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Total Synthesis and Structure Revision of Diplobifuranylone B

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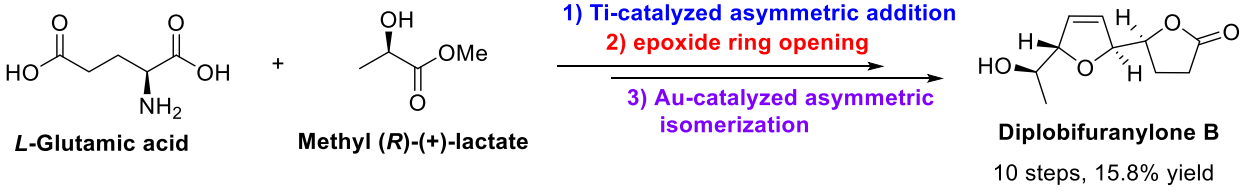


ABSTRACT: An asymmetric total synthesis of diplobifuranylone B was achieved in 10 steps for the longest linear sequence and in 15.8% overall yield from commercially available methyl (*R*)-(+)-lactate and *L*-glutamic acid. This synthesis features a stereoselective construction of the key 2,5-dihydrofuran 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**),[1] and diplobifuranylone C (**3**).[2] The structures of these natural products (**Figure 1**) were proposed based on UV, ^{1}H NMR, ^{13}C NMR, COSY, HMQC, HMBC, and NOESY spectroscopic experiments. The absolute configuration of the stereogenic carbinol C-6 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.

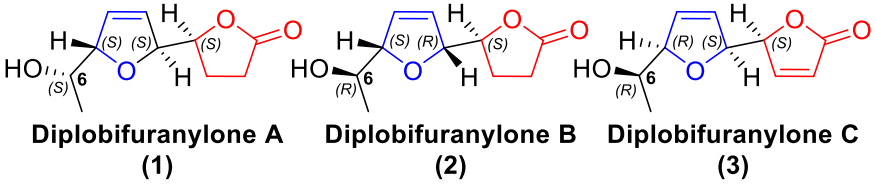
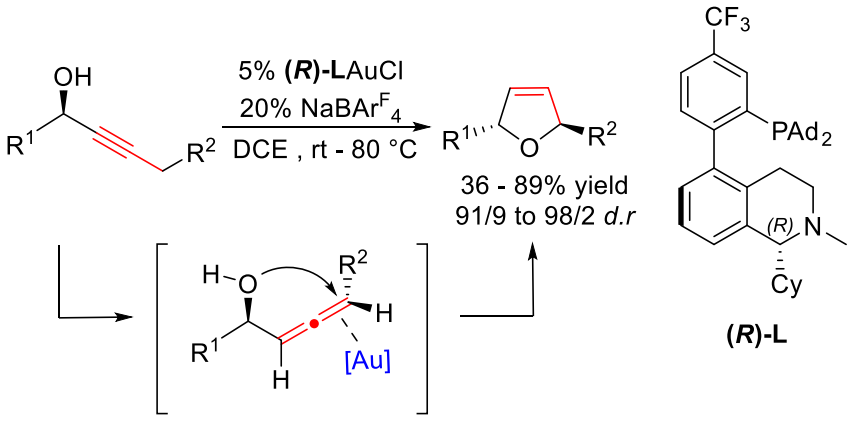


Figure 1. Diplobifuranylones produced by *Diplodia corticola*

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 a 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 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.

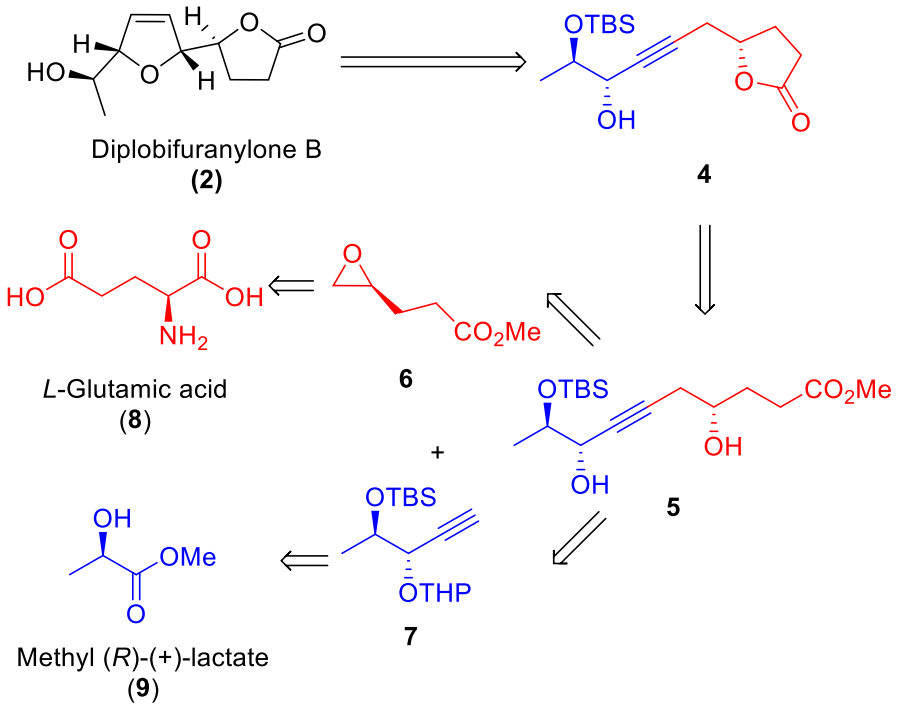
Scheme 1. Gold-Catalyzed Asymmetric Cycloisomerization of Chiral Propargylic Alcohol



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 the lactone **4** at the final stage. The lactone motif of **4** could be easily constructed through lactonization of the dihydroxyester **5**, which could, in turn, be prepared through an epoxide ring opening reaction between the epoxide **6** and the alkyne **7.**

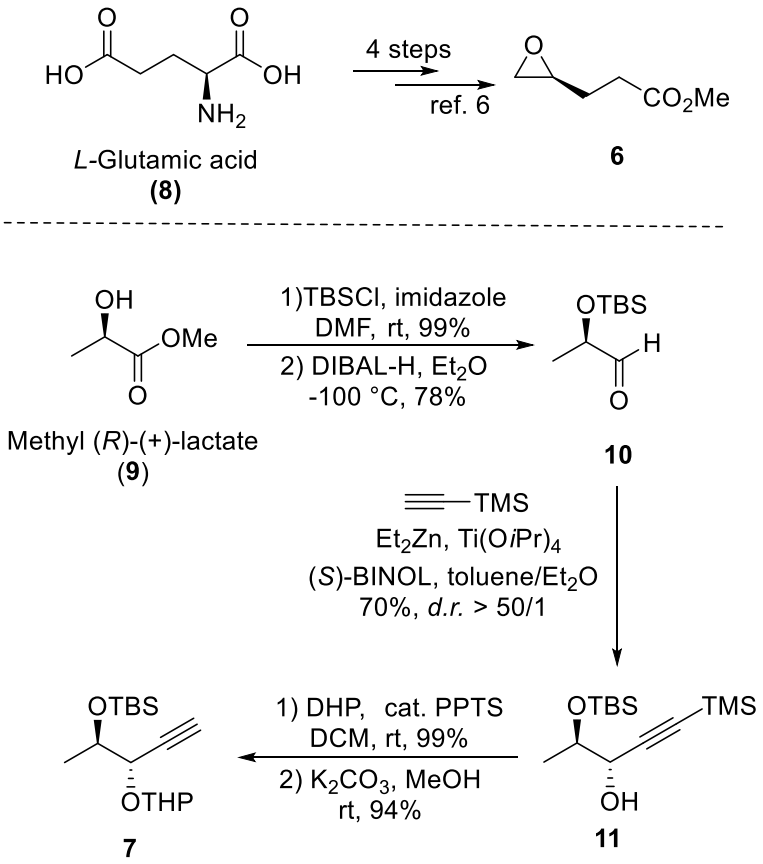
Scheme 2. Retrosynthetic Analysis



We commenced the synthesis with the preparation of the two fragments **6** and **7** (**Scheme 3**). **6** was prepared from *L*-glutamic acid (**8**) by following a reported four-steps 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. The 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 Ti(O*i*Pr)$_4$-BINOL complex[7] to afford the propargylic alcohol **11** in 70% isolated yield and *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.

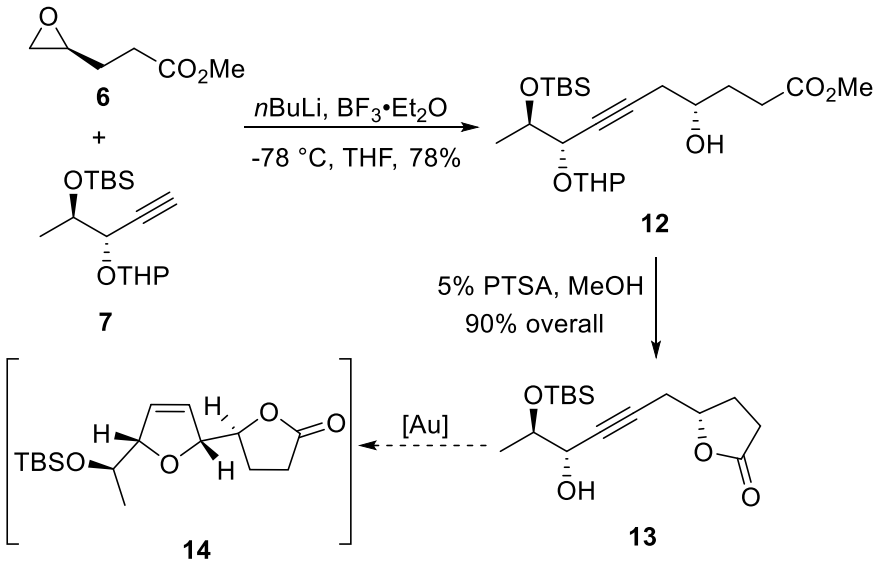
Scheme 3. Preparation of the chiral epoxide **6** and the alkyne **7**.



With these two chiral fragments in hand, we carried out the planned end game. As shown in **Scheme 4**, the BF_3-mediated ring opening[8] of the chiral epoxide **6** by deprotonated **7** delivered the γ-hydroxy ester **12** with the requisite carbon skeleton of the natural product. Removal of the THP group and lactonization were achieved in one step to give the lactone **13** in 90% overall yield. However, when **13** was subjected to the asymmetric gold catalysis for the construction of the 2,5-

dihydrofuran ring, the reaction was sluggish with most of the starting material **13** remained after 12 h; moreover, no desired product **14** was found in the reaction mixture.

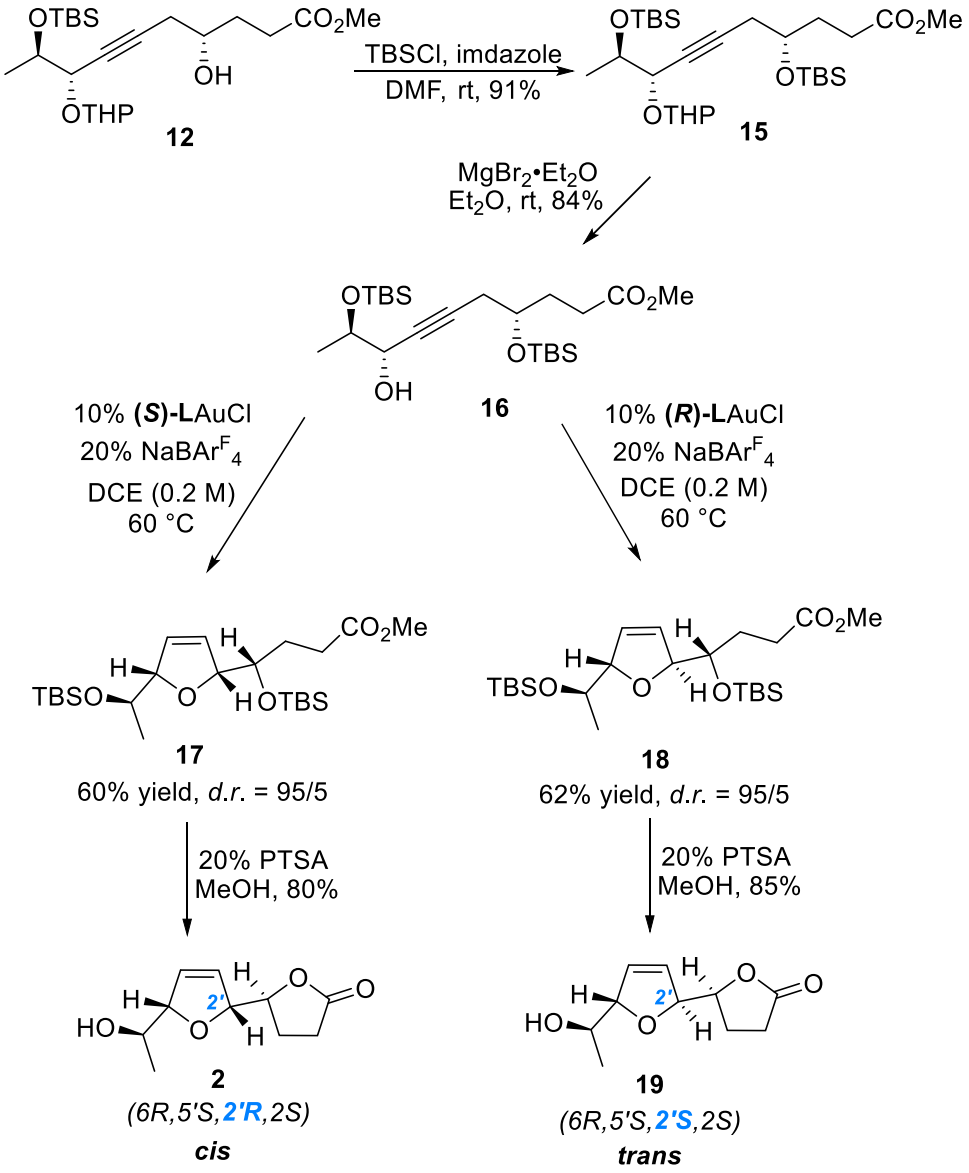
Scheme 4. Initial Attempt on the Total Synthesis of Diplobifuranylone B



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 synthesis sequence to have the 2,5-dihydrofuran ring installed before the lactonization step. To this end, we converted the 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*-*trig* 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 diplobifuranylone 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 ^{1}H and ^{13}C NMR spectra (**Table 1**) as well as optical rotation {$[\alpha]^{20}D = +24.7$ ($c = 1.06$, $CHCl_3$); lit. $[\alpha]^{20}D = -90.7$ ($c = 0.55$, $CHCl_3$)}of our synthetic compound (**2**) and what were reported.[1]

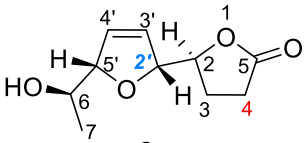
Scheme 5. Revised Route of Total Synthesis of Norminal Diplobifuranylone B



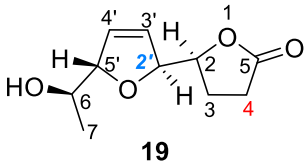
Our asymmetric gold catalysis permits easy access to the C2'-epimer of **2**, i.e., the *trans*-2,5-dihydrofuran **19** (**Scheme 5**) by simply employing the ligand enantiomer, i.e., (*R*)-**L**, in the

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 ^{1}H NMR, ^{13}C NMR, ^{1}H spin decouple, COSY, HMQC, and HMBC and the HR-MS measurement of **19** match those reported for diplobifuranylone B well except one surprising outlier in the ^{13}C data. The ^{13}C chemical shifts of **2**, **19**, and the parent γ-lactone[10] and those reported in the isolation paper are listed in **Table 1** for comparison. All 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 C4. For this outlier, the reported value is 22.9 ppm, but our measured value is 27.9 ppm, which is identical to that of the parent γ-lactone.[10] In addition, the chemical shift of the lactone C4 of diplobifuranylone A[1] is 28.2 ppm. We also performed a rather comprehensive literature search of γ-lactones possessing only one substituent at C-2, as in the case of diplobifuranylone B and found that the chemical shifts of the lactone C4 range from 26.9 ppm to 29.5 ppm.[11] In no example, the ^{13}C signal could shift to as high a field as 22.9 ppm. Unfortunately, we could not obtain the original ^{1}H and ^{13}C spectra of diplobifuranylone B. Considering that all 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 C4 ^{13}C chemical shift is a typo and should be 27.9 ppm.

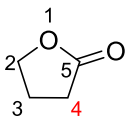
Table 1. ^{13}C NMR Comparison



2
(6R,5'S,2'R,2S)



19
(6R,5'S,2'S,2S)



20

Position	**2**	**19**	**20**	**Lit.**	Δ(**2-Lit.**) [a]	Δ(**19-Lit.**) [a]
2	81.04	80.12	68.49	80.1	+0.94	+0.02
3	23.54	23.75	22.06	23.7	-0.16	+0.05
4	**27.74**	**27.97**	**27.70**	**22.9**	**+4.84**	**+5.07**
5	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

[a] Calculated with the accuracy of the literature data extended to 0.01 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 Å and 3.99 Å, respectively. With both of these measurements less than 4 Å, the observed nOe might not be a reliable indicator of a *cis* configuration. The double coupling 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, while 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 experiments reveal that the coupling constants between H-2' and H-5' are 3.8 Hz and 5.8 Hz for **2** and **19**, respectively, which is consistent with our stereochemistry assignments. A related case is furanomycin (**29**) (**Figure 3**). The relative stereochemistry of its featured 2,5-dihydrofuran ring was initially assigned incorrectly as *cis* in **30** based on the coupling constant of 5.7 Hz between H-2 and H-5.[18] However, it was later determined to be *trans* upon its total synthesis[12] and X-ray diffraction studies.[19]

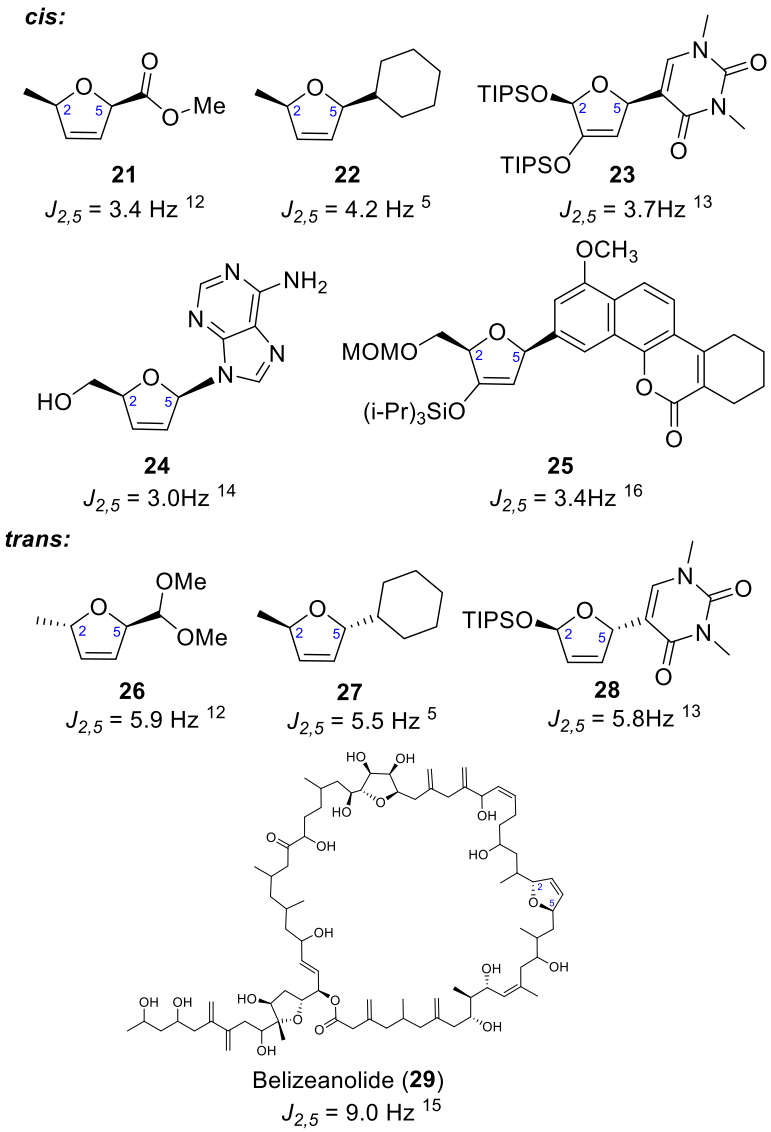


Figure 2. The long-range coupling constant between H-2 and H-5 ($J_{2,5}$) in the 2,5-dihydrofuran systems

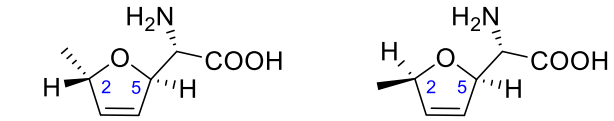


Figure 3. Structure of (+)-furanomycin and its initially misassigned *cis*-structure **30**.

CONCLUSION

In conclusion, an asymmetric total synthesis of diplobifuranylone 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 diplobifuranylone 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 diplobifuranylones.

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), 1,2-dichloroethane (HPLC grade) was 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). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz, 500 MHz and 600 MHz spectrometers using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 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 literature procedure [20]. 78% yield, colorless oil; ^{1}H 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); ^{1}H NMR is in accordance with literature[20].

(3S,4R)-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. 1.5 M Et_2Zn 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 Ti(O*i*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. 1.0 M tartaric acid 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 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. ^{1}H 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}C{^{1}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 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 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 stirring overnight. After reaction going to completion, sodium

bicarbonate solid was added into the reaction mixture and stirring for 30 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/Et_2O = 50:1), afforded compound **11-1** (805.6 mg, 99% yield, *d.r.* = 1/1) as a colorless liquid. ^{1}H 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}C{^{1}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, 30.2, 30.2, 25.8, 25.8, 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** (0.80g, 2.2 mmol) was dissolved in 10 mL MeOH, followed by adding K_2CO_3 (450 mg, 3.3 mmol) into this reaction mixture. The solution was stirred at room temperature for 1 h. 30 mL Et_2O was added into this reaction mixture, and then solid was removed via filtration through 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. ^{1}H 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}C{^{1}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, 30.2, 30.2, 25.8, 25.8, 25.5, 25.4, 20.2, 20.0, 18.9, 18.7, 18.2, 18.0, -4.55, -4.59, -4.59, -4.8.

Methyl (S)-3-(oxiran-2-yl)propanoate (**6**). Epoxide (**6**) was synthesized from *L*-glutamic acid (**8**) according to literature procedure [8]. 20% overall yield, colorless oil; ^{1}H 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). ^{1}H NMR is in accordance with literature[8].

Methyl (4*S*,8*S*,9*R*)-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 ℃, 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, $BF_3{\cdot}Et_2O$ (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 ℃ for 3 h, then quenched with *sat.* $NaHCO_3$(*aq*). The aqueous layer was extracted with Et_2O for three times. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was remove under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20:1 to hexane/EtOAc = 10 : 1 to hexane/EtOAc = 1:1), afforded compound **12** (1.68 g, 78% yield) as a colorless liquid. ^{1}H 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}C{^{1}H} NMR (101 MHz, CDCl3) δ 174.1, 174.1, 99.7, 94.8, 82.5, 82.0, 81.6, 80.1, 73.1, 71.2, 70.7, 70.3, 69.2, 69.2, 62.3, 61.8, 51.6, 51.6, 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* : $[M+Na]^+$ calculated for $C_{22}H_{40}O_6SiNa$ 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 quench by adding *sat.* $NaHCO_3$ (*aq*) into the mixture. The aqueous phase was extracted with Et_2O for four times. 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 silica gel (hexane/EtOAc = 20:1), afforded compound **15** (1.01 g, 91% yield) as a colorless liquid. ^{1}H 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 (dqd, *J* = 12.4, 6.2, 4.4 Hz, 2H), 3.85 – 3.79 (m, 3H), 3.65 (s, 6H), 3.49 (dqd, *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}C{^{1}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* : $[M+Na]^+$ calculated for $C_{28}H_{54}O_6Si_2Na$ 565.3357; Found 565.3362

Methyl (4S,8S,9R)-4,9-bis((tert-butyldimethylsilyl)oxy)-8-hydroxydec-6-ynoate (**16**). $MgBr_2{\cdot}Et_2O$ (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 reaction completion. 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. $[\alpha]^{20}_D$ = -22.7 (*c* = 1.19, $CHCl_3$); ^{1}H 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); $^{13}C\{^{1}H\}$ 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, 18.0, 18.0, -4.47, -4.55, -4.84, -4.86; HRMS (ESI-TOF) *m/z* : $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 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*)-**L**AuCl (13.2 mg), 20 mol% $NaBAr^F{}_4$ (26.4 mg) and 0.75 mL 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. $[\alpha]^{20}_D$ = -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* = 6.0Hz, 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); $^{13}C\{^{1}H\}$ 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*: $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 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*)-**L**AuCl (13.2 mg), 20 mol% $NaBAr^F{}_4$ (26.4 mg) and 0.75 mL 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. $[\alpha]^{20}_D$ = -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); $^{13}C\{^1H\}$ 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* : $[M+Na]^+$ calculated for $C_{23}H_{46}O_5Si_2Na$ 481.2781; Found 481.2786.

(S)-5-((2R,5S)-5-((R)-1-hydroxyethyl)-2,5-dihydrofuran-2-yl)dihydrofuran-2(3H)-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 starting material **17** 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 **2** (4.5 mg, 83% yield) as a colorless oil. $[\alpha]^{20}_D$ = +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); $^{13}C\{^1H\}$ 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:* $[M+Na]^+$ calculated for $C_{10}H_{14}O_4Na$ 221.0790; Found 221.0789; $J(H_2'\text{-}H_5')$ = 3.8 Hz.

(S)-5-((2S,5S)-5-((R)-1-hydroxyethyl)-2,5-dihydrofuran-2-yl)dihydrofuran-2(3H)-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 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 diplobifuranylone B (**19**) (7.0 mg, 73% yield) as a colorless oil. $[\alpha]^{20}_D$ = -132.4 (c = 0.55, $CHCl_3$); Literature[1] : $[\alpha]^{20}_D$ = -90.7 (c = 0.55, $CHCl_3$); ^{1}H 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, 1H), 2.47 (ddd, *J* = 17.7, 10.3, 6.4, 1H), 2.34 – 2.27 (m, 1H), 1.64 (br, s, 1H), 1.17 (d, *J* = 6.5 Hz); ^{13}C NMR{^{1}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*: $[M+Na]^+$ calculated for $C_{10}H_{14}O_4Na$ 221.0790; Found 221.0785; *J*(H_2'-H_5') = 5.8 Hz, *J*(H_2-H_2') = 2.8 Hz; Literature[1]: *J*(H_2'-H_5') = 5.5 Hz; *J*(H_2-H_2') = 2.8 Hz.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DFT Calculation and Spectra Data (PDF)

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Notes

The authors declare no competing financial interest.

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