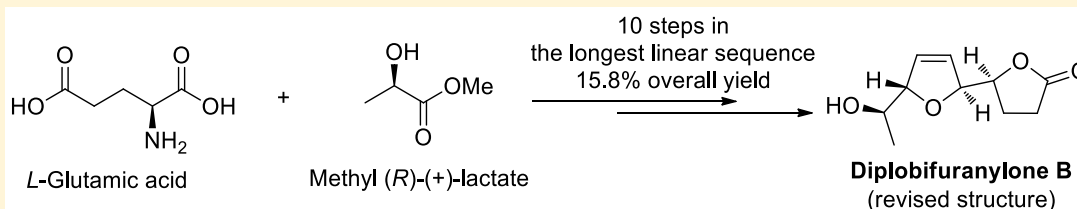


Total Synthesis and Structure Revision of Diplobifuranylone B

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Supporting Information



ABSTRACT: An asymmetric total synthesis of diplobifuranylone B was achieved in 10 steps for the longest linear sequence and in 15.8% overall yield from commercially available methyl (R)-(+)-lactate and L-glutamic acid. This synthesis features a stereoselective construction of the key 2,5-dihydrofuran ring in the natural product via a recently developed asymmetric gold catalysis. The stereochemical flexibility offered by the catalysis enables an expedient revision of the reported structure of diplobifuranylone B, where the relative stereochemistry of the 2,5-dihydrofuran moiety was previously misassigned as *cis* instead of *trans*.

INTRODUCTION

Diplobifuranylone B (**2**) was isolated from *Diplodia corticola*, a fungi species well known as a phytotoxin producer, in 2006.¹ Compounds of its family also include diplobifuranylone A (**1**) and diplobifuranylone C (**3**).² The structures of these natural

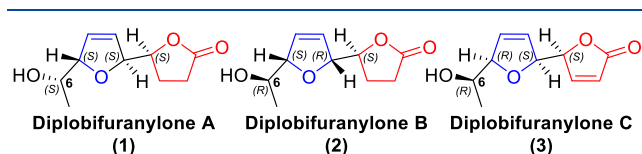
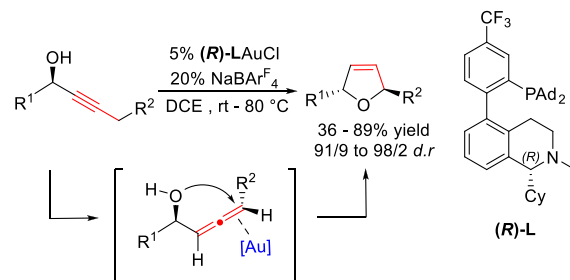


Figure 1. Diplobifuranylones produced by *Diplodia corticola*.

products (Figure 1) were proposed based on UV, ¹H NMR, ¹³C NMR, COSY, HMQC, HMBC, and NOESY spectroscopic experiments. The absolute configuration of the stereogenic carbinol C6 was deduced via the Mosher's method.³ The other stereogenic centers were determined using chiroptical methods in 2017.⁴ To date, the total synthesis of these secondary metabolites has not been reported.

Recently, our group reported a stereoselective strategy for the construction of chiral 2,5-dihydrofurans from chiral propargylic alcohols via asymmetric gold catalysis. In this chemistry, a designed chiral bifunctional biphenyl-2-yl phosphine ligand (**L**) enables a gold-catalyzed asymmetric isomerization of an alkyne into an allene.⁵ With chiral propargylic alcohol as the substrate, the gold-catalyzed isomerization generates an alcohol intermediate featuring a chiral allene motif, which undergoes tandem gold-catalyzed stereospecific cyclization to form a chiral 2,5-dihydrofuran with excellent diastereoselectivity (Scheme 1). Herein, we report the application of this chemistry as a key step toward a concise

Scheme 1. Gold-Catalyzed Asymmetric Cycloisomerization of Chiral Propargylic Alcohol



total synthesis of nominal diplobifuranylone B (**2**), which possesses a *cis* 2,5-dihydrofuran ring. The stereochemical flexibility offered by our gold catalysis permits a rapid structural revision of this reported natural product, which instead features a *trans*-dihydrofuran moiety.

RESULTS AND DISCUSSION

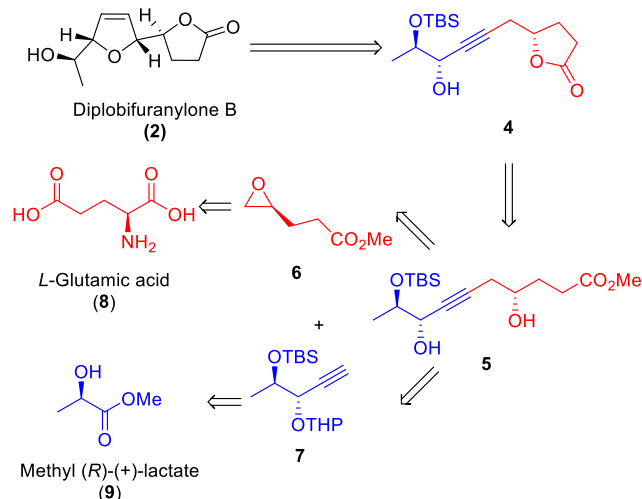
Our retrosynthetic analysis of nominal diplobifuranylone B (**2**) is shown in Scheme 2. A key step is the installation of the *cis*-2,5-dihydrofuran ring by the gold-catalyzed asymmetric isomerization/cyclization of lactone **4** at the final stage. The lactone motif of **4** could be easily constructed through lactonization of dihydroxyester **5**, which could, in turn, be prepared through an epoxide ring opening reaction between the epoxide **6** and the alkyne **7**.

We commenced the synthesis with the preparation of the two fragments **6** and **7** (Scheme 3). While the fragment **6** was

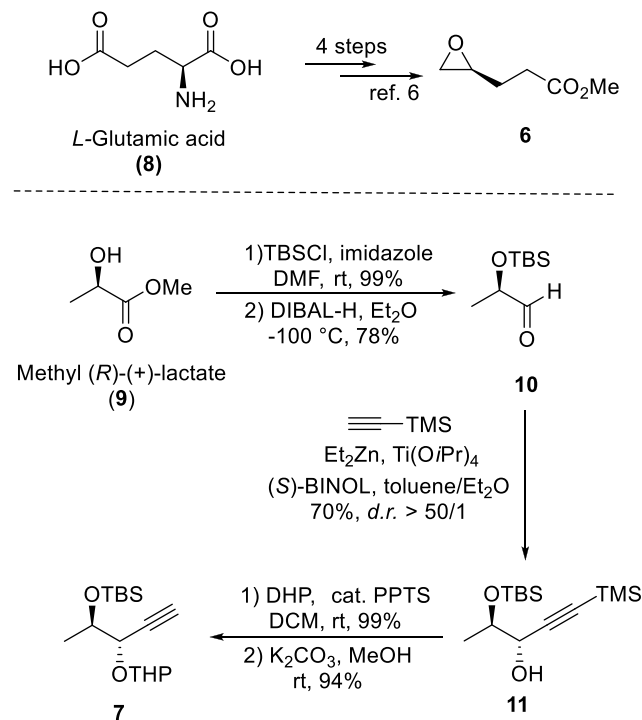
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Scheme 2. Retrosynthetic Analysis



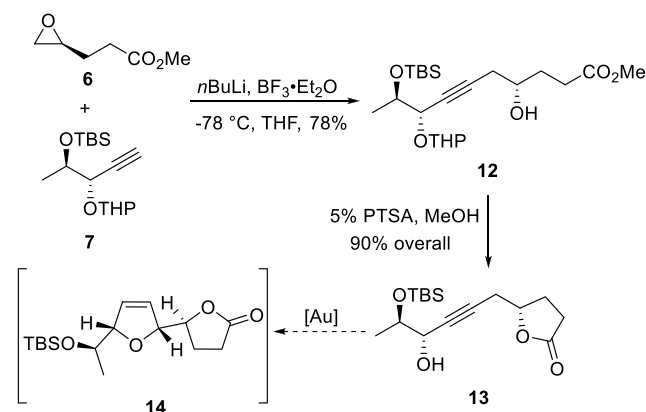
Scheme 3. Preparation of the Chiral Epoxide 6 and the Alkyne 7



prepared from L-glutamic acid (8) by following a reported four-step sequence,⁶ 7 was synthesized from methyl (R)-(+)-lactate (9) in five steps. The synthetic sequence began with a TBS group protection of 9, followed by a DIBAL-H reduction. α -siloxypropanal 10 was isolated in 78% overall yield. An asymmetric nucleophilic addition to 10 by ethynyltrimethylsilane was achieved in the presence of a stoichiometric $\text{Ti}(\text{O}i\text{Pr})_4$ -BINOL complex⁷ to afford propargylic alcohol 11 in 70% isolated yield and with d.r. > 50:1 upon careful column separation. THP protection of 11 followed by selective removal of the TMS group gave the desired terminal alkyne 7 in a combined 94% yield.

With these two chiral fragments in hand, we attempted to implement the initially designed synthetic route. As shown in Scheme 4, the BF_3 -mediated ring opening⁸ of the chiral

Scheme 4. Initial Attempt on the Total Synthesis of Diplobifuranyllone B

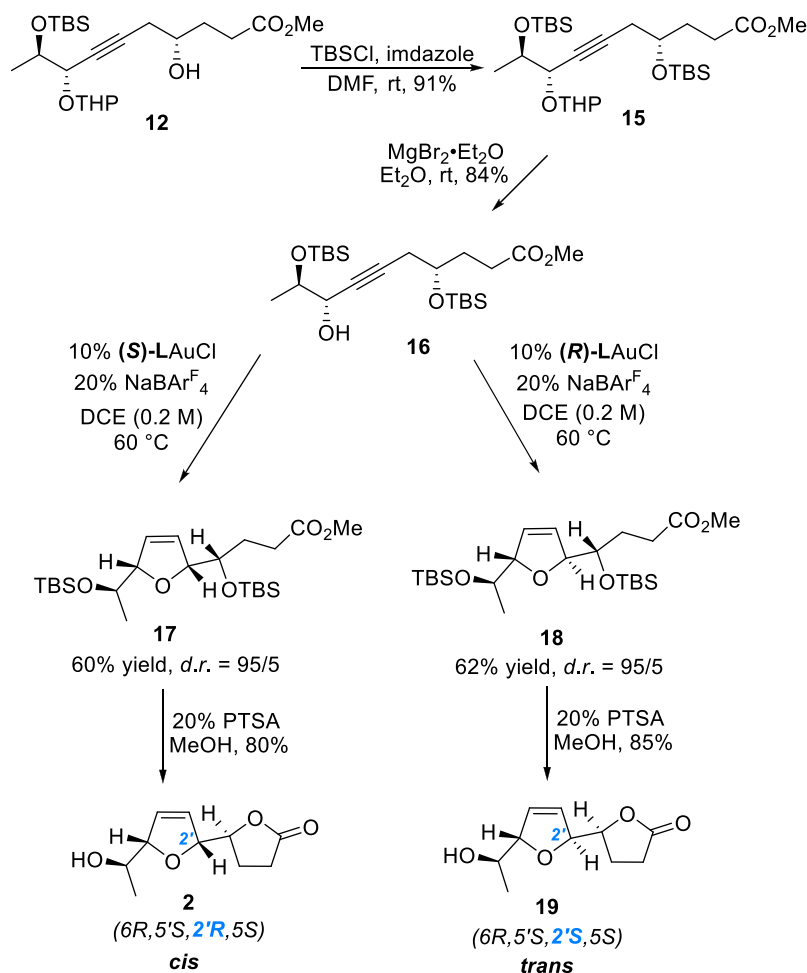


epoxide 6 by deprotonated 7 delivered γ -hydroxy ester 12 with the requisite carbon skeleton of the natural product. The removal of the THP group and lactonization were achieved in one step to give lactone 13 in 90% overall yield. However, when 13 was subjected to the asymmetric gold catalysis for the construction of 2,5-dihydrofuran ring, the reaction was sluggish with most of the starting material 13 remaining after 12 h; moreover, desired product 14 was not found in the reaction mixture.

We speculated that the strong electron-withdrawing nature of the lactone motif might affect the gold-catalyzed isomerization of alkyne to allene and hence decided to modify the synthetic sequence to have the 2,5-dihydrofuran ring installed before the lactonization step. To this end, we converted γ -hydroxy esters 12 to the desired propargylic alcohol 16 in 76% combined yield through a two-step sequence, i.e., TBS protection of the free hydroxyl group to avoid potential gold-catalyzed 5-*endo-dig* cyclization and subsequent selective deprotection of the THP group in the presence of magnesium bromide.⁹ To our delight, subjecting 16 to our asymmetric gold catalysis with (S)-L as the ligand afforded smoothly the 2,5-dihydrofuran product 17 in 60% yield and with a diastereomeric ratio of 95:5. One-pot removal of both TBS groups of 17 and lactonization in the presence of PTSA/MeOH completed the synthesis of the nominal diplobifuranyllone B (2) in 80% yield (Scheme 5). The absolute stereochemistry of C2' is assigned based on our previous report on chiral 2,5-dihydrofuran synthesis.⁵ To our surprise, there are obvious discrepancies between the ^1H and ^{13}C NMR spectra (Table 1) as well as the specific optical rotation $\{[\alpha]^{20}_{\text{D}} = +24.7$ ($c = 1.06$, CHCl_3); lit. $[\alpha]^{20}_{\text{D}} = -90.7$ ($c = 0.55$, CHCl_3)¹ of our synthetic compound (2) and what were reported.¹

Our asymmetric gold catalysis permits easy access to the C2'-epimer of 2, i.e., the *trans*-2,5-dihydrofuran 19 (Scheme 5) by simply employing the ligand enantiomer, i.e., (R)-L, in the conversion of 16. Indeed, by following the same two-step endgame, compound 19 was synthesized with comparable diastereoselectivity and efficiency to 2. Much to our delight, the spectroscopic data including ^1H NMR, ^{13}C NMR, ^1H spin decouple, COSY, HMQC, and HMBC and the HR-MS measurement of 19 match those reported for diplobifuranyllone B except one surprising outlier in the ^{13}C data. The ^{13}C chemical shifts of 2, 19, and the parent γ -lactone¹⁰ and those reported in the isolation paper are listed in Table 1 for

Scheme 5. Revised Route of Total Synthesis of Nominal Diplobifuranylone B

Table 1. ^{13}C NMR Comparison

position	2	19	20	lit.	$\Delta(2\text{-lit.})^a$	$\Delta(19\text{-lit.})^a$
5	81.04	80.12	68.49	80.1	+0.94	+0.02
4	23.54	23.75	22.06	23.7	-0.16	+0.05
3	27.74	27.97	27.70	22.9	+4.84	+5.07
2	176.39	177.24	177.81	177.2	-0.85	+0.04
2'	87.11	87.97		87.9	-0.79	+0.07
3'	129.50	128.79		128.7	+0.80	+0.09
4'	127.20	127.33		127.3	-0.10	+0.03
5'	91.00	91.01		90.9	+0.10	+0.11
6	69.08	69.09		69.1	-0.02	-0.01
7	18.92	17.94		17.9	+1.02	+0.04

^aCalculated with the accuracy of the literature data extended to 0.01 ppm.

comparison. All of the ^{13}C chemical shifts of **19** are within 0.11 ppm difference from the literature data, which are reported with accuracy down to the 0.1 ppm level and hence can be considered as identical except that of the lactone C3. For this outlier, the reported value is 22.9 ppm, but our measured value is 27.97 ppm, which is very close to that of the parent γ -lactone (i.e., 27.7 ppm).¹⁰ It is noted that the chemical shift of the

lactone C3 of diplobifuranylone **1** is 28.2 ppm. We also performed a rather comprehensive literature search of γ -lactones possessing only one substituent at C5, as in the case of diplobifuranylone **B** and found that the chemical shifts of the lactone C3 range from 26.9 to 29.5 ppm.¹¹ In none of the example, the ^{13}C signal could shift to as high a field as 22.9 ppm. Unfortunately, we could not obtain the original ^1H and

^{13}C spectra of diplobifuranyllone B. Considering that all of the other ^{13}C chemical shifts are essentially identical between the reported data and those of **19**, we feel confident to conclude that the reported C3 ^{13}C chemical shift is a typo and should be 27.9 ppm.

To understand the misassignment of the natural product's 2,5-dihydrofuran stereochemistry, we carefully examined the original reports.^{1,4} It was based on the NOESY, ROESY, and double decoupling experiments. Our DFT calculations reveal that the distances between H-2' and H-5' in the optimized structures of the cis (**2**) and the trans (**19**) isomers at the B3LYP//cc-pVDZ level are 3.50 and 3.99 Å, respectively. With both of these measurements being less than 4 Å, the observed nOe might not be a reliable indicator of a cis configuration. The double decoupling experiment revealed that the long-distance coupling constant between H-2' and H-5' is 5.5 Hz, which was suggested to corroborate the cis stereochemistry. However, this large long-range coupling constant is characteristic of *trans*-2,5-dihydrofurans.¹² Typically, the *J* values of *trans*-2,5-dihydrofurans are >5 Hz, whereas those of *cis*-2,5-dihydrofurans are <4 Hz. Some of the examples we found in the literature are listed in Figure 2.^{13–17} Our decoupling

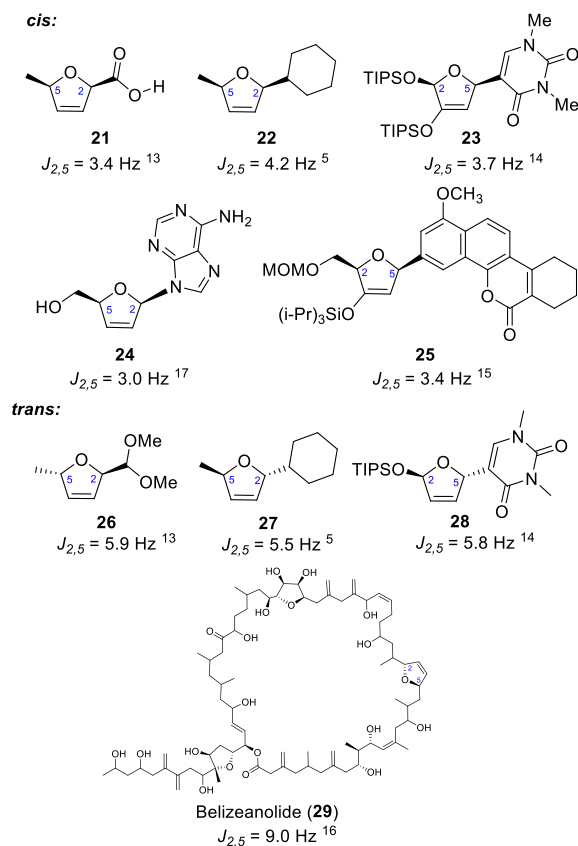


Figure 2. Long-range coupling constant between H-2 and H-5 ($J_{2,5}$) in the 2,5-dihydrofuran systems.

experiments reveal that the coupling constants between H-2' and H-5' are 3.8 and 5.8 Hz for **2** and **19**, respectively, which is consistent with our stereochemistry assignments. A related case is furanomycin (**30**) (Figure 3). The relative stereochemistry of its featured 2,5-dihydrofuran ring was initially assigned incorrectly as cis in **31** based on the coupling constant of 5.7 Hz between H-2 and H-5.¹⁸ However, it was later

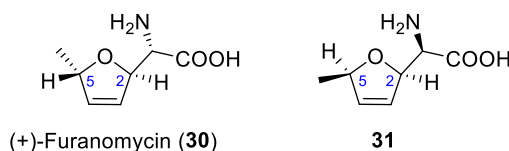


Figure 3. Structure of (+)-furanomycin and its initially misassigned cis-structure **31**.

determined to be trans upon its total synthesis¹³ and X-ray diffraction studies.¹⁹

CONCLUSIONS

In conclusion, an asymmetric total synthesis of diplobifuranyllone B was accomplished in 10 steps for the longest linear sequence and in 14 total steps from the commercially available methyl (*R*)-(+)-lactate and *L*-glutamic acid. The overall yield was 15.8%. The key 2,5-dihydrofuran moiety of the natural product is constructed via a recently published asymmetric gold catalysis. This work allows the revision of the structure of diplobifuranyllone B, in which the relative stereochemistry of its 2,5-dihydrofuran moiety is established as trans instead of the originally assigned cis. The total synthesis is convergent and should be applicable to the synthesis of other diplobifuranyllones.

EXPERIMENTAL SECTION

General Information. Ethyl acetate (ACS grade), hexanes (ACS grade), and diethyl ether (ACS grade) were purchased from Fisher Scientific and used without further purification. Anhydrous dichloromethane (HPLC grade) and 1,2-dichloroethane (HPLC grade) were purified by distillation over calcium hydride. Tetrahydrofuran, toluene, and *o*-xylene were distilled over sodium/benzophenone. Commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) using silicycle-precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230–400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on Varian 400, 500, and 600 MHz spectrometers using residue solvent peaks as internal standards (CDCl_3 , ^1H : 7.26 ppm; ^{13}C : 77.00 ppm).

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (10**).** Aldehyde (**10**) was synthesized from methyl (*R*)-(+)-lactate (**9**) according to the literature procedure.²⁰ The yield was 78%, colorless oil; ^1H NMR (600 MHz, CDCl_3) δ 9.61 (d, *J* = 1.3 Hz, 1H), 4.09 (qd, *J* = 6.8, 1.3 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^1H NMR is in accordance with the literature.²⁰

(3*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-(trimethylsilyl)pent-1-yn-3-ol (11**).** Propargylic alcohol (**11**) was synthesized from aldehyde (**10**) according to a modified literature procedure.²¹ Under N_2 protection, TMS acetylene (5.54 mL, 40 mmol) and 14 mL toluene were added into a Schlenk flask. Et_2Zn (1.5 M) in toluene (26.7 mL, 40 mmol) was added to the solution carefully. The mixture was heated to reflux for 1 h, during which time a large amount of white precipitate formed in the reaction flask. The mixture was cooled to room temperature, and (*S*)-BINOL (1.14 g, 4 mmol), Et_2O (80 mL), and $\text{Ti}(\text{O}i\text{Pr})_4$ (2.96 mL, 10 mmol) were added. After stirring for 1 h, aldehyde **9** (1.88 g, 10 mmol) was added, and the mixture was stirred overnight. Tartaric acid (1.0 M) was slowly added into the reaction mixture to quench the reaction and further stirring for 30 min. The mixture was partitioned in a separatory funnel and the aqueous portion was extracted three times with Et_2O . The combined organic extracts were washed with brine and dried over MgSO_4 . Filtration and concentration, followed by flash column chromatography on the silica gel (hexane/ Et_2O = 100:1 to hexane/ Et_2O = 10:1 gradient), afforded propargylic alcohol **11** (2.03 g, 70% yield, d.r. > 50:1) as a white solid. ^1H NMR (500 MHz, CDCl_3) δ 4.23 (dd, *J* = 5.1, 3.8 Hz, 1H), 3.91 (qd, *J* = 6.2, 3.9 Hz, 1H), 2.34 (d, *J* = 5.4 Hz, 1H), 1.22 (d, *J* = 6.2 Hz,

3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 103.7, 90.8, 71.0, 67.5, 25.8, 18.2, 18.0, -0.2, -4.4, -4.8. These data are in accordance with the literature.²¹

tert-Butyldimethyl(((2R,3S)-3-((tetrahydro-2H-pyran-2-yl)oxy)-5-(trimethylsilyl)pent-4-yn-2-yl)oxy)silane (11-1). Propargylic alcohol (11) (631.5 mg, 2.2 mmol) was dissolved in 10 mL of DCM. 3,4-Dihydro-2H-pyran (0.3 mL, 3.3 mmol) and pyridinium *p*-toluenesulfonate (28 mg, 0.11 mmol) were added into this solution and stirred overnight. When the reaction was near to completion, sodium bicarbonate solid was added into the reaction mixture and stirred for 30 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on the silica gel (hexane/ Et_2O = 50:1), afforded compound 11-1 (805.6 mg, 99% yield, d.r. = 1:1) as a colorless liquid. ^1H NMR (500 MHz, CDCl_3) δ 5.03 (t, J = 3.1 Hz, 1H), 4.85 (t, J = 3.2 Hz, 1H), 4.15 (d, J = 5.9 Hz, 1H), 4.13 (d, J = 5.1 Hz, 1H), 4.07–4.01 (m, 1H), 3.94–3.90 (m, 2H), 3.92–3.87 (m, 1H), 3.83–3.76 (m, 2H), 1.97–1.46 (m, 12H), 1.24 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.15 (s, 9H), 0.15 (s, 9H), 0.10–0.06 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 104.4, 103.2, 99.4, 94.6, 90.7, 89.8, 72.9, 71.3, 70.4, 61.9, 61.6, 30.22, 30.18, 25.84, 25.80, 25.52, 25.51, 20.4, 19.1, 18.9, 18.8, 18.1, 18.0, -0.08, -0.11, -4.51, -4.53, -4.7.

tert-Butyldimethyl(((2R,3S)-3-((tetrahydro-2H-pyran-2-yl)oxy)-pent-4-yn-2-yl)oxy)silane (7). Compound 11-1 (0.80 g, 2.2 mmol) was dissolved in 10 mL of MeOH, followed by the addition of K_2CO_3 (450 mg, 3.3 mmol) into this reaction mixture. The solution was stirred at room temperature for 1 h. Et_2O (30 mL) was added into this reaction mixture, and then the solid was removed via filtration through the silica gel pad (Et_2O as eluent). The solvent was removed under reduced pressure to afford terminal alkyne (7) (612.1 mg, 94% yield) as a colorless liquid. ^1H NMR (600 MHz, CDCl_3) δ 5.02 (t, J = 3.3 Hz, 1H), 4.84 (t, J = 3.4 Hz, 1H), 4.21 (t, J = 4.5 Hz, 1H), 4.21 (t, J = 4.6 Hz, 1H), 4.02 (ddd, J = 11.4, 9.5, 3.1 Hz, 1H), 3.98–3.94 (m, 1H), 3.94–3.90 (m, 1H), 3.82 (ddd, J = 11.0, 9.7, 2.9 Hz, 1H), 3.57–3.49 (m, 2H), 2.41 (d, J = 2.2 Hz, 1H), 2.33 (d, J = 2.1 Hz, 1H), 1.91–1.48 (m, 12H), 1.26 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 99.7, 94.8, 82.2, 81.1, 74.1, 73.4, 72.0, 71.3, 70.3, 69.9, 62.2, 61.7, 30.24, 30.20, 25.84, 25.78, 25.5, 25.4, 20.2, 20.0, 18.9, 18.7, 18.2, 18.0, -4.55, -4.89, -4.59, -4.8.

Methyl (S)-3-(Oxiran-2-yl)propanoate (6). Epoxide (6) was synthesized from L-glutamic acid (8) according to the literature procedure.⁸ The overall yield was 20%, colorless oil; ^1H NMR (600 MHz, CDCl_3) δ 3.63 (s, 3H), 2.95–2.90 (m, 1H), 2.72–2.69 (m, 1H), 2.46–2.43 (m, 1H), 2.43–2.38 (m, 2H), 1.96–1.87 (m, 1H), 1.76–1.67 (m, 1H). ^1H NMR is in accordance with the literature.⁸

Methyl (4S,8S,9R)-9-((tert-Butyldimethylsilyl)oxy)-4-hydroxy-8-((tetrahydro-2H-pyran-2-yl)oxy)dec-6-ynoate (12). Compound 12 was synthesized according to a modified literature procedure.⁸ Under nitrogen at -78°C , terminal alkyne (7) (2.09 g, 7.0 mmol) was dissolved in dry THF (5 mL), then *n*-BuLi (2.5 M in hexane, 2.8 mL, 7.0 mmol) was added. After 5 min, $\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.86 mL, 7.0 mmol) was added and 30 min later, epoxide (6) (650.7 mg, 5.0 mmol) was added. The reaction media was stirred at -78°C for 3 h, then quenched with sat. $\text{NaHCO}_3(\text{aq})$. The aqueous layer was extracted three times with Et_2O . The combined organic layers were washed with brine, dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on the silica gel (hexane/ EtOAc = 20:1 to hexane/ EtOAc = 10:1 to hexane/ EtOAc = 1:1), to afford compound 12 (1.68 g, 78% yield) as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ 4.97 (t, J = 3.2 Hz, 1H), 4.80 (t, J = 3.5 Hz, 1H), 4.19 (dt, J = 3.8, 1.8 Hz, 1H), 4.13 (dt, J = 4.1, 2.0 Hz, 1H), 4.02–3.92 (m, 2H), 3.88 (td, J = 6.2, 4.3 Hz, 2H), 3.79–3.70 (m, 2H), 3.66 (s, 6H), 3.53–3.46 (m, 2H), 2.53–2.26 (m, 8H), 1.96–1.44 (m, 16H), 1.20 (d, J = 6.5 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 0.07–0.04 (m, 12H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.14, 174.12, 99.7, 94.8, 82.5, 82.0, 81.6, 80.1, 73.1, 71.2, 70.7, 70.3, 69.17, 69.15, 62.3, 61.8, 51.59, 51.57, 31.1, 31.0, 30.5, 30.38, 30.36, 30.2, 27.97, 27.93,

25.76, 25.72, 25.42, 25.33, 20.32, 19.18, 19.12, 19.01, 18.1, 18.0, -4.56, -4.67, -4.75, -4.75; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{40}\text{O}_6\text{SiNa}$ 451.2492; found 451.2494.

Methyl (4S,8S,9R)-4,9-Bis((tert-Butyldimethylsilyl)oxy)-8-((tetrahydro-2H-pyran-2-yl)oxy)dec-6-ynoate (15). TBSCl (370.8 mg, 2.46 mmol) was added into a solution of 12 (878.9 mg, 2.05 mmol) and imidazole (279.1 mg, 4.10 mmol) in DMF (10 mL) at room temperature and stirred for 24 h. The reaction was quenched by the addition of sat. $\text{NaHCO}_3(\text{aq})$ into the mixture. The aqueous phase was extracted four times with Et_2O . The combined organic layer was washed with brine, dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on the silica gel (hexane/ EtOAc = 20:1), to afford compound 15 (1.01 g, 91% yield) as a colorless liquid. ^1H NMR (600 MHz, CDCl_3) δ 4.99 (t, J = 3.3 Hz, 1H), 4.85 (t, J = 3.4 Hz, 1H), 4.23 (dt, J = 4.1, 2.1 Hz, 1H), 4.19 (dt, J = 4.9, 1.9 Hz, 1H), 4.00 (ddd, J = 11.4, 9.5, 3.0 Hz, 1H), 3.89 (dq, J = 12.4, 6.2, 4.4 Hz, 2H), 3.85–3.79 (m, 3H), 3.65 (s, 6H), 3.49 (dq, J = 12.0, 4.1, 1.5 Hz, 2H), 2.44–2.29 (m, 8H), 2.03–1.95 (m, 2H), 1.89–1.77 (m, 4H), 1.75–1.45 (m, 10H), 1.22 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 0.89–0.85 (m, 36H), 0.09–0.03 (m, 24H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 174.0, 173.9, 99.4, 94.7, 82.6, 82.1, 79.2, 72.1, 71.7, 70.6, 70.2, 69.9, 69.8, 62.1, 61.6, 51.4, 31.4, 31.3, 30.26, 30.23, 29.62, 29.62, 27.63, 27.57, 25.80, 25.75, 25.72, 25.52, 25.46, 20.1, 19.02, 18.99, 18.5, 18.1, 18.00, 17.96, -4.56, -4.57, -4.65, -4.80, -4.88, -4.89; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{28}\text{H}_{54}\text{O}_6\text{Si}_2\text{Na}$ 565.3357; found 565.3362.

Methyl (4S,8S,9R)-4,9-Bis((tert-Butyldimethylsilyl)oxy)-8-hydroxydec-6-ynoate (16). $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ (1.44 g, 5.57 mmol) was added into a solution of 15 (859.8 mg, 1.58 mmol) in Et_2O and the reaction mixture was stirred at room temperature until the completion of the reaction. The solvent was removed and the residue was purified by flash column chromatography (hexane/ EtOAc = 20:1 to hexane/ EtOAc = 10:1) to give 16 (609.3 mg, 84% yield) as a colorless oil. $[\alpha]_D^{20}$ = -22.7 (c = 1.19, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 4.27–4.22 (m, 1H), 3.89 (qd, J = 6.2, 3.6 Hz, 1H), 3.84 (tt, J = 7.6, 4.3 Hz, 1H), 3.66 (s, 3H), 2.44–2.29 (m, 5H), 2.00 (dddd, J = 13.8, 9.1, 6.7, 3.9 Hz, 1H), 1.82 (dddd, J = 13.7, 8.9, 7.4, 6.1 Hz, 1H), 1.21 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 174.0, 83.0, 80.0, 71.2, 69.8, 67.1, 51.5, 31.4, 29.6, 27.5, 25.8, 18.03, 17.97, -4.47, -4.55, -4.84, -4.86; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{23}\text{H}_{46}\text{O}_5\text{Si}_2\text{Na}$ 481.2781; found 481.2796.

Methyl (S)-4-((tert-Butyldimethylsilyl)oxy)-4-((2R,5S)-5-((R)-1-((tert-Butyldimethylsilyl)oxy)ethyl)-2,5-dihydrofuran-2-yl)-butanoate (17). To a 2-dram vial were added sequentially 16 (68.0 mg, 0.15 mmol), 10 mol % (S)- LAuCl (13.2 mg), 20 mol % $\text{NaBAR}_4^{\text{F}}$ (26.4 mg), and 0.75 mL of dry dichloroethane (DCE). The reaction was stirred at 60°C for 50 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/ Et_2O = 20:1) to yield 17 (40.8 mg, 60% yield, d.r. = 95:5) as a colorless oil. $[\alpha]_D^{20}$ = -13.7 (c = 1.11, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 5.99–5.96 (m, 1H), 5.95–5.92 (m, 1H), 4.58–4.52 (m, 1H), 4.47–4.37 (m, 1H), 3.66 (s, 3H), 3.48 (qd, J = 4.3, 2.0 Hz, 2H), 2.47 (t, J = 8.0 Hz, 2H), 2.02–1.84 (m, 2H), 1.20 (d, J = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 174.3, 129.6, 129.5, 91.2, 88.2, 74.6, 72.4, 51.5, 29.3, 28.5, 25.8, 21.1, 18.04, 18.03, -4.23, -4.24, -4.5, -4.7; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{23}\text{H}_{46}\text{O}_5\text{Si}_2\text{Na}$ 481.2781; found 481.2770.

Methyl (S)-4-((tert-Butyldimethylsilyl)oxy)-4-((2S,5S)-5-((R)-1-((tert-Butyldimethylsilyl)oxy)ethyl)-2,5-dihydrofuran-2-yl)-butanoate (18). To a 2-dram vial were added sequentially 16 (68.0 mg, 0.15 mmol), 10 mol % (R)- LAuCl (13.2 mg), 20 mol % $\text{NaBAR}_4^{\text{F}}$ (26.4 mg), and 0.75 mL of dry dichloroethane (DCE). The reaction was stirred at 60°C for 50 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/ Et_2O = 20:1) to yield 18 (40.8 mg, 62% yield, d.r. = 95:5) as a colorless oil. $[\alpha]_D^{20}$ = -124.0

($c = 1.08$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 5.96 (dt, $J = 6.3$, 1.8 Hz, 1H), 5.85 (dt, $J = 6.3$, 1.8 Hz, 1H), 4.76 (tt, $J = 5.2$, 1.8 Hz, 1H), 4.55 (tt, $J = 6.0$, 1.8 Hz, 1H), 3.73–3.65 (m, 2H), 3.65 (s, 3H), 2.46 (ddd, $J = 15.8$, 10.2, 5.4 Hz, 1H), 2.30 (ddd, $J = 16.1$, 10.0, 6.1 Hz, 1H), 1.79 (tdt, $J = 9.9$, 6.1, 3.4 Hz, 1H), 1.64–1.54 (m, 1H), 1.15 (d, $J = 6.2$ Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 174.2, 129.5, 127.6, 90.9, 89.4, 73.5, 71.3, 51.5, 30.5, 27.3, 25.9, 25.8, 20.3, 18.11, 18.07, –4.32, –4.43, –4.84, –4.88; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{23}\text{H}_{46}\text{O}_5\text{Si}_2\text{Na}$ 481.2781; found 481.2786.

(*S*)-5-((2*R*,5*S*)-5-((*R*)-1-Hydroxyethyl)-2,5-dihydrofuran-2-yl)-dihydrofuran-2(3*H*)-one (**2**). *p*-Toluenesulfonic acid monohydrate (1.0 mg, 0.0055 mmol) was added into a solution of **17** (12.5 mg, 0.03 mol) in MeOH (0.3 mL). The mixture was stirred at room temperature until the starting material **17** was consumed. The solvent was removed under reduced pressure and the residue was dissolved in DCM and stirred for 1 h. Then, the solvent was removed again, and the residue was purified by flash column chromatography (hexane/EtOAc = 1:2) to yield **2** (4.5 mg, 83% yield) as a colorless oil. $[\alpha]_{\text{D}}^{20} = +24.7$ ($c = 1.06$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 6.07 (dt, $J = 6.6$, 1.7 Hz, 1H), 5.96 (dt, $J = 6.3$, 1.8 Hz, 1H), 4.85–4.81 (m, 1H), 4.74–4.71 (m, 1H), 4.53 (dt, $J = 7.3$, 5.8 Hz, 1H), 3.89 (dq, $J = 6.5$, 3.8 Hz, 1H), 2.61–2.49 (m, 2H), 2.39–2.31 (m, 1H), 2.19–2.11 (m, 1H), 1.22 (d, $J = 6.5$ Hz, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 176.4, 129.5, 127.2, 91.0, 87.1, 81.0, 69.1, 27.7, 23.5, 18.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{10}\text{H}_{14}\text{O}_4\text{Na}$ 221.0790; found 221.0789; $J(\text{H}_2' - \text{H}_5') = 3.8$ Hz.

(*S*)-5-((2*S*,5*S*)-5-((*R*)-1-Hydroxyethyl)-2,5-dihydrofuran-2-yl)-dihydrofuran-2(3*H*)-one (**19**). *p*-Toluenesulfonic acid monohydrate (2.0 mg, 0.01 mmol) was added into a solution of **18** (22.4 mg, 0.05 mol) in MeOH (0.5 mL). The mixture was stirred at room temperature until the starting material **18** has been consumed. The solvent was removed under reduced pressure, and the residue was dissolved in DCM and stirred for 1 h. Then, the solvent was removed again, and the residue was purified by flash column chromatography (hexane/EtOAc = 1:2) to yield diplobifuranylonone **B** (**19**) (7.0 mg, 73% yield) as a colorless oil. $[\alpha]_{\text{D}}^{20} = -132.4$ ($c = 0.55$, CHCl_3); literature¹: $[\alpha]_{\text{D}}^{20} = -90.7$ ($c = 0.55$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 6.01 (dt, $J = 6.3$, 2.0 Hz, 1H), 5.90 (dt, $J = 6.3$, 2.0 Hz, 1H), 4.97 (dtd, $J = 6.1$, 2.5, 1.7 Hz, 1H), 4.79 (dddd, $J = 5.9$, 3.7, 2.3, 1.5 Hz, 1H), 4.54 (ddd, $J = 8.0$, 5.3, 2.8 Hz, 1H), 3.90 (dq, $J = 6.5$, 3.4 Hz, 1H), 2.66 (ddd, $J = 17.7$, 10.1, 7.0 Hz, 1H), 2.47 (ddd, $J = 17.7$, 10.3, 6.4 Hz, 1H), 2.34–2.27 (m, 1H), 1.64 (br s, 1H), 1.17 (d, $J = 6.5$ Hz); ^{13}C NMR $\{^1\text{H}\}$ (126 MHz, CDCl_3) δ 177.2, 128.8, 127.3, 91.0, 88.0, 80.1, 69.1, 28.0, 23.8, 17.9; HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calculated for $\text{C}_{10}\text{H}_{14}\text{O}_4\text{Na}$ 221.0790; found 221.0785; $J(\text{H}_2' - \text{H}_5') = 5.8$ Hz, $J(\text{H}_5 - \text{H}_2) = 2.8$ Hz; literature¹: $J(\text{H}_5 - \text{H}_2) = 5.5$ Hz; $J(\text{H}_2 - \text{H}_2') = 2.8$ Hz.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01613.

DFT calculation and spectra data (PDF)

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Notes

The authors declare no competing financial interest.

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