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ORIGINAL ARTICLE

Development of a new air-stable structure-simplified nafuredin-γ analog as a potent and selective nematode complex I inhibitor

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Nafuredin-γ, obtained from natural nafuredin, has demonstrated a potent and selective inhibitory activity against nematode complex I. However, nafuredin-γ is unstable in air since its conjugated dienes are oxygen-labile. The instability in air was naturally solved by the synthesis of structure-simplified nafuredin-γ analogs without conjugated dienes. However, these modified analogs showed lower complex I inhibitory activities. Therefore, new air-stable structure-simplified nafuredin-γ analogs were designed and synthesized herein. Among all analogs synthesized, the one bearing a unique 1-azabicyclo[3.1.0]hexane scaffold showed the highest inhibitory activity (IC_{50} = 170 nM) while presenting high selectivity against nematode complex I.
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INTRODUCTION

Nafuredin (**1**)[1–3] was isolated from the fermentation broth of the fungal strain *Aspergillus niger* FT-0554 while screening for selective complex I inhibitors and proved to be a potent and selective inhibitor against nematode complex I. In addition, **1** demonstrated anthelmintic activity against *Haemonchus contortus* during *in vivo* trials with sheeps.[1] A total synthetic study of **1** subsequently identified a novel and structurally simpler γ-lactone compound, nafuredin-γ (**2**), which was generated from **1** under mild basic conditions.[4–6] Moreover, the nematode complex I inhibitory activity of **2** was identical to that of **1**. Therefore, nafuredin (**1**) and nafuredin-γ (**2**) holds promise as a selective antiparasitic agent. However, these compounds are disadvantageous in that they have poor air stability owing to the presence of oxygen-labile conjugated diene units (Figure 1). The total synthesis of **2** has been achieved by our group.[7] Several nafuredin-γ analogs were then synthesized using this total synthesis approach and their complex I inhibitory activities were examined. Consequently, the importance of the stereochemistries of C4 and C5 for the complex I inhibitory activity of these compounds was revealed. Next, we attempted the synthesis of structure-simplified nafuredin-γ analogs lacking the oxygen-labile conjugated diene units to solve the instability of **1** and **2** in air. Thus, we found that a new nafuredin-γ analog **3** obtained by a concise synthesis approach showed moderate complex I inhibitory activity while having high air stability (Figure 2).[8]

To improve the nematode complex I inhibitory activity of air-stable nafuredin-γ analogs, additional structure–activity relationship studies were carried out over **3**. Thus, the length of the isoprene unit as a side chain was changed originating new targets **4–6**. Additionally, the tetrahydrofuran (THF) unit was replaced by pyrrolidine or tetrahydrothiophene units to generate new targets **7** and **8** (Figure 2). Subsequent biological evaluation revealed some of the newly synthesized air-stable nafuredin-γ analogs to be more potent nematode complex I inhibitors than **3**. Herein, we report new structure–activity relationship studies of air-stable structure-simplified nafuredin-γ analogs as nematode complex I inhibitors.

RESULTS AND DISCUSSION

We first embarked on the synthesis of new analogs **4–6** by varying the length of the isoprene unit (Scheme 1) through our previously developed synthetic route.[8] *tert*-Butyldimethylsilyl protection, deacetylation by methanolysis and sharpless asymmetric epoxidation of a known allyl acetate **9**[9] gave chiral epoxyalcohol **10**, which was subjected to Appel reaction[10] to afford iodide **11**. Introduction of the side chain moiety was achieved by coupling the epoxyiodide **11** with the corresponding known sulfones **12–14**.[11,12] Subsequent Pd-catalyzed reductive desulfonylation[13] afforded **15–17** (the synthesis of intermediate **17** was not optimized. Because our primary interest was in evaluating the nematode complex I inhibitory activity of the new analog **6**.). Finally, deprotection of the *tert*-butyldimethylsilyl group and acid-catalyzed cyclization gave desired analogs **4–6**.

The inhibitory activities against nematode complex I of **4–6** were evaluated (Table 1, also see experimental section).[1,14] Analogs **4** and **5**, possessing shorter side chains ($n = 0$ or 1) than nafuredin-γ (**2**) and air-stable nafuredin-γ analog **3**, exhibited very low complex I

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inhibitory activities as compared with **3**. Analog **6** with a longer side chain ($n=3$) showed a moderate inhibitory activity and still lower than that of **3** ($n=2$). Therefore, analog **3** proved to have the optimum side chain length in terms of complex I inhibitory activity.

Next, we investigated the synthesis of new analogs **7** and **8** bearing pyrrolidine or tetrahydrothiophene units instead of THF (Scheme 2) while maintaining the same side chain of **3**. Coupling of iodide **9** with sulfone **18**[15] followed by Pd(0)-catalyzed desulfonation gave **19**, which

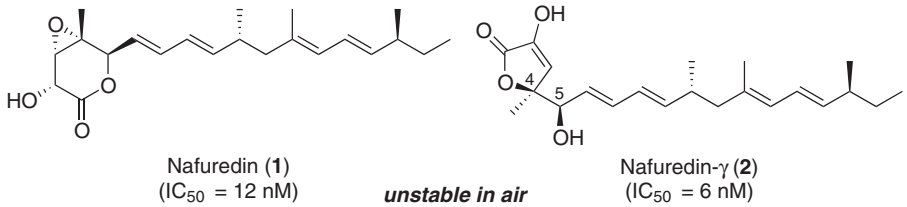


Figure 1 Structures and complex I inhibitory activities of nafuredin (**1**) and nafuredin-γ (**2**).

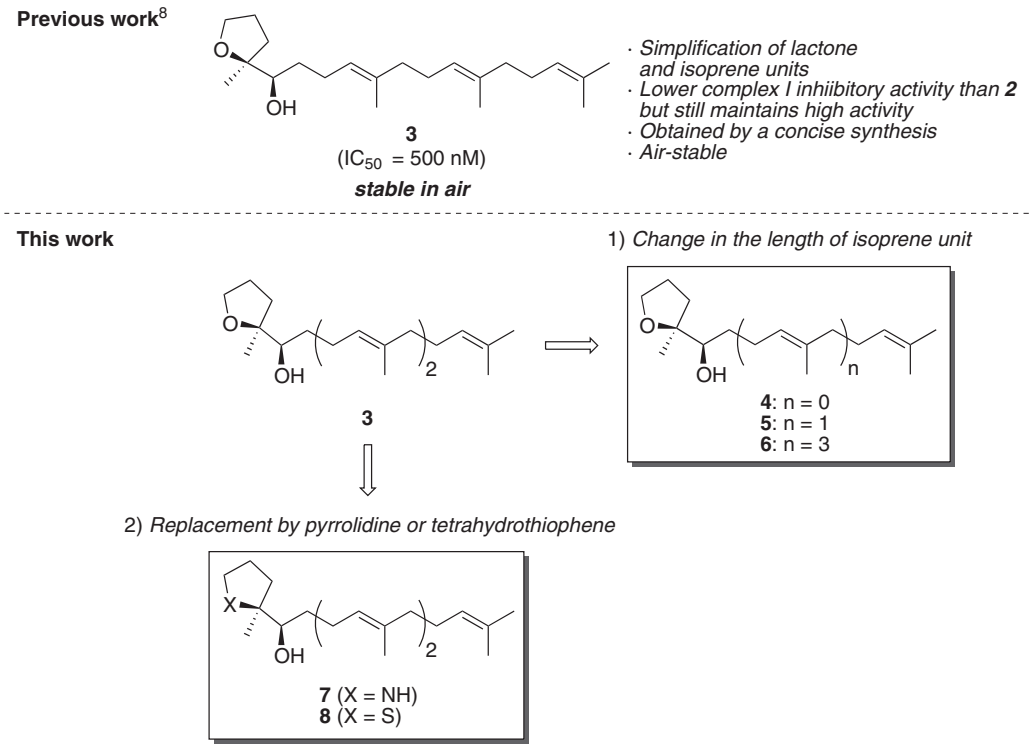
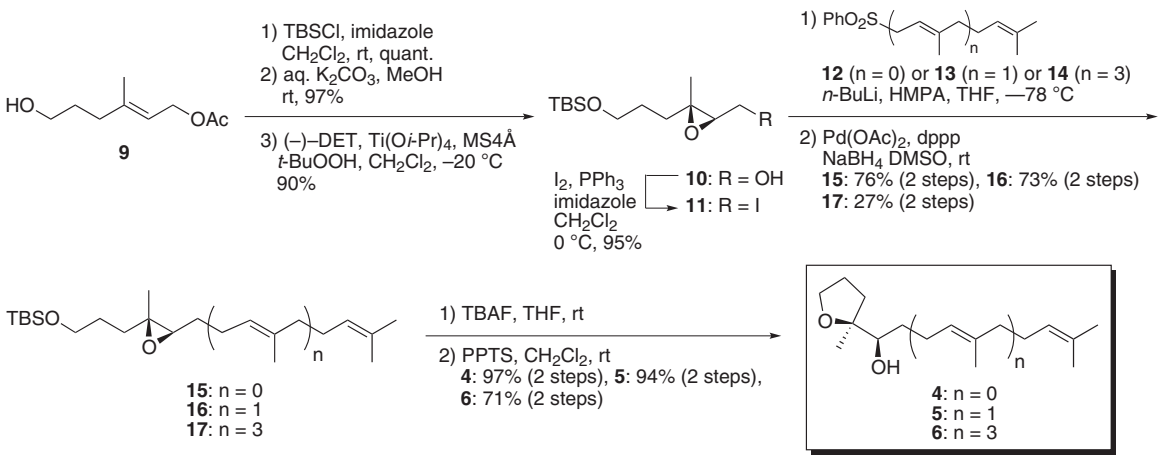
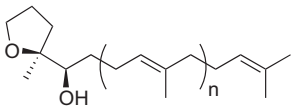


Figure 2 Air-stable structure-simplified nafuredin-γ analogs synthesized and designed by our group.



Scheme 1 Synthesis of air-stable structure-simplified nafuredin-γ analogs **4–6**.

Table 1 Inhibitory activities of 3–6 against nematode complex I

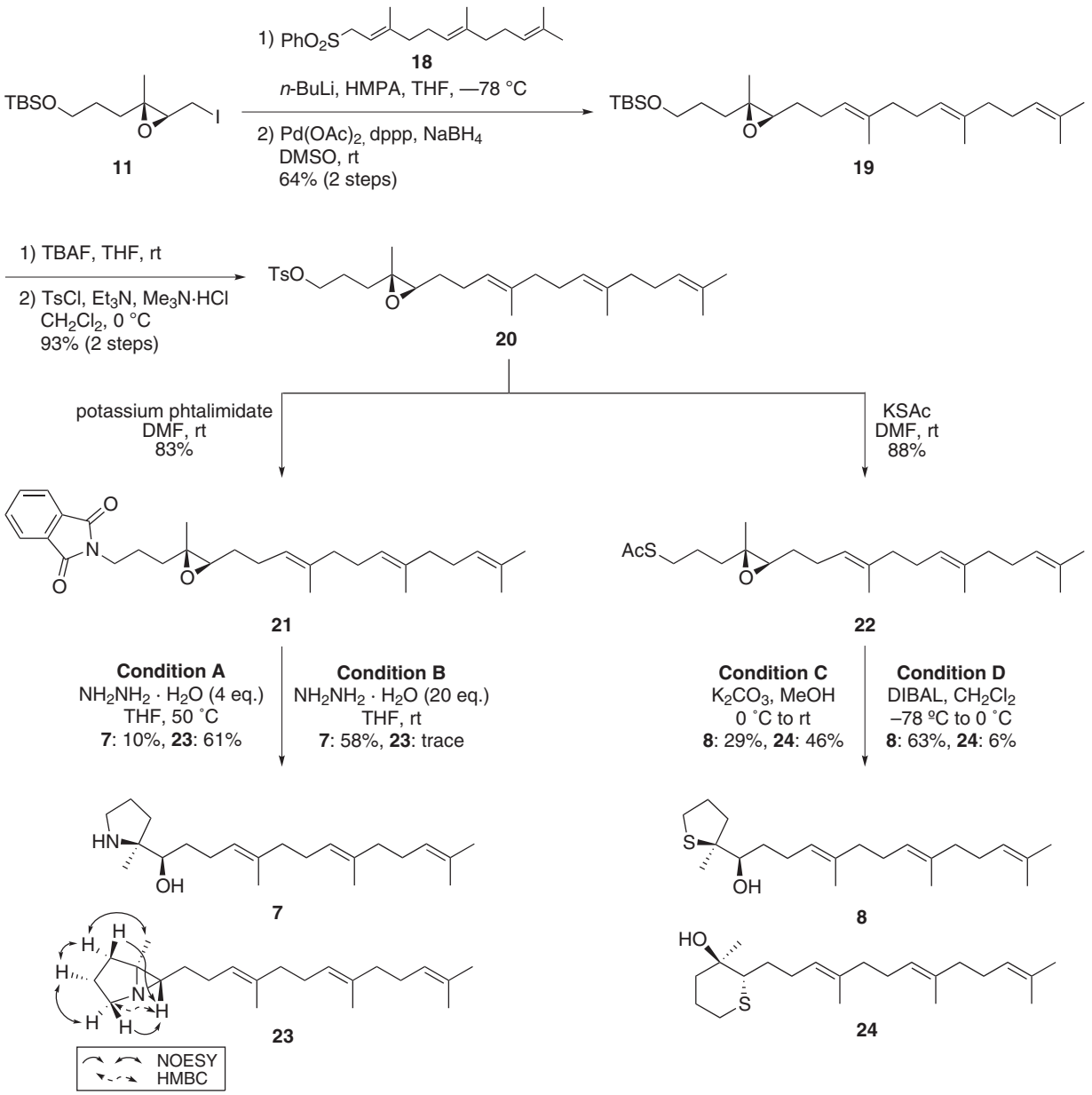


4 : n = 0
5 : n = 1
3 : n = 2
6 : n = 3

Compond	*IC_{50} (nM)*
4	$>4.0\times10^4$
5	2.3×10^3
3	5.0×10^2
6	8.0×10^2

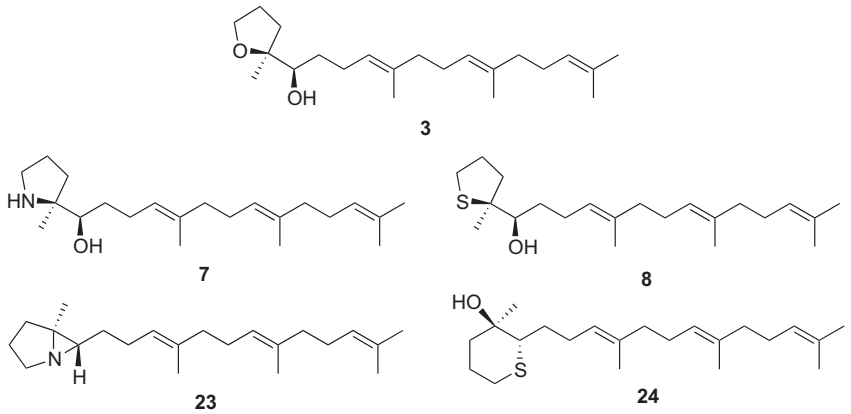
was subjected to deprotection of *tert*-butyldimethylsilyl ether and tosylation to afford tosylate **20**. S_N2 reaction of **20** with potassium phthalimide and potassium thioacetate yielded phthalimide **21** and thioacetate **22**, respectively.

First, phthalimide **21** was exposed to a solution of hydrazine (4 equiv.) in THF at 50 °C (Scheme 2, condition A) for synthesizing pyrrolidine analog **7**. Surprisingly, unexpected aziridine analog **23** bearing a unique 1-azabicyclo[3.1.0]hexane scaffold was obtained as a major product (61%) accompanied with desired pyrrolidine analog **7** (10%) as a minor product. The structure of aziridine analog **23** was determined by NOESY and HMBC spectroscopy. We speculated that aziridine analog **23** can be stereoselectively derived from desired pyrrolidine analog **7** via dehydration under high temperature conditions. This reaction was subsequently carried out at room temperature and the yield of **7** was slightly improved (27%) although **23** was also obtained in similar yield (23%) along with



Scheme 2 Synthesis of air-stable structure-simplified nafuredin-γ analogs **7**, **8**, **23** and **24**.

Table 2 Inhibitory activities of 7, 8, 23 and 24 against nematode complex I



Compond	*IC_{50} (nM)*
3	5.0×10^{2}
7	3.0×10^{2}
23	1.7×10^{2}
8	1.6×10^{3}
24	1.2×10^{3}

the recovered starting material **21** (28%) (data not shown). To completely consume the starting material, the reaction was carried out with higher concentrations of hydrazine (20 equiv.) at room temperature (Scheme 2, condition B) to afford the desired pyrrolidine analog **7** in 58% yield along with traces of the aziridine analog **23**.

With the thioacetate **22** in hand, the synthesis of tetrahydrothiophene analog **8** was also attempted. Methanolysis of **22** followed by epoxide-opening cyclization afforded a separable mixture of desired tetrahydrothiophene **8** (29%) and tetrahydro-2*H*-thiopyran **24** (46%) analogs (Scheme 2, condition C). In contrast to these results, diisobutylaluminum hydride reduction of **22** gave desired tetrahydrothiophene analog **8** (63%) as a major product accompanied with minor amounts of tetrahydro-2*H*-thiopyran analog **24** (6%) (Scheme 2, condition D). Tetrahydro-2*H*-thiopyran analog **24** is unfavorable according to the Baldwin rule.[16] However, the steric hindrance under condition C might prevail to give **24** as a major product. On the other hand, the regioselectivity under condition D would contribute to a greater stabilization of the partial positive charge at the more hindered end of the epoxide, resulting by coordination to the oxygen atom of the epoxide by aluminum species.

Table 2 shows the inhibitory activities against nematode complex I of novel analogs **7**, **8**, **23** and **24** (also see experimental section). The complex I inhibitory activity of pyrrolidine analog **7** slightly increased as compared with THF analog **3**. Interestingly, aziridine analog **23** exhibited the most potent complex I inhibitory activity ($IC_{50}=170$ nM) among all analogs synthesized. On the other hand, the complex I inhibitory activities of sulfur-containing analogs **8** and **24** greatly decreased as compared with to **3**. Aziridine analog **23** exhibited no inhibition activity against a bovine heart NADH oxidase including complexes I and III (>20 μM).[14] This result indicated that aziridine analog **23** is a potent and selective inhibitor against nematode complex I.

In conclusion, novel air-stable structure-simplified nafuredin-γ analogs, prepared by varying the length of side chain and by replacing the THF unit by pyrrolidine and tetrahydrothiophene, were designed and synthesized. In the course of the synthetic studies, we found out the new aziridine analog **23**, which is naturally stable in air and proved to be the most potent and selective inhibitor against nematode complex I among all analogs synthesized by our group. *In vivo* tests of aziridine analog **23** and further structure–activity relationship studies of the air-stable structure-simplified nafuredin-γ analogs are currently underway in our laboratory.

EXPERIMENTAL PROCEDURE

General

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere employing standard techniques for handling air-sensitive materials. Commercial reagents were used without further purification unless otherwise indicated. Organic solvents were distilled and dried over 3 or 4 Å molecular sieves. Cold baths were prepared as follows: 0 °C, wet ice/water; −78 °C, dry ice/acetone. Purifications by flash column chromatography were performed over silica gel 60 N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm Merck silica gel 60 F254 plates and the effluents were visualized by UV (254 nm) as well as by phosphomolybdic acid and *p*-anisaldehyde TLC stains. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H- and ^{13}C-NMR spectra were recorded using an internal deuterium lock on 400-MR, VNMRS-400 and UNITY-400 spectrometers (Agilent Technologies, Waldbornn, Germany). All NMR signals were reported in ppm relative to the internal reference standard provided by chloroform (that is, 7.26 or 77.0 ppm for the ^{1}H and ^{13}C spectra, respectively). Multiplicity data were presented as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = double doublet and dt = double triplet. Coupling constants (*J*) were reported in Hz. IR spectra were recorded on a FT/IR460-plus IR spectrometer (JASCO, Tokyo, Japan). Absorption data were given in wavenumbers (cm^{-1}). Optical rotations were recorded on a JASCO DIP-1000 polarimeter (JASCO, Tokyo, Japan) and reported as follows: $[\alpha]^{T}_{D}$, concentration (g per 100 ml), and solvent. High resolution mass spectra were obtained on JEOL JMS-700

Mstation, JEOL JMS-AX505HA and JEOL JMS-T100LP systems (JEOL, Tokyo, Japan) equipped with FAB, EI and ESI high-resolution mass spectrometers.

Enzyme assays

The nematode complex I (NADH-fumarate reductase) activity was measured in assay mixtures containing 50 mM potassium phosphate (pH 7.2), 10 mM β-D-glucose, 20 units of glucose oxidase, 26 units of catalase and 200 μM NADH.[1] The reaction is started by the addition of sodium fumarate (5 mM). The absorbance change at 340 nm (millimolar extinction coefficient of 6.2 for NADH) was followed. All inhibitory activities against nematode complex I (IC_{50} values) in Tables 1 and 2 were the average of three independent experiments.

((2*R*,3*R*)-3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-3-methyloxiran-2-yl)methanol (10)

To a solution of **9** (1.09 g, 6.30 mmol) in CH_2Cl_2 (63 ml) at 0 °C were added imidazole (515 mg, 7.56 mmol), *tert*-butyldimethylsilyl chloride (1.14 g, 7.56 mmol) and dimethylaminopyridine (38.5 mg, 0.320 mmol). The mixture was stirred for 1.5 h at room temperature, quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (70:1 hexane/EtOAc) afforded (*E*)-6-((*tert*-butyldimethylsilyl)oxy)-3-methylhex-2-en-1-yl acetate (**A**) (1.80 g, quant.) as a colorless oil: IR (neat) 3055, 1731, 1423, 1265, 741 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.28–5.24 (m, 1H), 4.48 (d, *J* = 7.4 Hz, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H), 1.94 (s, 3H), 1.61 (s, 3H), 1.58–1.51 (m, 2H), 0.80 (s, 9H), −0.05 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.1, 141.7, 118.4, 62.3, 59.1, 35.6, 30.6, 26.0, 20.8, 18.2, 16.2, −5.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{15}H_{31}O_3Si$ 287.2029, found 287.2024.

To a solution of **A** (3.49 g, 12.2 mmol) in MeOH (61 ml) at 0 °C was added aqueous K_2CO_3 (60 ml, 0.2 M). The mixture was stirred for 3 h at room temperature, diluted with H_2O and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (10:1 hexane/EtOAc) afforded (*E*)-6-((*tert*-butyldimethylsilyl)oxy)-3-methylhex-2-en-1-ol (**B**) (2.98 g, 97%) as a colorless oil: IR (neat) 3445, 2953, 2857, 2360, 1265, 1097, 743 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.41−5.37 (m, 1H), 4.11 (d, *J* = 6.6 Hz, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.03 (t, *J* = 7.7 Hz, 2H), 1.65 (s, 3H), 1.65–1.58 (m, 2H), 0.87 (s, 9H), 0.023 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.3, 123.4, 62.7, 59.2, 35.7, 30.9, 25.0, 18.3, 16.2, −5.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$ 245.1927, found 245.1931.

A mixture of $Ti(OiPr)_4$ (3.60 ml, 12.2 mmol) and 4 Å molecular sieves (1.19 g) in CH_2Cl_2 (76 ml) was treated with (−)-DET (2.09 ml, 12.2 mmol), and the resulting solution was vigorously stirred at −5 °C for 1 h. *tert*-Butyl hydroperoxide (5.0–6.0 M in decane, 4.88 ml, 24.4 mmol) was slowly added to the mixture, and the solution was stirred at −20 °C for 1 h. A solution of **B** (2.98 g, 12.2 mmol) in CH_2Cl_2 (46 ml) was added to the above mixture, and the solution was stirred at −20 °C for 1.5 h. After Me_2S (1.34 ml, 18.3 mmol) was added, the mixture was further stirred at −20 °C for 1 h. The resulting mixture was diluted with CH_2Cl_2, treated with celite (6.00 g) and $Na_2SO_4{\cdot}10H_2O$ (6.00 g), and subsequently stirred for 2 h at room temperature. The resulting suspension was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (5:1 hexane/EtOAc) to afford **10** (2.70 g, 90%) as a colorless oil: $[\alpha]^{23}_D$ +4.26 (*c* 1.00, $CHCl_3$); IR (neat) 3434, 3021, 1216, 769 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83–3.80 (m, 1H), 3.73–3.70 (m, 1H), 3.63–3.59 (m, 2H), 2.70 (dd, *J* = 6.7, 4.3 Hz, 1H), 1.67–1.52 (m, 4H), 1.30 (s, 3H), 0.88 (s, 9H), 0.039 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 62.9, 62.7, 61.3, 61.2, 34.9, 28.3, 26.0, 25.9, 25.8, 18.3, 16.8, −5.3, −5.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{29}O_3Si$ 261.1883, found 261.1886.

tert-Butyl(3-((2*R*,3*S*)-3-(iodomethyl)-2-methyloxiran-2-yl)propoxy) dimethylsilane (11)

To a solution of **10** (2.70 g, 10.4 mmol) in CH_2Cl_2 (100 ml) at 0 °C were added imidazole (2.04 g, 31.1 mmol), PPh_3 (4.08 g, 15.6 mmol) and I_2 (3.95 g, 15.6 mmol). The mixture was stirred for 50 min at 0 °C, quenched with saturated aqueous $Na_2S_2O_3$ and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (30:1 hexane/EtOAc) afforded **11** (3.66 g, 95%) as a colorless oil: $[\alpha]^{30}_D$ −32.0 (*c* 1.00, $CHCl_3$); IR (neat) 2953, 2857, 1253, 1101, 776, 616, 474 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.62–3.59 (td, *J* = 6.2, 2.3 Hz, 2H), 3.34 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.07 (dd, *J* = 8.6, 5.5 Hz, 1H), 2.97 (dd, *J* = 9.7, 8.6 Hz, 1H), 1.68–1.60 (m, 3H), 1.58–1.48 (m, 1H), 1.26 (s, 3H), 0.87 (s, 9H), 0.031 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 63.9, 62.7, 62.4, 34.7, 28.5, 26.0, 18.3, 15.7, 2.4, −5.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{28}O_2SiI$ 371.0915, found 371.0903.

((3-Methylbut-2-en-1-yl)sulfonyl)benzene (12)

To a solution of 1-bromo-3-methyl-2-butene (100 μl, 0.859 mmol) in dimethylformamide (8.6 ml) at room temperature were added $PhSO_2Na$ (169 mg, 1.03 mmol) and Bu_4NI (3.2 mg, 0.00859 mmol). The mixture was stirred for 1 h at room temperature, quenched with H_2O, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (10:1 hexane/EtOAc) afforded **12** (ref. 11; 115 mg, 82%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (m, 2H), 7.62–7.60 (m, 1H), 7.54–7.50 (m, 2H), 5.21–5.15 (m, 1H), 3.76 (d, *J* = 7.8 Hz, 2H), 1.69 (s, 3H), 1.30 (s, 3H).

(*tert*-Butyldimethyl(3-((2*R*,3*R*)-2-methyl-3-(4-methylpent-3-en-1-yl) oxiran-2-yl)propoxy)silane (15)

To a solution of **12** (200 mg, 0.540 mmol) in THF (4.0 ml) at −78 °C were added hexamethylphosphoramide (391 μl, 2.25 mmol) and *n*-BuLi (1.64 M in *n*-hexane, 550 μl, 0.900 mmol). After stirring for 1 h at −78 °C, a solution of **11** (94.6 mg, 0.450 mmol) in THF (2.0 ml) was added dropwise to the above mixture. The resulting mixture was stirred for 15 min at −78 °C, quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was briefly purified by flash column chromatography (10:1 hexane/EtOAc) to afford the corresponding coupling product, which was dissolved in DMSO (4.2 ml) and treated with Pd $(OAc)_2$ (24.2 mg, 0.108 mmol) and dppp (55.7 mg, 0.135 mmol). After stirring for 15 min at room temperature, $NaBH_4$ (24.5 mg, 0.648 mmol) was added to the mixture. The resulting mixture was stirred for 20 min at room temperature, quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (50:1 hexane/EtOAc) afforded **15** (107 mg, 2 steps, 76%) as a colorless oil: $[\alpha]^{30}_D$ −58.1 (*c* 1.00, $CHCl_3$); IR (neat) 3000, 1635, 1275, 1261, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.12 (t, *J* = 2.0 Hz, 1H), 3.60–3.56 (m, 2H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.15–2.09 (m, 2H), 1.68 (s, 3H), 1.63–1.44 (m, 6H), 1.59 (s, 3H), 1.23 (s, 3H), 0.88 (s, 9H), 0.022 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 132.3, 123.4, 63.2, 62.9, 60.8, 35.1, 28.9, 28.5, 25.9, 25.7, 25.0, 18.3, 17.6, 16.6, −5.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{18}H_{37}O_2Si$ 313.2554, found 313.2563.

(*R*)-5-Methyl-1-((*S*)-2-methyltetrahydrofuran-2-yl)hex-4-en-1-ol (4)

To a solution of **15** (81.3 mg, 0.270 mmol) in THF (2.7 ml) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 5.4 ml, 0.540 mmol). After stirring for 1 h at room temperature, the resulting mixture was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (2.7 ml) and treated with pyridinium *p*-toluenesulfonate (3.4 mg, 0.0135 mmol). After stirring for 30 min at room temperature, the reaction was quenched with

brine and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (25:1 hexane/EtOAc) afforded **4** (147 mg, 2 steps, 97%) as a colorless oil: $[\alpha]^{30}_D$ +32.6 (*c* 1.00, $CHCl_3$); IR (neat) 3435, 2349, 1635, 1260, 1051, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.15–5.11 (m, 1H), 3.91–3.80 (m, 2H), 3.53 (dd, *J*=10.5, 2.1 Hz, 1H), 2.36 (brs, 1H), 2.28–2.22 (m, 1H), 2.17–2.07 (m, 1H), 2.05–1.89 (m, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.50–1.42 (m, 2H), 1.38–1.30 (m, 1H), 1.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 132.0, 124.2, 85.8, 76.0, 67.9, 31.9, 30.6, 26.3, 25.7, 25.2, 23.1, 17.7; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{12}H_{23}O_2$ 199.1698, found 199.1698.

(*E*)-((3,7-Dimethylocta-2,6-dien-1-yl)sulfonyl)benzene (13)

To a solution of geraniol (200 μl, 1.14 mmol) in Et_2O (11 ml) at 0 °C was added PBr_3 (53 μl, 0.570 mmol). After stirring for 1.5 h at 0 °C, the resulting mixture was quenched with cold water and the aqueous phase was extracted with a 1:1 Et_2O:hexane mixture. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in DMF (11 ml) and treated with Bu_4NI (4.2 mg, 0.0114 mmol) and $PhSO_2Na$ (224 mg, 1.37 mmol). After stirring for 1.5 h at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (30:1 hexane/EtOAc) afforded **13** (ref. 11; 279 mg, 2 steps, 88%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.65–7.61 (m, 1H), 7.55–7.51 (m, 2H), 5.23 (dt, *J*=7.8, 1.0 Hz, 1H), 5.03–5.00 (m, 1H), 3.80 (d, *J*=7.8 Hz, 2H), 2.00–1.99 (m, 4H), 1.68 (s, 3H), 1.58 (s, 3H), 1.31 (s, 3H).

tert-Butyl(3-((2*R*,3*R*)-3-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-2-methyloxiran-2-yl)propoxy)dimethylsilane (16)

To a solution of **13** (147 mg, 0.530 mmol) in THF (7.9 ml) at −78 °C were added hexamethylphosphoramide (460 μl, 2.65 mmol) and *n*-BuLi (1.64 M in *n*-hexane, 646 μl, 1.06 mmol). After stirring for 1 h at −78 °C, a solution of **11** (291 mg, 0.790 mmol) in THF (3.0 ml) was added dropwise to the above mixture. The resulting mixture was stirred for 30 min at −78 °C, quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was briefly purified by flash column chromatography (20:1 hexane/EtOAc) to afford the corresponding coupling product, which was dissolved in DMSO (4.8 ml) and treated with Pd $(OAc)_2$ (25.9 mg, 0.106 mmol) and dppp (54.6 mg, 0.133 mmol). After stirring for 15 min at room temperature, $NaBH_4$ (40.1 mg, 1.06 mmol) was added to the mixture. The reaction was stirred for 20 min at room temperature, quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (40:1 hexane/EtOAc) afforded **16** (129 mg, 2 steps, 73%) as a colorless oil: $[\alpha]^{23}_D$ +2.77 (*c* 1.00, $CHCl_3$); IR (neat) 3055, 2986, 1636, 1422, 1265, 749 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.14 (dd, *J*=7.0, 1.2 Hz, 1H), 5.07 (dt, *J*=7.0, 1.6 Hz, 1H), 3.60–3.56 (m, 2H), 2.70 (t, *J*=6.3 Hz, 1H), 2.20–1.95 (m, 6H), 1.66 (s, 3H), 1.66–1.44 (m, 6H), 1.58 (s, 3H), 1.54 (s, 3H), 1.23 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.9, 131.3, 124.2, 123.2, 63.2, 62.9, 60.8, 39.7, 35.1, 28.9, 28.6, 26.6, 25.9, 25.7, 25.6, 24.8, 18.2, 17.7, 16.6, 16.0, −5.3; HRMS (EI) $[M]^+$ calcd for $C_{23}H_{44}O_2Si$ 380.3113, found 380.3111.

(*R*,*E*)-5,9-Dimethyl-1-((*S*)-2-methyltetrahydrofuran-2-yl)deca-4,8-dien-1-ol (5)

To a solution of **16** (243 mg, 0.70 mmol) in THF (7.0 ml) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 1.40 ml, 1.40 mmol). After stirring for 1 h at room temperature, the resulting mixture was quenched with brine and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (7.0 ml) and treated with pyridinium *p*-toluenesulfonate (8.8 mg, 0.035 mmol). After stirring for 1.5 h at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (20:1 hexane/EtOAc) afforded **5** (175 mg, 2 steps, 94%) as a colorless oil: $[\alpha]^{30}_D$ +4.62 (*c* 1.00, $CHCl_3$); IR (neat) 3452, 3055, 1636, 1422, 1265, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.16–5.07 (m, 2H), 3.91–3.80 (m, 2H), 3.59 (dd, *J*=10.0, 2.0 Hz, 1H), 2.35 (brs, 1H), 2.29–2.21 (m, 1H), 2.17–1.88 (m, 8H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.51–1.43 (m, 2H), 1.40–1.30 (m, 1H), 1.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.7, 131.3, 124.3, 124.0, 85.7, 76.0, 67.9, 39.7, 31.9, 30.6, 26.7, 26.3, 25.7, 25.0, 23.1, 17.7, 16; HRMS (FAB *m*-NBA) $[M+H]^+$ calcd for $C_{17}H_{31}O_2$ 267.2327, found 267.2324.

(((2*E*,6*E*,10*E*)-3,7,11,15-Tetramethylhexadeca-2,6,10,14-tetraen-1-yl)sulfonyl)benzene (14)

To a solution of geranyl geraniol (43.1 mg, 0.148 mmol) in Et_2O (3.0 ml) at 0 °C was added PBr_3 (7 μl, 0.0742 mmol). After stirring for 2 h at 0 °C, the resulting mixture was quenched with cold water and the aqueous phase was extracted with a 1:1 Et_2O:hexane mixture. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in DMF (3.0 ml) and treated with Bu_4NI (0.5 mg, 0.0015 mmol) and $PhSO_2Na$ (29.2 mg, 0.178 mmol). After stirring for 3 h at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (70:1 hexanes/EtOAc) afforded **14** (ref. 12; 38.0 mg, 2 steps, 63%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.65–7.61 (m, 1H), 7.55–7.30 (m, 2H), 5.19 (dt, *J*=8.2, 1.2 Hz, 1H), 5.11–5.03 (m, 3H), 3.80 (d, *J*=8.2 Hz, 2H), 2.09–1.92 (m, 12H), 1.67 (s, 3H), 1.65–1.58 (m, 9H), 1.25 (s, 3H).

tert-Butyldimethyl(3-((2*R*,3*R*)-2-methyl-3-((3*E*,7*E*,11*E*)-4,8,12,16-tetramethylheptadeca-3,7,11,15-tetraen-1-yl)oxiran-2-yl)propoxy)silane (17)

To a solution of **14** (32.0 mg, 0.0772 mmol) in THF (2.0 ml) at −78 °C were added hexamethylphosphoramide (67 μl, 0.386 mmol) and *n*-BuLi (1.64 M in *n*-hexane, 57 μl, 0.0926 mmol). After stirring for 1 h at −78 °C, a solution of **11** (291 mg, 0.790 mmol) in THF (3.0 ml) was added dropwise to the above mixture. The resulting mixture was stirred for 30 min at −78 °C, quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified briefly by flash column chromatography (10:1 hexane/EtOAc) to afford the corresponding coupling product, which was dissolved in DMSO (1.0 ml) and treated with Pd $(OAc)_2$ (3.7 mg, 0.154 mmol) and dppp (7.9 mg, 0.0193 mmol). After stirring for 15 min at room temperature, $NaBH_4$ (3.5 mg, 0.0926 mmol) was added to the mixture. The reaction was stirred for 30 min at room temperature, quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (40:1 hexane/EtOAc) afforded **17** (10.8 mg, 2 steps, 27%) as a colorless oil: $[\alpha]^{30}_D$ +0.93 (*c* 1.00, $CHCl_3$); IR (neat) 3054, 2986, 1635, 1423, 1265, 748 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.15–5.09 (m, 4H), 3.62–3.58 (m, 2H), 2.71 (t, *J*=6.2 Hz 1H), 2.16–2.00 (m, 14H), 1.68 (s, 3H), 1.65–1.46 (m, 6H), 1.62–1.58 (m, 12H), 1.24 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.9, 135.1, 134.9, 131.4, 124.4, 124.2, 124.1, 123.2, 63.2, 62.9, 60.8, 39.7, 35.1, 28.9, 28.5, 26.8, 26.6, 25.9, 25.7, 25.6, 24.9, 18.3, 17.7, 16.6, 16.0, −5.3; HRMS (EI) $[M]^+$ calcd for $C_{33}H_{60}O_2Si$ 516.4366, found 516.4363.

(*R*,4*E*,8*E*,12*E*)-5,9,13,17-Tetramethyl-1-((*S*)-2-methyltetrahydrofuran-2-yl)octadeca-4,8,12,16-tetraen-1-ol (6)

To a solution of **17** (9.0 mg, 0.0174 mmol) in THF (1.7 ml) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 35 μl,

0.0348 mmol). After stirring for 1 h at room temperature, the resulting mixture was quenched with brine and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (500 µl) and treated with pyridinium *p*-toluenesulfonate (0.1 mg, 0.00085 mmol). After stirring for 1 h at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (8:1 hexane/EtOAc) afforded **6** (5.0 mg, 2 steps, 71%) as a colorless oil: $[\alpha]^{28}_D$ −9.7 (*c* 1.00, $CHCl_3$); IR (neat) 3441, 3056, 2987, 1634, 1424, 1266, 752 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.16–5.07 (m, 4H), 3.91–3.80 (m, 2H), 3.53 (dd, *J*=10.1, 1.7 Hz, 1H), 2.35 (brs, 1H), 2.29–2.22 (m, 1H), 2.16–1.88 (m, 16H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 9H), 1.51–1.43 (m, 2H), 1.40–1.30 (m, 1H), 1.11 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8, 135.0, 134.9, 131.3, 124.4, 124.2, 124.1, 124.0, 85.8, 76.1, 67.9, 39.8, 39.7, 31.9, 30.6, 26.7, 26.6, 26.3, 25.7, 25.1, 23.1, 17.7, 16.1, 16.0, 15.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{27}H_{47}O_2$ 403.3570, found 403.3576.

tert-Butyldimethyl(3-((2*R*,3*R*)-2-methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)oxiran-2-yl)propoxy)silane (19)

To a solution of **18** (1.25 g, 3.60 mmol) in THF (20 ml) at −78 °C were added hexamethylphosphoramide (3.1 ml, 18.0 mmol) and *n*-BuLi (1.64 M in *n*-hexane, 4.4 ml, 7.20 mmol). After stirring for 1 h at −78 °C, a solution of **11** (1.60 mg, 4.30 mmol) in THF (10 ml) was added dropwise to the above mixture. The resulting mixture was stirred for 40 min at −78 °C, quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was briefly purified by flash column chromatography (20:1 hexane/EtOAc) to afford the corresponding coupling product, which was dissolved in DMSO (20 ml) and treated with Pd $(OAc)_2$ (176 mg, 0.720 mmol) and dppp (371 mg, 0.900 mmol). After stirring for 5 min at room temperature, $NaBH_4$ (272 mg, 7.20 mmol) was added to the mixture. The reaction was stirred for 50 min at room temperature, quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (70:1 hexane/EtOAc) afforded **19** (1.03 g, 2 steps, 64%) as a colorless oil: $[\alpha]^{30}_D$ +8.20 (*c* 1.00, $CHCl_3$); IR (neat) 3051, 2955, 1459, 1260, 739 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.17–5.07 (m, 3H), 3.69–3.51 (m, 2H), 2.72 (t, *J*=6.2 Hz, 1H), 2.14–1.96 (m, 10H), 1.68 (s, 3H), 1.65–1.49 (m, 6H), 1.62 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H), 1.25 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.9, 135.0, 131.2, 124.3, 124.1, 123.2, 63.2, 62.9, 60.8, 39.7, 35.1, 28.9, 28.6, 26.7, 26.6, 26.0, 25.8, 25.6, 24.8, 18.3, 17.7, 16.6, 16.0, 15.9, −5.3; HRMS (EI) $[M]^+$ calcd for $C_{28}H_{52}O_2Si$ 448.3737, found 448.3737.

3-((2*R*,3*R*)-2-Methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)oxiran-2-yl)propyl 4-methylbenzenesulfonate (20)

To a solution of **19** (350 mg, 0.780 mmol) in THF (8.0 ml) at room temperature was added tetrabutylammonium fluoride (1.0 M in THF, 2.3 µl, 3.34 mmol). After stirring for 0.5 h at room temperature, the resulting mixture was quenched with brine and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This residue was employed in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (8.0 ml) and treated with Et_3N (326 µl, 1.17 mmol), $Me_3N{\cdot}HCl$ (7.50 mg, 0.0780 mmol) and *p*-TsCl (223 mg, 1.17 mmol). After stirring for 45 min at 0 °C, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (10:1 hexane/EtOAc) afforded **20** (355 mg, 93%) as a colorless oil: $[\alpha]^{28}_D$ +10.3 (*c* 1.00, $CHCl_3$); IR (neat) 3055, 2986, 1600, 1423, 1265, 748 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 2H), 7.35–7.32 (m, 2H), 5.14–5.07 (m, 3H), 4.07–3.97 (m, 2H), 2.65 (dd, *J*=12.5, 6.2 Hz, 1H), 2.44 (s, 3H,), 2.16–1.94 (m, 10H), 1.78–1.70 (m, 2H) 1.67 (s, 3H), 1.60 (s, 3H), 1.59 (s, 6H), 1.57–1.48 (m, 4H), 1.19 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.7, 138.9, 136.1, 135.0, 133.1, 131.3, 129.8, 127.9, 124.3, 123.0, 70.3, 63.0, 60.0, 39.7, 34.4, 28.8, 26.7, 26.5, 25.7, 24.8, 24.6, 21.6, 17.7, 16.5, 16.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{29}H_{45}O_4S$ 489.3034, found 489.3039.

2-(3-((2*R*,3*R*)-2-Methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)oxiran-2-yl)propyl)isoindoline-1,3-dione (21)

To a solution of **20** (381 mg, 0.780 mmol) in DMF (19 ml) was added potassium phthalimide (173 mg, 0.936 mmol). After stirring for 15 min at room temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (10:1 hexane/EtOAc) afforded **21** (299 mg, 83%) as a colorless oil: $[\alpha]^{23}_D$ +4.95 (*c* 0.100, $CHCl_3$); IR (neat) 3020, 1712, 1216, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96–7.93 (m, 2H), 7.83–7.80 (m, 2H), 5.40–5.17 (m, 3H), 3.81–3.76 (m, 2H), 2.82 (t, *J*=6.2 Hz, 1H), 2.27–2.03 (m, 10H), 1.90–1.83 (m, 2H), 1.77 (s, 3H), 1.75–1.59 (m, 13H), 1.35 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.3, 136.0, 135.0, 133.9, 133.9, 133.8, 132.1, 131.2, 124.3, 124.1, 60.0, 60.2, 39.7, 39.6, 37.8, 35.9, 28.8, 26.7, 26.6, 25.6, 24.3, 24.2, 17.7, 16.5, 16.4, 16.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{30}H_{42}O_3N$ 465.3157, found 465.3165.

(*R*,4*E*,8*E*)-5,9,13-Trimethyl-1-((*S*)-2-methylpyrrolidin-2-yl)tetradeca-4,8,12-trien-1-ol (7)

To a solution of **21** (35.7 mg, 0.108 mmol) in THF (2.0 ml) was added $NH_2NH_2{\cdot}H_2O$ (67 µl, 2.16 mmol). After stirring for 2 days at room temperature, flash column chromatography (10:1 CH_2Cl_2/MeOH (1%NH_3 *aq.*)) afforded **7** (20.9 mg, 58%) as a colorless oil: $[\alpha]^{22}_D$ −3.15 (*c* 0.50, $CHCl_3$); IR (neat) 3437, 3055, 2982, 1634, 1424, 1266, 746 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.18–5.07 (m, 3H), 3.27 (dd, *J*=10.1, 1.9 Hz, 1H), 3.08–3.02 (m, 1H), 2.94–2.88 (m, 1H), 2.34–2.25 (m, 1H), 2.14–1.89 (m, 9H), 1.88–1.72 (m, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.56–1.44 (m, 1H), 1.42–1.21 (m, 2H), 0.87 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.4, 134.9, 131.3, 124.4, 124.3, 124.2, 76.2, 64.9, 45.7, 39.7, 39.6, 32.2, 30.7, 26.8, 26.6, 25.7, 24.6, 22.6, 17.8, 16.0, 15.9, 15.8; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{22}H_{40}ON$ 334.3103, found 334.3110.

(5*S*,6*S*)-5-Methyl-6-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)-1-azabicyclo[3.1.0]hexane (23)

To a solution of **21** (42.0 mg, 0.0906 mmol) in THF (1.8 ml) was added $NH_2NH_2{\cdot}H_2O$ (11.3 µl, 0.362 mmol). After stirring for 12 h at 50 °C, flash column chromatography (10:1 CH_2Cl_2/MeOH (1%NH_3 *aq.*)) afforded **23** (17.4 mg, 61%) and **7** (3.0 mg, 10%) as colorless oils: $[\alpha]^{21}_D$ −6.09 (*c* 1.00, $CHCl_3$); IR (neat) 3052, 2931, 2856, 1443, 1266, 745 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.17–5.11 (m, 3H), 2.92–2.87 (m, 1H), 2.61–2.87 (m, 1H), 2.43 (dd, *J*=10.5, 2.7 Hz, 1H), 2.20–1.92 (m, 10H), 1.75–1.63 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.65–1.58 (m, 1H), 1.60 (s, 6H), 1.53–1.28 (m, 3H), 1.15 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8, 135.0, 131.3, 124.3, 124.1, 123.8, 70.5, 64.5, 43.2, 39.7, 37.8, 29.7, 27.9, 26.7, 26.6, 25.7, 25.3, 23.7, 22.4, 17.7, 16.1, 16.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{22}H_{38}N$ 316.3008, found 316.3004.

S-(3-((2*R*,3*R*)-2-Methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-yl)oxiran-2-yl)propyl) ethanethioate (22)

To a solution of **20** (84.0 mg, 0.172 mmol) in DMF (1.00 ml) was added KSAc (98.1 mg, 0.859 mmol). After stirring for 30 min at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (30:1 hexane/EtOAc) afforded **22** (59.7 mg, 88%) as a colorless oil: $[\alpha]^{21}_D$ +0.027 (*c* 1.00, $CHCl_3$); IR (neat) 2965, 1694, 1448, 1383, 1133, 625 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.16–5.07 (m, 3H), 2.88–2.84 (m, 2H), 2.70 (t, *J*=6.4 Hz, 1H), 2.32 (s, 3H), 2.17–1.95 (m, 10H), 1.74–1.47 (m, 6H), 1.67 (d, *J*=0.8 Hz, 3H) 1.62 (s, 3H), 1.59 (s, 6H), 1.24 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.8, 136.2, 135.2, 131.4, 124.5, 124.3,

123.3, 63.3, 60.5, 60.5, 39.9, 39.8, 37.9, 30.8, 29.1, 26.9, 26.7, 25.8, 25.6, 25.0, 17.8, 16.7, 16.2, 14.3; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{24}H_{40}NaO_2S$ 415.2647, found 415.2655.

(*R*,4*E*,8*E*)-5,9,13-Trimethyl-1-((*S*)-2-methyltetrahydrothiophen-2-yl)tetradeca-4,8,12- trien-1-ol (8) and (2*R*,3*R*)-3-methyl-2-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1- yl)tetrahydro-2*H*-thiopyran-3-ol (24)

Methanolysis. To a solution of **22** (22.4 mg, 0.0570 mmol) in MeOH (500 µl) was added K_2CO_3 (47.3 mg, 0.342 mmol). After stirring for 1.5 h at room temperature, the reaction was quenched with H_2O and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (20:1 hexane/EtOAc) afforded **8** (6.00 mg, 29%) and **24** (8.40 mg, 46%) as colorless oils.

DIBAL reduction. To a solution of **22** (102 mg, 0.260 mmol) in CH_2Cl_2 (2.59 ml) was treated with DIBAL (1.03 M in *n*-hexane, 1.13 ml, 1.17 mmol) at −78 °C. After stirring for 1.5 h at 0 °C, MeOH was added dropwise at 0 °C to the resulting solution until the evolution of gas ceased. The mixture was diluted with CH_2Cl_2, treated with Celite (500 mg) and $Na_2SO_4{\cdot}10H_2O$ (500 mg), and then stirred for 1 h at 0 °C. The resulting suspension was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (15:1 hexane/EtOAc) to afford **8** (56.9 mg, 63%) and **24** (5.10 mg, 6%) as colorless oils.

8. $[\alpha]^{21}_D$ +0.028 (*c* 0.71, $CHCl_3$); IR (neat) 3450, 2927, 1636, 1377, 552 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.17–5.07 (m, 3H), 3.48 (dd, *J* = 1.8, 10.2 Hz, 1H), 2.94–2.81 (m, 2H), 2.32–2.23 (m, 1H), 2.20–1.93 (m, 12H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.71–1.51 (m, 2H), 1.43–1.34 (m, 1H), 1.38 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.8, 135.0, 131.3, 124.4, 124.2, 124.0, 76.6, 64.1, 39.7, 37.7, 33.7, 32.1, 31.0, 26.7, 26.7, 26.6, 25.7, 25.6, 17.7, 16.1, 16.0; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{22}H_{38}NaOS$ 373.2541, found 373.2534.

24. $[\alpha]^{21}_D$ −0.167 (*c* 0.52, $CHCl_3$); IR (neat) 3445, 2925, 1455, 1286, 548 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.13–5.10 (m, 3H), 2.47 (d, *J* = 11.6 Hz, 1H), 2.32–2.27 (m, 2H), 2.13–1.93 (m, 11H), 1.84–1.78 (m, 1H), 1.76–1.70 (m, 1H), 1.69–1.55 (m, 2H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 6H), 1.49–1.45 (m, 1H,), 1.25 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.2, 135.0, 131.3, 124.3, 124.1, 123.4, 69.4, 52.3, 39.7, 39.7, 36.0, 28.4, 26.7, 26.6, 26.4, 25.7, 25.4, 24.5, 23.9, 17.7, 16.1, 16.0; HRMS (ESI+) $[M+Na]^+$ calcd for $C_{22}H_{38}NaOS$ 373.2541, found 373.2531.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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