Bioorganic & Medicinal Chemistry 23 (2015) 932–943

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design, synthesis, and biological evaluation of air-stable nafuredin-γ analogs as complex I inhibitors

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ARTICLE INFO

Article history:
Received 10 December 2014
Revised 14 January 2015
Accepted 16 January 2015
Available online 22 January 2015

Keywords:
Nafuredin-γ
Air-stable analogs
Complex I inhibitor

ABSTRACT

Nafuredin-γ (**2**), converted from nafuredin (**1**) under mild basic conditions, demonstrates potent and selective inhibitory activity against helminth complex I. However, **2** is unstable in air because the conjugated dienes are oxygen-labile. To address this, we designed and synthesized air-stable nafuredin-γ analogs. Although the complex I inhibitory activities of all the new nafuredin-γ analogs were lower than that of **2**, all were in the high nM range (IC_{50}: 300–820 nM).

1. Introduction

Nafuredin (**1**)[1–3] was isolated from the fermentation broth of a fungal strain, *Aspergillus niger* FT-0554, during screening for selective complex I inhibitors and proved to be a potent and selective inhibitor against helminth complex I (Fig. 1). In addition, **1** demonstrated anthelmintic activity against *Haemonchus contortus* in in vivo trials with sheep.[1] Therefore, nafuredin (**1**) holds promise as a selective antiparasitic agent. A subsequent total synthetic study of **1** identified a novel and structurally simpler γ-lactone compound, nafuredin-γ (**2**), which was generated from **1** under mild basic conditions.[4,5] Moreover, the helminth complex I inhibitory activity of **2** was identical to that of **1**. The total synthesis of **2** has been achieved by our group;[6] 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 complex I inhibitory activity was revealed.[7]

On the other hand, nafuredin (**1**), nafuredin-γ (**2**), and their analogs are all unstable in air because the conjugated dienes are oxygen-labile. Therefore, these compounds must be stored as solutions in appropriate solvents. We addressed this instability by synthesizing the air-stable nafuredin-γ analogs **4**-**8** containing aromatic rings or non-conjugated (*E*)-olefins in the side chain (Fig. 2). The analogs **6**, **7**, and **8** were designed as structurally simpler analogs lacking one (compound **6**) or both (compounds **7** and **8**) of the stereogenic centers in the side chain. In particular, analog **8** is amenable to large scale synthesis. Although these new analogs contain a common saturated lactone moiety, the effect of removing the enol unit on complex I inhibitory activity had not been investigated.[8] Therefore, the synthesis and biological evaluation of **3**, in which the 2-hydroxy-α,β-unsaturated lactone moiety of **2** was replaced with the saturated lactone, was carried out first, followed by the synthesis of derivatives **4** to **8**. Herein, we report the design, synthesis, and biological evaluation of air-stable nafuredin-γ analogs as complex I inhibitors.

2. Results and discussion

2.1. Synthesis and complex I inhibitory activity of 3

We first synthesized new analog **3** using a convergent approach based on our synthesis of nafuredin-γ.[7] Starting chiral epoxide **9**[9] was converted to lactone **10** in 94% yield over 2 steps via ozonolysis, followed by Pinnick oxidation and lactonization through epoxide opening of the resulting carboxylic acid (Scheme 1). A two-step sequence of protecting group manipulations provided primary alcohol **11**. Dess–Martin oxidation of **11** gave aldehyde **12** (diastereopurity >99:1)[10] in 86% yield, which was subjected to Takai olefination to afford *E*-vinyl iodide **13** in 76% yield. Coupling partner boronate **16** was synthesized from known alcohol **14**.[4] Dess-Martin

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http://dx.doi.org/10.1016/j.bmc.2015.01.030
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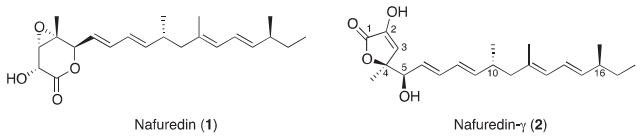


Figure 1.

oxidation of **14** followed by Takai olefination using Cl_2CHB(pinacolate)[11] afforded vinylboronic ester **16** with high diastereopurity (>99:1)[10] in 48% yield over 2 steps. With the required fragments **13** and **16** in hand, Suzuki coupling furnished the bis-diene **17**; exposure to acidic conditions provided the desired new nafuredin-γ analog **3** in 28% yield over 2 steps.[12]

The inhibitory activity of **3** against complex I (*Ascaris suum*) was evaluated; the IC_{50} value was 32 nM, indicating that replacement of 2-hydroxy-α,β-unsaturated lactone with the saturated lactone was tolerated and potent complex I inhibitory activity was retained.

2.2. Synthetic plan for new nafuredin-γ analogs 4–7

We next turned to synthesizing new nafuredin-γ analogs **4**–**7**, which were expected to be stable in air. The retrosynthetic analysis of analogs **4**–**7** is shown in Scheme 2. It was envisaged that these nafuredin-γ analogs could be synthesized by Suzuki coupling of the common vinyl iodide **13** with the arylboronic ester **18** or boronate intermediates **19**–**21** derived from the corresponding alkyl iodides.

2.3. Synthesis of new nafuredin-γ analog 4

The synthesis of **4** is shown in Scheme 3. Known 2-naphthol **22**[13] was converted to triflate **23** in 92% yield, which was subjected to Negishi coupling with $Zn(CN)_2$[14] to afford **24** in 78% yield. DIBAL reduction of **24** gave aldehyde **25** in 93% yield. The aldehyde **25** was coupled with an aryl lithium species derived from the known aryl bromide **26**[15] to afford the alcohol **27** in 99% yield. Removal of the benzylic hydroxyl group of **27** and deprotection of the MOM group gave phenol **29**, which was converted to arylboronic ester **18** via the triflate according to the Miyaura protocol.[16] The Suzuki coupling of **18** with vinyl iodide **13** afforded **30**. Finally, deprotection of the MOM group of **30** provided new nafuredin-γ-analog **4** in 38% yield (2 steps).[12]

2.4. Synthesis of new nafuredin-γ analogs 5, 6, and 7

Next, compounds **5** and **6**, containing non-conjugated (*E*)-olefins in the side chain, were synthesized. Lithium-iodide exchange of the known iodides **31** and **32**,[17] followed by treatment with

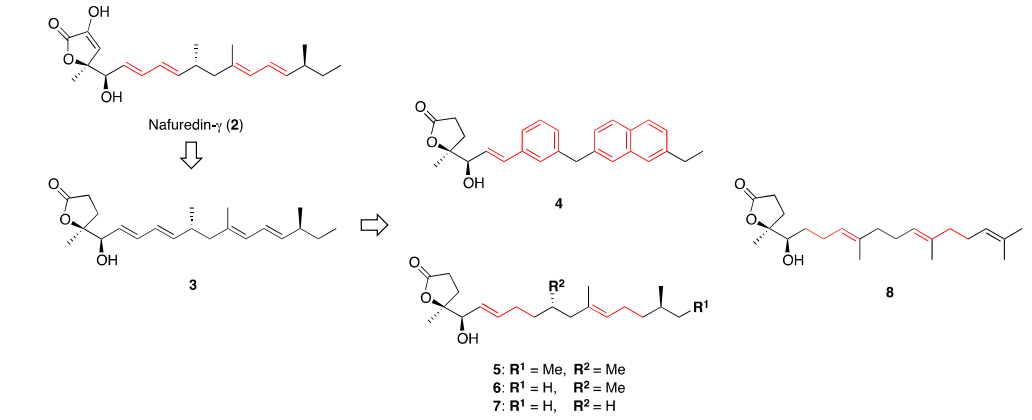
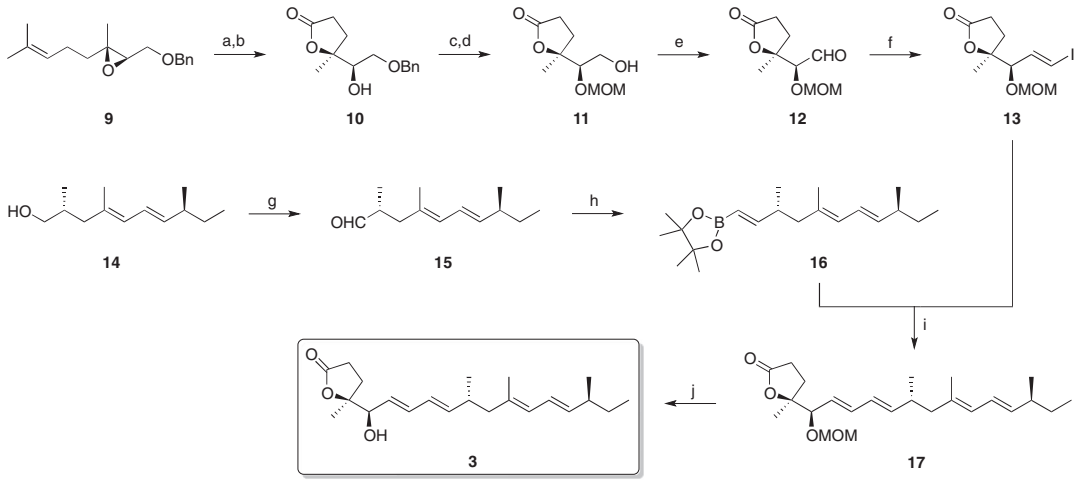
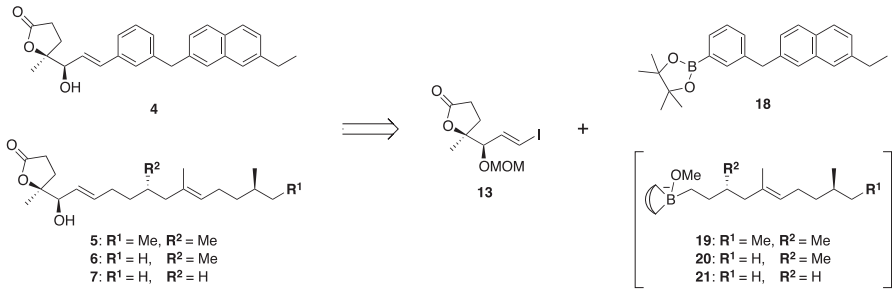


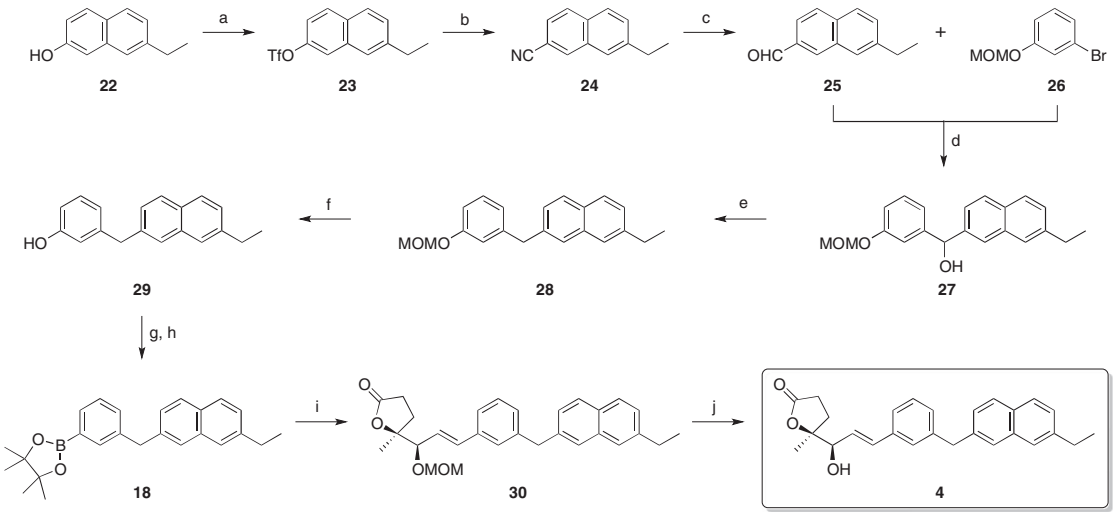
Figure 2.



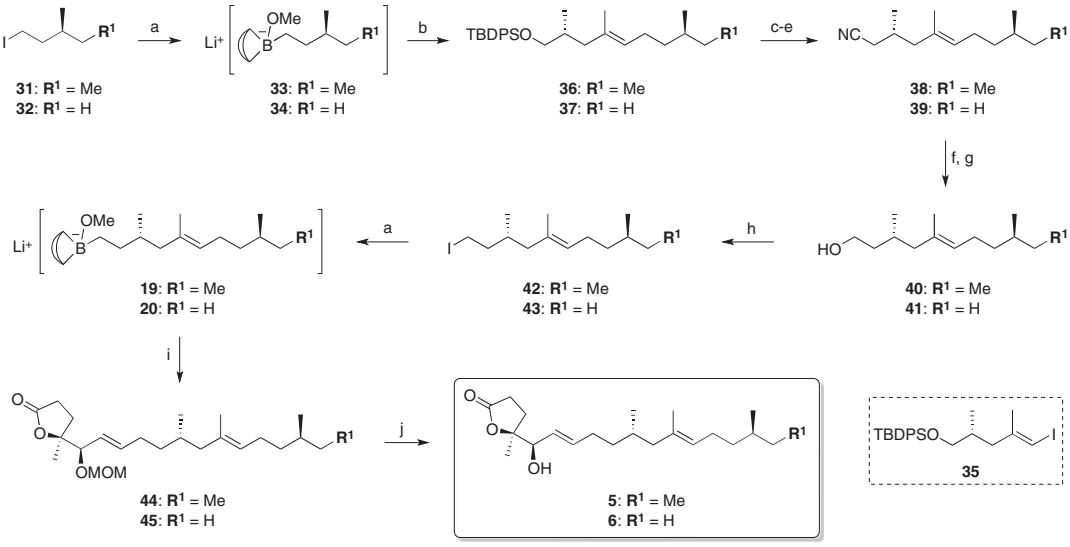
Scheme 1. Reagents and conditions: (a) O_3, CH_2Cl_2 rt, then Me_2S, −78 °C; (b) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O = 1:1, rt, 2 steps 94% (c) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 95%; (d) H_2, $Pd(OH)_2$/C, MeOH, rt, 90%; (e) DMP, CH_2Cl_2, rt, 86%; (f) $CrCl_2$, CHI_3, THF/dioxane, rt, 76% (g) DMP, CH_2Cl_2, rt; (h) $CrCl_2$, LiI, Cl_2CHB(pinacolate), THF, rt, 2 steps 48% (i) $Pd(PPh_3)_4$, PPh_3, 2 M Na_2CO_3 aq, toluene, EtOH, 80 °C; (j) CBr_4, *i*-PrOH, 70 °C, 2 steps 28%.



Scheme 2.

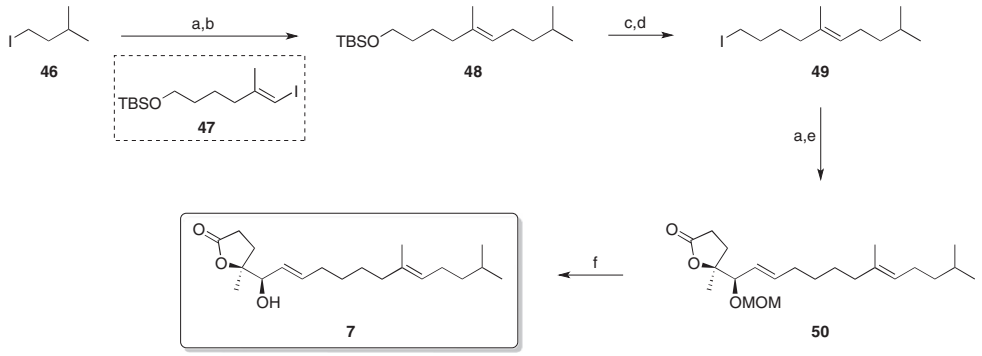


Scheme 3. Reagents and conditions: (a) Tf_2O, DMAP, 2,6-lutidine, CH_2Cl_2, rt, 92%; (b) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 150 °C, 78%; (c) DIBAL, CH_2Cl_2, −78 °C, 93%; (d) *t*-BuLi, THF, −78 °C, 99%; (e) Et_3SiH, TFA, CH_2Cl_2, rt, 75%; (f) CBr_4, *i*-PrOH, 75 °C, quant.; (g) Tf_2O, DMAP, 2,6-lutidine, CH_2Cl_2, rt, 99%; (h) $PdCl_2(dppf)$, bis(pinacolato)diboron, dppf, AcOK, dioxane, 80 °C, 93%; (i) **13**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, toluene, EtOH, 80 °C; (j) CBr_4, *i*-PrOH, 75 °C, 2 steps 38%.

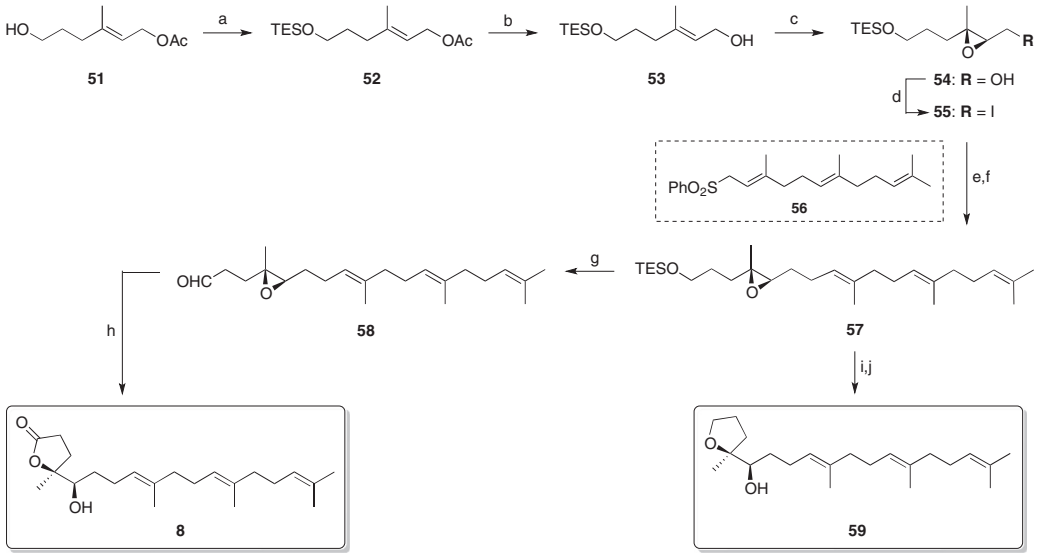


Scheme 4. Reagents and conditions: (a) *t*-BuLi, Et_2O, then 9-BBNOMe, THF, −78 °C to rt; (b) **35**, $PdCl_2(dppf)$, 3 M K_3PO_4 aq, dppp, DMF, rt, **36**: 93%, **37**: 83%; (c) TBAF, THF, rt; (d) *p*-TsCl, Et_3N, $Me_3N{\cdot}HCl$, CH_2Cl_2, 0 °C; (e) KCN, DMSO, 100 °C, **38**: 3 steps 83%; **39**: 3 steps 82%; (f) DIBAL, CH_2Cl_2, −78 °C; (g) $NaBH_4$, MeOH, 0 °C, **40**: 2 steps 81%; **41**: 2 steps 77%; (h) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, **42**: 86%; **43**: 90%; (i) **13**, $PdCl_2(dppf)$, 3 M K_3PO_4 aq, dppp, DMF, rt, **44**: 48%; **45**: 73%; (j) CBr_4, *i*-PrOH, 65 °C, **5**: 92%, **6**: 68%.

9-BBNOMe, gave boronate intermediates **33** and **34** (Scheme 4), which were subjected to *B*-alkyl Suzuki coupling[18] with known vinyl iodide **35**[19] to afford **36** (93%) and **37** (83%). The three-step conversions of **36** and **37** to nitriles **38** and **39** were successful. Stepwise reduction of the nitriles using DIBAL and $NaBH_4$ afforded primary alcohols **40** (81% over 2 steps) and **41** (77% over 2 steps). Subsequent iodination gave alkyl iodides **42** (86%) and **43** (90%) as precursors of the second *B*-alkyl Suzuki coupling. The coupling of boronate intermediates **19** and **20**, derived from iodides **42** and **43** by the same procedure as the preparation of **33** and **34**, with



Scheme 5. Reagents and conditions: (a) *t*-BuLi, Et_2O, then 9-BBNOMe, THF, −78 °C to rt; (b) **47**, $PdCl_2$(dppf), 3 M K_3PO_4 aq, dppp, DMF, rt, 83%; (c) TBAF, THF, rt, 93%; (d) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 91%; (e) **13**, $PdCl_2$(dppf), 3 M K_3PO_4 aq, dppp, DMF, rt; (f) CBr_4, *i*-PrOH, 65 °C, 2 steps, 44%.



Scheme 6. Reagents and conditions: (a) TESCl, imidazole, CH_2Cl_2, rt, 91%; (b) K_2CO_3 aq, MeOH, rt, 76%; (c) (−)-DET, Ti(O*i*-Pr)$_4$, MS4Å, *t*-BuOOH, CH_2Cl_2, −20 °C, 78%, 90% ee; (d) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 78%; (e) **56**, *n*-BuLi, HMPA, THF, −78 °C; (f) Pd(OAc)$_2$, dppp, $NaBH_4$, DMSO, rt, 2 steps 64%; (g) CrO_3, pyridine, CH_2Cl_2, rt, **58**: 54%; **59**: 5%; (h) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O = 1:1, rt, 86%; (i) TBAF, THF, rt; (j) PPTS, CH_2Cl_2, rt, 2 steps 89%.

vinyl iodide **13** in the presence of Pd catalyst afforded **44** (48%) and **45** (73%). Finally, deprotection of the MOM group under acidic conditions gave new nafuredin-γ analogs **5** (92%) and **6** (68%).[12]

The structurally simpler analog **7** was also synthesized (Scheme 5). TBS ether **48** was derived from commercially available alkyl iodide **46** and known vinyl iodide **47**[20] via *B*-alkyl Suzuki coupling in 83% yield. TBS-deprotection and iodination of compound **48** afforded alkyl iodide **49** in 85% yield over 2 steps. The coupling reaction between **49** and **13** followed by MOM-deprotection gave **7** in 44% yield over 2 steps.[12]

2.5. Synthesis of nafuredin-γ derivative 8

The synthesis of new nafuredin-γ derivative **8** is shown in Scheme 6. TES protection of known allyl acetate **51**[21] (91%) followed by solvolysis gave allyl alcohol **53** in 76% yield. Sharpless asymmetric epoxidation of **53** afforded chiral epoxy alcohol **54**[22] in 78% yield; the enantiomeric excess of **54** (90% ee) was determined using the improved Moscher procedure.[23] Iodination of **54** gave epoxy iodide **55** in 78% yield. Coupling reaction of **55** with a lithiated sulfone derived from sulfone **56**[24] followed by Pd-catalyzed reductive desulfoxylation[25] afforded **57** (2 steps, 64%). Oxidation of TES ether **57** under Collins conditions[26] gave desired aldehyde **58** in moderate yield (54%); a small amount of tetrahydrofuran **59** (5%) was also formed via cyclization prior to oxidation after desilylation of the TES ether. Finally, Pinnick oxidation of **58** gave the desired new nafuredin-γ derivative **8** in 86% yield. Although this completed the synthesis of all desired nafuredin-γ derivatives, tetrahydrofuran **59**, obtained as a by-product, was also an attractive compound for structure-activity relationship study. Therefore, conversion of **57** into **59** was achieved in high yield via deprotection of the TES ether, followed by cyclization under acidic conditions (2 steps, 89%).

2.6. Complex I inhibitory activities of the synthetic analogs

Complex I inhibitory activities of the new nafuredin-γ analogs **4**–**8** and **59** were evaluated (Table 1).[1,27] The IC_{50} values of

Table 1
Inhibitory activities of the synthesized nafuredin-γ analogs against complex I (*Ascaris suum*)

Compound	IC_{50} (nM)
Nafuredin-γ (**2**)	6
4	550
5	550
6	300
7	340
8	820
59	500

derivatives **4** and **5**, bearing aryl substituents and non-conjugated (*E*)-olefins, respectively, were both 550 nM. In addition, the structurally simpler analogs **6** and **7**, lacking one or both of the stereogenic centers in the side chain, respectively, showed complex I inhibitory activities similar to those of **4** and **5**. These results demonstrated that the methyl groups at C10 and C16, and their stereogenic centers in the side chain of the nafuredin-γ analogs, are not important for complex I inhibitory activity. Two structurally simpler analogues, **8** and **59**, were synthesized; the IC_{50} value of analog **8** was slightly larger than that of **59**. The complex I inhibitory activities of all the new nafuredin-γ analogs were lower than that of nafuredin-γ (**2**), but all were in the high nM range. As expected, these analogs were resistant to air oxidation.

3. Conclusion

In conclusion, we designed and synthesized new air-stable nafuredin-γ analogs. All the new analogs exhibited high inhibitory activity (nM) against complex I and were resistant to air oxidation. The efficient synthetic route of the structurally simplest nafuredin-γ analog, **59**, will be particularly helpful for scale-up synthesis for upcoming in vivo tests. Further SAR studies of nafuredin-γ analogs aimed at developing novel antiparasitic drugs are currently underway in our laboratory.

4. Experimental

4.1. General

IR spectra were obtained using a Horiba FT-710 spectrophotometer and JASCO FT/IR 460-plus. ^{1}H and ^{13}C NMR spectra were obtained using Agilent Technologies Mercury-300 and UNITY-400 spectrometers, and chemical shifts were reported on the δ scale based on internal TMS. MS spectra were measured with JEOL JMS-AX505HA, JMS-700 MStation, and JEOL JMS-T100LP spectrometers. Optical rotations were recorded on a JASCO DIP-1000 polarimeter. Commercial reagents and solvents were used without further purification unless otherwise indicated. Flash chromatography was carried out on silica gel 60N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm Merck silica gel 60 F254 plates and visualized by UV (254 nm) and cerium ammonium molybdenate or *p*-anisaldehyde.

4.1.1. (*S*)-5-[(*R*)-2-(Benzyloxy)-1-hydroxyethyl]dihydro-5-methylfuran-2(3*H*)-one (10)

Ozone was bubbled through a solution of **9**[9] (1.14 g, 4.40 mmol) in CH_2Cl_2 (44.0 mL) for 30 min at −78 °C. To remove residual ozone, oxygen was subsequently bubbled through the solution for 15 min at −78 °C and Me_2S (323 μL, 8.80 mmol) was added. After stirring for 1 h at room temperature, the reaction mixture was concentrated in vacuo. A solution of the crude aldehyde in *t*-BuOH (22.0 mL) and H_2O (22.0 mL) was treated with 2-methyl-2-butene (1.86 μL, 17.6 mmol), $NaH_2PO_4{\cdot}2H_2O$ (1.19 g, 13.2 mmol) and $NaClO_2$ (2.06 g, 13.2 mmol) at 0 °C. After stirring for 5 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq, then extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (3:2 hexanes/EtOAc) to afford **10** (969 mg, 2 steps, 94%) as a colorless oil.

$[\alpha]_D^{28}$ +4.55 (*c* 1.00, $CHCl_3$); IR (KBr) 3456, 3060, 3030, 2978, 2935, 2875, 1768, 1599, 1454, 1377, 1265, 1244, 1209, 1159, 1113, 1074, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 4.56 (s, 2H), 3.90–3.84 (m, 1H), 3.64 (dd, *J* = 9.7, 3.2 Hz, 1H), 3.50 (dd, *J* = 9.7, 7.3 Hz, 1H), 2.76–2.40 (m, 3H), 1.95–1.82 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 137.4, 128.5, 127.9, 127.8, 86.8, 74.4, 73.6, 70.1, 29.7, 29.0, 22.4; HRMS (FAB, *m*-NBA + NaI) $[M+Na]^+$ calcd for $C_{14}H_{18}O_4Na$ 273.1103, found 273.1109.

4.1.2. (*S*)-5-[(*R*)-2-(Benzyloxy)-1-(methoxymethoxy)ethyl] dihydro-5-methylfuran-2(3*H*)-one

A solution of **10** (1.94 g, 7.77 mmol) in CH_2Cl_2 (78.0 mL) was treated with *i*-Pr_2NEt (2.71 mL, 15.5 mmol) and MOMCl (1.17 mL, 15.5 mmol) at 0 °C. After stirring for 40 h at room temperature, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (3:1 hexanes/EtOAc) to afford (*S*)-5-[(*R*)-2-(benzyloxy)-1-(methoxymethoxy)ethyl]dihydro-5-methylfuran-2(3*H*)-one (2.18 g, 95%) as a colorless oil.

$[\alpha]_D^{24}$ −32.7 (*c* 0.10, $CHCl_3$); IR (KBr) 2941, 2895, 1772, 1454, 1371, 1246, 1207, 1157, 1109, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H) , 4.44 (d, *J* = 12.0 Hz, 1H) , 3.78 (dd, *J* = 4.9, 3.4 Hz, 1H), 3.69 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.60 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.37 (s, 3H), 2.71–2.45 (m, 3H), 1.93–1.79 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 137.7, 128.4, 127.8, 127.6, 96.9, 87.4, 80.1, 73.6, 69.9, 56.0, 29.6, 29.5, 23.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{16}H_{23}O_5$ 295.1545, found 295.1552.

4.1.3. (*S*)-Dihydro-5-[(*R*)-2-hydroxy-1-(methoxymethoxy)ethyl]-5-methylfuran-2(3*H*)-one (11)

A suspension of (*S*)-5-[(*R*)-2-(benzyloxy)-1-(methoxymethoxy)ethyl]dihydro-5-methylfuran-2(3*H*)-one (367 mg, 1.25 mmol) and 20% $Pd(OH)_2$/C (73 mg) in MeOH (13.0 mL) was vigorously stirred under a H_2 atmosphere at room temperature for 12 h. The catalyst was filtered through a pad of celite, and the celite was washed with Et_2O. The filtrate was concentrated in vacuo. The residue was purified by flash silica gel column chromatography (1:1 hexanes/EtOAc) to afford **11** (229 mg, 90%) as a colorless oil.

$[\alpha]_D^{25}$ +45.2 (*c* 0.10, $CHCl_3$); IR (KBr) 3473, 2949, 2895, 2829, 1768, 1456, 1415, 1385, 1292, 1209, 1157, 1099, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 3.75 (t, *J* = 9.1 Hz, 1H), 3.73–3.56 (m, 2H), 3.41 (s, 3H) , 3.02–3.00 (m, 1H), 2.62 (ddd, *J* = 17.8, 10.4, 7.1 Hz, 1H), 2.53 (ddd, *J* = 17.8, 10.4, 7.1 Hz, 1H), 2.44–2.39 (m, 1H), 1.89–1.84 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 98.0, 86.9, 86.4, 61.9, 56.0, 29.6, 29.3, 23.6; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_9H_{17}O_5$ 205.1076, found 205.1072.

4.1.4. (*S*)-2-[(*S*)-Tetrahydro-2-methyl-5-oxofuran-2-yl]-2-(methoxymethoxy)acetaldehyde (12)

A solution of **11** (333 mg, 1.63 mmol) in CH_2Cl_2 (16.3 mL) was treated with DMP (2.07 g, 4.90 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (1:1 hexanes/EtOAc) to afford **12** (282 mg, 86%) as a colorless oil.

$[\alpha]_D^{28}$ −49.4 (*c* 1.00, $CHCl_3$); IR (KBr) 3437, 2981, 2949, 2900, 2831, 2359, 1772, 1630, 1456, 1385, 1246, 1213, 1157, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.5 Hz, 1H), 4.70 (s, 2H), 4.05 (d, *J* = 1.5 Hz, 1H), 3.39 (s, 3H), 2.71 (ddd, *J* = 18.1, 10.3, 7.7 Hz, 1H), 2.56 (ddd, *J* = 18.1, 10.3, 5.6 Hz, 1H), 2.38 (ddd, *J* = 18.1, 10.3, 5.6 Hz, 1H), 1.93 (ddd, *J* = 18.1, 10.3,

7.7 Hz, 1H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 176.2, 97.3, 85.5, 84.9, 56.3, 29.6, 29.1, 23.8; HRMS (FAB, *m*-NBA + NaI) $[M+Na]^+$ calcd for $C_9H_{14}O_5Na$ 225.0739, found 225.0735.

4.1.5. (*S*)-Dihydro-5-[(*R*,*E*)-3-iodo-1-(methoxymethoxy)allyl]-5-methylfuran-2(3*H*)-one (13)

A solution of **12** (412 mg, 2.04 mmol) in THF/dioxane (10:1, 22.0 mL) was treated with $CrCl_2$ (1.50 g, 12.2 mmol) and CHI_3 (1.04 g, 2.65 mmol) at room temperature. After stirring for 13 h in the dark, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq, then stirred for 1 h. The reaction mixture was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (8:1 hexanes/EtOAc) to afford **13** (507 mg, 76%) as a colorless oil.

$[\alpha]_D^{19}$ −38.3 (*c* 0.1, $CHCl_3$); IR (KBr) 3514, 3446, 3055, 2983, 2952, 2889, 2825, 2359, 1774, 1606, 1450, 1290, 1248, 1209, 1157, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (d, *J* = 14.6 Hz, 1H), 6.41 (dd, *J* = 14.6, 7.7 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 4.09 (d, *J* = 7.7 Hz, 1H), 3.34 (s, 3H), 2.46–2.78 (m, 2H), 2.44–2.32 (m, 1H), 1.92–1.79 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 140.4, 94.1, 85.9, 82.6, 82.3, 56.0, 29.6, 28.6, 24.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{10}H_{16}IO_4$ 327.0093, found 327.0094.

4.1.6. 4,4,5,5-Tetramethyl-2-[(1*E*,3*R*,5*E*,7*E*,9*S*)-3,5,9-trimethylundeca-1,5,7-trienyl]-1,3,2-dioxaborolane (16)

A solution of **14**[4] (109 mg, 0.560 mmol) in CH_2Cl_2 (6.0 mL) was treated with DMP (471 mg, 1.11 mmol) at 0 °C. After stirring for 1.5 h at room temperature, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq, then the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude aldehyde **15** in THF (2.0 mL) was treated with Cl_2CHB(pinacolate)[9] (141 μg, 0.67 mmol) in THF (1.0 mL) solution and LiI (179 mg, 1.33 mmol) in THF (3.0 mL) at room temperature. After stirring for 15 h at room temperature, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq, then extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (40:1 hexanes/EtOAc) to afford **16** (82.5 mg, 2 steps, 48%) as a colorless oil.

$[\alpha]_D^{23}$ +38.4 (*c* 0.10, $CHCl_3$); IR (KBr) 2964, 2925, 2867, 1738, 1636, 1457, 1363, 1323, 1266, 1217, 1147, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (dd, *J* = 18.2, 6.7 Hz, 1H), 6.19 (ddd, *J* = 15.4, 10.8, 1.0 Hz, 1H), 5.77 (d, *J* = 10.8 Hz, 1H), 5.45 (dd, *J* = 15.4, 7.6 Hz, 1H), 5.39 (dd, *J* = 18.2, 1.4 Hz, 1H), 2.45–2.38 (m, 1H), 2.17 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.10–2.03 (m, 1H), 1.90 (dd, *J* = 13.3, 8.7 Hz, 1H), 1.71 (s, 3H), 1.35–1.28 (m, 2H), 1.26 (s, 12H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 138.4, 134.1, 126.8, 124.8, 83,0, 46.7, 38.5, 37.4, 28.8, 29.8, 24.7, 24.6, 20.9, 20.2, 18.9, 16.5, 11.8; HRMS (FAB, *m*-NBA) $[M]^+$ calcd for $C_{20}H_{35}O_2^{11}B$ 318.2734, found 318.2728.

4.1.7. (*S*)-Dihydro-5-[(1*R*,2*E*,4*E*,6*R*,8*E*,10*E*,12*S*)-1-hydroxy-6,8,12-trimethyltetradeca-2,4,8,10-tetraenyl]-5-methylfuran-2(3*H*)-one (3)

A solution of **13** (29.4 mg, 0.0900 mmol) and **16** (35.6 mg, 0.110 mmol) in toluene (1.8 mL) and EtOH (0.45 mL) was treated with $Pd(PPh_3)_4$ (5.4 mg, 4.70 μmol), PPh_3 (1.2 mg, 4.70 μmol) and 2 M Na_2CO_3 aq (1.1 mL) at room temperature. After stirring for 2 h at 80 °C, the reaction mixture was brought to room temperature and quenched with H_2O. The aqueous layer was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude MOM ether in *i*-PrOH (1.0 mL) was treated with CBr_4 (47.1 μg, 0.0142 mmol) at room temperature, then the temperature was immediately changed to 70 °C. After stirring for 4 h at 70 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (2:1 hexanes/EtOAc) to afford **3** (8.8 mg, 2 steps, 28%) as a colorless oil.

$[\alpha]_D^{25}$ +29.7 (*c* 0.10, $CHCl_3$); IR (KBr) 3431, 2960, 2924, 2860, 1767, 1658, 1455, 1379, 1260, 1204, 1085, 1022, 1379, 1260, 1204, 1085 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 15.4, 10.4 Hz, 1H), 6.17 (ddd, *J* = 15.2, 10.8, 0.9 Hz, 1H), 6.00 (dd, *J* = 15.4, 10.4 Hz, 1H), 5.76 (d, *J* = 10.8 Hz, 1H), 5.69 (dd, *J* = 15.4, 7.2, Hz, 1H), 5.50 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.45 (dd, *J* = 15.2, 7.9 Hz, 1H), 4.23 (d, *J* = 6.8 Hz, 1H), 2.67 (ddd, *J* = 18.0, 10.6, 6.5 Hz, 1H), 2.57 (ddd, *J* = 12.9, 10.2, 6.5 Hz, 1H), 2.44–2.37 (m, 2H), 2.11–2.02 (m, 2H), 1.95 (dd, *J* = 13.4, 7.9 Hz, 1H), 1.77 (ddd, *J* = 12.9, 10.2, 6.5 Hz, 1H), 1.70 (s, 3H), 1.36 (s, 3H), 1.33–1.27 (m, 2H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 142.6, 138.8, 134.9, 134.2, 127.2, 127.1, 126.5, 124.9, 88.4, 77.2, 47.7, 38.8, 35.0, 30.1, 29.7, 27.9, 24.0, 20.4, 19.8, 16.8, 12.0; HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{34}NaO_3$ 369.2405, found 369.2397.

4.1.8. 2-Ethylnaphthalen-7-yl trifluoromethanesulfonate (23)

A solution of **22**[13] (2.05 g, 11.9 mmol) in CH_2Cl_2 (60.0 mL) was treated with Tf_2O (3.00 mL, 17.8 mmol), 2,6-lutidine (2.78 mL, 23.8 mmol) and DMAP (727 mg, 5.95 mmol) at 0 °C. After stirring for 3 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq, then extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **23** (3.34 g, 92%) as a colorless oil.

IR (KBr) 3056, 2970, 2936, 2876, 2361, 1793, 1705, 1635, 1606, 1509, 1459, 1424, 1213, 1143, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 2.5 Hz, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.43 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.30 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 143.8, 133.7, 130.8, 130.2, 130.2, 128.5, 125.6, 125.6, 120.4, 118.7, 118.6, 117.2; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{12}F_3O_3S$ 305.0459, found 305.0457.

4.1.9. 2-Cyano-7-ethylnaphthalene (24)

A solution of **23** (103 mg, 0.340 mmol) in DMF (1.7 mL) was treated with $Zn(CN)_2$ (79.7 mg, 0.680 mmol) and $Pd(PPh_3)_4$ (39.2 mg, 0.0300 mmol) at room temperature. After stirring for 15 h at 150 °C, the reaction mixture was brought to room temperature and quenched with satd $NaHCO_3$ aq The reaction mixture was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (50:1 hexanes/EtOAc) to afford **24** (46.5 mg, 78%) as a white solid.

IR (KBr) 3055, 2974, 2935, 2874, 2226, 1631, 1603, 1508, 1458, 1369, 1341, 1317, 1268, 1197, 1175, 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.6 Hz, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.51 (dd, *J* = 8.6, 1.6 Hz, 1H), 2.85 (q, *J* =7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 133.6, 133.1, 132.5, 130.3, 128.8, 127.9, 126.0, 125.5, 119.4, 109.2, 28.9, 15.2; HRMS (EI) $[M]^+$ calcd for $C_{13}H_{11}ON$ 181.0891, found 181.0897.

4.1.10. 7-Ethylnaphthalene-2-carbaldehyde (25)

A solution of **24** (583 mg, 3.22 mmol) in CH_2Cl_2 (16.0 mL) was treated with DIBAL (1.03 M sol. in hexane, 6.43 mL, 6.43 mmol)

at −78 °C. After stirring for 0.5 h at −78 °C, the reaction mixture was quenched with 2 M HCl and diluted with EtOAc. The organic layer was washed with 2 M HCl and H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (200:1 hexanes/EtOAc) to afford **25** (3.34 g, 93%) as a white solid.

IR (KBr) 2971, 2935, 2871, 2821, 2721, 1694, 1603, 1458, 1375, 1338, 1270, 1205, 1169, 1123, 1058 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1H), 8.26 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 2.85 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 143.2, 134.9, 134.1, 134.1, 132.9, 130.4, 128.7, 127.9, 127.1, 121.9, 28.9, 15.3; HRMS (FAB, *m*-NBA+-NaI) $[M+Na]^+$ calcd for $C_{13}H_{12}ONa$ 207.0786, found 207.0790.

4.1.11. 2-Ethylnaphthalen-7-yl[3-(methoxymethoxy) phenyl]methanol (27)

A solution of **26**[15] (533 mg, 2.46 mmol) in THF (16.0 mL) was treated with *t*-BuLi (1.59 M sol. in pentane, 3.09 mL, 4.91 mmol) at −78 °C. After stirring for 10 min at −78 °C, **25** (302 mg, 1.63 mmol) in THF (8.6 mL) was added. After stirring for 1 h at −78 °C, the reaction mixture was quenched with satd NH_4Cl aq The aqueous layer was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (10:1 hexanes/EtOAc) to afford **27** (523 mg, 99%) as a white solid.

IR (KBr) 3448, 2964, 2347, 1633, 1605, 1511, 1486, 1451, 1403, 1314, 1246, 1207, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.66 (s, 1H), 7.42 (dd, J = 6.6 Hz, 1H), 7.37 (dd, J = 6.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.17 (s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.01–6.97 (m, 1H), 6.00 (d, J = 3.3 Hz, 1H), 5.20 (s, 2H), 3.50 (s, 3H), 2.86 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 145.4, 142.1, 141.0, 133.5, 131.3, 129.5, 128.0, 127.5, 127.2, 125.7, 124.7, 123.9, 120.2, 115.1, 114.7, 94.4, 76.2, 56.0, 29.0, 15.5 ; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{22}O_3Na$ 345.1467, found 345.1464.

4.1.12. 2-(3-(Methoxymethoxy)benzyl)-7-ethylnaphthalene (28)

A solution of **27** (281 mg, 0.870 mmol) in CH_2Cl_2 (9.0 mL) was treated with Et_3SiH (557 μL, 3.49 mmol) and TFA (134 μL, 1.74 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (100:1 hexanes/EtOAc) to afford **28** (201 mg, 75%) as a white solid.

IR (KBr) 2961, 2927, 1600, 1487, 1449, 1313, 1248, 1207, 1150, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.59 (br s, 1H), 7.57 (br s, 1H), 7.30 (dd, J = 8.4, 1.7 Hz, 1H), 7.27 (dd, J = 8.4, 1.7 Hz, 1H), 7.22 (ddd, J = 8.0, 7.7, 0.6 Hz, 1H), 6.93–6.87 (m, 3H), 5.16 (s, 2H), 4.11 (s, 2H), 3.48 (s, 3H), 2.81 (q, J = 7.6 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 142.7, 141.9, 138.3, 133.8, 130.5, 129.4, 127.8, 127.5, 126.8, 126.7, 126.6, 125.2, 122.6, 117.1, 113.7, 94.4, 56.0, 42.1, 29.0, 15.5; HRMS (FAB, *m*-NBA) $[M]^+$ calcd for $C_{21}H_{22}O_2$ 306.1620, found 306.1619.

4.1.13. 3-((2-Ethylnaphthalen-7-yl)methyl)phenol (29)

A solution of **28** (286 mg, 0.930 mmol) in *i*-PrOH (19.0 mL) was treated with CBr_4 (1.23 g, 3.73 mmol) at room temperature. After stirring for 0.5 h at 75 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (30:1 hexanes/EtOAc) to afford **29** (245 mg, quant.) as a white solid.

IR (KBr) 3376, 3046, 2964, 2928, 2870, 1595, 1488, 1455, 1349, 1264, 1153, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.57–7.56 (m, 2H), 7.31 (dd, J = 8.4, 1.6 Hz, 1H), 7.25 (dd, J = 8.4, 1.6 Hz, 1H), 7.16 (ddd, J = 7.6, 7.5, 0.9 Hz, 1H), 6.83–6.81 (m, 1H), 6.69–6.66 (m, 2H), 4.80–4.65 (br, 1H), 4.08 (s, 2H), 2.80 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 143.0, 142.0, 138.2, 133.8, 130.6, 129.6, 127.8, 127.5, 126.8, 126.7, 126.6, 125.2, 121.5, 115.9, 113.0, 41.9, 29.0, 15.5; HRMS (FAB, *m*-NBA) $[M]^+$ calcd for $C_{19}H_{18}O$ 262.1358, found 262.1363.

4.1.14. 3-((2-Ethylnaphthalen-7-yl)methyl)phenyl trifluoromethanesulfonate

A solution of **29** (298 mg, 1.13 mmol) in CH_2Cl_2 (11.0 mL) was treated with Tf_2O (229 μL, 1.36 mmol), 2,6-lutidine (199 μL, 1.70 mmol) and DMAP (69.4 mg, 0.580 mmol) at 0 °C. After stirring for 0.5 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford 3-((2-ethylnaphthalen-7-yl)methyl)-phenyl trifluoromethanesulfonate (441 mg, 99%) as a white solid.

IR (KBr) 3454, 2697, 2929, 2365, 1611, 1580, 1483, 1422, 1213, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.57–7.55 (m, 2H), 7.37 (dd, J = 7.7, 0.9 Hz, 1H), 7.34–7.31 (m, 1H), 7.26–7.19 (m, 2H), 7.14–7.11 (m, 2H), 4.17 (s, 2H), 2.81 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 144.2, 142.2, 136.9, 133.8, 130.7, 130.1, 129.0, 128.1, 127.6, 127.0, 126.8, 125.2, 121.8, 120.3, 118.9, 117.1, 41.6, 29.0, 15.5; HRMS (FAB, *m*-NBA) $[M]^+$ calcd for $C_{20}H_{17}F_3O_3S$ 394.0851, found 394.0851.

4.1.15. 2-(3-((2-Ethylnaphthalen-7-yl)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18)

A solution of 3-((2-ethylnaphthalen-7-yl)methyl)phenyl trifluoromethanesulfonate (201 mg, 0.510 mmol) in dioxane (5.1 mL) was treated with $PdCl_2$(dppf) (74.8 mg, 0.100 mmol), bis(pinacolato)diboron (160 mg, 0.610 mmol), dppf (56.6 mg, 0.100 mmol) and KOAc (150 mg, 1.53 mmol) at room temperature. After stirring for 12 h at 80 °C, the reaction mixture was quenched with H_2O and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **18** (176 mg, 93%) as a pale yellow solid.

IR (KBr) 2972, 2927, 2364, 1734, 1635, 1606, 1428, 1358, 1269, 1204, 1144, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.65 (m, 4H), 7.57–7.64 (m, 2H), 7.31–7.23 (m, 4H), 4.13 (s, 2H), 2.79 (q, J = 7.5 Hz, 2H), 1.34 (s, 12H), 1.32 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 140.3, 138.7, 135.3, 133.8, 132.6, 132.1, 130.5, 128.0, 127.7, 127.5, 126.8, 126.6, 126.5, 125.2, 83.7, 42.1, 29.7, 29.0, 24.8, 15.5; HRMS (FAB, *m*-NBA) $[M]^+$ calcd for $C_{25}H_{29}^{11}BO_2$ 372.2261, found 372.2259.

4.1.16. (*S*)-5-((*R*,*E*)-3-(3-((7-Ethylnaphthalen-2-yl)methyl) phenyl)-1-hydroxyallyl)-5-methyldihydrofuran-2(3*H*)-one (4)

A solution of **13** (40.2 mg, 0.123 mmol) and **18** (45.9 mg, 0.123 mmol) in toluene (2.5 mL) and EtOH (615 μL) was treated with a catalytic amount of $Pd(PPh_3)_4$ and 2 M Na_2CO_3 aq (1.5 mL) at room temperature. After stirring for 1 h at 80 °C, the reaction mixture was brought to room temperature and quenched with H_2O. The aqueous layer was extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude MOM ether in *i*-PrOH (1.5 mL) was treated with CBr_4 (61.5 μg, 0.185 mmol) at room tem-

perature. After stirring for 1 h at 75 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (5:1 hexanes/EtOAc) to afford **4** (18.7 mg, 2 steps 38%) as a white solid.

$[\alpha]_D^{26}$ −29.2 (*c* 0.10, $CHCl_3$); IR (KBr) 3425, 2925, 1762, 1633, 1452, 1077; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.56 (s, 2H), 7.31 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.27–7.13 (m, 5H), 6.72 (dd, *J* = 16.0, 0.9 Hz, 1H), 6.14 (dd, *J* = 16.0, 6.6 Hz, 1H), 4.80 (dd, *J* = 6.6, 0.9 Hz, 1H), 4.12 (s, 2H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.73–2.55 (m, 2H), 2.53–2.42 (m, 1H), 2.25–1.95 (br, 1H), 1.86–1.77 (m, 1H), 1.41 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, Acetone-d_6) δ 177.1, 142.8, 142.6, 139.8, 138.0, 134.9, 133.1, 131.6, 129.6, 129.2, 128.6, 128.6, 128.4, 128.2, 127.6, 127.4, 127.3, 126.0, 125.1, 88.2, 77.5, 42.4, 30.0, 29.5, 29.0, 23.8, 15.9; HRMS (ESI) $[M+Na]^+$ calcd for $C_{27}H_{28}O_3Na$ 423.1936, found 423.1936.

4.1.17. *tert*-Butyldiphenyl((2*R*,8*S*,*E*)-2,4,8-trimethyldec-4-enyloxy)silane (36)

A solution of **31**[17] (108 mg, 0.508 mmol) in Et_2O (5.0 mL) was treated with *t*-BuLi (1.55 M sol. in pentane, 0.700 mL, 1.09 mmol) at −78 °C. After stirring for 10 min at −78 °C, 9-BBNOMe (1.0 M sol. in hexane, 1.18 mL, 1.18 mmol) and THF (5.0 mL) were added. After stirring for 1.5 h at room temperature, the reaction mixture was treated with **35**[19] (110 mg, 0.231 mmol) in DMF (5.0 mL), 3 M K_3PO_4 aq (385 μL, 1.16 mmol), $PdCl_2$(dppf) (18.9 mg, 23.1 μmol) and dppf (12.8 mg, 23.1 μmol) at room temperature. After stirring for 13 h at room temperature, the reaction mixture was quenched with H_2O and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **36** (93.3 mg, 93%) as a colorless oil.

$[\alpha]_D^{25}$ +10.3 (c 1.00, $CHCl_3$); IR (KBr) 3062, 2957, 2925, 2862, 2361, 1463, 1436, 1383, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.42–7.34 (m, 6H), 5.08 (t, *J* = 7.0 Hz, 1H), 3.51–3.40 (m, 2H), 2.18 (dd, *J* = 12.8, 5.4 Hz, 1H), 1.97–1.93 (m, 2H), 1.82–1.78 (m, 1H), 1.72 (dd, *J* = 12.8, 8.4 Hz, 1H), 1.53 (s, 3H), 1.35–1.06 (m, 5H), 1.05 (s, 9H), 0.88–0.82 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.4, 133.3, 129.7, 127.8, 126.9, 69.0, 44.1, 36.9, 34.3, 34.0, 29.7, 27.1, 25.8, 19.6, 19.3, 16.9, 16.0, 11.6; HRMS (FAB, *m*-NBA) [M-*t*-Bu]$^+$ calcd for $C_{25}H_{35}OSi$ 379.2457, found 379.2453.

4.1.18. (3*R*,9*S*,*E*)-3,5,9-Trimethylundec-5-enenitrile (38)

A solution of **36** (442 mg, 1.02 mmol) in THF (10.0 mL) was treated with TBAF (1.0 M sol. in THF, 3.06 μL, 3.06 mmol) at room temperature. After stirring for 3 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude alcohol in CH_2Cl_2 (10.0 mL) was treated with *p*-TsCl (290 μg, 1.52 mmol), Et_3N (423 μL, 3.05 mmol) and Me_3N·HCl (9.7 mg, 0.102 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude tosylate in DMSO (10.0 mL) was treated with KCN (79.3 mg, 1.22 mmol) at room temperature. After stirring for 3.5 h at 100 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (200:1 hexanes/EtOAc) to afford **38** (175 mg, 3 steps, 83%) as a pale yellow oil.

$[\alpha]_D^{26}$ −13.4 (*c* 1.00, $CHCl_3$); IR (KBr) 3054, 2961, 2923, 2246, 1723, 1457, 1381, 1267 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (t, *J* = 7.0 Hz, 1H), 2.31 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.15 (dd, *J* = 16.5, 6.9 Hz, 1H), 2.07–1.89 (m, 5H), 1.53 (s, 3H), 1.40–1.06 (m, 5H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.89–0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7, 128.7, 119.2, 46.7, 36.7, 34.3, 29.6, 28.7, 25.7, 23.9, 19.7, 19.3, 15.9, 11.6; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{26}N$ 208.2065, found 208.2059.

4.1.19. (3*R*,9*S*,*E*)-3,5,9-Trimethylundec-5-en-1-ol (40)

A solution of **38** (174 mg, 0.840 mmol) in CH_2Cl_2 (8.4 mL) was treated with DIBAL (1.04 M sol. in hexane, 1.20 mL, 1.26 mmol) at −78 °C. After stirring for 1.5 h at −78 °C the reaction mixture was quenched with 2 M HCl and diluted with EtOAc. The organic layer was washed with 2 M HCl and H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude aldehyde in MeOH (8.4 mL) was treated with $NaBH_4$ (63.6 μg, 1.68 mmol) at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture was quenched with acetone and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (200:1 hexanes/EtOAc) to afford **40** (144 mg, 2 steps, 81%) as a pale yellow oil.

$[\alpha]_D^{27}$ +5.74 (*c* 1.00, $CHCl_3$); IR (KBr) 3331, 2958, 2921, 2231, 1662, 1457, 1379, 1057 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (dt, *J* = 7.0, 1.1 Hz, 1H), 3.74–3.60 (m, 2H), 2.01–1.90 (m, 3H), 1.82–1.67 (m, 3H), 1.64–1.53 (m, 1H), 1.57 (s, 3H), 1.38–1.24 (m, 4H), 1.19–1.06 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H) 0.85 (d, *J* = 5.7 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 126.8, 61.2, 48.0, 39.7, 36.7, 34.0, 29.4, 27.4, 25.5, 19.4, 19.1, 15.7, 11.4.; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{29}O$ 213.2218, found 213.2228.

4.1.20. (3*R*,9*S*,*E*)-1-Iodo-3,5,9-trimethylundec-5-ene (42)

A solution of **40** (70.3 mg, 0.331 mmol) in CH_2Cl_2 (5.0 mL) was treated with I_2 (126 mg, 0.497 mmol), PPh_3 (113 mg, 0.868 mmol) and imidazole (126 mg, 2.00 mmol) at 0 °C. After stirring for 10 min at 0 °C, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **42** (144 mg, 86%) as a pale yellow oil.

$[\alpha]_D^{27}$ −2.23 (*c* 1.00, $CHCl_3$); IR (KBr) 3437, 2958, 2919, 2154, 1637, 1456, 1379, 1256, 1215, 1177 cm^-; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dt, *J* = 7.0, 1.0 Hz, 1H), 3.31–3.12 (m, 2H), 2.06–1.91 (m, 3H), 1.90–1.64 (m, 3H), 1.63–1.51 (m, 1H), 1.58 (s, 3H), 1.42–1.26 (m, 3H), 1.22–1.05 (m, 2H), 0.91–0.81 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 127.4, 47.4, 40.8, 36.9, 34.2, 32.0, 29.7, 25.7, 19.4, 18.9, 16.0, 11.6, 5.6.; HRMS (EI) $[M]^+$ calcd for $C_{14}H_{27}I$ 322.1157, found 322.1155.

4.1.21. (*S*)-5-((1*R*,2*E*,6*S*,8*E*,12*S*)-1-(Methoxymethoxy)-6,8,12-trimethyltetradeca-2,8-dien-1-yl)-5-methyldihydrofuran-2(3*H*)-one (44)

A solution of **42** (152 mg, 0.160 mmol) in Et_2O (1.6 mL) was treated with *t*-BuLi (1.59 M sol. in pentane, 0.209 mL, 0.333 mmol) at −78 °C. After stirring for 10 min at −78 °C, 9-BBNOMe (1.0 M sol. in hexane, 0.359 mL, 0.832 mmol) and THF (1.6 mL) were added. After stirring for 1.5 h at room temperature, the reaction mixture was treated with **13** (43.4 mg, 0.133 mmol) in DMF (1.6 mL), 3 M K_3PO_4 aq (222 μL, 0.655 mmol), $PdCl_2$(dppf) (10.9 mg, 13.3 μmol) and dppf (7.4 mg, 13.3 μmol) at room temperature. After stirring for 17 h at room temperature, the reaction mixture was quenched with H_2O and diluted with EtOAc. The organic layer was washed

with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (50:1 hexanes/EtOAc) to afford **44** (25.2 mg, 48%) as a pale yellow oil.

$[\alpha]_D^{27}$ −53.49 (*c* 1.00, $CHCl_3$); IR (KBr) 3527, 2923, 1777, 1456, 1377, 1206, 1156, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.25 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.09 (t, *J* = 6.7 Hz, 1H), 4.67 (d, *J* = 6.7 Hz, 1H), 4.49 (d, *J* = 6.7 Hz, 1H), 4.06 (d, *J* = 8.2 Hz, 1H), 3.35 (s, 3H), 2.80–2.66 (m, 1H), 2.59–2.44 (m, 1H), 2.43–2.32 (m, 1H), 2.14–1.92 (m, 6H), 1.88–1.70 (m, 3H), 1.55 (s, 3H), 1.44–1.08 (m, 6H), 1.25 (s, 3H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.3, 134.2, 132.4, 124.0, 95.8, 89.9, 82.1, 55.6, 47.1, 39.0, 38.1, 32.9, 31.6, 28.8, 28.3, 28.2, 27.6, 24.4, 23.3, 21.5, 17.9, 16.6, 11.6; HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{42}NaO_4$ 417.2981, found 417.2972.

4.1.22. 4(*S*)-5-((1*R*,2*E*,6*S*,8*E*,12*S*)-1-Hydroxy-6,8,12-trimethyltetradeca-2,8-dien-1-yl)-5-methyldihydrofuran-2(3*H*)-one (5)

A solution of **44** (12.1 mg, 31.4 μmol) in *i*-PrOH (1.0 mL) was treated with CBr_4 (31.3 mg, 94.3 μmol) at room temperature. After stirring for 6 h at 65 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (5:1 hexanes/EtOAc) to afford **5** (10.1 mg, 92%) as a pale yellow oil.

$[\alpha]_D^{28}$ −3.00 (*c* 1.00, $CHCl_3$); IR (KBr) 3438, 2921, 1768, 1456, 1379, 1205, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88–5.80 (m, 1H), 5.42 (dd, *J* = 15.4, 7.0 Hz, 1H), 5.09 (t, *J* = 6.7 Hz, 1H), 4.18 (d, *J* = 7.0 Hz, 1H), 2.74–2.52 (m, 2H), 2.49–2.37 (m, 1H), 2.20–1.90 (m, 6H), 1.85–1.70 (m, 3H), 1.55 (s, 3H), 1.45–1.09 (m, 6H), 1.26 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H), 0.81 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 138.3, 134.2, 132.4, 124.0, 92.1, 77.9, 47.1, 39.0, 38.1, 32.9, 31.6, 28.8, 28.3, 28.2, 27.6, 24.4, 23.3, 21.5, 17.6, 16.6, 11.7; HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{38}NaO_3$ 373.2719, found 373.2705.

4.1.23. (*R*,*E*)-*tert*-Butyldiphenyl((2,4,8-trimethylnon-4-en-1-yl)oxy)silane (37)

According to the procedure for **36**. Yield: 83%.

$[\alpha]_D^{27}$ +7.40 (*c* 1.00, $CHCl_3$); IR (KBr) 3071, 3050, 2956, 2929, 2859, 1590, 1469, 1428, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.68 (m, 4H), 7.46–7.26 (m, 6H), 5.10 (t, *J* = 7.0 Hz, 1H, 3.52 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.46 (dd, *J* = 9.7, 6.3 Hz, 1H), 2.19 (dd, *J* = 12.9, 5.8 Hz, 1H), 1.97 (dd, *J* = 15.3, 7.0 Hz, 1H), 1.88–1.80 (m, 1H), 1.73 (dd, *J* = 12.9, 8.3 Hz, 1H), 1.59–1.49 (m, 1H), 1.56 (s, 3H), 1.24–1.17 (m, 2H) 1.08 (s, 9H), 0.87–0.85 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 134.1, 133.0, 129.5, 127.6, 126.5, 68.8, 43.8, 39.1, 33.7, 27.6, 26.9, 25.8, 22.6, 19.3, 16.7, 15.8; HRMS (FAB, *m*-NBA) $[M-^tBu]^+$ calcd for $C_{24}H_{33}OSi$ 365.2301, found 365.2312.

4.1.24. (*R*,*E*)-3,5,9-Trimethyldec-5-enenitrile (39)

According to the procedure for **38**. Yield: 3 steps, 82%.

$[\alpha]_D^{28}$ −25.05 (*c* 1.00, $CHCl_3$); IR (KBr) 3055, 2959, 2927, 2871, 1722, 1458, 1422, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (t, *J* = 7.0 Hz, 1H), 2.31 (dd, *J* = 16.6, 4.8 Hz, 1H), 2.14 (dd, *J* = 16.6, 6.7 Hz, 1H), 2.06–1.95 (m, 5H), 1.57 (s, 3H), 1.56–1.49 (m, 1H), 1.25–1.17 (m, 2H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.96–0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5, 128.4, 118.9, 46.4, 38.9, 28.4, 27.7, 25.8, 23.6, 22.5, 19.5, 15.6; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{24}N$ 194.1909, found 194.1905.

4.1.25. (*R*,*E*)-3,5,9-Trimethyldec-5-en-1-ol (41)

According to the procedure for **40**. Yield: 2 steps, 77%.

$[\alpha]_D^{29}$ −2.79 (*c* 1.00, $CHCl_3$); IR (KBr) 3393, 3052, 2956, 2925, 2871, 1637, 1459, 1265, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (t, *J* = 6.9 Hz, 1H), 3.73–3.64 (m, 2H), 2.02–1.94 (m, 3H), 1.83–1.68 (m, 2H), 1.62–1.48 (m, 1H) 1.58 (s, 3H), 1.38–1.26 (m, 1H), 1.24–1.17 (m, 3H), 0.91–0.83 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 126.7, 61.2, 48.0, 39.7, 39.0, 27.6, 27.4, 25.8, 22.6, 22.5, 19.4, 15.7; HRMS (EI) $[M]^+$ calcd for $C_{13}H_{26}O$ 198.1984, found 198.1991.

4.1.26. (*R*,*E*)-1-Iodo-3,5,9-trimethyldec-5-ene (43)

According to the procedure for **42**. Yield: 90%.

$[\alpha]_D^{29}$ −9.42 (*c* 1.00, $CHCl_3$); IR (KBr) 3055, 2984, 2960, 1636, 1425, 1382, 1265, 1216, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (dt, *J* = 7.2, 1.0 Hz, 1H), 3.30–3.13 (m, 2H), 2.02–1.94 (m, 3H), 1.90–1.68 (m, 3H), 1.62–1.50 (m, 2H) 1.58 (s, 3H), 1.25–1.18 (m, 2H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.82 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 127.1, 47.2, 40.5, 39.0, 31.7, 27.6, 25.8, 22.6, 18.6, 15.8, 5.5; HRMS (FAB, Thioglycerol+glycerol) $[M-H]^+$ calcd for $C_{13}H_{24}I$ 307.0928, found 307.0932.

4.1.27. (*S*)-5-((1*R*,2*E*,6*S*,8*E*)-1-(Methoxymethoxy)-6,8,12-trimethyltrideca-2,8-dien-1-yl)-5-methyldihydrofuran-2(3*H*)-one (45)

According to the procedure for **44**. Yield: 73%.

$[\alpha]_D^{29}$ −36.76 (*c* 1.00, $CHCl_3$); IR (KBr) 3021, 2957, 1766, 1667, 1423, 1265, 1217, 1031 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.23 (dd, *J* = 15.4, 8.4 Hz, 1H), 5.07 (t, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.48 (d, *J* = 6.7 Hz, 1H), 4.05 (d, *J* = 8.4 Hz, 1H), 3.34 (s, 3H), 2.78–2.66 (m, 1H), 2.57–2.49 (m, 1H), 2.47–2.36 (m, 1H), 2.16–1.89 (m, 4H), 1.88–1.35 (m, 5H), 1.53 (s, 3H), 1.33 (s, 3H), 1.28–1.08 (m, 4H), 0.87 (d, *J* = 6.7 Hz, 6H), 0.79 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 138.3, 134.2, 132.4, 124.0, 95.8, 89.9, 82.1, 55.6, 47.1, 39.0, 38.1, 32.9, 31.6, 28.8, 28.3, 28.2, 27.6, 24.4, 23.3, 21.5, 17.9, 16.6; HRMS (ESI) $[M+Na]^+$ calcd for $C_{23}H_{40}NaO_4$ 403.2824, found 403.2805.

4.1.28. (*S*)-5-((1*R*,2*E*,6*S*,8*E*)-1-Hydroxy-6,8,12-trimethyltrideca-2,8-dien-1-yl)-5-methyldihydrofuran-2(3*H*)-one (6)

According to the procedure for **5**. Yield: 68%.

$[\alpha]_D^{29}$ −10.07 (*c* 0.100, $CHCl_3$); IR (KBr) 3440, 3054, 1630, 1422, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (dt, *J* = 15.3, 6.9, 1.0 Hz, 1H), 5.41 (dd, *J* = 15.3, 7.0, 1.4 Hz, 1H), 5.08 (dt, *J* = 7.4, 1.2 Hz, 1H), 4.17 (d, *J* = 7.0 Hz, 1H), 2.69–2.54 (m, 2H), 2.46–2.38 (m, 1H), 2.17–1.94 (m, 4H), 1.82–1.72 (m, 1H), 1.64–1.49 (m, 3H), 1.55 (s, 3H), 1.43–1.29 (m, 1H), 1.35 (s, 3H), 1.24–1.09 (m, 4H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 138.3, 134.2, 132.4, 124.0, 92.1, 77.9, 47.1, 39.0, 38.1, 32.9, 31.6, 28.8, 28.3, 28.2, 27.6, 24.4, 23.3, 21.5, 17.6, 16.6; HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{36}NaO_3$ 359.2562, found 359.2573.

4.1.29. (*E*)-*tert*-Butyl((5,9-dimethyldec-5-en-1-yl)oxy) dimethylsilane (48)

A solution of **46** (156 μL, 1.19 mmol) in Et_2O (12.0 mL) was treated with *t*-BuLi (1.55 M sol. in pentane, 1.58 mL, 2.55 mmol) at −78 °C. After stirring for 10 min at −78 °C, 9-BBNOMe (1.0 M sol. in hexane, 2.76 mL, 2.76 mmol) and THF (12 mL) were added. After stirring for 1 h at room temperature, the reaction mixture was treated with **47**[17] (192 mg, 0.542 mmol) in DMF (12 mL), 3 M K_3PO_4 aq (903 μL, 2.71 mmol), $PdCl_2$(dppf) (44.3 mg, 54.2 μmol) and dppf (30.0 mg, 54.2 μmol) at room temperature. After stirring for 1.5 h at room temperature, the reaction mixture was quenched with H_2O and diluted with EtOAc. The organic layer was washed

with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **48** (135 mg, 83%) as a colorless oil.

IR (KBr) 3464, 2956, 2932, 2860, 1712, 1265, 1217, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (dt, J = 7.2, 1.3 Hz, 1H), 3.60 (t, J = 6.4 Hz, 2H), 2.00–1.94 (m, 4H), 1.58 (s, 3H), 1.56–1.39 (m, 5H), 1.25–1.17 (m, 2H), 0.89 (s, 9H), 0.88 (d, J = 6.6 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 130.2, 68.4, 44.7, 44.4, 37.7, 32.9, 31.2, 31.0, 29.3, 27.8, 23.6, 20.0, 0.0; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{18}H_{39}Osi$ 299.2770, found 299.2768.

4.1.30. (*E*)-5,9-Dimethyldec-5-en-1-ol

A solution of **48** (135 mg, 0.453 mmol) in THF (4.5 mL) was treated with TBAF (1.0 M sol. in THF, 0.904 µL, 0.904 mmol) at room temperature. After stirring for 2.5 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (30:1 hexanes/EtOAc) to afford (*E*)-5,9-dimethyldec-5-en-1-ol (77.1 mg, 93%) as a colorless oil.

IR (KBr) 3437, 2955, 2869, 1634, 1265, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (dt, J = 6.6, 1.1 Hz, 1H), 3.63 (t, J = 6.6 Hz, 2H), 2.00–1.93 (m, 4H), 1.88 (br s, 1H), 1.58 (s, 3H), 1.56–1.40 (m, 5H), 1.24–1.16 (m, 2H), 0.87 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 125.1, 62.9, 39.3, 39.1, 32.3, 27.6, 25.7, 24.0, 22.5, 15.7; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{12}H_{25}O$ 185.1905, found 185.1901.

4.1.31. (*E*)-1-Iodo-5,9-dimethyldec-5-ene (49)

A solution of (*E*)-5,9-dimethyldec-5-en-1-ol (77.1 mg, 0.419 mmol) in CH_2Cl_2 (2.0 mL) was treated with I_2 (160 mg, 0.629 mmol), PPh_3 (165 mg, 0.629 mmol) and imidazole (85.8 mg, 1.26 mmol) at 0 °C. After stirring for 2.5 h at room temperature, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (hexanes) to afford **49** (113 mg, 91%) as a pale yellow oil.

IR (KBr) 3019, 2958, 1711, 1265, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (dt, J = 7.2, 1.3 Hz, 1H), 3.19 (t, J = 7.2 Hz, 2H), 2.00–1.94 (m, 4H), 1.82–1.75 (m, 2H), 1.58 (s, 3H), 1.56–1.45 (m, 3H), 1.25–1.18 (m, 2H), 0.88 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 125.5, 39.0, 38.5, 33.0, 28.6, 27.6, 25.8, 22.6, 15.7, 7.2; HRMS (FAB, Thio G+G) $[M]^+$ calcd for $C_{12}H_{23}I$ 294.0844, found 294.0854.

4.1.32. (*S*)-5-((*R*, 2*E*, 8*E*)-1-Hydroxy-8,12-dimethyltrideca-2,8-dien-1-yl)-5-methyldihydro-furan-2(3*H*)-one (7)

A solution of **49** (47.6 µL, 0.162 mmol) in Et_2O (1.6 mL) was treated with *t*-BuLi (1.61 M sol. in pentane, 0.252 mL, 0.405 mmol) at −78 °C. After stirring for 10 min at −78 °C, 9-BBNOMe (1.0 M sol. in hexane, 0.432 mL, 0.432 mmol) and THF (1.6 mL) were added. After stirring for 1 h at room temperature, the reaction mixture was treated with **13** (43.9 mg, 0.135 mmol) in DMF (1.6 mL), 3 M K_3PO_4 aq (225 µL, 0.405 mmol), $PdCl_2$(dppf) (11.0 mg, 13.5 µmol) and dppf (7.5 mg, 13.5 µmol) at room temperature. After stirring for 18 h at room temperature, the reaction mixture was quenched with H_2O and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was semi-purified by flash silica gel column chromatography (30:1 hexanes/EtOAc) to afford crude **50**. A solution of crude **50** in *i*-PrOH (2.0 mL) was treated with CBr_4 (89.5 mg, 270 µmol) at room temperature. After stirring for 8 h at 65 °C, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (10:1 hexanes/EtOAc) to afford **7** (19.1 mg, 2 steps 44%) as a pale yellow oil.

$[\alpha]_D^{27}$ −15.25 (*c* 0.10, $CHCl_3$); IR (KBr) 3429, 2956, 2924, 2854, 1773, 1083 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–5.80 (m, 1H), 5.42 (dd, J = 15.4, 7.0 Hz, 1H), 5.09 (t, J = 6.7 Hz, 1H), 4.18 (d, J = 7.0 Hz, 1H), 2.74–2.52 (m, 2H), 2.49–2.37 (m, 1H), 2.20–1.90 (m, 6H), 1.85–1.70 (m, 1H) 1.65–1.50 (m, 1H), 1.55 (s, 3H), 1.45–1.09 (m, 6H), 1.26 (s, 3H), 0.82 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 136.4, 134.5, 126.0, 125.0, 88.1, 77.1, 39.4, 39.1, 32.3, 29.5, 27.6, 27.5, 27.4, 27.3, 25.6, 23.8, 22.6, 15.8; HRMS (ESI) $[M+Na]^+$ calcd for $C_{20}H_{34}NaO_3$ 345.2406, found 345.2416.

4.1.33. (*E*)-3-Methyl-6-((triethylsilyl)oxy)hex-2-en-1-yl acetate (52)

A solution of **51**[21] (345 mg, 2.03 mmol) in CH_2Cl_2 (20.0 mL) was treated with TESCl (0.408 mL, 2.43 mmol) and imidazole (276 mg, 4.05 mmol) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched with satd NH_4Cl aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (100:1 hexanes/EtOAc) to afford **52** (113 mg, 91%) as a colorless oil.

IR (neat) 3021, 2954, 2913, 2879, 1729, 1671, 1217, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35–5.31 (m, 1H), 4.56 (d, J = 7.0 Hz, 2H), 3.57 (t, J = 6.1 Hz, 2H), 2.07 (t, J = 7.8 Hz, 2H), 2.03 (s, 3H), 1.68 (s, 3H), 1.65–1.60 (m, 2H), 0.92 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.1, 118.2, 62.3, 61.4, 35.7, 30.7, 21.0, 16.4, 6.8, 4.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{15}H_{31}O_3Si$ 287.2038 found 287.2042.

4.1.34. (*E*)-3-Methyl-6-((triethylsilyl)oxy)hex-2-en-1-ol (53)

A solution of **52** (1.05 g, 3.67 mmol) in MeOH (18.0 mL) was treated with satd K_2CO_3 aq (18.0 mL, 0.2 M) at 0 °C. After stirring for 0.5 h at room temperature, the reaction mixture was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (5:1 hexanes/EtOAc) to afford **53** (312 mg, 76%) as a colorless oil.

IR (neat) 3021, 1477, 1424, 1216, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44–5.40 (m, 1H), 4.15 (dd, J = 6.8, 0.6 Hz, 2H), 3.60 (t, J = 6.7 Hz, 2H), 2.07 (t, J = 7.9 Hz, 2H), 1.68 (d, J = 0.6 Hz, 3H), 1.67–1.62 (m, 2H), 0.96 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 123.4, 62.5, 59.2, 35.7, 30.9, 16.2, 6.7, 4.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$ 245.1937 found 245.1935.

4.1.35. ((2″*R*,3″*R*)-3′-Methyl-3″-(3′-((triethylsilyl)oxy)propyl) oxiran-2″-yl)methanol (54)

A mixture of activated MS4Å (868 mg) and Ti(O*i*-Pr)$_4$ (1.05 mL, 3.55 mmol) in CH_2Cl_2 (45.0 mL) was treated with (−)-DET (0.760 mL, 4.44 mmol) at −5 °C. After stirring for 45 min at −5 °C, TBHP (5.0–6.0 M sol. in decane, 3.90 mL, 19.5 mmol) were added at −20 °C. After stirring for 1 h, **53** (2.17 g, 8.88 mmol) in CH_2Cl_2 (45.0 mL) was added and the mixture was stirred at −20 °C for 1 h. After Me_2S (0.975 mL, 13.3 mmol) was added, the mixture was further stirred at −20 °C for 1 h. The reaction mixture was diluted with Et_2O, treated with celite (6.51 g) and $Na_2SO_4 10H_2O$ (6.51 g) and stirred for 2 h at room temperature. The resulting suspension was filtered through a pad of celite, and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel column chromatography (2:1 hexanes/EtOAc) to afford **54** (1.83 mg, 78%) as a colorless oil.

$[\alpha]_D^{28}$ +2.47 (*c* 1.00, $CHCl_3$); IR (neat) 3450, 3021, 2957, 2878, 1476, 1423, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85–3.80 (m, 1H), 3.73–3.67 (m, 1H), 3.65–3.59 (m, 2H), 2.98 (dd, *J* = 6.7, 4.5 Hz, 1H), 1.70–1.53 (m, 4H), 1.31 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.1, 58.4, 57.1, 30.8, 24.2, 12.7, 2.7, 0.3, 0.2; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{29}O_3Si$ 261.1886 found 261.1880.

4.1.36. Triethyl(3′-((2′*R*,3′*S*)-3′-(iodomethyl)-2′-methyloxiran-2′-yl)propoxy)silane (55)

A solution of **54** (132 mg, 0.505 mmol) in CH_2Cl_2 (5.1 mL) was treated with I_2 (192 mg, 0.758 mmol), PPh_3 (199 mg, 0.758 mmol) and imidazole (103 mg, 1.52 mmol) at 0 °C. After stirring for 1.5 h at 0 °C, the reaction mixture was quenched with satd $Na_2S_2O_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (200:1 hexanes/EtOAc) to afford **55** (147 mg, 78%) as a colorless oil.

$[\alpha]_D^{27}$ −33.7 (*c* 1.00, $CHCl_3$); IR (neat) 3432, 1637, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.63–3.60 (m, 2H), 3.36 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.09 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.98 (dd, *J* = 9.8, 8.8 Hz, 1H), 1.74–1.60 (m, 3H), 1.53–1.46 (m, 1H), 1.28 (s, 3H), 0.98–0.93 (m, 9H), 0.62–0.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.9, 62.4, 62.3, 34.7, 28.5, 15.7, 6.8, 4.4, 2.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{13}H_{28}O_2SiI$ 371.0903, found 371.0910.

4.1.37. Triethyl(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 (57)

A solution of **56**[24] (93.7 μg, 0.270 mmol) in THF (7.0 mL) was treated with *n*-BuLi (1.64 M sol. in hexane, 0.659 mL, 1.08 mmol) and HMPA (0.470 mL, 2.70 mmol) at −78 °C. After stirring for 1 h at −78 °C, **55** (200 mg, 0.540 mmol) in THF (3.0 mL) was added. After stirring for 10 min at −78 °C, the reaction mixture was quenched with satd NH_4Cl aq and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was semi-purified by flash silica gel column chromatography (10:1 hexanes/EtOAc) to afford crude TES ether. A solution of crude TES ether in DMSO (2.7 mL) was treated with $Pd(OAc)_2$ (12.1 mg, 54.0 μmol) and dppp (27.8 mg, 0.0675 mmol) at room temperature. After stirring for 5 min at room temperature, $NaBH_4$ (12.3 mg, 0.324 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O, and diluted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (70:1 hexanes/EtOAc) to afford **57** (94.6 mg, 2 steps 64%) as a colorless oil.

$[\alpha]_D^{27}$ +4.47 (*c* 1.00, $CHCl_3$); IR (neat) 3020, 2958, 2877, 1425, 1384, 1216, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.18–5.07 (m, 3H), 3.63–3.58 (m, 2H), 2.72 (t, *J* = 6.4 Hz, 1H), 2.18–1.95 (m, 10H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.66–1.57 (m, 4H), 1.62 (s, 3H), 1.60 (s, 6H), 1.56–1.48 (m, 2H), 1.25 (s, 3H), 0.98–0.93 (m, 9H), 0.62–0.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.0, 131.3, 124.3, 124.1, 123.2, 63.2, 62.6, 60.8, 39.7, 35.1, 28.9, 28.6, 26.7, 26.6, 25.7, 24.9, 17.7, 16.6, 16.0, 6.8, 4.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{28}H_{53}O_2Si$ 449.3815, found 449.3807.

4.1.38. 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)propanal (58)

4.1.38.1. (*R*,4*E*,8*E*)-5,9,13-Trimethyl-1-((*S*)-2-methyltetrahydrofuran-2-yl)tetradeca-4,8,12-trien-1-ol (59)

A solution of pyridine (0.108 mL, 1.34 mmol) in CH_2Cl_2 (1.7 mL) was treated with CrO_3 (80.4 mg, 0.804 mmol) at room temperature. After stirring for 1 h, **57** (60.0 mg, 0.134 mmol) in CH_2Cl_2 (1.0 mL) was added. After stirring for 21 h at room temperature, the reaction mixture was filtered through a pad of celite, and the filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (10:1 hexanes/EtOAc) to afford **58** (23.9 mg, 54%) and **59** (2.2 mg, 5%) as colorless oils.

4.1.38.2. Data for 58.

$[\alpha]_D^{30}$ +8.58 (*c* 0.83, $CHCl_3$); IR (neat) 3020, 2927, 1724, 1431, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H), 5.16–5.07 (m, 3H), 2.74 (t, *J* = 6.4 Hz, 1H), 2.54–2.50 (m, 2H), 2.18–1.80 (m, 14H), 1.68 (d, *J* = 1.2 Hz, 3H), 1.62 (s, 3H), 1.60 (s, 6H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 136.1, 135.8, 135.1, 124.3, 124.0, 123.1, 63.0, 59.8, 39.7, 39.6, 39.1, 30.4, 28.7, 26.7, 26.6, 25.7, 24.8, 17.7, 16.7, 16.1, 16.0; HRMS (FAB, *m*-NAB) $[M+H]^+$ calcd for $C_{22}H_{37}O_2$ 333.2794, found 333.2799.

4.1.38.3. Data for 59.

$[\alpha]_D^{20}$ +5.16 (*c* 0.10, $CHCl_3$); IR (neat) 3448, 3058, 2389, 2089, 1636, 1449, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.16–5.07 (m, 3H), 3.91–3.80 (m, 2H), 3.53 (dd, *J* = 10.5, 1.6 Hz, 1H), 2.35 (br s, 1H), 2.29–2.22 (m, 1H), 2.16–1.87 (m, 12H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.51–1.43 (m, 2H), 1.39–1.30 (m, 1H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 134.9, 131.2, 124.4, 124.3, 124.2, 85.7, 76.0, 67.9, 39.7, 39.6, 31.9, 30.6, 26.7, 26.6, 26.3, 26.2, 25,7, 25.0, 17.6, 16.0, 15.9; HRMS (EI) $[M]^+$ calcd for $C_{22}H_{38}O_2$ 334.2871, found 334.2872.

4.1.39. (*S*)-5-((*R*,4′*E*,8′*E*)-1′-Hydroxy-5′,9′,13′-trimethyltetradeca-4′,8′,12′-trien-1′-yl)-5-methyldihydrofuran-2(3*H*)-one (8)

A solution of **58** (4.4 mg, 0.0132 mmol) in *t*-BuOH (0.132 mL) and H_2O (0.132 mL) was treated with 2-methyl-2-butene (5.6 μL, 0.0528 mmol), $NaClO_2$ (3.6 mg, 0.0396 mmol) and NaH_2PO_4 $2H_2O$ (6.2 mg, 0.0396 mmol) at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was quenched with satd NH_4Cl aq and was diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (7:1 hexanes/EtOAc) to afford **8** (3.8 mg, 86%) as a colorless oil.

$[\alpha]_D^{23}$ +8.67 (*c* 0.50, $CHCl_3$); IR (neat) 3448, 3022, 1766, 1639, 1426, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.14–5.07 (m, 3H), 3.68 (d, *J* = 10.2 Hz, 1H), 2.67–2.59 (m, 2H), 2.45–2.37 (m, 1H), 2.23–2.18 (m, 1H), 2.17–2.11 (m, 1H), 2.09–1.95 (m, 8H), 1.83–1.76 (m, 1H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.52–1.36 (m, 2H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 136.4, 135.1, 131.3, 124.4, 124.0, 123.2, 88.8, 75.4, 39.7, 39.8, 30.8, 29.3, 27.6, 26.7, 26.6, 24.5, 22.8, 17.7, 16.1, 16.0, 15.9; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{22}H_{37}O_3$ 349.2743, found 349.2745.

4.1.40. Improved synthesis of 59 from 57

A solution of **57** (14.3 mg, 0.0427 mmol) in THF (0.4 mL) was treated with TBAF (1.0 M sol. in THF, 85 μL, 0.0854 mmol) at room temperature. After stirring for 15 min at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. A solution of the crude alcohol in CH_2Cl_2 (0.5 mL) was treated with a catalytic amount of PPTS at room temperature. After stirring for 1 h at room temperature, the reaction mixture was quenched with satd $NaHCO_3$ aq and diluted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash silica gel column chromatography (8:1 hexanes/EtOAc) to afford **59** (12.7 mg, 2 steps, 89%) as a colorless oil.

Acknowledgments

This research was partially supported by JSPS KAKENHI Grant Number 2350132. We thank Ms. N. Sato and Dr. K. Nagai (Kitasato University) for kindly measuring NMR and MS spectra.

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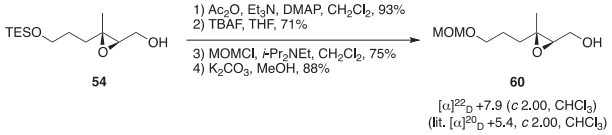
22. The absolute configuration of **54** was determined by conversion to the known MOM ether **60**, followed by comparison of the optical rotation of **60** to the literature value. Also see, Yadav, J. S.; Haldar, A.; Maity, T. *Eur. J. Org. Chem.* **2013**, 3076



54 **60**

$[\alpha]^{22}_{D}$ +7.9 (*c* 2.00, $CHCl_3$)
(lit. $[\alpha]^{20}_{D}$ +5.4, *c* 2.00, $CHCl_3$)

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