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One-Pot Synthesis of Multisubstituted Butyrolactonimidates: Total Synthesis of (−)-Nephrosteranic Acid

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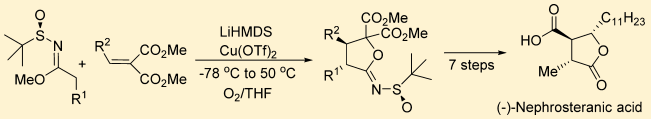
Supporting Information

ABSTRACT: Multisubstituted chiral butyrolactonimidates have been synthesized via a one-pot, three-step cascade reaction in which (*R*)-*N*-*tert*-butanesulfinyl imidates and *α*,*β*-unsaturated diesters undergo highly stereoselective Michael addition, anion-oxidative hydroxylation, and cyclization. The synthesized butyrolactonimidates are versatile intermediates for preparation of substituted butyrolactones and furans. The usefulness of this cascade reaction is demonstrated through the concise total synthesis of natural product (−)-nephrosteranic acid.



INTRODUCTION

The multisubstituted butyrolactone core structure is present in a diverse range of natural products with important biological activities (Figure 1, **1**−**8**).[1] For example, lignin enterolactone **1**, present in human urine, has been found to inhibit breast cancer and colon cancer.[2] Arctigenin (**2**) and isoarctigenin (**3**) potently inhibit HIV-type 1 integrase,[3] and parthenolide **4** has been tested in clinical trials because of its potent activities against pancreatic cancer, leukemia, and melanoma.[4] Paraconic acids **5** and **6** possess antifungal and antibacterial properties.[5] The whiskey lactone **7** and cognac lactone **8** are of tremendous commercial interest as potential key flavor components in aged alcoholic beverages.[6] Therefore, chiral multisubstituted butyrolactones have attracted considerable synthetic interest as important intermediates in natural product synthesis, food chemistry, and medicinal chemistry.

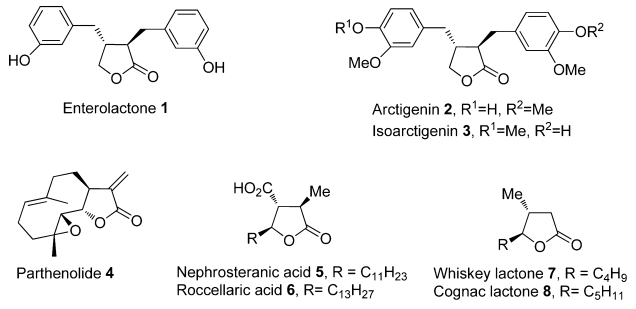
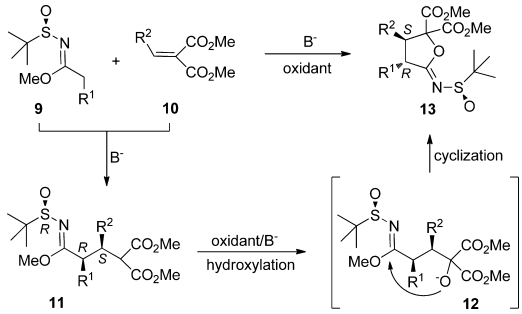


Figure 1. Representive natural products with a butyrolactone moiety.

These compounds have been synthesized by several methods involving chiral auxiliary induction[7] and asymmetric catalysis.[8] Most of these methods require multiple-step reaction with concomitant overall low yield. Here, we report the synthesis of multisubstituted chiral butyrolactonimidates **13** from (*R*)-*N*-*tert*-butanesulfinyl imidates **9**[9] and *α*,*β*-unsaturated diesters **10**[10] via a one-pot, three-step cascade reaction (Scheme 1) involving highly stereoselective Michael addition (**9** to **11**), followed by anion-oxidative hydroxylation (**11** to **12**) and oxygen anion cyclization (**12** to **13**). The synthesized butyrolactonimidates **13** are versatile precursors for preparing multisubstituted butyrolactones and furans.

Scheme 1



RESULTS AND DISCUSSION

In the planned cascade reaction, the first step of Michael addition simultaneously generates two stereocenters in target butyrolactonimidate **13**, which is key to ensure high diastereoselectivity and high yield for the overall cascade reaction. Therefore, we first sought to optimize the diastereoselectivity and yield for the Michael addition using

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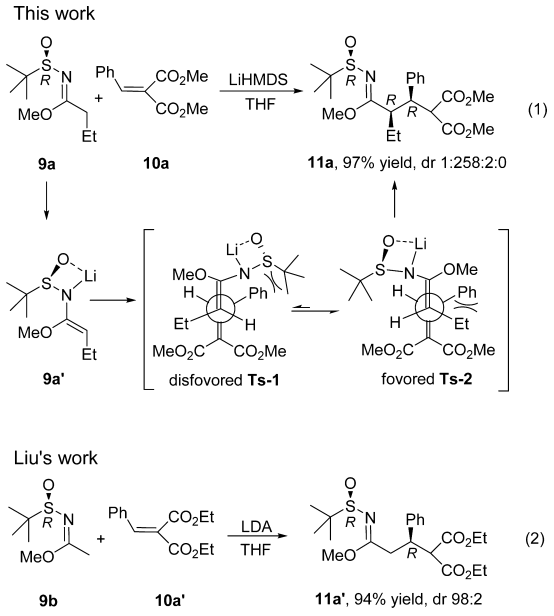
(*R*)-*N*-(*tert*-butanesylfinyl)propylimidate (**9a**) (R^1 = Et) and dimethyl 2-benzylidenemalonate (**10a**) (R^2 = Ph) as model substrates (Scheme 2, eq 1). Ellman et al., Kimpe et al., and

Scheme 2



Poisson et al. have, respectively, studied the α-alkylation, Mannich-type addition, and aldol addition of *N*-(*tert*-butanesulfinyl)imidates with excellent results.[11] Meanwhile, Liu et al.[12] reported a highly stereoselective Michael addition of **9b** to **10a**′ to give adduct **11a**′ containing a newly generated stereocenter with 98:2 dr and 94% yield (Scheme 2, eq 2). When we applied Liu's conditions to the Michael addition of **9a** to **10a** (1.2 equiv of LDA, −78 °C in THF, 0.05 M of **9a**), adduct **11a** was isolated in 89% yield as the dominant stereoisomer (dr 1:97:2:0 by LC−MS). X-ray analysis of a single crystal **11a**[13] (Figure 2) unambiguously showed the

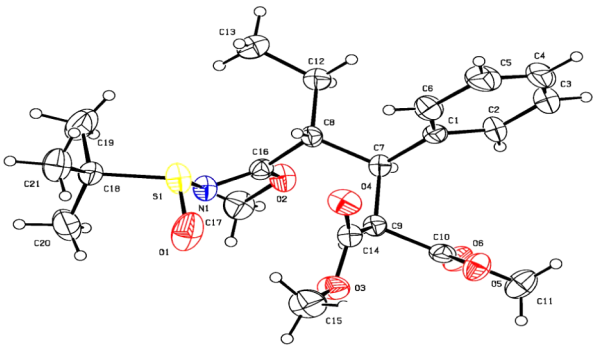
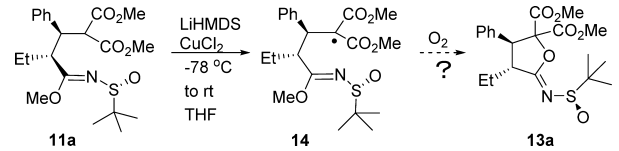


Figure 2. ORTEP drawing of compound **11a**.

absolute configuration of the newly generated stereocenters to be (*R*,*R*). Replacing the solvent THF with DME or ^{t}BuOMe while keeping LDA as the base substantially reduced dr values to 16:76:7:1 and 38:59:3:0, respectively. Replacing the LDA with LiHMDS in THF, excellent diastereoselectivity of **11a** (dr 1:258:2:0) and high yield (97%) were obtained. Concerning the excellent dr value in the Michael addition, a stereochemical addition model is proposed as shown in Scheme 2 (eq 1). In the presence of a strong base, the imidate **9a** was transferred to the dominant *cis* aza-enolate **9a**′ at low temperature. Addition of **9a**′ to diester **10a** occurred via transition state **Ts-2** rather than **Ts-1** to provide adduct **11a** with an (*R*,*R*)-configuration because there was a much stronger steric repulsion between the bulky *tert*-butanesulfinyl group of **9a** and the phenyl group of **10a** in **Ts-1** than the steric repulsion between the ethyl group of **9a** and the phenyl group of **10a** in **Ts-2**.

α-Hydroxy-β-dicarbonyl compounds are important building blocks in the syntheses of natural products and pharmaceutical substances. Although there are a number of methods for preparing α-hydroxyl β-ketone esters or α-hydroxyl diketones via diaza hydrolysis,[14] Baeyer−Villiger oxidation,[15] enol oxidization,[16] enol addition to nitroso compound,[17] and the anion-oxidative hydroxylation by employing metal salts such Mn, Ce, Pd, Co salts as oxidants,[18] to the best of our knowledge, these methods are limited to substrates with β-ketone esters or β-diketones, and the hydroxylation of diesters remains unexplored. We envisioned that if O_2 could be captured with a radical in **14** generated from **11a** by anion oxidation in the presence of oxidants, the butyrolactonimidate **13a** should be generated via subsequent peroxy bond reduction and oxygen anion cyclization (Scheme 3). Working on the

Scheme 3



hypothesis, we treated **11a** with 2.0 equiv of LiHMDS in THF at −78 °C for 1 h, after which we removed the septum, added solid oxidant $CuCl_2$, and maintained the reaction for 20 h under a nitrogen balloon at rt. To our delight, we indeed isolated the expected butyrolactonimidate **13a** in 14% yield from the initial experiment. Purposely replacing the nitrogen balloon with an oxygen balloon after adding $CuCl_2$ did not improve the yield. Albeit in low yield, successful generation of **13a** from **11a** encouraged us to investigate systematically the anion oxidative hydroxylation and cyclization of **11a** in order to optimize the synthesis of butyrolactonimidate **13a**.

We tested various oxidants usually used in radical coupling reactions of anion oxidation[19,20] under a condition of 3.0 equiv of LiHMDS, 3.0 equiv of oxidant, 50 °C, and 0.05 M of **11a** in THF (Table 1). Oxidants IBX, $PhI(OAc)_2$, and $FeCl_3$·DMF did not give **13a**, while I_2 provided **13a** in low 16% yield (entries 1−4). $CuCl_2$ and $CuBr_2$ afforded **13a** in 25% and 42% yield, respectively (entries 5 and 6). Using 3.0 equiv of $Cu(OTf)_2$ improved the yield to 82% (entry 7), and using higher or lower amounts of $Cu(OTf)_2$ significantly decreased yield (entries 8−10). Similarly, changing the amount of LiHMDS from 3.0 to 2.0 equiv or 4.0 equiv also decreased the yield (entries 11 and 12). Screening reactant concentrations showed that 0.01 M of **11a** gave the best yield of 92% (entries 7 and 13−15). Lowering the reaction temperature from 50 to 25 °C reduced the yield to 45% (entry 16).

After optimizing the conditions for the anion oxidative hydroxylation and cyclization (**11a** into **13a**), we combined the three steps of Michael addition, anion-oxidative hydroxylation, and cyclization into a one-pot procedure by adding 1.2 more equiv of LiHMDS, since at least 1.0 equiv of base was consumed in the first step of Michael addition. Therefore, the

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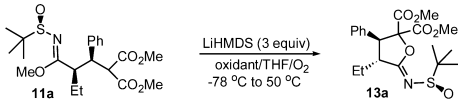
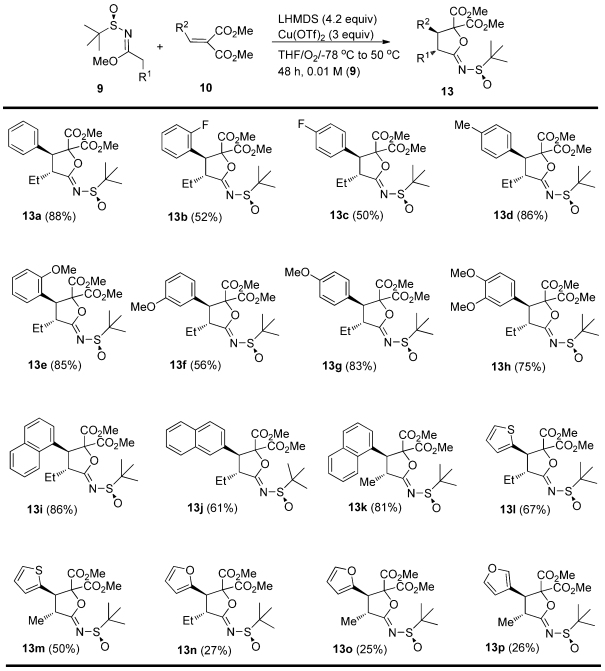
Table 1. Optimization of Conditions for Oxidative Cyclization of 13a[a]



entry	11a conc (M)	oxidant (equiv)	yield (%)
1	0.05	IBX (3.0)	NR
2	0.05	$PhI(OAc)_2$(3.0)	NR
3	0.05	$FeCl_3$·DMF (3.0)	NR
4	0.05	I_2 (3.0)	16
5	0.05	$CuCl_2$ (3.0)	25
6	0.05	$CuBr_2$ (3.0)	42
7	0.05	$Cu(OTf)_2$ (3.0)	82
8	0.05	$Cu(OTf)_2$ (1.0)	5
9	0.05	$Cu(OTf)_2$ (2.0)	53
10	0.05	$Cu(OTf)_2$ (3.5)	72
11[b]	0.05	$Cu(OTf)_2$ (3.0)	60
12[c]	0.05	$Cu(OTf)_2$ (3.0)	71
13	0.10	$Cu(OTf)_2$ (3.0)	73
14	0.01	$Cu(OTf)_2$ (3.0)	92
15	0.005	$Cu(OTf)_2$ (3.0)	85
16[d]	0.01	$Cu(OTf)_2$ (3.0)	45

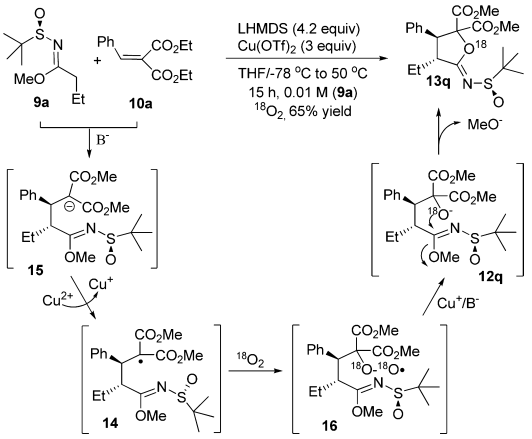
[a]Unless noted otherwise, reactions were performed under nitrogen at −78 °C in a solution of **11a** in THF to which 3.0 equiv of LiHMDS were added. The mixture was kept at −78 °C for 1 h. The septum was removed, oxidant was added, and the reaction vessel was covered with a nitrogen balloon. As a result, the reaction was exposed to air for a few minutes. The reaction temperature was then raised to 50 °C and maintained there for 48 h under a nitrogen balloon. [b]2.0 equiv of LiHMDS was used. [c]4.0 equiv of LiHMDS was used. [d]The reaction was conducted at 25 °C for 48 h.

Table 2. Synthesis of 13 in a One-Pot, Three-Step Cascade[a]



[a]General procedure for the one-pot cascade reaction: LiHMDS (4.2 equiv) was added to a solution of **9** (1.1 equiv, 0.01 M) in THF under nitrogen at −78 °C. After 30 min, a solution of **10** (1.0 equiv) in THF was added to the mixture, which was stirred at −78 °C for 3 h. Then 3 equiv of $Cu(OTf)_2$ were added after removing the septum, such that the reaction mixture was exposed to air for a few minutes. The reaction mixture was then warmed to 50 °C and maintained at that temperature for 48−60 h under a nitrogen balloon.

Scheme 4. Plausible Mechanism for the Cascade Reaction



cascade was carried out using 4.2 equiv of LiHMDS, 1.1 equiv of **9a**, 1.0 equiv of **10a** in 0.01 M THF, and 3.0 equiv of $Cu(OTf)_2$. These conditions led to **13a** in 88% yield (Table 2). Once again, replacing the nitrogen balloon with an oxygen balloon after addition of $Cu(OTf)_2$ did not improve the yield but resulted in production of more unidentified byproducts. We then tested the scope of the cascade reaction using substrates **9** and **10** with different R_1 and R_2, and we obtained the desired butyrolactonimidates **13b−m** in moderate to high yield. Using substrates **10** with a furan ring afforded the corresponding butyrolactonimidates **13n−p** in low yield. The excellent dr values for the Michael addition step were analyzed by a small portion of the reaction mixture. After workup, only one stereoisomer was isolated from all reactions described in Table 2 when the anion oxidative hydroxylation and cyclization were completed.

We postulated that the oxygen atom in **13** must originate from the air, consistent with the fact that the reaction is exposed to air for a few minutes when solid $Cu(OTf)_2$ is added after Michael addition. To test this idea, we performed the following experiment: instead of placing the normal nitrogen balloon on top of the reaction mixture after addition of $Cu(OTf)_2$, we used an oxygen isotope balloon. This accelerated the reaction, allowing it to reach completion within 15 h instead of the usual 48 h, and it decreased the yield of oxygen isotope-labeled adduct **13q** from 88% to 65%. Based on these results, we propose a plausible mechanism for the one-pot three-step cascade reaction (Scheme 4). After the first step of Michael addition, anion intermediate **15** is oxidized by Cu^{2+} to give radical intermediate **14**, which undergoes radical addition to $^{18}O_2$ to generate peroxy radical intermediate **16**. Reductive cleavage of the peroxy bond in **16** by Cu^+ and deprotonation under strongly basic conditions provide oxygen anion intermediate **12q**. Intramolecular cyclization of the oxygen anion with the imidate group in **12q** furnishes the butyrolactonimidate **13q**. The better yields with excess $Cu(OTf)_2$ (3 equiv) may arise from copper also participating as a Lewis acid to activate the unsaturated diester **10** or the sulfinylimidate **9**.

After using this one-pot method to generate butyrolactonimidates **13**, we explored their usefulness as versatile precursors for preparing multisubstituted butyrolactones and furans

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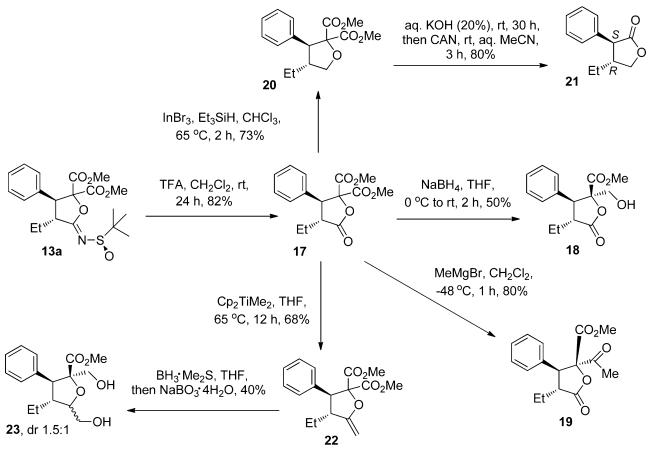
(Scheme 5). The chiral *tert*-butylsulfinyl moiety in **13a** was readily removed by TFA in CH_2Cl_2 to afford butyrolactone **17**.

Scheme 5. Conversion of Butyrolactonimidate 13a to Butyrolactones and Furans



The less hindered ester group opposite to the adjacent phenyl group in **17** was efficiently attacked by $NaBH_4$ to provide hydroxyl ester **18** and by methylmagnesium bromide to provide ketone ester **19**. Selective reduction of the lactone group in **17** using $InBr_3$ and Et_3SiH in $CHCl_3$ generated furan **20** in 73% yield.[21] Hydrolysis of the two ester groups in **20** followed by oxidative decarbonylation using CAN regenerated the lactone functionality to give lactone **21** in 80% yield. Optical rotation data indicated an absolute configuration of (*R*,*S*) for lactone **21**, consistent with the literature data.[8d] Heating **17** with Cp_2TiMe_2[22] in THF readily transformed lactone **17** into methylenefuran **22**. Hydroboration of **22** provided diol **23** as a mixture of two inseparable diastereomers.

To further demonstrate the synthetic usefulness of our cascade reaction, we applied it to the asymmetric total synthesis of natural product (−)-nephrosteranic acid **5** (Scheme 6).[8a,23] First we performed the cascade reaction between **9c** and **10g** under optimal conditions to afford butyrolactonimidate **13r** in 75% yield. Grignard reaction of **13r** with decylmagnesium bromide in THF at −40 °C provided ketone **24** in 53% yield. Decarbonylation of **24** with LiCl in DMF afforded **25** as a single diastereomer in 60% yield. Reduction of **25** with $NaBH_4$ in MeOH gave an inseparable mixture of two diastereomers **26** in 92% yield and 2:1 dr. Barton−McCombie deoxygenation of **26** generated **27** in 48% yield, from which the *tert*-butylsulfinyl group was removed using TFA, affording lactone **28** in 92% yield. Oxidation of the phenyl ring in **28** using $NaIO_4$ and $RuCl_3$ completed the total synthesis of (−)-nephrosteranic acid **5**.

CONCLUSION

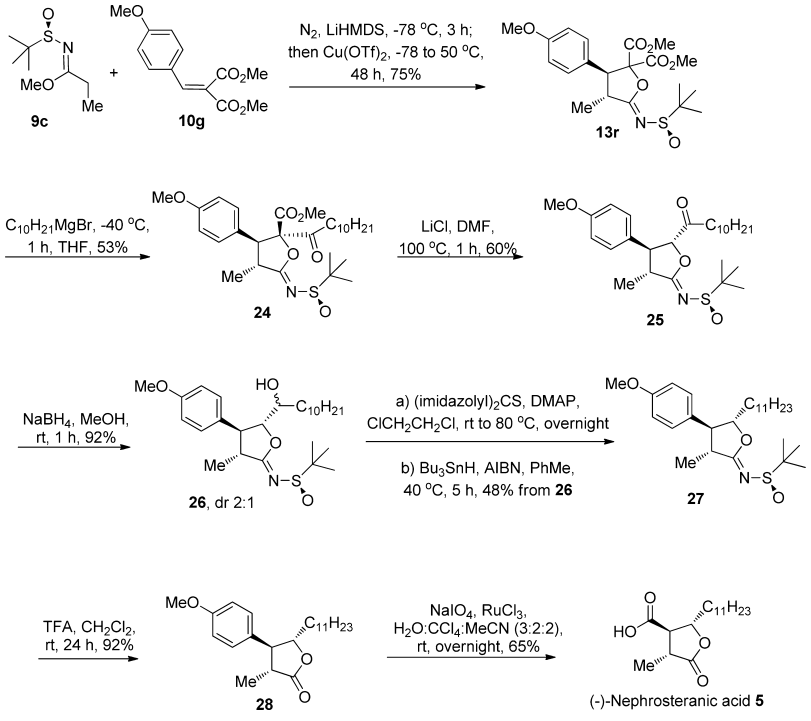
In summary, we have developed a one-pot, three-step cascade reaction in which (*R*)-*N*-*tert*-butanesulfinyl imidates **9** and *α*,*β*-unsaturated diesters **10** undergo highly stereoselective Michael addition, anion-oxidative hydroxylation, and oxygen anion cyclization. Complete diastereocontrol during the initial Michael addition ensures excellent stereoselectivity for the overall cascade. We show that the chiral butyrolactonimidates **13** synthesized using our approach are versatile intermediates for preparing multisubstituted butyrolactones and furans. We also use our approach to achieve the concise total synthesis of natural product (−)-nephrosteranic acid **5**.

EXPERIMENTAL SECTION

Experimental conditions and spectral data were published previously for compounds **9a** and **9c**[9] and **10a**−**m**.[10]

Dimethyl 2-((1*R*,2*R*)-2-((*E*)-(((*R*)-*tert*-Butylsulfinyl)imino)-(methoxy)methyl)-1-phenylbutyl)malonate (11a). Under N_2, to

Scheme 6. Synthesis of (−)-Nephrosteranic Acid 5



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a solution of **9a** (0.28 mmol, 1.1 equiv) in dry THF (3.7 mL) was added LiHMDS (1 M in THF, 0.30 mmol, 1.2 equiv) at −78 °C. After the resulting solution was maintained at −78 °C for 30 min, a solution of **10a** (0.25 mmol, 1.0 equiv) in THF (1 mL) was slowly added. The resulting solution was maintained at −78 °C for another 3 h. After the reaction was completed, the solution was quenched by pouring into aqueous NH_4Cl (5 mL). The aqueous layer was partitioned with EtOAc (15 mL × 3). The organic layer was separated, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo. Flash chromatography (silica gel) of the crude reaction mixture afforded pure product **11a**. Conditions for LC−MS analysis of the crude Michael addition product **11a**: mobile phase H_2O/CH_3CN (80:20); flow = 0.2 mL/min; detected by UV at 210 nm; retention time for stereoisomers: 7.27 min, 7.57 min, 7.77 min (major); dr 1:258:2:0. R_f = 0.35 (petroleum/EtOAc 3:1); 103 mg, 97% yield. A colorless crystal of **11a** for the X-ray analysis[13] was obtained by recrystallization from MeCN: mp 46−48 °C; $[\alpha]_D^{24}$ −179.4 (*c* 1.5, $CHCl_3$); IR (KBr) 2953, 2857, 1741, 1610, 1456, 1435, 1291, 1229, 1071, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.20 (m, 5H), 4.28 (d, *J* = 9.2 Hz, 1H), 3.76 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.27 (s, 3H), 1.45 (m, 1H), 1.25 (m, 9H), 1.25 (overlapped, 1H), 0.72 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 168.5, 168.1, 138.6, 129.1, 128.1, 127.2, 56.1, 56.0, 53.9, 52.3, 51.9, 49.4, 47.1, 24.1, 21.9, 11.5; HRMS (ESI-TOF) calcd for $C_{21}H_{31}NNaO_6S$ $[M + Na]^+$ 448.1770, found 448.1769.

General Procedure for Preparation of 13 via the One-Pot, Three-Step Cascade Reaction. Under N_2, to a solution of **9a** or **9c** (0.28 mmol, 1.1 equiv) in dry THF (23 mL) was added LiHMDS (1 M in THF, 1.05 mmol, 4.2 equiv) at −78 °C. After the resulting solution was maintained at −78 °C for 30 min, a solution of **10** (0.25 mmol, 1.0 equiv) in THF (1 mL) was slowly added. The resulting solution was maintained at −78 °C for another 3 h. The dr values for the first step of Michael addition were analyzed by LC−MS with a small portion of quenched sample. When the Michael addition was completed, $Cu(OTf)_2$ (0.75 mmol, 3.0 equiv) was added in one portion to the mixture at −78 °C along with exposure to air for 30 s to 5 min. Then the reaction mixture was warmed to ambient temperature slowly and kept at 50 °C charged with nitrogen balloon for 48−60 h. After the reaction was completed, the solution was allowed to cool to room temperature and quenched by pouring into aqueous NH_4Cl (5 mL). The aqueous layer was partitioned with EtOAc (15 mL × 3). The organic layer was separated, successively washed with HCl (1 N, 10 mL), water (10 mL), and aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), and filtered. The solvent was removed in vacuo. Flash chromatography (silica gel) of the crude reaction mixture afforded pure product **13**.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-phenyldihydrofuran-2,2(3H)-dicarboxylate (**13a**):* R_f = 0.20 (petroleum/EtOAc 4:1); 90 mg, 88% yield, yellow oil; $[\alpha]_D^{22}$ −48.0 (*c* 1.2, $CHCl_3$); IR (KBr) 2983, 1751, 1664, 1438, 1300, 1217, 1054, 757 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.44−7.33 (m, 5H), 4.26 (d, *J* = 11.6 Hz, 1H), 3.85 (s, 3H), 3.53 (m, 1H), 3.40 (s, 3H), 1.89 (m, 1H), 1.70 (m, 1H), 1.21 (s, 9H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 171.4, 166.2, 165.7, 134.2, 128.7, 128.5, 128.3, 90.0, 55.5, 53.0, 52.4, 51.7, 46.2, 23.0, 21.2, 10.5; HRMS (ESI-TOF) calcd for $C_{20}H_{27}NNaO_6S$ $[M + Na]^+$ 432.1451, found 432.1449.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(2-fluorophenyl)dihydrofuran-2,2(3H)-dicarboxylate (**13b**):* R_f = 0.30 (petroleum/EtOAc 5:1); 56 mg, 52% yield, light yellow oil; $[\alpha]_D^{24}$ −57.0 (*c* 0.5, $CHCl_3$); IR (KBr) 2962, 2926, 1752, 1666, 1457, 1297, 1236, 1202, 1090, 1057, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.04 (m, 4H), 4.35 (br s, 1H), 3.85 (s, 3H), 3.49 (br s, 3H), 3.40 (br s, 1H), 1.91 (br s, 1H), 1.71 (m, 1H), 1.28 (s, 9H), 0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 166.0, 165.6, 162.7−160.2 (d, *J* = 250.0 Hz), 130.2, 130.3−130.0 (d, *J* = 25.1 Hz), 124.4 (d, *J* = 3.0 Hz), 116.2 (d, *J* = 22.8 Hz), 89.3, 56.6, 54.9, 53.8, 53.0, 46.9, 23.8, 21.9, 11.1; HRMS (ESI-TOF) calcd for $C_{20}H_{26}FNNaO_6S$ $[M + Na]^+$ 450.1391, found 450.1388.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(4-fluorophenyl)dihydrofuran-2,2(3H)-dicarboxylate (**13c**):* R_f = 0.35 (petroleum/EtOAc 4:1); 53 mg, 50% yield, colorless oil; $[\alpha]_D^{24}$ −36.7 (*c* 0.3, $CHCl_3$); IR (KBr) 2962, 2927, 1750, 1666, 1513, 1459, 1439, 1301, 1220, 1090, 1057, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.04 (m, 2H), 4.10 (d, *J* = 12.8 Hz, 1H), 3.86 (s, 3H), 3.39 (s, 3H), 3.33 (m, 1H), 1.87 (m, 1H), 1.69 (m, 1H), 1.27 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.8−163.4 (d, *J* = 247.1 Hz), 130.2 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 20.7 Hz), 89.7, 56.5, 53.8, 52.9, 51.1, 46.4, 23.3, 21.9, 11.2; HRMS (ESI-TOF) calcd for $C_{20}H_{26}FNNaO_6S$ $[M + Na]^+$ 450.1391, found 450.1392.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(p-tolyl)dihydrofuran-2,2(3H)-dicarboxylate (**13d**):* R_f = 0.25 (petroleum/EtOAc 4:1); 91 mg, 86% yield, colorless oil; $[\alpha]_D^{24}$ −27.1 (*c* 0.8, $CHCl_3$); IR (KBr) 2959, 2925, 1750, 1665, 1438, 1300, 1238, 1089, 1055, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.06 (d, *J* = 11.6 Hz, 1H), 3.85 (s, 3H), 3.37 (s, 3H), 3.37 (overlapped, 1H), 2.33 (s, 3H), 1.87 (m, 1H), 1.68 (m, 1H), 1.28 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.3, 165.9, 138.3, 129.3, 128.3, 89.9, 56.4, 53.6, 52.8, 51.6, 46.4, 23.2, 21.8, 21.0, 12.0; HRMS (ESI-TOF) calcd for $C_{21}H_{29}NNaO_6S$ $[M + Na]^+$ 446.1608, found 446.1615.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(2-methoxyphenyl)dihydrofuran-2,2(3H)-dicarboxylate (**13e**):* R_f = 0.30 (petroleum/EtOAc 4:1); 93 mg, 85% yield, light yellow oil; $[\alpha]_D^{17}$ −43.9 (*c* 0.5, $CHCl_3$); IR (KBr) 2960, 1753, 1662, 1497, 1462, 1293, 1253, 1207, 1090, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m. 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.89 (m, 2H), 4.47 (br s, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.40 (brs, 4H), 3.40 (overlapped, 1H), 1.84 (br s, 1H), 1.67 (br s, 1H), 1.28 (s, 9H), 0.95 (brs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 165.9, 157.9, 129.5, 123.3, 120.6, 110.9, 110.7, 89.8, 56.3, 55.3, 53.7, 52.5, 47.8, 46.9, 21.9, 21.7, 11.2; HRMS $(M+H)^+$ calcd for $C_{21}H_{29}NO_7SH^+$ 440.1743, found 440.1730; HRMS (ESI-TOF) calcd for $C_{21}H_{29}NNaO_6S$ $[M + Na]^+$ 446.1608, found 446.1615.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(3-methoxyphenyl)dihydrofuran-2,2(3H)-dicarboxylate (**13f**):* R_f = 0.35 (petroleum/EtOAc 4:1); 61 mg, 56% yield, yellow oil; $[\alpha]_D^{22}$ −34.4 (*c* 0.6, $CHCl_3$); IR (KBr) 2961, 1749, 1663, 1458, 1263, 1091, 1054, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 1H), 6.84−6.76 (m, 3H), 4.01 (d, *J* = 12.0 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.31 (s, 3H), 3.31 (overlapped, 1H), 1.83 (m, 1H), 1.64 (m, 1H), 1.21 (s, 9H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.2, 159.8, 129.6, 120.2, 114.7, 113.8, 89.9, 56.4, 55.2, 53.7, 52.9, 51.8, 46.5, 23.3, 21.9, 11.2; HRMS (ESI-TOF) calcd for $C_{21}H_{30}NO_7S$ $[M + H]^+$ 440.1743, found 440.1750.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(4-methoxyphenyl)dihydrofuran-2,2(3H)-dicarboxylate (**13g**):* R_f = 0.20 (petroleum/EtOAc 4:1); 91 mg, 83% yield, colorless oil; $[\alpha]_D^{22}$ −47.1 (*c* 0.7, $CHCl_3$); IR (KBr) 2960, 2877, 1748, 1663, 1516, 1460, 1439, 1298, 1258, 1184, 1090, 1054, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.05 (d, *J* = 12.8 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.40 (s, 3H), 3.39 (s, 1H), 1.69 (m, 1H), 1.66 (m, 1H), 1.28 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 171.9, 166.3, 166.0, 159.6, 129.5, 114.0, 89.6, 56.4, 55.2, 53.6, 52.9, 51.2, 46.4, 23.2, 21.8, 11.2; HRMS (ESI-TOF) calcd for $C_{21}H_{30}NO_7S$ $[M + H]^+$ 440.1743, found 440.1752.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-3-(3,4-dimethoxyphenyl)-4-ethyldihydrofuran-2,2(3H)-dicarboxylate (**13h**):* R_f = 0.35 (petroleum/EtOAc 4:1); 88 mg, 75% yield, colorless oil; $[\alpha]_D^{23}$ −28.8 (*c* 0.4, $CHCl_3$); IR (KBr) 2960, 2934, 1749, 1663, 1520, 1462, 1265, 1204, 1090, 1056, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89−6.80 (m, 3H), 4.04 (d, *J* = 11.2 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.39 (m, 3H), 3.37 (overlapped, 1H), 1.88 (m, 1H), 1.69 (m, 1H), 1.28 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 166.4, 166.2, 153.2, 138.0, 105.5, 89.8, 60.8, 56.2, 53.7, 53.0, 51.9, 46.6, 23.3, 21.9, 11.3; HRMS (ESI-TOF) calcd for $C_{22}H_{31}NNaO_8S$ $[M + Na]^+$ 492.1668, found 492.1686.

*(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(naphthalen-1-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13i**):* R_f = 0.40 (petroleum/EtOAc 2:1); 98 mg, 86% yield, colorless oil; $[\alpha]_D^{23}$ −2.3 (*c* 0.9, $CHCl_3$); IR (KBr) 2961, 2918, 1750, 1663, 1437, 1296,

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1202, 1088, 798 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (brs, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.63 (m, 1H), 7.43 (m, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.53 (m, 1H), 5.15 (br s, 1H), 3.84 (s, 3H), 3.40 (br s, 1H), 3.16 (br s, 3H), 1.90 (br s, 1H), 1.69 (br s, 1H), 1.32(s, 9H), 0.93 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 166.1, 134.0, 132.2, 132.0, 129.1, 128.8, 126.7, 126.1, 124.7, 124.1, 123.4, 91.1, 56.6, 53.9, 52.5, 50.5, 45.6, 24.5, 22.0, 11.4; HRMS (ESI-TOF) calcd for $C_{24}H_{29}NNaO_6S$ $[M + Na]^+$ 482.1608, found 482.1614.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(naphthalen-2-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13j**): R_f = 0.35 (petroleum/EtOAc 2:1); 70 mg, 61% yield, colorless oil; $[\alpha]_D^{21}$ −15.1 (*c* 0.5, $CHCl_3$); IR (KBr) 2961, 2929, 1749, 1664, 1437, 1298, 1237, 1201, 1090, 1056, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 4H), 7.50 (m, 2H), 7.43 (d, J = 8.8 Hz, 1H), 4.28 (d, J = 12.0 Hz, 1H), 3.87 (s, 3H), 3.53 (br s, 1H), 3.25 (s, 3H), 1.92 (m, 1H), 1.73 (m, 1H), 1.30 (s, 9H), 0.92 (t. J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 166.4, 166.0, 133.2, 133.1, 128.4, 127.9, 127.6, 126.5, 125.7, 89.9, 56.5, 53.7, 52.9, 52.1, 46.6, 23.4, 21.9, 11.3; HRMS (ESI-TOF) calcd for $C_{24}H_{29}NNaO_6S$ $[M + Na]^+$ 482.1608, found 482.1595.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-methyl-3-(naphthalen-1-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13k**): R_f = 0.40 (petroleum/EtOAc 4:1); 90 mg, 81% yield, yellow oil; $[\alpha]_D^{19}$+39.1 (*c* 0.9, $CHCl_3$); IR (KBr) 2958, 2928, 1751, 1667, 1437, 1292, 1233, 1203, 1089, 1046, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.88−7.82 (m, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 4.98 (br s, 1H), 3.83 (s, 3H), 3.50 (br s, 1H), 3.26 (br s, 3H), 1.32 (s, 9H), 1.22 (overlapped, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 134.1, 129.3, 128.8, 126.7, 126.1, 124.7, 123.5, 90.3, 56.6, 53.9, 52.6, 48.3, 43.9, 21.9, 15.5; HRMS (ESI-TOF) calcd for $C_{23}H_{28}NO_6S$ $[M + H]^+$ 446.1632, found 446.1617.

(3R,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(thiophene-2-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13l**): R_f = 0.35 (petroleum/EtOAc 2:1); 70 mg, 67% yield, yellow oil; $[\alpha]_D^{24}$ −57.8 (*c* 0.2, $CHCl_3$); IR (KBr) 2960, 2929, 1749, 1666, 1437, 1031, 1255, 1199, 1092, 1056, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (overlapped, 1H), 7.08 (d, J = 3.2 Hz, 1H), 6.99 (t, J = 4.8 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 3.34 (br s, 1H), 1.91 (m, 1H), 1.78 (m, 1H), 1.27 (s, 9H), 0.99 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 166.0, 165.8, 136.4, 127.4, 127.1, 125.7, 89.5, 56.5, 53.8, 53.2, 47.8, 47.2, 22.9, 21.8, 11.0; HRMS (ESI-TOF) calcd for $C_{18}H_{26}NO_6S_2$ $[M + H]^+$ 416.1202, found 416.1227.

(3R,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-methyl-3-(thiophene-2-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13m**): R_f = 0.30 (petroleum/EtOAc 2:1); 50 mg, 50% yield, colorless oil; $[\alpha]_D^{20}$ −17.6 (*c* 0.4, $CHCl_3$); IR (KBr) 2958, 2927, 1749, 1668, 1455, 1437, 1292, 1231, 1200, 1092, 1059, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 1H), 7.09 (d, J = 2.8 Hz, 1H), 7.01 (m, 1H), 4.19 (d, J = 12.8 Hz, 1H), 3.89 (s, 3H), 3.46 (s, 3H), 3.42 (m, 1H), 1.37 (d, J = 6.4 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.6, 135.7, 127.5, 127.2, 125.9, 89.4, 56.5, 53.8, 53.2, 49.8, 42.0, 21.8, 14.6; HRMS (ESI-TOF) calcd for $C_{17}H_{24}NO_6S_2$ $[M + H]^+$ 402.1045, found 402.1027.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-4-ethyl-3-(furan-2-yl)dihydrofuran-2,2(3H)-dicarboxylate (**13n**): R_f = 0.45 (petroleum/EtOAc 1:1); 27 mg, 27% yield, yellow oil; $[\alpha]_D^{22}$ −58.8 (*c* 0.2, $CHCl_3$); IR (KBr) 2960, 2929, 1753, 1667, 1459, 1438, 1300, 1220, 1201, 1058, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.36 (dd, J = 16.0, 3.2 Hz, 2H), 4.15 (d, J = 12.4 Hz, 1H), 3.86 (s, 3H), 3.55 (s, 3H), 3.43 (m, 1H), 1.92 (m, 1H), 1.68 (m, 1H), 1.27 (s, 9H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.7, 147.4, 142.7, 111.0, 110.3, 87.8, 56.5, 53.8, 53.6, 46.3, 45.1, 23.2, 21.8, 10.8; HRMS (ESI-TOF) calcd for $C_{18}H_{25}NNaO_7S$ $[M + Na]^+$ 422.1244, found 422.1250.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-3-(furan-2-yl)-4-methyldihydrofuran-2,2(3H)-dicarboxylate (**13o**): R_f = 0.40 (petroleum/EtOAc 1:1); 24 mg, 25% yield, yellow oil; $[\alpha]_D^{23}$ +30.5 (*c* 0.2, $CHCl_3$); IR (KBr) 2959, 2918, 1753, 1668, 1456, 1438, 1292, 1221, 1091, 1221, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.37 (dd, J = 15.2, 3.2 Hz, 2H), 4.01 (d, J = 12.4 Hz, 1H), 3.68 (s, 3H), 3.55 (s, 3H), 3.49 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 146.9, 142.9, 110.9, 110.4, 89.0, 56.5, 53.8, 53.6, 48.6, 39.4, 21.8, 14.6; HRMS (ESI-TOF) calcd for $C_{17}H_{23}NNaO_7S$ $[M + Na]^+$ 408.1087, found 408.1095.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-butylsulfinyl)imino)-3-(furan-3-yl)-4-methyldihydrofuran-2,2(3H)-dicarboxylate (**13p**): R_f = 0.25 (petroleum/EtOAc 3:1); 25 mg, 26% yield, white solid; $[\alpha]_D^{22}$ −42.2 (*c* 0.2, $CHCl_3$); IR (KBr) 2958, 2926, 1750, 1667, 1456, 1294, 1233, 1090, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 18.0 Hz, 2H), 6.35 (s, 1H), 3.87 (s, 3H), 3.79 (d, J = 12.4 Hz, 1H), 3.52 (s, 3H), 3.27 (m. 1H), 1.33 (d, J = 7.2 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 166.3, 165.9, 143.6, 141.6, 118.3, 109.5, 89.3, 56.5, 53.7, 53.0, 46.0, 40.5, 30.9, 21.8, 14.5; HRMS (ESI-TOF) calcd for $C_{17}H_{23}NNaO_7S$ $[M + Na]^+$ 408.1087, found 408.1091.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-Butylsulfinyl)imino)-3-(4-methoxyphenyl)-4-methyldihydrofuran-2,2(3H)-dicarboxylate (**13r**). Compound **13r** was prepared according to the general procedure for preparation of **13** on a gram scale (**10g**, 3.95 g, 15.6 mmol) to afford 5.04 g (75% yield): light yellow amorphous powder; R_f = 0.30 (petroleum/EtOAc 2:1); $[\alpha]_D^{22}$ −3.7 (*c* 0.4, $CHCl_3$); IR (KBr) 2954, 1748, 1665, 1613, 1515, 1456, 1292, 1256, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (overlapped, 2H), 6.87 (d, J = 8.0 Hz, 2H), 3.9 (d, J = 12.4 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.40 (s, 3H), 3.40 (overlapped, 1H), 1.28 (s, 9H), 1.28 (overlapped, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.9, 159.7, 129.5, 114.1, 89.3, 56.5, 55.2, 53.7, 53.6, 52.9, 40.5, 21.8, 14.5; HRMS (ESI-TOF) calcd for $C_{20}H_{27}NNaO_7S$ $[M + Na]^+$ 448.1400, found 448.1410.

(3S,4R,Z)-Dimethyl 5-(((R)-tert-Butylsulfinyl)imino)-4-ethyl-3-phenyl-(^{18}O)-dihydrofuran-2,2(3H)-dicarboxylate (**13q**). Under N_2, to a solution of **9a** (0.28 mmol, 1.1 equiv) in dry degassed THF (13 mL) was added LiHMDS (1 M in THF, 1.05 mmol, 4.2 equiv) slowly. After the resulting solution was maintained at −78 °C for 30 min, a solution of **10a** (0.25 mmol, 1.0 equiv) in dry degassed THF (1 mL) was slowly added. When the Michael addition reaction was complete, the mixture was transferred to a solution of $Cu(OTf)_2$ (0.75 mmol, 3.0 equiv) in dry degassed THF (10 mL) via syringe, and the solution was kept at −78 °C and charged with $^{18}O_2$-gas balloon. The mixture was warmed to 50 °C for 15 h. After the reaction was completed, the solution was allowed to cool to ambient temperature and quenched by pouring into aqueous NH_4Cl (2 mL). The aqueous layer was partitioned with EtOAc (15 mL × 3). The organic layer was separated , washed with with HCl (1 N, 10 mL), water (10 mL), and then aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. Flash chromatography (silica gel) of the crude reaction mixture afforded pure product as colorless oil: R_f = 0.20 (petroleum/EtOAc 4:1); 68 mg, 65% yield; $[\alpha]_D^{17}$ −46.6 (*c* 0.7, $CHCl_3$); IR (KBr) 2959, 1750, 1665, 1457, 1438, 1299, 1193, 1092, 1047, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 5H), 4.14 (d, J = 7.2 Hz, 1H), 4.11 (s, 3H), 3.40 (m, 1H), 3.33 (s, 3H), 1.88 (m, 1H), 1.70 (m, 1H), 1.28 (s, 9H), 0.92 (t, 3H); HRMS (ESI-TOF) calcd for $C_{20}H_{27}NO_5{}^{18}OS$ $[M + H]^+$ 412.1680, found 412.1682.

(3S,4R)-Dimethyl 4-Ethyl-5-oxo-3-phenyldihydrofuran-2,2(3H)-dicarboxylate (**17**). To a solution of **13a** (66 mg, 0.16 mmol) in DCM (6.6 mL) cooled in an ice−water bath was added TFA (118 uL, 1.60 mmol). The mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of sat. $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (5 mL × 3), dried over Na_2SO_4 ,and then concentrated. The resulting residue was purified by column chromatography (silica gel) to give **17** (36 mg, 82%) as a white solid. R_f = 0.20 (petroleum/EtOAc 10:1); $[\alpha]_D^{23}$ +31.9 (*c* 0.2, DCM); IR (KBr) 2961, 2927, 1799, 1748, 1457, 1437, 1298, 1260, 1170, 1109, 1058, 933, 801, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.35 (m, 5H), 4.18 (d, J = 12.0 Hz, 1H), 3.85 (s, 3H), 3.37 (s, 3H), 3.18−3.21 (m, 1H), 1.78−1.83 (m, 1H), 1.68−1.73 (m, 1H), 0.91 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 166.5, 166.4, 134.0, 128.7, 128.4, 128.5, 86.3, 53.6, 52.9, 51.1, 44.1, 22.3, 10.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NaO_6$ $[M + Na]^+$ 329.0996, found 329.1006.

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*(2R,3S,4R)-Methyl 4-Ethyl-2-(hydroxymethyl)-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (**18**).* To a solution of **17** (60 mg, 0.2 mmol) in dry THF (6 mL) at 0 °C was added $NaBH_4$ (1.2 mg, 0.4 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of satd NaCl solution at 0 °C. The mixture was extracted with EtOAc (5 mL × 3), dried over Na_2SO_4, and then concentrated. The resulting residue was purified by column chromatography (silica gel) to give **18** (27 mg, 50%) as colorless oil: R_f = 0.20 (petroleum/EtOAc 2:1); $[\alpha]_D^{22}$ −22.8 (*c* 0.5, DCM); IR (KBr) 3450, 2965, 1779, 1745, 1639, 1458, 1258, 1188, 1065, 966, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.36 (m, 3H), 7.19 (d, *J* = 6.8 Hz, 2H), 4.04−4.09 (m, 1H), 3.90−3.95 (m, 1H), 3.78−3.82 (m, 1H), 3.46 (s, 3H), 3.29−3.32 (m, 1H), 1.20−2.03 (m, 1H) 1.81−1.83 (m, 1H), 1.68−1.71 (m, 1H), 0.893 (t, *J* = 7.6 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.9, 134.0, 129.0, 128.5, 127.9, 87.9, 62.0, 52.3, 49.9, 44.1, 22.4, 10.9; HRMS (ESI-TOF) calcd for $C_{15}H_{18}NaO_5$ $[M + Na]^+$ 301.1046, found 301.1059.

*(2R,3S,4R)-Methyl 2-Acetyl-4-ethyl-5-oxo-3-phenyltetrahydrofuran-2-carboxylate (**19**).* To a solution of **17** (100 mg, 0.33 mmol) in dry DCM (5 mL) at−48 °C was added MeMgBr (3 M in Et_2O, 220 uL, 0.66 mmol). The mixture was stirred at−48 °C for 1 h and was then quenched by the addition of satd NH_4Cl solution. The mixture was extracted with EtOAc (5 mL × 3), dried over Na_2SO_4, and then concentrated. The resulting residue was purified by column chromatography (silica gel) to give **19** (76 mg, 80%) as a white solid: R_f = 0.20 (petroleum/EtOAc 10:1); $[\alpha]_D^{23}$ +82.7 (*c* 0.4, DCM); IR (KBr) 2968, 2929, 2879, 1795, 1732, 1501, 1457, 1261, 1212, 1165, 1099, 1057, 998, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.34 (m, 5H), 4.12 (d, *J* = 11.6 Hz, 1H), 3.36 (s, 3H), 3.20−3.26 (m, 1H), 2.31 (s, 3H), 1.77−1.84 (m, 1H), 1.64−1.71 (m, 1H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0, 175.5, 166.9, 134.4, 128.7, 128.5, 128.3, 89.6, 52.8, 49.1, 44.6, 26.6, 22.5, 10.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NaO_5$ $[M + Na]^+$ 313.1046, found 313.1042.

*(3S,4R)-Dimethyl 4-Ethyl-3-phenyldihydrofuran-2,2(3H)-dicarboxylate (**20**).* To a freshly distilled $CHCl_3$ solution (2 mL) in a screw-capped vial under N_2 atmosphere were added successively **17** (40 mg, 0.13 mmol) in 0.5 mL of $CHCl_3$, a catalytic amount of $InBr_3$ (2.4 mg, 0.05 equiv), and Et_3SiH (84 uL, 0.52 mmol), and the vial was sealed with a cap containing a PTFE septum. During the stirring of the reaction mixture at 65 °C, the solution turned from colorless to yellow and then to orange. The reaction was monitored by TLC until consumption of the starting lactone. The mixture was added H_2O (3 mL) at room temperature, and the resulting orange suspension was stirred continuously until the color disappeared. The aqueous layer was extracted with CH_2Cl_2 (2 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and then evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel) to give the corresponding **20** (28 mg, 73%) as colorless oil: R_f = 0.20 (petroleum/acetone 20:1); $[\alpha]_D^{19}$ +2.8 (*c* 0.4, DCM); IR (KBr) 2957, 1742, 1498, 1436, 1286, 1219, 1115, 1071, 1036, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.30 (m, 4H), 7.22−7.25(m, 1H), 4.53 (t, *J* = 8.0 Hz, 1H), 3.87 (d, *J* = 10.4 Hz, 1H,), 3.80 (s, 3H), 3.65 (t, *J* = 9.2 Hz, 1H,), 3.24 (s, 3H), 2.70−2.76 (m, 1H), 1.50−1.55 (m, 1H), 1.29−1.37 (m, 1H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.8, 137.1, 128.7, 128.3, 127.5, 90.9, 74.6, 56.5, 53.1, 52.0, 46.4, 24.1, 12.6; HRMS (ESI-TOF) calcd for $C_{16}H_{20}NaO_5$ $[M + Na]^+$ 315.1203, found 315.1200.

*(3S,4R)-4-Ethyl-3-phenyldihydrofuran-2(3H)-one (**21**).* Compound **20** (28 mg, 0.096 mmol) was stirred vigorously with 20% aqueous KOH (2.5 mL) at room temperature for 30 h. After the resulting solution was washed with ether and cooled to 0 °C, the solution was adjusted to pH 2 with ice-cold 20% HCl and extracted with ether. Evaporation of ether provided the acid as white solid, which was used for the next step without further purification. The acid (36 mg) in acetonitrile (2 mL) was added to a solution of ceric ammonium nitrate (332 mg, 0.480 mmol) in water (0.6 mL), and the mixture was magnetically stirred vigorously for 3 h at room temperature. The reaction solution was poured into saturated aqueous NaCl (8 mL), and the resulting mixture was extracted with EtOAc (4 mL × 3). The combined extracts were washed with saturated brine (2 mL × 3) and then saturated aqueous $NaHCO_3$ (3 mL), dried (Na_2SO_4), and filtered. The crude product was purified by column chromatography (silica gel) to afford lactone **21** (13.5 mg, 80%) as a white solid: R_f = 0.20 (petroleum/EtOAc 20:1); $[\alpha]_D^{19}$ +37.3 (*c* 0.2, DCM) [lit.[8d] $[\alpha]_D^{25}$ +33.9 (*c* 1.0, DCM)]; IR (KBr) 2963, 2927, 1775, 1457, 1381, 1265, 1157, 1018, 801, 749, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.39 (m, 2H), 7.29−7.32 (m, 1H), 7.21−7.23 (m, 2H), 4.53−4.57 (dd, *J* = 8.8, 7.6 Hz, 1H), 3.97 (t, *J* = 8.8 Hz, 1H,), 3.38 (d, *J* = 10.8 Hz, 1H,), 2.55−2.61 (m, 1H), 1.68−1.74 (m, 1H), 1.46−1.54 (m, 1H), 0.90 (t, *J* = 7.6 Hz, 3H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 136.2, 128.9, 128.5, 127.7, 71.4, 52.6, 46.5, 24.8, 11.3; HRMS (ESI-TOF) calcd for $C_{12}H_{14}NaO_2$ $[M + Na]^+$ 213.0886, found 213.0896.

*(3S,4R)-Dimethyl 4-Ethyl-5-methylene-3-phenyldihydrofuran-2,2(3H)-dicarboxylate (**22**).* A mixture of **17** (30 mg, 0.099 mmol) in 1.5 mL of dry THF and 0.99 mmol of dimethyltitanocene (4.5 mL of a 0.22 M solution) was heated at 65 °C for 12 h under argon, with shielding light. The reaction was checked by TLC until consumption of the starting lactone. The reaction was quenched with 5% NaOH (3 mL) and saturated brine (3 mL). The resulting mixture was extracted with EtOAc (5 mL × 3). The extracts were concentrated under vacuum to give a brown oil. Column chromatography (silica gel) provided **22** (20 mg, 68%) as a white solid: R_f = 0.20 (petroleum/EtOAc 10:1). $[\alpha]_D^{19}$ +40.4 (*c* 0.3, DCM); IR (KBr) 2960, 1753, 1662, 1497, 1462, 1438, 1293, 1253, 1207, 1090, 1052, 936, 792, 758, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.31(m, 5H), 4.60 (s, 1H), 4.08 (s, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.82 (s, 3H), 3.32 (s, 3H), 3.19−3.21 (m, 1H), 1.61−1.65 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 167.7, 164.0, 136.5, 128.5, 128.4, 127.8, 90.1, 82.5, 53.6, 53.3, 52.3, 46.4, 24.5, 10.1; HRMS (ESI-TOF) calcd for $C_{17}H_{20}NaO_5$ $[M + Na]^+$ 327.1203, found 327.1210.

*(2R,3S,4R)-Methyl 4-Ethyl-2,5-bis(hydroxymethyl)-3-phenyltetrahydrofuran-2-carboxylate (**23**).* To a solution of **22** (22 mg, 0.072 mmol) in dry THF (1.0 mL) at 0 °C was added $BH_3{\cdot}Me_2S$ (12 uL, 0.216 mmol). The mixture was stirred at 0 °C for 5 h, and then a solution of $NaBO_3{\cdot}4H_2O$ (222 mg, 1.440 mmol) in water (2.2 mL) was added. The mixture was stirred at rt for 12 h, and then satd NaCl solution (2 mL) was added. The mixture was extracted five times with EtOAc, dried over Na_2SO_4, and then concentrated. The resulting residue was purified by column chromatography (silica gel) to give a white solid **23** (8 mg, 40%) as a mixture of two inseparable diastereomers (dr 1:1.5), R_f = 0.20 (petroleum/EtOAc 2:1). Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.31 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 4.16 (d, *J* = 9.6 Hz, 1H), 4.09 (d, *J* = 12.6 Hz, 1H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.88 (dd, *J* = 12.0, 10.8 Hz, 1H), 3.73 (overlapped, 1H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.29 (s, 3H), 2.97−3.02 (m, 1H), 2.80 (m, 1H, OH), 2.10−2.13 (m, 1H, OH), 1.42−1.47 (m, 2H), 0.78 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 136.3, 128.6, 128.2, 127.7, 89.5, 86.4, 63.8, 62.5, 56.0, 53.4, 52.0, 41.9, 23.5, 11.6. Minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (overlapped, 3H), 7.14 (d, *J* = 7.2 Hz, 2H), 4.61−4.63 (m, 1H, OH), 3.89 (m, 3H), 3.74−3.80 (m, 2H), 3.61 (d, *J* = 12.6 Hz, 1H), 3.37 (s, 3H), 3.03−3.08 (m, 1H), 2.90 (m, 1H, OH), 1.51−1.53 (m, 1H), 1.42−1.47 (m, 1H), 0.88 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 136.2, 128.5, 128.1, 127.6, 90.0, 81.6, 63.1, 62.9, 53.4, 53.2, 51.6, 45.6, 21.0, 13.4; HRMS (ESI-TOF) calcd for $C_{16}H_{22}NaO_5$ $[M + Na]^+$ 317.1359, found 317.1365.

*(2R,3S,4R,Z)-Methyl 5-(((R)-tert-Butylsulfinyl)imino)-3-(4-methoxyphenyl)-4-methyl-2-undecanoyltetrahydrofuran-2-carboxylate (**24**).* A freshly prepared Grignard reagent $BrMgC_{10}H_{21}$ (1 M in Et_2O, 4.5 mmol, 1.5 equiv) was added dropwise to a stirred suspension of **13r** (1.28 g, 3.0 mmol, 1.0 equiv) in dry THF (80 mL) under N_2 at −40 °C. After the reaction was stirred at −40 °C for 1 h, aqueous NH_4Cl (20 mL) was added at this temperature. The reaction mixture was warmed to room temperature and then extracted with EtOAc (30 mL × 3). The combined organic phases were washed with water and brine and then concentrated. Purification by chromatography (silica gel) afforded 0.85 g of **24** (53%) as colorless oil: R_f = 0.20 (petroleum/EtOAc 8:1); $[\alpha]_D^{27}$ −15.3 (*c* 0.4, $CHCl_3$); IR (KBr) 2927, 2855, 1733,

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1665, 1613, 1516, 1459, 1362, 1294, 1255, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 6.4 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.77 (overlapped, 1H), 3.36 (s, 3H), 3.38 (overlapped, 1H), 2.76 (dt, J = 18.0, 7.2 Hz, 1H), 2.48 (dt, J = 18.0, 7.2 Hz, 1H), 1.58 (m, 2H), 1.26−1.21 (26H), 0.85 (t, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.1, 172.2, 166.7, 159.4, 129.6, 125.1, 114.0, 93.3, 56.3, 55.2, 52.8, 52.2, 40.9, 39.1, 31.8, 29.5, 29.3, 29.2, 28.8, 23.1, 22.6, 21.8, 14.4, 14.0; HRMS (ESI-TOF) calcd for $C_{29}H_{45}NNaO_6S$ $[M + Na]^+$ 558.2865, found 558.2882.

*(R,Z)-N-((3R,4S,5R)-4-(4-Methoxyphenyl)-3-methyl-5-undecanoyldihydrofuran-2(3H)-ylidene)-2-methylpropane-2-sulfinamide (**25**).* LiCl (0.34 g, 8.0 mmol, 5 equiv) was added to a solution of **24** (0.85 g, 1.6 mmol, 1 equiv) in DMF (25 mL) at room temperature. The resulting suspension was heated at 100 °C for 1 h until TLC showed complete conversion of the substrate. Then water (10 mL) was added at room temperature, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered. The solvent was removed under reduced pressure. The residue was subjected to flash column chromatography to yield 0.45 g (60%) **25** as colorless oil: R_f = 0.20 (petroleum/EtOAc 6:1); $[\alpha]_D^{28}$ −71.0 (c 0.2, $CHCl_3$); IR (KBr) 2927, 2855, 1724, 1655, 1516, 1461, 1254, 1181, 1080, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.75 (d, J = 9.6 Hz, 1H), 3.79 (s, 3H), 3.03 (br s, 2H), 2.61 (m, 2H), 1.54 (m, 2H), 1.24 (26H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.0, 159.4, 128.7, 114.3, 89.3, 56.0, 55.3, 52.4, 45.4, 38.7, 31.9, 29.5, 29.4, 29.3, 29.0, 22.7, 22.6, 21.8, 14.1; HRMS (ESI-TOF) calcd for $C_{27}H_{43}NNaO_4S$ $[M + Na]^+$ 500.2805, found 500.2808.

*(R,Z)-N-((3R,4S,5R)-5-(1-Hydroxyundecyl)-4-(4-methoxyphenyl)-3-methyldihydrofuran-2(3H)-ylidene)-2-methylpropane-2-sulfinamide (**26**).* To a solution of **25** (450 mg, 0.94 mmol, 1.0 equiv) in MeOH (45 mL) was added a solution of $NaBH_4$ (40 mg, 1.04 mmol, 1.1 equiv) in EtOH (45 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then concentrated. The residue was taken up in EtOAc (100 mL). The mixture was washed with water (20 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to give an inseparable mixture of two diastereomers **26** (450 mg, 92%, 2:1 dr) as colorless oil, which was used for next step without purification. For the crude major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 4.60 (d, J = 8.8 Hz, 1H), 4.09 (m, 1H), 3.80 (s, 3H), 3.29 (t, J = 10.8 Hz, 1H), 2.91 (m, 1H), 1.44 (m, 1H), 1.30−1.07 (29H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 158.9, 131.2, 128.8, 114.4, 91.1, 70.3, 55.2, 47.9, 46.1, 31.8, 31.4, 29.5, 29.4, 29.3, 29.2, 22.6, 21.7, 14.1. Minor isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.35 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 3.45 (d, J = 8.4 Hz, 1H), 3.27 (t, J = 10.0 Hz, 1H), 2.99 (m, 1H), 1.62 (m, 1H), 1.30−1.07 (29H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 159.1, 129.2, 128.9, 114.5, 91.3, 70.0, 55.4, 50.7, 47.7, 34.2, 31.8, 29.5, 29.4, 29.3, 29.2, 25.8, 21.7, 14.0 cm^{-1}.

*(R,Z)-N-((3R,4S,5S)-4-(4-Methoxyphenyl)-3-methyl-5-undecyldihydrofuran-2(3H)-ylidene)-2-methylpropane-2-sulfinamide (**27**).* Step 1: Under N_2, to the solution of **26** (450 mg, 0.94 mmol, 1.0 equiv) in DCE (45 mL) were added $(imidazolyl)_2CS$ (836 mg, 4.70 mmol, 5.0 equiv) and a catalytic amount of DMAP (11 mg, 0.09 mmol, 0.1 equiv) at room temperature. The reaction temperature was gradually increased to 80 °C. After being stirred overnight, the reaction mixture was concentrated, diluted with EtOAc (100 mL), and washed with water (20 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to give pale yellow oil (335 mg).

Step 2: At room temperature, the pale yellow oil (335 mg, 0.57 mmol, 1.0 equiv) was dissolved in toluene (40 mL), to which were added Bu_3SnH (0.38 mL, 1.42 mmol, 2.5 equiv) and AIBN (28 mg, 0.17 mmol, 0.3 equiv) under N_2, and the mixture was kept at 40 °C for 5 h. When the reaction was completed, the reaction mixture was concentrated directly. Column purification gave **27** (175 mg, 48% over two steps) as oil: R_f = 0.20 (petroleum/EtOAc 6:1); $[\alpha]_D^{29}$ −61.3 (c 0.3, $CHCl_3$); IR (KBr) 2926, 2855, 1647, 1614, 1515, 1461, 1253, 1181, 1036 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.39 (m, 1H), 3.80 (s, 3H), 2.94 (m, 1H), 2.70 (t, J = 10.2 Hz, 1H), 1.65 (m, 2H), 1.46 (m, 2H), 1.33−1.20 (28H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 159.2, 128.7, 114.5, 88.9, 56.1, 55.6, 55.3, 46.0, 33.2, 31.9, 29.7, 29.6, 29.5, 29.3, 25.7, 22.7, 21.8, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{27}H_{45}NNaO_3S$ $[M + Na]^+$ 486.3012, found 486.3011.

*(3R,4S,5S)-4-(4-Methoxyphenyl)-3-methyl-5-undecyldihydrofuran-2(3H)-one (**28**).* TFA (0.28 mL, 3.80 mmol, 10 equiv) was added to the solution of **27** (175 mg, 0.38 mmol, 1 equiv) in DCM (20 mL) at 0 °C. The mixture was stirred overnight at room temperature. When the reaction was completed, aqueous $NaHCO_3$ (5 mL) was added slowly in an ice bath. The aqueous layer was partitioned with EtOAc (10 mL × 3). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel) of the reaction mixture gave 122 mg (92%) of pure product **28** as an oil: R_f = 0.20 (petroleum/EtOAc 35:1); $[\alpha]_D^{27}$ −4.3 (c 0.3, CHCl3); IR (KBr) 2926, 2854, 1777, 1613, 1515, 1462, 1253, 1180, 1036, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.31 (m, 1H), 3.81 (s, 3H), 2.73 (m, 2H), 1.64−1.19 (m, 23H), 0.87 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 159.2, 129.2, 128.6, 114.5, 84.5, 56.0, 55.3, 43.8, 33.4, 31.9, 29.7, 29.6, 29.5, 29.3, 25.6, 22.6, 14.1, 13.1; HRMS (ESI-TOF) calcd for $C_{23}H_{36}NaO_3$ $[M + Na]^+$ 383.2557, found 383.2568.

*(2S,3R,4R)-4-Methyl-5-oxo-2-undecyltetrahydrofuran-3-carboxylic Acid (**5**).* To a biphasic mixture of **28** (122 mg, 0.34 mmol, 1.00 equiv) and sodium peridate (870 mg, 4.08 mmol, 12.00 equiv) in a mixture solvent of H_2O/CCl_4/MeCN (3:2:2, 7 mL) was added $RuCl_3$ (0.02 mmol, 0.07 equiv) at 0 °C, and the reaction mixture turned yellow then red. After 0.5 h, the ice−water bath was removed, and the reaction mixture was stirred vigorously overnight while the reaction mixture turned black slowly. When the reaction was completed, DCM (10 mL) was added. The aqueous layer was partitioned with EtOAc (10 mL × 3). The organic layer was separated and washed with brine (10 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel) of the crude reaction mixture gave 65 mg (65%) of pure (−)-nephrosteranic acid **5** as a white amorphous powder: R_f = 0.20 (petroleum/EtOAc 3:1); $[\alpha]_D^{28}$ −26.7 (c 0.60, $CHCl_3$) [lit.[8a] $[\alpha]_D^{20}$ −27.2 (c 1.05, $CHCl_3$)]; IR (KBr) 2960, 2925, 2854, 1745, 1727, 1464, 1261, 1074, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (m,1H), 2.98 (m,1H), 2.70 (m, 1H), 1.80 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.43−1.26 (m, 20H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.5, 175.0, 79.3, 53.8, 39.8, 34.9, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.3, 22.7, 14.5, 14.1; HRMS (ESI-TOF) calcd for $C_{17}H_{29}O_4$ $[M + H]^+$ 297.2071, found 297.2069.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, chromatograms, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on synthesis and isolation of plant lignans, see: (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426. (b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top.*

DOI: 10.1021/jo5029166
J. Org. Chem. 2015, 80, 2494−2502

Curr. Chem. **2005**, *243*, 43. (c) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696. (d) Koch, S. S. C.; Chamberlin, A. R. In *Studies in Natural Product Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1995; Vol. *16*, p 687.

(2) Lin, X.; Switzer, B. R.; Denmark-Wahnefried, W. *Anticancer Res.* **2001**, *21*, 3995.

(3) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 86.

(4) (a) Barnard, E. A.; Skolnick, P.; Olsen, R. W.; Möhler, H.; Sieghart, W.; Biggio, G.; Braestrup, C.; Bateson, A. N.; Langer, S. Z. *Pharmacol. Rev.* **1998**, *50*, 291. (b) Bonnert, T. P.; Olsen, R. W. *Annu. Rev. Neurosci.* **1994**, *17*, 569. (c) Dunn, S. M. J.; Bateson, A. N.; Martin, I. L. *Int. Rev. Neurobiol* **1994**, *36*, 51.

(5) (a) Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod.* **1999**, *62*, 1565. (b) Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751.

(6) (a) Kepner, R. E.; Webb, A. D.; Muller, C. J. *Am. J. Enol. Viticult.* **1972**, *23*, 103. (b) Otsuka, K.; Zenibayashi, Y.; Itoh, M.; Totsuka, A. *Agric. Biol. Chem.* **1974**, *38*, 485. (c) Pollnitz, A. P.; Jones, G. P.; Sefton, M. A. *J. Chromatogr. A* **1999**, *857*, 239.

(7) (a) Ramachandran, P. V.; Nicponski, D. R.; Nair, H. N. G.; Helppi, M. A.; Gagare, P. D.; Schmidt, C. M.; Yip-Schneider, M. T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6911. (b) Ghosh, M. *Tetrahedron* **2007**, *63*, 11710. (c) Kaur, P.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 8231. (d) Hadri, A. E.; Abouabdellah, A.; Thomet, U.; Baur, R.; Furtmüller, R.; Sigel, E.; Sieghart, W.; Dodd, R. H. *J. Med. Chem.* **2002**, *45*, 2824. (e) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J. X. *J. Org. Chem.* **2002**, *67*, 1738.

(8) (a) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1257. (b) Steward, K. M.; Gentry, E. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 7329. (c) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1858. (d) Palomo, C.; Vera, S.; Mielgo, A.; Gmez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984. (e) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (f) Mandal, S. K.; Amin, S. k. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457. (g) Zhang, Q. H.; Lu, X. Y. *J. Am. Chem. Soc.* **2000**, *122*, 7604. (h) Cao, P.; Zhang, X. M. *J. Am. Chem. Soc.* **1999**, *121*, 7708. (i) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q. L. *J. Org. Chem.* **1996**, *61*, 9146.

(9) Colpaert, F.; Mangelinckx, S.; Verniest, G.; Kimpe, N. D. *J. Org. Chem.* **2009**, *74*, 3792.

(10) (a) Zhang, S.; Cheng, K.; Wang, X. H.; Yin, H. *Bioorg. Med. Chem.* **2012**, *20*, 6073. (b) Nickerson, D. M.; Mattson, A. E. *Chem.—Eur. J.* **2012**, *18*, 8310. (c) Mase, N.; Horibe, T. *Org. Lett.* **2013**, *15*, 1854. (d) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833.

(11) For studies on α-alkylation, Mannich-type adition, and aldol addition of *N*-*tert*-butanesulfinyl imidate, see: (a) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652. (b) Colpaert, F.; Mangelinckx, S.; Kimpe, N. D. *J. Org. Chem.* **2011**, *76*, 234. (c) Bartrum, H. E.; Viceriat, A.; Carret, S.; Poisson, J.-F. *Org. Lett.* **2014**, *16*, 1972.

(12) For studies on Michael addition of *N*-*tert*-butanesulfinyl imidate, see: Wang, J. F.; Zhou, Y.; Zhang, L.; Li, Z.; Chen, X. J.; Liu, H. *Org. Lett.* **2013**, *15*, 1508.

(13) A single crystal of **11a** was obtained by recrystallization from acetonitrile. Crystallographic data for **11a** ($C_{21}H_{31}N_1O_6S_1$, mp 46−48 °C) have been deposited with the Cambridge Crystallographic Data Centre (no. CCDC1000388). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. These data are also available in the Supporting Information.

(14) (a) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402. (b) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (c) Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288. (d) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021. (e) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254. (f) Zou, L. W.; Wang, B. M.; Mu, H. F.; Zhang, H. R.; Song, Y. M.; Qu, J. P. *Org. Lett.* **2013**, *15*, 3106.

(15) (a) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1985**, *26*, 3563. (b) Li, D.; Schröder, K.; Bitterlich, B.; Tse, M. K.; Beller, M. *Tetrahedron Lett.* **2008**, *49*, 5976. (c) Yu, J.; Cui, J.; Zhang, C. *Eur. J. Org. Chem.* **2010**, 7020.

(16) (a) Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, *20*, 1499. (b) Schultz, A. G.; Holoboski, M. A. *Tetrahedron Lett.* **1993**, *34*, 3021. (c) Duschek, A.; Kirsch, S. F. *Chem.—Eur. J.* **2009**, *15*, 10713. (d) Miao, C. B.; Wang, Y. H.; Xing, M. L.; Lu, X. W.; Sun, X. Q.; Yang, H. T. *J. Org. Chem.* **2013**, *78*, 11584.

(17) (a) Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1577. (b) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190. (c) Lu, M.; Zhu, D.; Lu, Y. P.; Zeng, X. F.; Tan, B.; Xu, Z. J.; Zhong, G. F. *J. Am. Chem. Soc.* **2009**, *131*, 4562.

(18) (a) Chuang, G. J.; Wang, W. K.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760. (b) Christoffers, J.; Werner, T.; Rössle, M. *Catal. Today* **2007**, *121*, 22. (c) Christoffers, J.; Kauf, T.; Werner, T.; Rössle, M. *Eur. J. Org. Chem.* **2006**, 2601. (d) Christoffers, J.; Werner, T.; Unger, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, 425. (e) Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668. (f) Watanabe, T.; Ishikawa, T. *Tetrahedron Lett.* **1999**, *40*, 7795.

(19) (a) Ivanoff, D.; Spassoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76. (b) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (c) Maryanoff, C. A.; Maryanoff, B. E. D.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839. (d) Dessau, R. M.; Heiba, E. I. *J. Org. Chem.* **1974**, *39*, 3457. (e) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (f) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487. (g) Frazier, R. H.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408. (h) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277.

(20) For recent developments and applications of the anion oxidative coupling reaction, see: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394−15396. (c) Baran, P. S.; C. Guerrero, A.; Ambhaikar, N. B.; Hafensteiner, B. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 606. (d) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083. (e) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (f) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (g) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568. (h) Zuo, Zh. W.; Xie, W. Q.; Ma, D. W. *J. Am. Chem. Soc.* **2010**, *132*, 13226. (i) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894. (j) Zuo, Zh. W.; Ma, D. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008. (k) Fan, F.; Xie, W. Q.; Ma, D. W. *Org. Lett.* **2012**, *14*, 1405. (l) Zhang, D.; Qin, Y. *Acta Chim. Sin.* **2013**, *71*, 13.

(21) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920.

(22) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Kates, M. J.; Schauble, J. H. *J. Org. Chem.* **1994**, *59*, 494.

(23) For isolation, see: (a) Asahina, Y.; Yanagita, M.; Sakurai, Y. *Ber. Dtsch. Chem. Ges. B* **1937**, *70*, 227. For synthesis, see: (b) Mao, B.; Geurts, K.; Fañanás-Mastral, M.; van Zijl, A. W.; Fletcher, S. P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2011**, *13*, 948. (c) Fernandes, R. A.; Chowdhury, A. K. *Eur. J. Org. Chem.* **2011**, 1106. (d) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. J. *Synth. Commun.* **2010**, *40*, 686. (e) Barreto, C. B., Jr.; Pereira, V. L. P. *Tetrahedron Lett.* **2009**, *50*, 6389. (f) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertranda, M. P. *Tetrahedron* **2007**, *63*, 77. (g) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem.—Eur. J.* **2004**, *10*, 4171. (h) Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313. (i) Chhor, R. B.; Nosse, B.; Söergel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem.—Eur. J.* **2003**, *9*, 260. (j) Barros, M. T.; Maycock, C. D.; Venture, M. R. *Org. Lett.* **2003**, *5*, 4097. (k) Jacobi, P. A.; Herradura, P. *Can. J. Chem.* **2001**, *79*, 1727. (l) Takahata, H.; Uchida, Y.; Momose, T. *J. Org. Chem.* **1995**, *60*, 5628. (m) Takahata, H.; Uchida, Y.; Momose, T. *Tetrahedron Lett.* **1994**, *35*, 4123.

DOI: 10.1021/jo5029166
J. Org. Chem. 2015, 80, 2494−2502