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Total synthesis of squafosacin F: stereodivergent approach to mono-tetrahydrofuran acetogenins†

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Annonaceous acetogenins have a wide range of potential biological activities. The development of simple and diversity-oriented approaches to their synthesis is therefore important. We have achieved the first total synthesis of squafosacin F and assigned its absolute configuration. The key steps were an acid-mediated tandem intramolecular double cyclization to build the hydroxy-flanked mono-tetrahydrofuran core and decoration with the desired functionalities of the target natural product *via* highly stereoselective reactions.

Introduction

In the past 35 years a vast number of annonaceous acetogenins have been isolated from the leaves, seeds, roots, and bark of tropical plants of the Annonaceae family.[1] Acetogenins consist of four substructures, namely an α,β-unsaturated-γ-lactone, one to three tetrahydrofuran (THF) units with flanking hydroxy groups, a long alkyl tail, and an alkyl spacer linking the γ-lactone and tetrahydrofuran moieties. Annonaceous acetogenins are well-known compounds with potent biological activities, *e.g.*, antiviral, antineoplastic, antimalarial, immunosuppressive, and anticoagulant effects.[2] Many of the biological activities of acetogenins are attributed to their inhibitory effects on mitochondrial NADH-ubiquinone oxidoreductase (complex I).[3] Detailed structure–activity relationship studies have shown that the γ-lactone moiety and the hydroxy-flanked tetrahydrofuran moiety alone do not inhibit mitochondrial complex I activity, but inhibitory activity occurs when these components are linked by an alkyl spacer. The presence of a polar functional group such as a hydroxy group on the alkyl spacer is not necessary. A chain length of C_{13} is important for achieving the most potent inhibitory activity.[4]

cis-Solamin is a particularly active mono-tetrahydrofuran acetogenin.[5] It was isolated from a root extract of *Annona muricata* L. and its structure was determined by Cavé *et al.* in 1998. It has a C13 spacer and therefore shows strong mitochondrial complex I inhibitory activity. Because of its unique structure and biological activity, many studies of syntheses of this compound and its analogs have been performed.[6] In 2018, we reported its formal synthesis *via* tandem cyclization of a diepoxy ester to achieve stereoselective formation of the hydroxy-flanked mono-tetrahydrofuran core.[7]

In 2008, Wu *et al.* isolated squafosacin F from *Annona squamosa* L. and determined its structure. This compound is a mono-tetrahydrofuran acetogenin with a C13 spacer (Fig. 1).[8]

Squafosacin F is a diastereomer of *cis*-solamin but its stereochemistry is still uncertain. The signals at δ_H 3.85 (3H)/δ_C 83.2, 82.1, and 71.8, and δ_H 3.40 (1H)/δ_C 74.3 in the ^{1}H and ^{13}C NMR spectra of this compound indicate that squafosacin F has a tetrahydrofuran moiety flanked by two hydroxy groups in *threo* and *erythro* configurations.[9] The relative configuration in the important tetrahydrofuran region could not be determined because of the complex signals at C-17 and C-18, and it was not possible to determine whether the configuration was *threo*/*cis*/*erythro* or *threo*/*trans*/*erythro*. However, the absolute configurations of the oxymethine group were identified as 15*S* and 20*S* by using the modified Mosher's method.[10] This showed that the tetrahydrofuran was in a *cis* configuration. On the basis of this analysis, the absolute configuration of squafosacin F was identified as either 15*S*/16*S*/19*R*/20*S* (**1**) or 15*S*/16*R*/19*S*/20*S* (**2**) (Fig. 2). Although squafosacin F is expected to have potent biological activity, similar to that of *cis*-solamin, the synthesis of squafosacin F has not yet been reported. We undertook the synthesis of squafosacin F to prove that our developed tandem cyclization, which was used in the formal synthesis of *cis*-solamin,[7] provides a comprehensive method for mono-tetrahydrofuran acetogenin synthesis. Here, report the first total synthesis of squafosacin F and determination of its absolute configuration.

Results and discussion

Our retrosynthetic analysis of the candidate compound **1** is shown in Scheme 1. We envisioned that **1** could be obtained from terminal alkene **A** *via* a ruthenium-catalyzed Alder–ene reaction[11] with ethyl (*S*)-4-hydroxypent-2-ynoate (**3**). We

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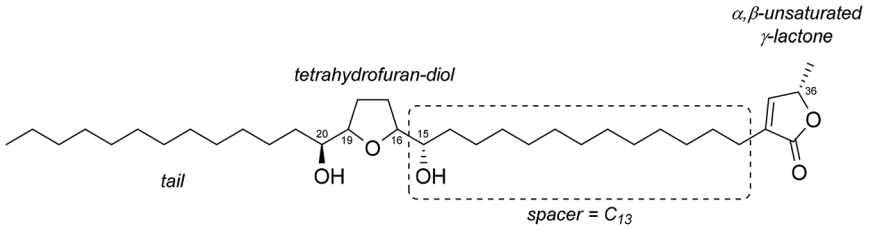


Fig. 1 Structure of mono-THF acetogenin squafosacin F.

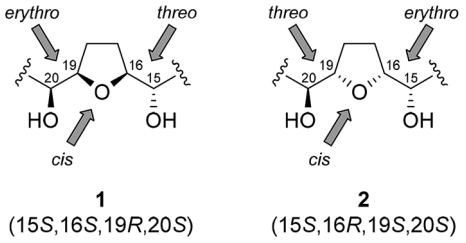
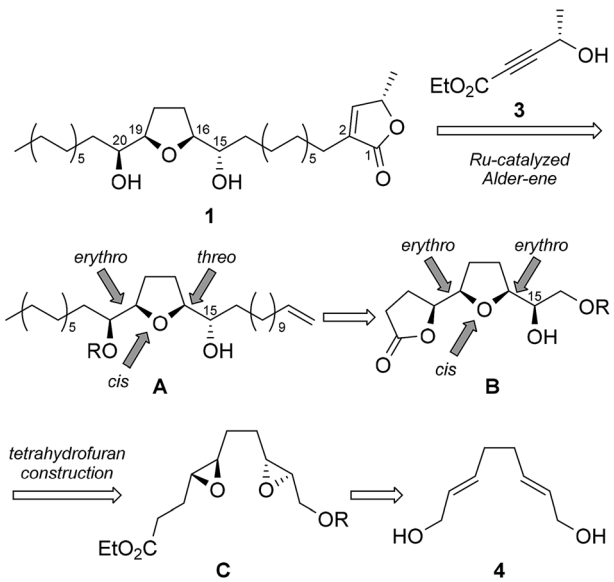


Fig. 2 Possible structures of *erythro*/*cis*/*threo* tetrahydrofuran-diol.

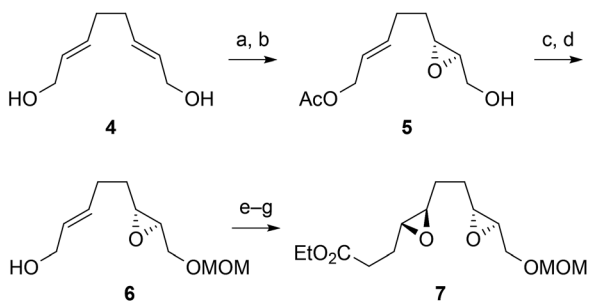


Scheme 1 Retrosynthetic analysis of **1**.

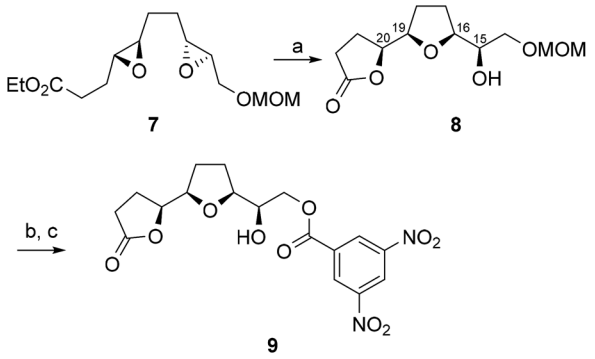
anticipated that the synthesis of *threo*/*cis*/*erythro* tetrahydrofurandiol **A** could achieved by elongation of the appropriate alkyl tail and introduction of the spacer unit *via* a stereoinversion at the C-15 position to give *erythro*/*cis*/*erythro* tetrahydrofuran-γ-lactone **B**. We expected that tetrahydrofuran-γ-lactone **B** could be obtained by using our developed acid-mediated tandem reaction for opening of the epoxide group in diepoxy ester **C**, which in turn could be synthesized by stepwise asymmetric epoxidation from the known allylic alcohol **4**.[12]

The synthesis of **1** started with the stereoselective synthesis of diepoxy ester **7** (Scheme 2). The symmetric *E*,*E*-diallylic alcohol **4** (ref. 12) was transformed to a monoacetate, which was then converted to epoxy alcohol **5** *via* a Sharpless asymmetric epoxidation under standard conditions.[13] The optical purity of **5** was determined to be >95% ee from the ^{1}H NMR spectrum in the presence of Chirabite-AR.[14] Protection of the primary hydroxy group in epoxy alcohol **5** with a methoxymethyl group and subsequent deacetylation gave *E*-allylic alcohol **6**, which was converted to an epoxy alcohol in 86% yield *via* sharpless asymmetric epoxidation. We obtained the unsaturated ester with excellent selectivity (>95 : 5, *E*/*Z*) by oxidation and then a Wittig reaction. Unexpected problems arose during reduction of the resulting unsaturated ester. Initially, we attempted to hydrogenate the double bond by using Pd/C, but the main reaction was epoxide ring opening and almost no diepoxy ester **7** was obtained (<5% yield). This problem was overcome by using a rhodium catalyst.[15] The order of addition of the reagents was important. Blowing hydrogen into a suspension of the unsaturated ester and Rh/Al_2O_3 in THF gave diepoxy ester **7** in moderate yield (51%) but was accompanied by formation of an epoxide-opened byproduct. Slow addition of the unsaturated ester to a suspension of pre-hydrogen-adsorbed Rh/Al_2O_3 in THF provided ester **7** in 80% yield over two steps from the epoxy alcohol. This suggests that hydrogen adsorption on the rhodium catalyst was not required for epoxide opening and that hydrogenation was faster than epoxide opening.

The ester was efficiently synthesized by catalytic hydrogenation using a rhodium catalyst with pre-stored hydrogen. NMR analysis of the diepoxy ester gave some unexpected results. In a previous study of *cis*-solamin synthesis,[7] tandem cyclization



Scheme 2 Synthesis of diepoxyester **7**. Reagents and conditions: (a) Ac_2O, pyridine, r.t., 52%; (b) TBHP, D-(−)-DIPT, $Ti(O^iPr)_4$, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 98% (>95% ee); (c) MOMCl, DIPEA, CH_2Cl_2, reflux; (d) K_2CO_3, MeOH, r.t., 88% (2 steps); (e) TBHP, D-(−)-DIPT, $Ti(O^iPr)_4$, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 86%; (f) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t. then $Ph_3P{=}CHCO_2Et$, r.t.; (g) H_2, Rh/Al_2O_3, THF, r.t., 80% (2 steps).



Scheme 3 Synthesis of tetrahydrofuran-γ-lactone **8**. Reagents and conditions: (a) 10-camphorsulfonic acid, H_2O, CH_2Cl_2, r.t., 91%; (b) 3,5-dinitrobenzoic acid, WSC, DMAP, CH_2Cl_2, r.t.; (c) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, −30 °C, 81% (2 steps).

caused by a small amount of an acid contaminant proceeded to form tetrahydrofuran-γ-lactone when NMR spectroscopic analysis of the corresponding diepoxy ester was performed in deuterated chloroform as the solvent. This observation triggered development of the acid-mediated tandem cyclization. However, in this case, diepoxy ester **7** was stable, despite the deuterated solvent, and no tetrahydrofuran-γ-lactone **8** was formed. This indicates that the acid sensitivity of the reaction using an *E*,*E*-diepoxide differed from that of the previously reported reaction using a *Z*,*Z*-diepoxide. Although a possible decrease in the reactivity was a concern, the tandem cyclization proceeded smoothly when *E*,*E*-diepoxy ester **7** was treated with 10-camphorsulfonic acid (0.2 equiv.) and water (1.0 equiv.) at room temperature in dichloromethane for 1.5 h; tetrahydrofuran-γ-lactone **8** was obtained with controlled stereochemistry at the C-15, C-16, C-19, and C-20 positions (91% yield; Scheme 3). The stereochemistry of **8** was confirmed by X-ray crystallographic analysis of the dinitrobenzoate **9**,[16] which was obtained by condensation of 3,5-dinitrobenzoic acid, removal of the methoxymethyl protecting group, and concomitant 1,2-acyl migration (Fig. 3).

This transformation can be explained by the mechanism shown in Scheme 4. First, acidic hydrolysis of the ester

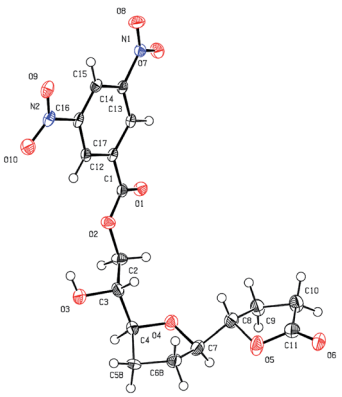
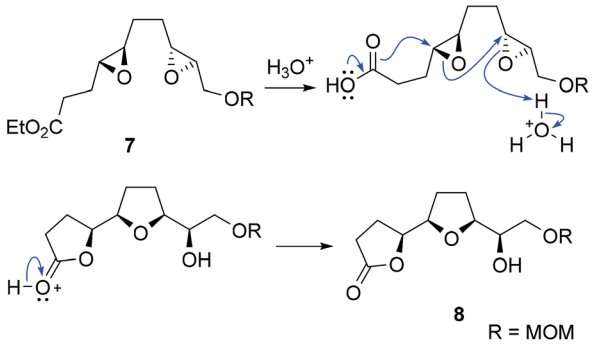


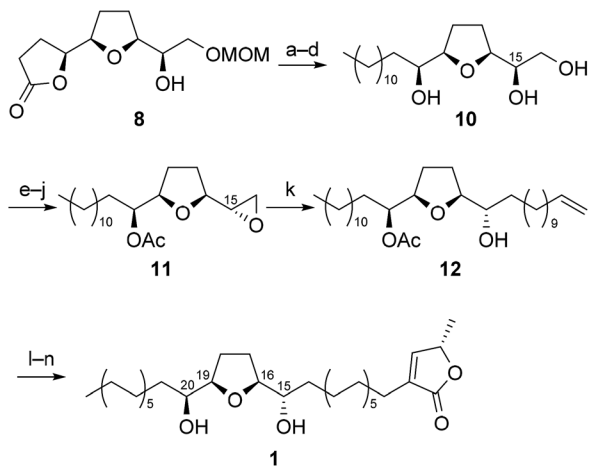
Fig. 3 ORTEP drawing of dinitrobenzoate **9**.



Scheme 4 Acid-catalyzed one-step construction of tetrahydrofuran-diol.

generates a carboxyl group *in situ*. The protonated epoxide oxygen acts as a leaving group, which leads to a sequential intramolecular S_N2-like cyclization of the carbonyl oxygen to form *erythro*/*cis*/*erythro* tetrahydrofuran-γ-lactone **8**.

Having obtained tetrahydrofuran-γ-lactone **8**, we introduced the appropriate alkyl linker, spacer, and γ-lactone to achieve the synthesis of **1**. First, we attached an alkyl linker to the tetrahydrofuran core. Half-reduction of **8** followed by a Wittig reaction of the resulting hemiacetal yielded an unsaturated alcohol as an inconsequential mixture (Scheme 5). Triol **10** was obtained by hydrogenation of the double bond, acid deprotection, protection as the acetonide derivative, and then treatment with acetic anhydride and pyridine to provide the corresponding acetate. Mild acidic deprotection of the acetonide and subsequent silylation of the resulting diol furnished the secondary alcohol, which underwent mesylation; subsequent treatment with



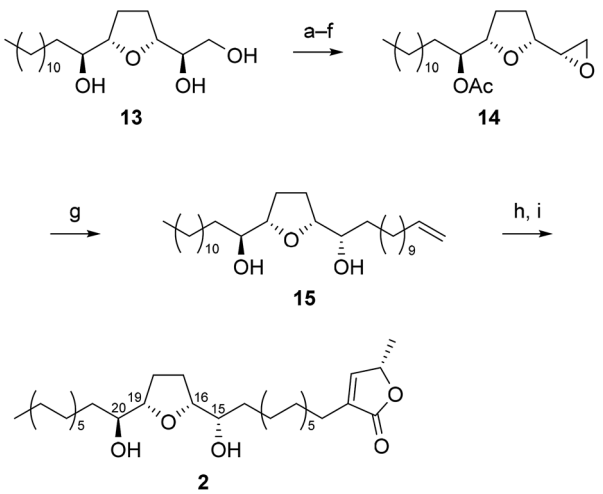
Scheme 5 Synthesis of **1**. Reagents and conditions: (a) DIBAH, CH_2Cl_2, −78 °C; (b) nonyltriphenylphosphonium bromide, BuLi, THF, 0 °C to r.t.; (c) H_2, Pd/C, MeOH, r.t.; (d) HCl, MeOH, 0 °C, 82% (4 steps); (e) 2,2-dimethoxypropane, *p*TsOH·H_2O, r.t.; (f) Ac_2O, pyridine, r.t.; (g) 80% AcOH, 50 °C; (h) TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t.; (i) MsCl, Et_3N, CH_2Cl_2, r.t.; (j) TBAF, THF, 50 °C, 87% (6 steps); (k) $CH_2{=}CH(CH_2)_9$-MgBr, CuI, THF, −60 °C, 79%; (l) DIBAH, CH_2Cl_2, −78 °C; (m) ethyl (*S*)-4-hydroxypent-2-ynoate (**3**), $CpRu(MeCN)_3PF_6$, DMF, r.t.; (n) $TsNHNH_2$, NaOAc, THF/H_2O, 60 °C, 65% (3 steps).

Table 1 Comparison of the ^{13}C NMR ($CDCl_3$) spectroscopic data for natural squafosacin F and synthetic **1** and **2**

Position	Natural squafosacin F δ^a [ppm]	Synthetic **1** δ^b [ppm]	Synthetic **2** δ^b [ppm]
1	173.9	173.9	173.9
2	134.3	134.4	134.2
3	25.3	25.2	25.2
4	27.4	27.4	27.3
5–13	25.6–29.7	25.7–29.7	26.0–29.7
14	33.2[c]	34.2[c]	33.1[c]
15	74.4	74.5	74.3
16	83.2	82.7	83.3
17	28.6	28.4	28.6
18	25.6	24.3	25.5
19	82.1	82.2	82.2
20	71.5	72.3	71.4
21	32.5[c]	33.1[c]	32.5[c]
22–29	25.6–29.7	25.7–29.7	26.0–29.7
30	31.9	31.9	31.9
31	22.7	22.7	22.6
32	14.1	14.1	14.1
33	148.9	148.8	148.8
34	77.4	77.4	77.4
35	19.2	19.2	19.2

[a] 100 MHz. [b] 125 MHz. [c] Assignments may be interchanged.

tetrabutylammonium fluoride at 0 °C for 10 min generated the alkoxide anion species *in situ*. The reaction mixture was warmed to 50 °C and then stirred at this temperature for 12 h. Subsequent cyclization to a sulfonate moiety proceeded smoothly in a one-pot system to afford epoxide **11** with complete inversion of the configuration at C-15. The conversion of epoxide **11** to **1** was performed by using the method reported by Brown *et al.*[17] Introduction of the alkyl spacer into epoxide **11** was achieved by a copper-catalyzed Grignard reaction to give terminal alkene **12**.



Scheme 6 Synthesis of **2**. Reagents and conditions: (a) 2,2-dimethoxypropane, *p*TsOH·H_2O, r.t.; (b) Ac_2O, pyridine, r.t.; (c) 80% AcOH, 50 °C; (d) TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t.; (e) MsCl, Et_3N, CH_2Cl_2, r.t.; (f) TBAF, THF, 50 °C, 75% (6 steps); (g) $CH_2{=}CH(CH_2)_9MgBr$, CuI, THF, −60 °C, 77%; (h) ethyl (*S*)-4-hydroxypent-2-ynoate (**3**), $CpRu(MeCN)_3PF_6$, DMF, r.t.; (i) $TsNHNH_2$, NaOAc, THF/H_2O, 60 °C, 89% (2 steps).

Deacetylation of **12** and a subsequent ruthenium-catalyzed Alder–ene reaction[11] with ethyl (*S*)-4-hydroxypent-2-ynoate (**3**) afforded the corresponding γ-lactone. Finally, reduction of the isolated double bond by using *p*-toluenesulfonylhydrazide and NaOAc furnished **1** with the 15*S*/16*S*/19*R*/20*S* configuration.

The ^1H NMR spectra of natural squafosacin F[8] and synthetic compound **1** are similar. However, careful comparison of the ^{13}C NMR spectra revealed minor discrepancies at three positions, namely C-14: δ_C 33.2 *vs.* 34.2; C-18: δ_C 25.6 *vs.* 24.3; and C-20: δ_C 71.5 *vs.* 72.3 (Table 1).

The differences between the ^{13}C NMR spectroscopic shifts were slight, therefore we synthesized another candidate compound, *i.e.*, **2**, from triol **13**, which was an intermediate in our previous synthesis of *cis*-solamin,[7] by using a similar reaction sequence to that shown in Scheme 6. Synthesis of **2** with the 15*S*/16*R*/19*S*/20*S* configuration was successful. Comparison of the ^{13}C NMR spectra showed that the spectrum of **2** was a better match than that of **1** for the spectrum of natural squafosacin F. The spectral and physical properties of **2**, namely the ^1H and ^{13}C NMR spectra, IR spectrum, HRMS results, and optical rotation, perfectly matched those of natural squafosacin F. The first total synthesis of squafosacin F (**2**) had therefore been accomplished and its absolute configuration was identified as 15*S*,16*R*,19*S*,20*S*,36*S*.

Conclusions

In conclusion, a diversity-oriented synthetic approach enabled the first total synthesis of squafosacin F (**2**) and the absolute configuration was established with the help of a ^{13}C NMR spectroscopic comparison of both possible configurations at C-16 and C-19. The salient features of the developed synthesis are tandem cyclization of a diepoxy ester with a Brønsted acid and **1**

equiv. of water, introduction of a long alkyl linker and spacer, and α,β-unsaturated-γ-lactone formation by a ruthenium-catalyzed Alder–ene reaction. In addition, our developed acid-mediated tandem cyclization can be used to control the stereochemistry of the tetrahydrofuran moiety flanked by two hydroxy groups by selecting an appropriate configuration of the diepoxy ester. This synthetic method can be used to construct natural mono-tetrahydrofuran acetogenins with various configurations. We hope that this strategy will open up a new approach to the preparation of natural mono-tetrahydrofuran acetogenins and of various analogs with similar structures.

Experimental section

General experimental procedures

Melting points (mp) were measured using the Yanaco melting point apparatus MP-S3 and were uncorrected. Optical rotations were measured with a JASCO P-1030 polarimeter. IR spectra were recorded with a JASCO FT-IR/620 spectrometer. Single crystal X-ray diffraction was recorded using a MacScience Co., Ltd DIP 2020 Image Plate. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Biospin AVANCE III HD 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) and a Bruker Biospin AVANCE III HD 500 (500 MHz for ^{1}H, 125 MHz for ^{13}C). The reported chemical shifts (δ) in parts per million (ppm) were relative to the internal $CHCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C); the coupling constant (J) values were measured in hertz. The coupling patterns are denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). HR-ESI-MS spectra were obtained using a Micromass LCT spectrometer with a time-of-flight (TOF) analyzer. Elemental analysis data were obtained using an Elementar Vario EL. Precoated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative thin-layer chromatography (TLC). Flash column chromatography was performed using Kanto Chemical silica gel 60N (spherical, natural) 40–50 μm. All reagents (Aldrich, Kanto, TCI, and Wako) and solvents were of commercial quality and were used as received.

(2*E*,6*E*)-8-Hydroxyocta-2,6-dien-1-yl acetate (16). To a stirred solution of (2*E*,6*E*)-octa-2,6-diene-1,8-diol (**4**) (1.00 g, 7.03 mmol) in pyridine (0.566 mL, 7.03 mmol) was added acetic anhydride (0.665 mL, 7.03 mmol) at room temperature. After stirring the mixture for 5 min, the reaction mixture was concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 4 : 1 to 0 : 1) to give monoacetate **16** (668 mg, 52% yield) as a colorless oil, diacetate (445 mg, 28% yield) as a colorless oil, and **4** (100 mg, 10% recovered yield): R_f 0.25 (hexane/EtOAc = 1 : 1); IR (neat) ν_{max} 3417, 3022, 2926, 2850, 1740, 1672, 1236, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (1H, m), 5.68–5.65 (2H, m), 5.59 (1H, m), 4.51 (2H, dd, J = 0.6, 6.4 Hz), 4.11–4.07 (2H, m), 2.17–2.14 (4H, m), 2.06 (3H, s), 1.54 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (C), 135.4 (CH), 131.9 (CH), 129.7 (CH), 124.4 (CH), 65.1 (CH_2), 63.6 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 21.0 (CH_3); MS (ESI-TOF) m/z 207 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{10}H_{16}O_3Na$ 207.0997, found 207.0994; anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.07; H, 8.80.

(*E*)-5-((2*R*,3*R*)-3-(Hydroxymethyl)oxiran-2-yl)pent-2-en-1-yl acetate (5). To a cold (−20 °C) suspension of 4 Å molecular sieves (2.79 g) in CH_2Cl_2 (40.0 mL) were added D-(−)-DIPT (0.478 mL, 2.27 mmol), $Ti(O^iPr)_4$ (0.446 mL, 1.51 mmol), and TBHP (6.50 M solution in CH_2Cl_2, 7.00 mL, 45.3 mmol). After stirring the mixture for 30 min at the same temperature, a solution of monoacetate **16** (2.79 g, 15.1 mmol) in CH_2Cl_2 (202 mL) was dropwised over 3.5 h. After stirring for 30 min, to the reaction mixture was added brine and then warmed to room temperature. After stirring for 30 min, the mixture was added $MgSO_4$ (1.06 g) and Celite (133 mg) and after stirring for 15 min, the mixture was passed through a pad of Celite and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 2 to 0 : 1) to give epoxyalcohol **5** (2.97 g, 98% yield, >95% ee) as a colorless oil: R_f 0.30 (hexane/EtOAc = 1 : 2); $[\alpha]_D^{25}$ +19.9 (*c* 1.68, $CHCl_3$); IR (neat) ν_{max} 3444, 2933, 1739, 1672, 1239 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78 (1H, m), 5.63 (1H, m), 4.52 (2H, d, J = 6.2 Hz), 3.89 (1H, ddd, J = 2.6, 5.2, 12.4 Hz), 3.64 (1H, m), 2.97 (1H, dt, J = 2.3, 5.8 Hz), 2.92 (1H, dt, J = 4.0, 2.6 Hz), 2.30–2.15 (2H, m), 2.06 (3H, s), 1.72–1.65 (2H, m), 1.61 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8 (C), 134.6 (CH), 124.8 (CH), 64.9 (CH_2), 61.6 (CH_2), 58.5 (CH), 55.3 (CH), 30.8 (CH_2), 28.6 (CH_2), 20.9 (CH_3); MS (ESI-TOF) m/z 223 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{10}H_{16}O_4Na$ 223.0946, found 223.0939; anal. calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.83; H, 8.14.

Determination of optical purity of synthetic (+)-epoxyalcohol 5. Before comparison between synthetic (+)-epoxyalcohol **5** and synthetic racemic epoxyalcohol *rac*-**5** with Chirabite-AR, we examined the effect of differing amounts of Chirabite-AR regarding *rac*-**5**, to determine sufficient signal separations between (+)- and (−)-**5**. Consequently, a mixture of *rac*-**5** with 100 mol% of Chirabite-AR was measured sequentially by 400 MHz ^{1}H NMR at room temperature in $CDCl_3$, the methine proton signal separations were observed between 3.92 to 3.86 ppm, and good enantiomeric discrimination was achieved for (+)- and (−)-**5**. NMR analysis of (+)-epoxyalcohol **5** under the same conditions as used to obtain the results indicated that no signal derived from (−)-**5** was observed. Therefore, the optical purity of synthetic (+)-**5** was determined as >95% ee.

(*E*)-5-((2*R*,3*R*)-3-((Methoxymethoxy)methyl)oxiran-2-yl)pent-2-en-1-ol (6). To a stirred solution of epoxyalcohol **5** (2.97 g, 12.8 mmol) in CH_2Cl_2 (74.0 mL) were added DIPEA (25.8 mL, 148 mmol) and MOMCl (3.37 mL, 44.4 mmol) at 0 °C, and then refluxed. After stirring for 3 h, the mixture was cooled to room temperature, and then quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with 1.0 M HCl aq., H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude MOM ether which was used for the next step without further purification.

To a stirred solution of the crude MOM ether in methanol (46.3 mL) was added K_2CO_3 (9.61 g, 69.5 mmol) at room temperature. After stirring the mixture for 30 min, the mixture was diluted with Et_2O, and then was passed through a pad of silica gel and then concentrated *in vacuo*. The residue was

purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 2) to give allylic alcohol **6** (2.65 g, 88% yield for 2 steps) as a colorless oil: R_f 0.60 (hexane/EtOAc = 1 : 2); $[\alpha]_D^{25}$ +16.5 (*c* 0.83, $CHCl_3$); IR (neat) ν_{max} 3433, 2991, 2933, 2863 cm^{-1}; ^1H N/MR ($CDCl_3$, 400 MHz) δ 5.72–5.69 (2H, m), 4.66 (1H, d, J = 7.5 Hz), 4.64 (1H, d, J = 7.5 Hz), 4.12–4.08 (2H, m), 3.70 (1H, dd, J = 3.8, 11.6 Hz), 3.57 (1H, dd, J = 5.4, 11.6 Hz), 3.38 (3H, s), 2.94 (1H, ddd, J = 2.3, 3.8, 5.8 Hz), 2.86 (1H, dt, J = 2.1, 5.8 Hz), 2.30–2.18 (2H, m), 1.71–1.67 (2H, m), 1.52 (1H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 131.4 (CH), 130.0 (CH), 96.5 (CH_2), 67.8 (CH_2), 63.4 (CH_2), 56.7 (CH), 55.9 (CH), 55.3 (CH_3), 31.1 (CH_2), 28.6 (CH_2); MS (ESI-TOF) *m*/*z* 225 $[M + Na]^+$ (100); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{18}O_4Na$ 225.1103, found 225.1104; anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.21; H, 8.97.

Ethyl 3-((2*R*,3*R*)-3-(2-((2*R*,3*R*)-3-((methoxymethoxy)methyl) oxiran-2-yl)ethyl)oxiran-2-yl)propanoate (7). To a stirred solution of epoxyalcohol **6** (1.69 g, 7.74 mmol) in CH_2Cl_2 (155 mL) were added $NaHCO_3$ (2.60 g, 30.9 mmol) and Dess-Martin periodinane (6.57 g, 15.5 mmol) at room temperature. After stirring for 40 min, the mixture was added Ph_3PCHCO_2Et (4.04 g, 11.6 mmol) at same temperature. After stirring for 15 min, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with 10% aqueous Na_2SO_3 solution, H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude α,β-unsaturated ester which was used for the next step without further purification.

After a suspension of 5% Rh/Al_2O_3 (308 mg) in THF (268 mL) was stirred under hydrogen atmosphere at room temperature for 30 min, a solution of above crude α,β-unsaturated ester in THF (40.0 mL) was added to the stirred suspension. After stirring for 2 h, argon was blown into the reaction mixture in order to remove hydrogen and then diluted with Et_2O, filtered through silica gel pad, and concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2 : 1) to give bisepoxyester **7** (1.15 g, 51% yield for 2 steps) as a colorless oil: R_f 0.30 (hexane/EtOAc = 1 : 1); $[\alpha]_D^{25}$ +39.5 (*c* 0.28, $CHCl_3$); IR (neat) ν_{max} 2981, 2935, 1733, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.66 (1H, d, J = 7.6 Hz), 4.64 (1H, d, J = 7.6 Hz), 4.14 (2H, q, J = 7.2 Hz), 3.73 (1H, dd, J = 3.5, 11.7 Hz), 3.56 (1H, dd, J = 5.5, 11.7 Hz), 3.37 (3H, s), 2.96 (1H, ddd, J = 2.3, 3.5, 5.6 Hz), 2.90 (1H, m), 2.80–2.74 (2H, m), 2.47–2.41 (2H, m), 1.96 (1H, m), 1.82–1.60 (5H, m), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8 (C), 96.6 (CH_2), 67.7 (CH_2), 60.5 (CH_2), 58.0 (CH), 57.5 (CH), 56.7 (CH), 55.5 (CH), 55.3 (CH_3), 30.4 (CH_2), 28.2 (CH_2), 28.0 (CH_2), 27.1 (CH_2), 14.2 (CH_3); MS (ESI-TOF) *m*/*z* 311 $[M + Na]^+$ (100); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{24}O_6Na$ 311.1471, found 311.1459; anal. calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.16; H, 8.29.

(2*S*,2′*R*,5′*S*)-5′-((*R*)-1-Hydroxy-2-(methoxymethoxy)ethyl)hexahydro-[2,2′-bifuran]-5(2*H*)-one (8). To a stirred solution of bisepoxyester **7** (35.1 mg, 0.122 mmol) in CH_2Cl_2 (0.700 mL) was added a solution of (±)-10-camphorsulfonic acid (5.7 mg, 0.0244 mmol) in CH_2Cl_2 (1.70 mL) and H_2O (0.0022 mL, 0.122 mmol) at room temperature. After stirring for 2 h, the reaction mixture was concentrated and then purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 10) to give tetrahydrofuran **8** (28.9 mg, 91% yield) as a colorless oil: R_f 0.30 (hexane/EtOAc = 1 : 4); $[\alpha]_D^{25}$ +14.4 (*c* 0.83, $CHCl_3$); IR (neat) ν_{max} 3434, 2948, 2889, 1767, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.67 (1H, d, J = 7.0 Hz), 4.66 (1H, d, J = 7.0 Hz), 4.44 (1H, m), 3.99 (1H, m), 3.90 (1H, m), 3.75–3.67 (2H, m), 3.57 (1H, m), 3.39 (3H, s), 2.69 (1H, brd, J = 4.0 Hz), 2.60–2.45 (2H, m), 2.30 (1H, m), 2.15–1.92 (4H, m), 1.80 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (C), 97.2 (CH_2), 81.2 (CH), 80.2 (CH), 79.9 (CH), 72.3 (CH), 70.4 (CH_2), 55.5 (CH_3), 28.1 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 23.9 (CH_2); MS (ESI-TOF) *m*/*z* 283 $[M + Na]^+$ (100); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{20}O_6Na$ 283.1158, found 283.1150; anal. calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.23; H, 7.81.

(*R*)-2-Hydroxy-2-((2*R*,2′*S*,5*S*)-5′-oxooctahydro-[2,2′-bifuran]-5-yl)ethyl 3,5-dinitrobenzoate (9). To a stirred solution of tetrahydrofuran **8** (20.0 mg, 0.0769 mmol) in CH_2Cl_2 (2.56 mL) were added WSC (88.5 mg, 0.462 mmol), DMAP (2.8 mg. 0.0231 mol), and 3,5-dinitrobenzoic acid (48.9 mg, 0.231 mmol) at room temperature. After stirring for 15 min, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude dinitrobenzoate which was used for the next step without further purification.

To a solution of above crude dinitrobenzoate in CH_2Cl_2 (2.56 mL) were added Me_2S (0.256 mL, 3.50 mmol) and $BF_3 \cdot OEt_2$ (0.0285 mL, 0.230 mmol) at −30 °C. After stirring for 1.5 h, the reaction mixture was quenched with Et_3N (0.0107 mL, 0.0769 mmol) and warmed to room temperature. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 2) to give dinitrobenzoate **9** (25.5 mg, 81% yield for two steps) as a white needle: ^1H NMR ($CDCl_3$, 400 MHz) δ 9.24 (1H, m), 9.19–9.15 (2H, m), 4.63 (1H, dd, J = 3.0, 11.6 Hz), 4.57–4.43 (2H, m), 4.20–3.92 (3H, m), 2.60–2.53 (2H, m), 2.40–2.22 (2H, m), 2.18–1.92 (4H, m), 1.52 (1H, bs); ESI-MS *m*/*z* 433 $[M + Na]^+$ (100); HR-ESI-MS *m*/*z* 433.0858 (calcd for $C_{17}H_{18}N_2O_{10}Na$, 433.0859).

(*R*)-1-((2*S*,5*R*)-5-((*S*)-1-Hydroxytridecyl)tetrahydrofuran-2-yl) ethane-1,2-diol (10). To a stirred solution of tetrahydrofuran **8** (794 mg, 3.05 mmol) in CH_2Cl_2 (61.0 mL) was added DIBAH (1.02 M solution in hexane, 8.97 mL, 9.15 mmol) at −78 °C. After stirring for 30 min, the reaction mixture was added $Na_2SO_4 \cdot 10H_2O$ (50.0 mg) slowly, diluted with CH_2Cl_2, and then warmed to room temperature. After stirring for 24 h, the mixture was added $MgSO_4$. After stirring for 15 min, the resulting mixture passed through a pad of Na_2SO_4 and then concentrated *in vacuo* to give a crude hemiacetal which was used for the next step without further purification.

To a stirred suspension of nonyltriphenylphosphonium bromide (8.00 g, 17.0 mmol) in THF (41.0 mL) was added BuLi (1.64 M solution in hexane, 9.30 mL, 15.3 mmol) dropwise at 0 °C and the mixture was stirred for 1.5 h at same temperature.

A solution of the above crude hemiacetal in THF (20.0 mL) was then added to the mixture at 0 °C and then warmed to room temperature. After stirring for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, diluted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was passed through a pad of silica gel (hexane/EtOAc = 1 : 1) and then concentrated *in vacuo* to give a crude diol which was used for the next step without further purification.

To a solution of above crude diol in MeOH (117 mL) was added Pd/C (5%, 117 mg), and then was stirred under H_2 atmosphere. After stirring for 1 h, the reaction mixture was diluted with Et_2O and passed through a pad of silica gel and then concentrated *in vacuo*. The residue was passed through a pad of silica gel (hexane/EtOAc = 1 : 2) and then concentrated *in vacuo*. The residue was passed through a pad of silica gel (toluene/EtOAc = 2 : 1) and then concentrated *in vacuo* to give a crude diol which was used for the next step without further purification.

To a solution of above crude diol in CH_2Cl_2 (22.1 mL) were added Me_2S (7.37 mL, 99.6 mmol) and $BF_3{\cdot}OEt_2$ (1.36 mL, 11.0 mmol) at −30 °C. After stirring for 30 min, the reaction mixture was quenched with Et_3N (3.08 mL, 22.1 mmol) and warmed to room temperature. The mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 4 to 0 : 1) to give triol **10** (575 mg, 57% yield for four steps) as a white plate: R_f 0.30 ($CHCl_3$/MeOH = 15 : 1); mp 76−77 °C; $[\alpha]_D^{25}$ +2.7 (*c* 1.04, $CHCl_3$); IR (KBr) ν_{max} 3393, 3283, 2925, 2850, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.99 (1H, dt, J = 4.1, 7.1 Hz), 3.89 (1H, m), 3.87–3.81 (2H, m), 3.71 (1H, dd, J = 3.9, 11.2 Hz), 3.61 (1H, dd, J = 6.4, 11.2 Hz), 2.00–1.87 (3H, m), 1.82 (1H, m), 1.54–1.20 (22H, m), 0.88 (3H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.4 (CH), 80.2 (CH), 73.4 (CH), 72.2 (CH), 63.9 (CH_2), 33.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2) × 2, 29.64 (CH_2), 29.63 (CH_2), 29.61 (CH_2), 29.56 (CH_2), 29.3 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 24.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3); MS (ESI-TOF) *m*/*z* 353 $[M + Na]^+$ (100); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{38}O_4Na$ 353.2668, found 353.2672; anal. calcd for $C_{19}H_{38}O_4$: C, 69.05; H, 11.59. Found: C, 69.28; H, 11.54.

(*S*)-1-((2*R*,5*S*)-5-((*S*)-Oxiran-2-yl)tetrahydrofuran-2-yl)tridecyl acetate (11). To a stirred solution of triol **10** (102 mg, 0.309 mmol) in 2,2-dimethoxypropane (10.3 mL) was added *p*TsOH·H_2O (5.9 mg, 0.0310 mmol) at room temperature. After stirring for 4 h, the mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude acetonide which was used for the next step without further purification.

Acetic anhydride (3.10 mL, 32.8 mmol) was added to a stirred solution of the above crude acetonide in pyridine (3.10 mL, 38.5 mmol) at room temperature. After stirring for 12 h, the mixture was concentrated *in vacuo* to give a crude acetate which was used for the next step without further purification.

To the above crude acetate was added 80% AcOH aq. (3.10 mL) at room temperature. The mixture was warmed to 50 °C and after 40 min recooled to room temperature. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude diol which was used for the next step without further purification.

To a stirred solution of the above crude diol in CH_2Cl_2 (0.618 mL) were added Et_3N (0.258 mL, 1.85 mmol), TBSCl (140 mg, 0.929 mmol), and DMAP (3.8 mg, 0.0311 mmol) at 0 °C and then warmed to room temperature. After stirring for 3.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude TBS ether which was used for the next step without further purification.

To a stirred solution of the above crude TBS ether in CH_2Cl_2 (3.10 mL) were added Et_3N (0.172 mL, 1.23 mmol) and MsCl (0.048 mL, 0.620 mmol) at 0 °C and then warmed to room temperature. After stirring for 45 min, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude mesylate which was used for the next step without further purification.

To a stirred solution of the above crude mesylate in THF (3.10 mL) were added TBAF (1.00 M solution in THF, 0.773 mL, 0.773 mmol) at room temperature. After stirring for 1 h, the mixture was warmed to 50 °C and stirred for 12 h. The mixture was diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 6 : 1) to give epoxide **11** (95.3 mg, 87% yield for six steps) as a white waxy solid: R_f 0.60 (hexane/EtOAc = 1 : 1); mp 31–32 °C; $[\alpha]_D^{25}$ −10.5 (*c* 0.19, $CHCl_3$); IR (KBr) ν_{max} 2925, 2854, 1741, 1466, 1370, 1239 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.98 (1H, ddd, J = 4.4, 4.7, 8.8 Hz), 3.93 (1H, m), 3.83 (1H, m), 2.94 (1H, ddd, J = 2.6, 4.3, 7.1 Hz), 2.73 (1H, dd, J = 4.3, 5.2 Hz), 2.65 (1H, dd, J = 2.6, 5.2 Hz), 2.07 (3H, s), 2.05–1.76 (4H, m), 1.37–1.15 (22H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (C), 80.8 (CH), 78.7 (CH), 74.4 (CH), 53.8 (CH), 44.0 (CH_2), 31.9 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2) × 2, 29.6 (CH_2), 29.5 (CH_2) × 2, 29.3 (CH_2), 28.1 (CH_2), 26.8 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 14.1 (CH_3); MS (ESI-TOF) *m*/*z* 377 $[M + Na]^+$ (100); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{38}O_4Na$ 377.2668, found 377.2664; anal. calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 70.97; H, 10.95.

(*S*)-1-((2*R*,5*S*)-5-((*S*)-1-Hydroxytridec-12-en-1-yl) tetrahydrofuran-2-yl)tridecyl acetate (12). At −60 °C, undec-10-enylmagnesium bromide (0.40 M solution in THF, 1.40 mL, 0.560 mmol) was added dropwise to a suspension of CuI (53.8 mg, 0.283 mmol) in THF (0.40 mL). The mixture was warmed to −30 °C and after 20 min recooled to −60 °C whereupon a solution of epoxide **11** (50.1 mg, 0.141 mmol) in THF (1.00 mL) was added dropwise. The mixture was allowed to warm to −20 °C over 4 h. Saturated aqueous NH_4Cl solution/NH_3 (8 : 1, 1.40 mL) was added to the reaction mixture. The mixture was diluted with Et_2O, washed with saturated aqueous

NH_4Cl solution, H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 7 : 1) to give alcohol **12** (56.8 mg, 79% yield) as a colorless oil: R_f 0.35 (hexane/EtOAc = 7 : 1); $[\alpha]_D^{25}$ −11.4 (*c* 0.75, $CHCl_3$); IR (neat) ν_{max} 3545, 2925, 2854, 1742, 1640, 1466, 1370, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.81 (1H, ddt, J = 10.1, 16.9, 6.8 Hz), 3.98 (1H, dt, J = 4.9, 5.7 Hz), 3.73 (1H, q, J = 6.2 Hz), 3.32 (1H, dt, J = 5.7, 6.3 Hz), 2.07 (3H, s), 2.06–2.00 (2H, m), 1.94–1.75 (3H, m), 1.68 (1H, m), 1.59–1.17 (44H, m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (C), 139.3 (CH), 114.1 (CH_2), 82.8 (CH), 80.5 (CH), 74.5 (CH), 74.1 (CH), 33.8 (CH_2), 31.9 (CH_2), 31.1 (CH_2), 29.7 (CH_2), 29.65 (CH_2), 29.62 (CH_2) × 2, 29.57 (CH_2) × 4, 29.54 (CH_2), 29.47 (CH_2) × 2, 29.46 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 25.4 (CH_2), 22.7 (CH_2), 21.2 (CH_3), 14.1 (CH_3); MS (ESI-TOF) m/z 531 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{32}H_{60}O_4Na$ 531.4389, found 531.4391; anal. calcd for $C_{32}H_{64}O_4$: C, 75.54; H, 11.89. Found: C, 75.37; H, 11.84.

(*S*)-3-((*S*)-13-Hydroxy-13-((2*S*,5*R*)-5-((*S*)-1-hydroxytridecyl) tetrahydrofuran-2-yl)tridecyl)-5-methylfuran-2(5*H*)-one (1). To a stirred solution of alcohol **12** (24.1 mg, 0.0474 mmol) in CH_2Cl_2 (0.948 mL) was added DIBAH (1.03 M solution in hexane, 0.0920 mL, 0.0893 mmol) at −78 °C. After stirring for 45 min, the reaction mixture was added $Na_2SO_4 \cdot 10H_2O$ (100 mg) slowly, diluted with Et_2O, and then warmed to room temperature. After stirring for 30 min, the mixture was added $MgSO_4$. After stirring for 15 min, the resulting mixture passed through a pad of Na_2SO_4 and then concentrated *in vacuo* to give a crude diol which was used for the next step without further purification.

$[CpRu(CH_3CN)_3]^+PF_6^-$ (2.1 mg, 0.00484 mmol) was added to a stirred solution of the above crude diol and (*S*)-4-hydroxypent-2-ynoate **3** (10.1 mg, 0.0711 mmol) in DMF (0.948 mL). The solution was allowed to stir at room temperature for 1 h before the reaction mixture was diluted with Et_2O and passed through a plug of silica gel. The mixture was washed with 1.0 M HCl aq., H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude butenolide.

To a solution of the above crude butanolide and $TsNHNH_2$ (618 mg, 3.32 mmol) in DME (4.80 mL) was added a solution of NaOAc (311 mg, 3.79 mmol) in H_2O (4.80 mL). The mixture was heated at 80 °C for 12 h, and then cooled to room temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 1) to give butenolide **1** (17.4 mg, 65% yield for three steps) as a white waxy solid: R_f 0.40 (hexane/EtOAc = 1 : 1); mp 89−90 °C; $[\alpha]_D^{25}$ +13.2 (*c* 0.19, $CHCl_3$); IR (KBr) ν_{max} 3450, 2920, 2849, 1734, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.98 (1H, dt, J = 1.5, 1.6 Hz), 4.99 (1H, ddq, J = 6.8, 13.6, 1.7 Hz), 3.90 (1H, dt, J = 3.2, 7.3 Hz), 3.83 (1H, m), 3.81 (1H, m), 3.44 (1H, m), 2.27 (1H, dt, J = 8.1, 1.7 Hz), 2.25 (1H, dt, J = 8.1, 1.7 Hz), 1.98–1.90 (2H, m), 1.88–1.66 (4H, m), 1.58–1.19 (44H, m), 1.40 (3H, d, J = 6.9 Hz), 0.88 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9 (C), 148.8 (CH), 134.4 (C), 82.7 (CH), 82.2 (CH), 77.4 (CH), 74.5 (CH), 72.3 (CH), 34.2 (CH_2), 33.1 (CH_2), 31.9 (CH_2), 29.69 (CH_2) × 2, 29.66 (CH_2) × 3, 29.64 (CH_2), 29.60 (CH_2), 29.57 (CH_2) × 2, 29.56 (CH_2) × 2, 29.5 (CH_2), 29.34 (CH_2), 29.28 (CH_2), 29.2 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.9 (CH_2), 28.7 (CH_2), 25.2 (CH_2), 24.3 (CH_2), 22.7 (CH_2), 19.2 (CH_3), 14.1 (CH_3); MS (ESI-TOF) m/z 587 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{35}H_{64}O_5Na$ 587.4651, found 587.4655; anal. calcd for $C_{35}H_{64}O_5$: C, 74.42; H, 11.42. Found: C, 74.32; H, 11.55.

(*S*)-1-((2*S*,5*R*)-5-((*S*)-Oxiran-2-yl)tetrahydrofuran-2-yl)tridecyl acetate (14). To a stirred solution of triol **13** (12.2 mg, 0.0369 mmol) in 2,2-dimethoxypropane (1.20 mL) was added *p*$TsOH \cdot H_2O$ (0.7 mg, 0.00368 mmol) at room temperature. After stirring for 12 h, the mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude acetonide which was used for the next step without further purification.

Acetic anhydride (0.369 mL, 3.90 mmol) was added to a stirred solution of the above crude acetonide in pyridine (0.369 mL, 4.58 mmol) at room temperature. After stirring for 12 h, the mixture was concentrated *in vacuo* to give a crude acetate which was used for the next step without further purification.

To the above crude acetate was added 80% AcOH aq. (0.369 mL) at room temperature. The mixture was warmed to 50 °C and after 40 min recooled to room temperature. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude diol which was used for the next step without further purification.

To a stirred solution of the above crude diol in CH_2Cl_2 (0.0740 mL) were added Et_3N (0.0310 mL, 0.222 mmol), TBSCl (16.7 mg, 0.111 mmol), and DMAP (0.5 mg, 0.00409 mmol) at 0 °C and then warmed to room temperature. After stirring for 3.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude TBS ether which was used for the next step without further purification.

To a stirred solution of the above crude TBS ether in CH_2Cl_2 (0.369 mL) were added Et_3N (0.0206 mL, 0.148 mmol) and MsCl (0.00571 mL, 0.0738 mmol) at 0 °C and then warmed to room temperature. After stirring for 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude mesylate which was used for the next step without further purification.

To a stirred solution of the above crude mesylate in THF (0.369 mL) were added TBAF (1.00 M solution in THF, 0.0923 mL, 0.0923 mmol) at room temperature. After stirring for 1 h, the mixture was warmed to 50 °C and stirred for 12 h. The mixture was diluted with Et_2O, washed with H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 2 : 1) to give epoxide **14** (9.8 mg, 75% yield for six steps) as a colorless oil: R_f 0.55 (hexane/EtOAc = 1 : 1); $[\alpha]_D^{25}$ −13.4 (*c* 0.95, $CHCl_3$); IR (neat) ν_{max} 2925, 2854, 1739, 1467, 1372, 1240, 1075, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.87 (1H, dt, J = 7.7, 5.3 Hz), 4.06 (1H,

dt, J = 5.3, 6.6 Hz), 3.91 (1H, dt, J = 4.8, 6.6 Hz), 2.99 (1H, ddd, J = 2.7, 4.0, 4.8 Hz), 2.79 (1H, dd, J = 4.0, 4.9 Hz), 2.58 (1H, dd, J = 2.7, 4.9 Hz), 2.09 (3H, s), 2.06–1.96 (2H, m), 1.76 (1H, m), 1.65 (1H, m), 1.35–1.19 (22H, m), 0.88 (3H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (C), 80.1 (CH), 78.9 (CH), 75.1 (CH), 53.1 (CH), 45.3 (CH_2), 31.9 (CH_2), 31.0 (CH_2), 29.6 (CH_2), 29.6 (CH_2) × 2, 29.5 (CH_2), 29.4 (CH_2) × 2, 29.3 (CH_2), 27.8 (CH_2), 27.6 (CH_2), 25.4 (CH_2), 22.6 (CH_2), 21.1 (CH_3), 14.1 (CH_3); MS (ESI-TOF) m/z 377 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{38}O_4Na$ 377.2668, found 377.2671; anal. calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.08; H, 10.72.

(*S*)-1-((2*R*,5*S*)-5-((*S*)-1-Hydroxytridecyl)tetrahydrofuran-2-yl) tridec-12-en-1-ol (15). At −60 °C, undec-10-enylmagnesium bromide (1.00 M solution in THF, 11.0 mL, 11.0 mmol) was added dropwise to a suspension of CuI (1.05 g, 5.51 mmol) in THF (30.0 mL). The mixture was warmed to −30 °C and after 20 min recooled to −60 °C whereupon a solution of epoxide **14** (649 mg, 1.83 mmol) in THF (6.60 mL) was added dropwise. The mixture was allowed to warm to −20 °C over 4 h. Saturated aqueous NH_4Cl solution/NH_3 (8 : 1, 36.6 mL) was added to the reaction mixture. The mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl solution, H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 7 : 1) to give alcohol **15** (658 mg, 77% yield) as a white waxy solid: R_f 0.20 (hexane/EtOAc = 4 : 1); mp 75−76 °C; $[\alpha]_D^{25}$ −9.3 (c 0.77, $CHCl_3$); IR (KBr) ν_{max} 3434, 2918, 2850, 1642, 1467 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (1H, ddt, J = 10.2, 17.1, 6.6 Hz), 4.99 (1H, ddt, J = 2.2, 17.1, 1.6 Hz), 4.92 (1H, ddt, J = 2.2, 10.2, 1.2 Hz), 3.87 (1H, ddd, J = 3.4, 6.0, 9.2 Hz), 3.85–3.77 (2H, m), 3.39 (1H, dt, J = 5.4, 6.6 Hz), 2.16–1.79 (8H, m), 1.63 (1H, m), 1.57–1.19 (39H, m), 0.88 (3H, t, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2 (CH), 114.1 (CH_2), 83.2 (CH), 82.1 (CH), 74.3 (CH), 71.5 (CH), 33.8 (CH_2), 33.2 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 29.71 (CH_2), 29.66 (CH_2), 29.64 (CH_2), 29.63 (CH_2), 29.61 (CH_2), 29.57 (CH_2), 29.56 (CH_2) × 2, 29.53 (CH_2), 29.47 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 14.0 (CH_3); MS (ESI-TOF) m/z 489 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{30}H_{58}O_3Na$ 489.4284, found 489.4284; anal. calcd for $C_{30}H_{58}O_3$: C, 77.19; H, 12.52. Found: C, 76.91; H, 12.22.

(*S*)-3-((*S*)-13-Hydroxy-13-((2*R*,5*S*)-5-((*S*)-1-hydroxytridecyl) tetrahydrofuran-2-yl)tridecyl)-5-methylfuran-2(5*H*)-one (2). $[CpRu(CH_3CN)_3]^+PF_6^-$ (22.3 mg, 0.0513 mmol) was added to a stirred solution of the above crude diol and (*S*)-4-hydroxypent-2-ynoate **3** (110 mg, 0.774 mmol) in DMF (5.10 mL). The solution was allowed to stir at room temperature for 1 h before the reaction mixture was diluted with Et_2O and passed through a plug of silica gel. The mixture was washed with 1.0 M HCl aq., H_2O, and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo* to give a crude butenolide.

To a solution of the above crude butanolide and $TsNHNH_2$ (3.83 g, 20.6 mmol) in DME (25.7 mL) was added a solution of NaOAc (2.11 g, 25.7 mmol) in H_2O (25.7 mL). The mixture was heated at 80 °C for 3 h, and then cooled to room temperature. The mixture was diluted with Et_2O, washed with H_2O and brine, dried over anhydrous $MgSO_4$ and Na_2SO_4, and then concentrated *in vacuo*. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 1 : 1) to give butenolide **2** (260 mg, 89% yield for two steps) as a white waxy solid: R_f 0.40 (hexane/EtOAc = 1 : 1); mp 86−87 °C; $[\alpha]_D^{25}$ +4.5 (c 0.39, $CHCl_3$); IR (KBr) ν_{max} 3440, 2920, 2851, 1740, 1469 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.98 (1H, dt, J = 1.6, 1.5 Hz), 4.99 (1H, ddq, J = 6.8, 13.6, 1.6 Hz), 3.87 (1H, ddd, J = 3.4, 6.0, 9.3 Hz), 3.82 (1H, dt, J = 8.2, 6.7 Hz), 3.80 (1H, ddd, J = 3.6, 6.8, 9.3 Hz), 3.39 (1H, dt, J = 6.5, 6.7 Hz), 2.27 (1H, dt, J = 8.0, 1.6 Hz), 2.25 (1H, dt, J = 8.0, 1.6 Hz), 2.02–1.81 (2H, m), 1.92 (2H, brs), 1.68–1.56 (2H, m), 1.54–1.18 (44H, m), 1.40 (3H, d, J = 6.8 Hz), 0.88 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.9 (C), 148.8 (CH), 134.3 (C), 83.2 (CH), 82.1 (CH), 77.4 (CH), 74.3 (CH), 71.6 (CH), 33.2 (CH_2), 32.6 (CH_2), 31.9 (CH_2), 29.70 (CH_2), 29.66 (CH_2) × 2, 29.64 (CH_2), 29.62 (CH_2), 29.60 (CH_2), 29.57 (CH_2) × 3, 29.6 (CH_2), 29.53 (CH_2), 29.49 (CH_2), 29.34 (CH_2), 29.28 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 19.2 (CH_3), 14.1 (CH_3); MS (ESI-TOF) m/z 587 $[M + Na]^+$ (100); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{35}H_{64}O_5Na$ 587.4651, found 587.4659; anal. calcd for $C_{35}H_{64}O_5$: C, 74.42; H, 11.42. Found: C, 74.17; H, 11.31.

Conflicts of interest

There are no conflicts to declare.

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