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The total synthesis and biological evaluation of nafuredin-γ and its analogues

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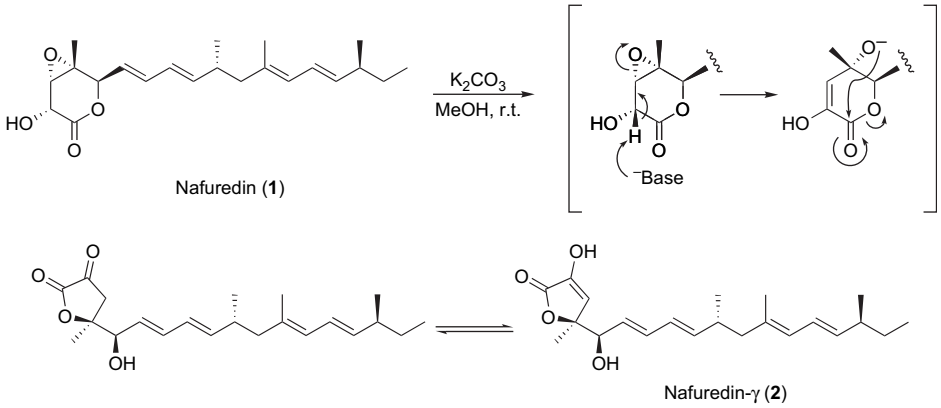
ABSTRACT

Nafuredin (**1**) is converted to nafuredin-γ (**2**) under mild basic conditions and both compounds exhibit the same inhibitory activity and selectivity against NADH-fumarate reductase (complex I). The total synthesis of **2** was achieved by a convergent approach using Stille coupling. The structural elements required for inhibitory activity against NADH-fumarate reductase (complex I) were then investigated by evaluation of nafuredin-γ (**2**) and its structural analogues.

1. Introduction

Nafuredin (**1**)[1,2] was isolated from the fermentation broth of a fungal strain, *Aspergillus niger* FT-0554, in the course of our screening for NADH-fumarate reductase (NFRD) inhibitors, and is potentially a selective antiparasitic agent. Nafuredin inhibited NFRD of *Ascaris suum* with an IC_{50} value of 12 nM and showed selective inhibition of the target enzyme complex I in helminth mitochondria. In addition, nafuredin demonstrated anthelmintic activity against *Haemonchus contortus* in in vivo trials with sheep.[1] These useful biological activities of **1** attracted our attention, and we previously reported the elucidation of the absolute configuration[3] and the total synthesis[4] of **1**.

During the course of our synthetic studies, we discovered that under mild basic conditions, nafuredin (**1**) was converted to a novel γ-lactone derivative (**2**), which existed as a mixture of keto–enol tautomers (Scheme 1).[5] We named this γ-lactone derivative (**2**) nafuredin-γ. Since nafuredin-γ (**2**) is not detected at all in the aforementioned fermentation broth, it must not be produced directly by the above strain and must be formed from **1** under basic conditions via β-elimination of the epoxide followed by translactonization. Because the conversion of **1** to **2** likely occurs under



Scheme 1. Proposed mechanism of the conversion of nafuredin (**1**) to nafuredin-γ (**2**).

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the NFRD assay conditions, we expected **2** to also have inhibitory activity against NFRD. Our tests indeed showed that **2** possessed the same inhibitory activity and selectivity as **1**, suggesting it may be an active form of **1**. This finding led us to embark on the total synthesis of nafuredin-γ (**2**)[6] and allowed structural simplification of the lactone moiety in the structure–activity relationship studies of **1**. We provide herein a detailed account of the total synthesis and the structure–activity relationship studies of nafuredin-γ (**2**).

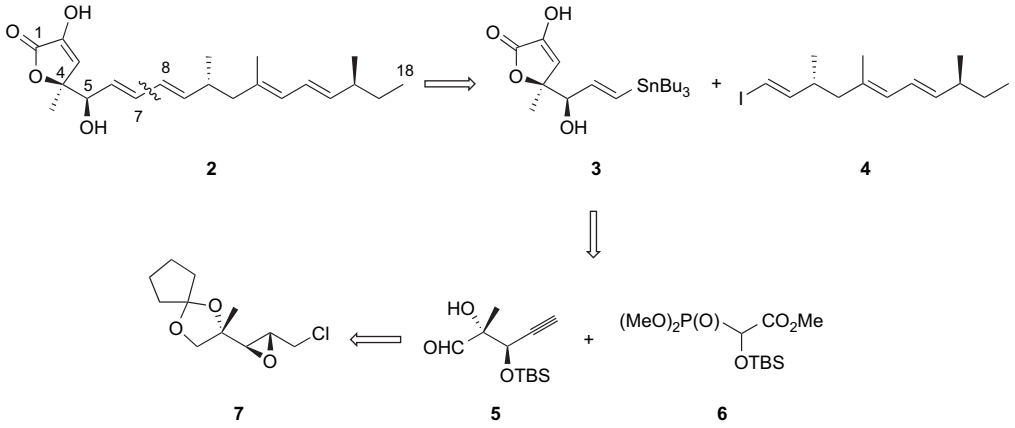
2. Results and discussion

2.1. Total synthesis of nafuredin-γ (2)

As outlined in Scheme 2, our retrosynthetic strategy toward nafuredin-γ (**2**) is convergent and involves the assembly of the C1–C7 segment **3** and the C8–C18 segment **4**,[4] which will be joined in the final step by Stille coupling. This route provides a simple and efficient method to synthesize various nafuredin-γ analogues with modifications of the side chain moiety and also promises to be especially effective for the synthesis of C4 and/or C5 stereoisomers of nafuredin-γ (**2**). The enol lactone **3** will be constructed by Horner–Wadsworth–Emmons reaction of aldehyde **5** with known phosphonate **6**[7] followed by hydrostannylation. The aldehyde **5** will be derived from the epoxy chloride **7**, which will be constructed by Sharpless asymmetric epoxidation[8] and dihydroxylation[9] as key reactions.

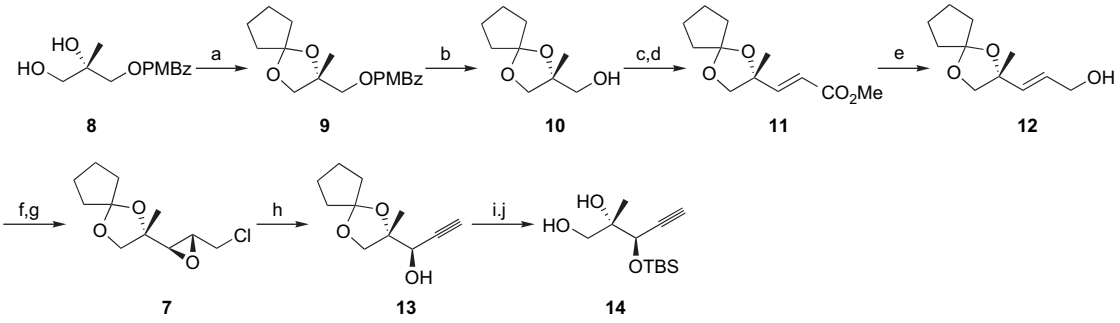
The known diol **8** (97% ee)[10] was used as the precursor to aldehyde **5** as shown in Scheme 3. Acetalization of **8** with cyclopentanone in the presence of a catalytic amount of TsOH in benzene caused serious racemization by transesterification of the *p*-methoxybenzoyl ester. However, treatment with cyclopentanone dimethylacetal in the presence of $Sc(OTf)_3$ catalyst[11] gave **9** almost quantitatively without loss of stereochemical integrity. Cleavage of the *p*-methoxybenzoyl ester with sodium methoxide in methanol produced **10** in 97% yield. Oxidation of **10** with Dess–Martin periodinane[12] followed by Wittig reaction with methyl (triphenylphosphoranylidene)acetate furnished **11** in 75% yield over 2 steps. The resulting ester was reduced with DIBAL to give allyl alcohol **12** in 94% yield. Sharpless asymmetric epoxidation of **12** using (+)-diethyl tartrate provided the corresponding epoxide (94% de), which was then converted to chloride **7** by treatment with NCS and Ph_3P in the presence of an excess amount of 2-methyloxirane as a chloride ion scavenger in 94% yield over 2 steps. This reaction in the absence of 2-methyloxirane gave a mixture of undesired products formed by addition of chloride ion to the epoxide. Base-induced elimination[13] of **7** with *n*-BuLi furnished **13** in 99% yield. Silyl ether protection of **13** with TBSOTf and 2,6-lutidine followed by hydrolysis of the cyclopentylidene acetal with 70% aqueous AcOH led to diol **14** in 87% yield over 2 steps.

Oxidation of the primary alcohol in **14** with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and trichloroisocyanuric acid[14]

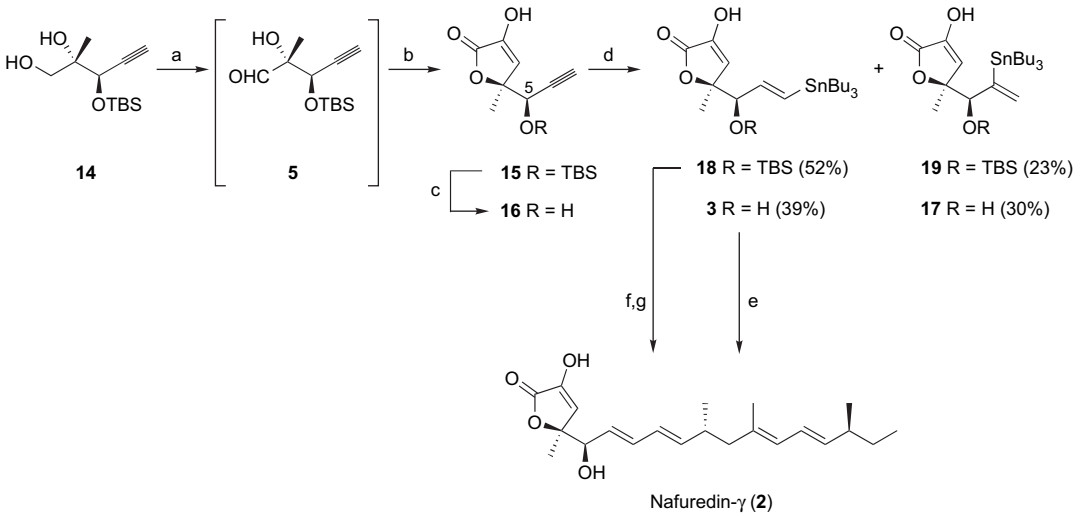


Scheme 2. Retrosynthesis of nafuredin-γ (**2**).

gave the desired aldehyde **5** (Scheme 4), while DMSO oxidation (Swern conditions and Parikh–Doering conditions), Dess–Martin oxidation, and TEMPO–NaClO–KBr oxidation caused decomposition of the product. The use of trichloroisocyanuric acid as a co-oxidant in the TEMPO oxidation of **14** was crucial for high yield



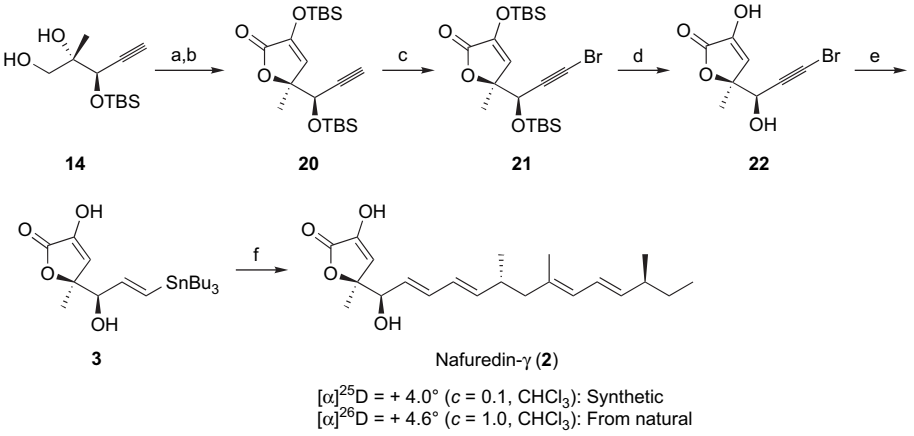
Scheme 3. Reagents and conditions: (a) cat. $Sc(OTf)_3$, 1,1-dimethoxycyclopentane, MeCN, rt, 99%; (b) NaOMe, MeOH, rt, 97%; (c) Dess–Martin periodinane, CH_2Cl_2, rt; (d) $Ph_3P{=}CHCO_2Me$, benzene, reflux, 75% (2 steps); (e) DIBAL, CH_2Cl_2, −78 °C, 94%; (f) (+)-DET, $Ti(Oi\text{-}Pr)_4$, TBHP, CH_2Cl_2, −20 °C; (g) NCS, PPh_3, 2-methyloxirane, CH_2Cl_2, rt, 94% (2 steps); (h) *n*-BuLi, THF, −40 °C, 99%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt; (j) 70% aq AcOH, rt, 87% (2 steps).



Scheme 4. Reagents and conditions: (a) cat. TEMPO, trichloroisocyanuric acid, CH_2Cl_2, 0 °C; (b) **6**, DBU, LiCl, MeCN, 0 °C, 75% (2 steps); (c) HF·pyridine, THF, rt, 91%; (d) Bu_3SnH, cat. $PdCl_2(PPh_3)_2$, THF, 0 °C; (e) **4**, cat. $PdCl_2(MeCN)_2$, NMP, 50 °C, 72%; (f) **4**, cat. $PdCl_2(MeCN)_2$, NMP, $Ph_2P(O)O^-Bu_4N^+$, 50 °C, 63%; (g) HF·pyridine, THF, rt, 85%.

and reproducibility. Aldehyde **5** was subjected to the next reaction without further purification because of its instability. Horner–Wadsworth–Emmons reaction of **5** with the known phosphonate **6**[7] in the presence of DBU and LiCl[15] afforded γ-lactone **15** in 75% yield over 2 steps. γ-Lactone **15** was treated with HF·pyridine to give **16** in 91% yield. Subsequent palladium-catalyzed hydrostannylation[16] of **16** with Bu_3SnH and $PdCl_2(PPh_3)_2$ proceeded nonregioselectively, yielding the desired *E*-alkenylstannane **3** (39%) and its regioisomer **17** (30%). After separation by silica gel chromatography, Stille coupling[17] between **3** and vinyl iodide **4** in the presence of $PdCl_2(MeCN)_2$ gave nafuredin-γ (**2**) in 72% yield.

Next, we focused on the high regioselectivity of palladium-catalyzed hydrostannylation of alkynyl bromides reported by Guibé et al.[19] Bromination of the terminal alkynes **15** and **16** led to decomposition of the substrates. Therefore, TBS protected enol ether **20** was constructed by oxidation of **14** followed by Horner–Wadsworth–Emmons reaction with **6** and LHMDS (75% yield, 2 steps). Enol ether **20** afforded alkynyl bromide **21** quantitatively upon treatment with NBS and $AgNO_3$[20] (Scheme 5). Removal of the TBS ether group with HF·pyridine gave enol **22** quantitatively. Subsequent palladium-catalyzed hydrostannylation of **22** provided the desired *E*-alkenylstannane **3** in 71% yield with high regioselectivity



Scheme 5. Reagents and conditions: (a) cat. TEMPO, trichloroisocyanuric acid, CH_2Cl_2, 0 °C; (b) **6**, LHMDS, THF, 0 °C, 75% (2 steps); (c) cat. $AgNO_3$, NBS, acetone, rt, 100%; (d) HF·pyridine, THF, rt, 100%; (e) Bu_3SnH, cat. $PdCl_2(PPh_3)_2$, THF, 0 °C, 71%; (f) **4**, cat. $PdCl_2(MeCN)_2$, NMP, 50 °C, 72%.

Although the total synthesis of **2** was achieved, a more effective hydrostannylation procedure with higher regioselectivity was required for large-scale synthesis of **2**. We therefore examined hydrostannylation of the TBS ether **15**, which provided **18** in 52% yield along with its regioisomer **19** (23%). However, subsequent Stille coupling of **18** with **4** did not proceed well under the same conditions (20% yield). Addition of $Ph_2P(O)O^-Bu_4N^+$[18] improved the yield of the coupled product (63%), affording nafuredin-γ (**2**) in 85% yield after removal of the TBS ether group with HF·pyridine. Unfortunately, these moderate yields in hydrostannylation and Stille coupling were still far from satisfactory.

(**3**/**17**=15:1). This was converted to nafuredin-γ (**2**) in good yield as mentioned above. Synthetic nafuredin-γ (**2**) was identical to that derived from natural nafuredin (**1**) in all respects ($[\alpha]_D$, ^1H and ^{13}C NMR, IR, FABMS, and inhibitory activity against NFRD).

2.2. Synthesis of analogues of nafuredin-γ (2)

Our continued efforts on the structure–activity relationships of **2** led to the synthesis of new analogues **23**–**25** (Fig. 1) using our strategy for the total synthesis of nafuredin-γ.[6] These new nafuredin-γ analogues are the C4-epimer (**23**), the C5-epimer (**24**), and

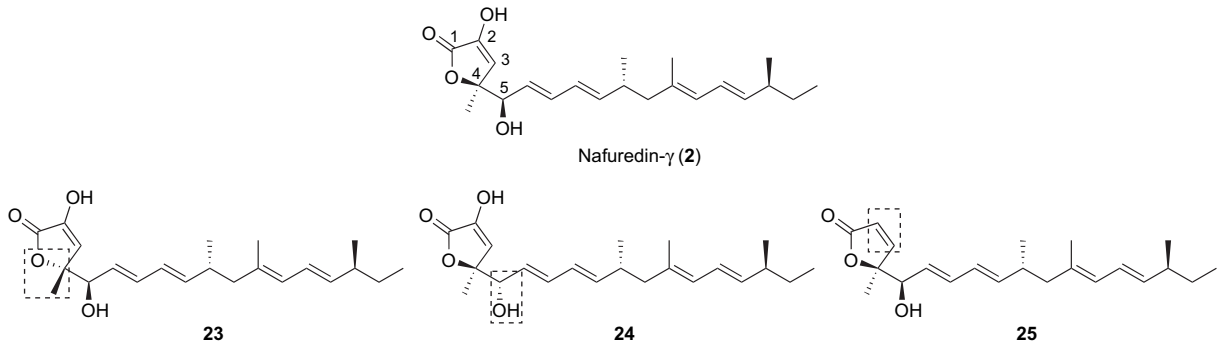


Figure 1. Chemical structures of nafuredin-γ (**2**) and new nafuredin-γ analogues (**23**–**25**).

the 2-dehydroxy-α,β-unsaturated lactone (**25**). These analogues were selected in order to elucidate the requirements of the C4 and C5 stereochemistries and the enol in **2** for inhibitory activity against NADH-fumarate reductase (complex I).

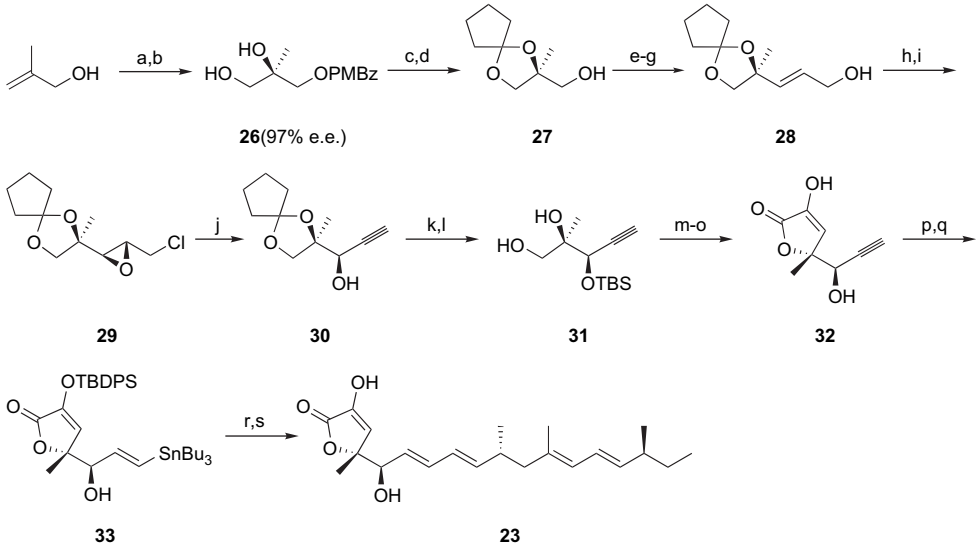
The synthesis of the C4-epimer (**23**) started from methallyl alcohol, which was readily converted into the chiral diol **26**[10] (97% ee) through asymmetric dihydroxylation (Scheme 6). The $Sc(OTf)_3$-catalyzed acetalization of **26** followed by cleavage of the *p*-methoxybenzoyl ester with sodium methoxide furnished alcohol **27**. Subsequent Dess–Martin oxidation and Wittig reaction afforded the corresponding α,β-unsaturated ester, which was reduced with DIBAL to give allyl alcohol **28**. Sharpless asymmetric epoxidation of **28** using (+)-diethyl tartrate provided the corresponding epoxy alcohol, which was further converted to chloride **29** by treatment with NCS and Ph_3P in the presence of 2-methyloxirane. Base-induced elimination of **29** with *n*-BuLi furnished propargyl alcohol **30**. A two-step sequence of protecting group manipulations provided diol **31**. Oxidation of the primary alcohol in **31** with TEMPO gave the corresponding aldehyde, which was subjected to Horner–Wadsworth–Emmons reaction using **6**, followed by deprotection of the silyl ethers to produce 2-hydroxy-α,β-unsaturated lactone **32**. After the enol of **32** was protected as a TBDPS ether to facilitate handling and NMR assignment of the substrate, hydrostannylation afforded the desired *E*-alkenylstannane **33** as the major product. Stille coupling with the vinyl iodide **4** in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ and subsequent deprotection of the silyl enol ether gave the desired C4-epimer (**23**).

We next synthesized the C5-epimer (**24**) as shown in Scheme 7. Allyl alcohol **12**, an advanced intermediate in the total synthesis of **2**, was converted into chloride **34** by Sharpless asymmetric epoxidation using (−)-diethyl tartrate followed by chlorination of the resulting epoxy alcohol. Further transformations from the chloride **34** to the C5-epimer (**24**) were achieved in the same manner as the synthesis of **23**.

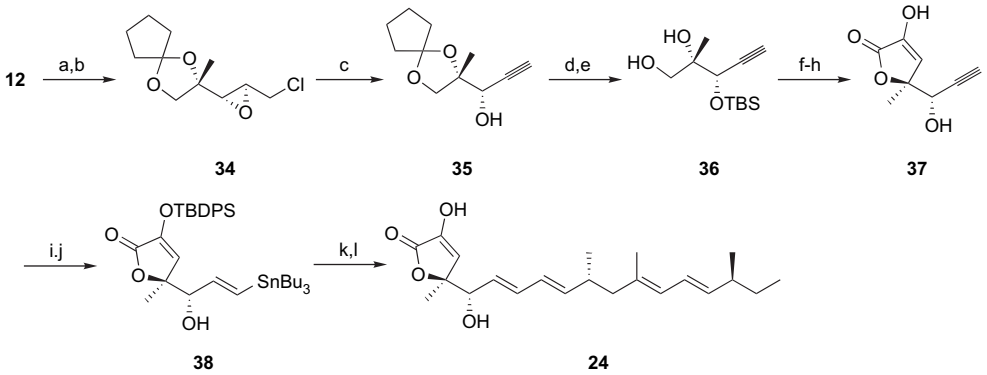
Finally, we investigated the synthesis of the 2-dehydroxy-α,β-unsaturated lactone (**25**) (Scheme 8). Diol **14** was oxidized with TEMPO to furnish the corresponding aldehyde, which was subjected to Still–Gennari olefination[21] followed by deprotection of the silyl ether to give α,β-unsaturated lactone **39**. Hydrostannylation of **39** led to the desired *E*-alkenylstannane **40**. Stille coupling between **40** and the vinyl iodide **4** in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ gave the desired 2-dehydroxy-α,β-unsaturated lactone (**25**). Although the regioselectivities and yields of several reactions in the synthesis of nafuredin-γ analogues were unsatisfactory, priority was given to their biological evaluation.

2.3. Biological evaluation of the new nafuredin-γ analogues

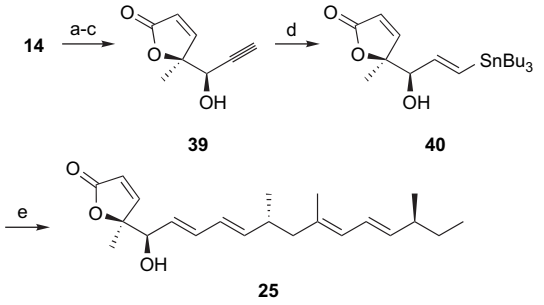
With the nafuredin-γ analogues **23**–**25** in hand, the inhibitory activity against NFRD of *A. suum* was evaluated and the results are



Scheme 6. Reagents and conditions: (a) PMBzCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, quant.; (b) $(DHQ)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O, 0 °C, 95%; (c) cat. $Sc(OTf)_3$, 1,1-dimethoxycyclopentane, MeCN, rt, 84%; (d) NaOMe, MeOH, rt, 73%; (e) Dess–Martin periodinane, CH_2Cl_2, rt; (f) $Ph_3P{=}CHCO_2Et$, benzene, 80 °C, 75% (2 steps); (g) DIBAL, CH_2Cl_2, −78 °C, 82%; (h) (+)-DET, $Ti(Oi\text{-}Pr)_4$, TBHP, CH_2Cl_2, −20 °C; (i) NCS, PPh_3, 2-methyloxirane, CH_2Cl_2, rt, 86% (2 steps); (j) *n*-BuLi, THF, −40 °C, 99%; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%; (l) 70% aq AcOH, rt, 78%; (m) cat. TEMPO, trichloroisocyanuric acid, CH_2Cl_2, 0 °C; (n) LHMDS, **6**, THF, −78 °C; (o) HF·pyridine, THF, rt, 52% (3 steps); (p) TBDPSCl, Et_3N, THF, rt, 56%; (q) cat. $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 0 °C, 47%; (r) cat. $PdCl_2(MeCN)_2$, **4**, NMP, 50 °C, 32%; (s) HF·pyridine, THF, rt, 85%.



Scheme 7. Reagents and conditions: (a) (−)-DET, Ti(Oi-Pr)$_4$, TBHP, CH_2Cl_2, −20 °C; (b) NCS, PPh_3, 2-methyloxirane, CH_2Cl_2, rt, 92% (2 steps); (c) *n*-BuLi, THF, −40 °C, 97%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; (e) AcOH, rt, 86%; (f) cat. TEMPO, trichloroisocyanuric acid, CH_2Cl_2, 0 °C; (g) LHMDS, **6**, THF, −78 °C; (h) HF·pyridine, THF, rt, 49% (3 steps); (i) TBDPSCl, Et_3N, THF, rt, 65%; (j) cat. $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, 0 °C, 73%; (k) cat. $PdCl_2(MeCN)_2$, **4**, NMP, 50 °C, 28%; (l) HF·pyridine, THF, rt, 84%.



Scheme 8. Reagents and conditions: (a) cat. TEMPO, trichloroisocyanuric acid, CH_2Cl_2, 0 °C; (b) LHMDS, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, 0 °C; (c) HF·pyridine, THF, rt, 55% (3 steps); (d) cat. $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt, 68%; (e) cat. $PdCl_2(MeCN)_2$, **4**, NMP, 50 °C, 70%.

Table 1
Inhibitory activity of the nafuredin-γ analogues against NFRD of *Ascaris suum*

Compound	IC_{50} (nM)
Nafuredin-γ (**2**)	6
23	7
24	120
25	8

summarized in Table 1. Surprisingly, both the IC_{50} values of the C4-epimer (**23**) and the 2-dehydroxy-α,β-unsaturated lactone (**25**) were nearly identical to that of nafuredin-γ (**2**). However, NFRD inhibitory activity of the C5-epimer (**24**) decreased more than ten times. Therefore, it was concluded that the stereochemistry at C4 and the presence of the enol (or 2-ketone) are not important, but the C5 stereochemistry is valuable for the inhibitory activity against NADH-fumarate reductase (complex I).

3. Summary

We have discovered nafuredin-γ (**2**), a proposed active form of nafuredin (**1**), and achieved its first total synthesis. This enabled construction of the diverse nafuredin-γ analogues **23**–**25**. The structure–activity relationship studies of **2** revealed that the C4 stereochemistry and the enol (or 2-ketone) functionality as structural elements are not required as structural elements, but the stereochemistry of the C5 hydroxy group is important for the NFRD inhibitory activity of **2**. These results will allow further structural simplification of the lactone moiety and lead to the development of shorter and more efficient syntheses for new nafuredin-γ analogues. Additional structure–activity relationship studies of **2** are in progress and will be reported in due course.

4. Experimental

4.1. General information

Commercial reagents were used without further purification unless otherwise indicated. Organic solvents were distilled and dried over 3 Å or 4 Å molecular sieves. Reactions were performed in flame-dried glassware under positive Ar pressure unless otherwise indicated. Cold baths were generated as follows: 0 °C, wet ice/water; −78 °C, dry ice/acetone. Flash chromatography was performed on silica gel 60 N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm E. Merck silica gel 60 F_{254} plates and visualized by UV light (254 nm) and cerium ammonium molybdenate.

4.2. Conversion of nafuredin (1) to nafuredin-γ (2)

Compound **1** (10.0 mg) was dissolved in MeOH (0.28 mL), and $CaCO_3$ (2.0 mg) was added to the solution. After the solution was stirred at room temperature for 30 min, EtOAc (10 mL) and a saturated aqueous NaCl solution (10 mL) were added. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield **2**[5] (9.3 mg, 93%).

4.3. Total synthesis of nafuredin-γ (2)

*4.3.1. (S)-(2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl)methyl 4-methoxybenzoate (**9**)*

To a solution of **8** (1.75 g, 7.29 mmol) in MeCN (70 mL) were added 1,1-dimethoxycyclopentane (2.00 mL, 14.5 mmol) and $Sc(OTf)_3$ (31.3 mg, 72.9 μmol) at room temperature. The resulting solution was stirred for 1 h and diluted with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (30:1 hexanes/EtOAc) afforded **9** (2.21 g, 99%) as a colorless oil. $[\alpha]_D^{23}$ +2.8 (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2733, 1770, 1558, 1157, 1110 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.99 (d, 2H, *J*=8.9 Hz), 6.91 (d, 2H, *J*=8.7 Hz), 4.25 (d, 1H, *J*=11.2 Hz), 4.17 (d, 1H, *J*=11.2 Hz), 4.02 (d, 1H, *J*=8.6 Hz), 3.84 (s, 3H), 3.67 (d, 1H, *J*=8.6 Hz), 1.76 (m, 8H), 1.38 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 165.9, 163.4, 131.6, 122.3, 119.7, 113.6, 78.9,

71.8, 67.8, 55.3, 37.3, 37.1, 23.6, 23.3, 22.2; HRMS (FAB, *m*-NBA) M^+ calcd for $C_{17}H_{22}O_5$: 306.1467, found: 306.1465.

*4.3.2. (R)-(2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl)methanol (**10**)*

To a stirred solution of **9** (1.87 g, 6.11 mmol) in MeOH (20 mL) was added NaH (60% in oil, 49.8 mg, 1.22 mmol). The resulting solution was stirred for 45 min at room temperature, diluted with H_2O, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (5:1 hexanes/EtOAc) afforded **10** (1.02 g, 97%) as a colorless oil. $[\alpha]_D^{23}$ +5.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3327, 2732, 1234, 1103, 1024 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.88 (d, 1H, *J*=8.6 Hz), 3.59 (d, 1H, *J*=8.6 Hz), 3.45 (m, 2H), 2.26 (br s, 1H), 1.75 (m, 8H), 1.32 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 119.3, 80.7, 71.1, 66.9, 37.1, 23.5, 23.1, 21.7; HRMS (FAB, *m*-NBA) M^+ calcd for $C_9H_{16}O_3$: 172.1099, found: 172.1103.

*4.3.3. (R,E)-Methyl 3-(2-methyl-1,4-dioxaspiro[4.4]nonan-2-yl)acrylate (**11**)*

To a solution of **10** (762 mg, 4.43 mmol) in CH_2Cl_2 (45 mL) was added Dess–Martin periodinane (2.40 g, 5.76 mmol) at room temperature. After 1 h, the reaction was quenched with saturated aqueous solutions of $Na_2S_2O_3$ and $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. This residue was employed in the next reaction without further purification.

To a solution of the resulting aldehyde in benzene (45 mL) was added (carbomethoxymethylene)triphenylphosphorane (2.2 g, 6.64 mmol). The reaction was refluxed for 1 h and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc) afforded **11** (751 mg, 75% for 2 steps) as a yellow oil. $[\alpha]_D^{25}$ −54.0 (*c* 0.1, $CHCl_3$); IR (KBr) 2973, 2871, 1726, 1662, 1303, 1170, 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.95 (d, 1H, *J*=15.5 Hz), 6.07 (d, 1H, *J*=15.5 Hz), 3.84 (d, 1H, *J*=8.2 Hz), 3.76 (d, 1H, *J*=8.2 Hz), 3.74 (s, 3H), 1.76 (m, 8H), 1.40 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.8, 150.5, 120.1, 119.6, 79.6, 74.0, 51.6, 37.0, 36.8, 24.4, 23.4, 23.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{12}H_{19}O_4$: 227.1283, found: 227.1272.

*4.3.4. (R,E)-3-(2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl)prop-2-en-1-ol (**12**)*

To a solution of **11** (1.66 g, 7.35 mmol) in CH_2Cl_2 (70 mL) was added dropwise DIBAL (1.0 M solution in hexane, 22 mL, 22.0 mmol) at −78 °C. After stirring for 0.5 h, the reaction mixture was quenched with MeOH, diluted with CH_2Cl_2, and treated with Celite (20 g) and $Na_2SO_4{\cdot}10H_2O$ (20 g). The resulting mixture was stirred for 2 h at room temperature and then filtered through a pad of Celite. The filtrates were concentrated in vacuo. The residue was purified by column chromatography (3:1 hexanes/EtOAc) to give **12** (1.37 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ −6.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3428, 2973, 2871, 1334, 1106, 975 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.91 (dt, 1H, *J*=15.5, 4.9 Hz), 5.79 (d, 1H, *J*=15.5 Hz), 4.17 (t, 2H, *J*=4.9 Hz), 3.77 (d, 1H, *J*=8.2 Hz), 3.72 (d, 1H, *J*=8.2 Hz), 1.75 (m, 8H), 1.37 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 143.3, 128.5, 119.5, 79.6, 74.6, 62.7, 37.2, 37.0, 24.4, 23.3; HRMS (FAB, *m*-NBA) M^+ calcd for $C_{11}H_{18}O_3$: 198.1256, found: 198.1254.

*4.3.5. (S)-2-[(2R,3R)-3-(Chloromethyl)oxiran-2-yl]-2-methyl-1,4-dioxaspiro[4.4]nonane (**7**)*

To a mixture of MS 4 Å (3.00 g) and (+)-DET (1.70 mL, 9.83 mmol) in CH_2Cl_2 (15 mL) was added dropwise titanium tetraisopropoxide (2.30 mL, 7.86 mmol) at −5 °C. After 20 min, TBHP (5.0 M in decane, 3.20 mL, 16.3 mmol) was added dropwise to the mixture at −20 °C. After stirring for 20 min at −20 °C, the resulting mixture was treated with a solution of **12** (1.40 g, 7.07 mmol) in CH_2Cl_2 (7 mL) and then stirred at −20 °C for 15 h. The reaction was diluted with Et_2O (11 mL), warmed to room temperature, and treated with Celite (10.0 g) and $Na_2SO_4{\cdot}10H_2O$ (10.0 g). After stirring for 2 h at room temperature, the resulting mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (1:1 hexanes/EtOAc) to give a mixture of the corresponding epoxy alcohol and a small amount of (+)-DET. This mixture was employed in the next reaction without further purification.

To a solution of the mixture in CH_2Cl_2 (70 mL), NCS (1.60 g, 11.9 mmol), triphenylphosphine (3.10 g, 11.9 mmol), and 2-methyloxirane (980 μL, 14.0 mmol) were added. The reaction mixture was stirred for 10 min at room temperature and concentrated in vacuo. Flash chromatography (40:1 hexanes/EtOAc) afforded **7** (1.54 g, 94% for 2 steps) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 0.1, $CHCl_3$); IR (KBr) 2969, 2873, 1336, 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.92 (d, 1H, *J*=8.6 Hz), 3.66 (d, 1H, *J*=8.6 Hz), 3.58 (d, 2H, *J*=5.3 Hz), 3.22 (dt, 1H, *J*=5.3, 2.0 Hz), 2.99 (d, 1H, *J*=2.0 Hz), 1.74 (m, 8H), 1.29 (s, 3H, 4-Me); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 119.9, 77.9, 71.8, 61.7, 54.3, 44.0, 36.9, 36.7, 23.5, 23.2, 21.4; HRMS (FAB, *m*-NBA) M^+ calcd for $C_{11}H_{17}O_3Cl$: 232.0866, found: 232.0868.

*4.3.6. (R)-1-[(S)-2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl]prop-2-yn-1-ol (**13**)*

To a solution of **7** (1.53 g, 6.61 mmol) in THF (66 mL) was added *n*-BuLi (1.6 M in hexane, 20 mL, 33.0 mmol) at −78 °C. The reaction mixture was stirred for 2 h at −40 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (10:1 hexanes/EtOAc) afforded **13** (1.28 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ −12.0 (*c* 0.1, $CHCl_3$); IR (KBr) 3444, 3307, 2971, 2875, 1336, 1106, 1051 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.32 (dd, 1H, *J*=4.0, 2.0 Hz), 4.19 (d, 1H, *J*=8.7 Hz), 3.68 (d, 1H, *J*=8.7 Hz), 2.46 (d, 1H, *J*=2.0 Hz), 2.33 (br d, 1H, *J*=4.0 Hz), 1.77 (m, 8H), 1.40 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 120.1, 82.0, 81.7, 74.0, 70.8, 66.3, 37.0, 36.9, 23.6, 23.1, 20.8; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{11}H_{17}O_3$: 197.1178, found: 197.1183.

*4.3.7. (2S,3R)-3-(tert-Butyldimethylsilyloxy)-2-methylpent-4-yne-1,2-diol (**14**)*

To a solution of **13** (1.29 g, 6.56 mmol) in CH_2Cl_2 (65 mL) were added TBSOTf (3.00 mL, 13.1 mmol) and 2,6-lutidine (2.30 mL, 19.6 mmol) at 0 °C. After 30 min at room temperature, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. This residue was employed in the next reaction without further purification.

The residue was dissolved in 70% aqueous AcOH solution (31 mL). The reaction mixture was stirred for 10 h at room temperature, quenched with a saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded **14** (1.40 g, 87% for 2 steps) as a colorless oil. $[\alpha]_D^{23}$ −45.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3300, 2929, 2863, 1239, 1185, 1130, 1025 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.35 (d, 1H, *J*=2.0 Hz), 3.86 (d, 1H, *J*=11.2 Hz), 3.43 (d, 1H, *J*=11.2 Hz), 2.64 (br s, 2H), 2.47 (d, 1H, *J*=2.0 Hz), 1.19 (s, 3H), 0.89 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 82.3, 74.8, 73.9, 69.2, 66.8, 25.6, 19.8, 18.0, −4.8, −5.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{12}H_{25}O_3Si$: 245.1573, found: 245.1569.

*4.3.8. (S)-5-[(R)-1-(tert-Butyldimethylsilyloxy)prop-2-ynyl]-3-hydroxy-5-methylfuran-2(5H)-one (**15**)*

To a solution of **14** (161 mg, 657 μmol) in CH_2Cl_2 (6.6 mL) were added TEMPO (20.5 mg, 131 μmol) and trichloroisocyanuric acid (153 mg, 657 μmol) at room temperature. The resulting solution was stirred for 30 min and diluted with a saturated aqueous

$NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude aldehyde **5** was subjected to the next reaction without further purification.

To a solution of **6** (511 mg, 1.64 mmol) in CH_3CN (4.0 mL) were added LiCl (63.8 mg, 1.51 mmol) and DBU (210 μL, 1.51 mmol) at 0 °C. After stirring for 30 min, a solution of the crude aldehyde **5** in THF (1.3 mL) was slowly added dropwise over 60 min to the reaction mixture at 0 °C. After 5 min, the resulting solution was quenched with a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (7:1 hexanes/EtOAc) afforded **15** (140 mg, 75% for 2 steps) as a colorless oil. $[\alpha]_D^{24}$ −69.3 (*c* 0.5, $CHCl_3$); IR (KBr) 3369, 3284, 2947, 2868, 1786, 1664, 1462, 1392, 1317, 1252, 1184, 1093, 989, 935, 849, 783, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) enol δ 9.80 (s, 1H), 6.21 (s, 1H), 4.37 (d, 1H, *J*=2.2 Hz), 2.50 (d, 1H, *J*=2.2 Hz), 1.57 (s, 3H), 0.86 (s, 9H), 0.13 (s, 3H), 0.1 (s, 3H); ketone δ 4.39 (d, 1H, *J*=2.2 Hz), 3.26 (d, 1H, *J*=18.8 Hz), 2.55 (d, 1H, *J*=2.2 Hz), 2.41 (d, 1H, *J*=18.8 Hz), 1.69 (s, 3H), 0.83 (s, 9H), 0.14 (s, 3H), 0.1 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) as a keto–enol mixture, δ 191.5, 169.4, 160.2, 142.8, 128.3, 119.2, 86.3, 83.7, 81.2, 80.5, 76.1, 74.9, 68.5, 67.0, 41.1, 25.5, 25.4, 22.7, 20.7, 18.2, 18.0, −5.1, −5.4; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{14}H_{23}O_4Si$: 283.1366, found: 283.1371.

4.3.9. (S)-3-Hydroxy-5-[(R)-1-hydroxyprop-2-ynyl]-5-methylfuran-2(5H)-one (**16**)

A solution of **15** (17.1 mg, 0.06 mmol) in THF (1.2 mL) was treated with HF·pyridine (600 μL) and stirred for 24 h at room temperature. The resulting mixture was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) afforded **16** (9.30 mg, 91%) as a colorless oil. $[\alpha]_D^{22}$ −55.1 (*c* 0.5, CH_3OH); IR (KBr) 3288, 2997, 2941, 2902, 2123, 1743, 1658, 1566, 1446, 1385, 1233, 1203, 1134, 1051, 978, 918, 868, 825, 781, 721, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 1H), 4.31 (d, 1H, *J*=2.3 Hz), 2.49 (d, 1H, *J*=2.3 Hz), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 143.9, 119.1, 85.6, 80.5, 74.8, 66.0, 20.9; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_8H_8O_4Na$: 191.0320, found: 191.0325.

4.3.10. (S)-3-Hydroxy-5-[(R,E)-1-hydroxy-3-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**3**) and (S)-3-hydroxy-5-[(S)-1-hydroxy-2-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**17**)

To a stirred solution of **16** (36.4 mg, 217 μmol) in THF (4.3 mL) were added tributyltin hydride (120 μL, 0.43 mmol) and $PdCl_2(PPh_3)_2$ (4.4 mg, 10.8 μmol). The resulting mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was purified by column chromatography (7:1 hexanes/EtOAc) to give **3** (38.9 mg, 39%) and **17** (30.0 mg, 30%) as white solids.

Compound **3**: see Section 4.3.15.

Compound **17**: mp 69–72 °C; $[\alpha]_D^{22}$ −10.1 (*c* 0.5, $CHCl_3$); IR (KBr) 3469, 3194, 3086, 2951, 2920, 2856, 1739, 1687, 1645, 1415, 1336, 1273, 1219, 1124, 1068, 1034, 985, 937, 785, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) enol δ 9.75 (s, 1H), 6.38 (dd, 1H, *J*=19.2, 1.3 Hz), 5.97 (dd, 1H, *J*=19.2, 5.5 Hz), 4.20 (br d, 1H, *J*=4.9 Hz), 1.55–1.42 (m, 6H), 1.45 (s, 3H), 1.39–1.25 (m, 6H), 0.94–0.83 (m, 6H), 0.89 (t, 9H, *J*=7.2 Hz); ketone δ 6.50 (dd, 1H, *J*=19.2, 1.5 Hz), 6.14 (s, 1H), 5.94 (dd, 1H, *J*=19.2, 5.3 Hz), 4.31 (br d, 1H, *J*=4.7 Hz), 3.00 (d, 1H, *J*=18.8 Hz), 2.29 (d, 1H, *J*=18.8 Hz), 1.57 (s, 3H), 1.55–1.42 (m, 6H), 1.39–1.25 (m, 6H), 0.94–0.83 (m, 6H), 0.89 (t, 9H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) as a keto–enol mixture, δ 192.2, 169.4, 160.6, 143.6, 142.7, 142.5, 135.5, 133.5, 120.3, 86.8, 84.3, 78.5, 78.3, 40.0, 29.0, 27.2, 23.5, 21.1, 13.7, 9.6; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{20}H_{36}O_4SnNa$: 483.1533, found: 483.1534.

4.3.11. (S)-5-[(R,E)-1-(tert-Butyldimethylsilyloxy)-3-(tributylstannyl)allyl]-3-hydroxy-5-methylfuran-2(5H)-one (**18**) and (S)-5-[(S)-1-(tert-butyldimethylsilyloxy)-2-(tributylstannyl)allyl]-3-hydroxy-5-methylfuran-2(5H)-one (**19**)

To a stirred solution of **15** (18.0 mg, 63.8 μmol) in THF (640 μL) were added tributyltin hydride (50 μL, 19.1 μmol) and $PdCl_2(PPh_3)_2$ (1.3 mg, 3.19 μmol). The resulting mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was purified by column chromatography (7:1 hexanes/EtOAc) to give **18** (19.1 mg, 52%) and **19** (8.4 mg, 23%) as colorless oils.

Compound **18**: $[\alpha]_D^{24}$ −32.5 (*c* 0.5, $CHCl_3$); IR (KBr) 2952, 2927, 2858, 1786, 1462, 1385, 1306, 1254, 1184, 1086, 1001, 849, 781, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) enol δ 9.63 (s, 1H), 6.32 (dd, 1H, *J*=19.1, 1.3 Hz), 5.91 (dd, 1H, *J*=19.1, 5.9 Hz), 4.09 (dd, 1H, *J*=5.9, 1.3 Hz), 1.57–1.42 (m, 6H), 1.39 (s, 3H), 1.36–1.24 (m, 6H), 0.93–0.79 (m, 6H), 0.88 (t, 9H, *J*=7.3 Hz), 0.81 (s, 9H), −0.02 (s, 3H); ketone δ 6.43 (dd, 1H, *J*=19.1, 1.3 Hz), 6.08 (s, 1H), 5.85 (dd, 1H, *J*=19.1, 5.9 Hz), 4.18 (dd, 1H, *J*=5.9, 1.3 Hz), 2.99 (d, 1H, *J*=18.6 Hz), 2.23 (d, 1H, *J*=18.6 Hz), 1.57–1.42 (m, 6H), 1.52 (s, 3H), 1.36–1.24 (m, 6H), 0.93–0.79 (m, 6H), 0.88 (t, 9H, *J*=7.3 Hz), 0.81 (s, 9H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) as a keto–enol mixture, δ 192.2, 169.7, 160.6, 145.5, 144.1, 142.3, 136.0, 133.3, 120.3, 87.1, 84.3, 80.4, 79.5, 40.3, 29.1, 27.2, 25.7, 23.5, 20.8, 18.0, 13.7, 9.6, −4.5, −4.6, −5.2, −5.4; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{26}H_{50}O_4SiSnNa$: 597.2398, found: 597.2404.

Compound **19**: $[\alpha]_D^{24}$ −18.8 (*c* 0.5, $CHCl_3$); IR (KBr) 3477, 3346, 2957, 2927, 2858, 1753, 1687, 1658, 1462, 1384, 1255, 1219, 1153, 1070, 937, 866, 839, 781, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) enol δ 6.19 (s, 1H), 6.08 (m, 1H), 5.43 (dd, 1H, *J*=2.5, 1.0 Hz), 4.20 (s, 1H), 1.51–1.41 (m, 6H), 1.38–1.25 (m, 6H), 1.31 (s, 3H), 1.04–0.81 (m, 24H), 0.03 (s, 6H), −0.04 (s, 6H); ketone δ 6.16 (m, 1H), 5.50 (dd, 1H, *J*=2.5, 1.0 Hz), 4.41 (s, 1H), 3.14 (d, 1H, *J*=18.8 Hz), 2.19 (d, 1H, *J*=18.8 Hz), 1.51–1.41 (m, 6H), 1.49 (s, 3H), 1.38–1.25 (m, 6H), 1.04–0.81 (m, 24H), 0.03 (s, 6H), −0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) as a keto–enol mixture, δ 192.3, 169.4, 160.4, 153.1, 152.2, 141.8, 131.1, 128.8, 122.5, 87.1, 84.9, 81.9, 40.0, 29.0, 28.9, 27.4, 27.3, 25.8, 25.7, 24.5, 20.0, 18.1, 18.0, 13.6, 13.5, 12.4, 12.3, −4.3, −4.0, −5.2, −5.5; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{26}H_{50}O_4SiSnNa$: 597.2398, found: 597.2404.

4.3.12. (S)-3-(tert-Butyldimethylsilyloxy)-5-[(R)-1-(tert-butyldimethylsilyloxy)prop-2-ynyl]-5-methylfuran-2(5H)-one (**20**)

To a solution of **14** (63.0 mg, 257 μmol) in CH_2Cl_2 (2.6 mL) were added TEMPO (8.03 mg, 51.4 μmol) and trichloroisocyanuric acid (59.7 mg, 257 μmol) at room temperature. The resulting solution was stirred for 30 min and diluted with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude aldehyde **5** was subjected to the next reaction without further purification.

To a solution of **6** (201 mg, 646 μmol) in THF (1.3 mL) was added LHMDS (1.0 M solution in THF, 590 μL, 590 μmol) at 0 °C. After stirring for 30 min, a solution of the crude aldehyde **5** in THF (1.3 mL) was slowly added dropwise over 30 min to the reaction mixture at 0 °C. After 5 min, the resulting solution was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (50:1 hexanes/EtOAc) afforded **20** (76.4 mg, 75% for 2 steps) as a colorless oil. $[\alpha]_D^{23}$ −65.2 (*c* 3.1, $CHCl_3$); IR (KBr) 2933, 2858, 1760, 1656, 1257, 1130, 1079, 842 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.20 (s, 1H), 4.34 (d, 1H, *J*=2.0 Hz), 2.48 (d, 1H, *J*=2.0 Hz), 1.53 (s, 3H), 0.96 (s, 9H), 0.87 (s, 9H), 0.25 (s, 6H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.5, 143.4, 124.6, 84.3, 81.5, 74.7, 67.2, 25.5, 25.4, 20.9, 18.2, 18.0, −4.8, −4.9, −5.0, −5.3; HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{20}H_{37}O_4Si_2$: 397.2230, found: 397.2227.

*4.3.13. (S)-5-[(R)-3-Bromo-1-(tert-butyldimethylsilyloxy)prop-2-ynyl]-3-(tert-butyldimethylsilyloxy)-5-methylfuran-2(5H)-one (**21**)*

To a stirred solution of **20** (227 mg, 573 μmol) in acetone (5.7 mL) were added NBS (111 mg, 631 μmol) and silver(I) nitrate (11.0 mg, 57.3 μmol). The resulting solution was stirred for 1 h at room temperature, filtered through a pad of silica gel, and concentrated in vacuo. The residue was purified by column chromatography (50:1 hexanes/EtOAc) to give **21** (272 mg, 100%) as a colorless oil. $[\alpha]_D^{23}$ −52.8 (*c* 2.7, $CHCl_3$); IR (KBr) 2931, 2859, 1753, 1652, 1259, 1078 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.16 (s, 1H), 4.34 (s, 1H), 1.51 (s, 3H), 0.96 (s, 9H), 0.86 (s, 9H), 0.24 (s, 6H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.4, 143.4, 124.8, 84.2, 77.8, 68.4, 46.9, 25.5, 25.4, 20.9, 18.2, 18.0, −4.8, −4.9, −5.0, −5.3; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{20}H_{35}O_4BrSi_2Na$: 497.1154, found: 497.1173.

*4.3.14. (S)-5-[(R)-3-Bromo-1-hydroxyprop-2-ynyl]-3-hydroxy-5-methylfuran-2(5H)-one (**22**)*

To a stirred solution of **21** (273 mg, 576 μmol) in THF (6 mL) was added HF·pyridine (2 mL). The resulting solution was stirred for 24 h at room temperature, filtered through a pad of silica gel, and concentrated in vacuo. The residue was purified by column chromatography (2:1 hexanes/EtOAc) to give **22** (142 mg, 100%) as a colorless oil. $[\alpha]_D^{23}$ −30.7 (*c* 1.0, MeOH); IR (KBr) 3322, 3153, 2991, 2877, 1743, 1662, 1201, 1132, 1018 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) enol δ 6.21 (s, 1H), 4.46 (s, 1H), 1.07 (s, 3H); ketone δ 4.53 (s, 1H), 3.25 (d, 1H, *J*=19.1 Hz), 2.49 (d, 1H, *J*=19.1 Hz), 1.59 (s, 3H); HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_8H_7O_4BrNa$: 268.9425, found: 268.9417.

*4.3.15. (S)-3-Hydroxy-5-[(R,E)-1-hydroxy-3-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**3**)*

To a stirred solution of **22** (48.0 mg, 195 μmol) in THF (2 mL) was added tributyltin hydride (500 μL, 1.85 mmol). The resulting mixture was stirred for 30 min at room temperature and then concentrated in vacuo. The residue was purified by column chromatography (7:1 hexanes/EtOAc) to give **3** (63.8 mg, 71%) as a white solid. Mp 78–80 °C; $[\alpha]_D^{22}$ −32.9 (*c* 0.5, $CHCl_3$); IR (KBr) 3539, 3454, 3369, 3140, 3074, 2920, 2858, 1732, 1653, 1458, 1377, 1294, 1201, 1144, 1061, 993, 870, 787, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) enol δ 9.75 (s, 1H), 6.38 (dd, 1H, *J*=19.2, 1.3 Hz), 5.97 (dd, 1H, *J*=19.2, 5.5 Hz), 4.20 (br d, 1H, *J*=4.9 Hz), 1.55–1.42 (m, 6H), 1.45 (s, 3H), 1.39–1.25 (m, 6H), 0.94–0.83 (m, 6H), 0.89 (t, 9H, *J*=7.2 Hz); ketone δ 6.50 (dd, 1H, *J*=19.2, 1.5 Hz), 6.14 (s, 1H), 5.94 (dd, 1H, *J*=19.2, 5.3 Hz), 4.31 (br d, 1H, *J*=4.7 Hz), 3.00 (d, 1H, *J*=18.8 Hz), 2.29 (d, 1H, *J*=18.8 Hz), 1.57 (s, 3H), 1.55–1.42 (m, 6H), 1.39–1.25 (m, 6H), 0.94–0.83 (m, 6H), 0.89 (t, 9H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) as a keto–enol mixture, δ 192.2, 169.4, 160.6, 143.6, 142.7, 142.5, 135.5, 133.5, 120.3, 86.8, 84.3, 78.5, 78.3, 40.0, 29.0, 27.2, 23.5, 21.1, 13.7, 9.6; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{20}H_{36}O_4SnNa$: 483.1533, found: 483.1528.

*4.3.16. Nafuredin-γ (**2**)*

To a stirred solution of **3** (16.4 mg, 35.6 μmol) and **4** (14.7 mg, 46.3 μmol) in *N*-methyl pyrrolidinone (NMP) (500 μL) was added bisacetonitriledichloropalladium (1.00 mg, 3.85 μmol). The resulting mixture was stirred for 30 min at 50 °C, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded **2** (9.24 mg, 72%) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 0.1, $CHCl_3$); IR (KBr) 3374, 2960, 2925, 2858, 1754, 1737, 1660, 1261, 1101 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) enol δ 6.30 (dd, 1H, *J*=15.5, 10.2 Hz), 6.18 (dd, 1H, *J*=14.8, 10.9 Hz), 6.15 (s, 1H), 6.00 (dd, 1H, *J*=15.5, 10.2 Hz), 5.76 (d, 1H, *J*=10.9 Hz), 5.70 (dd, 1H, *J*=15.5, 7.3 Hz), 5.50 (dd, 1H, *J*=15.5, 7.3 Hz), 5.46 (dd, 1H, *J*=14.8, 7.6 Hz), 4.25 (d, 1H, *J*=7.3 Hz), 2.43–2.36 (m, 1H), 2.12–1.91 (m, 3H), 1.70 (s, 3H), 1.46 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, *J*=6.6 Hz), 0.97 (s, 3H, *J*=6.7 Hz), 0.86 (t, 3H, *J*=7.6 Hz); ketone δ 6.30 (dd, 1H, *J*=15.5, 10.2 Hz), 6.18 (dd, 1H, *J*=14.8, 10.9 Hz), 6.00 (dd, 1H, *J*=15.5, 10.2 Hz), 5.76 (d, 1H, *J*=10.9 Hz), 5.70 (dd, 1H, *J*=15.5, 7.3 Hz), 5.50 (dd, 1H, *J*=15.5, 7.3 Hz), 5.46 (dd, 1H, *J*=14.8, 7.6 Hz), 4.21 (m, 1H), 3.03 (d, 1H, *J*=18.8 Hz), 2.43–2.36 (m, 1H), 2.32 (d, 1H, *J*=18.8 Hz), 2.12–1.91 (m, 3H), 1.70 (s, 3H), 1.54 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, *J*=6.6 Hz), 0.97 (s, 3H, *J*=6.7 Hz), 0.86 (t, 3H, *J*=7.6 Hz); HRMS (FAB, *m*-NBA) $[M+H]^+$ calcd for $C_{22}H_{33}O_4$: 361.2379, found: 361.2372.

4.4. Synthesis of nafuredin analogues 23, 24, and 25

*4.4.1. Synthesis of **26**, **27**, and **28***

These compounds were prepared according to the syntheses of **8**, **10**, and **12**.

*4.4.2. (R)-2-[(2R,3R)-3-(Chloromethyl)oxiran-2-yl]-2-methyl-1,4-dioxaspiro[4.4]nonane (**29**)*

According to the conversion of **12** into **7**, **28** (537 mg, 2.71 mmol) gave **29** (541 mg, 86% for 2 steps) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 3.90 (d, 1H, *J*=8.9 Hz), 3.63 (dd, 1H, *J*=11.5, 6.4 Hz), 3.61 (d, 1H, *J*=8.9 Hz), 3.52 (dd, 1H, *J*=11.5, 6.4 Hz), 3.28 (dt, 1H, *J*=6.4, 2.0 Hz), 2.90 (d, 1H, *J*=2.0 Hz), 1.78–1.56 (m, 8H), 1.33 (s, 3H).

*4.4.3. (R)-1-[(R)-2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl]prop-2-yn-1-ol (**30**)*

According to the conversion of **7** into **13**, **29** (541 mg, 2.33 mmol) afforded **30** (453 mg, 99%) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 4.31 (dd, 1H, *J*=4.6, 2.2 Hz), 4.03 (d, 1H, *J*=8.9 Hz), 3.68 (d, 1H, *J*=8.9 Hz), 2.46 (d, 1H, *J*=2.2 Hz), 2.39 (d, 1H, *J*=4.6 Hz), 1.84–1.59 (m, 8H), 1.42 (s, 3H).

*4.4.4. (2R,3R)-3-(tert-Butyldimethylsilyloxy)-2-methylpent-4-yne-1,2-diol (**31**)*

According to the conversion of **13** into **14**, **30** (454 mg, 2.32 mmol) furnished **31** (435 mg, 77% for 2 steps) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) δ 4.42 (d, 1H, *J*=2.2 Hz), 3.68 (dd, 1H, *J*=11.4, 6.3 Hz), 3.56 (dd, 1H, *J*=11.4, 5.3 Hz), 2.61 (s, 1H), 2.48 (d, 1H, *J*=2.2 Hz), 2.07 (br s, 1H), 1.21 (s, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H).

*4.4.5. (R)-3-Hydroxy-5-[(R)-1-hydroxyprop-2-ynyl]-5-methylfuran-2(5H)-one (**32**)*

To a solution of **31** (436 mg, 1.79 mmol) in CH_2Cl_2 (17.8 mL) were added TEMPO (5.60 mg, 35.7 μmol) and trichloroisocyanuric acid (415 mg, 1.79 mmol) at 0 °C. After 35 min at 0 °C, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. This crude aldehyde was employed in the next reaction without further purification.

To a solution of **6** (1.40 g, 4.46 mmol) in THF (17.8 mL) was added LHMDS (1.0 M solution in THF, 4.12 mL, 4.12 mmol) at 0 °C. After stirring for 30 min, a solution of the crude aldehyde in THF (17.8 mL) was slowly added dropwise over 30 min to the reaction mixture at 0 °C. After 10 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. This crude lactone was employed in the next reaction without further purification.

A solution of the crude lactone in THF (8.8 mL) was treated with HF·pyridine (200 μL) and stirred for 24 h at room temperature. The resulting mixture was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (1:1 hexanes/EtOAc) afforded **32** (155 mg, 52% for 3 steps) as a colorless oil. ^1H NMR (270 MHz, $CDCl_3$) enol δ 6.25 (s, 1H), 4.36 (s, 1H), 2.56 (d, 1H,

J=2.0 Hz), 1.62 (s, 3H); ketone δ 4.42 (m, 1H), 3.31 (d, 1H, J=19.4 Hz), 2.63 (d, 1H, J=2.0 Hz), 2.55 (d, 1H, J=19.4 Hz), 1.72 (s, 3H).

4.4.6. (*R*)-3-(*tert*-Butyldiphenylsilyloxy)-5-[(*R*,*E*)-1-hydroxy-3-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**33**)

To a solution of **32** (155 mg, 0.92 mmol) in THF (9.2 mL) were added Et_3N (193 μL, 1.39 mmol) and TBDPSCl (288 μL, 1.11 mmol) at room temperature. The reaction mixture was stirred for 40 min, quenched with a saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (5:1 hexanes/EtOAc) afforded the corresponding TBDPS enol ether (210 mg, 56%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.71–7.40 (m, 10H), 5.62 (s, 1H), 4.04 (d, 1H, J=2.3 Hz), 2.35 (d, 1H, J=2.3 Hz), 1.33 (s, 3H), 1.13 (s, 9H).

The TBDPS enol ether (210 mg, 0.52 mmol) was dissolved in THF (4.9 mL) and treated with $PdCl_2(PPh_3)_2$ (10.1 mg, 24.4 μmol) and Bu_3SnH (262 μL, 0.974 mmol) at 0 °C. After 1 h, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (50:1 hexanes/EtOAc) afforded **33** (303 mg, 47%) as a white solid. Mp 49–50 °C; $[\alpha]_D^{24}$ +31.4 (c 0.5, $CHCl_3$); IR (KBr) 3427, 2924, 2858, 1749, 1647, 1462, 1433, 1238, 1200, 1109, 1068, 833, 754, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 4H), 7.50–7.38 (m, 6H), 5.96 (dd, 1H, J=19.0, 1.0 Hz), 5.60 (dd, 1H, J=19.0, 6.0 Hz), 5.50 (s, 1H), 3.67 (m, 1H), 2.02 (d, 1H, J=3.0 Hz), 1.46–1.36 (m, 6H), 1.29–1.19 (m, 6H), 1.16 (s, 3H), 1.12 (s, 9H), 0.88–0.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 143.4, 142.3, 135.5, 135.4, 134.1, 130.5, 130.4, 128.0, 127.6, 85.3, 80.1, 29.0, 27.1, 26.2, 19.4, 18.7, 13.6, 9.4; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{36}H_{54}O_4SiSnNa$: 721.2711, found: 721.2700.

4.4.7. C4-epimer (**23**)

To a solution of **33** (65.2 mg, 93.3 mmol) in NMP (2 mL) were added **4** (39.0 mg, 0.123 mmol) and $PdCl_2(MeCN)_2$ (2.40 mg, 9.43 μmol). After stirring for 1.5 h at 50 °C, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc) afforded the corresponding coupling product (17.9 mg, 32%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.71–7.41(m, 10H), 6.25 (m, 1H), 6.18 (m, 1H), 6.17 (s, 1H), 6.01 (m, 1H), 5.74 (d, 1H, J=10.7 Hz), 5.59 (m, 1H), 5.58 (m, 1H), 5.39 (m, 1H), 4.10 (m, 1H), 2.40 (m, 1H), 2.31 (m, 1H), 1.93 (m, 2H), 1.67 (s, 3H), 1.32 (s, 3H), 1.25 (m, 2H), 0.93 (d, 3H, J=6.6 Hz), 0.90 (d, 3H, J=6.8 Hz), 0.80 (t, 3H, J=7.4 Hz), 0.79 (s, 9H).

The coupling product (17.9 mg, 29.9 mmol) was dissolved in THF (5 mL) and treated with HF·pyridine (200 μL). After stirring for 24 h at room temperature, the resulting mixture was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded the C4-epimer (**23**) (9.20 mg, 85%) as a colorless oil. $[\alpha]_D^{27}$ +114.3 (c 0.52, $CHCl_3$); IR (KBr) 3446, 2961, 2925, 2860, 2360, 2300, 1749, 1717, 1698, 1683, 1653, 1636, 1558, 1540, 1521, 1507, 1488, 1456, 1418, 1376, 1203, 1130, 1078, 991, 970 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) enol δ 6.27 (dd, 1H, J=15.5, 10.4 Hz), 6.17 (dd, 1H, J=15.2, 11.1 Hz), 6.15 (s, 1H), 6.00 (dd, 1H, J=15.2, 10.4 Hz), 5.76 (d, 1H, J=11.1 Hz), 5.69 (dd, 1H, J=15.2, 7.3 Hz), 5.50–5.43 (m, 2H), 4.12 (d, 1H, J=8.0 Hz), 2.46–2.37 (m, 1H), 2.12–1.94 (m, 3H), 1.70 (s, 3H), 1.47 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, J=6.6 Hz), 0.97 (d, 3H, J=6.8 Hz), 0.86 (t, 3H, J=7.4 Hz); ketone δ 6.27 (dd, 1H, J=15.5, 10.4 Hz), 6.17 (dd, 1H, J=15.2, 11.1 Hz), 6.00 (dd, 1H, J=15.2, 10.4 Hz), 5.76 (d, 1H, J=11.1 Hz), 5.69 (dd, 1H, J=15.2, 7.3 Hz), 5.50–5.43 (m, 2H), 4.06 (d, 1H, J=8.0 Hz), 3.08 (d, 1H, J=18.6 Hz), 2.51 (d, 1H, J=18.6 Hz), 2.46–2.37 (m, 1H), 2.12–1.94 (m, 3H), 1.70 (s, 3H), 1.53 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, J=6.6 Hz), 0.97 (d, 3H, J=6.8 Hz), 0.86 (t, 3H, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) as a keto–enol mixture, δ 191.9, 160.6, 144.0, 143.0, 138.8, 138.7, 137.5, 135.4, 134.0, 133.9, 126.9, 126.8, 125.9, 125.2, 124.7, 120.7, 87.3, 83.2, 78.2, 77.4, 47.4, 47.3, 43.8, 38.6, 34.8, 29.8, 29.7, 23.4, 20.2, 19.8, 19.6, 16.5, 11.8; HRMS (FAB, *m*-NBA) $[M+Na]^+$ calcd for $C_{22}H_{32}O_4Na$: 383.2198, found: 383.2192.

4.4.8. (*S*)-2-[(2*S*,3*S*)-3-(Chloromethyl)oxiran-2-yl]-2-methyl-1,4-dioxaspiro[4.4]nonane (**34**)

According to the conversion of **12** into **7**, **12** (2.17 g, 10.9 mmol) was subjected to Sharpless epoxidation using (−)-DET followed by chlorination to afford **34** (2.34 g, 92% for 2 steps) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.91 (d, 1H, J=8.9 Hz), 3.74 (dd, 1H, J=11.5, 5.3 Hz), 3.62 (d, 1H, J=8.9 Hz), 3.51 (dd, 1H, J=11.5, 5.3 Hz), 3.28 (ddd, 1H, J=10.7, 5.3, 1.7 Hz), 2.89 (d, 1H, J=1.7 Hz), 1.86–1.56 (m, 8H), 1.33 (s, 3H).

4.4.9. (*S*)-1-[(*S*)-2-Methyl-1,4-dioxaspiro[4.4]nonan-2-yl]prop-2-yn-1-ol (**35**)

According to the conversion of **29** into **30**, **34** (2.34 g, 10.1 mmol) gave **35** (1.92 g, 97%) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.31 (dd, 1H, J=4.6, 2.0 Hz), 4.03 (d, 1H, J=8.9 Hz), 3.68 (d, 1H, J=8.9 Hz), 2.45 (d, 1H, J=2.0 Hz), 2.39 (d, 1H, J=4.6 Hz), 1.84–1.67 (m, 8H), 1.42 (s, 3H).

4.4.10. (2*S*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpent-4-yne-1,2-diol (**36**)

According to the conversion of **30** into **31**, **35** (1.92 g, 9.79 mmol) gave **36** (1.98 g, 83% for 2 steps) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.42 (d, 1H, J=2.3 Hz), 3.68 (dd, 1H, J=11.3, 6.9 Hz), 3.55 (dd, 1H, J=11.3, 5.9 Hz), 2.60 (s, 1H), 2.48 (d, 1H, J=2.3 Hz), 2.11–2.04 (m, 1H), 1.24 (s, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H).

4.4.11. (*S*)-3-Hydroxy-5-[(*S*)-1-hydroxyprop-2-ynyl]-5-methylfuran-2(5H)-one (**37**)

According to the conversion of **31** into **32**, **36** (1.03 g, 4.22 mmol) gave **37** (347 mg, 49% for 3 steps) as a yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.25 (s, 1H, enol), 4.42 (br s, 1H, ketone), 4.36 (br s, 1H, enol), 3.13 (d, 1H, J=19.3 Hz, ketone), 2.56 (d, 1H, J=2.0 Hz), 2.54 (d, 1H, J=19.3 Hz, ketone), 1.71 (s, 3H).

4.4.12. (*S*)-3-(*tert*-Butyldiphenylsilyloxy)-5-[(*S*,*E*)-1-hydroxy-3-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**38**)

According to the conversion of **32** into **33**, **37** (199 mg, 1.18 mmol) gave **38** (389 mg, 47% for 2 steps) as a white solid. Mp 61–62 °C; $[\alpha]_D^{23}$ −37.5 (c 0.5, $CHCl_3$); IR (KBr) 3425, 2954, 2924, 2858, 1749, 1645, 1462, 1431, 1240, 1198, 1109, 1068, 833, 754, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 4H), 7.50–7.38 (m, 6H), 5.96 (dd, 1H, J=19.0, 1.0 Hz), 5.60 (dd, 1H, J=19.0, 6.0 Hz), 5.50 (s, 1H), 3.67 (m, 1H), 2.02 (d, 1H, J=3.0 Hz), 1.46–1.36 (m, 6H), 1.29–1.19 (m, 6H), 1.16 (s, 3H), 1.12 (s, 9H), 0.88–0.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 143.4, 142.3, 135.5, 135.4, 134.1, 130.5, 130.4, 128.0, 127.6, 85.3, 80.1, 29.0, 27.1, 26.2, 19.4, 18.7, 13.6, 9.4; HRMS (FAB, *m*-NBA+NaI) $[M+Na]^+$ calcd for $C_{36}H_{54}O_4SiSnNa$: 721.2711, found: 721.2719.

4.4.13. C5-epimer (**24**)

To a solution of **38** (35.3 mg, 0.051 mmol) in NMP (1.01 mL) were added **4** (20.9 mg, 0.066 mmol) and $PdCl_2(MeCN)_2$ (1.31 mg, 5.00 μmol). After stirring for 4 h at 50 °C, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (20:1 hexanes/EtOAc) afforded the corresponding coupling product (8.50 mg, 28%) as a colorless oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.48–7.41 (m, 6H), 6.24–6.15 (dd, 1H, J=15.0, 10.2 Hz), 5.90–5.82 (m, 2H), 5.77 (d, 1H, J=10.2 Hz), 5.63–5.54 (dd, 1H, J=14.8, 7.3 Hz), 5.51 (s, 1H), 5.51–5.43 (dd, 1H, J=15.3, 7.8 Hz), 5.17–5.09 (dd, 1H, J=14.2, 6.9 Hz), 3.73 (d, 1H,

J=7.3 Hz), 2.38 (m, 1H), 2.05 (m, 1H), 1.94 (m, 1H), 1.71 (s, 3H), 1.62 (m, 1H), 1.35–1.26 (m, 2H), 1.20 (s, 3H), 1.12 (s, 9H), 0.99 (d, 3H, J=6.9 Hz), 0.95 (d, 3H, J=6.6 Hz), 0.86 (t, 3H, J=7.1 Hz).

The coupling product (22.3 mg, 37.0 μmol) was dissolved in THF (373 μL) and treated with HF·pyridine (200 μL). After stirring for 24 h at room temperature, the resulting mixture was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (4:1 hexanes/EtOAc) afforded the C5-epimer (**24**) (11.2 mg, 84%) as a colorless oil. $[\alpha]_D^{27}$ +46.0 (c 1.12, $CHCl_3$); IR (KBr) 3566, 2962, 2924, 2860, 2360, 2342, 1771, 1750, 1717, 1699, 1684, 1653, 1636, 1558, 1540, 1521, 1507, 1489, 1457, 1418, 1396, 1203, 1130, 1064, 991 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) enol δ 6.27 (dd, 1H, J=15.3, 10.5 Hz), 6.18 (dd, 1H, J=15.0, 10.8 Hz), 6.13 (s, 1H), 6.01 (dd, 1H, J=15.0, 10.5 Hz), 5.76 (d, 1H, J=11.0 Hz), 5.65 (dd, 1H, J=15.0, 8.5 Hz), 5.55–5.43 (m, 2H), 4.08 (d, 1H, J=8.0 Hz), 2.45–2.39 (m, 1H), 2.15–1.92 (m, 3H), 1.71 (s, 3H), 1.46 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, J=6.5 Hz), 0.97 (d, 3H, J=6.5 Hz), 0.86 (t, 3H, J=7.4 Hz); ketone δ 6.27 (dd, 1H, J=15.3, 10.5 Hz), 6.18 (dd, 1H, J=15.0, 10.8 Hz), 6.01 (dd, 1H, J=15.0, 10.5 Hz), 5.76 (d, 1H, J=11.0 Hz), 5.65 (dd, 1H, J=15.0, 8.5 Hz), 5.55–5.43 (m, 2H), 4.06 (d, 1H, J=8.0 Hz), 3.07 (d, 1H, J=18.6 Hz), 2.51 (d, 1H, J=18.6 Hz), 2.45–2.39 (m, 1H), 2.15–1.92 (m, 3H), 1.71 (s, 3H), 1.52 (s, 3H), 1.32 (m, 2H), 0.99 (d, 3H, J=6.5 Hz), 0.97 (d, 3H, J=6.5 Hz), 0.86 (t, 3H, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) as a keto–enol mixture, δ 191.9, 160.7, 143.9, 142.9, 138.7, 138.6, 137.4, 135.4, 134.0, 133.8, 126.9, 126.7, 126.6, 125.9, 125.2, 124.7, 120.9, 87.3, 83.3, 78.1, 77.4, 47.4, 47.3, 43.8, 38.6, 34.8, 29.8, 29.7, 23.4, 20.2, 19.7, 19.5, 16.5, 11.8; HRMS (FAB, m-NBA) $[M+Na]^+$ calcd for $C_{22}H_{32}O_4Na$: 383.2198, found: 383.2195.

4.4.14. (S)-5-[(R)-1-Hydroxyprop-2-ynyl]-5-methylfuran-2(5H)-one (**39**)

To a solution of **14** (228 mg, 0.932 mmol) in CH_2Cl_2 (9.3 mL) were added TEMPO (2.90 mg, 18.7 μmol) and trichloroisocyanuric acid (217 mg, 0.932 mmol) at 0 °C. After stirring for 1 h, the resulting mixture was filtered through a pad of Celite and the filtrate was washed with a saturated aqueous $NaHCO_3$ solution. The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. This crude aldehyde was employed in the next reaction without further purification.

To a solution of $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (400 μL, 1.86 mmol) was added LHMDS (1.60 mL, 1.60 mmol) at 0 °C. After 30 min, a solution of the crude aldehyde was added dropwise to the resulting mixture at 0 °C. The reaction mixture was stirred for 10 min, quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (40:1 hexanes/EtOAc) afforded the corresponding α,β-unsaturated lactone (139 mg, 56% for 2 steps) as a colorless oil. $[\alpha]_D^{23}$ −175.9 (c 0.5, $CHCl_3$); IR (KBr) 2945, 2864, 1768, 1254, 1113, 976, 843, 783, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 1H, J=5.7 Hz), 6.12 (d, 1H, J=5.7 Hz), 4.43 (d, 1H, J=2.2 Hz), 2.54 (d, 1H, J=2.2 Hz), 1.57 (s, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.9, 122.5, 89.7, 81.1, 75.1, 66.6, 25.5, 19.8, 18.0, −5.1, −5.4; HRMS (FAB, m-NBA) $[M+H]^+$ calcd for $C_{14}H_{23}O_3Si$: 267.1416, found: 267.1418.

A solution of the α,β-unsaturated lactone (139 mg, 0.524 mmol) in THF (5.2 mL) was treated with HF·pyridine (1.5 mL) and stirred for 12 h at room temperature. The resulting mixture was filtered through a pad of silica gel and concentrated in vacuo. Flash chromatography (2:1 hexanes/EtOAc) afforded **39** (79.0 mg, 99%) as a colorless oil. $[\alpha]_D^{24}$ −142.0 (c 0.5, $CHCl_3$); IR (KBr) 3543, 3300, 3251, 3111, 2993, 2933, 2885, 2121, 1720, 1641, 1444, 1390, 1308, 1238, 1122, 1059, 974, 895, 825, 696, 573, 534, 422, 409, 401 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, 1H, J=5.7 Hz), 6.16 (d, 1H, J=5.7 Hz), 4.52 (dd, 1H, J=2.2, 6.2 Hz), 3.12 (br s, 1H), 2.58 (d, 1H, J=2.2 Hz), 1.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 156.7, 122.7, 89.7, 79.8, 76.0, 65.9, 20.0; HRMS (FAB, m-NBA) $[M+H]^+$ calcd for $C_8H_9O_3$: 153.0552, found: 153.0553.

4.4.15. (S)-5-[(R,E)-1-Hydroxy-3-(tributylstannyl)allyl]-5-methylfuran-2(5H)-one (**40**)

To a solution of **39** (79.0 mg, 0.52 mmol) and $PdCl_2(PPh_3)_2$ (10.7 mg, 26.0 μmol) in THF (5.2 mL) was added dropwise Bu_3SnH (420 μL, 1.56 mmol) at room temperature. After 10 min, the resulting mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (5:1 hexanes/EtOAc) afforded **40** (157 mg, 68%) as a colorless oil. $[\alpha]_D^{24}$ −35.0 (c 0.5, $CHCl_3$); IR (KBr) 3458, 2920, 2858, 1753, 1458, 1377, 1288, 1242, 1176, 1107, 999, 960, 877, 822, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1H, J=5.8 Hz), 6.38 (dd, 1H, J=19.2, 1.5 Hz), 6.08 (d, 1H, J=5.8 Hz), 6.01 (dd, 1H, J=19.2, 5.3 Hz), 4.19 (m, 1H), 2.33 (br d, 1H, J=5.1 Hz), 1.76–1.44 (m, 6H), 1.44 (s, 3H), 1.42–1.24 (m, 6H), 0.92–0.86 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.4, 143.6, 133.2, 121.7, 90.3, 77.8, 29.0, 27.2, 19.7, 13.6, 9.5; HRMS (FAB, m-NBA) $[M+H]^+$ calcd for $C_{20}H_{37}O_3Sn$: 445.1765, found: 445.1769.

4.4.16. 2-Dehydroxy-α,β-unsaturated lactone (**25**)

To a solution of **40** (89.7 mg, 0.202 mmol) in NMP (2.00 mL) were added **4** (83.5 mg, 0.263 mmol) and $PdCl_2(MeCN)_2$ (5.20 mg, 20.6 μmol). After stirring for 1.5 h at 50 °C, the reaction mixture was quenched with H_2O and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Flash chromatography (3:1 hexanes/EtOAc) afforded the 2-dehydroxy-α,β-unsaturated lactone (**25**) (50.9 mg, 70%) as a colorless oil. $[\alpha]_D^{27}$ −8.5 (c 2.1, $CHCl_3$); IR (KBr) 3446, 2961, 2924, 2872, 2360, 1750, 1653, 1558, 1540, 1507, 1488, 1456, 1376, 1237, 1110, 992, 966, 818 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, 1H, J=6.0 Hz), 6.30 (dd, 1H, J=15.2, 10.5 Hz), 6.17 (dd, 1H, J=15.0, 11.08 Hz), 6.09 (d, 1H, J=6.0 Hz), 6.00 (dd, 1H, J=15.2, 10.5 Hz), 5.76 (d, 1H, J=10.9 Hz), 5.69 (dd, 1H, J=15.2, 7.3 Hz), 5.54 (dd, 1H, J=15.2, 6.6 Hz), 5.45 (dd, 1H, J=15.0, 7.7 Hz), 4.25 (d, 1H, J=6.7 Hz), 2.45–2.37 (m, 1H), 2.11–2.03 (m, 1H), 1.96 (dd, 2H, J=13.4, 7.8 Hz), 1.70 (s, 3H), 1.46 (s, 3H), 1.35–1.29 (m, 2H), 0.99 (d, 3H, J=6.8 Hz), 0.97 (d, 3H, J=6.7 Hz), 0.86 (t, 3H, J=7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 158.0, 142.8, 138.7, 134.7, 134.0, 126.9, 126.8, 126.2, 124.7, 121.9, 90.6, 75.7, 47.4, 38.6, 34.8, 29.8, 20.2, 20.1, 19.6, 16.5, 11.8; HRMS (FAB, m-NBA) $[M+Na]^+$ calcd for $C_{22}H_{32}O_3Na$: 367.2249, found: 367.2250.

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