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Synthesis of solamin type mono-THF acetogenins using cross-metathesis

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ABSTRACT

The total synthesis of mono-THF acetogenins, *cis*-solamin A and B, and reticulatacin, was accomplished starting with muricatacin. The backbone of the mono-THF acetogenins was constructed by olefin cross-metathesis between the tetrahydrofuran moiety and γ-lactone moiety. An enzymatic kinetic transesterification procedure was successfully applied to the synthesis of an optically pure γ-lactone moiety. Notably, *cis*-THF compounds were obtained without using protective groups.

1. Introduction

Annonaceous acetogenins[1] exhibit a broad spectrum of biological activities including cytotoxic, antitumor, pesticidal, antifeedant, and immunosuppressive effects and contain either adjacent and non-adjacent tetrahydrofuran or tetrahydropyran rings and α,β-unsaturated γ-lactone rings. These compounds are thought to target the NADH-ubiquinone oxidoreductase (complex I) in mammalian and insect mitochondrial electron transport systems[2] and/or ubiquinone-linked NAD(P)H oxidase in cytoplasmic membranes of cancer cells.[3]

Their structural diversity and numerous biological properties have encouraged total synthesis.[4] We have already reported the stereoselective synthesis of acetogenins, such as solamin, murisolin, rollicosin, and pyranicin starting from muricatacin using a Sonogashira coupling reaction of the THF acetylene unit and butenolide vinyl iodide moiety as a key step.[1b] Curran,[5a] Tanaka,[5b] and Sinha[5c] were disclosed the synthesis of libraries of the THF moiety of acetogenins is important to search for drug discovery as a pioneer work. To obtain an acetogenin library for the evaluation of inhibitory activity against mitochondrial complex I, we have developed a simple route for the synthesis of mono-THF acetogenins in the course of our recent research regarding mitochondrial complex I inhibitors based on acetogenin structures. In the previous communication, we reported the total synthesis of *cis*-solamin A using a practical route containing no protection/deprotection steps.[6] Therefore, we selected the most simple mono-THF acetogenins, *cis*-solamin A (**1**) and B (**2**), and reticulatacin (**3**) as targets. *cis*-Solamin was isolated from the roots of *Annnona muricata* by Gleye et al. in 1998[7] (Fig. 1). The relative stereochemistry of the THF-diol part was determined to be *threo*–*cis*–*threo*, and the absolute structure of *cis*-solamin was expected to be either *cis*-solamin A (**1**) or *cis*-solamin B (**2**). Because of diverse biological activities and an unique biosynthetic mechanism, the total synthesis of *cis*-solamin was conducted by four groups, Stark's,[8] Donohoe's,[9] Brown's,[10] and Makabe's groups.[11] Synthetic *cis*-solamin A (**1**) and *cis*-solamin B (**2**) both showed remarkable inhibitory effects against mitochondrial complex I with an IC_{50} value of 2.2 and 2.1 nM, respectively.[11] In 2006, Hu et al. reported that natural *cis*-solamin is a mixture of two tetra-epimeric diastereoisomers consisting of *cis*-solamin A (**1**) and *cis*-solamin B (**2**).[12] Reticulatacin (**3**) was isolated from *Annnona reticulata* by McLaughlin in 1990.[13] The relative stereochemistry of the THF-diol part was determined to be *threo*–*trans*–*threo*, and it has a weak inhibitory effect (IC_{50}=20 nM).[14]

We herein report the synthesis of three stereoisomers of the THF unit and transesterification of butenolide using a cross metathesis reaction to obtain *cis*-solamin A (**1**) and B (**2**), and reticulatacin (**3**).

2. Results and discussion

Our method centers on the construction of the mono-THF segment via an olefin cross metathesis reaction[15,16] of the THF–allylic

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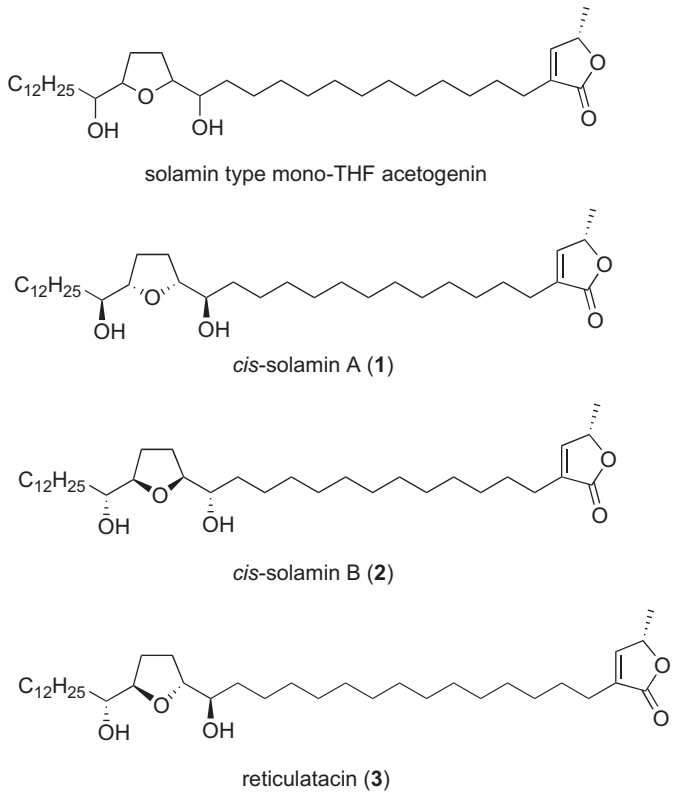
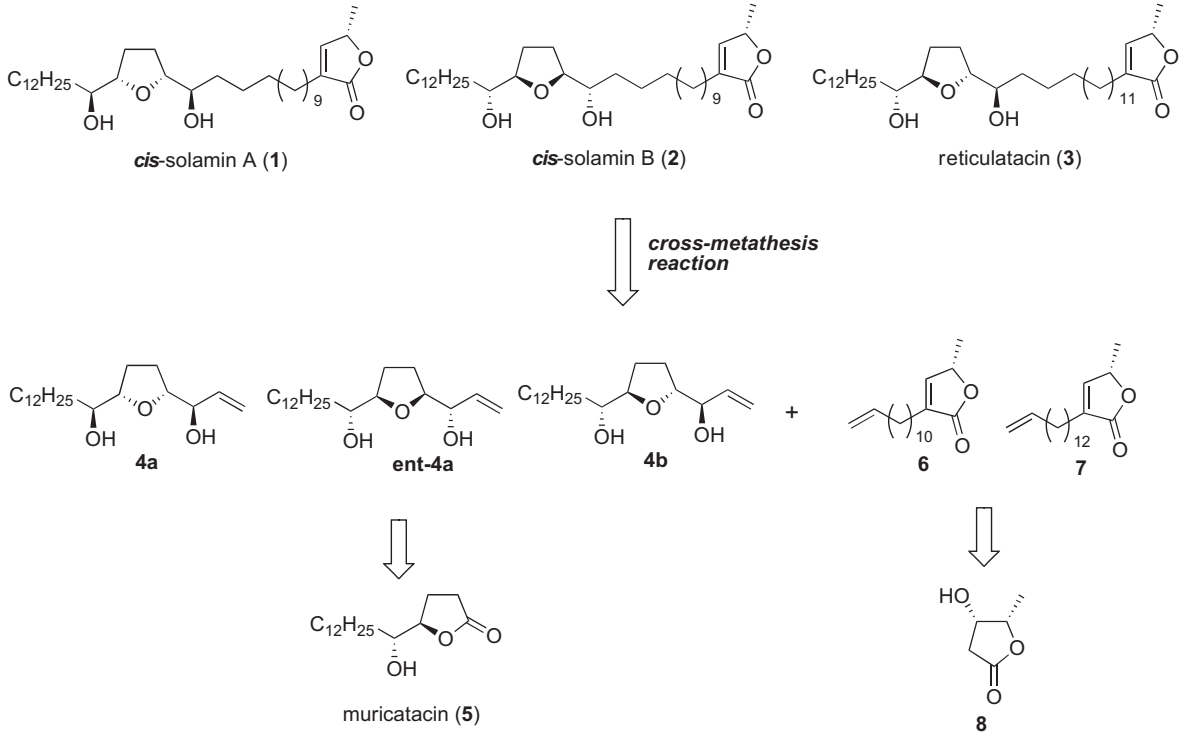


Figure 1. mono-THF acetogenins, *cis*-solamin A (**1**), B (**2**), and reticulatacin (**3**).

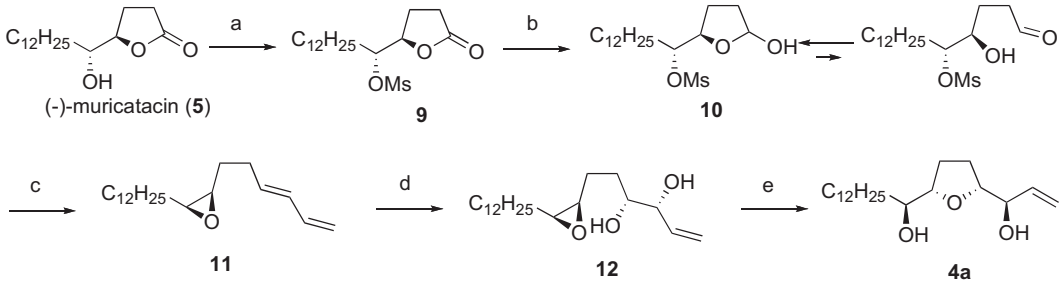
alcohol component and the γ-lactone moiety with the terminal double bond. Recently, Mootoo et al. applied the cross-metathesis strategy for a synthesis of mono-THF acetogenins.[17] An attractive aspect of this strategy is the convergent assembly of the mono-THF and lactone components. In view of the variety of natural and unnatural analogues available for the investigation of structure-activity relationships, this strategy can provide chemical libraries easily. For the metathesis reaction, an allylic alcohol **4** containing unprotected hydroxy groups is employed, and thus the alcohol **4** is prepared from a known compound, enantiopure muricatacin (**5**) checked by mosher method after recrystallization in hexane,[18] via Horner Emmons type olefination followed by an asymmetric dihydroxylation and Grignard reaction. The metathesis counterpart γ-lactone **6** or **7** is synthesized by the alkylation of an enantiopure hydroxy lactone **8**, which is prepared by an enzymatic kinetic transesterification[19] of the racemic lactone (±)-**8**. Since the racemic lactone (±)-**8** can be easily obtained by two-step reactions from commercially available *trans*-3-pentenenitrile, the enzymatic route can provide an optically pure lactone[20] with practical procedures (Scheme 1).

Synthesis of the THF–allylic alcohol **4a** is shown in Scheme 2. (−)-Muricatacin (**5**) was converted to a mesyl compound using $MsCl/Et_3N$ and the subsequent reduction with DIBAL-H in THF gave the hemi-acetal **10** in 57% yield in two steps. Horner Emmons type olefination and epoxidation of **10** using an excess of the lithium salt of diethyl allylphosphate gave an epoxy-*E*-diene **11** with a ratio of more than 20:1 (*E*/*Z*) in 64% overall yield as an inseparable mixture. Asymmetric dihydroxylation (AD-mix β)[21] of **11** and subsequent treatment with a catalytic amount of *p*-TsOH in CH_2Cl_2 afforded the desired THF–allylic alcohol **4a** as a major product in 52% yield with a minor regioisomer (26% yield). The diastereomeric excess of **4a** was determined to be >98%de. In addition, a enantiomer of **4a** was prepared from (+)-muricatacin (*ent*-**5**). Using this route, THF–allylic alcohol analogues varying in stereostructure could be similarly prepared with specific combinations of muricatacin analogues and asymmetric dihydroxylation reagents.

The α,β-unsaturated ester **13** starting from (−)-muricatacin (**5**) reported by us[22] was converted to **4b** and **4c** using cyclization with epoxide and oxidative degradation of the diol moiety to give the aldehyde **15** followed by a Grignard reaction in 55% yield for **16** and

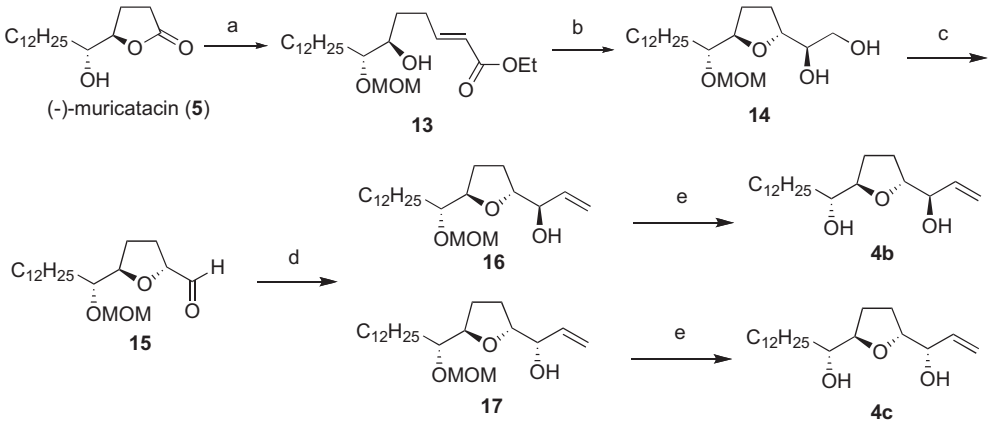


Scheme 1. Synthetic plan for mono-THF acetogenins.



Scheme 2. Synthesis of **4a**. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 82%, (b) DIBAL-H, THF, −40 °C, 69%. (c) $(EtO)_2P(O)CH_2CHCH_2$, *n*-BuLi, HMPA, THF, −40 °C to 0 °C, 64%. (d) AD-mix β, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0 °C. (e) *p*-TsOH (cat.), CH_2Cl_2, 52% (two steps).

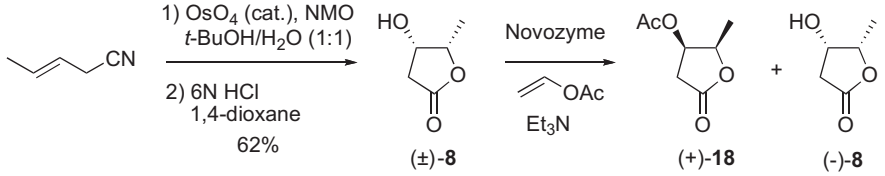
22% yield for **17**, respectively. MOM-deprotection of **16** and **17** afforded **4b** and **4c** as counterparts of the cross-metathesis, easily (Scheme 3).



Scheme 3. Synthesis of **4b** and **4c**. (a) Ref. 19; (b) (i) DIBAL-H, THF, (ii) m-CPBA, CH_2Cl_2. (c) $NaIO_4$, THF/H_2O, 46% (three steps). (d) Vinylmagnesium bromide, THF, 0 °C, 55% (**16**), 22% (**17**). (e) concd HCl, MeOH, 85% for **4b**, 82% for **4c**.

The optically active γ-lactone (−)-**8** was prepared by employing a lipase-mediated kinetic transesterification.[19] The necessary racemic substrate (±)-**8** was synthesized by the OsO_4-catalyzed dihydroxylation of commercially available *trans*-3-pentenenitrile and subsequent hydrolysis-lactonization (6 N HCl at 80 °C) in 62% overall yield. A variety of lipases were tested under different conditions Lipase PS, Lipase AY, Lipase A, Lipase M, and Novozyme. Novozyme (*Candida antarctica*, Novo) provided the best results concerning both conversion yield and enantioselectivity. With 4 h of treatment with Novozyme in the presence of vinyl acetate in toluene containing 5% Et_3N,[20] the hydroxy lactone (±)-**8** gave the acetoxy lactone (+)-**18** and hydroxy lactone (−)-**8** in nearly quantitative yields with high enantiomeric excess[23,24,25] (Table 1, entry 7).

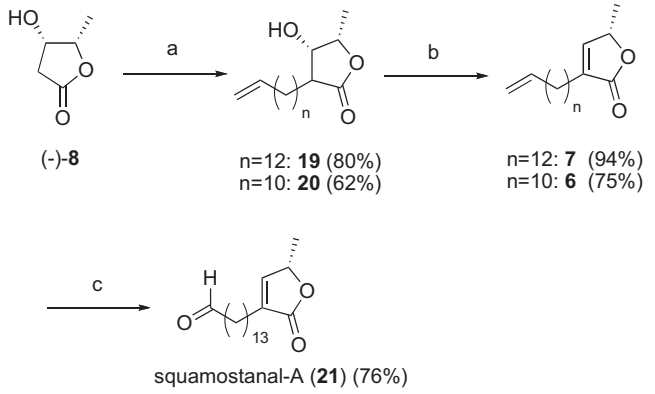
Table 1
Kinetic transesterification of racemic-**8**



Entry	Solvent	Time (h)	Acetate (−)-**8**		Alcohol (−)-**8**	
			Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	None	4	46	77	52	82
2	THF	4	34	90	45	82
3	MeCN	4	24	83	68	32
4	CH_2Cl_2	4	28	95	43	95
5	*t*-BuOMe	4	44	95	48	98
6	AcOEt	4	49	98	50	98
7	Toluene	4	48	98	50	99

[a] Isolation yield after silica gel chromatography.
[b] Determined by HPLC using CHIRALCEL OD-H column (hexane-*i*-PrOH, 90:10) after transformation to the corresponding benzoate.

Alkylation of the sodium enolate of the hydroxy lactone (−)-**8** with alkyl iodide gave **19** and **20** in 80% and 62% yields as a diastereomeric mixture (10:1), respectively. Treatment of **19** or **20** with MsCl/Et_3N in CH_2Cl_2 and the addition of DBU in situ at room temperature afforded the unsaturated γ-lactones **7** and **6** in good yield as a single product. In order to determine the absolute configuration of the resolution products, **7** was converted to squamostanal-A (**21**),[26] a product of the oxidative degradation of acetogenins isolated from *Annona squamosa* L. Oxidative cleavage of the terminal double bond of **7** by treatment with catalytic OsO_4/co-oxidant NMO and the addition of $NaIO_4$ afforded squamostanal-A (**21**) in 76% yield. The specific rotation of the synthetic **21** ($[\alpha]_D^{28}$ +24) is nearly identical to the authentic value ($[\alpha]_D^{28}$ +21). Spectroscopic data for the synthetic squamostanal-A (**21**) were also identical to those for the authentic sample.[27] Thus the absolute configuration of the hydroxy lactone obtained by the kinetic transesterification was confirmed undoubtedly to be (−)-**8** (Scheme 4).



Scheme 4. Synthesis of the lactone moiety **7** and **6**, and squamostanal-A (**21**). Reagents and conditions: (a) $CH_2CH(CH_2)_{12}I$ or $CH_2CH(CH_2)_{10}I$, NaHMDS, THF, −78 °Cto rt, 80% for **19** and 62% for **20**. (b) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt then DBU, rt, 94% for **7** and 75% for **6**. (c) OsO_4 (cat.), NMO, THF/H_2O, 0 °C to rt, then $NaIO_4$, rt, 76%.

A cross metathesis of the allylic alcohol **4a** and lactone **6** with a first generation Grubbs' catalyst or Schrock catalyst (20 mol %, CH_2Cl_2) for 10 h at ambient temperature produced the desired product **22** in 5% and 8% yields, respectively. The second generation Grubbs' catalyst in CH_2Cl_2 proceeded at 40 °C to give the desired **22** as a single *E*-isomer in 52% yield (78% yield based on the starting material **3** consumed) as well as the lactone homo-dimer (ca. 20% yield). In addition, the acetogenin backbone structures **23** and **24** were obtained by the same procedure in moderate yields, respectively.

Finally, selective hydrogenation of the double bond with *p*-$TsNHNH_2$[28] gave *cis*-solamin A (**1**) and B (**2**) and reticulatacin (**3**) in 95%, 93%, and 91% yields, respectively (Scheme 5). Spectroscopic data for the products were identical with those reported by our group.[10]

In conclusion, we have achieved the total synthesis of *cis*-solamin A (**1**) and B (**2**) and reticulatacin (**3**). Notably, the synthesis of **1** and **2** was accomplished using a practical route containing no protection/deprotection steps. The route should be effective for the construction of acetogenin libraries diverse in stereochemistry around hydroxylated THF rings as well as alkyl chain lengths for structure–activity relationship studies on the inhibitory activities of acetogenins against mitochondrial complex I.

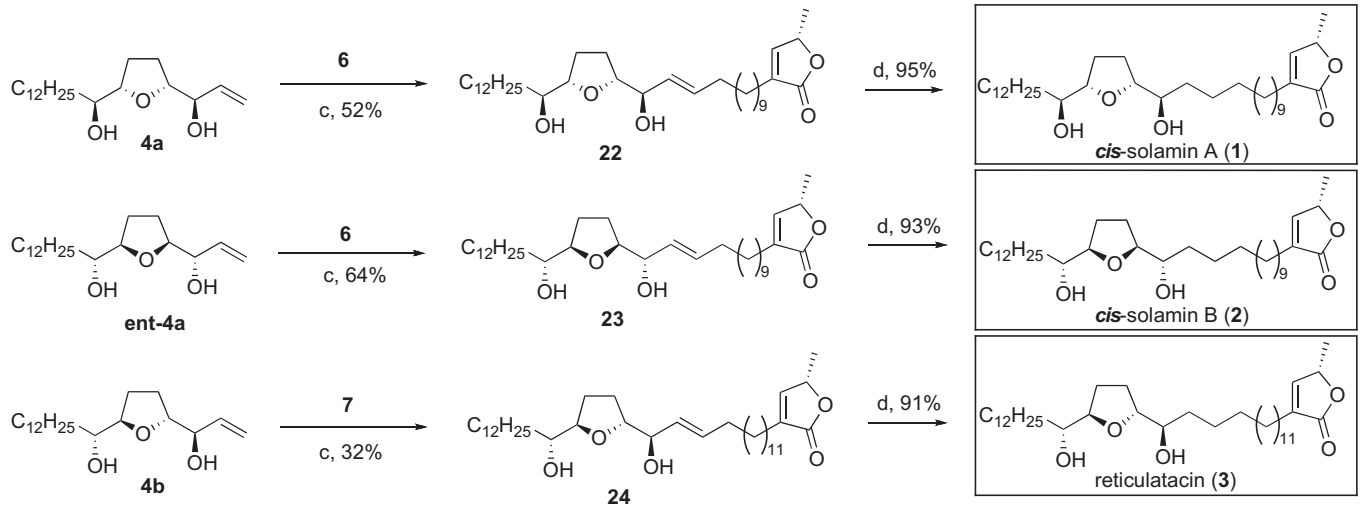
3. Experimental

3.1. General

All manipulations were conducted under an inert atmosphere (N_2). All solvents were of reagent grade. THF was distilled from sodium and benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. All commercial reagents were of the highest purity available. Analytical TLC was performed on silica gel (60 F_{254}, Plates 0.25 mm). Column chromatography was carried out on Wakogel 60 (particle size, 0.063–0.200 mm). Analytical HPLC was performed on a Hitachi La-chlome Elite System instrument (OD 256 nm) equipped with the Daicel CHIRALCEL OD-H (4.6×150 mm). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AM-300. Chemical shifts are expressed in parts per million relative to TMS (0 ppm) or $CHCl_3$ (7.26 ppm for ^1H and 77.0 ppm for ^{13}C). IR spectra were obtained on a HORIBA FREEXACT-II FT-710 spectrometer. Optical rotations were recorded on a HORIBA SEPA-300 at the sodium D line. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were obtained on either a JOEL JMS-HX-211A or a JMS-HX-110A (EI or FAB).

3.2. Synthesis

*3.2.1. (1R,2′R)-(5′-Oxotetrahydrofuran-2-yl)tridecylmethansulfonate (**9**).* To a solution of the (−)-muricatacin **5** (2.00 g, 7.03 mmol) in



Scheme 5. Total synthesis of *cis*-solamin A (**1**), *cis*-solamin B (**2**), and reticulatacin (**3**). Reagents and conditions: (c) lactone unit, Grubbs' catalyst (second generation), CH_2Cl_2, 40 °C, 12 h. (d) *p*-$TsNHNH_2$, NaOAc, ethylene glycol dimethyl ether, reflux.

CH_2Cl_2 (40 ml) was added Et_3N (2.92 ml, 21.0 mmol) and MsCl (0.810 ml, 10.5 mmol) at 0 °C. The mixture was warmed to room temperature, stirred for 30 min, and partitioned between H_2O (40 ml) and CH_2Cl_2 (40 ml). The organic layer was washed with H_2O (40 ml) and brine (40 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 hexane/AcOEt) to give **9** (2.09 g, 5.77 mmol, 82%) as a colorless oil. $[\alpha]_D^{29}$ −12.0 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2916, 2848, 1786, 1346, 1173, 1165, 931. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, 3H, *J*=6.9 Hz), 1.26 (br s, 18H), 1.46 (br s, 2H), 1.75 (m, 2H), 2.12 (m, 1H), 2.35 (m, 1H), 2.48–2.70 (m, 2H), 3.12 (s, 3H), 4.61 (dt, 1H, *J*=7.2, 5.4 Hz), 4.79 (t, 1H, *J*=5.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 24.1, 24.7, 27.9, 29.16, 29.20, 29.22, 29.4, 29.46, 29.50, 30.7, 31.8, 39.0, 79.4, 83.3, 175.9. HRFABMS *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{36}O_5S$: 363.2205; found: 363.2205.

*3.2.2. (1R,2′R)-(5-Hydroxytetrahydrofuran-2-yl)tridecyl methansulfonate (**10**).* To a solution of the mesylate **9** (2.09 g, 5.77 mmol) in THF (20 ml) was added dropwise DIBAL-H (1.0 M solution in hexane; 6.00 ml, 6.00 mmol) at −40 °C and the mixture stirred for 1 h. MeOH (10 ml) and ether (100 ml) were then added and the solution warmed to room temperature. After filtration on a Celite pad, the organic layer was washed with H_2O (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane/AcOEt) to give the hemi-acetal **10** (1.45 g, 3.98 mmol, 69%) as a colorless oil. $[\alpha]_D^{28}$ +7.1 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3513, 2924, 2854, 1466, 1350, 1173, 941, 922. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.9 Hz), 1.26 (br s, 18H), 1.44 (br s, 2H), 1.59 (m, 2H), 1.73–2.18 (m, 4H), 3.10(s, 1.8H), 3.16 (s, 1.2H), 3.70 (br s, 1H), 4.09 (dt, 0.6H, *J*=7.8, 6.9 Hz), 4.30 (q, 0.4H, *J*=6.9 Hz), 4.53 (q, 0.6H, *J*=6.3 Hz), 4.65 (td, 0.4H, *J*=8.1, 4.8 Hz), 5.51 (d, 0.6H, *J*=3.3 Hz), 5.58 (dd, 0.4H, *J*=4.8, 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.5, 24.7, 24.8, 25.7, 26.1, 29.16, 29.22, 29.4, 29.5, 31.2, 31.3, 31.7, 32.8, 33.8, 38.7, 38.9, 78.4, 80.9, 85.3, 88.0, 98.4, 98.5. HRCIMS *m*/*z* $[M-OH]^+$ calcd for $C_{18}H_{35}O_4S$: 347.2256; found: 347.2254.

*3.2.3. (7R,8S)-7,8-Epoxyicosa-1,3-diene (**11**).* To a solution of diethyl allylphosphonate (300 mg, 3.42 mmol) and *n*-BuLi (1.6 M solution in hexane; 2.13 ml, 3.42 mmol) in THF (10 ml) were added dropwise the hemi-acetal **10** (234 mg, 0.642 mmol) and HMPA (1 ml) at −40 °C and the mixture was warmed to 0 °C. After 30 min of stirring, H_2O (5 ml) and ether (10 ml) were added. The organic layer was washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20:1 hexane/AcOEt) to give the epoxy diene **11** (150 mg, 0.411 mmol, 64%) as a colorless oil. $[\alpha]_D^{29}$ +0.9 (*c* 0.3, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2924, 2854, 1464, 1261, 804. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, 3H, *J*=7.8 Hz), 1.27–1.70 (m, 22H), 2.02 (m, 2H), 2.22 (m, 2H), 2.93 (m, 2H), 4.98 (d, 1H, *J*=10.5 Hz), 5.11 (d, 1H, *J*=16.8 Hz), 5.73 (dt, 1H, *J*=15.0, 6.9 Hz), 6.10 (dt, 1H, *J*=15.0, 10.5 Hz), 6.31 (dt, 1H, *J*=16.8, 10.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.6, 27.6, 27.9, 29.4, 29.57, 29.64, 29.7, 30.0, 30.3, 31.9, 32.8, 37.1, 56.6, 57.3, 115.4, 131.7, 133.8, 137.0. HRFABMS *m*/*z* $[M+H]^+$ calcd for $C_{20}H_{37}O$: 293.2844; found: 293.2850.

*3.2.4. (2R,5S,1′R,1″S)-2-(1′-Hydroxy-2′-propenyl)-5-(1″-hydroxytridecyl) tetrahydrofuran (**4a**).* To a solution of the epoxy diene **11** (150 mg, 0.411 mmol) in *t*-BuOH/H_2O (1:1, 3 ml) were added AD-mix β (863 mg, 0.617 mmol) and methanesulfonamide (59 mg, 0.617 mmol) at 0 °C. After stirring at 4 °C for 24 h, aq $NaHSO_3$ (5 ml) and AcOEt (10 ml) were added. The organic layer was washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. To a solution of crude product in CH_2Cl_2 (5 ml) was added a *p*-TsOH (2 mg). The mixture was stirred for 2 h at room temperature and saturated $NaHCO_3$ aq (10 ml) and AcOEt (20 ml) were added to the mixture. The organic layer was washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (1:1 hexane/AcOEt) to give the THF diol **4a** (70 mg, 0.214 mmol, 52%) as a colorless oil. $[\alpha]_D^{29}$ +9.4 (*c* 0.3, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3398, 2924, 1465, 1070, 924, 721. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.9 Hz), 1.26 (br s, 20H), 1.45 (br s, 2H), 1.71–1.99 (m, 4H), 2.79 (br s, 1H), 2.94 (br s, 1H), 3.44 (m, 1H), 3.84 (m, 1H), 3.89 (m, 1H), 3.97 (d, 1H, *J*=6.0 Hz), 5.20 (d, 1H, *J*=10.5 Hz), 5.35 (d, 1H, *J*=17.4 Hz), 5.87 (ddd, 1H, *J*=17.4, 10.5, 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.7, 27.8, 27.9, 29.3, 29.59, 29.61, 29.64, 29.7, 31.9, 34.1, 74.3, 75.8, 82.3, 83.1, 116.7, 137.5. HRFABMS *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{38}O_3Na$: 349.2719; found: 349.2723.

Enantiomer of **4a**: $[\alpha]_D^{29}$ −10.2 (*c* 0.3, $CHCl_3$).

*3.2.5. (2R,5R,1′R,1″S)-2-(1′,2′-Dihydroxyethyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran(**14**).* To a solution of ethyl ester (80 mg, 0.199 mmol) in THF (2 ml) was added DIBAL-H (1.0 ml, 1.0 mmol; 1.0 M solution in hexane) at −78 °C. After 15 min of stirring, MeOH (0.30 ml) was added and the mixture was warmed to room temperature. The mixture was filtrated through a Celite pad, concentrated in vacuo, and purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give allyl alcohol (50 mg, 0.139 mmol, 70%) as a colorless oil. To a solution of allyl alcohol (50 mg, 0.139 mmol) in CH_2Cl_2 (5 ml) was added m-CPBA (50 mg) at room temperature. After 1 h of stirring, saturated $Na_2S_2O_3$ aq was added. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (AcOEt) to give the diastereomeric diol **14** (40 mg, 0.107 mmol, 77%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3398, 2924, 2854, 1466, 1149, 1101, 1038, 918. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.6 Hz), 1.26 (m, 20H), 1.51–2.01 (m, 6H), 3.40 (s, 3H), 3.45 (m, 1H), 3.58–4.01 (m, 5H), 4.68 (d, 1H, *J*=6.8 Hz), 4.79 (d, 1H, *J*=6.8 Hz).[29]

*3.2.6. (2R,5R,1′R,1″S)-2-(1′-Hydroxy-2′-propenyl)-5-(1″-methoxymethoxy-tridecyl)tetrahydrofuran(**16**) and (2R,5R,1′S,1″R)-2-(1′-hydroxy-2′-propenyl)-5-(1″-methoxymethoxytridecyl)tetrahydrofuran (**17**).* To a solution of the diol **14** (906 mg, 2.42 mmol) in THF/H_2O (4:1; 20 ml) was added $NaIO_4$ (1.04 g, 4.84 mmol) at 0 °C. After 1 h of stirring, H_2O was added. The organic layer was washed with brine (30 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. To a solution of crude product in THF was added vinylmagnesium bromide (4.85 ml; 4.85 mmol; 1 M solution in THF) at 0 °C. The mixture was stirred for 30 min at 0 °C and saturated NH_4Cl and ether were added. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 hexane/AcOEt) to give the diastereomeric allyl alcohol **16** (456 mg, 1.23 mmol, 55%) and **17** (182 mg, 0.491 mmol, 22%) as a colorless oil. Compound **16**: $[\alpha]_D^{25}$ +14 (*c* 0.2, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3452, 3078, 2924, 2854, 1466, 1149, 1101, 1038, 920, 721. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=7.1 Hz), 1.25 (m, 20H), 1.42 (m, 2H), 1.68 (m, 2H), 1.84 (m, 2H), 3.40 (s, 3H), 3.47 (m, 1H), 3.99 (m, 3H), 4.69 (d, 1H, *J*=5.4 Hz), 4.79 (d, 1H, *J*=5.4 Hz), 5.19 (dd, 1H, *J*=10.7, 3.9 Hz), 5.34 (dd, 1H, *J*=17.3, 7.6 Hz), 5.79 (ddd, 1H, *J*=17.3, 10.3, 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.2, 26.1, 28.5, 29.2, 29.5, 29.7, 31.1, 31.8, 38.6, 55.6, 70.8, 72.2, 79.8, 82.7, 114.4, 140.5. HREIMS $[M-OH]^+$ calcd for $C_{22}H_{41}O_3$: 353.3056, found: 353.3051.

Compound **17**: $[\alpha]_D^{25}$ +19 (*c* 0.3, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3429, 3082, 2924, 2854, 1466, 1037, 921. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.9 Hz), 1.26 (br s, 20H), 1.43 (m, 2H), 1.61 (m, 2H), 1.89 (m, 2H), 3.39 (m, 1H), 3.85 (m, 1H), 4.00 (m, 2H), 4.40 (m, 1H), 4.67 (d, 1H, *J*=6.9 Hz), 4.80 (d, 1H, *J*=6.9 Hz), 5.11 (d, 1H, *J*=9.0 Hz), 5.28 (d, 1H, *J*=17.1 Hz), 5.92 (ddd, 1H, *J*=17.1, 9.0, 5.1 Hz). ^{13}C NMR

(75 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.2, 26.1, 28.5, 29.2, 29.5, 29.7, 31.1, 31.8, 38.6, 55.6, 69.4, 69.9, 79.9, 81.9, 96.5, 113.9, 140.8. HREIMS $[M-OH]^+$ calcd for $C_{22}H_{41}O_3$: 353.3056, found: 353.3045.

*3.2.7. (2S,5R,1′R,1″R)-2-(1′-Hydroxy-2′-propenyl)-5-(1″-hydroxydodecyl)tetra-hydrofuran (**4b**).* To a solution of the allyl alcohol **16** (456 mg, 1.23 mmol) in MeOH (10 ml) was added concd HCl (two drops). After 24 h of stirring at room temperature, H_2O (20 ml) and AcOEt (30 ml) were added. The organic layer was washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (2:1 hexane/AcOEt) to give the diol **4b** (321 mg, 0.984 mmol, 85%) as a colorless oil. $[\alpha]_D^{25}$ +3.1 (*c* 0.3, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3437, 2924, 2854, 1463, 1068, 925, 721. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.9 Hz), 1.26 (br s, 20H), 1.38 (m, 3H), 1.71 (m, 1H), 1.88 (m, 2H), 1.97 (m, 1H), 3.41 (m, 1H), 3.43 (d, 1, *J*=5.1 Hz), 3.85 (m, 2H), 3.98 (m, 1H), 5.21 (ddt, 1H, *J*=10.5, 3.0, 1.5 Hz), 5.36 (ddt, 1H, *J*=17.1, 6.0, 1.5 Hz), 5.81 (ddd, 1H, *J*=17.1, 10.5, 6.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.6, 28.4, 29.4, 29.6, 29.7, 31.9, 33.3, 33.5, 73.3, 74.3, 81.8, 83.6, 116.6, 136.2. HREIMS $[M-OH]^+$ calcd for $C_{20}H_{37}O_2$: 309.2794, found: 309.2806.

*3.2.8. (2S,5R,1′S,1″R)-2-(1′-Hydroxy-2′-propenyl)-5-(1″-hydroxytridecyl)tetrahydrofuran (**4c**).* To a solution of **16** (182 mg, 0.495 mmol) in MeOH (5 ml) was added concd HCl (two drops). After stirring 24 h of stirring at room temperature, H_2O (10 ml) and EtOAc (20 ml) were added. The organic layer was washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (4:1 hexane/AcOEt) to give the diol **4c** (133 mg, 0.406 mmol, 82%) as a colorless oil. $[\alpha]_D^{25}$ +13 (*c* 0.7, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3398, 3082, 2924, 2854, 1466, 1068, 921, 721. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.6 Hz), 1.26 (m, 18H), 1.63 (m, 5H), 1.90 (m, 3H), 2.47 (br s, 1H), 2.72 (br s, 1H), 3.40 (m, 1H), 3.85 (m, 2H), 4.01 (m, 1H), 4.47 (m, 1H), 5.15 (dd, 1H, *J*=10.5, 1.2 Hz), 5.32 (dd, 1H, *J*=17.1, 1.2 Hz), 5.93 (ddd, 1H, *J*=17.1, 10.5, 5.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.6, 26.2, 28.5, 29.4, 29.6, 29.7, 31.2, 33.2, 38.3, 69.2, 70.3, 74.3, 82.0, 83.4, 114.4, 140.6. HRFABMS $[M-OH]^+$ calcd for $C_{20}H_{35}O_2$: 307.2674, found: 307.2637.

3.2.9. 3,4-Dihydroxy-pentanenitrile. To a solution of 3-pentenenitrile (4.04 g, 49.8 mmol) in *t*-BuOH/H_2O (1:1, 100 ml) were added *N*-methyl morphorine-*N*-oxide (6.19 ml, 59.8 mmol) and OsO_4 (1 M in H_2O, five drops) at room temperature. The mixture was stirred for 12 h, and the reaction was quenched by adding $NaHSO_4$. After extraction with AcOEt, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (1:2 hexane/AcOEt) to give 3,4-dihydroxy-pentanenitrile (3.52 g, 30.6 mmol, 61%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3363, 2978, 2935, 2254, 1641, 1417, 1149, 1066, 999. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (d, 3H, *J*=6.3 Hz), 2.28 (br s, 1H), 2.58 (dd, 1H, *J*=16.8, 6.3 Hz), 2.64 (dd, 1H, *J*=16.8, 5.7 Hz), 2.97 (br s, 1H), 3.71–3.86 (m, 2H).

*3.2.10. 4-Hydroxy-5-methyldihydrofuran-2(3H)-one (±**8**).* To a solution of 3,4-dihydroxy-pentanenitrile (6.21 g, 54.0 mmol) in 1,4-dioxane (30 ml) was added 6 N HCl (30 ml) at room temperature. The mixture was stirred for 12 h at 80 °C, and after extraction with ethyl acetate, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (1:2 hexane/AcOEt) to give the hydroxy γ-lactone ±-**8** (4.32 g, 37.2 mmol, 69%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3367, 2995, 2939, 1770, 1649, 1346, 1240, 1174, 1057, 945. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.26 (dd, 3H, *J*=6.6, 1.5 Hz), 2.38 (d, 1H, *J*=17.7 Hz), 2.71 (ddd, 1H, *J*=17.7, 5.4, 0.6 Hz), 3.97 (br s, 1H), 4.31 (m, 1H), 4.48 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.2, 39.0, 68.7, 81.5, 177.1. HRFABMS *m*/*z* $[M+H]^+$ calcd for $C_5H_9O_3$: 117.0552; found: 117.0551.

*3.2.11. (4S,5S)-4-Hydroxy-5-methyldihydrofuran-2(3H)-one {(−)-**8**} and (4R,5R)-4-acetoxy-5-methyldihydrofuran-2(3H)-one {(+)-**18**}.* A suspension of the hydroxy γ-lactone ±-**8** (100 mg, 0.854 mmol), vinyl acetate (0.5 ml), and Novozyme435 (50 mg) in toluene (5 ml) was stirred at room temperature for 4 h. The mixture was filtrated through a Celite pad, concentrated in vacuo, and purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give the acetoxy-γ-lactone (+)-**18** (65 mg, 0.410 mmol, 48%) as a colorless oil and the hydroxy-γ-lactone (−)-**8** (50 mg, 0.427 mmol, 50%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2992, 1786, 1743, 1234, 1056, 933. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (d, 3H, *J*=6.3 Hz), 2.12 (s, 3H), 2.57 (d, 1H, *J*=18.3 Hz), 2.97 (dd, 1H, *J*=18.3, 6.0 Hz), 4.76 (m, 1H), 5.46 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 20.3, 36.2, 70.8, 78.6, 169.6, 174.0 HRFABMS *m*/*z* $[M+H]^+$ calcd for $C_7H_{11}O_4$: 159.0657; found: 159.0654. The enantiomeric excess was determined to be 98%ee for (+)-**18** and 99%ee for (−)-**8** by HPLC after transformation to the corresponding benzoate.

*3.2.12. (3RS,4S,5S)-4-Hydroxy-5-methyl-3-(13′-tetradecyl)dihydrofuran-2(3H)-one (**19**).* To a solution of the lactone (−)-**8** (270 mg, 2.33 mmol) in THF (3 ml) was added 1 M NaHMDS (5.83 ml, 5.83 mmol; 1 M solution in THF) at −78 °C. The mixture was stirred for 30 min, and 1-iodo-11-tetradecene (500 mg, 1.55 mmol) in THF/HMPA (1:1, 2 ml) was added at −78 °C. After stirring at −40 °C for 12 h, the mixture was hydrolyzed with 1 M HCl (5 ml). Following extraction with ethyl acetate, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (1:2 hexane/AcOEt) to give the hydroxy γ-lactone **19** (385 mg, 1.24 mmol, 80%) as a colorless oil. $[\alpha]_D^{25}$ −436 (*c* 1.2, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3452, 3076, 2925, 2854, 1755, 1641, 1466, 1342, 1188, 1055, 995, 908. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (m, 18H), 1.40 (d, 2.4H, *J*=6.6 Hz), 1.42 (d, 0.6H, *J*=6.6 Hz), 1.57–1.76 (m, 2H), 2.04 (q, 2H, *J*=6.6 Hz), 2.55 (m, 1H), 4.19 (br s, 0.8H), 4.31 (br s, 0.2H), 4.46 (dq, 0.2H, *J*=12.9, 3.0 Hz), 4.63 (qd, 0.8H, *J*=6.6, 6.0 Hz), 4.94 (m, 2H), 5.81 (ddt, 1H, *J*=16.8, 10.2, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 13.8, 23.2, 27.2, 27.5, 28.4, 28.9, 29.1, 29.29, 29.34, 29.39, 29.47, 29.51, 33.7, 47.6, 49.2, 71.0, 73.8, 78.7, 79.3, 114.0, 139.1, 178.4.

*3.2.13. (5S)-5-Methyl-3-(13′-tetradecenyl)furan-2(5H)-one (**7**).* To a solution of the lactone **19** (385 mg, 1.24 mmol) in CH_2Cl_2 (2 ml) were added Et_3N (514 μl, 3.72 mmol) and MsCl (144 μl, 1.86 mmol) at 0 °C. The mixture was stirred for 30 min, and DBU (552 μl, 3.72 mmol) was added at 0 °C. After 1 h of stirring at room temperature, H_2O (2 ml) was added. Following extraction with chloroform, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (4:1 hexane/AcOEt) to give the lactone **7** (341 mg, 1.17 mmol, 94%) as a colorless oil. $[\alpha]_D^{25}$ +37 (*c* 0.8, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3072, 2920, 2854, 1751, 1448, 1311, 1147, 1078, 908, 750, 688. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (m, 20H), 1.40 (d, 3H, *J*=6.6 Hz), 1.55 (m, 2H), 2.03 (q, 2H, *J*=6.8 Hz), 2.26 (t, 2H, *J*=7.3 Hz), 4.91–5.02 (m, 3H), 5.81 (ddt, 1H, *J*=16.8, 10.2, 6.6 Hz), 6.99 (d, 1H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 25.2, 27.4, 28.9, 29.08, 29.14, 29.3, 29.42, 29.45, 29.50, 33.7, 77.3, 114.1, 134.3, 139.2, 148.8, 173.8. HREIMS *m*/*z* $[M]^+$ calcd for $C_{19}H_{32}O_2$: 292.2402; found: 292.2389.

*3.2.14. Squamostanal-A (**21**).* To a solution of the lactone **7** (336 mg, 1.21 mmol) in THF/H_2O (4:1, 24 ml) were added *N*-methylmorpholine *N*-oxide (50% in H_2O; 368 mg, 1.57 mmol) and OsO_4 (2 mg) at room temperature. After 5 min of stirring, $NaIO_4$ (1.31 g, 6.13 mmol) was added. The mixture was stirred for 3 h and H_2O

(20 ml) and AcOEt (20 ml) were added. The organic layer was washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give squamostanal-A (**21**) (432 mg, 1.21 mmol, 100%) as a wax. $[\alpha]_D^{25}$ +24.4 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 2925, 2854, 1751, 1724, 1448, 1197, 721. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (m, 18H), 1.39 (d, 3H, *J*=6.8 Hz), 1.70 (m, 2H), 2.26 (t, 2H, *J*=7.7 Hz), 2.42 (td, 3H, *J*=7.3, 2.0 Hz), 4.98 (qd, 1H, *J*=6.8, 1.7 Hz), 6.98 (d, 1H, *J*=1.7 Hz), 9.77 (t, 1H, *J*=2.0 Hz). HREIMS *m*/*z* $[M-2H]^+$ calcd for $C_{18}H_{30}O_3$: 292.2039; found: 292.2036. The spectral data were well consistent with the corresponding values reported for natural or synthetic squamostanal-A.

*3.2.15. (3RS,4S,5S)-3-(11′-Dodecyl)-4-hydroxy-5-methyldihydrofuran-2(3H)-one (**20**).* To a solution of lactone (−)-**8** (202 mg, 1.74 mmol) in THF (3 ml) was added 1 M NaHMDS (4.35 ml, 4.35 mmol) at −78 °C. The mixture was stirred for 30 min, and 1-iodo-11-dodecene (768 mg, 2.61 mmol) in THF/HMPA (1:1, 2 ml) was added at −78 °C. After stirring at −40 °C for 12 h, the mixture was hydrolyzed with 1 M HCl (5 ml). Following extraction with AcOEt, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (1:2 hexane/AcOEt) to give the hydroxy γ-lactone **20** (335 mg, 1.08 mmol, 62%) as a colorless oil. $[\alpha]_D^{25}$ −436 (*c* 1.2, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3452, 3076, 2925, 2854, 1755, 1641, 1466, 1342, 1188, 1055, 995, 908. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (m, 18H), 1.40 (d, 2.4H, *J*=6.6 Hz), 1.42 (d, 0.6H, *J*=6.6 Hz), 1.57–1.76 (m, 2H), 2.04 (q, 2H, *J*=6.6 Hz), 2.55 (m, 1H), 4.19 (br s, 0.8H), 4.31 (br s, 0.2H), 4.46 (dq, 0.2H, *J*=12.9, 3.0 Hz), 4.63 (qd, 0.8H, *J*=6.6, 6.0 Hz), 4.94 (m, 2H), 5.81 (ddt, 1H, *J*=16.8, 10.2, 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.6, 13.8, 23.2, 27.2, 27.5, 28.4, 28.9, 29.1, 29.29, 29.34, 29.39, 29.47, 29.51, 33.7, 47.6, 49.2, 71.0, 73.8, 78.7, 79.3, 114.0, 139.1, 178.4. HRFABMS *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{31}O_3$: 283.2273; found: 283.2278.

*3.2.16. (5S)-3-(11′-Dodecenyl)5-methylfuran-2(5H)-one (**6**).* To a solution of the lactone **20** (60 mg, 0.193 mmol) in CH_2Cl_2 (2 ml) were added Et_3N (80 ml, 0.579 mmol) and MsCl (30 ml, 0.386 mmol) at 0 °C. The mixture was stirred for 30 min, and DBU (86 ml, 0.579 mmol) was added at 0 °C. After 1 h of stirring at room temperature, H_2O (2 ml) was added. Following extraction with chloroform. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (4:1 hexane/AcOEt) to give the lactone **6** (42 mg, 0.144 mmol, 75%) as a colorless oil. $[\alpha]_D^{25}$ +35 (*c* 0.8, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3076, 2978, 2925, 2854, 1759, 1641, 1464, 1319, 1200, 1076, 908. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (m, 18H), 1.40 (d, 3H, *J*=6.9 Hz), 1.55 (m, 2H), 2.04 (q, 2H, *J*=6.9 Hz), 2.26 (t, 2H, *J*=7.5 Hz), 4.91–5.02 (m, 3H), 5.81 (ddt, 1H, *J*=16.8, 10.2, 6.6 Hz), 6.99 (d, 1H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.2, 25.2, 27.4, 28.9, 29.08, 29.14, 29.3, 29.42, 29.45, 29.50, 33.7, 77.3, 114.1, 134.3, 139.2, 148.8, 173.8. HRFABMS *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{28}O_2Na$: 287.1987; found: 287.1989.

*3.2.17. (1‴S,2″R,5S,5″S,13′R)-3-{13′-Hydroxy-13′-[5″-(1‴-hydroxytridecyl)tetrahydrofuran-2″-yl]-11′-tridecyl}-5-methyl-2,5-dihydrofuran-2-one (**22**).* To a solution of the THF diol **4a** (20 mg, 0.0572 mmol) and lactone **6** (33 mg, 0.115 mmol) in CH_2Cl_2 (2 ml) was added a second generation Grubbs' catalyst (5 mg, 0.018 mmol) at room temperature. The mixture was stirred for 12 h at 40 °C and concentrated in vacuo. The crude product was purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give **22** (17 mg, 0.030 mmol, 52%) as a wax. $[\alpha]_D^{25}$ +12 (*c* 0.4, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3431, 2924, 2852, 1757, 1458, 1319, 1074, 1028, 970. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.9 Hz), 1.26 (32H, m), 1.41 (3H, t, *J*=6.9 Hz), 1.45–1.63 (6H, m), 1.78 (2H, m), 1.91 (2H, m), 2.04 (2H, q, *J*=6.9 Hz), 2.27 (2H, dd, *J*=7.7, 1.5 Hz), 2.50 (2H, br s), 3.42 (1H, q, *J*=5.4 Hz), 3.87 (2H, m), 4.99 (1H, qq, *J*=4.8, 1.8 Hz), 5.46 (1H, dd, *J*=15.6, 6.9 Hz), 5.75 (1H, dt, *J*=15.3, 6.9 Hz), 6.98 (1H, d, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 19.2, 22.7, 25.2, 25.7, 27.4, 27.91, 27.94, 29.06, 29.14, 29.27, 29.34, 29.41, 29.47, 29.51, 29.63, 29.65, 29.7, 31.9, 32.33, 34.14, 74.3, 75.9, 76.6, 82.6, 83.1, 128.9, 134.4, 134.5, 148.8, 173.9. HRFABMS $[M+Na]^+$ calcd for $C_{35}H_{62}O_5Na$: 585.4495, found: 585.4487.

*3.2.18. (1‴R,2″S,5S,5″R,13′S)-3-{13′-Hydroxy-13′-[5″-(1‴-hydroxytridecyl)tetrahydrofuran-2″-yl]-11′-tridecyl}-5-methyl-2,5-dihydrofuran-2-one (**23**).* To a solution of the THF diol *ent*-**4a** (10 mg, 0.0286 mmol) and lactone **6** (18 mg, 0.063 mmol) in CH_2Cl_2 (2 ml) was added a second generation Grubbs' catalyst (5 mg, 0.018 mmol) at room temperature. The mixture was stirred for 12 h at 40 °C and concentrated in vacuo. The crude product was purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give **23** (10 mg, 0.018 mmol, 64%) as a wax. $[\alpha]_D^{25}$ +14 (*c* 0.3, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3409, 2924, 2854, 1755, 1466, 1319, 1076, 1026. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.9 Hz), 1.26 (m, 32H), 1.41 (t, 3H, *J*=6.9 Hz), 1.47–1.57 (m, 4H), 1.76 (m, 2H), 1.92 (m, 2H), 2.04 (q, 2H, *J*=6.9 Hz), 2.27 (t, 2H, *J*=7.2 Hz), 2.56 (br s, 2H), 3.44 (m, 1H), 3.82–3.93 (m, 3H), 4.99 (qd, 1H, *J*=6.6, 1.5 Hz), 5.46 (dd, 1H, *J*=15.3, 6.9 Hz), 5.75 (dt, 1H, *J*=15.3, 6.9 Hz), 6.98 (d, 1H, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 19.2, 22.7, 25.2, 25.7, 27.4, 27.9, 29.1, 29.2, 29.4, 29.4, 29.5, 29.6, 29.7, 31.2, 32.3, 34.1, 74.3, 75.9, 82.6, 83.1, 128.9, 134.4, 134.6, 148.8, 173.9. HRFABMS $[M+H]^+$ calcd for $C_{35}H_{62}O_5$: 562.4597, found: 562.4597.

*3.2.19. cis-Solamin-A (**1**).* To a refluxing solution of **22** (10 mg, 0.018 mmol) and *p*-toluenesulfonylhydrazide (138 mg, 0.895 mmol) in ethylene glycol–diethyl ether (15 ml) was added a solution of sodium acetate (88 mg, 1.07 mmol) in H_2O (20 ml) over a period of 4 h. After cooling to room temperature, the mixture was extracted with diethyl ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1:1 hexane/AcOEt) to give *cis*-solamin-A (**1**) (9 mg, 0.017 mmol, 95%) as a colorless solid. Mp=66–68 °C; $[\alpha]_D^{25}$ +26 (*c* 0.5, $CHCl_3$) [lit.[10] $[\alpha]_D^{21}$ +26 (*c* 0.45, $CHCl_3$)]. IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 1320, 1110, 1080, 1030, 960, 840, 750, 715. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.6 Hz), 1.20–2.05 (48H, m), 1.41 (3H, d, *J*=6.6 Hz), 2.27 (2H, t, *J*=7.3 Hz), 2.39 (2H, br s), 3.41 (2H, m), 3.81 (2H, m), 4.99 (1H, dq, *J*=6.7, 1.6 Hz), 6.98 (1H, d, *J*=1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 19.2, 22.7, 25.2, 25.7, 27.4, 28.2, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 30.3, 31.9, 32.5, 34.0, 34.2, 74.4, 77.4, 82.7, 134.4, 148.8, 173.9. HRFABMS $[M+H]^+$ calcd for $C_{35}H_{64}O_5$: 564.4753, found: 564.4720.

*3.2.20. cis-Solamin-B (**2**).* To a refluxing solution of **23** (10 mg, 0.018 mmol) and *p*-toluenesulfonylhydrazide (138 mg, 0.895 mmol) in ethylene glycol–diethyl ether (15 ml) was added a solution of sodium acetate (88 mg, 1.07 mmol) in H_2O (20 ml) over a period of 4 h. After cooling to room temperature, the mixture was extracted with diethyl ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1:1 hexane/AcOEt) to give *cis*-solamin-B (**2**) (8 mg, 0.015 mmol, 93%) as a colorless solid. Mp=63–66 °C. $[\alpha]_D^{25}$ +42 (*c* 0.5, $CHCl_3$) [lit.[10] $[\alpha]_D^{21}$ +42 (*c* 0.5, $CHCl_3$)]. IR (film) ν_{max} cm^{-1}: 3420, 2920, 2850, 1760, 1470, 13,230, 1110, 1080, 1030, 960. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, *J*=6.6 Hz), 1.20–2.05 (m, 48H), 1.41 (d, 3H, *J*=6.6 Hz), 2.00 (br s, 1H), 2.27 (t, 2H, *J*=7.3 Hz), 2.35 (br s, 1H), 3.42 (m, 2H), 3.81 (m, 2H), 4.99 (dq, 1H, *J*=6.7, 1.6 Hz), 6.98 (d, 1H, *J*=1.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1,

19.2, 22.7, 25.2, 25.7, 27.4, 28.2, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9, 32.5, 34.0, 34.2, 74.4, 77.4, 82.7, 134.4, 148.8, 173.9. HRFABMS $[M+Na]^+$ calcd for $C_{35}H_{64}O_5Na$: 587.4651, found: 587.4650.

*3.2.21. Reticulatacin (**3**).* To a solution of the THF diol **4b** (20 mg, 0.0572 mmol) and lactone **7** (30 mg, 0.103 mmol) in CH_2Cl_2 (2 ml) was added a second generation Grubbs' catalyst (5 mg, 0.018 mmol) at room temperature. The mixture was stirred for 12 h at 40 °C and concentrated in vacuo. The crude product was purified with column chromatography on silica gel (2:1 hexane/AcOEt) to give **24** (11 mg, 0.0185 mmol, 32%) as a wax. To a refluxing solution of **24** (11 mg, 0.0185 mmol) and *p*-toluenesulfonylhydrazide (142 mg, 0.925 mmol) in ethylene glycol–diethyl ether (10 ml) was added a solution of sodium acetate (94 mg, 1.11 mmol) in H_2O (20 ml) over a period of 4 h. After cooling to room temperature, the mixture was extracted with diethyl ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1:1 hexane/AcOEt) to give reticulatacin (**3**) (10 mg, 0.0168 mmol, 91%) as a colorless solid. Mp=78–81 °C [lit.[11] [Mp=80–80.5 °C]; $[\alpha]_D^{25}$ +25 (*c* 0.5, $CHCl_3$) [lit.[11] $[\alpha]_D^{21}$ +26 (*c* 0.5, $CHCl_3$)]. IR (film) ν_{max} cm^{-1}: 3413, 2916, 2850, 1753, 1738, 1471, 1323, 1079, 717. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J*=6.6 Hz), 1.26 (38H, m), 1.41 (3H, d, *J*=6.6 Hz), 1.54 (2H, m), 1.68 (1H, m), 1.93 (3H, m), 2.26 (2H, tt, *J*=8.6, 1.5 Hz), 2.32 (1H, br s), 3.40 (1H, br s), 3.84 (3H, m), 4.99 (1H, qq, *J*=5.4, 1.8 Hz), 6.98 (1H, q, *J*=1.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.2, 19.3, 22.8, 25.3, 25.4, 25.7, 26.1, 27.5, 28.7, 28.8, 29.3, 29.40, 29.44, 29.6, 29.7, 29.8, 32.0, 32.7, 33.4, 33.6, 71.2, 74.1, 74.4, 82.3, 82.7, 83.3, 134.5, 148.9, 174.0. HRFABMS $[M+H]^+$ calcd for $C_{37}H_{69}O_5$: 593.5145, found: 593.5151.

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References and notes

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23. *trans*-4-Benzolyoxy-5-methyl-2(3*H*)-furanone: to a solution of the hydroxy-γ-lactone 8 (100 mg, 0.861 mmol) in CH_2Cl_2 (2 ml) were added Et_3N (0.360 ml, 2.58 mmol) and benzoyl chloride (0.150 ml, 1.29 mmol) at 0 °C and the mixture warmed to room temperature. After 2 h of stirring, H_2O (5 ml) and CH_2Cl_2 (10 ml) were added. The organic layer was washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified with column chromatography on silica gel (4:1 hexane–AcOEt) to give benzoyloxy-γ-lactone (186 mg, 0.846 mmol, 95%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 2995, 1795, 1722, 1271, 1111, 1026, 947, 710. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (d, 3H, *J*=6.6 Hz), 2.76 (dd, 1H, *J*=18.3, 1.2 Hz), 3.04 (dd, 1H, *J*=18.3, 6.3 Hz), 4.84 (qd, 1H, *J*=6.6, 4.2 Hz), 5.72 (ddd, 1H, *J*=6.3, 4.2, 1.2 Hz), 7.48 (t, 2H, *J*=7.8 Hz), 7.62 (tt, 1H, *J*=7.8, 1.2 Hz), 8.05 (dd, 2H, *J*=7.8, 1.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 36.7, 71.6, 79.2, 128.6, 128.9, 129.7, 133.7, 165.5, 174.1. HREIMS *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}O_4$: 220.0736; found: 220.0725. The enantiomeric excess of benzoyloxy-γ-lactone was determined by HPLC using a CHIRALCEL OD-H column (0.46 cm φ×25 cm); elution with 10% *i*-PrOH in hexane, t_R=17.4 min for (+)-isomer, t_R=19.6 min for (−)-isomer.
24. Asymmetric dihydroxylation of *trans*-3-pentenenitrile provided a 3,4-dihydroxypentanenitrile, which showed 80% ee in a HPLC-based analysis of the corresponding benzoate.
25. Kinetic hydrolysis of the racemic acetate (±-**18**) with Novozyme in 0.2 M Na–phosphate buffer did not give satisfactory results in terms of yield and enantiomeric excess.
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