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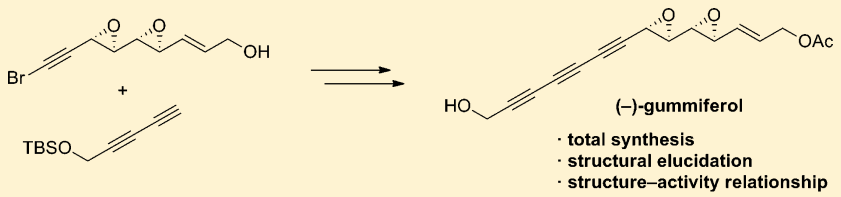
Total Synthesis, Structural Elucidation, and Structure–Cytotoxic Activity Relationship of (−)-Gummiferol

Hiroyoshi Takamura,*[,†] Hiroko Wada,[†] Nan Lu,[†] Osamu Ohno,[‡] Kiyotake Suenaga,[‡] and Isao Kadota*[,†]

[†]Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushimanaka, Kita-ku, Okayama 700-8530, Japan

[‡]Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan

Supporting Information



ABSTRACT: A highly stereoselective and stereodivergent synthesis of two possible diastereomers of (−)-gummiferol was achieved, wherein the stepwise epoxidation and Cadiot–Chodkiewicz reaction were utilized for the construction of the diepoxide moiety and triacetylene part, respectively. Detailed comparison of their ^{1}H and ^{13}C NMR data and specific rotation with those of the natural product unambiguously elucidated the absolute stereostructure of gummiferol. In addition, the cytotoxic activity of the synthesized gummiferol, its stereoisomers, and its truncated analogues was evaluated, which clearly indicates that (1) the absolute configuration of the diepoxide moiety has little influence on the cytotoxic activity against human cancer cells and (2) the triacetylene unit is the crucial structural element required for exerting the cytotoxic activity.

INTRODUCTION

Conjugated acetylenes are common structural units found in a large number of natural products, many of which exhibit the potent and diverse biological activities such as antibacterial,[1] antiparasitic,[2] and insecticidal.[3] These polyacetylenes also show HIV-1 integrase-inhibitory effect[4] and cytotoxicity toward a wide range of cell lines.[5]

In 1995, Wall and co-workers isolated (−)-gummiferol as a new conjugated acetylenic compound from the 50% MeOH/$CHCl_3$ extract of the leaves of *Adenia gummifera* collected in Mazowe, Zimbabwe, by the cytotoxicity-guided fractionation.[6] The cytotoxicity of gummiferol was evaluated by using 13 mammalian cancer cell lines, which revealed that this molecule exhibited the strong cytotoxicity against P388 murine leukemia cell line (ED_{50} = 0.03 μg/mL) and U373 human glioma cell line (ED_{50} = 0.05 μg/mL). The planar structure of gummiferol, which has featured the conjugated triacetylene unit and its neighboring diepoxide moiety, was determined by the analyses of HRMS, IR, UV, and NMR measurements including ^{1}H–^{1}H COSY, HMQC, and HMBC (Figure 1). The *trans*-configurations at the C8/C9 and C10/C11 two epoxide moieties were inferred from the observation of small coupling constants ($^{3}J_{8,9}$ and $^{3}J_{10,11}$ = 2.0 Hz). However, the stereostructure of gummiferol, that is, the absolute configuration of the two contiguous epoxide moieties, was not clarified. Therefore, we embarked on the synthetic study of (−)-gummiferol toward the structural elucidation.[7] In 2011, as a preliminary communication, we reported the stereoselective total synthesis of two possible diastereomers of (−)-gummiferol, which has culminated in the stereochemical elucidation of this natural product.[8] In this article, we describe the details of our total synthesis of (−)-gummiferol including the examination of Cadiot–Chodkiewicz reaction for the efficient introduction of the conjugated triacetylene moiety. Furthermore, we also report the synthesis of the structurally simplified analogues of gummiferol and a growth-inhibitory activity of the synthesized gummiferol, its stereoisomers, and its truncated analogues against human cancer cells.

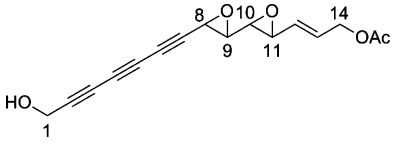


Figure 1. Planar structure of (−)-gummiferol.

RESULTS AND DISCUSSION

Synthetic Strategy of 5a and 5b. Toward the structural determination of (−)-gummiferol, we initially envisioned the stereoselective and stereodivergent synthesis[9] of two possible diastereomers of this natural product, **5a** and **5b**, as depicted in Scheme 1. We planned to introduce the stereochemistries at

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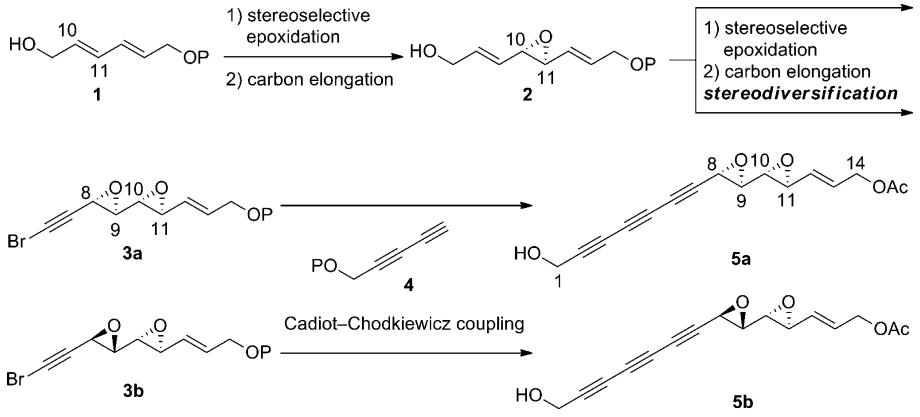
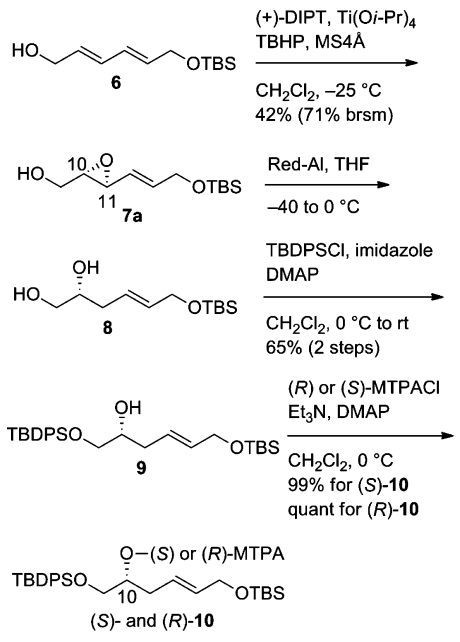
Scheme 1. Synthetic Strategy of 5a and 5b



the C8 to C11 positions by utilizing the stepwise epoxidation. Thus, stereoselective epoxidation of allylic alcohol **1** and subsequent carbon elongation would give epoxide **2**. The same procedure, which includes the stereodiversification step, would be applied to the allylic alcohol **2** to afford diepoxides **3a** and **3b**, respectively. The conjugated triacetylene unit could be constructed by Cadiot–Chodkiewicz coupling[10] through a combination of the bromoacetylenes **3a** and **3b** and diacetylene **4** to provide the target molecules **5a** and **5b**, respectively.

Stereoselective Synthesis of *syn*-Diepoxide 5a. First, we investigated the stereoselective synthesis of the *syn*-diepoxide **5a**. Sharpless asymmetric epoxidation[11] with (+)-diisopropyl tartrate (DIPT) was applied to the known dienol **6**[12] to yield epoxy alcohol **7a** as a single stereoisomer (Scheme 2). The optical purity of **7a** was determined by the ^{1}H NMR comparison between its derivatized (*R*)-MTPA ester and the (*R*)-MTPA ester prepared from the racemic epoxy alcohol, which was synthesized by epoxidation of **6** with *m*-CPBA. The epoxy alcohol **7a** was derivatized for the unambiguous configurational determination. Thus, **7a** was subjected to the Red-Al reduction in THF, wherein the corresponding 1,3-diol was expected to be obtained,[13] to produce 1,2-diol **8** as the sole product. The plausible rationale of this outcome of the regioselective epoxide opening is the C–O bond activation at the C11 position by the neighboring π-orbital. Selective protection of the primary hydroxy group of **8** provided TBDPS ether **9**. Treatment of the secondary alcohol **9** with MTPACl/Et_3N/DMAP afforded MTPA esters (*S*)- and (*R*)-**10**, respectively. The modified Mosher method[14] was utilized to elucidate the stereochemistry at the C10 position. Thus, the ^{1}H–^{1}H COSY spectra of (*S*)- and (*R*)-**10** were analyzed, and the $\Delta\delta_{S-R}$ values were calculated (Figure 2). The signs at the left side of the C10 position were negative, and those at the right side were positive. Therefore, the absolute stereochemistry of **10** was elucidated to be 10*R*, which led to the configurational assignment of **7a**.

Scheme 2. Synthesis of 7a and Its Derivatization for the Structural Elucidation



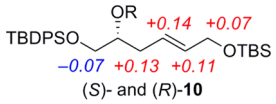


Figure 2. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**10**. R = MTPA. MTPA = α-methoxy-β-(trifluoromethyl)phenylacetyl.

We next carried out the stereoselective introduction of the 8,9-epoxide moiety and its stereochemical assignment. Parikh–Doering oxidation[15] of **7a** and subsequent two-carbon elongation under the Masamune–Roush conditions[16] afforded α,β-unsaturated ester **11** in 80% yield in two steps (Scheme 3). The ester **11** was transformed to alcohol **12** through the corresponding aldehyde by the stepwise DIBAL-H reduction, wherein 1.1 equiv of the reagent was used in each step because the epoxide opening was observed as a side reaction in the case of 2.2 equiv. The second epoxidation was carried out under the Sharpless conditions[11] with (+)-DIPT to yield *syn*-diepoxide **13a** in 80% yield as a single diastereomer. The configurational establishment of the resulting 8,9-epoxide moiety of **13a** was performed by the derivatization and the modified Mosher method.[14] Thus, the double bond of **13a** was reduced with diimide, in order to decrease the reactivity at the C11 position in the next Red-Al reduction, to provide alkane **14**. Chemo- and regioselective reduction of the 8,9-epoxide moiety of **14** with Red-Al[13] produced the desired 1,3-diol. The primary alcohol was selectively protected to give TBDPS ether **15**. The secondary alcohol **15** was converted to MTPA esters (*S*)- and (*R*)-**16** quantitatively by the standard conditions. In the

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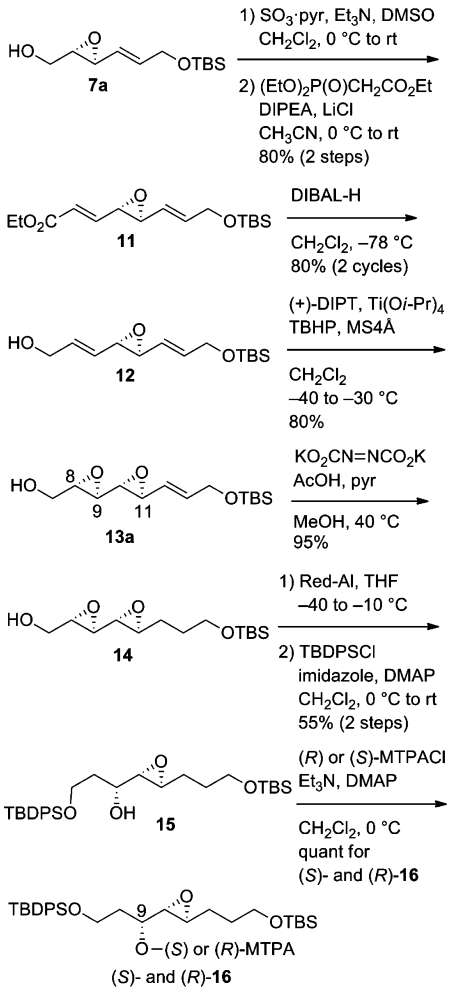
Scheme 3. Synthesis of 13a and Its Derivatization for the Structural Elucidation



observed $\Delta\delta_{S-R}$ values of the (*S*)- and (*R*)-**16**, the signs at the left side of the C9 position proved to be positive, and those at the right side were elucidated to be negative (Figure 3). Therefore, the absolute configuration at the C9 position of **16** was assigned to be *R*, which culminated in the structural determination of the 8,9-epoxide moiety of **13a**.

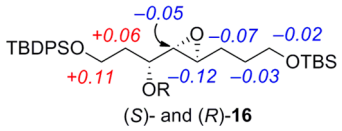
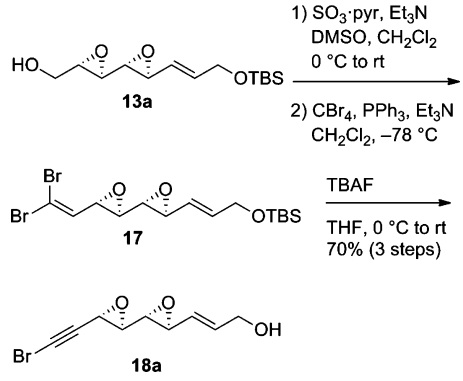


Figure 3. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**16**. R = MTPA.

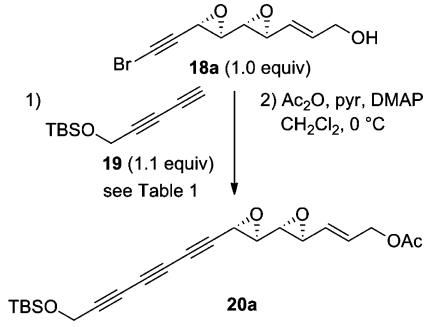
Transformation of the alcohol **13a** to the coupling precursor **18a** is described in Scheme 4. Parikh–Doering oxidation[15] of **13a** afforded the corresponding aldehyde. The initial attempt to convert the aldehyde to dibromoalkene **17** under the standard Corey–Fuchs conditions[17] provided a mixture of products because of the epoxide opening side reaction.[18] After the detailed investigation, it was proven that the addition of Et_3N was effective and the dibromoalkene **17** was obtained as the sole product.[19] Removal of the TBS group and dehydrobromination were carried out simultaneously with an excess amount of TBAF to afford the bromoacetylene **18a**.[19b] We next

Scheme 4. Synthesis of 18a



examined the Cadiot–Chodkiewicz reaction[10] between **18a** and diacetylene **19** (Table 1).[20] When we treated **18a** (1.0 equiv)

Table 1. Cadiot–Chodkiewicz Coupling between 18a and 19



entry	conditions	yield (%)[a]
1	CuI, $(Ph_3P)_2PdCl_2$, pyrrolidine, rt	0
2	CuCl, NH_2OH·HCl, $EtNH_2$, MeOH, rt	20
3	CuCl, NH_2OH·HCl, $EtNH_2$, MeOH, 0 °C	40
4	CuCl, NH_2OH·HCl, $EtNH_2$, MeOH, −78 °C	67

[a]Isolated yield in two steps.

and **19** (1.1 equiv) with CuI/$(Ph_3P)_2PdCl_2$ in pyrrolidine according to Alami protocol,[21] the reaction yielded the complex mixture (entry 1). The use of CuCl/NH_2OH·HCl/$EtNH_2$ at room temperature gave the desired cross-coupling product (entry 2).[22] Treatment of the resulting allylic alcohol with Ac_2O/pyridine/DMAP and purification by silica gel column chromatography afforded acetate **20a** in 20% yield in two steps. Although the desired product **20a** was obtained, we observed the formation of several byproducts in the first step. Therefore, we carried out the Cadiot–Chodkiewicz reaction at 0 °C to provide **20a** in 40% yield (entry 3). The chemical yield of **20a** could be improved to 67% by lowering the reaction temperature to −78 °C (entry 4). It is noteworthy that the reactive propargylic and vinylic epoxides as well as the free allylic alcohol of **18a** could be tolerated under the reaction conditions. Finally, deprotection of the TBS moiety of **20a** with HF·pyr produced the *syn*-diepoxide **5a**, quantitatively (Scheme 5).

Stereoselective Synthesis of *anti*-Diepoxide 5b. Next, we examined the stereoselective synthesis of the *anti*-diepoxide **5b** by using a transformation similar to that toward **5a**. The allylic alcohol **12** was subjected to the Sharpless asymmetric epoxidation[11] with (−)-DIPT to give epoxy alcohol **13b** in 81% yield as the sole product (Scheme 6). The diastereomeric purity

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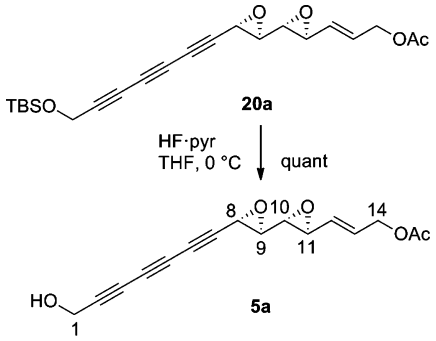
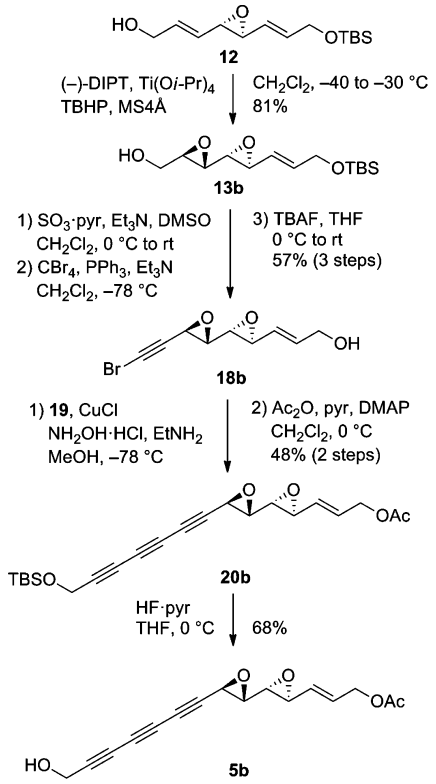
Scheme 5. Synthesis of 5a



Scheme 6. Synthesis of 5b



of **13b** was judged by the ^{1}H and ^{13}C NMR data, which deviated obviously from those of **13a**. Parikh–Doering oxidation,[15] dibromo-olefination utilizing Corey–Fuchs protocol in the presence of Et_3N,[17,19] and TBS deprotection/dehydrobromination afforded allylic alcohol **18b** in 57% yield in three steps. The bromoacetylene **18b** was reacted with diacetylene **19** under the optimized conditions of Cadiot–Chodkiewicz reaction[10] to form the desired coupling product. Acetylation of the resulting allylic alcohol provided acetate **20b** in 48% yield from **18b**. Finally, desilylation of **20b** was performed to produce the *anti*-diepoxide **5b**.

Structural Elucidation of (−)-Gummiferol. With two possible diastereomers of (−)-gummiferol in hand, we next submitted these two synthetic products to the detailed 2D NMR analysis. Tables 2 and 3 describe chemical shifts and their deviations of natural gummiferol[6] and the synthesized diepoxides **5a** and **5b** in the ^{1}H and ^{13}C NMR spectra, respectively. The ^{1}H and ^{13}C NMR data of **5a** were in excellent agreement with those of natural gummiferol. On the other hand, the ^{1}H and ^{13}C NMR data of the synthetic *anti*-diepoxide

Table 2. ^{1}H NMR Chemical Shifts and Their Deviations of Natural (−)-Gummiferol and the Synthetic Products 5a and 5b[a]

position	natural[b]	5a[c]	5b[c]	$\Delta(\delta_N-\delta_{5a})$[d]	$\Delta(\delta_N-\delta_{5b})$[d]
1	4.34	4.36	4.36	−0.02	−0.02
8	3.46	3.44	3.43	+0.02	+0.03
9	3.35	3.34	3.27	+0.01	+0.08
10	3.04	3.02	2.92	+0.02	+0.12
11	3.39	3.38	3.35	+0.01	+0.04
12	5.49	5.49	5.48	0.00	+0.01
13	6.05	6.04	6.04	+0.01	+0.01
14	4.58	4.59	4.58	−0.01	0.00
14-COCH_3	2.09	2.08	2.08	+0.01	+0.01

[a]Chemical shifts are reported in parts per million with reference to tetramethylsilane. [b]Data from ref 6. Recorded at 500 MHz. [c]Recorded at 400 MHz. [d]δ_N, δ_{5a}, and δ_{5b} are chemical shifts of the natural product and the synthetic products **5a** and **5b**, respectively.

Table 3. ^{13}C NMR Chemical Shifts and Their Deviations of Natural (−)-Gummiferol and the Synthetic Products 5a and 5b[a]

position	natural[b]	5a[c]	5b[c]	$\Delta(\delta_N-\delta_{5a})$[d]	$\Delta(\delta_N-\delta_{5b})$[d]
1	51.3	51.5	51.5	−0.2	−0.2
2	77.2	77.2	77.2	0.0	0.0
3	70.1	70.4	70.4	−0.3	−0.3
4	62.4	62.6	62.8	−0.2	−0.4
5	62.8	62.7	62.6	+0.1	+0.2
6	69.0	69.0	69.2	0.0	−0.2
7	73.9	74.0	73.7	−0.1	+0.2
8	43.1	43.1	43.5	0.0	−0.4
9	57.5	57.5	58.7	0.0	−1.2
10	56.2	56.2	57.1	0.0	−0.9
11	55.2	55.1	55.9	+0.1	−0.7
12	129.4	129.3	129.1	+0.1	+0.3
13	130.5	130.4	130.5	+0.1	0.0
14	63.6	63.5	63.5	+0.1	+0.1
14-$COCH_3$	170.8	170.4	170.4	+0.4	+0.4
14-$COCH_3$	20.9	20.9	20.9	0.0	0.0

[a]Chemical shifts are reported in parts per million with reference to tetramethylsilane. [b]Data from ref 6. Recorded at 125 MHz. [c]Recorded at 100 MHz. [d]δ_N, δ_{5a}, and δ_{5b} are chemical shifts of the natural product and the synthetic products **5a** and **5b**, respectively.

5b were clearly different from those of the natural product. It was proven that there were the critical differences in the chemical shifts at the C9 and C10 positions between natural gummiferol and the synthetic **5b**: $\Delta(\delta_N-\delta_{5b})$ = +0.08 (H-9), +0.12 (H-10), −1.2 (C-9), −0.9 (C-10). The measured specific rotation of the synthetic adduct **5a**, $[\alpha]_D^{28}$ −62.5 (*c* 0.07, CH_3OH), was consistent with the reported value of natural (−)-gummiferol, $[\alpha]_D^{25}$ −170 (*c* 0.2, CH_3OH).[6,23] Therefore, the absolute configuration of (−)-gummiferol was elucidated to be that depicted in **5a**.

Synthesis of 5c and 5b. Having elucidated the absolute configuration of (−)-gummiferol by the chemical synthesis of two possible diastereomers **5a** and **5b**, we next turned our attention to the structure–activity relationship of gummiferol. First, we decided to elucidate the influence on the biological activity by the stereostructure of the diepoxide moiety. Therefore, in addition to the diepoxides **5a** and **5b**, their enantiomers **5c** and **5d** were also synthesized through the common synthetic intermediate **7b**, which was obtained by the

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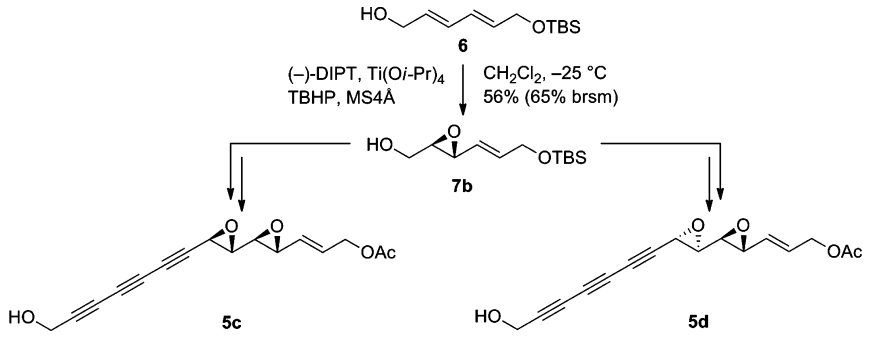
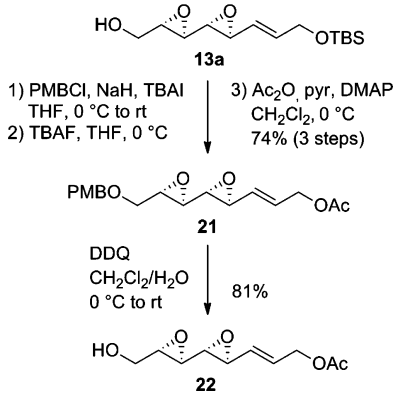
Scheme 7. Synthesis of 5c and 5d



Sharpless epoxidation[11] with (−)-DIPT of **6**, as shown in Scheme 7.

Synthesis of Analogues. We next tried to synthesize the structurally simplified analogues corresponding to the diepoxide and triacetylene moieties. Synthesis of the truncated diepoxide analogue **22** is described in Scheme 8. Protection of

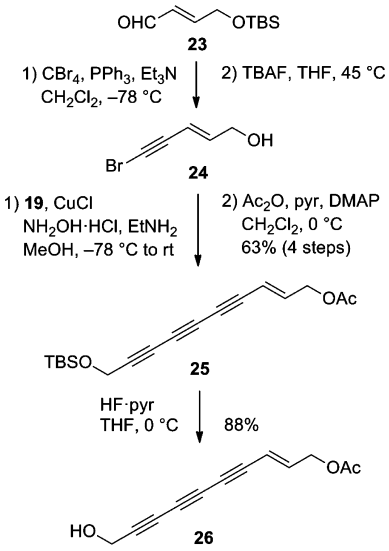
Scheme 8. Synthesis of 22



the epoxy alcohol **13a**, which is the synthetic intermediate toward (−)-gummiferol (**5a**), as the PMB ether, removal of the TBS protective group, and acetylation of the resulting alcohol gave acetate **21**. Oxidative deprotection of the PMB moiety with DDQ afforded the structurally simplified diepoxide analogue **22** in 81% yield.

Next, we investigated the synthesis of the truncated triacetylene analogues **26**, **29**, and **33** on the basis of the Cadiot−Chodkiewicz cross-coupling.[10] Dibromo-olefination of the known aldehyde **23**[12] under the modified Corey−Fuchs conditions[17,19] followed by deprotection of the TBS group and dehydrobromination with TBAF provided bromoacetylene **24** (Scheme 9). The bromoacetylene **24** was coupled with the diacetylene **19** to yield the desired triacetylene. Treatment of the resulting alcohol with Ac_2O/pyr/DMAP gave acetate **25** in 63% yield in four steps. The TBS group was removed with HF·pyr to produce the first structurally simplified triacetylene analogue **26**. The other two truncated triacetylene analogues **29** and **33** were also synthesized, as depicted in Scheme 10. Parikh−Doering oxidation[15] of the dienol **6** afforded dienal **27** in 89% yield. The aldehyde **27** was transformed to triacetylene **28** by the following four-step sequence: (1) one-carbon elongation with CBr_4/PPh_3 in the presence of Et_3N,[17,19] (2) TBS removal and dehydrobromination in one-pot, (3) Cadiot−Chodkiewicz coupling[10] of the corresponding bromoalkyne with **19**, and (4) acetylation of the resulting alcohol. The final

Scheme 9. Synthesis of 26



deprotection of **28** with HF·pyr proceeded smoothly to give the second truncated triacetylene analogue **29**, which is the two-carbon elongated diacetylene analogue of **26**. Investigation on the synthesis of **33** was also commenced from the allylic alcohol **6**. Chemoselective epoxidation of **6** took place with *m*CPBA to provide epoxy alcohol **30** in 78% yield as the racemate. The epoxy alcohol **30** was converted to the third structurally simplified triacetylene analogue **33**, which is the monoepoxidized compound of **29**, through **31** and **32** as the synthetic intermediates by using the similar sequence to that toward **29**.

Evaluation of the Cytotoxicity of (−)-Gummiferol, Its Stereoisomers, and Its Analogues. With (−)-gummiferol (**5a**), its stereoisomers **5b**−**5d**, and its truncated analogues **22**, **26**, **29**, and **33** in hand, we evaluated the growth-inhibitory activity of these compounds by using the MTT assay with HL60 human leukemia cells and HeLa S_3 human cervical cancer cells. The cells were treated in 96-well plates with various concentrations of the compounds for 72 h. The results are shown in Table 4. Interestingly, (−)-gummiferol (**5a**) and its stereoisomers **5b**−**5d** exhibited the similar activity without regard to the stereostructure of the diepoxide moiety (IC_{50} = 1.22−3.61 μM for HL60 cells and 6.76−19.1 μM for HeLa S_3 cells). The structurally simplified diepoxide analogue **22** was inactive against both HL60 and HeLa S_3 cells (IC_{50} >100 μM). On the other hand, the truncated triacetylene analogue **26** retained the growth-inhibitory activity (IC_{50} = 12.3 μM for HL60 cells and 31.6 μM for HeLa S_3 cells). The cytotoxic activity of the other two triacetylene analogues **29** and **33**

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Scheme 10. Synthesis of 29 and 33

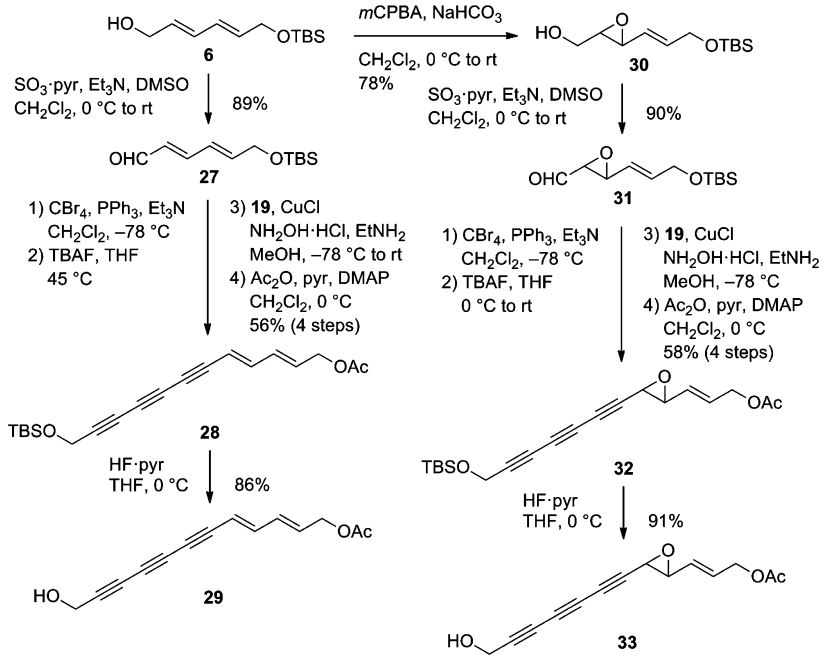

Table 4. Growth-Inhibitory Activity of (−)-Gummiferol, Its Stereoisomers, and Its Structural Analogues against Human Cancer Cells[a]

compounds	HL60	HeLa S_3
5a	1.22	6.76
5b	1.62	8.61
5c	1.23	6.68
5d	3.61	19.1
22	>100	>100
26	12.3	31.6
29	4.63	22.4
33	4.75	17.4
25	4.48	19.3
28	19.4	50.9
32	7.40	20.6

[a] IC_{50} values in μM.

proved to be slightly increased in comparison with that of **26**. Furthermore, to elucidate the influence on the cytotoxic activity by the propargylic alcohol moieties of **26**, **29**, and **33**, we evaluated the growth-inhibitory activity of the TBS ethers **25**, **28**, and **32**, and it was found that these compounds also exhibited the cytotoxic activity against both HL60 and HeLa S_3 cells. These results revealed the following two points concerning the structure−activity relationship: (1) The stereochemistry of the diepoxide moiety has little influence on the growth-inhibitory activity. (2) The triacetylene unit is essential for exerting the growth inhibition.

CONCLUSION

First, we have synthesized two possible diastereomers of (−)-gummiferol, **5a** and **5b**, in a highly stereoselective and stereodivergent manner. In the synthetic route, two contiguous epoxide parts were stereoselectively introduced by the Sharpless asymmetric epoxidation conditions. The resulting stereochemistries of the synthetic products in the epoxidation steps were unambiguously determined by the derivatization and the modified Mosher method. The Cadiot−Chodkiewicz reactions between the bromoacetylenes and the diacetylene were efficiently applied to the construction of the triacetylene unit. The detailed comparison of the synthetic **5a** and **5b** and the natural product in the ^1H and ^{13}C NMR data and specific rotation revealed the absolute configuration of (−)-gummiferol to be that shown in **5a**.

Besides **5a** and **5b**, their enantiomers **5c** and **5d** were also synthesized for elucidating the stereostructure−activity relationship of gummiferol. Moreover, its skeletal analogues **22**, **25**, **26**, **28**, **29**, **32**, and **33** were synthesized as the structurally simplified diepoxide and triacetylene analogues, respectively. The growth-inhibitory activity of these synthetic products against HL60 and HeLa S_3 cells was evaluated, establishing that (1) the stereostructure of the diepoxide unit has little effect on the cytotoxic activity and (2) the presence of the triacetylene moiety is crucial for the cytotoxic activity.

EXPERIMENTAL SECTION

Epoxy Alcohol 7a. To a suspension of powdered MS4Å (400 mg) in CH_2Cl_2 (40 mL) were added (+)-DIPT (0.27 mL, 1.32 mmol), $Ti(O\textit{i}\text{-}Pr)_4$ (0.26 mL, 0.877 mmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 2.9 mL, 17.4 mmol) at −25 °C. The mixture was stirred at the same temperature for 30 min, and a solution of allylic alcohol **6** (2.00 g, 8.77 mmol) in CH_2Cl_2 (5.0 mL + 3.0 mL + 2.0 mL) was added. After the resulting mixture was stirred at −25 °C for 4 h, the reaction was quenched with 3 M aqueous NaOH. The mixture was stirred at room temperature for 1 h. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 6:1) gave epoxy alcohol **7a** (901 mg, 42%) as a light yellow oil and allylic alcohol **6** (816 mg, 41% recovery). Epoxy alcohol **7a**: R_f = 0.39 (hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ −27.1 (*c* 0.10, $CHCl_3$); IR (neat) 3434, 2954, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.03 (dt, *J* = 15.4, 4.4 Hz, 1 H), 5.50 (ddt, *J* = 15.4, 8.0, 2.0 Hz, 1 H), 4.20 (dd, *J* = 4.4, 2.0 Hz, 2 H), 3.96 (ddd, *J* = 12.7, 5.4, 2.4 Hz, 1 H), 3.70 (ddd, *J* = 12.7, 7.8, 3.9 Hz, 1 H), 3.44 (dd, *J* = 8.0, 2.4 Hz, 1 H), 3.09 (dt, *J* = 3.9, 2.4 Hz, 1 H), 1.60 (dd, *J* = 7.8, 5.4 Hz, 1 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 125.9, 62.8, 61.2, 60.0, 55.3, 26.0, 18.6, −5.2, −5.2;

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HRMS (ESI−TOF) calcd for $C_{12}H_{24}O_3SiNa$ $[M + Na]^+$ 267.1393, found 267.1385.

TBDPS Ether 9. To a solution of epoxy alcohol **7a** (50.0 mg, 0.205 mmol) in THF (2.0 mL) was added Red-Al (65% in toluene, 0.31 mL, 1.00 mmol) at −40 °C. After the mixture was stirred at 0 °C for 5 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was diluted with EtOAc and washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1, 2:1) gave diol **8** (40.5 mg), which was used for the next reaction without further purification.

To a solution of diol **8** obtained above (40.5 mg) in CH_2Cl_2 (1.5 mL) were added DMAP (32.6 mg, 0.237 mmol), imidazole (32.2 mg, 0.474 mmol), and TBDPSCl (82 μL, 0.316 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 25:1, 10:1, 4:1) gave TBDPS ether **9** (61.9 mg, 65% in two steps) as a yellow oil: R_f = 0.67 (hexane/EtOAc = 4:1); $[\alpha]_D^{22}$ +1.2 (*c* 0.77, $CHCl_3$); IR (neat) 3412, 2956, 2930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.44−7.37 (m, 6 H), 5.67−5.56 (m, 2 H), 4.10 (d, *J* = 3.7 Hz, 2 H), 3.78−3.75 (m, 1 H), 3.67 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.54 (dd, *J* = 10.2, 6.8 Hz, 1 H), 2.43 (br s, 1 H), 2.23 (t, *J* = 6.4 Hz, 2 H), 1.07 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 133.1, 132.2, 129.7, 127.7, 126.2, 71.5, 67.4, 63.7, 36.1, 26.9, 26.0, 19.3, 18.5, −5.0; HRMS (ESI−TOF) calcd for $C_{28}H_{44}O_3Si_2Na$ $[M + Na]^+$ 507.2727, found 507.2733.

MTPA Ester (*S*)-10. To a solution of alcohol **9** (2.8 mg, 5.77 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (1.4 mg, 11.5 μmol), Et_3N (1.1 μL, 8.00 μmol), and (*R*)-MTPACl (1.3 μL, 6.93 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 45:1) gave MTPA ester (*S*)-**10** (4.0 mg, 99%) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 10:1); $[\alpha]_D^{23}$ −7.7 (*c* 0.19, $CHCl_3$); IR (neat) 2954, 2928, 1748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.32 (m, 15 H), 5.64−5.52 (m, 2 H, H-12 and H-13), 5.25−5.20 (m, 1 H, H-10), 4.06 (d, *J* = 4.4 Hz, 2 H, H_2-14), 3.74−3.66 (m, 2 H, H_2-9), 3.54 (s, 3 H), 2.55−2.41 (m, 2 H, H_2-11), 1.01 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 135.5, 135.4, 133.4, 133.0, 132.8, 132.2, 129.7, 129.5, 129.4, 128.2, 127.6, 127.6, 127.4, 124.2, 77.2, 76.8, 64.0, 63.4, 55.5, 33.5, 26.8, 26.0, 19.2, 18.5, −5.2; HRMS (ESI−TOF) calcd for $C_{38}H_{51}F_3O_5Si_2Na$ $[M + Na]^+$ 723.3125, found 723.3130.

MTPA Ester (*R*)-10. To a solution of the alcohol **9** (2.8 mg, 5.77 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (1.4 mg, 11.5 μmol), Et_3N (1.1 μL, 8.00 μmol), and (*S*)-MTPACl (1.3 μL, 6.93 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 45:1) gave MTPA ester (*R*)-**10** (4.1 mg, quant) as a colorless oil: R_f = 0.45 (hexane/EtOAc = 10:1); $[\alpha]_D^{26}$ +26.7 (*c* 0.72, $CHCl_3$); IR (neat) 2954, 2930, 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.29 (m, 15 H), 5.53−5.39 (m, 2 H, H-12 and H-13), 5.27−5.20 (m, 1 H, H-10), 4.01−3.98 (m, 2 H, H_2-14), 3.77 (dd, *J* = 5.6, 2.2 Hz, 2 H, H_2-9), 3.55 (s, 3 H), 2.35 (t, *J* = 6.3 Hz, 2 H, H_2-11), 1.04 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 135.5, 135.4, 133.3, 133.0, 132.8, 132.4, 129.8, 129.8, 129.4, 128.6, 128.3, 127.7, 127.4, 124.0, 77.2, 76.8, 64.4, 63.4, 55.5, 33.3, 26.8, 26.0, 19.3, 18.4, −5.1; HRMS (ESI−TOF) calcd for $C_{38}H_{51}F_3O_5Si_2Na$ $[M + Na]^+$ 723.3125, found 723.3135.

α,β-Unsaturated Ester 11. To a solution of alcohol **7a** (998 mg, 4.09 mmol) in CH_2Cl_2 (40 mL) and DMSO (13 mL) were added Et_3N (1.3 mL, 12.3 mmol) and SO_3·pyr (1.30 g, 8.18 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding aldehyde (865 mg), which was used for the next reaction without further purification.

To a solution of $(EtO)_2P(O)CH_2CO_2Et$ (1.6 mL, 7.12 mmol) in CH_3CN (27 mL) were added DIPEA (1.8 mL, 10.7 mmol), LiCl (602 mg, 14.2 mmol), and the aldehyde obtained above (865 mg) in CH_3CN (5.0 mL + 3.0 mL + 1.0 mL) at 0 °C. After the mixture was stirred at room temperature for 30 min, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave α,β-unsaturated ester **11** (1.02 g, 80% in two steps) as a colorless oil: R_f = 0.63 (hexane/EtOAc = 4:1); $[\alpha]_D^{22}$ −43.2 (*c* 1.00, $CHCl_3$); IR (neat) 2955, 2930, 1723, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 15.6, 6.8 Hz, 1 H), 6.13 (d, *J* = 15.6 Hz, 1 H), 6.03 (dt, *J* = 15.3, 4.4 Hz, 1 H), 5.50 (ddt, *J* = 15.3, 7.7, 1.9 Hz, 1 H), 4.22−4.17 (m, 4 H), 3.38−3.32 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 143.7, 135.8, 125.3, 123.7, 62.7, 60.7, 60.6, 58.2, 26.0, 18.4, 14.3, −5.2, −5.2; HRMS (ESI−TOF) calcd for $C_{16}H_{28}O_4SiNa$ $[M + Na]^+$ 335.1655, found 335.1648.

Allylic Alcohol 12. To a solution of α,β-unsaturated ester **11** (18.4 mg, 59.0 μmol) in CH_2Cl_2 (1.0 mL) was added DIBAL-H (1.03 M solution in hexane, 63 μL, 64.9 μmol) at −78 °C. After the mixture was stirred at the same temperature for 10 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 20:1, 10:1, 4:1) gave the corresponding aldehyde (16.4 mg), which was used for the next reaction without further purification.

To a solution of the aldehyde obtained above (16.4 mg) in CH_2Cl_2 (1.0 mL) was added DIBAL-H (1.03 M solution in hexane, 63 μL, 64.9 μmol) at −78 °C. After the mixture was stirred at the same temperature for 10 min, the reaction was quenched with MeOH. The mixture was filtered through a Celite pad and washed with EtOAc. Concentration and column chromatography (hexane/EtOAc = 10:1, 4:1) gave allylic alcohol **12** (12.7 mg, 80% in two cycles) as a colorless oil: R_f = 0.35 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ −32.1 (*c* 0.87, $CHCl_3$); IR (neat) 3409, 2954, 2929, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, *J* = 15.4, 4.4 Hz, 1 H), 6.00 (dt, *J* = 15.4, 4.4 Hz, 1 H), 5.54−5.46 (m, 2 H), 4.20−4.17 (m, 4 H), 3.29−3.27 (m, 2 H), 1.36 (br s, 1 H), 0.91 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 134.2, 128.0, 126.1, 62.8, 62.7, 59.9, 59.6, 26.0, 18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{14}H_{26}O_3SiNa$ $[M + Na]^+$ 293.1549, found 293.1545.

Epoxy Alcohol 13a. To a suspension of powdered MS4Å (130 mg) in CH_2Cl_2 (10 mL) were added (+)-DIPT (0.17 mL, 0.843 mmol), $Ti(Oi\text{-}Pr)_4$ (0.17 mL, 0.562 mmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 1.8 mL, 10.8 mmol) at −30 °C. The mixture was stirred at the same temperature for 30 min, and a solution of allylic alcohol **12** (151 mg, 0.558 mmol) in CH_2Cl_2 (3.0 mL + 1.0 mL + 1.0 mL) was added at −40 °C. After the resulting mixture was stirred at −40 °C for 17 h and at −30 °C for further 8 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. After the concentration, the mixture was diluted with Et_2O and 3 M aqueous NaOH was added to the mixture. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **13a** (127 mg, 80%) as a colorless oil: R_f = 0.42 (hexane/EtOAc = 1:1); $[\alpha]_D^{20}$ −61.2 (*c* 0.98, $CHCl_3$); IR (neat) 3435, 2954, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 4.4 Hz, 1 H), 5.46 (ddt, *J* = 15.6, 7.8, 2.0 Hz, 1 H), 4.19 (dd, *J* = 4.4, 2.0 Hz, 2 H), 3.96 (ddd, *J* = 12.7, 4.4, 2.2 Hz, 1 H), 3.70 (ddd, *J* = 12.7, 7.8, 3.6 Hz, 1 H), 3.39 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.17 (dt, *J* = 3.6, 2.2 Hz, 1 H), 3.07 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.92 (dd, *J* = 4.4, 2.0 Hz, 1 H), 1.82 (br s, 1 H), 0.90 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 125.4, 62.7, 60.5, 57.9, 55.7, 55.5, 53.3, 25.9,

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18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{14}H_{26}O_4SiNa$ $[M + Na]^+$ 309.1498, found 309.1496.

Alkane 14. To a mixture of alkene **13a** (10.0 mg, 34.9 μmol), pyridine (0.54 mL, 5.58 mmol), and $KO_2CN{=}NCO_2K$ (542 mg, 2.79 mmol) in MeOH (2.0 mL) was added AcOH (0.32 mL, 5.58 mmol) at 40 °C. After the mixture was stirred at the same temperature for 6 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave alkane **14** (9.6 mg, 95%) as a yellow oil: R_f = 0.60 (hexane/EtOAc = 1:1); $[\alpha]_D^{22}$ −34.9 (*c* 0.20, $CHCl_3$); IR (neat) 3435, 2954, 2928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99−3.96 (m, 1 H), 3.71−3.69 (m, 3 H), 3.16 (dt, *J* = 4.4, 2.2 Hz, 1 H), 3.04 (dd, *J* = 4.6, 2.2 Hz, 1 H), 3.00−2.97 (m, 1 H), 2.76 (dd, *J* = 4.6, 2.2 Hz, 1 H), 1.74−1.57 (m, 5 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 60.6, 56.2, 55.9, 55.7, 53.7, 29.1, 28.2, 26.0, 18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{14}H_{28}O_4SiNa$ $[M + Na]^+$ 311.1655, found 311.1653.

TBDPS Ether 15. To a solution of epoxy alcohol **14** (12.0 mg, 41.5 μmol) in THF (0.6 mL) was added Red-Al (65% in toluene, 62 μL, 0.208 mmol) at −40 °C. After the mixture was allowed to warm to −10 °C for 2 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:1) gave the corresponding diol (11.0 mg), which was used for the next reaction without further purification.

To a solution of the diol obtained above (11.0 mg) in CH_2Cl_2 (0.5 mL) were added DMAP (5.4 mg, 44.0 μmol), imidazole (3.0 mg, 44.0 μmol), and TBDPSCl (7.6 μL, 29.3 μmol) at 0 °C. After the mixture was stirred at room temperature for 7 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave TBDPS ether **15** (12.1 mg, 55% in two steps) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 4:1); $[\alpha]_D^{24}$ −3.2 (*c* 0.33, $CHCl_3$); IR (neat) 3419, 2954, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.46−7.37 (m, 6 H), 3.93−3.80 (m, 3 H), 3.67−3.60 (m, 2 H), 2.99−2.96 (m, 1 H), 2.78 (dd, *J* = 4.6, 2.2 Hz, 1 H), 2.63 (d, *J* = 4.6 Hz, 1 H), 1.85−1.75 (m, 2 H), 1.67−1.58 (m, 4 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.5, 129.7, 127.7, 69.6, 62.6, 61.6, 61.5, 55.9, 36.2, 29.8, 29.2, 28.3, 26.9, 26.0, 19.2, −5.2; HRMS (ESI−TOF) calcd for $C_{30}H_{48}O_4Si_2Na$ $[M + Na]^+$ 551.2989, found 551.2988.

MTPA Ester (*S*)-16. To a solution of alcohol **15** (1.7 mg, 3.21 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (0.8 mg, 6.42 μmol), Et_3N (0.6 μL, 4.50 μmol), and (*R*)-MTPACl (0.7 μL, 3.85 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*S*)-**16** (2.5 mg, quant) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 7:1); $[\alpha]_D^{24}$ −14.3 (*c* 0.23, $CHCl_3$); IR (neat) 2953, 2929, 1751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4 H), 7.54−7.52 (m, 2 H), 7.39−7.35 (m, 9 H), 5.27−5.22 (m, 1 H, H-9), 3.75−3.70 (m, 2 H, H_2-7), 3.61−3.56 (m, 2 H, H_2-14), 3.47 (s, 3 H), 2.88 (dd, *J* = 6.5, 2.1 Hz, 1 H, H-10), 2.79−2.76 (m, 1 H, H-11), 2.07−1.88 (m, 2 H, H_2-8), 1.61−1.51 (m, 4 H, H_2-12 and H_2-13), 1.06 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 135.4, 135.4, 133.3, 133.2, 132.1, 130.0, 129.5, 128.3, 127.7, 127.4, 77.2, 73.8, 62.4, 59.4, 58.4, 56.4, 55.4, 33.8, 29.1, 28.2, 26.9, 26.0, 19.2, 18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{40}H_{55}F_3O_6Si_2Na$ $[M + Na]^+$ 767.3387, found 767.3378.

MTPA Ester (*R*)-16. To a solution of alcohol **15** (1.3 mg, 2.45 μmol) in CH_2Cl_2 (0.2 mL) were added DMAP (0.6 mg, 4.90 μmol), Et_3N (0.5 μL, 3.43 μmol), and (*S*)-MTPACl (0.6 μL, 2.94 μmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave MTPA ester (*R*)-**16** (2.0 mg, quant) as a colorless oil: R_f = 0.41 (hexane/EtOAc = 7:1); $[\alpha]_D^{27}$ +28.0 (*c* 0.23, $CHCl_3$); IR (neat) 2954, 2929, 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.70 (m, 1 H), 7.64−7.60 (m, 4 H), 7.53−7.51 (m, 1 H), 7.45−7.29 (m, 9 H), 5.20−5.15 (m, 1 H, H-9), 3.66−3.56 (m, 4 H, H_2-7 and H_2-14), 3.57 (s, 3 H), 2.93 (dd, *J* = 7.3, 2.0 Hz, 1 H, H-10), 2.91−2.89 (m, 1 H, H-11), 1.93−1.80 (m, 2 H, H_2-8), 1.66−1.51 (m, 4 H, H_2-12 and H_2-13), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 135.5, 135.4, 134.7, 133.4, 133.3, 132.3, 129.7, 129.4, 128.3, 127.7, 127.2, 77.2, 74.5, 62.4, 59.2, 58.5, 57.1, 55.6, 34.0, 29.1, 28.2, 26.9, 26.0, 19.2, 18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{40}H_{55}F_3O_6Si_2Na$ $[M + Na]^+$ 767.3387, found 767.3381.

Bromoacetylene 18a. To a solution of alcohol **13a** (18.6 mg, 64.9 μmol) in CH_2Cl_2 (1.0 mL) and DMSO (0.3 mL) were added Et_3N (45 μL, 0.325 mmol) and SO_3·pyr (41.3 mg, 0.260 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 5:1) gave the corresponding aldehyde (15.1 mg), which was used for the next reaction without further purification.

To a solution of CBr_4 (70.3 mg, 0.212 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (111 mg, 0.425 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (59 μL, 0.425 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, the aldehyde obtained above (15.1 mg) in CH_2Cl_2 (0.6 mL + 0.4 mL) was added at −78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 20:1) gave dibromoalkene **17** (22.4 mg), which was used for the next reaction without further purification.

To a solution of dibromoalkene **17** obtained above (22.4 mg) in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 0.20 mL, 0.200 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. Concentration and column chromatography (hexane/EtOAc = 4:1) gave bromoacetylene **18a** (11.1 mg, 70% in three steps) as a colorless amorphous solid: R_f = 0.23 (hexane/EtOAc = 1:1); $[\alpha]_D^{24}$ −89.9 (*c* 0.90, $CHCl_3$); IR (neat) 3354, 3012, 2949, 2225, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 15.6, 5.0 Hz, 1 H), 5.46 (ddt, *J* = 15.6, 7.8, 1.7 Hz, 1 H), 4.20−4.18 (m, 2 H), 3.40 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.38 (d, *J* = 2.0 Hz, 1 H), 3.27 (dd, *J* = 3.4, 2.0 Hz, 1 H), 2.99 (dd, *J* = 3.4, 2.0 Hz, 1 H), 1.55 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 126.5, 75.8, 62.5, 57.0, 56.5, 55.3, 45.4, 43.6; HRMS (ESI−TOF) calcd for $C_9H_9BrO_3Na$ $[M + Na]^+$ 268.9613, found 268.9611.

Acetate 20a. To a solution of $EtNH_2$ (70% aqueous solution, 0.5 mL) in MeOH (0.7 mL) was added CuCl (2.0 mg, 19.9 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (8.3 mg, 0.119 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **19** (8.5 mg, 43.7 μmol) in MeOH (0.3 mL + 0.2 mL) at room temperature, and the mixture was stirred at the same temperature for 20 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **18a** (10.1 mg, 39.7 μmol) in MeOH (0.3 mL + 0.2 mL) at −78 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave the corresponding triacetylene (9.9 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (9.9 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc

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= 7:1) gave acetate **20a** (10.6 mg, 67% in two steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ −77.7 (*c* 0.30, $CHCl_3$); IR (neat) 2954, 2930, 2216, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.9 Hz, 1 H), 5.48 (ddd, *J* = 15.6, 7.8, 1.2 Hz, 1 H), 4.58 (dd, *J* = 5.9, 1.2 Hz, 2 H), 4.39 (s, 2 H), 3.44 (d, *J* = 2.0 Hz, 1 H), 3.38 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.33 (dd, *J* = 3.2, 2.0 Hz, 1 H), 3.01 (dd, *J* = 3.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.4, 129.3, 77.8, 73.6, 69.5, 69.1, 63.5, 63.1, 62.0, 57.5, 56.2, 55.1, 52.1, 43.1, 25.8, 20.9, 18.3, −5.1; HRMS (ESI−TOF) calcd for $C_{22}H_{28}O_5SiNa$ $[M + Na]^+$ 423.1604, found 423.1613.

Diepoxide 5a. To a solution of TBS ether **20a** (1.2 mg, 2.99 μmol) in THF (0.2 mL) was added HF·pyr (5.0 μL) at 0 °C. After the mixture was stirred at the same temperature for 40 min, HF·pyr (2.0 μL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was diluted with Et_2O. The mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave diepoxide **5a** (1.6 mg, quant) as a light yellow amorphous solid: R_f = 0.40 (hexane/EtOAc = 1:1); $[\alpha]_D^{28}$ −62.5 (*c* 0.07, CH_3OH); IR (neat) 3410, 3015, 2925, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.6 Hz, 1 H), 5.49 (ddt, *J* = 15.6, 7.8, 1.4 Hz, 1 H), 4.59 (dd, *J* = 5.6, 1.4 Hz, 2 H), 4.36 (d, *J* = 5.8 Hz, 2 H), 3.44 (d, *J* = 2.0 Hz, 1 H), 3.38 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.34 (dd, *J* = 3.2, 2.0 Hz, 1 H), 3.02 (dd, *J* = 3.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 1.69 (t, *J* = 5.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.4, 129.3, 77.2, 74.0, 70.4, 69.0, 63.5, 62.7, 62.6, 57.5, 56.2, 55.1, 51.5, 43.1, 20.9; HRMS (ESI−TOF) calcd for $C_{16}H_{14}O_5Na$ $[M + Na]^+$ 309.0739, found 309.0731.

Epoxy Alcohol 13b. To a suspension of powdered MS4Å (20 mg) in CH_2Cl_2 (1.0 mL) were added (−)-DIPT (22 μL, 0.110 mmol), $Ti(Oi\text{-}Pr)_4$ (22 μL, 73.2 μmol), and TBHP (ca. 6.0 M solution in 2,2,4-trimethylpentane, 0.23 mL, 1.38 mmol) at −30 °C. The mixture was stirred at the same temperature for 30 min, and a solution of allylic alcohol **12** (19.8 mg, 73.2 μmol) in CH_2Cl_2 (0.8 mL + 0.2 mL) was added at −40 °C. After the resulting mixture was stirred at −40 °C for 8 h and at −30 °C for further 8 h, the reaction was quenched with saturated aqueous sodium potassium tartrate. The mixture was filtered through a Celite pad and washed with EtOAc. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. After the concentration, the mixture was diluted with Et_2O and 3 M aqueous NaOH was added to the mixture. The mixture was stirred at 0 °C for 30 min. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **13b** (17.0 mg, 81%) as a colorless oil: R_f = 0.34 (hexane/EtOAc = 1:1); $[\alpha]_D^{22}$ −2.7 (*c* 1.14, $CHCl_3$); IR (neat) 3435, 2954, 2929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (dt, *J* = 15.6, 4.2 Hz, 1 H), 5.43 (ddt, *J* = 15.6, 7.9, 2.0 Hz, 1 H), 4.17 (dd, *J* = 4.2, 2.0 Hz, 2 H), 3.95−3.92 (m, 1 H), 3.67−3.64 (m, 1 H), 3.34 (dd, *J* = 7.9, 2.2 Hz, 1 H), 3.13 (dt, *J* = 4.2, 2.2 Hz, 1 H), 3.04 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.2 Hz, 1 H), 1.76 (br s, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 125.2, 62.7, 60.8, 58.0, 56.5, 56.5, 53.7, 26.0, 18.4, −5.2; HRMS (ESI−TOF) calcd for $C_{14}H_{26}O_4SiNa$ $[M + Na]^+$ 309.1498, found 309.1490.

Bromoacetylene 18b. To a solution of alcohol **13b** (16.6 mg, 57.9 μmol) in CH_2Cl_2 (1.0 mL) and DMSO (0.3 mL) were added Et_3N (40 μL, 0.289 mmol) and SO_3·pyr (36.7 mg, 0.231 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1) gave the corresponding aldehyde (11.6 mg), which was used for the next reaction without further purification.

To a solution of CBr_4 (51.0 mg, 0.155 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (81 mg, 0.310 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (43 μL, 0.310 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, the aldehyde obtained above (11.6 mg) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at −78 °C. The mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 30:1, 20:1) gave the corresponding dibromoalkene (18.0 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (18.0 mg) in THF (0.4 mL) was added TBAF (1.0 M solution in THF, 0.16 mL, 0.160 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Concentration and column chromatography (hexane/EtOAc = 2:1) gave bromoacetylene **18b** (8.1 mg, 57% in three steps) as a colorless amorphous solid: R_f = 0.24 (hexane/EtOAc = 2:1); $[\alpha]_D^{21}$ −9.0 (*c* 0.62, $CHCl_3$); IR (neat) 3354, 3006, 2949, 2224, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (dt, *J* = 15.6, 5.1 Hz, 1 H), 5.45 (ddt, *J* = 15.6, 7.8, 1.7 Hz, 1 H), 4.19 (dd, *J* = 5.1, 1.7 Hz, 2 H), 3.40−3.34 (m, 2 H), 3.22 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.0 Hz, 1 H), 1.58 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 126.2, 75.5, 62.4, 58.1, 57.2, 56.1, 45.7, 44.1; HRMS (ESI−TOF) calcd for $C_9H_9BrO_3Na$ $[M + Na]^+$ 268.9613, found 268.9617.

Acetate 20b. To a solution of $EtNH_2$ (70% aqueous solution, 0.4 mL) in MeOH (0.7 mL) was added CuCl (1.6 mg, 16.3 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (6.8 mg, 97.8 μmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **19** (6.9 mg, 35.9 μmol) in MeOH (0.2 mL + 0.2 mL) at room temperature, and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **18b** (8.0 mg, 32.6 μmol) in MeOH (0.2 mL + 0.2 mL) at −78 °C, and the mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding triacetylene (5.5 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (5.5 mg) in CH_2Cl_2 (0.5 mL) were added pyridine (12 μL, 0.149 mmol), Ac_2O (10 μL, 0.106 mmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave acetate **20b** (6.3 mg, 48% in two steps) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 1:1); $[\alpha]_D^{23}$ −1.5 (*c* 0.44, $CHCl_3$); IR (neat) 2954, 2929, 2217, 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.8 Hz, 1 H), 5.47 (ddt, *J* = 15.6, 7.6, 1.4 Hz, 1 H), 4.58 (dd, *J* = 5.8, 1.4 Hz, 2 H), 4.39 (s, 2 H), 3.42 (d, *J* = 2.0 Hz, 1 H), 3.35 (dd, *J* = 7.6, 2.0 Hz, 1 H), 3.26 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.92 (dd, *J* = 4.1, 2.0 Hz, 1 H), 2.08 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.5, 129.1, 77.8, 73.3, 69.5, 69.4, 63.4, 63.2, 62.0, 58.7, 57.1, 55.8, 52.1, 43.5, 25.8, 20.9, 18.3, −5.1; HRMS (ESI−TOF) calcd for $C_{22}H_{28}O_5SiNa$ $[M + Na]^+$ 423.1604, found 423.1610.

Diepoxide 5b. To a solution of TBS ether **20b** (5.0 mg, 12.4 μmol) in THF (2.5 mL) was added HF·pyr (5.0 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·pyr (2.0 μL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was diluted with Et_2O. The mixture was washed with saturated aqueous $NaHCO_3$, H_2O, and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1, 7:1) gave diepoxide **5b** (2.4 mg, 68%) as a light yellow amorphous solid: R_f = 0.43 (hexane/EtOAc = 1:1); $[\alpha]_D^{23}$ +32.0 (*c* 0.12, CH_3OH); IR (neat) 3448, 2920, 2214, 1711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.8 Hz, 1 H), 5.48 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H), 4.58 (dd, *J* = 5.8, 1.5 Hz, 2 H), 4.36 (d, *J* = 6.1 Hz, 2 H), 3.43 (d, *J* = 2.0 Hz, 1 H), 3.35 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.27 (dd, *J* = 4.2, 2.0 Hz, 1 H), 2.92 (dd, *J* = 4.2, 2.0 Hz, 1 H), 2.08 (s, 3 H), 1.67 (br t, *J* = 6.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 130.5, 129.1, 77.2, 73.7, 70.4, 69.2, 63.5, 62.8, 62.6, 58.7, 57.1, 55.9, 51.5,

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43.5, 20.9; HRMS (ESI−TOF) calcd for $C_{16}H_{14}O_5Na$ $[M + Na]^+$ 309.0739, found 309.0743.

Epoxy Alcohol 7b: Light yellow oil; $[\alpha]_D^{29}$ +25.7 (*c* 1.21, $CHCl_3$); HRMS (ESI−TOF) calcd for $C_{12}H_{24}O_3SiNa$ $[M + Na]^+$ 267.1393, found 267.1396; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of epoxy alcohol **7a**.

Diepoxide 5c: Light yellow amorphous solid; $[\alpha]_D^{25}$ +76.0 (*c* 0.03, CH_3OH); HRMS (ESI−TOF) calcd for $C_{16}H_{14}O_5Na$ $[M + Na]^+$ 309.0739, found 309.0743; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of diepoxide **5a**.

Diepoxide 5d: Light yellow amorphous solid; $[\alpha]_D^{23}$ −32.0 (*c* 0.12, CH_3OH); HRMS (ESI−TOF) calcd for $C_{16}H_{14}O_5Na$ $[M + Na]^+$ 309.0739, found 309.0739; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of diepoxide **5b**.

Acetate 21. To a suspension of NaH (60% dispersion in oil, 9.5 mg, 0.197 mmol, washed with hexane in advance) in THF (1.0 mL) was added alcohol **13a** (16.2 mg, 56.4 μmol) in THF (0.7 mL + 0.3 mL) at 0 °C. To the mixture were added PMBCl (23 μL, 0.169 mmol) and TBAI (10.3 mg, 28.0 μmol) at the same temperature. After the mixture was stirred for 12 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and the mixture was diluted with EtOAc. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1, 8:1) gave the corresponding PMB ether (19.7 mg), which was used for the next reaction without further purification.

To a solution of the TBS ether obtained above (19.7 mg) in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 97 μL, 97.0 μmol) at 0 °C. The mixture was stirred for 3 h at the same temperature. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 1:1) gave the corresponding alcohol (12.6 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (12.6 mg) in CH_2Cl_2 (0.8 mL) were added pyridine (4.5 μL, 56.1 μmol), Ac_2O (4.9 μL, 51.8 μmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1, 3:1) gave acetate **21** (13.9 mg, 74% in three steps) as a colorless oil: R_f = 0.36 (hexane/EtOAc = 2:1); $[\alpha]_D^{31}$ −42.7 (*c* 0.66, $CHCl_3$); IR (neat) 3000, 2934, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2 H), 6.88 (d, *J* = 8.3 Hz, 2 H), 6.02 (dt, *J* = 15.6, 5.8 Hz, 1 H), 5.50 (ddt, *J* = 15.6, 7.8, 1.5 Hz, 1 H), 4.58 (dd, *J* = 5.8, 1.5 Hz, 2 H), 4.49 (d, *J* = 4.2 Hz, 2 H), 3.80 (s, 3H), 3.71 (dd, *J* = 11.7, 2.0 Hz, 1 H), 3.52 (dd, *J* = 11.7, 4.0 Hz, 1 H), 3.37 (dd, *J* = 7.8, 2.0 Hz, 1 H), 3.18 (dt, *J* = 4.2, 2.0 Hz, 1 H), 2.96 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.91 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.3, 130.0, 129.8, 129.7, 129.3, 113.8, 73.1, 68.8, 63.6, 57.9, 55.3, 54.9, 54.6, 53.5, 20.9; HRMS (ESI−TOF) calcd for $C_{18}H_{22}O_6Na$ $[M + Na]^+$ 357.1314, found 357.1312.

Alcohol 22. To a solution of PMB ether **21** (11.0 mg, 32.9 μmol) in CH_2Cl_2 (1.0 mL) and H_2O (30 μL) was added DDQ (14.9 mg, 65.8 μmol) at 0 °C. The mixture was stirred at the same temperature for 2 h and at room temperature for 1 h. The mixture was diluted with EtOAc. The mixture was washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, H_2O, and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 2:1) gave alcohol **22** (5.7 mg, 81%) as a colorless oil: R_f = 0.21 (hexane/EtOAc = 1:1); $[\alpha]_D^{28}$ −62.0 (*c* 0.25, $CHCl_3$); IR (neat) 3457, 2925, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 15.6, 5.9 Hz, 1 H), 5.51 (ddt, *J* = 15.6, 7.6, 1.2 Hz, 1 H), 4.59 (dd, *J* = 5.9, 1.2 Hz, 2 H), 3.97 (dd, *J* = 13.0, 2.2 Hz, 1 H), 3.72 (dd, *J* = 13.0, 3.4 Hz, 1 H), 3.39 (dd, *J* = 7.6, 2.0 Hz, 1 H), 3.18 (dt, *J* = 3.4, 2.2 Hz, 1 H), 3.10 (dd, *J* = 4.4, 2.2 Hz, 1 H), 2.94 (dd, *J* = 4.4, 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 129.9, 129.9, 63.6, 60.5, 57.8, 55.8, 54.9, 53.1, 20.9; HRMS (ESI−TOF) calcd for $C_{10}H_{14}O_5Na$ $[M + Na]^+$ 237.0739, found 237.0734.

Acetate 25. To a solution of CBr_4 (150 mg, 0.451 mmol) in CH_2Cl_2 (1.0 mL) was added PPh_3 (237 mg, 0.902 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (0.13 mL, 0.902 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **23** (22.6 mg, 0.113 mmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at −78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1) gave the corresponding dibromoalkene (39.2 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (39.2 mg) in THF (2.0 mL) was added TBAF (1.0 M solution in THF, 0.44 mL, 0.440 mmol) at room temperature. The mixture was stirred at 45 °C for 18 h and diluted with Et_2O. The mixture was washed with saturated aqueous NH_4Cl, H_2O, and brine and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding TBS-deprotected dibromoalkene and bromoacetylene **24** (36.3 mg). The same procedure was repeated twice to give bromocetylene **24** (17.3 mg), which was used for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 0.9 mL) in MeOH (1.5 mL) was added CuCl (5.3 mg, 54.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added $NH_2OH{\cdot}HCl$ (22.5 mg, 0.324 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **19** (73.4 mg, 0.378 mmol) in MeOH (0.4 mL + 0.4 mL) at room temperature, and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added bromoacetylene **24** (17.3 mg, 0.108 mmol) in MeOH (0.4 mL + 0.4 mL) at −78 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was allowed to warm to room temperature for 3 h. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave the corresponding triacetylene (20.5 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (20.5 mg) in CH_2Cl_2 (3.0 mL) were added pyridine (45 μL, 0.335 mmol), Ac_2O (40 μL, 0.424 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave acetate **25** (22.5 mg, 63% in four steps) as a yellow oil: R_f = 0.69 (hexane/EtOAc = 2:1); IR (neat) 2953, 2929, 2860, 2173, 1746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (dt, *J* = 16.1, 5.4 Hz, 1 H), 5.78 (dt, *J* = 16.1, 1.7 Hz, 1 H), 4.63 (dd, *J* = 5.4, 1.7 Hz, 2 H), 4.40 (s, 2 H), 2.09 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 141.7, 111.0, 79.0, 75.5, 74.5, 69.8, 66.4, 63.4, 62.6, 52.2, 25.8, 20.8, 18.3, 5.1; HRMS (ESI−TOF) calcd for $C_{18}H_{24}O_3SiNa$ $[M + Na]^+$ 339.1393, found 339.1388.

Alcohol 26. To a solution of TBS ether **25** (22.5 mg, 71.1 μmol) in THF (2.0 mL) was added HF·pyr (0.10 mL) at 0 °C. After the mixture was stirred at the same temperature for 1 h, HF·pyr (0.10 mL) was added. The mixture was stirred at 0 °C for further 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was diluted with Et_2O. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1, 3:1) gave alcohol **26** (12.6 mg, 88%) as a yellow oil: R_f = 0.37 (hexane/EtOAc = 2:1); IR (neat) 3418, 2925, 2187, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (dt, *J* = 16.1, 5.6 Hz, 1 H), 5.78 (dt, *J* = 16.1, 2.0 Hz, 1 H), 4.64 (dd, *J* = 5.6, 2.0 Hz, 2 H), 4.37 (s, 2 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 141.9, 110.8, 78.1, 75.4, 74.9, 70.7, 66.0, 63.4, 63.2, 51.6, 20.8; HRMS (ESI−TOF) calcd for $C_{12}H_{10}O_3Na$ $[M + Na]^+$ 225.0528, found 225.0519.

Dienal 27. To a solution of dienol **6** (24.2 mg, 0.106 mmol) in CH_2Cl_2 (1.5 mL) and DMSO (0.5 mL) were added Et_3N (80 μL, 0.578 mmol) and $SO_3{\cdot}pyr$ (76.4 mg, 0.481 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over

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Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 10:1) gave dienal **27** (24.2 mg, 89%) as a colorless oil: R_f = 0.54 (hexane/EtOAc = 4:1); IR (neat) 2954, 2929, 1685, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (d, J = 8.0 Hz, 1 H), 7.12 (dd, J = 15.3, 11.0 Hz, 1 H), 6.58−6.51 (m, 1 H), 6.31 (dt, J = 15.1, 4.4 Hz, 1 H), 6.08 (dd, J = 15.3, 8.0 Hz, 1 H), 4.33 (dd, J = 4.4, 1.5 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 151.4, 144.2, 131.1, 127.0, 62.9, 25.9, 18.4, −5.3; HRMS (ESI−TOF) calcd for $C_{12}H_{22}O_2SiNa$ $[M + Na]^+$ 249.1287, found 249.1283.

Acetate 28. To a solution of CBr_4 (142 mg, 0.428 mmol) in CH_2Cl_2 (1.5 mL) was added PPh_3 (225 mg, 0.856 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (0.12 mL, 0.856 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **27** (24.2 mg, 0.107 mmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at −78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 50:1, 30:1) gave the corresponding dibromoalkene (39.7 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (39.7 mg) in THF (2.0 mL) was added TBAF (1.0 M solution in THF, 0.42 mL, 0.420 mmol) at room temperature. The mixture was stirred at 45 °C for 20 h and diluted with Et_2O. The mixture was washed with saturated aqueous NH_4Cl, H_2O, and brine, and then dried over Na_2SO_4. Concentration gave the mixture of the corresponding TBS-deprotected dibromoalkene and TBS-deprotected bromoacetylene (42.3 mg). The same procedure was repeated once to give the corresponding TBS-deprotected bromocetylene (31.3 mg), which was used for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 1.3 mL) in MeOH (3.0 mL) was added CuCl (5.1 mg, 52.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (21.7 mg, 0.312 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **19** (70.7 mg, 0.364 mmol) in MeOH (0.7 mL + 0.3 mL) at room temperature, and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added the bromoacetylene obtained above (31.3 mg) in MeOH (0.7 mL + 0.3 mL) at −78 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was allowed to warm to room temperature for 3 h. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 5:1) gave the corresponding triacetylene (18.8 mg), which was used for the next reaction without further purification.

To a solution of the alcohol obtained above (18.8 mg) in CH_2Cl_2 (2.0 mL) were added pyridine (24 μL, 0.179 mmol), Ac_2O (20 μL, 0.212 mmol), and DMAP (1.0 mg, 8.19 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave acetate **28** (20.5 mg, 56% in four steps) as a yellow oil: R_f = 0.60 (hexane/EtOAc = 2:1); IR (neat) 2954, 2929, 2173, 1744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, J = 15.4, 10.8 Hz, 1 H), 6.33 (dd, J = 15.1, 10.8 Hz, 1 H), 5.93 (dt, J = 15.1, 6.0 Hz, 1 H), 5.66 (d, J = 15.4 Hz, 1 H), 4.64 (d, J = 6.0 Hz, 2 H), 4.41 (s, 2 H), 2.09 (s, 3 H), 0.91 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.1, 131.9, 131.6, 110.2, 79.5, 76.3, 70.0, 67.4, 64.1, 63.9, 62.9, 52.3, 25.8, 20.9, 18.3, −5.1; HRMS (ESI−TOF) calcd for $C_{20}H_{26}O_3SiNa$ $[M + Na]^+$ 365.1549, found 365.1549.

Alcohol 29. To a solution of TBS ether **28** (11.2 mg, 32.7 μmol) in THF (1.2 mL) was added HF·pyr (40 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·pyr (50 μL) was added. The mixture was stirred at 0 °C for further 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was diluted with Et_2O. The mixture was washed with H_2O and brine and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave alcohol **29** (6.4 mg, 86%) as a yellow oil: R_f = 0.52 (hexane/EtOAc = 1:1); IR (neat) 3508, 2912, 2173, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, J = 15.6, 11.0 Hz, 1 H), 6.33 (dd, J = 15.3, 11.0 Hz, 1 H), 5.94 (dt, J = 15.3, 6.1 Hz, 1 H), 5.66 (d, J = 15.6 Hz, 1 H), 4.64 (d, J = 6.1 Hz, 1 H), 4.38 (s, 2 H), 2.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 145.3, 131.9, 131.8, 110.1, 78.6, 77.2, 70.9, 67.0, 64.1, 63.9, 63.5, 51.6, 20.9; HRMS (ESI−TOF) calcd for $C_{14}H_{12}O_3Na$ $[M + Na]^+$ 251.0684, found 251.0689.

Epoxy Alcohol 30. To a solution of allylic alcohol **6** (297 mg, 1.30 mmol) in CH_2Cl_2 (17 mL) were added $NaHCO_3$ (179 mg, 2.13 mmol) and *m*CPBA (69−75%, 306 mg, 1.22−1.33 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 4:1) gave epoxy alcohol **30** (243 mg, 78%) as a light yellow oil: HRMS (ESI−TOF) calcd for $C_{12}H_{24}O_3SiNa$ $[M + Na]^+$ 267.1393, found 267.1396; IR, ^1H NMR, and ^{13}C NMR spectra were identical to those of epoxy alcohol **7a**.

Aldehyde 31. To a solution of alcohol **30** (15.7 mg, 64.1 μmol) in CH_2Cl_2 (0.6 mL) and DMSO (0.2 mL) were added Et_3N (45 μL, 0.321 mmol) and SO_3·pyr (40.7 mg, 0.256 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave aldehyde **31** (14.0 mg, 90%) as a colorless oil: R_f = 0.57 (hexane/EtOAc = 1:1); IR (neat) 3439, 2954, 2929, 1730, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, J = 6.1 Hz, 1 H), 6.12 (dt, J = 15.6, 4.2 Hz, 1 H), 5.49 (ddt, J = 15.6, 7.8, 2.0 Hz, 1 H), 4.21 (dd, J = 4.2, 2.0 Hz, 2 H), 3.68 (dd, J = 7.8, 2.0 Hz, 1 H), 3.30 (dd, J = 6.1, 2.0 Hz, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 137.4, 123.3, 62.5, 60.8, 56.2, 25.9, 18.4, −5.3; HRMS (ESI−TOF) calcd for $C_{13}H_{26}O_4SiNa$ $[M + Na]^+$ 297.1498, found 297.1500.

Acetate 32. To a solution of CBr_4 (75.3 mg, 0.227 mmol) in CH_2Cl_2 (0.8 mL) was added PPh_3 (119 mg, 0.454 mmol) at 0 °C. The mixture was stirred at the same temperature for 15 min, and Et_3N (63 μL, 0.454 mmol) was added to the resulting mixture at 0 °C. After the mixture was stirred at the same temperature for 5 min, aldehyde **31** (13.7 mg, 56.7 μmol) in CH_2Cl_2 (0.3 mL + 0.2 mL) was added at −78 °C. The mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 20:1) gave the corresponding dibromoalkene (21.7 mg), which was used for the next reaction without further purification.

To a solution of the dibromoalkene obtained above (21.7 mg) in THF (0.7 mL) was added TBAF (1.0 M solution in THF, 0.22 mL, 0.220 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding bromoacetylene (9.7 mg), which was used for the next reaction without further purification.

To a solution of $EtNH_2$ (70% aqueous solution, 0.6 mL) in MeOH (1.0 mL) was added CuCl (2.4 mg, 24.0 μmol) at room temperature that resulted in the formation of a blue solution. To the resulting mixture was added NH_2OH·HCl (10.0 mg, 0.144 mmol) at room temperature to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To the resulting mixture was added diacetylene **19** (10.2 mg, 52.7 μmol) in MeOH (0.2 mL + 0.2 mL) at room temperature, and the mixture was stirred at the same temperature for 10 min that resulted in the formation of a yellow suspension. To the resulting mixture was added the bromoacetylene obtained above (9.7 mg) in MeOH (0.2 mL + 0.2 mL) at −78 °C, and the mixture was stirred at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 3:1) gave the corresponding triacetylene (11.1 mg), which was used for the next reaction without further purification.

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To a solution of the alcohol obtained above (11.1 mg) in CH_2Cl_2 (0.6 mL) were added pyridine (3.7 μL, 45.5 μmol), Ac_2O (4.0 μL, 42.0 μmol), and DMAP (0.8 mg, 6.55 μmol) at 0 °C. The mixture was stirred at the same temperature for 20 min. The mixture was diluted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 8:1) gave acetate **32** (11.8 mg, 58% in four steps) as a yellow oil: R_f = 0.63 (hexane/EtOAc = 2:1); IR (neat) 2954, 2930, 2216, 1745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, J = 15.6, 5.6 Hz, 1 H), 5.46 (ddt, J = 15.6, 7.3, 1.2 Hz, 1 H), 4.58 (br d, J = 5.6 Hz, 2 H), 4.39 (s, 2 H), 3.58 (dd, J = 7.3, 1.2 Hz, 1 H), 3.33 (d, J = 1.2 Hz, 1 H), 2.09 (s, 3 H), 0.90 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 131.1, 128.4, 77.8, 73.9, 69.5, 69.2, 63.3, 63.2, 62.1, 59.5, 52.1, 47.2, 25.8, 20.8, 18.3, −5.1; HRMS (ESI−TOF) calcd for $C_{20}H_{26}O_4SiNa$ $[M + Na]^+$ 381.1498, found 381.1501.

Alcohol 33. To a solution of TBS ether **32** (11.5 mg, 32.1 μmol) in THF (1.0 mL) was added HF·pyr (30 μL) at 0 °C. After the mixture was stirred at the same temperature for 2 h, HF·pyr (15 μL) was added. After the mixture was stirred at 0 °C for 1 h, HF·pyr (15 μL) was added. The mixture was stirred at the same temperature for 30 min. The mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over Na_2SO_4. Concentration and column chromatography (hexane/EtOAc = 7:1, 4:1) gave alcohol **33** (7.3 mg, 91%) as a yellow oil: R_f = 0.82 (hexane/EtOAc = 1:1); IR (neat) 3436, 2925, 2214, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, J = 15.6, 5.6 Hz, 1 H), 5.46 (ddt, J = 15.6, 7.6, 1.5 Hz, 1 H), 4.59 (dd, J = 5.6, 1.5 Hz, 2 H), 4.36 (br s, 2 H), 3.59 (dd, J = 7.6, 2.0 Hz, 1 H), 3.34 (d, J = 2.0 Hz, 1 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 131.2, 128.4, 76.9, 74.3, 70.4, 69.1, 63.3, 62.8, 62.7, 59.5, 51.5, 47.1, 20.9; HRMS (ESI−TOF) calcd for $C_{14}H_{12}O_4Na$ $[M + Na]^+$ 267.0633, found 267.0634.

Cell Growth-Inhibitory Activity. HL60 cells were cultured at 37 °C with 5% CO_2 in RPMI (Nissui, Tokyo, Japan) supplemented with 10% heat-inactivated fetal bovine serum (FBS; Sigma-Aldrich Co., St. Louis, MO), 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$. HeLa S_3 cells were cultured at 37 °C with 5% CO_2 in MEM (Nissui) supplemented with 10% heat-inactivated FBS, 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$. HL60 cells were seeded at 1×10^4 cells/well in 96-well plates (Iwaki, Tokyo, Japan). HeLa S_3 cells were seeded at 4×10^3 cells/well in 96-well plates and cultured overnight. Various concentrations of compounds were then added, and cells were incubated for 72 h. Cell proliferation was measured by the MTT assay.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for new compounds and $^1H-^1H$ COSY, HMQC, and HMBC spectra for compounds **5a** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: takamura@cc.okayama-u.ac.jp, kadota-i@cc.okayama-u.ac.jp.

Notes

The authors declare no competing financial interest.

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