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Stereocontrolled Synthesis of a Possible Stereoisomer of Laurenidificin and a Formal Total Synthesis of (+)-Aplysiallene Featuring a Stereospecific Ring Contraction

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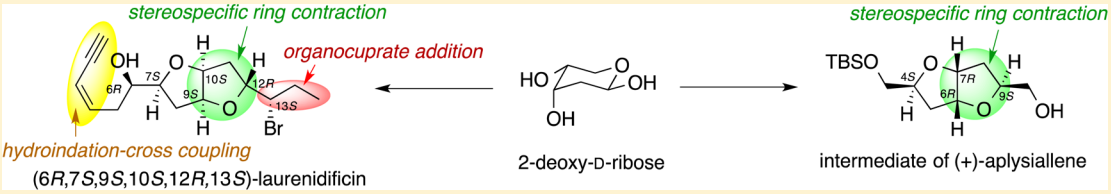
Supporting Information



ABSTRACT: We report a highly stereocontrolled total synthesis of one of the possible stereoisomers of laurenidificin. Highlights of the synthesis include the formation of the 2,6-dioxabicyclo[3.3.0]octane framework by a stereospecific bromolactonization−α-bromination−ring contraction sequence, followed by a stereoselective propargylation, an insertion of the *Z*-enyne side chain by a hydroindation/cross coupling reaction, and ethylation at C13 with an organocuprate reagent. While the synthetic compound was not identical to the natural product, the absolute stereochemistry of the natural product was proposed on the basis of NMR analyses. Moreover, a formal total synthesis of (+)-aplysiallene was achieved by extending the ring contraction strategy.

INTRODUCTION

Halogenated C_{15}-acetogenins are widely distributed in red algae *Laurencia* species.[1] More than 180 compounds have been elucidated since the first discovery of laurencia by the Irie group in 1965.[2] Structurally, most of them contain small- or medium-sized ether rings ranging from 4 to 12 members and one or more bromine or chlorine atoms. Murai and co-workers proposed biogenetic pathways of brominated C_{15}-acetogenins on the basis of enzymatic reactions with commercially available lactoperoxidase (LPO) or partially purified bromoperoxidase (BPO) isolated from natural *Laurencia* species.[3] They suggested that an enzyme-bound bromonium ion, generated by the two-electron oxidation of bromide ion with BPO and hydrogen peroxide, provoked bromoetherification of unsaturated molecules to give rise to a variety of cyclic bromoether products. Importantly, the acyclic (6*S*,7*S*)- or (6*R*,7*R*)-laurediols are suggested to be biosynthetic precursors of the brominated C_{15}-acetogenins.[3,4]

Among this family, laurenenynes A (**1*E***) and B (**1*Z***),[5] laurenidificin (**2**),[6] (−)-kumausallene (**3**),[7] and (−)-aplysiallene (**4**)[8] are grouped into the 2,6-dioxabicyclo[3.3.0]octane class (Figure 1). A notable structural feature is that a thermodynamically unfavorable conjugated *Z*-enyne or an unusual bromoallene side chain is bound to a cis-fused bicyclic core. In addition, there are more than five chiral centers as well as double-bond isomerism, which expands the structural diversity of this class.[9] While the bioactivities of **1**, **2**, and **3** remain unknown, it is reported that **4** exhibited Na^+/K^+ ATPase inhibitory activity at IC_{50} = 15.0 μM.[8e] Their structural complexity, unrevealed biological activity, and limited availability from natural sources have made them attractive synthetic targets.[8d,e,10−13] To date, one racemic and two asymmetric total syntheses of **3** and two asymmetric total syntheses of **4** have been reported by the groups of Overman,[10] Evans,[11] Tang,[12] Pagenkopf,[8d] and Fujioka,[8e] respectively, while total syntheses of **1** and **2** have yet to be achieved.[13] Laurenidificin (**2**) was discovered from

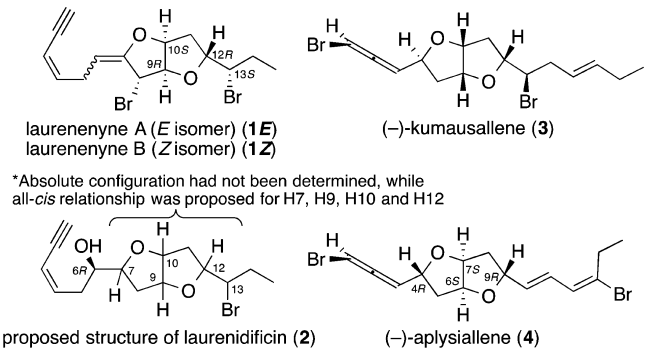


Figure 1. Examples of brominated C_{15}-acetogenins bearing 2,6-dioxabicyclo[3.3.0]octane skeletons.

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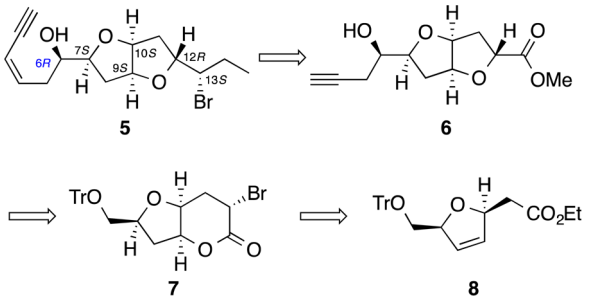
Laurencia nidifica 10 years after the discovery of **1**.[6] While its structure and the absolute configuration at C6 were determined by NMR methods, the remaining stereochemistries from C7 to C13 including the relationships between C6 and C7, and C12 and C13 were not elucidated. By considering the NOE correlations observed from H9, H10 to H12 and H7, a cis relationship was proposed for H7, H9, H10, and H12.[6] However, this stereochemical prediction is not definitive, as it is known that the structure determination by the NOE method occasionally leads to misassignment of the relative stereochemistry.[14] Indeed, the originally proposed structure of aplysiallene[8a−c] was revised by the Pagenkopf group through the total synthesis of putative stereoisomers.[8d] Thus, unequivocal confirmation of the proposed structure by the total synthesis remains of great importance, in particular, in the area of marine-derived halogenated natural products.[15] In this context, we undertook a synthetic study to determine all the stereochemistry of **2** and to develop a general synthetic route of this class of natural products. Herein, we report a highly stereocontrolled total synthesis of one of the possible stereoisomers of laurenidificin featuring stereospecific ring contraction. While our effort did not culminate in full assignment of the structure of the natural product, the relative stereochemistry between C6 and C7 was suggested on the basis of NMR analyses, which led to a prediction of the most plausible structure of laurenidificin. Moreover, a highly stereospecific ring contraction strategy was extended to the formal total synthesis of (+)-aplysiallene (*ent*-**4**).

RESULTS AND DISCUSSION

To begin, the unidentified stereochemistry from C9 to C13 in **2** was assumed to be the same as that of **1***E* and **1***Z* by considering their structural similarities and the biogenetic viewpoint. In short, structure **5** was selected as the initial synthetic target (Scheme 1). It was planned that the

Scheme 1. Retrosynthetic Analysis of 5



thermodynamically unfavorable *Z*-enyne side chain could be introduced by a hydroindation/cross-coupling sequence onto alkyne **6** by following Oshima's method.[16] Recently, we demonstrated that the base-induced ring contraction (i.e., oxy-Favorskii rearrangement) of bicyclic α-bromolactones was a powerful method to obtain cis-fused bicyclic hydrofurans with an α-substituent of the ether oxygen.[17,18] This method was successfully applied to the total synthesis of (±)-communiol E.[17] Since the main backbone of **5** was similar to that of communiol E, we decided to apply this methodology to the formation of the dioxabicyclo[3.3.0]octane framework of **5**.[19] Thus, α-bromolactone **7** was planned as a precursor to **6**. It was expected that **7** would be obtained from the known ester **8**[20] via one-carbon elongation, halolactonization, reduction, and α-bromination. We envisioned that the entire synthetic sequence would be stereospecific due to the inflexible molecular architecture of the intermediates, which would provide **5** in a stereocontrolled manner.

The synthesis commenced with DIBAL-H reduction and Wittig olefination of the known ester **8** that was prepared from 2-deoxy-D-ribose in three steps[20] (Scheme 2). More than 3 equiv of the Wittig reagent with the addition of aldehyde at low temperature was necessary to obtain enol ether **9** in good yield. The product **9** was submitted to hydrolysis under acidic conditions followed by Lindgren−Kraus oxidation[21] to provide the requisite carboxylic acid **10**. The stage was now set for the consecutive stereospecific reactions involving halolactonization, α-bromination of the resultant lactone, and ring contraction. In the hope that this method could be applied to both laurenidificin (**2**) and laurenenynes (**1**), the latter of which bears the bromine substituent at C8, bromolactonization was planned rather than iodolactonization. After exploration of several conditions, Braddock's conditions with NBS and tetramethylguanidine as the organocatalyst[22] turned out to be appropriate. While the isolated yield of the bromolactone after silica gel or Florisil chromatography was about 60%, NMR studies in deuterated solvent ($CDCl_3$) indicated clean conversion without forming considerable byproducts. The use of freshly distilled $CHCl_3$ enhanced reproducibility, which suggested that a small amount of EtOH contained as a stabilizer of $CHCl_3$ induced side reactions such as ethanolysis of the lactone to give the ring-opening product. Since the bromolactone was unstable on silica gel, it was submitted to radical reduction without purification to give the bicyclic lactone **11** in 84% isolated yield over two steps.

Next, we focused our attention on α-bromination to set up the rearrangement. The lactone **11** was treated with LiHMDS and TMSCl to generate a silyl ketene acetal, which was treated with NBS at −78 °C to provide α-bromolactone **7** as a single stereoisomer. In accordance with the previous results, addition of NBS occurred at the less-hindered convex face.[17] Since the product **7** was again unstable, it was submitted, without chromatography, to the ring contraction in the presence of K_2CO_3 in MeOH at −78 °C to room temperature. Remarkably, the expected bicyclic ether **12** was obtained as the sole stereoisomer in almost quantitative yield without epimerization at C12.[23] It appears that the *R*-configuration at C12 arose from backside attack of alkoxide **A**, generated by methanolysis of the lactone, on the 12*S*-configured secondary bromide. The syn relationship between H6 and H12 was confirmed by the NOE enhancement after detritylation of **12** with TsOH/MeOH to give alcohol **12a** (91% yield from **11**, Figure 2). The C6-alcohol **12a** was then oxidized with Dess−Martin periodinane[24] in the presence of $NaHCO_3$ as the acid scavenger to afford aldehyde **13**.

Next, our attention was focused on the synthesis of the *Z*-enyne side chain by employing hydroindation chemistry.[16,25] To introduce the requisite alkyne terminal, propargylation of **13** was carried out with propargyl bromide and zinc dust using 1,2-dibromoethane as the activator of zinc.[26] Remarkably, the 6*R*-configured alcohol **6** was exclusively produced in 67% yield. The absolute configuration at C6 was later determined by the modified Mosher method (vide infra). It is likely that the complete diastereoselectivity is set by the *Re* face addition of the organozinc reagent via the Felkin−Anh conformation **B** (Figure 3).[27] This selectivity was in accordance with the

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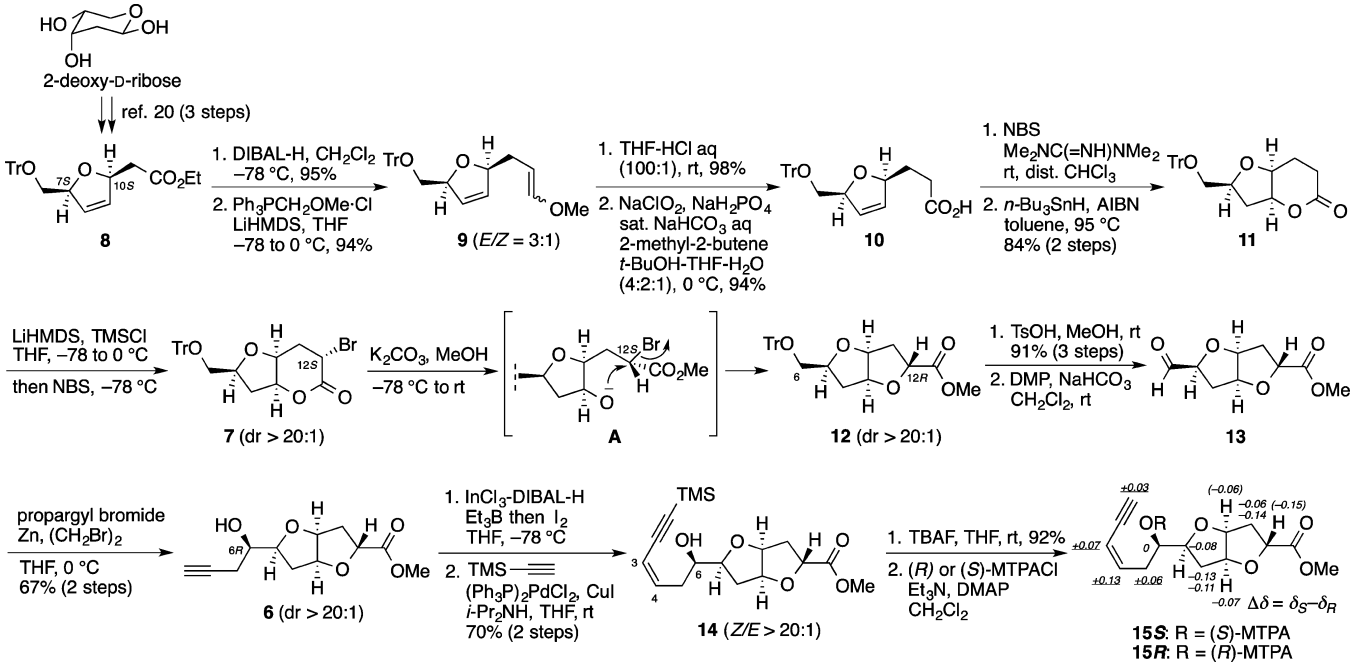
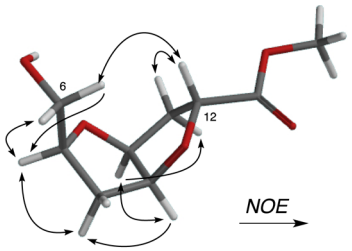
Scheme 2. Stereocontrolled Synthesis of the Dioxabicyclo[3.3.0]octane Framework and Insertion of the Enyne Moiety





12a

Figure 2. NOE correlations for **12a**. The energy-minimized structure was obtained by the molecular mechanics calculation with MMFF force field.

previous results, where propargylation under Barbier conditions tended to occur from the *Re* face of the carbonyl group.[28]

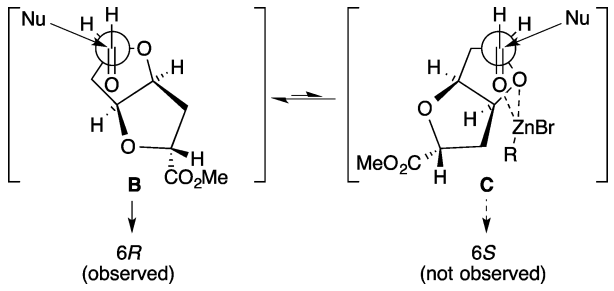


Figure 3. Stereochemical outcome for propargylation (**13** → **6**).

With the desired 6*R*-hydroxy alkyne **6** in hand, the *Z*-selective hydroindation/cross-coupling sequence[16] was examined after optimizing the reaction conditions with a model study (Scheme 3). Thus, alkyne **6** was treated with $HInCl_2$, generated from anhydrous $InCl_3$ and DIBAL-H, in the presence of Et_3B at −78 °C for 3 h. The vinylindium intermediate was then trapped by molecular iodine to afford the corresponding vinyl iodide, which was, without purification, coupled with ethynyltrimethylsilane under Hagihara−Sonogashira conditions[29] to provide the desired *Z*-enyne **14** as a single isomer in 70% overall yield for two steps. The coupling constant, J_{H3-H4} = 11 Hz, indicated the *Z*-configuration with respect to the C3−C4 olefin. To make the process more efficient, the one-pot operation was attempted with a model substrate **II** (Scheme 3). Thus, the solutions of (iodoethynyl)-trimethylsilane, $Pd_2(dba)_3{\cdot}CHCl_3$, and tri-2-furylphosphine were added sequentially to the transient vinylindium solution (**D**) at room temperature. The desired *Z*-enyne **IV** was obtained in 42% yield, together with a slight amount of alkene **V** (4% yield). While the one-pot process was not applied to the actual substrate **6**, this preliminary achievement offers a promising approach to *Z*-enyne structures starting from terminal alkynes.[30] Back to Scheme 2, after desilylation of **14** with TBAF and conversion to the corresponding MTPA esters **15*S*** and **15*R***, the stereochemistry at C6 was determined by the modified Mosher method.[31] The signs of $\Delta\delta_{H(S-R)}$ values for **15** and the MTPA derivatives of **2**[6] were all identical, which suggested that both compounds had the 6*R*-configuration.

The remaining tasks were insertion of the C14−C15 carbon chain and bromination at C13. At first, the C6-hydroxyl group of **14** was protected as the TES ether (Scheme 4). Next, the methyl ester was carefully reduced with DIBAL-H to afford the aldehyde. The next ethylation was, however, problematic. When EtLi was added in THF at 0 °C,[17] the reaction produced a complex mixture of unidentifiable products, among which the desired ethylation product was isolated in only 2% yield after HPLC. Therefore, we searched for more efficient conditions with model studies. After extensive screening of organometallic nucleophiles (EtMgBr, EtLi), additives ($CuBr{\cdot}SMe_2$, $CuBr{\cdot}SMe_2/BF_3{\cdot}Et_2O$, CuI, CuCN, $CuCN/BF_3{\cdot}Et_2O$), solvents (THF, ether), and temperatures (from −78 to 0 °C), either a 2:1 combination of EtMgBr and $CuBr{\cdot}SMe_2$ or a 2:1:1 combination of EtLi, CuCN, and $BF_3{\cdot}Et_2O$ was found to be suitable.[32] Application of the latter conditions (two cycles) gave rise to ethylation product **16** as the only detectable stereoisomer.[33] The C13-stereochemistry was again confirmed by the

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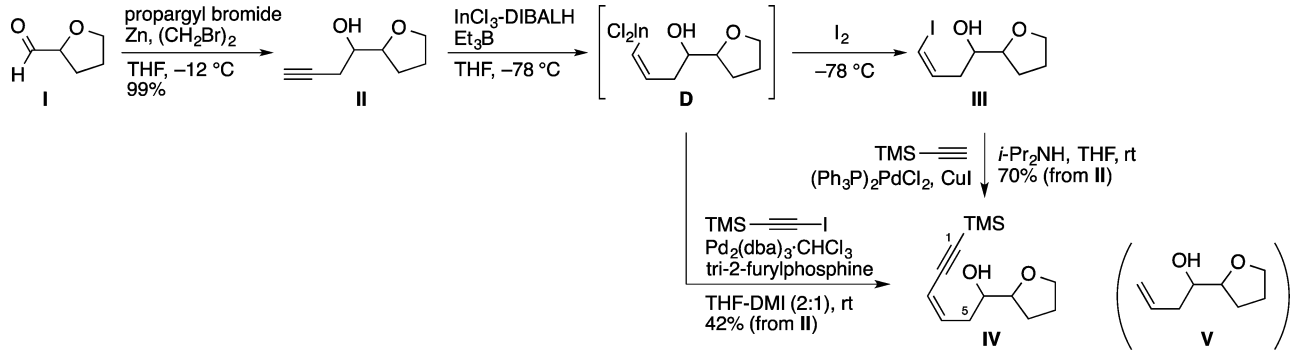
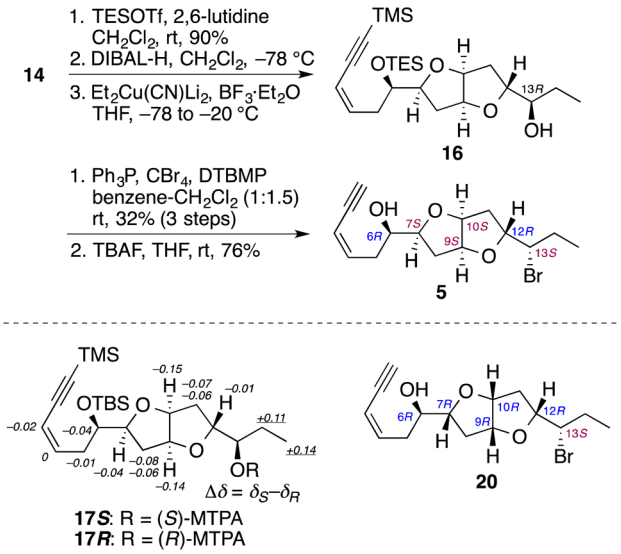
Scheme 3. Model Studies To Construct the *Z*-Enyne Moiety of Laurenidificin



Scheme 4. Total Synthesis of a Possible Stereoisomer of Laurenidificin (5)



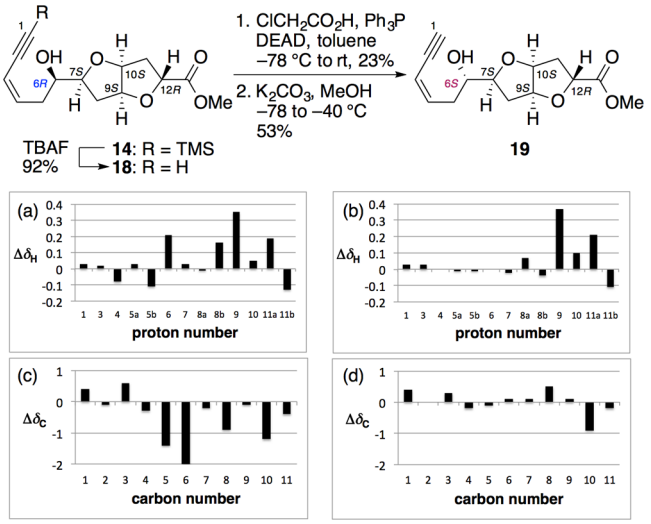


Figure 4. Chemical shift differences between the synthetic compound (**18** or **19**) and the natural laurenidificin. The *x*-axis represents proton or carbon number. The *y*-axis shows chemical shift differences in ppm. (a) $\Delta\delta_H$ = **18** − (natural product). (b) $\Delta\delta_H$ = **19** − (natural product). (c) $\Delta\delta_C$ = **18** − (natural product). (d) $\Delta\delta_C$ = **19** − (natural product).

modified Mosher method (**17*S*** and **17*R***),[31] which revealed that, to our delight, the major product had the desired 13*R*-configuration.[34] The product **16** was subjected to bromination[10−12] with Ph_3P and CBr_4 in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to provide the expected bromide in 32% overall yield for three steps.[35] While the assignment of the stereochemistry at C13 was not possible at this stage, the general S_N2 reaction mode tentatively defined the absolute configuration of C13 as 13*S*.[36] Finally, two silyl groups were simultaneously removed by TBAF to furnish the target molecule **5**.

Contrary to our initial expectations, comparison of the NMR data suggested that **5** was not identical to the natural product.[6,37] In whole, substantial differences in the chemical shifts and the coupling constants were observed, which indicated that the shapes of the two molecules were considerably different. While the stereochemistry at C6 was the same in both, a large difference in the chemical shifts for H6 was observed (δ 3.69 and δ 3.92 for **2** and **5**, respectively). This observation implied that the relative stereochemistry around the C6 center was not the same. To deduce the stereochemical relationship between C6 and C7, the 6*S*-configured alcohol **19** was synthesized from the corresponding 6*R*-alcohol **14** via Mitsunobu inversion with monochloroacetic acid[38,39] (Figure 4). Proton and carbon chemical shift differences ($\Delta\delta_H$ and $\Delta\delta_C$) between the synthetic compound (**18** or **19**) and the natural product (**2**) suggested that **19**, rather than **18**, was more analogous to the natural product, specifically because of the relationship around the C6 center (a vs b, and c vs d). Additionally, the $\Delta\delta_H$ values at C9 in both **18** and **19** exceeded 0.3 ppm, which indicated that the steric environments of the bicyclic core were different. By taking these results and the reported NOE data[6] (vide supra), as well as a possible biosynthetic route,[5,40] into consideration, the most plausible structure of laurenidificin was proposed as **20** with 6*R*,7*R*,9*R*,-10*R*,12*R*,13*S*-configurations (Scheme 4).[41,42] Toward the synthesis of **20**, it would be essential to find an ingenious method for constructing all-cis stereochemistry regarding hydrogens on the dioxabicyclo[3.3.0]octane ring and to obtain an alternative starting material that can readily access the 7*R*-configuration.[43]

Having proved the great potential of the ring contraction strategy for the synthesis of the cis-fused dioxabicyclo[3.3.0]-octane class of halogenated acetogenins, we then extended the strategy to the other stereochemical type. As shown in Figure 1, (−)-aplysiallene (**4**) has a trans relationship with respect to H4 and H6, and H7 and H9,[8d] which seemed ideal for executing the ring contraction reaction. With the established strategy described in Scheme 2 in hand, we decided to carry out the synthesis of (+)-aplysiallene (*ent*-**4**)[8e] bearing the 4*S*,6*R*,7*R*,9*S*-

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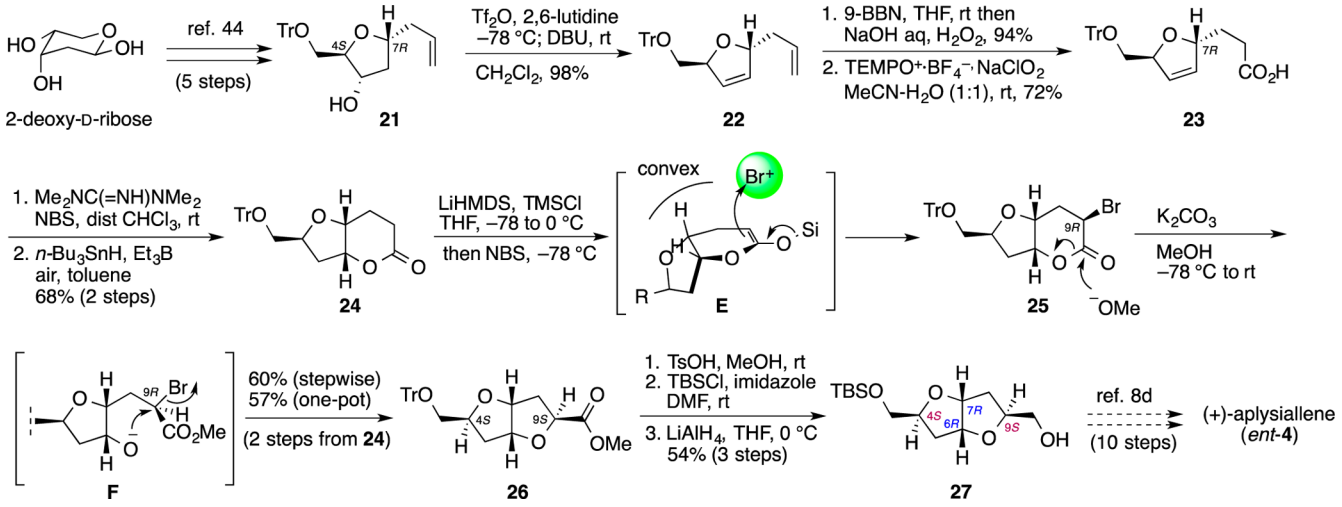
Scheme 5. Formal Total Synthesis of (+)-Aplysiallene (*ent*-4)



configurations. The synthesis again began with 2-deoxy-D-ribose by following the report of Schomaker and Borhan (Scheme 5).[44] A reliable five-step conversion afforded secondary alcohol **21** with the 7*R*-configuration in 68% overall yield. Dehydration of **21** with triflic anhydride followed by hydroboration/oxidation and oxidation with a TEMPO oxoammonium salt/$NaClO_2$ system[45] provided carboxylic acid **23**, whose stereochemistry at C7 was epimeric to that of **10**. Bromolactonization[22] of **23** and reduction with *n*-Bu_3SnH using Et_3B/air as the radical initiator gave rise to the somewhat unstable bicyclic lactone **24**. Subsequent bromination of **24** occurred at the convex face of the bicyclic molecule (**E**) to provide *β*-bromolactone **25** as an only detectable stereoisomer. The ring contraction proceeded through alkoxide **F** in an S_N2 fashion, affording the expected bicycle ether **26** with the 9*S*-configuration in 60% overall yield from **24**. It should be noted that a bromination/ring contraction sequence was achieved in one-pot to provide **26** in 57% overall yield. In the latter case, a small amount of 9-*epi*-**26** was detected (5% yield), which might be arising from epimerization at C9 in **25** under basic conditions.[17] The cis-relationship between H4 and H9 on **26** was confirmed by a strong NOE enhancement of H9 upon irradiation of H4 (Figure 5). The product **26** was then converted into alcohol **27** via a deprotection−reprotection sequence followed by ester reduction with $LiAlH_4$. The NMR spectra of **27** matched those of *ent*-**27** that was prepared in the course of total synthesis of (−)-aplysiallene (**4**).[8d]

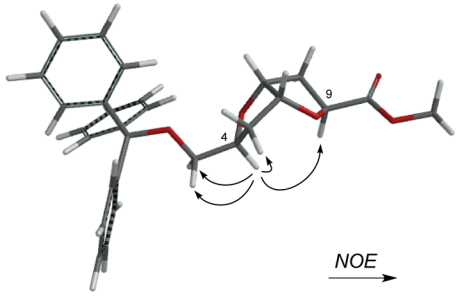


Figure 5. NOE correlations for **26**. The energy-minimized structure was obtained by the molecular mechanics calculation with the MMFF force field.

CONCLUSIONS

In summary, we have achieved a stereocontrolled total synthesis of one possible stereoisomer of laurenidificin, which led to the prediction of the stereochemistry of the natural product. Our synthesis features the formation of the 2,6-dioxabicyclo[3.3.0]-octane framework by a stereospecific bromolactonization−*α*-bromination−ring contraction sequence, followed by a stereoselective propargylation, an insertion of the *Z*-enyne side chain by a hydroindation/cross coupling reaction, and ethylation with an organocuprate reagent. Furthermore, we extended the ring contraction method to the formation of the other stereoisomer (cf. **26**), which constituted a formal total synthesis of (+)-aplysiallene. The overall transformations from carboxylic acids (**10** and **23**) to the ring contraction products (**12** and **26**) were reliable and beneficial for the construction of the branched bicyclic ethers condensed with five-membered rings. Of particular note is that all synthetic sequences from the known substrates were stereoselective and free from separation of stereoisomers. Additional studies directed toward the total synthesis of the most plausible structure of laurenidificin and application of the present method to other halogenated acetogenins are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Techniques. All reactions utilizing air- or moisture-sensitive reagents were performed under an atmosphere of argon or nitrogen. Commercially available dry solvents were used for DMF, CH_2Cl_2, THF, and MeOH. Triethylamine, pyridine, 1,1,1,3,3,3-hexamethyldisilazane, and TMSCl were distilled from CaH_2. *n*-Bu_3SnH was distilled by a Kugelrohr apparatus without a drying agent. *i*-Pr_2NH was distilled from KOH. $CHCl_3$ was distilled from $CaCl_2$. NBS was recrystallized from water. Ph_3P was recrystallized from EtOAc/MeOH. CBr_4 was recrystallized from EtOH. TEMPO$^+BF_4^-$ was prepared according to literature method.[46] Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60-F254) that were analyzed by fluorescence upon 254 nm irradiation or by staining with *p*-anisaldeyde/AcOH/H_2SO_4/EtOH, $12MoO_3{\cdot}H_3PO_4$/EtOH, or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$/$H_2SO_4$. The products were purified by either open chromatography on silica gel (spherical, neutral, 70−230 *μ*m) or flash chromatography on silica gel (spherical, neutral, 40−50 *μ*m) and, if necessary, HPLC with a prepacked column using *n*-hexane/EtOAc as eluent. NMR spectra were recorded with a 300 MHz (^{1}H, 300 MHz; ^{13}C, 75 MHz) or a 400 MHz (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C)

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for $CDCl_3$. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet. Infrared spectra were recorded with a FT/IR spectrometer and are reported as wavenumber (cm^{-1}). Low- and high-resolution FAB mass spectra were recorded with a double-focusing magnetic sector mass spectrometer in positive or negative ion mode. High-resolution ESI, APCI, and APPI mass spectra were recorded with an Orbitrap analyzer in positive or negative ion mode. The carbon numbering described in the peak assignments corresponds to that of laurenidificin and aplysiallene. The NMR peak assignments were confirmed by $^1H-^1H$ COSY analysis.

Synthetic Procedures and Analytical Data. *(4S,5R)-5-((Trityloxy)methyl)tetrahydrofuran-2,4-diol.*[47] In a 500 mL round-bottom flask was placed 2-deoxy-D-ribose (17.3 g, 129 mmol). The substrate was dried by coevaporation with dry pyridine (3 × 8 mL) and then dissolved in the same anhydrous solvent (146 mL). Trityl chloride (43.2 g, 155 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (112 mg, 0.913 mmol) were added, and the resulting solution was stirred for 23 h at 50 °C. Then the solution was cooled to 0 °C and quenched with water. The resulting mixture was evaporated to remove most of pyridine before extraction with EtOAc (2×). The combined organic layer was washed with saturated $KHSO_4$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 4 → 1) to give the title compound (19.9 g, 53.0 mmol, 41%) as a colorless amorphous solid that contained a small amount of inseparable isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.20 (m, 15H), 5.62 (t, 1H, J = 5.0 Hz), 4.36 (td, 1H, J = 4.8, 1.2 Hz), 4.27 (br t, 1H, J = 6.5 Hz), 3.15 (dd, 1H, J = 9.9, 4.5 Hz), 3.11 (dd, 1H, J = 9.9, 5.0 Hz), 2.19 (dt, 1H, J = 14, 5.4 Hz), 2.04 (br d, 1H, J = 14 Hz).

Ethyl 2-((2R,4S,5R)-4-Hydroxy-5-((trityloxy)methyl)-tetrahydrofuran-2-yl)acetate.[20a] In a three-necked round-bottom flask was placed *t*-BuOK (4.18 g, 37.2 mmol). THF (62 mL) was added and the suspension was cooled to 0 °C. Ethyl diethylphosphonoacetate (6.86 mL, 34.6 mmol) was added and the mixture was stirred at 0 °C for 30 min. Then a solution of (4*S*,5*R*)-5-((trityloxy)methyl)tetrahydrofuran-2,4-diol (10.0 g, 26.6 mmol) in THF (89 mL) was added and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched by the addition of saturated NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (hexane/EtOAc = 5 → 3 → 2) followed by flash chromatography (*n*-hexane/EtOAc = 6 → 4 → 2) to give the title compound (8.76 g, 19.6 mmol, 67%) as a colorless amorphous solid and its diastereomer (2.21 g, 4.94 mmol, 17%) as a colorless amorphous solid. Data for title compound: ^1H NMR (300 MHz, $CDCl_3$) δ 7.47−7.41 (m, 6H), 7.33−7.20 (m, 9H), 4.61−4.51 (m, 1H), 4.36−4.30 (m, 1H), 4.15 (q, 2H, J = 7.2 Hz), 3.93 (ddd, 1H, J = 5.7, 4.5, 2.4 Hz), 3.24 (dd, 1H, J = 9.6, 4.5 Hz), 3.09 (dd, 1H, J = 9.6, 5.7 Hz), 2.66 (dd, 1H, J = 15, 7.2 Hz), 2.51 (dd, 1H, J = 15, 6.0 Hz), 2.06 (ddd, 1H, J = 13, 5.4, 2.1 Hz), 1.84 (ddd, 1H, J = 13, 9.9, 6.3 Hz), 1.75 (d, 1H, J = 3.6 Hz), 1.25 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 143.9, 128.8, 128.0, 127.2, 86.9, 85.9, 74.8, 74.7, 64.8, 60.7, 40.9, 40.7, 14.3. Data for diastereomer: 7.47−7.37 (m, 6H), 7.33−7.20 (m, 9H), 4.50 (qui, 1H, J = 6.5 Hz), 4.35−4.28 (m, 1H), 4.16 (q, 2H, J = 7.2 Hz), 4.08−4.03 (m, 1H), 3.24 (dd, 1H, J = 9.6, 4.5 Hz), 3.09 (dd, 1H, J = 9.6, 6.3 Hz), 2.73 (dd, 1H, J = 16, 6.6 Hz), 2.65 (dd, 1H, J = 16, 6.0 Hz), 2.47 (d, 1H, J = 5.1 Hz), 2.45 (dt, 1H, J = 13, 6.9 Hz), 1.78 (ddd, 1H, J = 13, 6.3, 4.8 Hz), 1.26 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 143.9, 128.8, 128.0, 127.2, 87.0, 84.9, 74.9, 64.7, 60.7, 40.9, 39.9, 14.3.

*Ethyl 2-((2S,5S)-5-((Trityloxy)methyl)-2,5-dihydrofuran-2-yl)-acetate (**8**).*[20b] To a solution of ethyl 2-((2*R*,4*S*,5*R*)-4-hydroxy-5-((trityloxy)methyl)tetrahydrofuran-2-yl)acetate (5.00 g, 11.2 mmol) in CH_2Cl_2 (112 mL) were added 2,6-lutidine (3.89 mL, 33.6 mmol) and Tf_2O (2.83 mL, 16.8 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C, followed by the addition of DBU (16.7 mL, 112 mmol). The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution. After removal of CH_2Cl_2 by evaporation, the residue was extracted with *n*-hexane/EtOAc (5/1) (2×). The combined organic layer was washed with 1 M aqueous HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 10) to give alkene **8** (3.70 g, 8.63 mmol, 77%) as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.44 (m, 6H, Tr), 7.33−7.20 (m, 9H, Tr), 5.94 (ddd, 1H, J = 6.3, 2.1, 1.5 Hz, H8), 5.85 (br dt, 1H, J = 6.3, 1.8 Hz, H9), 5.28−5.22 (m, 1H, H10), 5.00−4.95 (m, 1H, H7), 4.16 (q, 2H, J = 7.1 Hz, OEt), 3.20 (dd, 1H, J = 9.6, 5.4 Hz, H6), 3.11 (dd, 1H, J = 9.6, 4.5 Hz, H6), 2.72 (dd, 1H, J = 15, 7.2 Hz, H11), 2.55 (dd, 1H, J = 15, 6.3 Hz, H11), 1.26 (t, 3H, J = 7.1 Hz, OEt); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 144.1, 130.2, 128.9, 128.8, 127.9, 127.1, 86.6, 86.0, 82.7, 67.0, 60.7, 42.2, 14.4; FT-IR (film on ZnSe) 3058, 3022, 2981, 2868, 1729, 1597, 1491, 1449, 1373, 1300, 1262, 1220, 1173, 1076 cm^{-1}; HRMS (FAB) m/z calcd for $C_{28}H_{28}O_4$ $[M + Na]^+$ 451.1885, found 451.1915.

*(2S,5S)-2-(3-Methoxyallyl)-5-((trityloxy)methyl)-2,5-dihydrofuran (**9**).* To a solution of ester **8** (5.77 g, 13.5 mmol) in CH_2Cl_2 (112 mL) was added DIBAL-H (1.04 M in *n*-hexane, 15.5 mL, 16.2 mmol) through a dropping funnel over 20 min at −78 °C. After 10 min at −78 °C, the reaction mixture was quenched by the addition of saturated Rochelle salt solution. The resulting mixture was stirred at room temperature until two phases were clearly separated (3 h). After removal of CH_2Cl_2 by evaporation, the residue was extracted with *n*-hexane (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5 → 2) to give aldehyde (4.92 g, 12.8 mmol, 95%) as a colorless amorphous solid and a small amount of the corresponding alcohol (202 mg, 0.522 mmol, 4%). Data for aldehyde: $[\alpha]_D^{27}$ −60.6 (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (t, 1H, J = 1.8 Hz, CHO), 7.47−7.20 (m, 15H, Tr), 5.90 (ddd, 1H, J = 6.3, 2.1, 1.5 Hz, H5), 5.86 (ddd, 1H, J = 6.0, 2.1, 1.2 Hz, H4), 5.35−5.28 (m, 1H, H3), 5.01−4.95 (m, 1H, H6), 3.19 (dd, 1H, J = 9.6, 5.3 Hz, H7), 3.13 (dd, 1H, J = 9.6, 4.1 Hz, H7), 2.79 (ddd, 1H, J = 17, 7.5, 2.1 Hz, H2), 2.68 (ddd, 1H, J = 17, 5.1, 1.5 Hz, H2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 144.0, 129.9, 128.8, 127.9, 127.1, 86.5, 86.1, 81.2, 66.7, 50.6; FT-IR (film on ZnSe) 3086, 3058, 3023, 2921, 2867, 1725, 1596, 1492, 1449, 1360, 1265, 1219, 1183, 1154, 1090 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{26}H_{24}O_3Na$ $[M + Na]^+$ 407.1618, found 407.1611.

To a suspension of (methoxymethyl)triphenylphosphonium chloride (15.2 g, 44.5 mmol) in THF (60 mL) was added fleshly prepared LiHMDS (0.5 M in THF, 76.2 mL, 38.1 mmol) through a dropping funnel over 20 min at 0 °C. After completion of the addition, the mixture was stirred for 1 h at 0 °C. The suspension was then cooled to −78 °C followed by the addition of aldehyde (4.88 g, 12.7 mmol) in THF (67 mL) over 20 min. The resulting mixture was gradually warmed to 0 °C and stirred for 2 h. The reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and extracted with ether (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 100 → 50 → 10) to give enol ether **9** (4.91 g, 11.9 mmol, 94%, E/Z = 3:1) as a colorless solid. The following analytical data was collected as a mixture of stereoisomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.46 (m, 6H, Tr), 7.32−7.19 (m, 9H, Tr), 6.31 (br d, 0.75H, J = 13 Hz, H13), 5.91 (dt, 0.25H, J = 6.3, 1.4 Hz, H13), 5.88−5.76 (m, 2H, H8, H9), 5.01−4.95 (m, 1H, H7), 4.89−4.80 (m, 1H, H10), 4.70 (dt, 0.75H, J = 13, 7.6 Hz, H12), 4.44 (dt, 0.25H, J = 7.5, 6.3 Hz, H12), 3.55 (s, 0.75H, OMe), 3.44 (s, 2.25H, OMe), 3.200 (dd, 0.25H, J = 9.3, 6.0 Hz, H6), 3.193 (dd, 0.75H, J = 9.3, 5.7 Hz, H6), 3.070 (dd, 0.25H, J = 9.3, 4.5 Hz, H6), 3.065 (dd, 0.75H, J = 9.6, 4.2 Hz, H6), 2.40−2.12 (m, 2H, H11); FT-IR (film on ZnSe) 3086, 3059, 3033, 2929, 2862, 1656, 1596, 1491, 1449, 1389, 1358, 1215, 1153, 1132, 1075 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{28}H_{28}O_3Na$ $[M + Na]^+$ 435.1931, found 435.1920.

*3-((2S,5S)-5-((Trityloxy)methyl)-2,5-dihydrofuran-2-yl)propanoic Acid (**10**).* To a solution of enol ether **9** (4.91 g, 11.9 mmol) in THF

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(120 mL) was added 1 M aqueous HCl (1.2 mL). The mixture was stirred at room temperature for 13 h. After dilution with Et_2O, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution. The resulting mixture was stirred for 1 h before extraction with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 2) to give aldehyde (4.64 g, 11.6 mmol, 98%) as a pale yellow amorphous solid: $[\alpha]_D^{25}$ −53.3 (*c* 1.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, 1H, *J* = 1.5 Hz, H13), 7.49−7.45 (m, 6H, Tr), 7.33−7.20 (m, 9H, Tr), 5.84−5.78 (m, 2H, H8, H9), 4.99−4.94 (m, 1H, H7), 4.94−4.87 (m, 1H, H10), 3.20 (dd, 1H, *J* = 9.6, 5.7 Hz, H6), 3.11 (dd, 1H, *J* = 9.6, 4.2 Hz, H6), 2.54 (td, 2H, *J* = 7.5, 1.5 Hz, H12), 2.00 (dtd, 1H, *J* = 14, 7.5, 4.2 Hz, H11), 1.84 (dq, 1H, *J* = 14, 7.5 Hz, H11); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 144.1, 130.6, 128.9, 128.6, 127.9, 127.1, 86.6, 85.7, 85.3, 67.2, 40.0, 28.6; FT-IR (film on ZnSe) 3085, 3057, 3032, 2921, 2863, 2724, 1724, 1596, 1492, 1449, 1410, 1389, 1372, 1321, 1220, 1183, 1154 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{27}H_{26}O_3Na$ [M + Na]$^+$ 421.1774, found 421.1764.

To a solution of aldehyde (4.64 g, 11.6 mmol) in THF (35 mL) were added *t*-BuOH (69 mL), 2-methyl-2-butene (6.42 mL, 60.5 mmol), and saturated aqueous $NaHCO_3$ solution (23.4 mL). After cooling at 0 °C, a premixed solution of NaH_2PO_4 (4.36 g, 36.3 mmol) and $NaClO_2$ (3.28 g, 36.3 mmol) in water (17 mL) was added. The resulting mixture was stirred for 20 min at 0 °C before addition of $CHCl_3$ and 1 M aqueous HCl. The organic layer was separated and the aqueous phase was extracted with $CHCl_3$ (2×). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 5 → 2 containing 3% MeOH) to give carboxylic acid **10** (4.55 g, 11.0 mmol, 94%) as a colorless solid: $[\alpha]_D^{24}$ −26.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.45 (m, 6H, Tr), 7.33−7.19 (m, 9H, Tr), 5.83−5.78 (m, 2H, H8, H9), 5.00−4.93 (m, 1H, H7), 4.94−4.88 (m, 1H, H10), 3.19 (dd, 1H, *J* = 9.6, 6.0 Hz, H6), 3.10 (dd, 1H, *J* = 9.6, 4.2 Hz, H6), 2.47 (t, 2H, *J* = 7.6 Hz, H12), 1.99 (dtd, 1H, *J* = 15, 7.6, 4.1 Hz, H11), 1.84 (dq, 1H, *J* = 15, 7.4 Hz, H11); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.8, 144.1, 130.5, 128.9, 128.5, 127.9, 127.1, 86.5, 85.8, 85.3, 67.2, 31.2, 30.0; FT-IR (film on ZnSe) 3087, 3057, 3023, 2925, 2867, 1708, 1597, 1491, 1449, 1414, 1217, 1183, 1157, 1034 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{27}H_{26}O_4Na$ [M + Na]$^+$ 437.1723, found 437.1713.

*(2S,3aS,7aS)-2-((Trityloxy)methyl)hexahydro-5H-furo[3,2-b]-pyran-5-one (**11**).* To a solution of carboxylic acid **10** (215 mg, 0.519 mmol) in fleshly distilled $CHCl_3$ (5.2 mL) were added 1,1,3,3-tetramethylguanidine (19.5 μL, 0.156 mmol) and NBS (140 mg, 0.785 mmol). The mixture was stirred for 2.5 h at room temperature and quenched by the addition of saturated aqueous Na_2SO_3 solution. The resulting mixture was extracted with ether (2×), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Bromolactone was obtained as a yellow amorphous solid (256 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.18 (m, 15H, Tr), 4.98 (br d, 1H, *J* = 4.8 Hz, H9), 4.43 (q, 1H, *J* = 4.2 Hz, H10), 4.24−4.17 (m, 2H, H7, H8), 3.37 (dd, 1H, *J* = 10, 3.0 Hz, H6), 3.28 (dd, 1H, *J* = 10, 4.8 Hz, H6), 2.67 (ddd, 1H, *J* = 17, 12, 5.7 Hz, H12), 2.45 (dt, 1H, *J* = 17, 5.1 Hz, H12), 2.28−2.05 (m, 2H, H11); FT-IR (film on ZnSe) 3087, 3057, 3022, 2925, 2873, 1756, 1597, 1490, 1449, 1414, 1379, 1357, 1317, 1246, 1218, 1182, 1157 cm^{-1}.

The crude bromolactone (256 mg) was dissolved in toluene (5.2 mL) followed by the addition of *n*-Bu_3SnH (0.18 mL, 0.69 mmol) and AIBN (17.6 mg, 0.107 mmol). The mixture was warmed to 95 °C and stirred for 1 h. Then the reaction mixture was cooled to room temperature and quenched by the addition of saturated aqueous KF solution. The resulting mixture was vigorously stirred for 16 h and filtered through a pad of Celite. The filter cake was thoroughly washed with EtOAc, and the filtrate was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by 10% w/w KF−Florisil chromatography[48] (*n*-hexane/EtOAc = 6 → 1 → 0.5) to give lactone **11** (181 mg, 0.437 mmol, 84%) as a colorless solid: $[\alpha]_D^{26}$ +5.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.44 (m, 6H, Tr), 7.34−7.20 (m, 9H, Tr), 4.87 (ddd, 1H, *J* = 7.2, 4.5, 2.7 Hz, H9), 4.17−4.08 (m, 2H, H7, H10), 3.27 (dd, 1H, *J* = 9.9, 6.3 Hz, H6), 3.16 (dd, 1H, *J* = 9.9, 3.9 Hz, H6), 2.62 (ddd, 1H, *J* = 17, 11, 6.0 Hz, H12), 2.50−2.34 (m, 2H, H8, H12), 2.23−2.04 (m, 2H, H11), 1.93 (ddd, 1H, *J* = 14, 7.5, 2.7 Hz, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 143.9, 128.8, 127.9, 127.2, 86.7, 81.6, 77.3, 74.3, 65.9, 37.3, 25.8, 23.4; FT-IR (film on ZnSe) 3058, 3020, 2918, 2869, 1733, 1596, 1490, 1449, 1377, 1315, 1315, 1293, 1259, 1218, 1185, 1158 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{27}H_{26}O_4Na$ [M + Na]$^+$ 437.1723, found 437.1712.

*Methyl (2R,3aS,5S,6aS)-5-(Hydroxymethyl)hexahydrofuro[3,2-b]-furan-2-carboxylate (**12a**).* To a solution of lactone **11** (376 mg, 0.907 mmol) in THF (4.6 mL) was added LiHMDS (0.5 M solution in THF, 2.4 mL, 1.2 mmol) at −78 °C. After 1 h at −78 °C, TMSCl (173 μL, 1.36 mmol) was added and the resultant mixture was warmed to 0 °C. After 30 min, the solution was again cooled to −78 °C followed by the addition of NBS (275 mg, 1.54 mmol) in THF (4.5 mL). The reaction mixture was stirred for 1 h at −78 °C and quenched by the addition of pH 7 phosphate buffer. The resulting mixture was extracted with ether (2×), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Bromolactone **7** (568 mg) was obtained as a pale yellow amorphous solid. As the product was unstable on silica gel, it was submitted to the next reaction without further purification. To a solution of crude bromolactone **7** (568 mg) in MeOH (19 mL) was added K_2CO_3 (252 mg, 1.82 mmol) at −78 °C. The suspension was warmed to room temperature and stirred for 20 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give methyl ester **12** (418 mg) as a pale yellow amorphous solid. An analytical sample was obtained by column chromatography (*n*-hexane/EtOAc = 5 → 2): $[\alpha]_D^{28}$ −9.1 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.45 (m, 6H, Tr), 7.33−7.20 (m, 9H, Tr), 4.83 (ddd, 1H, *J* = 6.3, 3.9, 2.1 Hz, H9), 4.61−4.56 (m, 2H, H10, H12), 4.18 (qd, 1H, *J* = 6.9, 3.9 Hz, H7), 3.75 (s, 3H, OMe), 3.26 (dd, 1H, *J* = 9.9, 6.6 Hz, H6), 3.09 (dd, 1H, *J* = 9.9, 3.9 Hz, H6), 2.53 (dd, 1H, *J* = 14, 6.6 Hz, H11), 2.25 (ddd, 1H, *J* = 14, 8.1, 6.6 Hz, H8), 2.06 (ddd, 1H, *J* = 14, 9.6, 4.8 Hz, H11), 1.87 (ddd, 1H, *J* = 14, 6.9, 2.1 Hz, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 144.1, 128.9, 127.9, 127.1, 86.6, 85.4, 84.0, 79.8, 76.6, 66.4, 52.3, 37.7, 36.3; FT-IR (film on ZnSe) 3086, 3057, 3020, 2951, 2871, 1754, 1596, 1496, 1450, 1362, 1322 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{28}H_{28}O_5Na$ [M + Na]$^+$ 467.1829, found 467.1823.

To a solution of crude methyl ether **12** (418 mg) in MeOH (9 mL) was added $TsOH{\cdot}H_2O$ (86.3 mg, 0.454 mmol). After 1.5 h at room temperature, the reaction mixture was quenched by the addition of Et_3N (635 μL, 4.56 mmol). The resulting mixture was concentrated and directly purified by flash chromatography (*n*-hexane/EtOAc/MeOH = 20/100/3 → 10/100/3) to give alcohol **12a** (167 mg, 0.826 mmol, 91% for three steps) as a colorless oil: $[\alpha]_D^{26}$ +22.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (ddd, 1H, *J* = 6.6, 3.9, 2.4 Hz, H9), 4.68 (dd, 1H, *J* = 9.0, 6.6 Hz, H12), 4.55 (t, 1H, *J* = 4.2 Hz, H10), 4.09 (qd, 1H, *J* = 7.0, 3.3 Hz, H7), 3.75 (s, 3H, OMe), 3.72 (dd, 1H, *J* = 12, 3.3 Hz, H6), 3.59 (dd, 1H, *J* = 12, 6.3 Hz, H6), 2.50 (dd, 1H, *J* = 14, 6.9 Hz, H11), 2.26 (ddd, 1H, *J* = 14, 7.2, 6.9 Hz, H8), 2.07 (ddd, 1H, *J* = 14, 9.3, 5.1 Hz, H11), 1.89 (ddd, 1H, *J* = 14, 7.2, 2.1 Hz, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 85.6, 84.0, 81.0, 76.7, 65.0, 52.4, 37.4, 35.0; FT-IR (film on ZnSe) 3477, 2958, 2928, 2855, 1743, 1442, 1373, 1260, 1213, 1173 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_9H_{15}O_5$ [M + H]$^+$ 203.0914, found 203.0913.

*Methyl (2R,3aS,5S,6aS)-5-((R)-1-Hydroxybut-3-yn-1-yl)-hexahydrofuro[3,2-b]furan-2-carboxylate (**6**).* To a solution of alcohol **12a** (10.4 mg, 0.0514 mmol) in CH_2Cl_2 (1.0 mL) were added $NaHCO_3$ (34.5 mg, 0.411 mmol) and Dess−Martin periodinane (65.3 mg, 0.154 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 1.5 h. After dilution with CH_2Cl_2 (1.5 mL), the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. The resulting mixture was stirred for 30 min and extracted

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with CH_2Cl_2 (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give aldehyde **13** as a pale yellow solid (9.5 mg). As the polarity of **13** was very high and exhibited tailing on TLC, aldehyde **13** was submitted to the next reaction without purification. Data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, 1H, J = 1.2 Hz, CHO), 4.81−4.76 (m, 2H, H9, H12), 4.68 (t, 1H, J = 7.8 Hz, H10), 4.41 (br dd, 1H, J = 9.6, 2.4 Hz, H7), 3.74 (s, 3H, OMe), 2.72 (br dd, 1H, J = 14, 7.8 Hz, H11), 2.51 (br dd, 1H, J = 14, 3.0 Hz, H8), 2.36 (ddd, 1H, J = 14, 9.9, 3.9 Hz, H8), 2.24 (ddd, 1H, J = 14, 7.8, 4.8 Hz, H11).

To a suspension of Zn dust (124 mg, 1.91 mmol) in THF (2 mL) was added 1,2-dibromoethane (18.9 μL, 0.219 mmol). The suspension was heated at reflux for 6 min, followed by the addition of propargyl bromide (71.6 μL, 0.950 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, followed by the addition of crude aldehyde (9.5 mg) in THF (1.5 mL). The resulting mixture was stirred for 15 min at 0 °C and quenched by the addition of saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 1/10) to give alcohol **6** (7.6 mg, 0.032 mmol, 67%, dr >20:1) as a colorless viscous oil: $[\alpha]_D^{25}$ −4.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.86 (ddd, 1H, J = 6.3, 3.9, 2.1 Hz, H9), 4.66 (dd, 1H, J = 9.0, 6.9 Hz, H12), 4.54 (br dd, 1H, J = 4.5, 4.2 Hz, H10), 4.03 (td, 1H, J = 7.4, 5.4 Hz, H7), 3.87 (td, 1H, J = 6.0, 5.7 Hz, H6), 3.76 (s, 3H, OMe), 2.50 (dd, 1H, J = 14, 6.9 Hz, H11), 2.47−2.44 (m, 2H, H5), 2.29 (ddd, 1H, J = 14, 7.5, 6.3 Hz, H8), 2.13 (ddd, 1H, J = 14, 7.2, 2.1 Hz, H8), 2.09 (ddd, 1H, J = 14, 9.0, 4.8 Hz, H11), 2.05 (t, 1H, J = 2.9 Hz, H3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 85.5, 83.9, 82.1, 80.2, 76.6, 71.1, 70.9, 52.4, 37.4, 33.9, 23.9 cm^{-1}; FT-IR (film on ZnSe) 3473, 3280, 2952, 2911, 2118, 1957, 1747, 1440, 1373, 1287, 1261, 1216, 1171 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{12}H_{17}O_5$ [M + H]$^+$ 241.1071, found 241.1062.

*Methyl (2R,3aS,5S,6aS)-5-((R,Z)-1-Hydroxy-6-(trimethylsilyl)hex-3-en-5-yn-1-yl)hexahydrofuro[3,2-b]furan-2-carboxylate (**14**).* In a 20 mL two-necked round-bottom flask was placed $InCl_3$ (74.8 mg, 0.338 mmol). The solid was thoroughly dried by a heat-gun in vacuo. THF (1 mL) was added and the suspension was cooled to −78 °C. DIBAL-H (1.0 M solution in *n*-hexane, 0.317 mL, 0.317 mmol) was added over 6 min and the mixture was stirred for 30 min at −78 °C. A solution of alcohol **6** (29.2 mg, 0.122 mmol) in THF (1 mL) and Et_3B (1 M solution in THF, 61.0 μL, 0.0610 mmol) were added sequentially, and the resulting mixture was stirred for 3 h at −78 °C. Iodine (186 mg, 0.733 mmol) was then added in one portion and the stirring was continued for 15 min at −78 °C. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution followed by saturated aqueous $Na_2S_2O_3$ solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give vinyl iodide as a yellow oil (44.9 mg), which was used for the next reaction without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38−6.28 (m, 2H, H3, H4), 4.87 (ddd, 1H, J = 6.6, 4.2, 2.7 Hz, H9), 4.68 (dd, 1H, J = 8.7, 6.6 Hz, H12), 4.52 (t, 1H, J = 4.8 Hz, H10), 3.97−3.89 (m, 2H, H6, H7), 3.76 (s, 3H, OMe), 2.52 (dd, 1H, J = 14, 6.9 Hz, H11), 2.35−2.13 (m, 4H, H5, H8), 2.09 (ddd, 1H, J = 14, 8.7, 4.8 Hz, H11).

In a 20 mL two-necked round-bottom flask were placed $(Ph_3P)_2PdCl_2$ (8.6 mg, 0.024 mmol), CuI (4.6 mg, 0.024 mmol), ethynyltrimethylsilane (33.8 μL, 0.244 mmol), and *i*-Pr_2NH (51.8 μL, 0.366 mmol). A solution of vinyl iodide (44.9 mg) in THF (2 mL) was added and the mixture was stirred for 1 h at room temperature. An additional portion of $(Ph_3P)_2PdCl_2$ (0.8 mg, 2 μmol) was added and the stirring was continued for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 1) to give enyne **14** (29.0 mg, 0.0857 mmol, 70% for two steps, *Z*/*E* > 20:1) as a yellow oil: $[\alpha]_D^{27}$ +20.2 (*c* 0.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (ddd, 1H, J = 11, 8.4, 6.6 Hz, H4), 5.60 (dt, 1H, J = 11, 1.4 Hz, H3), 4.88 (ddd, 1H, J = 6.9, 4.2, 2.7 Hz, H9), 4.67 (dd, 1H, J = 9.0, 6.6 Hz, H12), 4.51 (dd, 1H, J = 4.8, 4.2 Hz, H10), 3.96−3.85 (m, 2H, H6, H7), 3.75 (s, 3H, OMe), 2.58 (dddd, 1H, J = 14, 8.4, 6.0, 1.2 Hz, H5), 2.50 (dd, 1H, J = 14, 6.6 Hz, H11), 2.52−2.38 (m, 1H, H5), 2.27 (dt, 1H, J = 14, 6.9 Hz, H8), 2.12 (ddd, 1H, J = 14, 7.8, 3.0 Hz, H8), 2.07 (ddd, 1H, J = 14, 9.2, 4.8 Hz, H11), 0.18 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 140.1, 111.9, 101.6, 99.8, 85.4, 83.6, 83.0, 76.5, 71.1, 52.4, 37.3, 34.4, 32.9, 0.1; FT-IR (film on ZnSe) 3508, 3025, 2952, 2897, 2148, 1743, 1616, 1436, 1370, 1249, 1210, 1171 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{17}H_{27}O_5Si$ [M + H]$^+$ 339.1622, found 339.1615.

*Methyl (2R,3aS,5S,6aS)-5-((R,Z)-1-Hydroxyhex-3-en-5-yn-1-yl)-hexahydrofuro[3,2-b]furan-2-carboxylate (**18**).* To a solution of enyne **14** (28.2 mg, 0.0833 mmol) in THF (0.8 mL) was added TBAF (1 M solution in THF, 125 μL, 0.125 mmol). The mixture was stirred for 30 min at room temperature and directly subjected to flash chromatography (*n*-hexane/EtOAc = 1 → 0.5) to give alcohol **18** (20.5 mg, 0.0770 mmol, 92%) as a yellow oil: $[\alpha]_D^{26}$ +9.9 (*c* 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.09 (dddd, 1H, J = 11, 7.8, 6.9, 0.9 Hz, H4), 5.57 (ddt, J = 11, 2.6, 1.5 Hz, H3), 4.86 (ddd, 1H, J = 6.6, 3.9, 2.4 Hz, H9), 4.67 (dd, 1H, J = 8.9, 6.8 Hz, H12), 4.51 (t, 1H, J = 4.5 Hz, H10), 3.94−3.85 (m, 2H, H6, H7), 3.75 (s, 3H, OMe), 3.11 (d, 1H, J = 1.8 Hz, H1), 2.57 (dddd, 1H, J = 14, 8.1, 5.1, 1.2 Hz, H5), 2.49 (dd, 1H, J = 14, 6.8 Hz, H11), 2.49−2.37 (m, 1H, H5), 2.26 (dt, 1H, J = 14, 6.9 Hz, H8), 2.11 (ddd, 1H, J = 14, 7.2, 2.4 Hz, H8), 2.07 (ddd, 1H, J = 14, 9.2, 5.1 Hz, H11); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.1, 110.8, 85.4, 83.6, 83.1, 82.3, 80.2, 76.5, 71.3, 52.4, 37.3, 34.4, 33.0; FT-IR (film on ZnSe) 3490, 3291, 3028, 2952, 2898, 2095, 1746, 1616, 1436, 1375, 1286, 1261, 1216, 1170 cm^{-1}. HRMS (APCI-pos) *m*/*z* calcd for $C_{14}H_{19}O_5$ [M + H]$^+$ 267.1227, found 267.1228.

*Methyl (2R,3aS,5S,6aS)-5-((R,Z)-1-(((S)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-3-en-5-yn-1-yl)hexahydrofuro[3,2-b]-furan-2-carboxylate (**15S**).* To a solution of alcohol **18** (3.2 mg, 12 μmol) in CH_2Cl_2 (0.5 mL) were added DMAP (5.9 mg, 0.049 mmol), Et_3N (2.5 μL, 0.018 mmol), and (*R*)-(−)-MTPACl (4.5 μL, 0.024 mmol). The mixture was stirred for 3 h at room temperature. As TLC indicated incomplete esterification, additional portions of DMAP (5.9 mg, 0.049 mmol), Et_3N (47.6 μL, 0.342 mmol), and (*R*)-(−)-MTPACl (4.5 μL, 0.024 mmol) were added, and the mixture was stirred at 80 °C for 17 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (*n*-hexane/EtOAc = 2) to give (*S*)-MTPA ester **15S** (1.5 mg, 3.1 μmol, 26%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H, Ph), 7.42−7.37 (m, 3H, Ph), 6.02 (br dt, 1H, J = 11, 7.5 Hz, H4), 5.59 (ddt, J = 11, 2.1, 1.6 Hz, H3), 5.34 (dt, 1H, J = 6.9, 5.7 Hz, H6), 4.81 (ddd, 1H, J = 7.2, 4.2, 2.7 Hz, H9), 4.45 (t, 1H, J = 4.7 Hz, H10), 4.37 (dd, 1H, J = 9.3, 6.6 Hz, H12), 3.90 (ddd, 1H, J = 8.1, 6.9, 6.0 Hz, H7), 3.75 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.15 (br d, 1H, J = 2.4 Hz, H1), 2.80 (br t, 2H, J = 7.2 Hz, H5), 2.31 (br dd, 1H, J = 14, 6.9 Hz, H11), 2.18 (dt, 1H, J = 14, 6.9 Hz, H8), 1.97 (ddd, 1H, J = 15, 9.3, 5.4 Hz, H11), 1.83 (ddd, 1H, J = 14, 8.1, 2.7 Hz, H8); FT-IR (film on ZnSe) 3287, 3064, 3032, 2954, 2853, 1747, 1492, 1451, 1440, 1369, 1268, 1218, 1171, 1122, 1085, 1019 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{24}H_{29}O_7NF_3$ [M + NH_4]$^+$ 500.1891, found 500.1867.

*Methyl (2R,3aS,5S,6aS)-5-((R,Z)-1-(((R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-3-en-5-yn-1-yl)hexahydrofuro-[3,2-b]furan-2-carboxylate (**15R**).* To a solution of alcohol **18** (2.3 mg, 8.3 μmol) in CH_2Cl_2 (0.3 mL) were added DMAP (4.4 mg, 0.036 mmol), Et_3N (1.4 μL, 0.010 mmol), and (*S*)-(+)-MTPACl (3.2 μL, 0.017 mmol). The mixture was stirred for 30 min at room temperature and quenched by the addition of water. The resulting mixture was extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 2) to give (*R*)-MTPA ester **15R** (2.8 mg, 5.8 μmol, 67%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.51 (m, 2H, Ph), 7.43−7.37 (m, 3H, Ph), 5.89 (dtd, 1H, J = 9.9, 6.3, 0.9 Hz, H4), 5.52 (ddt, J = 11, 2.1, 1.5 Hz, H3), 5.34 (ddd, 1H, J = 6.6, 5.7, 4.8 Hz, H6), 4.88 (ddd, 1H, J = 7.5, 4.2, 3.3 Hz, H9), 4.52 (dd, 1H, J = 9.6, 6.9 Hz, H12), 4.51 (t, 1H, J = 4.7 Hz, H10), 3.98 (ddd, 1H, J = 8.7, 6.9, 4.5 Hz, H7), 3.74 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.12 (dd, 1H, J = 2.4, 0.9 Hz, H1),

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2.77 (br dt, 1H, J = 15, 5.7 Hz, H5), 2.73 (br dt, 1H, J = 15, 7.2 Hz, H5), 2.45 (dd, 1H, J = 14, 6.9 Hz, H11), 2.31 (dt, 1H, J = 14, 6.9 Hz, H8), 2.03 (ddd, 1H, J = 14, 9.6, 5.1 Hz, H11), 1.94 (ddd, 1H, J = 14, 9.0, 3.0 Hz, H8); FT-IR (film on ZnSe) 3292, 3064, 3030, 2952, 2852, 1752, 1494, 1451, 1440, 1367, 1259, 1217, 1172, 1122, 1087 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{24}H_{29}O_7NF_3$ $[M + NH_4]^+$ 500.1891, found 500.1873.

*(R)-1-((2R,3aS,5S,6aS)-5-((R,Z)-1-((tert-Butyldimethylsilyl)oxy)-6-(trimethylsilyl)hex-3-en-5-yn-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-propyl (S)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (**17S**).* To a solution of alcohol **14** (19.4 mg, 0.0573 mmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (27 μL, 0.30 mmol) and TBSOTf (15 μL, 0.086 mmol). After 40 min at room temperature, 2,6-lutidine (6.6 μL, 0.057 mmol) and TBSOTf (5.0 μL, 0.029 mmol) were additionally added. After 1 h, 2,6-lutidine (17 μL, 0.14 mmol) and TBSOTf (10 μL, 0.057 mmol) were added. After 40 min, 2,6-lutidine (20 μL, 0.17 mmol) and TBSOTf (15 μL, 0.086 mmol) were additionally added. After 30 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution. The resulting mixture was extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (n-hexane/EtOAc = 5) to give TBS ether (21.6 mg, 0.0478 mmol, 83%) as a colorless oil: $[\alpha]_D^{28}$ −18.1 (c 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (dt, 1H, J = 11, 7.5 Hz, H4), 5.55 (dt, 1H, J = 11, 1.4 Hz, H3), 4.88 (ddd, 1H, J = 7.5, 4.8, 3.3 Hz, H9), 4.62 (dd, 1H, J = 9.9, 6.3 Hz, H12), 4.46 (t, 1H, J = 4.8 Hz, H10), 3.91 (td, 1H, J = 5.4, 4.5 Hz, H6), 3.75 (s, 3H, OMe), 3.72 (ddd, 1H, J = 9.0, 6.3, 4.2 Hz, H7), 2.55−2.48 (m, 2H, H5), 2.42 (dd, 1H, J = 14, 6.3 Hz, H11), 2.22 (dt, 1H, J = 14, 6.9 Hz, H8), 2.06−1.93 (m, 2H, H8, H11), 0.88 (s, 9H, TBS), 0.18 (s, 9H, TMS), 0.08 (s, 6H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 140.5, 111.3, 101.9, 99.3, 85.3, 83.1, 82.8, 76.2, 71.8, 52.3, 37.5, 36.1, 34.2, 25.9, 18.2, 0.1, −4.3; FT-IR (film on ZnSe) 3030, 2955, 2929, 2897, 2858, 2149, 1759, 1744, 1472, 1463, 1437, 1389, 1361, 1251, 1208, 1173, 1091 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{23}H_{41}O_5Si_2$ $[M + H]^+$ 453.2487, found 453.2479.

To a solution of TBS ether (22.0 mg, 0.0486 mmol) in CH_2Cl_2 (2 mL) was added DIBAL-H (1.0 M solution in n-hexane, 73 μL, 0.073 mmol) at −78 °C. After 1.2 h at −78 °C, an additional portion of DIBAL-H (1.0 M solution in n-hexane, 73 μL, 0.073 mmol) was added and the stirring was continued for 1 h at −78 °C. The reaction mixture was quenched by the addition of saturated aqueous Rochelle salt solution and then stirred at room temperature until two phases were clearly separated. The mixture was extracted with n-hexane/EtOAc (5:1) (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Aldehyde was obtained as a colorless oil (21.7 mg), which was used for the next reaction without purification. Data for aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H, CHO), 5.99 (ddd, 1H, J = 11, 7.5 Hz, H4), 5.56 (dt, 1H, J = 11, 1.2 Hz, H3), 4.83 (ddd, 1H, J = 7.5, 4.2, 3.6 Hz, H9), 4.50−4.44 (m, 2H, H10, H12), 3.91 (ddd, 1H, J = 11, 6.6, 5.4 Hz, H6), 3.74 (ddd, 1H, J = 11, 6.6, 4.2 Hz, H7), 2.56−2.50 (m, 2H, H5), 2.32 (dd, 1H, J = 14, 6.6 Hz, H11), 2.23 (dd, 1H, J = 14, 6.6 Hz, H8), 2.02 (ddd, 1H, J = 14, 9.0, 3.3 Hz, H8), 1.87 (ddd, 1H, J = 14, 10, 5.1 Hz, H11), 0.89 (s, 9H, TBS), 0.19 (s, 9H, TMS), 0.08 (s, 6H, TBS).

To a solution of CuBr·SMe_2 (108 mg, 0.527 mmol) in THF (1 mL) was added EtMgBr (1.0 M solution in THF, 1.03 mL, 1.03 mmol) at −78 °C. After 1 h at −78 °C, the crude aldehyde (21.7 mg) in THF (2 mL) was added and the resulting mixture was gradually warmed to 0 °C. After 23.5 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (n-hexane/EtOAc = 20 → 5) to give a 1.9:1 mixture of 13R-alcohol and starting aldehyde (8.2 mg), a 1:1 mixture of 13S-alcohol and aldehyde (4.1 mg), and recovered aldehyde (4.7 mg). The calculated yields of 13R-alcohol, 13S-alcohol, and starting aldehyde were 25%, 10%, and 46%, respectively. The mixtures were additionally purified by normal-phase HPLC using n-hexane/EtOAc as eluent for the spectral analyses. Data for 13R-alcohol: $[\alpha]_D^{28}$ −20.9 (c 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (dt, 1H, J = 11, 7.5 Hz, H4), 5.55 (dt, 1H, J = 11, 1.2 Hz, H3), 4.72 (dt, 1H, J = 7.8, 4.4 Hz, H9), 4.44 (t, 1H, J = 5.1 Hz, H10), 3.99 (dt, 1H, J = 11, 5.1 Hz, H12), 3.93 (dt, 1H, J = 5.7, 5.1 Hz, H6), 3.67 (ddd, 1H, J = 9.6, 6.3, 4.2 Hz, H7), 3.36 (dt, 1H, J = 7.2, 5.4 Hz, H13), 2.55−2.49 (m, 2H, H5), 2.19 (ddd, 1H, J = 14, 7.2, 6.3 Hz, H8), 2.01 (dd, 1H, J = 13, 5.1 Hz, H11), 1.93 (ddd, 1H, J = 14, 9.6, 3.9 Hz, H8), 1.69 (ddd, 1H, J = 13, 10, 5.1 Hz, H11), 1.48 (quint, 2H, J = 7.2 Hz, H14), 0.99 (t, 3H, J = 7.2 Hz, H15), 0.90 (s, 9H, TBS), 0.19 (s, 9H, TMS), 0.09 (s, 3H, TBS), 0.08 (s, 3H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 111.2, 102.0, 99.3, 84.0, 83.8, 82.4, 80.5, 74.8, 71.8, 36.2, 35.7, 34.6, 27.2, 26.0, 18.3, 10.2, 0.14, −4.22, −4.26; FT-IR (film on ZnSe) 3483, 3025, 2956, 2929, 2897, 2858, 2150, 1472, 1463, 1436, 1389, 1361, 1251, 1189, 1081, 1005 cm^{-1}; HRMS (ESI-neg) m/z calcd for $C_{24}H_{45}O_4Si_2$ $[M + H]^+$ 453.2851, found 453.2846. Data for 13S-alcohol: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dt, 1H, J = 11, 7.7 Hz, H4), 5.55 (br d, 1H, J = 11 Hz, H3), 4.75 (br dt, 1H, J = 8.2, 4.4 Hz, H9), 4.43 (br t, 1H, J = 4.8 Hz, H10), 4.07 (ddd, 1H, J = 10, 4.9, 3.0 Hz, H12), 3.97−3.91 (m, 1H, H6), 3.81−3.76 (m, 1H, H13), 3.66 (ddd, 1H, J = 10, 6.0, 4.0 Hz, H7), 2.55−2.49 (m, 2H, H5), 2.21 (ddd, 1H, J = 13, 7.9, 6.0 Hz, H11), 1.96−1.77 (m, 3H, H8 × 2, H11), 1.44−1.36 (m, 2H, H14), 0.99 (t, 3H, J = 7.5 Hz, H15), 0.90 (s, 9H, TBS), 0.19 (s, 9H, TMS), 0.09 (s, 3H, TBS), 0.08 (s, 3H, TBS); FT-IR (film on ZnSe) 3470, 3026, 2957, 2929, 2896, 2857, 2149, 1728, 1472, 1463, 1435, 1407, 1389, 1361, 1251, 1076 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{24}H_{45}O_4Si_2$ $[M + H]^+$ 453.2851, found 453.2841.

To a solution of 13R-alcohol (2.2 mg, 4.9 μmol) in CH_2Cl_2 (1 mL) were added DMAP (2.6 mg, 21 μmol), Et_3N (6.8 μL, 49 μmol), and (R)-(−)-MTPACl (1.8 μL, 9.7 μmol). The mixture was stirred for 21 h at room temperature and quenched by the addition of 3-(dimethylamino)propylamine (1.2 μL, 9.7 μmol). The resulting mixture was stirred for 30 min before concentration. The residue was purified by flash chromatography (n-hexane/EtOAc = 10 → 2) to give (S)-MTPA ester **17S** (0.9 mg, 1.4 μmol, 27%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.58 (m, 2H, Ph), 7.40−7.37 (m, 3H, Ph), 5.97 (dt, 1H, J = 11, 7.8 Hz, H4), 5.54 (br d, 1H, J = 11 Hz, H3), 5.02 (dt, 1H, J = 7.2, 5.7 Hz, H13), 4.61 (ddd, 1H, J = 7.8, 5.1, 3.9 Hz, H9), 4.25 (t, 1H, J = 5.1 Hz, H10), 4.17 (dt, 1H, J = 9.6, 5.7 Hz, H12), 3.89 (td, 1H, J = 5.4, 4.2 Hz, H6), 3.64 (ddd, 1H, J = 9.3, 6.6, 4.5 Hz, H7), 3.56 (br s, 3H, OMe), 2.53−2.46 (m, 2H, H5), 2.11 (ddd, 1H, J = 14, 7.2, 6.3 Hz, H8), 1.98 (dd, 1H, J = 14, 5.4 Hz, H11), 1,86 (ddd, 1H, J = 14, 9.3, 3.6 Hz, H8), 1.76−1.66 (m, 2H, H14), 1.49 (ddd, 1H, J = 14, 9.6, 5.4 Hz, H11), 0.97 (t, 3H, J = 7.4 Hz, H15), 0.86 (s, 9H, TBS), 0.19 (s, 9H, TMS), 0.06 (s, 3H, TBS), 0.04 (s, 3H, TBS); FT-IR (film on ZnSe) 2954, 2929, 2885, 2858, 2149, 1750, 1472, 1463, 1452, 1388, 1361, 1252, 1171, 1124, 1081, 1020 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{34}H_{55}O_6NF_3Si_2$ $[M + NH_4]^+$ 686.3515, found 686.3502.

*(R)-1-((2R,3aS,5S,6aS)-5-((R,Z)-1-((tert-Butyldimethylsilyl)oxy)-6-(trimethylsilyl)hex-3-en-5-yn-1-yl)hexahydrofuro[3,2-b]furan-2-yl)-propyl (R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate (**17R**).* To a solution of 13R-alcohol (3.0 mg, 6.6 μmol) in CH_2Cl_2 (1 mL) were added DMAP (3.4 mg, 28 μmol), Et_3N (9.2 μL, 66 μmol), and (S)-(+)-MTPACl (2.5 μL, 13 μmol). The mixture was stirred for 21 h at room temperature and quenched by the addition of 3-(dimethylamino)propylamine (1.7 μL, 13 μmol). The resulting mixture was stirred for 30 min before concentration. The residue was purified by flash chromatography (n-hexane/EtOAc = 7 → 5 → 2) to give (R)-MTPA ester **17R** (1.7 mg, 2.5 μmol, 38%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (m, 2H, Ph), 7.40−7.35 (m, 3H, Ph), 5.97 (dt, 1H, J = 11, 7.5 Hz, H4), 5.56 (br d, 1H, J = 11 Hz, H3), 5.07 (td, 1H, J = 8.1, 3.6 Hz, H13), 4.75 (dt, 1H, J = 8.4, 4.2 Hz, H9), 4.40 (t, 1H, J = 5.1 Hz, H10), 4.18 (ddd, 1H, J = 10, 6.9, 4.8 Hz, H12), 3.93 (ddd, 1H, J = 6.6, 5.7, 3.9 Hz, H6), 3.67 (ddd, 1H, J = 9.6, 6.0, 3.9 Hz, H7), 3.59 (br s, 3H, OMe), 2.54−2.47 (m, 2H, H5), 2.19 (ddd, 1H, J = 13, 7.5, 6.0 Hz, H8), 2.05 (dd, 1H, J = 13, 5.1 Hz, H11), 1.92 (ddd, 1H, J = 13, 9.6, 4.2 Hz, H8), 1.67−1.50 (m, 3H, H11, H14), 0.86 (s, 9H, TBS), 0.83 (t, 3H, J = 7.5 Hz, H15), 0.19 (s, 9H, TMS), 0.07 (s, 3H, TBS), 0.05 (s, 3H, TBS); FT-IR (film on

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ZnSe) 2955, 2929, 2898, 2857, 2150, 1751, 1471, 1464, 1452, 1389, 1361, 1251, 1185, 1169, 1126, 1081, 1021 cm^{-1}; HRMS (ESI-pos) *m/z* calcd for $C_{34}H_{55}O_6NF_3Si_2$ $[M + NH_4]^+$ 686.3515, found 686.3503.

Tetrahydro-2-furancarboxaldehyde (I).[49] To a solution of $(COCl)_2$ (2.58 mL, 30.1 mmol) in CH_2Cl_2 (15 mL) was added a solution of DMSO (4.25 mL, 49.9 mmol) in CH_2Cl_2 (68 mL) through a dropping funnel over 40 min at −78 °C. After 20 min, a solution of tetrahydrofurfuryl alcohol (2.53 g, 24.8 mmol) in CH_2Cl_2 (50 mL) was added through a dropping funnel over 20 min. After 10 min at −78 °C, Et_3N (17.8 mL, 128 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was quenched by the addition of water and extracted with CH_2Cl_2 (3×). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was passed through a short plug of silica gel and eluted with *n*-hexane/EtOAc (7:3). The fractions containing aldehyde were concentrated, and the residue was distilled with a Kugelrohr apparatus to give aldehyde **I** (1.52 g, 15.2 mmol, 61%, bp 90 °C/2.7 kPa) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, 1H, *J* = 1.8 Hz, H6), 4.27 (ddd, 1H, *J* = 8.7, 6.0, 1.8 Hz, H7), 3.94 (t, 2H, *J* = 6.6 Hz, H10), 2.21−1.83 (m, 4H, H8, H9).

(Z)-1-(Tetrahydrofuran-2-yl)-6-(trimethylsilyl)hex-3-en-5-yn-1-ol (IV). To a mixture of Zn dust (1.54 g mg, 23.6 mmol) and propargyl bromide (1.31 mL, 17.4 mmol) was added a solution of aldehyde **I** (590 mg, 5.89 mmol) in THF (20 mL). The mixture was cooled to −12 °C and stirred for 2 h. An additional portion of progargyl bromide (0.22 mL, 2.95 mL) was added and the mixture was stirred for 10 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with ether (8×). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, water, and brine; dried over anhydrous $MgSO_4$; filtered; and concentrated to give propargyl alcohol **II** as a pale yellow oil (818 mg, 5.83 mmol, 99%, dr = 3.1:1), which was used for the next reaction without purification. For the major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 3.94−3.71 (m, 4H, H6, H7, H10), 2.45 (dd, 2H, *J* = 6.0, 2.7 Hz, H5), 2.04 (t, 1H, *J* = 2.7 Hz, H3), 1.97−1.80 (m, 4H, H8, H9).

Stepwise Method. In a 30 mL two-necked round-bottom flask was placed $InCl_3$ (300 mg, 1.36 mmol). The solid was thoroughly dried by a heat-gun in vacuo. THF (4 mL) was added and the suspension was cooled to −78 °C. DIBAL-H (1.03 M solution in *n*-hexane, 1.28 mL, 1.32 mmol) was added with a gastight syringe over 10 min and the resulting mixture was stirred for 30 min at −78 °C. A solution of alcohol **II** (75.0 mg, 0.535 mmol) in THF (2.5 mL) and Et_3B (1 M solution in THF, 100 μL, 0.100 mmol) were added in this order, and the resulting mixture was stirred for 2.5 h at −78 °C. Iodine (766 mg, 3.02 mmol) was then added in one portion and the stirring was continued for 50 min at −78 °C. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution followed by saturated aqueous $Na_2S_2O_3$ solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give vinyl iodide **III** as a yellow oil (143 mg), which was used for the next reaction without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 6.38−6.30 (m, 2H, H3, H4), 3.97−3.74 (m, 4H, H6, H7, H10), 2.40−2.28 (m, 2H, H5), 1.99−1.85 (m, 4H, H8, H9).

In a 30 mL two-necked round-bottom flask were placed $(Ph_3P)_2PdCl_2$ (38.1 mg, 0.0543 mmol), CuI (20.6 mg, 0.108 mmol), ethynyltrimethylsilane (152 μL, 1.08 mmol), and *i*-Pr_2NH (0.230 mL, 1.62 mmol). A solution of vinyl iodide **III** (143 mg) in THF (5.4 mL) was added and the mixture was stirred for 30 min at room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by repeated flash chromatography (*n*-hexane/EtOAc = 15 → 10 then *n*-hexane/EtOAc = 20 → 5) to give enyne **IV** (89.2 mg, 0.374 mmol, 70% from **II**, *Z*/*E* > 20) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (ddd, 1H, *J* = 11, 8.1, 6.6 Hz, H4), 5.59 (dt, 1H, *J* = 11, 1.6 Hz, H3), 3.92−3.72 (m, 4H, H6, H7, H10), 2.59 (dddd, 1H, *J* = 14, 8.3, 5.6, 1.2 Hz, H5), 2.44 (dddd, 1H, *J* = 14, 7.8, 6.6, 1.6 Hz, H5), 2.02−1.82 (m, 4H, H8, H9), 0.19 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 111.6, 101.8, 99.6, 81.9, 71.6, 68.8, 34.2, 26.2, 25.1, 0.09; FT-IR (film on ZnSe) 3435, 3025, 2962, 2898, 2873, 2149, 1613, 1442, 1408, 1393, 1368, 1318, 1292, 1250, 1185, 1119 cm^{-1}; HRMS (ESI-pos) *m/z* calcd for $C_{13}H_{23}O_2Si$ $[M + H]^+$ 239.1462, found 239.1461.

One-Pot Method. In a 20 mL two-necked round-bottom flask was placed $InCl_3$ (121 mg, 0.547 mmol). The solid was thoroughly dried by a heat-gun in vacuo. THF (1.6 mL) was added and the suspension was cooled to −78 °C. DIBAL-H (1.03 M solution in *n*-hexane, 0.50 mL, 0.52 mmol) was added with a gastight syringe over 6 min and the mixture was stirred for 30 min at −78 °C. A solution of alcohol **II** (27.9 mg, 0.199 mmol) in THF (2 mL) and Et_3B (1 M solution in THF, 100 μL, 0.100 mmol) were added in this order, and the resulting mixture was stirred for 2.5 h at −78 °C. Then the solution was warmed to room temperature, followed by the addition of iodoethynyltrimethylsilane (108 mg, 0.482 mmol) in 1,3-dimethyl-2-imidazolidinone (DMI, 1.5 mL) and a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (4.5 mg, 4.4 μmol) and tri-2-furylphosphine (TFP, 5.0 mg, 0.022 mmol) in THF (2 mL). The resulting mixture was stirred for 15 min at room temperature. Additional portions of iodoethynyltrimethylsilane (155 mg + 70.8 mg, 0.692 mmol + 0.316 mmol) in DMI (1 mL + 1 mL) and a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (4.5 mg, 4.4 μmol) and TFP (5.0 mg, 0.020 mmol) in THF (2 mL) were added, and the resulting mixture was stirred for 14 h. The reaction mixture was quenched by the addition of water and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by the repeated flash chromatography (*n*-hexane/EtOAc = 5 then *n*-hexane/EtOAc = 10) to give an 11:1 mixture of enyne **IV** (20.0 mg, 0.0839 mmol, 42%, *Z*/*E* > 20) and alkene **V** (1.1 mg, 0.0075 mmol, 4%) as a pale yellow oil.

(R,Z)-1-((2S,3aS,5R,6aS)-5-((S)-1-Bromopropyl)hexahydrofuro-[3,2-b]furan-2-yl)hex-3-en-5-yn-1-ol (5). To a solution of alcohol **14** (20.5 mg, 0.0606 mmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (35.0 μL, 0.302 mmol) and TESOTf (27.0 μL, 0.120 mmol). The mixture was stirred for 30 min at room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ solution at 0 °C. The resulting mixture was extracted with EtOAc (2×). The combined organic layer was washed with 1 M aqueous HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5) to give TES ether (24.6 mg, 0.0543 mmol, 90%) as a colorless oil: $[\alpha]_D^{26}$ −0.487 (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (dt, 1H, *J* = 11, 7.5 Hz, H4), 5.56 (dt, 1H, *J* = 11, 1.2 Hz, H3), 4.88 (ddd, 1H, *J* = 7.5, 4.2, 3.3 Hz, H9), 4.63 (dd, 1H, *J* = 9.6, 6.3 Hz, H12), 4.47 (t, 1H, *J* = 4.8 Hz, H10), 3.91 (td, 1H, *J* = 6.0, 4.8 Hz, H6), 3.76 (s, 3H, OMe), 3.78−3.69 (m, 1H, H7), 2.54 (t, 2H, *J* = 6.9 Hz, H5), 2.44 (dd, 1H, *J* = 14, 6.3 Hz, H11), 2.24 (dt, 1H, *J* = 14, 7.2 Hz, H8), 2.07−1.94 (m, 2H, H8, H11), 0.96 (t, 9H, *J* = 8.1 Hz, TES), 0.62 (q, 6H, *J* = 8.1 Hz, TES), 0.187 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 140.6, 111.3, 102.0, 99.4, 85.3, 83.3, 83.0, 76.3, 72.2, 52.3, 37.6, 36.1, 34.5, 7.03, 5.22, 0.12; FT-IR (film on ZnSe) 3024, 2952, 2913, 2877, 2149, 1759, 1460, 1438, 1415, 1250, 1209, 1173, 1089 cm^{-1}; HRMS (ESI-pos) *m/z* calcd for $C_{23}H_{41}O_5Si_2$ $[M + H]^+$ 453.2487, found 453.2488.

To a solution of TES ester (55.9 mg, 0.123 mmol) in CH_2Cl_2 (1.2 mL) was added DIBAL-H (1.0 M solution in *n*-hexane, 0.190 mL, 0.190 mmol) at −78 °C. After 30 min at −78 °C, the reaction mixture was quenched by the addition of saturated aqueous Rochelle salt solution. The resulting mixture was stirred at room temperature until two phases were clearly separated. The mixture was extracted with *n*-hexane/EtOAc (5:1) (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Aldehyde was obtained as a pale yellow oil (50.4 mg), which was used for the next reaction without purification. Data for aldehyde: ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, 1H, *J* = 1.6 Hz, H13), 6.01 (dt, 1H, *J* = 11, 7.6 Hz, H4), 5.56 (dt, 1H, *J* = 11, 1.2 Hz, H3), 4.83 (ddd, 1H, *J* = 7.2, 4.0, 3.2 Hz, H9), 4.50−4.45 (m, 2H, H10, H12), 3.90 (td, 1H, *J* = 6.0, 4.4 Hz, H6), 3.76 (ddd, 1H, *J* = 8.8, 6.8, 4.8 Hz, H7), 2.56 (m, 2H, H5), 2.34 (dd, 1H, *J* = 13, 6.4 Hz, H11), 2.26 (dt, 1H, *J* = 13, 6.4 Hz,

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H8), 2.04 (dd, 1H, J = 13, 8.8, 3.2 Hz, H8), 1.89 (ddd, 1H, J = 13, 10, 5.2 Hz, H11), 0.97 (t, 9H, J = 7.6 Hz, TES), 0.63 (q, 6H, J = 7.6 Hz, TES), 0.19 (s, 9H, TMS).

To a suspension of CuCN (107 mg, 1.19 mmol) in THF (6 mL) was added EtLi (0.5 M solution in benzene−cyclohexane, 4.8 mL, 2.4 mmol) at −78 °C. After 20 min at −78 °C, BF_3·Et_2O (0.15 mL, 1.2 mmol) was added. After 30 min at −78 °C, the crude aldehyde (50.4 mg) in THF (6 mL) was added. The resulting mixture was gradually warmed to −30 °C and stirred at that temperature for 1 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5 → 1) to give an approximately 1:1 mixture of alcohol **16** and aldehyde (43.5 mg). This mixture was again subjected to the ethylation conditions to consume all of the starting material. Thus, to a suspension of CuCN (93.8 mg, 1.05 mmol) in THF (6 mL) was added EtLi (0.5 M solution in benzene−cyclohexane, 4.1 mL, 2.1 mmol) at −78 °C. After 30 min at −78 °C, BF_3·Et_2O (0.13 mL, 1.0 mmol) was added. After 40 min at −78 °C, the above-mentioned mixture of **16** and aldehyde (43.5 mg) in THF (4 mL) was added. The resulting mixture was gradually warmed to −30 °C and stirred at that temperature for 20 h. The reaction mixture was additionally stirred for 4 h at −20 °C, quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5 → 1) to give a 5:1 inseparable mixture of **16** and aldehyde (24.7 mg). NMR data for **16** (peaks were selected from the mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (dt, 1H, J = 11, 7.2 Hz, H4), 5.56 (br d, 1H, J = 11 Hz, H3), 4.71 (dt, 1H, J = 8.4, 4.4 Hz, H9), 4.46 (t, 1H, J = 5.0 Hz, H10), 3.99 (dt, 1H, J = 10, 5.6 Hz, H12), 3.92 (td, 1H, J = 6.0, 4.4 Hz, H6), 3.69 (ddd, 1H, J = 9.6, 6.4, 4.4 Hz, H7), 3.37 (dt, 1H, J = 7.2, 5.2 Hz, H13), 2.54 (t, 2H, J = 6.8 Hz, H5), 2.22 (dt, 1H, J = 14, 8.0 Hz, H8), 2.03 (dd, 1H, J = 13, 4.8 Hz, H11), 1.97−1.88 (m, 1H, H8), 1.69 (ddd, 1H, J = 13, 10, 5.6 Hz, H11), 1.49 (m, 2H, H14), 1.00 (t, 3H, J = 7.2 Hz, H15), 0.97 (t, 9H, J = 7.6 Hz, TES), 0.63 (q, 6H, J = 7.6 Hz, TES), 0.19 (s, 9H, TMS).

To a solution of **16** and aldehyde (5:1, 24.7 mg) in benzene (1.2 mL) were added Ph_3P (143 mg, 0.544 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (113 mg, 0.549 mmol), and a solution of CBr_4 (181 mg, 0.547 mmol) in CH_2Cl_2 (1.8 mL). After 3 h at room temperature, the reaction mixture was concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 10 → 3) to give 13*S*-bromide (20.6 mg, 0.0399 mmol) as a colorless oil: $[\alpha]_D^{26}$ −15 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dt, 1H, J = 11, 7.2 Hz, H4), 5.56 (br d, 1H, J = 11 Hz, H3), 4.78 (dt, 1H, J = 8.0, 4.0 Hz, H9), 4.44 (t, 1H, J = 5.0 Hz, H10), 4.16 (ddd, 1H, J = 10, 6.8, 5.6 Hz, H12), 3.98−3.91 (m, 2H, H6, H13), 3.71 (ddd, 1H, J = 9.2, 6.4, 4.4 Hz, H7), 2.54 (br t, 2H, J = 6.8 Hz, H5), 2.28 (dd, 1H, J = 13, 5.2 Hz, H11), 2.20 (dt, 1H, J = 14, 6.8 Hz, H8), 2.01−1.94 (m, 2H, H8, H14), 1.82−1.69 (m, 2H, H11, H14), 1.07 (t, 3H, J = 7.2 Hz, H15), 0.97 (t, 9H, J = 8.0 Hz, TES), 0.63 (q, 6H, J = 8.0 Hz, TES), 0.19 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 111.2, 102.0, 99.4, 84.6, 83.6, 82.5, 80.2, 72.0, 61.4, 37.9, 36.1, 34.9, 28.9, 12.1, 7.09, 5.23, 0.13; FT-IR (film on ZnSe) 3022, 2956, 2913, 2877, 2149, 1459, 1433, 1416, 1380, 1250, 1197, 1165, 1079 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{24}H_{44}O_3BrSi_2$ $[M + H]^+$ 515.2007, found 515.2014.

To a solution of 13*S*-bromide (7.6 mg, 0.015 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 37 μL, 0.037 mmol). After 30 min at room temperature, the reaction mixture was quenched by the addition of saturated NH_4Cl solution at 0 °C. The resulting mixture was extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 3) to give alcohol **5** (3.7 mg, 0.011 mmol, 76%) as a pale yellow oil: $[\alpha]_D^{26}$ −8.6 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (dt, 1H, J = 11, 7.2 Hz, H4), 5.58 (br dd, 1H, J = 11, 2.0 Hz, H3), 4.78 (ddd, 1H, J = 6.4, 4.0, 2.8 Hz, H9), 4.48 (t, 1H, J = 4.4 Hz, H10), 4.23 (dt, 1H, J = 9.2, 6.0 Hz, H12), 3.97 (ddd, 1H, J = 9.2, 6.0, 3.6 Hz, H13), 3.92 (m, 1H, H6), 3.90 (ddd, 1H, J = 7.6, 6.8, 3.2 Hz, H7), 3.11 (d, 1H, J = 2.4 Hz, H1), 2.57 (m, 1H, H5), 2.45 (m, 1H, H5), 2.35 (dd, 1H, J = 14, 5.6 Hz, H11), 2.20 (dt, 1H, J = 14, 6.8 Hz, H8), 2.07 (ddd, 1H, J = 14, 7.6, 2.8 Hz, H8), 1.96 (ddq, 1H, J = 15, 7.4, 3.6 Hz, H14), 1.90 (ddd, 1H, J = 14, 9.2, 4.8 Hz, H11), 1.71 (ddq, 1H, J = 15, 9.2, 7.4 Hz, H14), 1.06 (t, 3H, J = 7.4 Hz, H15); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 110.7, 84.6, 84.1, 82.7, 82.3, 80.8, 80.2, 71.2, 61.7, 37.6, 34.4, 33.3, 28.7, 12.2; FT-IR (film on ZnSe) 3292, 2969. 2934, 2925, 2877, 2853, 1734, 1718, 1458, 1437, 1278, 1167, 1073, 1063 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{15}H_{22}O_3Br$ $[M + H]^+$ 329.0747, found 329.0745.

*Methyl (2R,3aS,5S,6aS)-5-((S,Z)-1-Hydroxyhex-3-en-5-yn-1-yl)-hexahydrofuro[3,2-b]furan-2-carboxylate (**19**).* To a solution of alcohol **18** (15.0 mg, 0.0563 mmol) in toluene (0.5 mL) was added a solution of Ph_3P (44.3 mg, 0.169 mmol) and $ClCH_2CO_2H$ (16.0 mg, 0.169 mmol) in toluene (1.4 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C, followed by the addition of diethyl azodicarboxylate (40% in toluene, 76.8 μL, 0.169 mmol). The resulting mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was directly subjected to flash chromatography (hexane/EtOAc = 3 → 2 → 1) to give an inseparable mixture of chloroacetate and diethyl hydrazine-1,2-dicarboxylate (derived from DEAD) (24.4 mg). The yield of chloroacetate was calculated to be 23% on the basis of the ^{1}H NMR analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (dtd, 1H, J = 14, 6.3, 0.9 Hz, H4), 5.58 (ddt, 1H, J = 11, 2.1, 1.4 Hz, H3), 5.16 (td, 1H, J = 7.5, 4.5 Hz, H6), 4.83 (ddd, 1H, J = 6.0, 3.9, 1.8 Hz, H9), 4.80 (dd, 1H, J = 9.0, 7.2 Hz, H12), 4.55 (t, 1H, J = 4.2 Hz, H10), 4.11 (s, 2H, $-CH_2Cl$), 4.07−4.00 (m, 1H, H7), 3.75 (s, 3H, OMe), 3.13 (br d, 1H, J = 1.6 Hz, H1), 2.76−2.56 (m, 2H, H5), 2.50 (dd, 1H, J = 14, 7.2 Hz, H11), 2.30 (ddd, 1H, J = 14, 8.4, 6.0 Hz, H8), 2.06 (ddd, 1H, J = 14, 8.7, 4.5 Hz, H11), 1.96 (ddd, 1H, J = 14, 6.3, 1.8 Hz, H8).

To a solution of the above product (24.4 mg) in MeOH (1 mL) was added K_2CO_3 (1.8 mg, 0.013 mmol) at −78 °C. The mixture was gradually warmed to −40 °C over 4 h and stirred at that temperature for 19 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 2 → 1) followed by normal-phase HPLC using *n*-hexane/EtOAc as eluent to give alcohol **19** (1.8 mg, 6.8 μmol, 12% for two steps) as a colorless oil: $[\alpha]_D^{24}$ +1.1 (*c* 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (dtd, 1H, J = 11, 7.8, 1.2 Hz, H4), 5.58 (ddt, 1H, J = 11, 2.4, 1.5 Hz, H3), 4.88 (ddd, 1H, J = 6.3, 3.9, 2.1 Hz, H9), 4.67 (dd, 1H, J = 9.3, 6.9 Hz, H12), 4.56 (dd, 1H, J = 4.8, 4.2 Hz, H10), 3.85 (q, 1H, J = 7.2 Hz, H7), 3.76 (s, 3H, OMe), 3.69 (td, 1H, J = 6.6, 5.4 Hz, H6), 3.11 (br dd, 1H, J = 2.4, 0.9 Hz, H1), 2.53 (ddd, 2H, J = 7.8, 6.6, 1.5 Hz, H5), 2.51 (dd, 1H, J = 14, 6.9 Hz, H11), 2.32 (ddd, 1H, J = 14, 7.5, 6.6 Hz, H8), 2.09 (ddd, 1H, J = 14, 9.0, 4.8 Hz, H11), 1.91 (ddd, 1H, J = 14, 7.2, 2.4 Hz, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.2, 110.5, 85.6, 83.9, 83.4, 82.3, 80.3, 77.4, 73.4, 52.4, 37.5, 35.8, 34.3; FT-IR (film on ZnSe) 3474, 3272, 3030, 2952, 2093, 1752, 1439, 1377, 1287, 1262, 1216, 1173, 1091 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{14}H_{19}O_5$ $[M + H]^+$ 267.1227, found 267.1222.

tert-Butyl(((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-5-methoxytetrahydrofuran-2-yl)methoxy)dimethylsilane.[44] To a solution of 2-deoxy-D-ribose (5.01 g, 37.4 mmol) in MeOH (100 mL) was added anhydrous HCl (4 M solution in CPME, 0.30 mL, 1.2 mmol) at room temperature. After 2 h, the reaction mixture was quenched by the addition of solid $BaCO_3$ and stirred for 1 h to neutralize the remaining acid. The mixture was filtered through a pad of Celite and the filtrate was concentrated to give methyl acetal (5.70 g) as a yellow oil. The acetal (5.70 g) was dissolved in DMF (100 mL) and treated with imidazole (12.5 g, 184 mmol) and TBSCl (12.8 g, 84.9 mmol). After 17 h at room temperature, the reaction mixture was quenched by the addition of water and extracted with Et_2O (5×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open

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chromatography (*n*-hexane/EtOAc = 40) to give the title compound (13.1 g, 34.8 mmol, 93% for two steps) as a 1.2:1 diastereomeric mixture: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (dd, 0.45H, J = 5.1, 3.0 Hz, H7 minor), 4.97 (dd, 0.55H, J = 5.7, 2.7 Hz, H7 major), 4.37 (td, 0.45H, J = 6.0, 3.9 Hz, H5 minor), 4.17 (ddd, 0.55H, J = 8.1, 6.0, 5.1 Hz, H5 major), 3.87 (m, 1H, H4), 3.76 (dd, 0.55H, J = 11, 3.0 Hz, H3 major), 3.66 (dd, 0.55H, J = 11, 4.5 Hz, H3 major), 3.66−3.56 (m, 0.9H, H3 minor), 3.37 (s, 1.65H, OMe major), 3.33 (s, 1.35H, OMe minor), 2.34 (ddd, 0.55H, J = 14, 8.4, 6.0 Hz, H6 major), 2.09 (ddd, 0.45H, J = 13, 6.6, 2.7 Hz, H6 minor), 2.01 (dt, 0.45H, J = 13, 5.4 Hz, H6 minor), 1.79 (ddd, 0.55H, J = 14, 5.1, 2.7 Hz, H6 major), 0.904, 0.895, 0.876 (s, 18H total, *t*-Bu), 0.069, 0.066, 0.060, 0.050 (s, 12H total, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.3, 104.7, 87.2, 84.7, 72.5, 71.4, 64.3, 62.9, 55.3, 55.1, 42.0, 41.9, 26.10, 26.07, 25.9, 18.55, 18.51, 18.15, 18.11, −4.44, −4.55, −4.65, −4.70, −5.07, −5.22, −5.24.

(2R,3S,5R)-5-Allyl-2-(hydroxymethyl)tetrahydrofuran-3-ol.[44] To a solution of the above methyl acetal (13.1 g, 34.8 mmol) in CH_2Cl_2 (35 mL) were added allyltrimethylsilane (8.3 mL, 52 mmol) and a solution of $SnBr_4$ (15.3 g, 34.8 mmol) in CH_2Cl_2 at −78 °C. The mixture was gradually warmed to room temperature and stirred for 2 h in total. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution and thoroughly extracted with EtOAc (5×) (insoluble solid particles were removed by decantation or filtration). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. TLC and NMR analyses indicated that the product consisted of a mixture of alkenyl bis-TBS ether, alkenyl mono-TBS ether, and alkenyl diol (title compound). This mixture was dissolved in THF (15 mL) and treated with TBAF (1.0 M solution in THF, 69.5 mL, 69.5 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 17 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (5×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 1 → 0.3) to give the title compound (4.70 g, 29.7 mmol, 85% for two steps) as a brownish oil that contained a small amount of tetrabutylammonium hydroxide (~7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1H, H9), 5.16−5.06 (m, 2H, H10), 4.31 (td, 1H, J = 6.9, 5.4 Hz), 4.12 (m, 1H), 3.85 (td, 1H, J = 5.4, 4.2 Hz), 3.72 (dd, 1H, J = 12, 4.2 Hz, H3), 3.63 (dd, 1H, J = 12, 5.1 Hz, H3), 2.50−2.28 (m, 3H), 1.71 (ddd, 1H, J = 13, 7.8, 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 117.7, 84.8, 77.8, 72.8, 62.6, 40.7, 40.2.

*(2R,3S,5R)-5-Allyl-2-((trityloxy)methyl)tetrahydrofuran-3-ol (**21**).*[44] To a solution of the above diol (2.83 g, 17.9 mmol) in CH_2Cl_2 (18 mL) were added pyridine (2.89 mL, 35.8 mmol), trityl chloride (5.49 g, 19.7 mmol), and *N*,*N*-dimethyl-4-aminopyridine (15.3 g, 34.8 mmol) at room temperature. After 13 h, the reaction mixture was quenched by the addition of water, concentrated to remove CH_2Cl_2, and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 15 → 10 → 5) to give monotrityl ether **21** (6.13 g, 15.3 mmol, 86%) as a viscous oil and bis-trityl ether (1.18 g, 1.83 mmol, 10%) as a colorless solid. Data for **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.19 (m, 15H), 5.83 (m, 1H), 5.16−5.06 (m, 2H), 4.26 (m, 1H), 4.13 (m, 1H), 3.98 (dt, 1H, J = 5.4, 4.8 Hz), 3.28 (dd, 1H, J = 9.6, 4.8 Hz), 3.09 (dd, 1H, J = 9.3, 6.0 Hz), 2.48−2.26 (m, 3H), 1.66 (ddd, 1H, J = 13, 8.1, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 134.7, 128.8, 128.0, 127.2, 117.5, 87.0, 83.8, 77.9, 75.1, 64.9, 40.7, 39.8.

*(2R,5S)-2-Allyl-5-((trityloxy)methyl)-2,5-dihydrofuran (**22**).* To a solution of alcohol **21** (6.13 g, 15.3 mmol) in CH_2Cl_2 (153 mL) were added 2,6-lutidine (5.33 mL, 45.9 mmol) and Tf_2O (3.77 mL, 23.0 mmol) at −78 °C. After 30 min, DBU (22.8 mL, 153 mmol) was added and the resulting mixture was warmed to room temperature. After 2 h, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution, concentrated to remove CH_2Cl_2, and extracted with EtOAc (2×). The combined organic layer was washed with 1 M aqueous HCl and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 15 → 10) to give diene **22** (5.75 g, 15.0 mmol, 98%) as a yellow viscous oil: $[\alpha]_D^{28}$ −141 (*c* 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.43 (m, 6H, Tr), 7.31−7.19 (m, 9H, Tr), 5.89 (s, 2H, H5, H6), 5.84 (m, 1H, H9), 5.16−5.06 (m, 2H, H10), 5.04−4.94 (m, 2H, H4, H7), 3.16 (dd, 1H, J = 9.3, 4.8 Hz, H3), 3.09 (dd, 1H, J = 9.3, 5.1 Hz, H3), 2.40−2.34 (m, 2H, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 134.4, 130.8, 128.9, 128.5, 127.9, 127.1, 117.3, 86.5, 85.5, 85.4, 66.7, 40.7; FT-IR (film on ZnSe) 3058, 3033, 3023, 2977, 1641, 1597, 1492, 1449, 1356, 1318, 1218, 1184, 1154, 1075 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{27}H_{26}O_2Na$ $[M + Na]^+$ 405.1825, found 405.1810.

*3-((2R,5S)-5-((Trityloxy)methyl)-2,5-dihydrofuran-2-yl)propanoic Acid (**23**).* To a solution of diene **22** (7.20 g, 18.8 mmol) in THF (5 mL) was added 9-BBN (0.5 M solution in THF, 46 mL, 23 mmol) over 10 min at room temperature. After 3 h, the mixture was cooled to 0 °C followed by the addition of 1 M aqueous NaOH (67.5 mL, 67.5 mmol) and 30% aqueous H_2O_2 (27.0 mL, 264 mmol). The resulting mixture was stirred for 3 h at room temperature, concentrated to remove THF, and extracted with ether (3×). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 2) to give the primary alcohol (7.10 g, 17.7 mmol, 94%) as a colorless oil: $[\alpha]_D^{28}$ −169 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.43 (m, 6H, Tr), 7.32−7.18 (m, 9H, Tr), 5.85 (s, 2H, H5, H6), 5.05−4.94 (m, 2H, H4, H7), 3.73−3.60 (m, 2H, H10), 3.15 (dd, 1H, J = 9.3, 4.8 Hz, H3), 3.10 (dd, 1H, J = 9.3, 4.5 Hz, H3), 2.35 (br s, 1H, OH), 1.82−1.55 (m, 4H, H8, H9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 131.1, 128.8, 128.1, 127.9, 127.0, 86.5, 86.1, 85.3, 66.6, 63.0, 32.8, 28.9; FT-IR (film on ZnSe) 3432, 3084, 3057, 3033, 2919, 2867, 1597, 1491, 1449, 1378, 1356, 1318, 1266, 1219, 1183, 1154, 1073 cm^{-1}; HRMS (ESI-pos) m/z calcd for $C_{27}H_{28}O_3Na$ $[M + Na]^+$ 423.1931, found 423.1914.

To a mixture of alcohol (3.10 g, 7.74 mmol), $NaClO_2$ (2.62 g, 23.2 mmol), and $TEMPO^+BF_4^-$ (0.376 g, 1.55 mmol) were added distillated water (13 mL) and MeCN (13 mL). A slightly exothermic reaction occurred and the reaction vessel was immersed in a water bath. After 1 h at room temperature, the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution and extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by open chromatography (*n*-hexane/EtOAc = 5 → 2 → 1 containing 3% MeOH) to give carboxylic acid **23** (2.31 g, 5.58 mmol, 72%) as a colorless solid: $[\alpha]_D^{24}$ −103 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.42 (m, 6H, Tr), 7.32−7.19 (m, 9H, Tr), 5.91−5.81 (m, 2H, H5, H6), 5.07−4.98 (m, 2H, H4, H7), 3.15 (dd, 1H, J = 9.6, 4.8 Hz, H3), 3.10 (dd, 1H, J = 9.6, 4.5 Hz, H3), 2.48 (t, 2H, J = 7.5 Hz, H9), 2.05 (m, 1H, H8), 1.87 (m, 1H, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 144.2, 130.2, 129.1, 128.9, 127.9, 127.1, 86.6, 85.6, 85.0, 66.6, 30.3, 29.5; FT-IR (film on ZnSe) 3084, 3057, 3033, 2925, 2867, 1735, 1708, 1596, 1491, 1449, 1217, 1155, 1075 cm^{-1}; HRMS (ESI-neg) m/z calcd for $C_{27}H_{25}O_4$ $[M - H]^+$ 413.1758, found 413.1766.

*(2S,3aR,7aR)-2-((Trityloxy)methyl)hexahydro-5H-furo[3,2-b]-pyran-5-one (**24**).* To a solution of carboxylic acid **23** (93.4 mg, 0.225 mmol) in freshly distilled $CHCl_3$ (2.3 mL) were added 1,1,3,3-tetramethylguanidine (8.5 μL, 68 μmol) and NBS (61.2 mg, 0.344 mmol). The mixture was stirred for 1.5 h at room temperature and quenched by the addition of saturated aqueous Na_2SO_3 solution. The resulting mixture was extracted with ether (2×), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Bromolactone was obtained as a colorless amorphous solid (103 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.42 (m, 6H, Tr), 7.34−7.19 (m, 9H, Tr), 5.01 (br d, 1H, J = 3.9 Hz, H6), 4.73 (q, 1H, J = 3.9 Hz, H7), 4.53 (br d, 1H, J = 3.0 Hz, H5), 4.16 (td, 1H, J = 6.0, 3.6 Hz, H4), 3.53 (dd, 1H, J = 9.6, 5.4 Hz, H3), 3.27 (dd, 1H, J = 9.6, 6.6 Hz, H3), 2.63 (ddd, 1H, J = 17, 11, 5.7 Hz, H9), 2.45 (dt, 1H, J = 17, 5.1 Hz, H9), 2.22−2.02 (m, 2H, H8).

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The crude bromolactone (103 mg) was dissolved in toluene (2 mL) followed by the addition of *n*-Bu_3SnH (55 μL, 0.21 mmol) and Et_3B (1.0 M solution in *n*-hexane, 209 μL, 0.209 mmol). Air was introduced into the reaction vessel and the mixture was stirred for 5 min at room temperature. Additional *n*-Bu_3SnH (11 μL, 0.042 mmol) and Et_3B (105 μL, 0.105 mmol) were added, and the resulting mixture was stirred for 10 min. The reaction mixture was quenched by the addition of saturated aqueous KF solution and vigorously stirred for 2 h. The mixture was extracted with EtOAc (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by 10% w/w KF−Florisil chromatography[48] (*n*-hexane only → *n*-hexane/EtOAc = 5 → 1) to give lactone **24** (64.3 mg, 0.155 mmol, 68%) as a pale yellow oil. The yield was calculated by NMR analysis, as the sample contained a small amount of organotin byproducts. An analytical sample was obtained by further purification by silica gel chromatography: $[\alpha]_D^{29}$ −4.35 (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.41 (m, 6H, Tr), 7.33−7.19 (m, 9H, Tr), 4.96 (m, 1H, H6), 4.43−4.35 (m, 2H, H4, H7), 3.27 (dd, 1H, *J* = 9.9, 3.9 Hz, H3), 3.10 (dd, 1H, *J* = 9.9, 4.5 Hz, H3), 2.67 (ddd, 1H, *J* = 17, 11, 6.3 Hz, H9), 2.43 (dt, 1H, *J* = 17, 5.4 Hz, H9), 2.28−2.11 (m, 4H, H5, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 144.0, 128.8, 128.0, 127.2, 86.9, 82.8, 77.8, 73.9, 66.0, 36.9, 25.4, 23.9; FT-IR (film on ZnSe) 3086, 3057, 3020, 2930, 2871, 1745, 1596, 1490, 1449, 1368, 1319, 1240, 1170, 1078, 1052, 1034 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{27}H_{26}O_4Na$ $[M + Na]^+$ 437.1723, found 437.1709.

*Methyl (2S,3aR,5S,6aR)-5-((Trityloxy)methyl)hexahydrofuro[3,2-b]furan-2-carboxylate (**26**). Stepwise Method.* To a solution of lactone **24** (172 mg, 0.420 mmol) in THF (4.2 mL) was added LiHMDS (0.5 M solution in THF, 2.2 mL, 1.1 mmol) at −78 °C. After 1 h at −78 °C, TMSCl (69 μL, 0.55 mmol) was added and the resultant mixture was warmed to 0 °C. After 30 min, the solution was again cooled to −78 °C followed by the addition of NBS (112 mg, 0.630 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at −78 °C and quenched by the addition of pH 7 phosphate buffer. The resulting mixture was extracted with ether (2×), and the combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Bromolactone **25** (207 mg) was obtained as a brownish amorphous solid. As the product was unstable on silica gel, it was submitted to the next reaction without further purification. To a solution of crude **25** (207 mg) in MeOH (8.4 mL) was added K_2CO_3 (590 mg, 4.27 mmol) at −78 °C. The suspension was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl solution, and brine; dried over anhydrous $MgSO_4$; filtered; and concentrated to give methyl ester **26** (112 mg, 0.253 mmol, 60%) as a yellow oil. The yield was calculated by NMR analysis, as the sample contained a small amount of organotin byproducts. An analytical sample was obtained by further purification by silica gel chromatography: $[\alpha]_D^{27}$ −7.92 (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.42 (m, 6H, Tr), 7.32−7.19 (m, 9H, Tr), 4.90 (t, 1H, *J* = 4.2 Hz, H6), 4.80 (t, 1H, *J* = 4.2 Hz, H7), 4.65 (dd, 1H, *J* = 8.7, 7.2 Hz, H9), 4.32 (m, 1H, H4), 3.76 (s, 3H, OMe), 3.18 (dd, 1H, *J* = 9.6, 4.2 Hz, H3), 3.08 (dd, 1H, *J* = 9.6, 4.8 Hz, H3), 2.50 (dd, 1H, *J* = 14, 6.9 Hz, H8), 2.20 (dd, 1H, *J* = 14, 5.7 Hz, H5), 2.16 (ddd, 1H, *J* = 14, 8.7, 5.4 Hz, H8), 1.88 (ddd, 1H, *J* = 14, 9.0, 5.1 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 144.1, 128.8, 127.9, 127.1, 86.7, 85.6, 83.5, 79.0, 66.1, 52.3, 38.7, 37.0; FT-IR (film on ZnSe) 3086, 3057, 3033, 2951, 2870, 1753, 1597, 1492, 1449, 1365, 1280, 1213, 1167, 1090, 1035 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{28}H_{28}O_5Na$ $[M + Na]^+$ 467.1829, found 467.1820.

One-Pot Method. To a solution of lactone **24** (33.6 mg, 0.0811 mmol) in THF (0.8 mL) was added LiHMDS (0.5 M solution in THF, 422 μL, 0.211 mmol) at −78 °C. After 2 h at −78 °C, TMSCl (15 μL, 0.12 mmol) was added and the resultant mixture was warmed to 0 °C. After 30 min, the solution was again cooled to −78 °C followed by the addition of NBS (22.0 mg, 0.126 mmol) in THF (0.5 mL). The reaction mixture was stirred for 1.3 h at −78 °C, at which point MeOH (2 mL) and K_2CO_3 (112 mg, 0.812 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 1 h before the addition of water at 0 °C. The resultant mixture was extracted with EtOAc (2×). The combined organic layer was washed with saturated aqueous NH_4Cl solution and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5 → 3) to give methyl ester **26** (15.3 mg, 0.0344 mmol, 42%) as a yellow oil and a 3:1 diastereomeric mixture of **26** and 9-*epi*-**26** (7.1 mg, 0.016 mmol, 19%).

*((2S,3aR,5S,6aR)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-hexahydrofuro[3,2-b]furan-2-yl)methanol (**27**).* To a solution of trityl ether **26** (30.2 mg, 0.0729 mmol) in MeOH (0.7 mL) was added $TsOH·H_2O$ (7.9 mg, 0.042 mmol). After 1.5 h at room temperature, the reaction mixture was quenched by the addition of Et_3N (51 μL, 0.37 mmol). The resulting mixture was concentrated and directly purified by flash chromatography (*n*-hexane/EtOAc = 0.5 → 0.1 → 0.1 containing 3% MeOH) to give alcohol (19.7 mg, quant) as a colorless oil: $[\alpha]_D^{27}$ −8.42 (*c* 1.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (t, 1H, *J* = 4.2 Hz, H6), 4.74 (br t, 1H, *J* = 4.5 Hz, H7), 4.64 (m, 1H, H9), 4.22 (dtd, 1H, *J* = 10, 4.8, 3.0 Hz, H4), 3.78 (dd, 1H, *J* = 12, 3.0 Hz, H3), 3.75 (s, 3H, OMe), 3.49 (dd, 1H, *J* = 12, 4.8 Hz, H3), 2.45 (br dd, 1H, *J* = 14, 7.2 Hz, H8), 2.17 (ddd, 1H, *J* = 14, 8.4, 5.1 Hz, H8), 2.15 (br dd, 1H, *J* = 14, 5.7 Hz, H5), 1.89 (ddd, 1H, *J* = 14, 10, 4.8 Hz, H5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 85.8, 83.5, 80.1, 77.7, 64.2, 52.3, 38.8, 35.5; FT-IR (film on ZnSe) 3525, 2959, 2923, 1748, 1436, 1374, 1288, 1207, 1167 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_9H_{15}O_5$ $[M + H]^+$ 203.0914, found 203.0910.

To a solution of the above alcohol (19.7 mg) in DMF (1 mL) were added imidazole (16.8 mg, 0.247 mmol) and TBSCl (10.7 mg, 0.0710 mmol) at room temperature. After 15 h, the reaction mixture was diluted with Et_2O and water. The resulting mixture was extracted with ether (2×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the corresponding TBS ether (15.6 mg): H NMR (300 MHz, $CDCl_3$) δ 4.88 (br t, 1H, *J* = 4.5 Hz, H6), 4.72 (br t, 1H, *J* = 4.2 Hz, H7), 4.63 (br dd, 1H, *J* = 9.0, 6.9 Hz, H9), 4.19 (m, 1H, H4), 3.75 (s, 3H, OMe), 3.70 (dd, 1H, *J* = 11, 3.6 Hz, H3), 3.58 (dd, 1H, *J* = 11, 3.9 Hz, H3), 2.45 (br dd, 1H, *J* = 14, 6.9 Hz, H8), 2.15 (br dd, 1H, *J* = 14, 6.3 Hz, H5), 2.10 (ddd, 1H, *J* = 14, 9.0, 5.1 Hz, H8), 1.93 (ddd, 1H, *J* = 14, 9.0, 5.1 Hz, H5), 0.89 (s, 9H, TBS), 0.05 (s, 6H, TBS).

To a solution of crude TBS ether (15.6 mg) in THF (1 mL) was added $LiAlH_4$ (7.9 mg, 0.20 mmol) at 0 °C. After 30 min at 0 °C, the reaction mixture was quenched by the addition of cold water. After the addition of EtOAc and saturated aqueous Rochelle salt solution, the resulting mixture was stirred for 2 h before it was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give alcohol **27** (11.3 mg, 0.0392 mmol, 54% for three steps) as a colorless oil, which did not need further purification: $[\alpha]_D^{29}$ −7.41 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.74−4.69 (m, 2H), 4.25−4.15 (m, 2H), 3.78 (dd, 1H, *J* = 12, 3.0 Hz), 3.68 (dd, 1H, *J* = 11, 4.2 Hz), 3.59 (dd, 1H, *J* = 11, 4.2 Hz), 3.49 (dd, 1H, *J* = 12, 5.1 Hz), 2.08 (m, 1H), 1.97−1.79 (m, 3H), 0.89 (s, 9H, TBS), 0.05 (s, 6H, TBS); ^1H NMR (300 MHz, C_6D_6) δ 4.46 (br t, 1H, *J* = 4.4 Hz), 4.38 (br t, 1H, *J* = 4.5 Hz), 4.11 (br ddt, 1H, *J* = 9.5, 5.4, 3.8 Hz), 4.02 (m, 1H), 3.59 (dd, 1H, *J* = 11, 3.9 Hz), 3.51 (dd, 1H, *J* = 12, 3.0 Hz), 3.47 (dd, 1H, *J* = 11, 4.2 Hz), 3.20 (dd, 1H, *J* = 12, 4.8 Hz), 2.00 (dd, 1H, *J* = 13, 5.7 Hz), 1.84 (dd, 1H, *J* = 13, 5.7 Hz), 1.70 (ddd, 1H, *J* = 13, 9.3, 5.4 Hz), 1.54 (ddd, 1H, *J* = 13, 9.9, 5.1 Hz), 0.98 (s, 9H, TBS), 0.07 (s, 6H, TBS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.6, 80.7, 80.0, 65.6, 64.3, 36.9, 36.2, 26.1, 18.5, −5.16, −5.21; ^{13}C NMR (75 MHz, C_6D_6) δ 84.7, 84.5, 80.7, 80.4, 65.8, 64.2, 37.2, 36.5, 26.1, 18.6, −5.1, −5.2; FT-IR (film on ZnSe) 3450, 2952, 2928, 2858, 1472, 1464, 1437, 1388, 1361, 1254, 1140, 1098, 1047 cm^{-1}; HRMS (ESI-pos) *m*/*z* calcd for $C_{14}H_{29}O_4Si$ $[M + H]^+$ 289.1830, found 289.1823.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02595.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds, NOE spectra for **12a** and **26**, and chemical shift tables for **5** and natural products (PDF)

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Notes

The authors declare no competing financial interest.

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(33) Although the precise diastereomeric ratio was not determined due to the complexity of the NMR spectrum of the crude products, it

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was apparent that contamination by the minor diastereomer was marginal, if any.
(34) The stereochemical analysis was performed with the corresponding C6-TBS ethers (**17*S*** and **17*R***). To facilitate desilylation in the final step, the TES ether was later prepared and carried forward.
(35) Previous researchers had met difficulties in bromination of the similar secondary alcohols (refs 10a, 10c, 11, and 12). In our hands, the reaction yields varied according to the purity of reagents, polarity of substrates, and the ratio of solvents (benzene vs CH_2Cl_2).
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(39) The low yield of **19** is attributed to the formation of the elimination product (C5−C6 olefin) in the first step (59% yield).
(40) Suzuki et al. reported in ref 5 that "many halogenated C_{15} non-terpenoids isolated from various *Laurencia* species contained (12*R*,13*S*)- or (12*S*,13*R*)-configuration and were suggested to arise from (6*S*,7*S*)- or (6*R*,7*R*)-laurediol, reflecting the (12*E*)-double bond in both precursors". In line with this suggestion, we proposed the 13*S*-configuration as the most plausible stereochemistry of laurenidificin. However, we cannot completely exclude the possiblity of the 13*R*-configuration, as it was reported that two metabolites from Japanese *Laurencia pinnata*, namely laurepinnacin and isolaurepinnacin, had 12*R*,13*R*- and 12*S*,13*S*-configuration, respectively. The latter two natural productes were suggested to arise from (3*E*,6*Z*,9*Z*,12*Z*)-pentadeca-3,6,9,12-tetraen-1-yne, which was a plausible biogenetic precursor of laurediol. (a) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081. (b) Fukuzawa, A.; Honma, T.; Takasugi, Y.; Murai, A. *Phytochemistry* **1993**, *32*, 1435.
(41) To gain insight into the stereochemical relationship between C12 and C13, 13-*epi*-**5** was tentatively synthesized from alcohol **16** by oxidation [AZADO, $PhI(OAc)_2$], reduction ($NaBH_4$, EtOH, 13*S*:13*R* = 2.6:1), bromination (Ph_3P, CBr_4, DTBMP, 13*R*:13*S* = 2.6:1), and deprotection (TBAF), albeit on a small scale. The signals from H10 to H15 were slightly different, but conclusive evidence for the relationship between C12 and C13 could not be obtained because the signals did not match the corresponding signals of laurenenynes A and B. Additional studies to address these stereochemical issues are ongoing and will be reported in due course.
(42) One reviewer pointed out that our approach was relevant to the previous research including structure determination of 2,2′-bifuranyl natural products. The Burton groups used DFT calculations of NMR chemical shifts combined with close analysis of NMR data by a synthetic method, while the Britton group used only the synthetic approach to predict the candidate stereochemistry of the natural product. (a) Shepherd, D. J.; Broadwith, P. A.; Dyson, B. S.; Paton, R. S.; Burton, J. W. *Chem. - Eur. J.* **2013**, *19*, 12644. (b) Holmes, M. T.; Britton, R. *Chem. - Eur. J.* **2013**, *19*, 12649.
(43) As can be seen from our synthetic route in Scheme 2, the 7*S*-configuration of **5** is derived from the C4-stereochemistry of 2-deoxy-D-ribose. In theory, the use of 2-deoxy-L-ribose as the starting material will afford the 7*R*-isomers. However, the latter substrate is more expensive than the former, and therefore, substitution of the starting material to the cheaper one is desirable.
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