2′-thiodiethanethiol as the nucleophile.

The ^{1}H and ^{13}C NMR spectra of aza analogues **2**, **3**, and **4** show the presence of some minor contamination, which is believed to be diastereomers resulting from epimerization in the butenolide unit after the elimination of phenylsulfenic acid at elevated temperatures. No such epimerization was observed in aza analogue **1**, nor in thio analogues **5** and **6**, where the unsaturated lactone ring was formed at room temperature. Despite all of the investigations concerning the lactone ring unit of the acetogenins, there does not seem to be a consensus about the exact structural requirement for biological activity.[38]

Biological Evaluation

The antiproliferative activity of analogues **1**–**6** against the HeLa cell line are given in Table 1 as the concentration of compound necessary to give one-half the maximum response (ED_{50}). Rotenone, a known complex I inhibitor,[39] was used as a reference. After 24 h of treatment, all of the aza analogues (i.e., **1**–**4**) showed cytotoxicity $ED_{50} < 10$ μM, and performed more effectively than rotenone (ED_{50} = 77.5 μM). The thio analogues (i.e., **5** and **6**) had less effect on cell growth than the aza analogues, and they needed concentrations of around 100 μM or higher to reach the effective dose.

The best result was obtained with *N*,*N*′-dimethylated diamine analogue **3**, which, at a concentration of 3 μM, had a

Table 1. Antiproliferative activity of compounds **1**–**6** against the HeLa cell line.[a]

Entry	Compound	ED_{50} [μM][b]
1	**1**	5.7
2	**2**	8.2
3	**3**	3.1
4	**4**	7.7
5	**5**	91.0
6	**6**	>100
7	rotenone[c]	77.5

[a] HeLa cell line, human epitheloid cervix carcinoma. [b] ED_{50}, effective dose. [c] Rotenone was used as reference as a complex I inhibitor.

cytotoxicity of 34.7 ± 4.4%, and at 5 μM had a cytotoxicity of 91.9 ± 3.3% (ED_{50} = 3.1 μM). Based on our findings, the epimerization of the α,β-unsaturated lactone ring in **3** did not seem to have a great effect on its biological activity, as the antiproliferative activity of **3** falls in the same range as its non-methylated counterpart **1** (ED_{50} = 5.7 μM), for which no epimerization was detected. *N*-Methylated analogue **4** and non-methylated analogue **2** had similar effective doses of 7.7 μM and 8.2 μM, respectively. It seems that aza analogues with diamine moieties, whether methylated or not, are more cytotoxic than monoamine analogues.

Conclusions

Four aza analogues **1**–**4** and two thio analogues **5** and **6** were synthesized according to a general synthetic scheme that allows facile variability of the central heteroatom-containing portion of the molecule. Hydrolytic kinetic resolution of bis-epoxides was successfully used to establish two remote stereocentres with high enantio- and diastereoselectivity in a single step. All the analogues synthesized underwent preliminary in vitro studies against the HeLa cell line. While the aza analogues showed a 50% cell-viability reduction at concentrations under 10 μM, the thio analogues had less effect, needing concentrations of around 100 μM or above to reach an effective dose. Although we observed epimerization in the α,β-unsaturated lactone ring for aza analogues **2**–**4**, the bioassay studies did not show significant differences in activity between analogues **2**–**4** and the non-epimerized analogue **1**.

Experimental Section

Cell Culture: Human cervical cancer cell line HeLa (American Type Culture Collection via LGC, Sweden) was cultured in Dulbecco's Modified Eagle Medium (DMEM) with high glucose and with L-glutamine. The medium was supplemented with 10% fetal bovine serum (FBS), sodium pyruvate (1 mM), penicillin (100 U/mL), streptomycin (100 μg/mL) and 1% nonessential amino acids (further denoted as complete medium; PAA Laboratories GmbH, Austria). Cell cultures were cultivated at 37 °C in a humidified 5% CO_2 incubator.

In vitro Proliferation Assay: Long-term toxicity was evaluated using an MTS[40] proliferation assay (CellTiter 96® Aqueous One Solution Cell Proliferation Assay, Promega, Madison, WI, USA). The MTS assay measures the activity of mitochondrial dehydrogenases by measuring their conversion of tetrazolium salts into formazan. Briefly, the cells were seeded in 96-well plates at a density 1×10^4 cells per well in DMEM-high glucose medium (100 μL) 1 d before treatment. The test compounds were diluted with DMSO (0.01 mM–10 mM). The cells were treated with the serial dilutions of the test compounds (not exceeding 1% v/v in final concentration), and the treated cells were incubated for 24 h at 37 °C in a humidified chamber in an atmosphere containing 5% CO_2. Rotenone, a classical complex I inhibitor, was used as a positive control. MTS was added to cells according to the manufacturer's general protocol. The quantity of formazan produced was measured colourimetrically by absorbance at 490 nm on a Tecan Sunrise microplate absorbance reader, and is directly proportional to the number of living cells in culture. All experiments were performed in triplicate, and the relative cell viability (%) was expressed as the percent absorbance of the control (cells treated with 1% DMSO).

General Remarks: ^1H and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz, respectively. For compound **1**, the ^{13}C NMR spectrum was recorded at 201.2 MHz. The chemical shifts for the ^1H and ^{13}C NMR spectra are given in ppm, and are calibrated using residual solvent signals (for ^1H, $CDCl_3$: δ = 7.26 ppm, and for ^{13}C, $CDCl_3$: δ = 77.0 ppm). The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br. s, broad singlet; vt, virtual triplet. Reactions were monitored by thin-layer chromatography (TLC), and TLC plates were visualized either by UV detection or by staining with $KMnO_4$ or phosphomolybdic acid solution. Purification of reaction products was done by flash chromatography using silica gel 60 (0.040–0.063 mm, 230–400 mesh). In HPLC analysis, signals were detected by a diode-array detector. For HRMS analysis, an LTQ Orbitrap analyser was used. An FTIR spectrophotometer (ATR) was used for IR analysis. All reagents and solvents were obtained from commercial sources and were used without further purification.

1,2-Epoxydodecane (9): A solution of 1-dodecene **10** (1500 mg, 8.91 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and *m*CPBA (17.82 mmol, 3994 mg, >77% purity) was added. The reaction mixture was stirred for 16 h at room temp., then it was quenched with $Na_2S_2O_3$ (satd. aq.). The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was redissolved in petroleum ether, and the solution was filtered and then concentrated in vacuo to dryness. The residue was purified by flash chromatography on silica (5% EtOAc in petroleum ether) to give **9** (1626 mg, 99%) as a clear oil. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 2.87 (m, 1 H), 2.71 (dd, J = 5.0, 4.0 Hz, 1 H), 2.43 (dd, J = 5.0, 2.7 Hz 1 H), 1.54–1.17 (m, 18 H), 0.85 (vt, 3 H). The ^1H NMR spectroscopic data is in agreement with the data for commercially available 1,2-epoxydodecane.

(*S*)-1,2-Epoxydodecane [(*S*)-9]: (*S*,*S*)-(salen)cobalt(II) (28 mg, 0.047 mmol) was dissolved in toluene (0.5 mL), and AcOH (10 μL, 0.18 mmol) was added. The solution was stirred at room temp. open to air for 1 h, and then it was concentrated in vacuo to dryness. The residue was dissolved in THF (0.5 mL), and 1,2-epoxydodecane **9** (862 mg, 4.67 mmol) was added. The mixture was cooled to 0 °C and stirred for 5 min. Then H_2O (46 μL, 2.57 mmol) was added at 0 °C. The reaction mixture was stirred at room temp. for 16 h, then it was concentrated in vacuo to dryness. The residue was purified by column chromatography on silica (10% EtOAc in petroleum ether) to give product (*S*)-**9** (423 mg, 49%) as a beige oil. $[\alpha]_D^{23}$ = –6.6 (c = 0.3, CH_2Cl_2) {ref.[41] for (*R*)-1,2-epoxydo-

decane: $[a]_D^{23}$ = +6.0 (*c* = 0.3, CH_2Cl_2)}. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 2.84 (m, 1 H), 2.67 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.39 (dd, *J* = 5.0, 2.7 Hz, 1 H), 1.51–1.16 (m, 18 H), 0.83 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 52.3, 47.0, 32.4, 31.8, 29.56, 29.52 (two overlapping signals), 29.42, 29.2, 25.9, 22.6, 14.0 ppm. IR: $\tilde{\nu}$ = 2924, 2854, 1465, 914, 833, 721 cm^{-1}. The *er* of 99.9:0.1 was measured from a tosyl derivative of (*S*)-**9** by HPLC analysis [CHIRALPAK IA column, 2% *i*PrOH in hexane, 1.0 mL/min; *R* isomer 38.8 min (minor), *S* isomer 49.1 (major)]. See Supporting Information for further details.

1,2:13,14-Diepoxytetradecane (14): *m*CPBA (3.30 g, 14.74 mmol, >77% purity) was added in one portion to a cooled (0 °C) solution of 1,13-tetradecadiene **15** (1.14 g, 5.89 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at 0 °C for 30 min, then it was allowed to warm to room temp. and stirred for a further 2 h. After TLC indicated that the starting material had been consumed, $Na_2S_2O_3$ (20% aq.; 50 mL) was added, and the mixture was stirred for 5 min. Further $Na_2S_2O_3$ (20% aq.; 30 mL) and CH_2Cl_2 (30 mL) were added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in hexanes, and the solution was filtered. Purification by flash column chromatography on silica (10% EtOAc in hexanes) gave product **14** (1.23 g, 92%) as a beige oil. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 2.86 (m, 2 H), 2.70 (dd, *J* = 5.0, 4.0 Hz, 2 H), 2.42 (dd, *J* = 5.0, 2.7 Hz, 2 H), 1.53–1.17 (m, 20 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 52.2, 46.9, 32.3, 29.4–29.3, 25.8 ppm. IR: $\tilde{\nu}$ = 2933, 2854, 1461, 1407, 1257, 836 cm^{-1}. HRMS: calcd. for $C_{14}H_{26}O_2$ $[M + H]^+$ 227.2005; found 227.1999.

(2*R*,13*S*)-13,14-Epoxytetradecane-1,2-diol (13): (*S*,*S*)-(salen)cobalt(II) (14 mg, 22 μmol) was dissolved in CH_2Cl_2 (1 mL), and AcOH (5 μL, 90 μmol) was added. The mixture was stirred at room temp. open to air for 1 h, during which time the colour turned from dark red to brown. Then the solution was concentrated to dryness in vacuo. The residue was redissolved in THF (2 mL), and this solution was added to bis-epoxide **14** (510 mg, 2.25 mmol). The solution was cooled to 0 °C, and H_2O (38 μL, 2.14 mmol) was added. The reaction mixture was stirred at room temp. for 16 h. Then the mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica (2–6% MeOH in CH_2Cl_2) to give **13** (250 mg, 44% from theoretical 50% yield) as a white solid. R_f (**13**) = 0.8 in 50% EtOAc/petroleum ether [R_f (**14**) = 0.3 in 50% EtOAc/petroleum ether; R_f (tetrol) = 0.9 in 10% MeOH/CH_2Cl_2], m.p. 60–61.3 °C. $[a]_D^{20}$ = –6.0 (*c* = 1.15, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.75–3.62 (m, 2 H), 3.43 (m, 1 H), 2.90 (m, 1 H), 2.74 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1 H), 2.05 (br. s, 1 H), 1.93 (br. s, 1 H), 1.56–1.22 (m, 20 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 72.2, 66.6, 52.3, 47.0, 33.0, 32.3, 29.5, 29.4–29.3, 29.2, 25.8, 25.4 ppm. IR: $\tilde{\nu}$ = 3475, 3313, 2916, 2850, 1469, 1072, 848 cm^{-1}. HRMS: calcd. for $C_{14}H_{28}O_3$ $[M + H]^+$ 245.2111; found 245.2106.

The stereomeric ratios for **13** were determined by chiral HPLC analysis after derivatization. The *dr* of 97:3 was measured after tosylation of **13** to give **21** (Phenomenex LUX Cellulose-1 column, 10% *i*PrOH in hexane, 1.5 mL/min, major isomer 8.83 min, minor isomer 9.94 min). The *er* of 99.3:0.7 was measured after preparation of a thiol derivative (Phenomenex LUX Cellulose-1 column, 20% *i*PrOH in hexane, 1.5 mL/min, minor isomer 14.5 min, major isomer 17.3 min). For further details, see Supporting Information.

(*R*)-2-Hydroxy-12-[(*S*)-oxiran-2-yl]dodecyl-4-methylbenzenesulfonate (21): Epoxy-diol **13** (178 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (5 mL), and Bu_2SnO (3 mg, 14 μmol), Et_3N (101 μL, 0.72 mmol), and *p*TsCl (145 mg, 0.76 mmol) were added. The reaction mixture was stirred for 17 h at room temp. Then the mixture was diluted with CH_2Cl_2, and $NaHCO_3$ (satd. aq.) was added. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica (1–2% MeOH in CH_2Cl_2) to give product **21** (253 mg, 87%) as a white solid, m.p. 58–60 °C. $[a]_D^{20}$ = –8.2 (*c* = 1.15, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.79–7.75 (m, 2 H), 7.35–7.31 (m, 2 H), 4.00 (dd, *J* = 9.9, 2.8 Hz, 1 H), 3.85 (dd, *J* = 9.9, 7.0 Hz, 1 H), 3.79 (m, 1 H), 2.88 (m, 1 H), 2.72 (m, 1 H), 2.44 (m, 1 H), 2.42 (br. s, 3 H), 2.30 (br. s, 1 H), 1.53–1.17 (m, 20 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.9, 132.6, 129.8, 127.8, 73.9, 69.3, 52.3, 47.0, 32.5, 32.3, 29.4, 29.3, 25.8, 25.1, 21.5 ppm. IR: $\tilde{\nu}$ = 3374, 2923, 2854, 1596, 1357, 1176, 960, 836, 813, 736, 667 cm^{-1}. HRMS: calcd. for $C_{21}H_{34}O_5S$ $[M + H]^+$ 399.2199; found 399.2192.

(*R*)-2-(*tert*-Butyldimethylsilyloxy)-12-[(*S*)-oxiran-2-yl]dodecyl-4-methylbenzenesulfonate (22): Tosylate **21** (677 mg, 1.70 mmol) was dissolved in dry DMF (10 mL), and imidazole (289 mg, 4.25 mmol) and TBDMSCl (512 mg, 3.40 mmol) were added at 0 °C. The reaction mixture was stirred at room temp. overnight. Then the mixture was diluted with EtOAc, and brine was added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with $NaSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica (10% EtOAc in hexanes) to give product **22** (643 mg, 73%) as a clear oil. $[a]_D^{20}$ = –0.5 (*c* = 1.2, $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.79–7.75 (m, 2 H), 7.34–7.30 (m, 2 H), 3.90–3.76 (m, 3 H), 2.88 (m, 1 H), 2.72 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1 H), 2.43 (br. s, 3 H), 1.55–1.12 (m, 20 H), 0.82 (br. s, 9 H), 0.01 (br. s, 3 H), –0.004 (br. s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.6, 132.9, 129.7, 127.8, 73.1, 69.8, 52.2, 46.9, 33.9, 32.3, 29.45, 29.40, 29.37, 29.32, 25.8, 25.6, 24.6, 21.5, 17.9, –4.6, –4.9 ppm. IR: $\tilde{\nu}$ = 2927, 2858, 1365, 1180, 836, 779 cm^{-1}. HRMS: calcd. for $C_{27}H_{48}O_5SSi$ $[M + H]^+$ 513.3064; found 513.3050.

(*R*)-13-*tert*-Butyldimethylsilyloxy-14-iodo-(*S*)-1,2-epoxytetradecane (11): A concentrated reaction mixture of tosylate **22** (570 mg, 1.11 mmol) and NaI (250 mg, 1.66 mmol) in DMF (1 mL) was stirred overnight at 60 °C. Then the mixture was concentrated to dryness on a rotary evaporator, and the residue was purified by column chromatography on silica (5% EtOAc in hexanes) to give product **11** (429 mg, 82%) as a clear oil. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 3.53 (m, 1 H), 3.19 (m, 2 H), 2.90 (m, 1 H), 2.74 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1 H), 1.64–1.21 (m, 20 H), 0.90 (br. s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 71.4, 52.3, 47.1, 36.9, 32.4, 29.5 (overlapping signals), 29.4, 25.9, 25.8, 24.9, 18.0, 14.0, –4.3, –4.5 ppm. IR: $\tilde{\nu}$ = 2928, 2854, 1465, 1253, 1083, 836, 775 cm^{-1}. HRMS: calcd. for $C_{20}H_{41}IO_2Si$ $[M + H]^+$ 469.1993; found 469.1978.

(5*S*)-3-{(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-12-[(*S*)-oxiran-2-yl]-dodecyl}-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (7): *n*-Butyllithium (2.5 M; 308 μL, 0.77 mmol) was added to a cooled solution of *N*,*N*-diisopropylamine (108 μL, 0.77 mmol) in THF (0.5 mL) under an argon atmosphere, and the mixture was stirred for 30 min at 0 °C. The LDA solution was then transferred to lactone **12** (147 mg, 0.70 mmol) by cannula, and the resulting solution was stirred for a further 30 min at 0 °C. Then iodide **11** (301 mg, 0.64 mmol) was dissolved in HMPA (1.1 mL) and THF (0.5 mL), and this solution was added to the reaction mixture by cannula.

The reaction mixture was warmed to room temp. and stirred overnight. Then the solution was diluted with EtOAc, NH_4Cl (satd. aq.) was added, and the phases were separated. The organic phase was extracted three times with EtOAc, washed with brine, dried with $MgSO_4$ and filtered. After concentration in vacuo, the residue was purified by flash chromatography (6% EtOAc in petroleum ether) to give **7** (261 mg, 78%) as a colourless oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 2 H), 7.40–7.29 (m, 3 H), 4.58 (m, 0.3 H, minor isomer), 4.50 (m, 0.7 H, major isomer), 4.24 (m, 0.7 H, major), 3.84 (m, 0.3 H, minor), 3.03 (dd, J = 14.0, 7.6 Hz, 0.7 H), 2.89 (m, 1 H), 2.72 (m, 1 H), 2.44 (dd, J = 5.0, 2.7 Hz, 1 H), 2.09–1.79 (m, 3 H), 1.55–1.15 (m, 25 H), 0.88 (br. s, 9 H, major), 0.85 (br. s, 3 H, minor), 0.15 (br. s, 3 H), 0.11 (br. s, 3 H), 0.03 (br. s, 1 H, minor), 0.01 (br. s, 1 H, minor) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.4 (major), 175.0 (minor), 136.9, 136.6, 130.4 (minor), 129.8 (minor), 129.6 (minor), 129.5 (major), 128.9 (major), 128.8 (major), 73.5 (minor), 73.2 (major), 70.2 (minor), 69.4 (major), 55.4 (major), 55.0 (minor), 52.2, 47.0, 42.0 (minor), 41.6 (minor), 41.2 (major), 39.5 (major), 38.4 (major), 37.9 (minor), 32.4, 29.6 (major), 29.5 (minor), 29.4–29.3 (overlapping signals), 25.9–25.8 (overlapping signals), 24.3; 21.2 (major), 20.3 (minor), 17.9, –3.79 (minor), –3.87 (major), –4.16 (minor) ppm. IR: $\tilde{\nu}$ = 2927, 2854, 1762, 1253, 1184, 1002, 833, 775, 694 cm^{-1}. HRMS: calcd. for $C_{31}H_{52}O_4SSi$ [M + H]$^+$ 549.3428; found 549.3417.

(*S*)-3-{(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-12-[(*S*)-oxiran-2-yl]-dodecyl}-5-methylfuran-2(5*H*)-one (8): A solution of **7** (91 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) was cooled to –20 °C and *m*CPBA (41 mg, 0.18 mmol, >77% purity) was added. The reaction mixture was stirred at –20 °C for 1.5 h. Then the reaction was quenched with $Na_2S_2O_3$ (satd. aq.), and the mixture was allowed to warm to room temp. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (8% EtOAc in petroleum ether) to give **8** (64 mg, 88%) as a clear oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.11 (m, 1 H), 4.99 (m, 1 H), 3.93 (m, 1 H), 2.89 (m, 1 H), 2.72 (dd, J = 5.0, 4.0 Hz, 1 H), 2.45 (dd, J = 5.0, 2.7 Hz, 1 H), 2.41 (m, 2 H), 1.55–1.19 (m, 23 H), 0.86 (br. s, 9 H), 0.04 (br. s, 3 H), 0.01 (br. s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.9, 151.4, 130.8, 77.4, 70.1, 52.3, 47.0, 36.9, 32.7, 32.4, 29.6, 29.5, 29.49, 29.48, 29.46, 29.3, 25.9, 25.8, 25.1, 18.9, 18.0, –4.4 ppm. IR: $\tilde{\nu}$ = 2927, 2854, 1755, 1462, 1319, 1253, 1072, 833, 775 cm^{-1}. HRMS: calcd. for $C_{25}H_{46}O_4Si$ [M + H]$^+$ 439.3238; found 439.3228.

(5*S*)-3-{(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]tetradec-13-en-1-yl}-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (18):[42] A mixture of diol **20** (400 mg, 1.75 mmol), Bu_2SnO (17 mg, 0.07 mmol), Et_3N (244 μL, 1.75 mmol), and *p*TsCl (334 mg, 1.75 mmol) was stirred at room temp. overnight. Then the mixture was diluted with EtOAc and filtered, and brine was added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. Then the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo to dryness. The crude tosylate (637 mg, 95%) was used in the next step without further purification.

The tosylate (604 mg, 1.57 mmol) was dissolved in dry DMF (2.5 mL), and imidazole (268 mg, 3.94 mmol) and TBDMSCl (261 mg, 1.73 mmol) were added. The reaction mixture was stirred at room temp. for 5.5 h. Then EtOAc and brine were added, the phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography (5% EtOAc in petroleum ether) to give the silylated product (644 mg, 82%).

The silylated compound (580 mg, 1.16 mmol) and NaI (874 mg, 5.83 mmol) were added to acetone (3 mL), and the mixture was heated at 65 °C overnight. Then the reaction mixture was cooled to room temp., and EtOAc and brine were added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography (3% EtOAc in petroleum ether) to give the iodated product (458 mg, 86%).

LDA (1.5 M; 323 μL, 0.58 mmol) was added to a cooled solution of lactone **12** (121 mg, 0.58 mmol) in THF (2 mL) under an argon atmosphere, and the mixture was stirred at 0 °C. Then the iodated compound (240 mg, 0.53 mmol) in HMPA (510 μL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred overnight at room temp. Then EtOAc and NH_4Cl (satd. aq.) were added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography on silica (3% EtOAc in petroleum ether) to give alkylated product **18** (210 mg, 74%) as an inseparable mixture of diastereomers. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2 H), 7.40–7.30 (m, 3 H), 5.81 (m, 1 H), 4.96 (m, 2 H), 4.60 (m, 0.3 H), 4.51 (m, 0.7 H), 4.25 (m, 0.7 H), 3.85 (m, 0.7 H), 3.04 (dd, J = 14.0, 7.6 Hz, 0.7 H), 2.08–1.80 (m, 5 H), 1.49–1.18 (m, 21 H), 0.90 (br. s, 5 H), 0.87 (br. s, 4 H), 0.15 (br. s, 2 H), 0.12 (br. s, 2 H), 0.03 (br. s, 1 H), 0.01 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 175.0, 139.1, 137.0, 136.6, 129.5, 128.9, 128.8, 114.0, 73.6, 73.2, 70.2, 69.4, 55.4, 42.0, 41.1, 39.4, 38.5, 33.7, 29.7, 29.5–29.4, 29.1, 28.8, 25.9, 25.9, 24.4, 21.3, 17.9, –3.8, –3.9 ppm. IR: $\tilde{\nu}$ = 2927, 2854, 1762, 1462, 1438, 1253, 1180, 837, 775, 748, 690 cm^{-1}. The analytical data is in agreement with that reported in the literature.[42]

(5*S*)-3-{(2*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13,14-dihydroxytetradecyl}-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (23): Compound **18** (531 mg, 0.99 mmol) was added to a cooled (0 °C) mixture of $K_2OsO_2(OH)_4$ (1.5 mg, 0.004 mmol), $(DHQD)_2PHAL$ (15 mg, 0.02 mmol), $K_3[Fe(CN)_6]$ (984 mg, 2.99 mmol), and K_2CO_3 (441 mg, 3.19 mmol) in *t*BuOH/H_2O (1:1, 20 mL). The reaction mixture was stirred at 4 °C overnight. Solid $Na_2S_2O_3{\cdot}5H_2O$ was added, and then the mixture was stirred for a further 1 h. Then the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to dryness. Diol **23** (560 mg, 99% crude yield) was used in the next step without further purification. Compound **23** is a 1:3 mixture of diastereomers, the signals of the major diastereomer are given: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 2 H), 7.25–9.19 (m, 3 H), 4.41 (m, 1 H), 4.14 (m, 1 H), 3.59–3.50 (m, 2 H), 3.48 (dd, J = 11.2, 2.6 Hz, 1 H), 3.27 (dd, J = 11.2, 7.7 Hz, 1 H), 2.93 (dd, J = 14.0, 7.7 Hz, 1 H), 1.98–1.68 (m, 3 H), 1.39–1.05 (m, 23 H), 0.79 (br. s, 6 H), 0.75 (br. s, 3 H), 0.04 (br. s, 3 H), 0.01 (br. s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 136.4, 130.1, 129.4, 128.8, 73.2, 72.0, 69.2, 66.5, 55.2, 41.0, 39.2, 38.3, 32.9, 30.9, 29.5–29.2, 25.8–25.7, 25.4, 24.2, 21.1, 17.8, –3.9 ppm. IR: $\tilde{\nu}$ = 3367, 2924, 2854, 1766, 1462, 1253, 1184, 1064, 1006, 833, 775, 748, 690 cm^{-1}. HRMS: calcd. for $C_{31}H_{54}O_5SSi$ [M + H]$^+$ 567.3534; found 567.3536.

(5*S*)-3-{(*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-12-[(*R*)-oxiran-2-yl]-dodecyl}-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (16):

Bu_2SnO (10 mg, 0.04 mmol), Et_3N (146 μL, 1.05 mmol), and *p*TsCl (200 mg, 1.05 mmol) were added to a solution of **23** (560 mg, 0.99 mmol) in CH_2Cl_2 (9 mL), and the mixture was stirred overnight at room temp. Then the mixture was filtered, and CH_2Cl_2 and brine were added. The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography (10–15% EtOAc in petroleum ether) to give the tosylated product (681 mg, 94%) as a beige oil.

K_2CO_3 (275 mg, 1.99 mmol) was added to a cooled (0 °C) solution of the tosylated compound (681 mg, 0.94 mmol) in MeOH (15 mL). The reaction mixture was stirred for 10 h, and HCl (1 M) was then added until neutral pH was reached. The mixture was diluted with EtOAc, and $NaHCO_3$ (satd. aq.) was added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography (5% EtOAc in petroleum ether) to give product **16** (403 mg, 73% over three steps from **23**) as a beige oil.

(*S*)-1-[(2-Aminoethyl)amino]dodecan-2-ol (24):[26] A solution of epoxide (*S*)-**9** (105 mg, 0.57 mmol) and ethylene-1,2-diamine (196 mg, 3.25 mmol) in EtOH (10 mL) was stirred at 50 °C for 4 h. Then the reaction mixture was diluted with CH_2Cl_2, and brine was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo to dryness. The residue was purified by flash chromatography on silica (10:2:0.5 of $CHCl_3$/MeOH/NH_4OH) to give **24** (137 mg, 99%). ^{1}H NMR (400.1 MHz, $CDCl_3$, CD_3OD): δ = 3.39 (m, 1 H), 2.56–2.33 (m, 7 H), 2.23 (dd, *J* = 12.0, 9.2 Hz, 1 H), 1.23–0.93 (m, 18 H), 0.61 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, CD_3OD): δ = 70.2, 55.6, 51.7, 41.1, 35.8, 32.3, 30.1, 30.0 (overlapping signals), 29.7, 26.0, 23.0, 14.2 ppm. IR: $\tilde{\nu}$ = 3113, 2916, 2846, 1465, 1114, 925, 837 cm^{-1}. HRMS: calcd. for $C_{14}H_{32}N_2O$ $[M + H]^+$ 245.2587; found 245.2581.

(*S*)-3-{(2*R*,13*S*)-2,13-Dihydroxy-14-[(2-{[(*S*)-2-hydroxydodecyl]-amino}ethyl)amino]tetradecyl}-5-methylfuran-2(5*H*)-one (1): A mixture of epoxide **8** (36 mg, 82 μmol), amine **24** (40 mg, 164 μmol), and $La(OTf)_3$ hydrate (5 mg, 8.5 μmol) in *i*PrOH (0.7 mL) was stirred at 40 °C for 2 d, and the reaction was monitored by TLC analysis. Then the mixture was concentrated to dryness in vacuo, and the residue was purified by flash chromatography (5–10% MeOH in CH_2Cl_2) to give the coupled product as a clear oil (37 mg, 65%).

The product (20 mg, 30 μmol) was then dissolved in MeOH (1 mL), and AcCl (22 μL, 300 μmol) was added. The reaction mixture was stirred overnight, and then excess $NaHCO_3$ was added. The mixture was filtered through a Celite plug, and the filtrate was concentrated to dryness in vacuo. The residue was purified by flash chromatography on silica (10–30% MeOH in CH_2Cl_2) to give **1** (12 mg, 73%) as a beige waxy solid. ^{1}H NMR (400.1 MHz, $CDCl_3$, CD_3OD): δ = 6.96 (m, 1 H), 4.74 (m, 1 H), 3.52–3.40 (m, 2 H), 3.33 (m, 1 H), 2.90–2.49 (m, 6 H), 2.15–1.95 (m, 2 H), 1.17–0.86 (m, 41 H), 0.53 (vt, 3 H) ppm. ^{13}C NMR (201.2 MHz, $CDCl_3$): δ = 174.9, 152.0, 130.9, 78.2, 70.5, 69.9, 69.9, 51.4, 44.9, 37.3, 34.8, 33.3, 31.9, 29.6–29.3, 25.6, 25.4, 22.6, 19.0, 14.1 ppm. IR: $\tilde{\nu}$ = 3329, 2920, 2850, 1747, 1458, 1080, 1026 cm^{-1}. HRMS: calcd. for $C_{33}H_{64}N_2O_5$ $[M + H]^+$ 569.4888; found 569.4875.

(*S*)-*N*-(2-Hydroxydodecyl)-2-nitrobenzenesulfonamide (25): A solution of epoxide (*S*)-**9** (369 mg, 2.0 mmol), 2-nitrobenzenesulfonamide (809 mg, 4.0 mmol), TEBA (46 mg, 0.2 mmol), and K_2CO_3 (28 mg, 0.2 mmol) in 1,4-dioxane (1.0 mL) was heated at 90 °C for 20 h. The mixture was then cooled to room temperature, diluted with CH_2Cl_2, and washed with brine. The organic phase was dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica (2% MeOH in CH_2Cl_2) to give **25** (724 mg, 94%) as a yellow waxy solid, m.p. 56.5–57.9 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 8.13 (m, 1 H), 7.87 (m, 1 H), 7.75–7.68 (m, 2 H), 5.74 (dd, *J* = 7.1, 5.0 Hz, 1 H), 3.74 (m, 1 H), 3.24 (ddd, *J* = 12.9, 7.1, 3.2 Hz, 1 H), 2.94 (ddd, *J* = 12.9, 8.0, 5.0 Hz, 1 H), 1.88 (br. s, 1 H), 1.46–1.20 (m, 18 H), 0.88 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 148.1, 133.60, 133.59, 132.7, 131.1, 125.4, 70.4, 49.2, 34.7, 31.9, 29.56, 29.53, 29.46, 29.44, 29.3, 25.3, 22.7, 14.1 ppm. IR: $\tilde{\nu}$ = 3540, 3350, 2930, 2857, 1545, 1367, 1168 cm^{-1}. HRMS: calcd. for $C_{18}H_{30}N_2O_5S$ $[M + Na]^+$ 409.1768; found 409.1762.

***N*-{(2*S*,13*R*)-13-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-14-[(5*S*)-5-methyl-2-oxo-3-(phenylthio)tetrahydrofuran-3-yl]tetradecyl}-*N*-[(*S*)-2-hydroxydodecyl]-2-nitrobenzenesulfonamide (26):** K_2CO_3 (23 mg, 166 μmol) was added to a solution of nosylamide **25** (51 mg, 133 μmol) and epoxide **7** (36 mg, 66 μmol) in 1,4-dioxane (0.4 mL), and the reaction mixture was stirred at 90 °C for 12 d. Then the mixture was concentrated to dryness in vacuo. The residue was purified by flash chromatography on silica (50% EtOAc in petroleum ether) to give product **26** (28 mg, 45%) as a beige oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.97 (m, 1 H), 7.76–7.66 (m, 2 H), 7.62 (m, 1 H), 7.59–7.50 (m, 2 H), 7.41–7.29 (m, 3 H), 4.60 (m, 0.2 H, minor isomer), 4.51 (m, 0.8 H, major isomer), 4.24 (m, 0.8 H), 4.03–3.92 (m, 2 H), 3.65–3.55 (m, 2 H), 3.09–2.97 (m, 3 H), 2.11–1.79 (m, 3 H), 1.49–1.16 (m, 41 H), 0.89 (br. s, 7 H), 0.86 (m, 5 H), 0.15 (br. s, 2 H), 0.11 (br. s, 2 H), –0.03 (br. s, 1 H), –0.02 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.6, 175.1 (minor), 148.4, 137.0, 136.6, 133.7, 132.1, 131.6, 130.7, 130.4, 129.9, 129.6 (minor), 129.5, 128.96, 128.91, 124.2, 73.6 (minor), 73.3, 71.64, 71.63, 70.3 (minor), 70.2, 69.5, 57.4, 55.4, 55.0 (minor), 42.4 (minor), 41.7 (minor), 41.2, 39.5, 38.5, 37.9 (minor), 34.7, 34.6 (minor), 31.8, 29.7, 29.6, 29.5–29.4 (overlapping signals), 29.2, 25.99, 25.97, 25.3, 25.2, 24.4, 22.6, 21.3, 20.3 (minor), 18.0, 14.0, –3.7 (minor), –3.8, –4.1 (minor) ppm. IR: $\tilde{\nu}$ = 3344, 2924, 2854, 1762, 1543, 1350, 1165, 1002, 833 cm^{-1}. HRMS: calcd. for $C_{49}H_{82}N_2O_9S_2Si$ $[M + H]^+$ 935.5303; found 935.5302.

(5*S*)-3-((2*R*,13*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-hydroxy-14-{[(*S*)-2-hydroxydodecyl]amino}tetradecyl)-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (27): 1-Decanethiol (32 μL, 149 μmol) and DBU (23 μL, 149 μmol) were added to a solution of **26** (27 mg, 29 μmol) in DMF (0.4 mL). The reaction mixture was stirred overnight, then it was diluted with EtOAc, and brine was added. The phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated to dryness in vacuo. The residue was purified by flash chromatoghraphy on silica (3% MeOH in CH_2Cl_2) to give **27** (21 mg, 95%) as a yellow oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2 H), 7.39–7.30 (m, 3 H), 5.24 (br. s, 3 H), 4.60 (m, 0.2 H), 4.51 (m, 0.8 H), 4.25 (m, 0.8 H), 4.04–3.88 (m, 2 H), 3.04 (dd, *J* = 14.2, 7.7 Hz, 1 H), 3.00–2.71 (m, 4 H), 2.14–1.78 (m, 3 H), 1.56–1.14 (m, 41 H), 0.89 (br. s, 7 H), 0.86 (vt, 5 H), 0.15 (br. s, 2 H), 0.11 (br. s, 2 H), 0.03 (br. s, 1 H), 0.02 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.6, 175.1 (minor), 137.0, 136.6, 130.4, 129.6, 128.9, 73.6 (minor), 73.3, 70.2 (minor), 69.5, 67.8, 55.5, 54.5, 54.4, 41.1, 39.4, 38.5, 35.0, 31.9, 29.8–29.5, 29.3, 25.9, 25.4, 24.4, 22.7, 21.3, 18.0, 14.1, –3.8 ppm. IR: $\tilde{\nu}$ = 3357, 2911, 2849, 1762, 1462, 1439, 1379, 1341, 1253, 1182, 1020, 845, 760, 752 cm^{-1}. HRMS: calcd. for $C_{43}H_{79}NO_5SSi$ $[M + H]^+$ 750.5521; found 750.5517.

(*S*)-3-((2*R*,13*S*)-2,13-Dihydroxy-14-{[(*S*)-2-hydroxydodecyl]-amino}tetradecyl)-5-methylfuran-2(5*H*)-one (2): Compound **27** (29 mg, 39 μmol) was dissolved in CH_2Cl_2 (2.5 mL), and $MeSO_3H$ (5 μL, 77 μmol) was added. The mixture was stirred for 20 min, and then it was concentrated to dryness in vacuo. The residue was redissolved in CH_2Cl_2 (2 mL), the solution was cooled to –20 °C, and a solution of *m*CPBA (11 mg, 47 μmol, >77% purity) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred for 1.5 h at –20 °C, then it was quenched with $Na_2S_2O_3$ (20% aq.; 5 mL). The mixture was brought to room temp. and stirred for a further 15 min. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was then redissolved in toluene (2 mL) and heated at reflux for 3.5 h. Then the reaction mixture was brought to room temperature and concentrated to dryness. The residue was purified by flash chromatography (3–10% MeOH in CH_2Cl_2) to give the unsaturated product (12 mg) as a beige oil, and final product **2** (13 mg, 63%). Data for **2**: ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.19 (m, 1 H), 5.06 (m, 0.3 H), 4.95 (m, 0.7 H), 4.13–3.96 (m, 2 H), 3.84 (m, 0.7 H), 3.16–2.87 (m, 4 H), 2.56–2.37 (m, 2 H), 1.53–1.11 (m, 38 H), 0.87 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.7, 151.9, 151.0, 131.2, 128.2, 81.8, 78.0, 70.5, 69.9, 68.5, 67.0, 54.7, 37.4, 34.9, 33.3, 31.9, 29.6–29.3, 25.4, 25.3, 24.9, 23.3, 22.6, 19.0, 14.1 ppm. IR: $\tilde{\nu}$ = 3352, 2909, 2847, 1742, 1462, 1211, 1041, 753 cm^{-1}. HRMS: calcd. for $C_{31}H_{59}NO_5$ $[M + H]^+$ 526.4466; found 526.4467.

(*R*)-1-{Methyl[2-(methylamino)ethyl]amino}dodecan-2-ol (28): Epoxide (*R*)-**9** (306 mg, 1.66 mmol) was dissolved in *i*PrOH (0.5 mL), and *N*,*N*′-dimethylethylene-1,2-diamine (900 μL, 8.30 mmol) was added. The reaction mixture was warmed to 40 °C, and stirred for 18 h. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give product **28** (295 mg, 65%) as a colourless waxy substance. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.61 (m, 1 H), 2.83 (br. s, 2 H), 2.72–2.58 (m, 3 H), 2.46 (m, 1 H), 2.42 (br. s, 3 H), 2.28 (m, 1 H), 2.26 (br. s, 3 H), 1.50–1.16 (m, 18 H), 0.85 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 67.5, 63.8, 56.9, 49.3, 42.8, 36.1, 34.8, 31.8, 29.7, 29.5, 29.2, 25.6, 22.6, 14.0 ppm. IR: $\tilde{\nu}$ = 3410, 2920, 2850, 2796, 1462, 1361, 1303, 1064, 1045, 1022, 960, 867, 779 cm^{-1}. HRMS: calcd. for $C_{16}H_{36}N_2O$ $[M + H]^+$ 273.2900; found 273.2900.

(5*S*)-3-{(2*R*,13*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-hydroxy-14-[(2-{[(*R*)-2-hydroxydodecyl](methyl)amino}ethyl)(methyl)amino]-tetradecyl}-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (29): Epoxide **16** (74 mg, 136 μmol) and amine **28** (44 mg, 163 μmol) were dissolved in *i*PrOH (0.3 mL), and the mixture was heated at 50 °C for 4 d. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give product **29** (73 mg, 65%) as a beige oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.59–7.51 (m, 2 H), 7.40–7.29 (m, 3 H), 4.59 (m, 0.3 H), 4.51 (m, 1 H), 4.24 (m, 1 H), 3.72–3.60 (m, 2 H), 3.03 (dd, *J* = 13.9, 7.6 Hz,1 H), 2.75–2.64 (m, 2 H), 2.42–2.24 (m, 10 H), 2.09–1.78 (m, 3 H), 1.51–1.06 (m, 41 H), 0.89 (br. s, 7 H), 0.87–0.83 (m, 5 H), 0.14 (br. s, 2 H), 0.10 (br. s, 2 H), 0.02 (m, 1 H), 0.01 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 175.0 (minor isomer), 136.9, 136.6, 129.5, 128.9, 128.8, 73.6 (minor), 73.2, 70.2 (minor), 69.4, 68.0 (minor), 67.8, 63.3, 55.3, 54.5, 43.6, 42.8, 42.4, 41.1, 39.4, 38.5, 34.7, 31.8, 29.7–29.4, 29.2, 25.9–25.9, 25.6, 24.4, 22.6, 21.2, 17.9, 14.0, –3.8 ppm. IR: $\tilde{\nu}$ = 3402, 2922, 2851, 1764, 1462, 1250, 1180, 1061, 833, 773 cm^{-1}. HRMS: calcd. for $C_{47}H_{88}N_2O_5SSi$ $[M + H]^+$ 822.6289; found 822.6272.

(*S*)-3-{(2*R*,13*R*)-2,13-Dihydroxy-14-[(2-{[(*R*)-2-hydroxydodecyl]-(methyl)amino}ethyl)(methyl)amino]tetradecyl}-5-methylfuran-2(5*H*)-one (3): $MeSO_3H$ (10 μL, 154 μmol) was added to a solution of **29** (43 mg, 52 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 15 min, then it was concentrated to dryness in vacuo. The residue was redissolved in CH_2Cl_2 (1.5 mL), the solution was cooled to –20 °C, and a solution of *m*CPBA (14 mg, 63 μmol, >77 purity) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred for 2 h at –20 °C, then it was quenched with $Na_2S_2O_3$ (20% aq.). The mixture was brought to room temp. and stirred for a further 15 min. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was then redissolved in toluene (1.5 mL) and heated at reflux for 4 h. Then the reaction mixture was brought to room temp. and concentrated to dryness. The residue was purified by flash chromatography (5–10% MeOH in CH_2Cl_2) to give the product with an α,β-unsaturated lactone ring and an intact silyl group (26 mg), and also final product **3** (6 mg). The silyl-ether-bearing compound (26 mg, 37 μmol) was dissolved in MeOH (1.5 mL), and AcCl (20 μL, 281 μmol) in MeOH (1.0 mL) was added. The mixture was stirred for 16 h under argon. The reaction was quenched by the addition of solid $NaHCO_3$, then the mixture was filtered, and the filtrate was concentrated to dryness in vacuo. The residue was purified by flash chromatography (2–10% MeOH in CH_2Cl_2) to give **3** (combined yield: 27 mg, 87%) as a beige oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.16 (m, 1 H), 4.98 (m, 0.4 H), 4.88 (m, 0.6 H), 3.93 (m, 0.7 H), 3.81–3.72 (m, 2 H), 3.11–2.84 (m, 4 H), 2.76–2.63 (m, 4 H), 2.60 (br. s, 6 H), 2.35 (m, 1 H), 1.44–1.06 (m, 43 H), 0.78 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.0, 152.2, 151.2, 130.7, 81.9, 78.1, 69.3, 66.6, 65.5, 62.2, 61.9, 52.8, 42.1, 41.7, 37.0, 34.4, 33.1, 32.7, 31.7, 29.4–29.0, 25.3, 25.2, 25.1, 24.7, 22.7, 22.4, 18.6, 13.8 ppm. IR: $\tilde{\nu}$ = 3387, 2924, 2854, 1747, 1458, 1199, 1072 cm^{-1}. HRMS: calcd. for $C_{35}H_{68}N_2O_5$ $[M + H]^+$ 597.5201; found 597.5195.

(*R*)-1-(Methylamino)dodecan-2-ol (30): A solution of epoxide (*R*)-**9** (273 mg, 1.48 mmol) and methylamine (8 M in EtOH; 930 μL, 7.44 mmol) was heated at 50 °C for 9 h. Then the mixture was concentated in vacuo, and the residue was purified by flash chromatography (10% MeOH in CH_2Cl_2) to give product **30** (209 mg, 65%) as a white solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.63–3.50 (m, 3 H), 2.53 (d, *J* = 11.9, 3.2 Hz, 1 H), 2.41 (d, *J* = 11.9, 9.2 Hz, 1 H), 2.35 (br. s, 3 H), 1.43–1.10 (m, 18 H), 0.79 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 68.9, 68.8, 57.4, 35.8, 35.2, 31.7, 29.6, 29.4, 29.1, 25.6, 22.5, 13.9 ppm. IR: $\tilde{\nu}$ = 3417, 3286, 2916, 2846, 1469, 910, 891, 864, 717 cm^{-1}. HRMS: calcd. for $C_{13}H_{29}NO$ $[M + H]^+$ 216.2321; found 216.2320.

(5*S*)-3-((2*R*,13*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-hydroxy-14-{[(*R*)-2-hydroxydodecyl](methyl)amino}tetradecyl)-5-methyl-3-(phenylthio)dihydrofuran-2(3*H*)-one (31): A solution of epoxide **16** (100 mg, 182 μmol) and amine **30** (109 mg, 506 μmol) in *i*PrOH (2 mL) was heated at 50 °C for 19 h. Then the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (2% MeOH in petroleum ether) to give product **31** (128 mg, 92%) as a beige oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 2 H), 7.42–7.29 (m, 3 H), 4.60 (m, 0.2 H), 4.51 (m, 0.8 H), 4.25 (m, 0.8 H), 3.73–3.62 (m, 2 H), 3.04 (dd, *J* = 14.1, 7.6 Hz, 0.8 H), 2.84 (br. s, 2 H), 2.48–2.25 (m, 8 H), 2.09–1.78 (m, 3 H), 1.50–1.17 (m, 41 H), 0.89 (br. s, 7 H), 0.87–0.84 (m, 5 H, overlap), 0.14 (br. s, 2 H), 0.11 (br. s, 2 H), 0.04–0.01 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.5, 175.1 (minor isomer), 137.0, 136.6, 130.3, 129.5, 128.9, 128.8, 73.6, 73.3, 70.2, 69.4, 68.0, 67.5, 65.4, 63.8, 55.4, 55.0, 43.6, 42.3, 41.8, 41.6, 41.1, 39.4,

38.5, 37.9, 34.9, 34.9, 31.8, 29.7, 29.5–29.4, 29.3, 25.9, 25.6, 25.5, 24.4, 22.6, 21.3, 17.9, 14.0, –3.8 ppm. IR: $\tilde{\nu}$ = 3410, 2924, 2854, 1766, 1462, 1253, 1184, 1053, 1006, 833, 775 cm^{-1}. HRMS: calcd. for $C_{44}H_{81}NO_5SSi$ $[M + H]^+$ 764.5677; found 764.5672.

(*S*)-3-((2*R*,13*R*)-2,13-Dihydroxy-14-{[(*R*)-2-hydroxydodecyl]-(methyl)amino}tetradecyl)-5-methylfuran-2(5*H*)-one (4): $MeSO_3H$ (8 μL, 120 μmol) was added to a solution of amine **31** (51 mg, 67 μmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 15 min, and then it was concentrated to dryness in vacuo. Then the solid was redissolved in CH_2Cl_2 (2.0 mL), the solution was cooled to –20 °C, and a solution of *m*CPBA (18 mg, 81 μmol, >77% purity) in CH_2Cl_2 (1.0 mL) was added. The reaction mixture was stirred 30 min at –20 °C, and then it was quenched with $Na_2S_2O_3$ (20% aq.). The mixture was brought to room temp. and stirred for a further 15 min. The phases were separated, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was then redissolved in toluene (4.0 mL) and heated at reflux for 2 h. Then the reaction mixture was brought to room temp. and concentrated to dryness. The residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give the unsaturated product still containing a silyl ether (20 mg), and also final product **4** (9 mg). The silyl-ether-bearing compound (20 mg, 31 μmol) was dissolved in MeOH (1 mL), and AcCl (11 μL, 155 μmol) was added. The mixture was stirred for 12 h under argon. The reaction was quenched by the addition of solid $NaHCO_3$, then the mixture was filtered, and the filtrate was concentrated to dryness in vacuo. The residue was purified by flash chromatography (10% MeOH in CH_2Cl_2) to give **4** (13 mg; combined yield: 22 mg, 60%) as a beige oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.18 (m, 1 H), 5.05 (m, 0.3 H), 4.95 (m, 0.7 H), 4.06 (m, 1 H), 3.92–3.79 (m, 2 H), 2.85–2.35 (m, 7 H), 1.53–1.17 (m, 41 H), 0.87 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.6, 174.6, 151.8, 150.9, 131.2, 131.1, 81.8, 77.9, 69.9, 67.0, 66.7, 66.1, 65.3, 64.1, 43.5, 37.3, 35.0–34.8, 33.3, 33.3, 31.8, 30.9, 29.6–29.1, 25.5–25.4, 24.8, 23.3, 22.6, 19.0, 14.0 ppm. IR: $\tilde{\nu}$ = 3363, 2924, 2854, 1751, 1458, 1373, 1056, 732 cm^{-1}. HRMS: calcd. for $C_{32}H_{61}NO_5$ $[M + H]^+$ 540.4622; found 540.4605.

(*S*)-1-[(2-Mercaptoethyl)thio]dodecan-2-ol (32): $InCl_3$ (43 mg, 0.19 mmol) and 1,2-ethanedithiol (822 μL, 9.77 mmol) were added to a solution of epoxide (*S*)-**9** (360 mg, 1.95 mmol) in *i*PrOH (1.5 mL). The reaction mixture was stirred for 1 h, then after TLC indicated that the epoxide had been consumed the mixture was concentrated to dryness in vacuo. The residue was purified by flash chromatography (2% EtOAc in petroleum ether) to give **32** (334 mg, 61%) as a white solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.62 (m, 1 H), 2.79–2.66 (m, 5 H), 2.54 (br. s, 1 H), 2.41 (dd, *J* = 13.6, 8.7 Hz, 1 H), 1.52–1.17 (m, 18 H), 0.85 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 69.6, 40.0, 36.2, 36.1, 31.8, 29.5, 29.5–29.4, 29.2, 28.6 25.6, 24.7, 22.5, 14.0 ppm. IR: $\tilde{\nu}$ = 3360, 2916, 2850, 1465, 1087, 1049, 721 cm^{-1}. HRMS: calcd. $C_{14}H_{30}OS_2$ $[M + Na]^+$ 301.1630; found 301.1626 ppm.

(*S*)-3-{(2*R*,13*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-hydroxy-14-[(2-{[(*S*)-2-hydroxydodecyl]thio}ethyl)thio]tetradecyl}-5-methylfuran-2(5*H*)-one (33): A mixture of epoxide **8** (41 mg, 94 μmol), sulfide **32** (52 mg, 189 μmol), and $InCl_3$ (2 mg, 9.4 μmol) in *i*PrOH (0.5 mL) was stirred at room temp. for 21 h, and then the mixture was concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc in petroleum ether) to give product **33** (39 mg, 58%) as a clear oil. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.11 (m, 1 H), 4.99 (m, 1 H), 3.94 (m, 1 H), 3.70–3.61 (m, 2 H), 2.79–2.72 (dd, *J* = 13.7, 3.4 Hz, 2 H), 2.76 (br. s, 4 H), 2.48 (dd, *J* = 13.7, 8.8 Hz, 2 H), 2.41 (m, 2 H), 1.53–1.19 (m, 48 H), 0.89–0.83 (m, 12 H), 0.04 (br. s, 3 H), 0.01 (br. s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.9, 151.4, 130.8, 77.4, 70.2, 69.7, 40.3, 36.9, 36.2, 32.7, 32.6, 31.8, 29.6, 29.59–29.51, 29.2, 25.8, 25.7, 25.1, 22.6, 18.9, 18.0, 14.0, –4.4 ppm. HRMS: calcd. for $C_{39}H_{76}O_5S_2Si$ $[M + H]^+$ 717.4976; found 717.4971.

(*S*)-3-{(2*R*,13*S*)-2,13-Dihydroxy-14-[(2-{[(*S*)-2-hydroxydodecyl]-thio}ethyl)thio]tetradecyl}-5-methylfuran-2(5*H*)-one (5): Compound **33** (33 mg, 46 μmol) was dissolved in MeOH (0.3 mL), and AcCl (33 μL, 464 μmol) in MeOH (0.2 mL) was added at room temp. under an argon atmosphere. The mixture was stirred for 50 min, and the reaction progress was monitored by TLC analysis. When the starting material had been consumed, solid $NaHCO_3$ was added, and after stirring for 5 min, the mixture was filtered through a silica plug. The filtrate was concentrated in vacuo to dryness. The residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give **5** (24 mg, 89%) as a white solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.18 (m, 1 H), 5.06 (qd, *J* = 6.8, 1.4 Hz, 1 H), 3.84 (m, 1 H), 3.65 (m, 2 H), 2.77 (m, 5 H), 2.57–2.32 (m, 5 H), 1.53–1.39 (m, 6 H), 1.43 (d, *J* = 6.8 Hz, 3 H), 1.36–1.22 (m, 32 H), 0.87 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.6, 151.8, 131.2, 77.9, 70.0, 69.7, 69.7, 40.3, 37.3, 36.3, 33.3, 32.5, 31.9, 29.6–29.3, 25.7, 25.5, 22.6, 19.1, 14.1 ppm. IR: $\tilde{\nu}$ = 3421, 2916, 2850, 1739, 1465, 1323, 1199, 1080, 1026, 721 cm^{-1}. HRMS: calcd. for $C_{33}H_{62}O_5S_2$ $[M + H]^+$ 603.4111; found 603.4113.

(*S*)-1-({2-[(2-Mercaptoethyl)thio]ethyl}thio)dodecan-2-ol (34): 2,2′-Thiodiethanethiol (332 μL, 2.54 mmol) was added to a solution of epoxide (*S*)-**9** (156 mg, 0.84 mmol) and $InCl_3$ (18 mg, 84 μmol) in *i*PrOH (2 mL), and the mixture was stirred at room temp. for 1.5 d. Then the mixture was concentrated in vacuo, and the residue was purified by flash chromatography (5% EtOAc in petroleum ether) to give **34** (153 mg, 53%) as an opaque waxy solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.64 (m, 1 H), 2.82–2.67 (m, 9 H), 2.48 (dd, *J* = 13.6, 8.6 Hz, 1 H), 2.38 (br. s, 1 H), 1.72 (m, 1 H), 1.54–1.18 (m, 18 H), 0.86 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 69.6, 40.3, 36.2, 32.5, 32.2, 31.8, 29.56, 29.54, 29.53, 29.50, 29.2, 25.6, 24.7, 22.6, 14.0 ppm. IR: $\tilde{\nu}$ = 3433, 2916, 2846, 1465, 1423, 1199, 1087, 1049, 721, 678 cm^{-1}. HRMS: calcd. for $C_{16}H_{34}OS_3$ $[M + H]^+$ 339.1844; found 339.1838.

(*S*)-3-[(2*R*,13*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-hydroxy-14-({2-[(2-{[(*S*)-2-hydroxydodecyl]thio}ethyl)thio]ethyl}thio)tetradecyl]-5-methylfuran-2(5*H*)-one (35): Sulfide **34** (32 mg, 95 μmol) was added to a solution of **8** (27 mg, 63 μmol) and $InCl_3$ (2 mg, 12 μmol) in CH_2Cl_2 (0.6 mL), and the mixture was stirred overnight at room temp. Then the mixture was concentrated in vacuo, and the residue was purified by flash chromatography (20% EtOAc in petroleum ether) to give **35** (33 mg, 68%) as an opaque waxy solid. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.12 (m, 1 H, major isomer), 7.10 (m, 0.06 H, minor isomer), 5.00 (m, 1 H), 3.94 (m, 1 H), 3.70–3.61 (m, 2 H), 2.80–2.73 (m, 10 H), 2.50 (dd, *J* = 13.6, 8.6 Hz, 2 H), 2.42 (m, 2 H), 1.53–1.19 (m, 52 H), 0.90–0.83 (m, 14 H), 0.05 (br. s, 3 H), 0.02 (br. s, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.0, 151.4, 130.8, 77.4, 70.2, 69.8, 40.3, 36.9, 36.3, 32.7, 32.5, 32.4, 31.8, 29.69, 29.62–29.5 (overlapping signals), 29.3, 25.8, 25.7, 25.1, 22.6, 18.9, 18.0, 14.0, –4.44, –4.45 ppm. IR: $\tilde{\nu}$ = 3448, 2924, 2854, 1751, 1462, 1253, 1076, 1026, 837, 775 cm^{-1}. HRMS: calcd. for $C_{41}H_{80}O_5S_3Si$ $[M + H]^+$ 777.5009; found 777.5016.

(*S*)-3-[(2*R*,13*S*)-2,13-Dihydroxy-14-({2-[(2-{[(*S*)-2-hydroxydodecyl]thio}ethyl)thio]ethyl}thio)tetradecyl]-5-methylfuran-2(5*H*)-one (6): Compound **35** (18 mg, 23 μmol) was dissolved in MeOH (1 mL), and AcCl (16 μL, 0.23 mmol) was added. The mixture was

stirred overnight at room temp. Solid $NaHCO_3$ was added, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give **6** (12 mg, 77%) as a white solid. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.17 (m, 1 H), 5.05 (m, 1 H), 3.84 (m, 1 H), 3.70–3.60 (m, 2 H), 2.79–2.73 (m, 10 H), 2.53–2.45 (m, 2 H), 2.27 (br. s, 3 H), 1.54–1.20 (m, 43 H), 0.87 (vt, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.5, 151.7, 131.2, 77.9, 69.9, 69.83, 69.82, 40.3, 37.4, 36.3, 36.2, 33.3, 32.5, 32.4, 31.8, 29.6, 29.59, 29.58, 29.55, 29.49, 29.48, 29.46, 29.3, 25.7, 25.6, 25.5, 22.6, 19.1, 14.0 ppm. IR: $\tilde{\nu}$ = 3425, 2916, 2846, 1739, 1465, 1423, 1319, 1195, 1083, 1029, 736, 721 cm^{-1}. HRMS: calcd. for $C_{35}H_{66}O_5S_3$ $[M + H]^+$ 663.4145; found 663.4141.

Supporting Information (see footnote on the first page of this article): Determination of enantiomeric ratio for (*S*)-**9**, determination of enantiomeric and diastereomeric ratios for epoxy-diol **13**, ^1H and ^{13}C NMR spectra for compounds **1**–**8**, **11** and **22**–**35**, HRMS spectra for aza and thio analogues **1**–**6**.

Acknowledgments

The authors thank the Estonian Ministry of Education (project No. SF0180073s08 and SF0180027s08), the Archimedes Foundation (project No. 3.2.0501.10-0004), and the European Regional Development Fund through the Center of Excellence in Chemical Biology, Estonia for financial support. We are also grateful to Dr. Tõnis Pehk (National Institute of Chemical Physics and Biophysics, Tallinn, Estonia) for his help with NMR spectra, and Prof. Peter Somfai (Lund University, Sweden) for critically reading the manuscript.

[1] For recent reviews of isolated and synthesized acetogenins, see: a) C.-C. Liaw, T.-Y. Wu, F.-R. Chang, Y.-C. Wu, *Planta Med.* **2010**, *76*, 1390–1404; b) A. Bermejo, B. Figadère, M.-C. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269–303; c) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540.

[2] D. J. Morré, R. de Cabo, C. Farley, N. H. Oberlies, J. L. McLaughlin, *Life Sci.* **1994**, *56*, 343–348.

[3] a) P. S. Soltis, D. E. Soltis, *Am. J. Bot.* **2004**, *91*, 1614–1626; b) R. F. Thorne, *Bot. Rev.* **2000**, *66*, 441–647.

[4] J. L. McLaughlin, *J. Nat. Prod.* **2008**, *71*, 1311–1321.

[5] S. D. Jolad, J. J. Hoffmann, K. H. Schram, J. R. Cole, *J. Org. Chem.* **1982**, *47*, 3151–3153.

[6] a) T. Motoyama, H. Yabunaka, H. Miyoshi, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2089–2092; b) T. Hamada, N. Ichimaru, M. Abe, D. Fujita, A. Kenmochi, T. Nishioka, K. Zwicker, U. Brandt, H. Miyoshi, *Biochemistry* **2004**, *43*, 3651–3658; c) M. Abe, A. Kenmochi, N. Ichimaru, T. Hamada, T. Nishioka, H. Miyoshi, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 779–782; d) K. Kuwabara, M. Takada, J. Iwata, K. Tatsumoto, K. Sakamoto, H. Iwamura, H. Miyoshi, *Eur. J. Biochem.* **2000**, *267*, 2538–2546; e) H. Shimada, J. B. Grutzner, J. F. Kozlowski, J. L. McLaughlin, *Biochemistry* **1998**, *37*, 854–866.

[7] a) N. Kojima, T. Morioka, D. Urabe, M. Yano, Y. Suga, N. Maezaki, A. Ohashi-Kobayashi, Y. Fujimoto, M. Maeda, T. Yamori, T. Yoshimitsu, T. Tanaka, *Bioorg. Med. Chem.* **2010**, *18*, 8630–8641; b) N. Kojima, T. Tanaka, *Molecules* **2009**, *14*, 3621–3661; c) V. Coothankandaswamy, Y. Liu, S.-C. Mao, J. B. Morgan, F. Mahdi, M. B. Jekabsons, D. G. Nagle, Y.-D. Zhou, *J. Nat. Prod.* **2010**, *73*, 956–961.

[8] M. Abe, A. Kubo, S. Yamamoto, Y. Hatoh, M. Murai, Y. Hattori, H. Makabe, T. Nishioka, H. Miyoshi, *Biochemistry* **2008**, *47*, 6260–6266.

[9] a) N. Kojima, T. Fushimi, N. Maezaki, T. Tanaka, T. Yamori, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1637–1641; b) R. A. Duval, G. Lewin, E. Peris, N. Chahboune, A. Garofano, S. Dröse, D. Cortes, U. Brandt, R. Hocquemiller, *Biochemistry* **2006**, *45*, 2721–2728; c) R. A. Duval, E. Poupon, V. Romero, E. Peris, G. Lewin, D. Cortes, U. Brandt, R. Hocquemiller, *Tetrahedron* **2006**, *62*, 6248–6257; d) S. Arndt, U. Emde, S. Bäurle, T. Friedrich, L. Grubert, U. Koert, *Chem. Eur. J.* **2001**, *7*, 993–1005; e) S. Hoppen, U. Emde, T. Friedrich, L. Grubert, U. Koert, *Angew. Chem.* **2000**, *112*, 2181–2184; *Angew. Chem. Int. Ed.* **2000**, *39*, 2099–2101.

[10] Y. Chen, J.-W. Chen, S.-S. Xu, Y. Wang, X. Li, B.-C. Cai, N.-B. Fan, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2717–2719.

[11] A. Guadaño, C. Gutiérrez, E. de la Peña, D. Cortes, A. González-Coloma, *J. Nat. Prod.* **2000**, *63*, 773–776.

[12] For further reading on acetogenin mimics containing polyether units, see: a) Z.-J. Yao, H.-P. Wu, Y.-L. Wu, *J. Med. Chem.* **2000**, *43*, 2484–2487; b) B.-B. Zeng, Y. Wu, Q. Yu, Y.-L. Wu, Y. Li, X.-G. Chen, *Angew. Chem.* **2000**, *112*, 2010–2013; *Angew. Chem. Int. Ed.* **2000**, *39*, 1934–1937; c) S. Jiang, Y. Li, X.-G. Chen, T.-S. Hu, Y.-L. Wu, Z.-J. Yao, *Angew. Chem.* **2004**, *116*, 333–338; *Angew. Chem. Int. Ed.* **2004**, *43*, 329–334; d) H.-X. Liu, G.-R. Huang, H.-M. Zhang, S. Jiang, J.-R. Wu, Z.-J. Yao, *ChemBiolChem.* **2007**, *8*, 172–177; e) Q. Xiao, Y. Liu, Y. Qiu, G. Zhou, C. Mao, Z. Li, Z.-J. Yao, S. Jiang, *J. Med. Chem.* **2011**, *54*, 525–533.

[13] H. Konno, N. Hiura, H. Makabe, M. Abe, H. Miyoshi, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 629–632.

[14] a) Q. Xiao, Y. Liu, Y. Qiu, Z. Yao, G. Zhou, Z.-J. Yao, S. Jiang, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3613–3615; b) M. Wang, J.-K. Shen, *Chin. J. Synth. Chem.* **2006**, *14*, 337–341.

[15] S. Jiang, Z.-H. Liu, G. Sheng, B.-B. Zeng, X.-G. Cheng, Y.-L. Wu, Z.-J. Yao, *J. Org. Chem.* **2002**, *67*, 3404–3408.

[16] H.-X. Liu, F. Shao, G.-Q. Li, G.-L. Xun, Z.-J. Yao, *Chem. Eur. J.* **2008**, *14*, 8632–8639.

[17] a) C. Jacob, *Nat. Prod. Rep.* **2006**, *23*, 851–863; b) T. A. M. Gulder, B. S. Moore, *Curr. Opin. Microbiol.* **2009**, *12*, 252–260.

[18] D. L. Howard, H. G. Kjaergaard, *Phys. Chem. Chem. Phys.* **2008**, *10*, 4113–4118.

[19] a) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; b) L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362; c) P. Kumar, V. Naidu, P. Gupta, *Tetrahedron* **2007**, *63*, 2745–2785.

[20] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.

[21] a) H. Lebel, E. N. Jacobsen, *Tetrahedron Lett.* **1999**, *40*, 7303–7306; b) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Org. Lett.* **2005**, *7*, 1983–1985.

[22] a) S. Chow, W. Kitching, *Tetrahedron: Asymmetry* **2002**, *13*, 779–793; b) S. Chow, W. A. Koening, W. Kitching, *Eur. J. Org. Chem.* **2004**, 1198–1201; c) X. Li, C. E. Burrell, R. J. Staples, B. Borhan, *J. Am. Chem. Soc.* **2012**, *134*, 9026–9029.

[23] J. Bredihhina, P. Villo, K. Andersons, L. Toom, L. Vares, *J. Org. Chem.* **2013**, *78*, 2379–2385.

[24] a) P. Duret, B. Figadère, R. Hocquemiller, A. Cavé, *Tetrahedron Lett.* **1997**, *38*, 8849–8852; b) J. A. Marshall, H. Jiang, *J. Org. Chem.* **1999**, *64*, 971–975.

[25] The ratio of enantiomers was determined by chiral GC analysis using a permethylated β-cyclodextrin column (30 m × 0.25 mm ID × 0.25 μm film thickness, Chrompack).

[26] L. Toom, P. Villo, I. Liblikas, L. Vares, *Synth. Commun.* **2008**, *38*, 4295–4313.

[27] For the determination of *er*, see Exp. Sect. for (*S*)-**9** and Supporting Information.

[28] For the determination of *er* and *dr*, see Exp. Sect. for **13** and Supporting Information. For the characterization of the thiol derivative, see ref.[23]

[29] M. J. Martinelli, N. K. Nayyar, E. D. Moher, U. P. Dhokte, J. M. Pawlak, R. Vaidyanathan, *Org. Lett.* **1999**, *1*, 447–450.

[30] White's lactone **12** was synthesized from (*S*)-propylene oxide and (phenylthio)acetic acid in good yield according to a known procedure, see: J. D. White, T. C. Somers, G. N. Reddy, *J. Org. Chem.* **1992**, *57*, 4991–4998.
[31] H. Tominaga, N. Maezaki, M. Yanai, N. Kojima, D. Urabe, R. Ueki, T. Tanaka, *Eur. J. Org. Chem.* **2006**, 1422–1429.
[32] G. J. Florence, J. C. Morris, R. G. Murray, J. D. Osler, V. R. Reddy, T. K. Smith, *Org. Lett.* **2011**, *13*, 514–517.
[33] H. Zhao, J. S. T. Gorman, B. L. Pagenkopf, *Org. Lett.* **2006**, *8*, 4379–4382.
[34] a) J. S. Yadav, A. R. Reddy, A. V. Narsaiah, B. V. S. Reddy, *J. Mol. Catal. A* **2007**, *261*, 207–212; b) T. Ollevier, E. Nadeau, *Tetrahedron Lett.* **2008**, *49*, 1546–1550.
[35] Additionally to the conditions for aminolysis of epoxides explored in ref.[26], transition metal chlorides $FeCl_3$, $ZrCl_4$, $ZnCl_2$, and $InCl_3$ were tested, as well as triflates $Sc(OTf)_3$, $La(OTf)_3$, $Yb(OTf)_3$, and $Bi(OTf)_3$. At room temp., these Lewis acids all catalysed the reaction to give the desired product in ca. 30% yield. Microwave conditions were also investigated with $Bi(OTf)_3$, but this led to the formation of by-products.
[36] S. C. Miller, T. S. Scanlan, *J. Am. Chem. Soc.* **1997**, *119*, 2301–2302.
[37] J. S. Yadav, B. V. S. Reddy, G. Baishya, *Chem. Lett.* **2002**, *9*, 906–907.
[38] N. Kojima, M. Abe, Y. Suga, K. Ohtsuki, T. Tanaka, H. Iwasaki, M. Yamashita, H. Miyoshi, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1217–1219. See also the literature references given under ref.[9]
[39] N. Li, K. Ragheb, G. Lawler, J. Sturgis, B. Rajwa, J. A. Melendez, J. P. Robinson, *J. Biol. Chem.* **2003**, *278*, 8516–8525.
[40] MTS: 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium salt.
[41] D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond, A. J. P. White, *Chem. Commun.* **2009**, 1082–1084.
[42] K. J. Quinn, L. Islamaj, S. M. Couvertier, K. E. Shanley, B. L. Mackinson, *Eur. J. Org. Chem.* **2010**, 5943–5945.

Received: May 24, 2013
Published Online: September 9, 2013

