

Total Synthesis and Cytotoxicity of (+)- and (−)-Goniodiol and 6-*epi*-Goniodiol. Construction of α,β-Unsaturated Lactones by Ring-Closing Metathesis

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(+)-Goniodiol, a potent and selective cytotoxin, and (−)-6-*epi*-goniodiol, as well as their enantiomers, have been synthesized starting from cinnamyl alcohol. The key steps of the synthesis were Sharpless asymmetric epoxidation and cyclization of an acrylate derivative using ring-closing metathesis reaction. The cytotoxicity of both enantiomers of goniodiol and 6-*epi*-goniodiol against HL-60 cells was examined.

(+)-Goniodiol (**1**) was isolated from the leaves and twigs of *Goniothalamus sesquipedalis* (Annonaceae)[1,2] and from the stem bark of *Goniothalamus giganteus* (Annonaceae),[3] as a potent and selective cytotoxic compound against human lung carcinoma A-549 ($ED_{50} = 0.12\,\mu g\,mL^{-1}$)[2] and P-388 murine leukemia cells ($IC_{50} = 4.56\,\mu g\,mL^{-1}$).[4] Because of the unique structural features and potent biological activities, several groups have accomplished the synthesis of these compounds.[5–9] Honda and co-workers constructed the δ-lactone moiety using ring enlargement of furylmethanol.[4] Vatéle and co-workers[5] used the Ghosez method.[10] Recently, we have communicated the synthesis of α,β-unsaturated lactones from acrylate derivatives using Grubbs' reagents **3** and **4**.[11] This methodology can be applied to the synthesis of **1** and 6-*epi*-goniodiol (**2**),[9,12] and at the same time we are intrested in the biological activities of these compounds. During our work, unfortunately, we became to know that a similar synthetic work was published in 2002 and 2003.[9] However, we studied the selectivity of ring-opening of the epoxide and also the stereochemistry at the 6-position, and a biological study about both enantiomers of goniodiol and 6-*epi*-goniodiol was also carried out. Now, we report the details of the total synthesis of both (+)- and (−)-**1** and **2** starting from cinnamyl alcohol (**5**), as well as their biological activities (Chart 1).

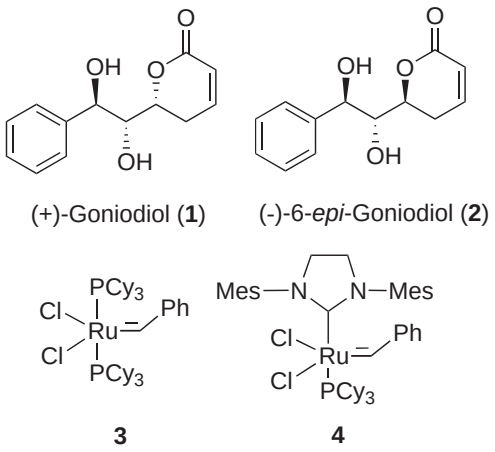

Chart 1.

Results and Discussion

The Sharpless asymmetric epoxidation[13] of cinnamyl alcohol (**5**) provided 2,3-epoxyalcohol **6**[6,13] in 95% yield. The enantio excess of **6** (in the case of (+)-dietyl tartrate (DET)) was determined by GC as 93.8% ee (Fig. 1). The reaction of alcohol **6** with *tert*-butyldiphenylchlorosilane (TBDPSCl) and triethylamine in the presence of *N*,*N*-dimethylaminopyridine (DMAP) provided the silyl ether **7**[6] in 99% yield. Cleavage of the oxirane ring of **7** with *p*-toluenesulfonic acid in THF–H_2O (5:1) afforded a mixture of diol **8** in 66% yield. Protection of the diol **8** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid followed by deprotection with tetrabutylammonium fluoride provided alcohols **9**[6] and **10**[6] (3.5:1.0) in 58% overall yield. The stereochemistry of the alcohols was determined by the NMR spectrum, because the dimethyl groups of alcohol **9**[6] appeared at $\delta = 27.0$ and 24.5 ($\Delta\delta = 2.5$) in the ^{13}C NMR spectrum. On the other hand, the dimethyl groups of alcohol **10**[6] appeared at $\delta = 27.1$ and 27.0 ($\Delta\delta = 0.1$) in the ^{13}C NMR spectrum.[14] From the above results, the structure of alcohol **9** should be *anti*-form and that of alcohol **10**, *syn*-form.[6] These isomers were presumably produced due to the S_N1 mechanism, because it is at the benzylic position. Therefore, epoxide **6**[6] was treated with benzoic acid in the presence of $Ti(O^iPr)_4$ in CH_2Cl_2 to yield a benzoate **11** as the sole product in 83% yield.[15] After protection of the primary alcohol with TBDPS, benzoate **12** was hydrolyzed with Cs_2CO_3 in MeOH:H_2O (8:1) followed by protection of the diol with acetonide to afford compound **14**[6] in 89% yield in three steps. Deprotection of the silyl ether and Dess–Martin oxidation gave aldehyde **15**[6,9,16] in 65% yield (2 steps). The results of allylation of this aldehyde are summarized in Table 1. The best result was obtained using Grignard reagent in ether to give in 71% yield in the ratio of 3:7 in favor of **16b**.[9] Therefore, we next studied the oxidation–reduction methodology.

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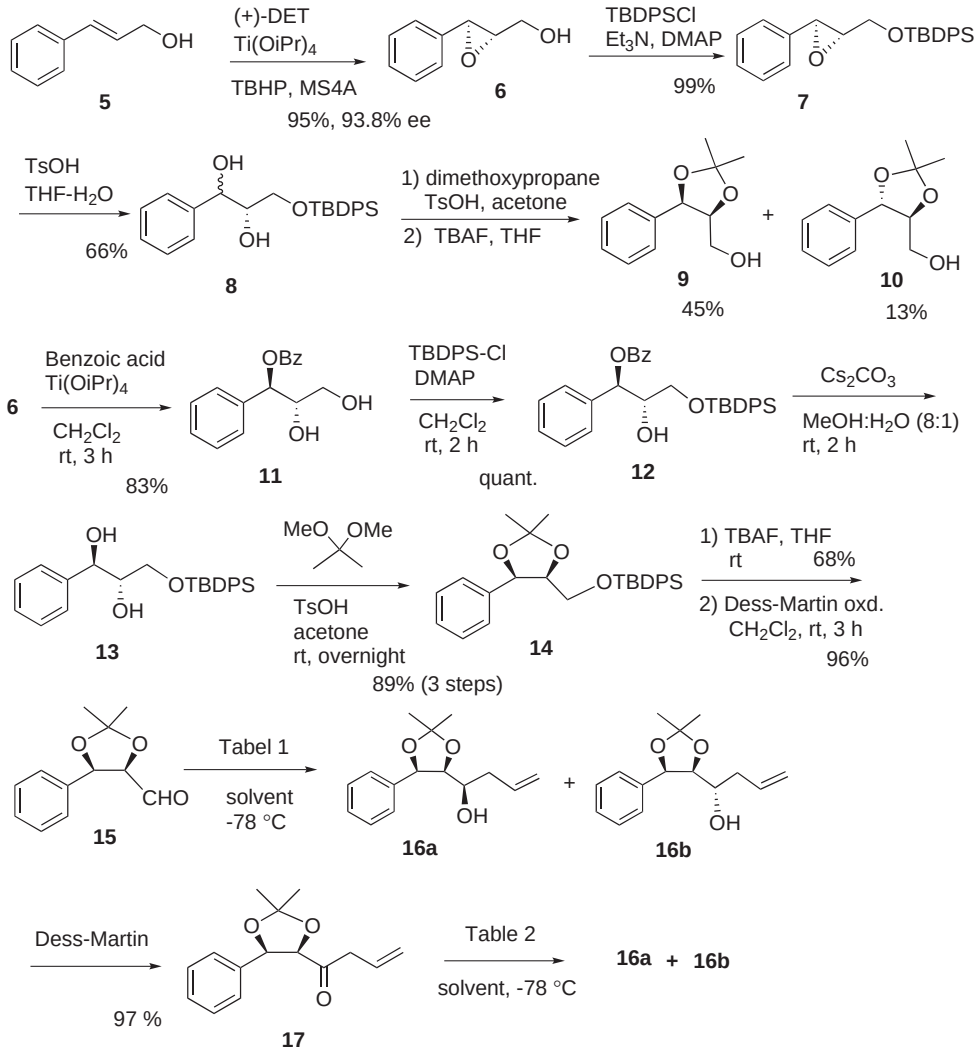

Fig. 1. Preparation of alcohols **16a** and **16b** from cinnamyl alcohol (**5**).

Table 1. Allylation of Aldehyde **15**

Entry	Reagent	Solvent	Time/h	Yields/%	Ratio/% (GC-MS)		
					16a	**16b**	**15**
1	MgBr	THF	6	67	38	62	
2	MgBr	Et_2O	2	71	30	70	
3	(-)-Ipc$_2$B	THF	4	15	63	37	
4	B	CH_2Cl_2	3	68	42	58	
5	Sn	MeOH	6	—	30	38	17

A mixture of **16a**[9] and **16b**[9] was oxidized with Dess–Martin periodinane and ketone **17** was reduced, whose results are listed in Table 2. In Entry 6, when $LiBEt_3H$ was used in THF, compound **16a**[9] was obtained as a major product in the ratio of 73:27 in 85% yield. Thus, this method turned out to compensate the selectivity of both compounds.

A mixture of alcohols **16a**[9] and **16b**[9] was treated with acryloyl chloride to give acrylates **18a**[9] and **18b**[9] in 47 and 18% (isolation yields), respectively (Fig. 2). After separation with column chromatography, acrylate **18a**[9] was treated with 5 mol % of Grubbs' reagent **3** in CH_2Cl_2 (5 mM) to provide α,β-unsaturated lactone **19a**[9] in 90% yield. It is worth mentioning that Ti(O^iPr)$_4$ was not necessary in this reaction, although many reports pointed out that the use of Ti(O^iPr)$_4$

Table 2. Reduction of Ketone **17**

Entry	Reagent	Solvent	Time/h	Yield/%	Ratio/% (GC-MS)		
					16a	**16b**	**17**
1	L-Selectride	THF	2.5	77	60	40	
2	DIBAL	THF	2	quant.	42	58	
3	$Zn(BH_4)_2$	Et_2O	2.5	—	21	17	58
4	LAH	Et_2O	1	50	72	28	
5	$NaBH_4$	Et_2O	1	75	52	48	
6	$LiBEt_3H$	THF	1	85	73	27	
7	$LiBH_4$	THF	1	77	73	27	
8	$LiBH_4$ + LiBr	THF	4	84	70	30	

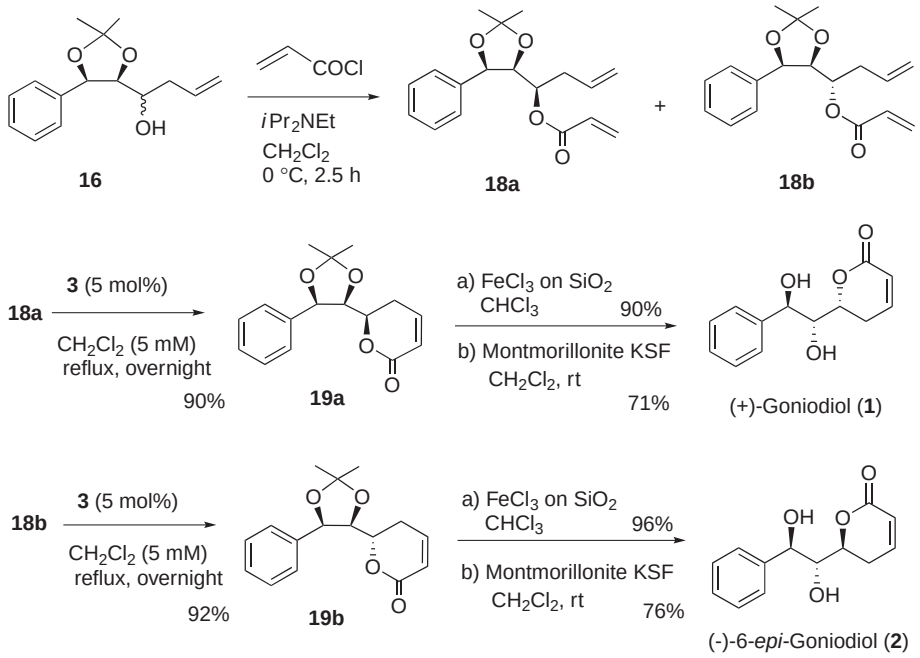

Fig. 2. Synthesis of goniodiol (**1**) and 6-*epi*-goniodiol (**2**).

was essential for cyclization reactions.[17] Similarly, acrylate **18b**[9] was treated with 5 mol % of Grubbs' reagent **3** in CH_2Cl_2 (5 mM) to provide α,β-unsaturated lactone **19b**[9] in 92% yield. NOEs were observed between one of the methyl groups of the acetonide and two oxymethine protons at C-7 and C-8 positions of **19a**[9] and **19b**,[9] supporting the results by ^{13}C NMR experiment described above. However, the stereochemistry of the 6-position was not determined at this stage. Deprotection of lactone **19a**[9] with $FeCl_3$ on silica-gel in $CHCl_3$[18] provided goniodiol [**1**, $[\alpha]_D$ +72.4 (*c* 0.68, $CHCl_3$), lit. +75.8 ($CHCl_3$),[2] +72.1 ($CHCl_3$)[9]] in 90% yield. The spectral data of **1** was completely identical with those of the natural product reported in the literature.[2,3,9] Similarly, lactone **19b**[9] provided 6-*epi*-goniodiol [**2**, $[\alpha]_D$ −40.1 (*c* 2.8, $CHCl_3$), lit. −47.4 ($CHCl_3$)[9]] in 96% yield. The yields of deprotection of acetonide using $FeCl_3$ on silica-gel[18] varied depending on the grade of the reagent prepared. Thus, we have found that Montmorillonite KSF in CH_2Cl_2[19] worked constantly to afford **1** in 71% and **2** in 76% yield, respectively. Ring-closing metathesis reaction of **18a**[9] and **18b**[9] smoothly proceeded using Grubbs' catalyst **3** as described above. These results well agreed with our previous report on simpler α,β-unsaturated lactones.[11]

In order to test the possibility, we synthesized the precursors **21**[17a] and **24**[17a] from aldehyde **20** (Fig. 3). Attempted cyclization of **21**[17a] or **24**[17a] using **3** did not work at all, although these reactions were reported.[17a,20] However, when new-generation catalyst **4** (20 mol %) was used, lactones **22**[17a] and **23**[17a] were obtained in 41 and 50% yields. Similarly, compound **24**[17a] afforded **25**[17a,20] and **26**[17a,20] in 42 and 50% yields on treatment of **24** with **4** in CH_2Cl_2. Therefore, the choice of the catalyst, **3** or **4**, may depend upon the functionality of the substrates. The reason why **21** and **24** did not cyclize into lactones using **3** is not clear now. However, the presence of the acetonide moiety nearby both the olefins might have impeded the reaction. The stereochemistry of compounds **22**, **23**, **25**, and **26** was determined by NOESY spectra. The methyl group of the acetonide at $\delta = 1.30$ in compound **23** had NOEs into H-5, H-6, and H-7β, and the one at $\delta = 1.37$ had NOE into H-7α. On the other hand, the methyl group at $\delta = 1.35$ in compound **22** had NOE into H-6β, and the one at $\delta = 1.47$ had NOE into H-5. Therefore, compound **22** should have 5*S*,6*R* configuration, and **23** must be 5*R*,6*R*, respectively. The methyl group at $\delta = 1.36$ in compound **25** had NOEs into H-7β and H-8β, and the one at $\delta = 1.42$ had NOEs into H-6 and H-8α. While in the

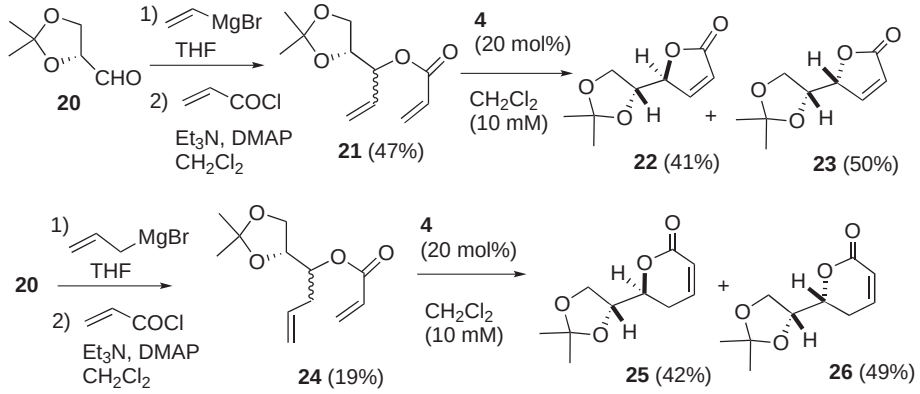

Fig. 3. Preparation of α,β-unsaturated lactones.

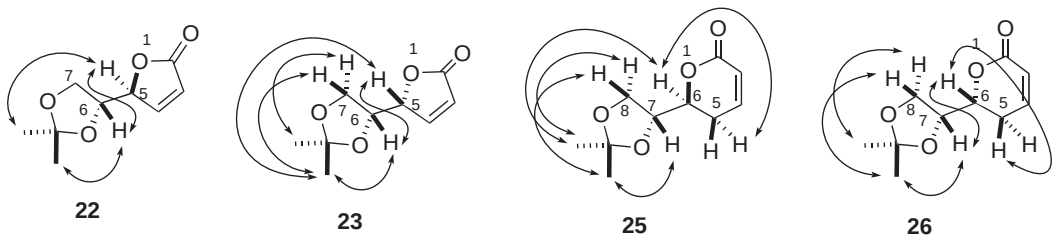

Fig. 4. Selected NOEs detected for compounds **22**, **23**, **25**, and **26**.

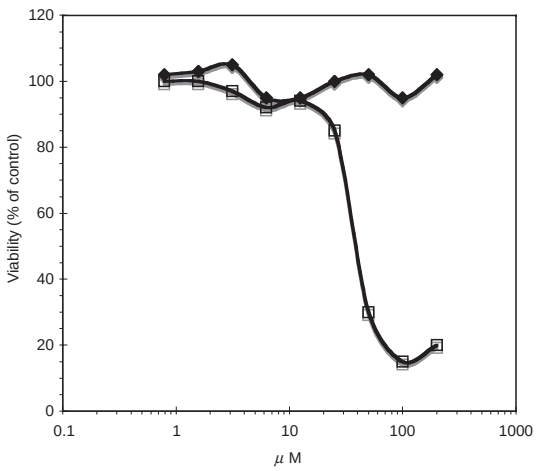

Fig. 5. Cytotoxicity of (+)-goniodiol (**1**) (□) and (−)-6-*epi*-goniodiol (**2**) (●) against HL-60 cells.

case of compound **26**, the methyl group at $\delta = 1.38$ had NOEs into H-7β and H-8β, and the one at $\delta = 1.46$ had NOE into H-8α. Therefore, compound **25** was established as 6*S*,7*R* and **26** as 6*R*,7*R*, respectively (Fig. 4).

The biological activity of the synthesized compounds was tested using HL-60 cell by WST-8 assay.[21] Cytotoxicity (IC_{50}) of (+)-goniodiol (**1**) was shown to be 40 μM in HL-60 cells. However, (−)-6-*epi*-goniodiol (**2**) has no cytotoxicity in HL-60 cells ($IC_{50} > 200$ μM). It is worth mentioning that two structurally closely related compounds, **1** and **2**, showed completely different activities against HL-60 cells (Fig. 5). This is presumably because both compounds adopt different conformations. Therefore, we next studied their conformations by calculation of the steric energies. Calculation of the global minimum of (+)-goniodiol (**1**) by CONFLEX[22] resulted in the conformation of **1a**, whose population was 57%. On the other hand, the global minimum conformation of (−)-6-*epi*-goniodiol (**2**) was **2a**, whose population was 89%. Their conformations were expressed with CPK models (Fig. 7). In the case of **1a**, the hydrophilic functions, namely, four oxygen atoms, were exposed outside of the molecule in one side. However, in the case of **2a**, oxygen atoms randomly exist in the molecule. We suspect that this difference in conformation might be the main reason for the biological activity. Therefore, we further synthesized the enantiomers of (+)-**1** and (−)-**2** (specific rotations of (−)-goniodiol (**1e**) and (+)-6-*epi*-goniodiol (**2e**) as well as compounds on the way to them were described in the Experimental). The values of cytotoxic activity of (−)-**1e** and (+)-**2e** were almost the same as those of (+)-**1** and (−)-**2**, respectively. The results are shown in Fig. 6. Thus, the absolute configuration did not affect the biological activity. The conformations are presumably important for displaying biological activities.

Experimental

General. All reactions were carried out under argon atmosphere. Anhydrous solvents were purchased from Kanto Chemical Co., Inc. Reagents were purchased at the highest commercial quality and used without further purification. The IR spectra were measured on a JASCO FT/IR 500 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 600, a JEOL ECP-400, or a Varian Gemini 200 spectrometer. The solvent used for NMR spectra was $CDCl_3$ unless otherwise stated. MS spectra were measured on a JEOL JMS 700 MStation spectrometer. Silica-gel BW-300 (200–400 mesh, Fuji Silycia) was used for column chromatography, and silica-gel $60F_{254}$ plate (0.25 mm, Merck) were used for TLC.

Synthesis of 3-Benzoyloxy-3-phenylpropane-1,2-diol (11). To a stirred solution of epoxide **6**[6] (5.0 g, 33.3 mmol) in CH_2Cl_2

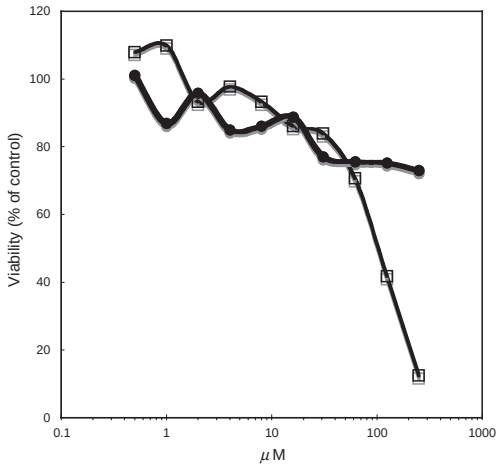

Fig. 6. Cytotoxicity of (−)-goniodiol (**1e**) (□) and (+)-6-*epi*-goniodiol (**2e**) (●) against HL-60 cells.

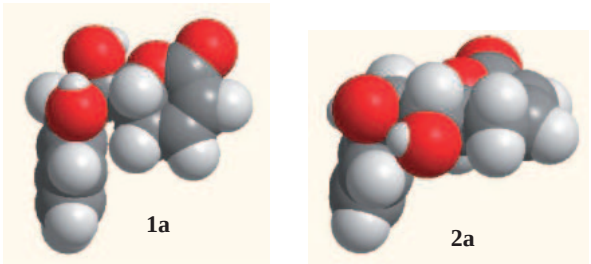

Fig. 7. Most stable conformation of (+)-goniodiol (**1**) and (−)-6-*epi*-goniodiol (**2**) displayed by CPK model.

(180 mL) was added benzoic acid (4.48 g, 1.1 equiv) and $Ti(iPrO)_4$ (10.42 mL, 1.1 equiv), successively and the mixture was stirred for 3 h at rt. After addition of 15% aqueous tartaric acid solution, the mixture was extracted with ethyl acetate. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford benzoate **11** (7.54 g, 83%). **11**; $[\alpha]_D^{18}$ +23.8 (*c* 1.18, $CHCl_3$); FT-IR: 3400 cm^{-1}; ^1H NMR (200 MHz) δ 3.15 (2H, –OH), 3.64 (2H, m), 4.03 (1H, m), 5.93 (1H, d, $J = 7.0$ Hz), 7.43 (8H, m), 8.03 (2H, d, $J = 7.0$ Hz); ^{13}C NMR (50 MHz) δ 62.7 (CH_2), 74.0 (CH), 76.0 (CH), 127.3 (CH), 128.5 (CH), 128.6 (CH, C), 128.7 (CH), 129.8 (CH), 133.4 (CH), 137.1 (C), 165.9 (CO); MS (CI) *m/z* 273 $[M + H]^+$, 212, 181, 151 (base), 133, 105, 58, 56; HRMS (CI) Found *m/z* 273.1121 $[M + H]^+$ $C_{16}H_{17}O_4$ requires 273.1127. *ent*-**11**; $[\alpha]_D^{18}$ −25.4 (*c* 1.01, $CHCl_3$).

Synthesis of 1-Benzoyloxy-3-*t*-butyldiphenylsilyloxy-1-phenylpropan-2-ol (12). A solution of diol **11** (6.1 g, 25.4 mmol) in DMF (82 mL) was treated with imidazole (2.6 g, 1.5 equiv) and TBDPSCl (7.92 mL, 1.2 equiv) at rt for 3 h. Water was added and the mixture was extracted with ether. The organic solution was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford **12** (13.0 g, quant.). **12**; FT-IR: 3500, 1720 cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (9H, s), 2.48 (1H, d, $J = 5.7$ Hz), 3.81 (1H, dd, $J = 10.5$, 4.2 Hz), 3.87 (1H, dd, $J = 10.5$, 5.4 Hz), 4.17 (1H, m), 6.05 (1H, d, $J = 6.9$ Hz), 7.35 (14H, m), 7.67 (4H, m), 7.98 (2H, m); ^{13}C NMR (50 MHz) δ 19.2 (C), 26.8 (CH_3), 64.1 (CH_2), 73.6 (CH), 75.8 (CH), 127.4 (CH), 127.8 (CH), 128.3 (CH), 128.4 (C), 129.7 (CH), 129.8 (C), 129.9 (CH), 130.0 (CH), 132.8 (CH), 135.5 (CH), 137.3 (C), 165.2 (CO); MS (CI) *m/z* 511 $[M + H]^+$, 493, 453, 433, 389, 353, 311 (base), 269, 253, 233, 199, 191, 105, 91; HRMS (CI) Found *m/z* 511.2306 $[M + H]^+$ $C_{32}H_{35}O_4Si$ requires 511.2304.

Synthesis of 3-*t*-Butyldiphenylsilyloxy-1-phenylpropane-1,2-diol (13). A solution of benzoate **12** (117.6 mg, 0.231 mmol) in MeOH:H_2O (8:1, 10 mL) was treated with Cs_2CO_3 (76 mg, 0.234 mmol, 1.0 equiv) at rt for 3 h. Sat. NH_4Cl solution was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford diol **13**[6] (50.9 mg, 54%).

Synthesis of 4-(*t*-Butyldiphenylsilyloxy)methyl-2,2-dimethyl-5-phenyl-1,3-dioxolane (14). A solution of diol **13** (725.1 mg, 1.79 mmol) in acetone (50 mL) was treated with 2,2-dimethoxypropane (0.44 mL, 3.57 mmol, 2.0 equiv) and TsOH (92 mg) at rt overnight. Sat. aqueous $NaHCO_3$ solution was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford **14**[6] (737.4 mg, 92%). $[\alpha]_D^{18.5}$ −48.7 (*c* 1.19, $CHCl_3$). *ent*-**14**; $[\alpha]_D^{19}$ +49.8 (*c* 1.36, $CHCl_3$).

Synthesis of (4*S*,5*R*)-(2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)methanol (9). A solution of acetonide **14** (594.6 mg, 1.33 mmol) in THF (50 mL) was treated with TBAF (1 M THF solun., 2.67 mL, 2.67 mmol, 2.0 equiv) at rt overnight. The solvent was evaporated and the residue was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford **9**[6] (202.8 mg, 68%).

Synthesis of 2,2-Dimethyl-5-phenyl-1,3-dioxolane-4-carbaldehyde (15). A solution of alcohol **9** (87.8 mg, 0.422 mmol) in CH_2Cl_2 (10 mL) was treated with Dess–Martin reagent (363 mg, 0.856 mmol, 2.0 equiv) and $NaHCO_3$ (111 mg, 1.33 mmol, 3.1 equiv) at rt for 1.5 h. A 25% sodium thiosulfate aqueous solution and then sat. $NaHCO_3$ aqueous solution were added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give aldehyde **15**[6,9] (83.5 mg, 96%).

Allylation of 2,2-Dimethyl-5-phenyl-1,3-dioxolane-4-carbaldehyde (15). Entry 1: To a stirred solution of aldehyde **15** (170.4 mg, 0.819 mmol) in THF (34 mL) was added allylmagnesium bromide (1 M Et_2O solun.; 4.13 mL, 4.13 mmol, 5.0 equiv) at −78 °C and the mixture was stirred for 6 h. Sat. NH_4Cl aqueous solution was added and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a residue. The residue was purified by silica-gel column chromatography (hexane–EtOAc, in gradient) to afford **16a**[9] and **16b**[9] (38:62, 137.0 mg, 67%). Entry 2: Similarly, aldehyde **15** (21.1 mg, 0.102 mmol) in Et_2O (5 mL) was treated with allylmagnesium bromide (1 M Et_2O soln., 0.50 mL, 0.50 mmol, 5.0 equiv) at −78 °C for 2 h to afford **16a** and **16b** (30:70, 18.0 mg, 71%). Entry 3: Aldehyde **15** (58.9 mg, 0.290 mol) in CH_2Cl_2 (5 mL) was treated with 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaboralane (0.16 mL, 0.871 mmol, 3.0 equiv) at −78 °C for 3 h to afford **16a** and **16b** (42:58, 48.6 mg, 68%). Entry 4: Aldehyde **15** (20.9 mg, 0.101 mmol) in MeOH (5 mL) was treated with tetraallyltin (0.01 mL, 0.0412 mmol, 0.4 equiv) at rt for 6 h to afford a mixture of **16a**, **16b**, and **15** (30:38:17, 25.0 mg).

1-(2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)-3-buten-1-one (17). A solution of alcohol **16** (162.7 mg, 0.656 mmol) in CH_2Cl_2 (25 mL) was treated with Dess–Martin reagent (557 mg, 1.31 mmol, 2.0 equiv) and $NaHCO_3$ (165 mg, 1.97 mmol, 3.0 equiv) at rt overnight. A 25% aqueous sodium thiosulfate solution and sat. $NaHCO_3$ aqueous solution were added. The mixture was extracted with ether and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to yield ketone **17** (157.1 mg, 97%); FT-IR: 1720, 1640 cm^{-1}; ^1H NMR (200 MHz) δ 1.50 (3H, s), 1.80 (3H, s), 2.70 (1H, dd, $J = 18.4$, 6.6 Hz), 2.87 (1H, dd, $J = 18.4$, 6.6 Hz), 4.75 (1H, d, $J = 17.4$ Hz), 4.83 (1H, d, $J = 8.4$ Hz), 4.96 (1H, d, $J = 9.8$ Hz), 5.40 (1H, m), 5.48 (1H, d, $J = 8.4$ Hz), 7.30 (5H, br s); ^{13}C NMR (50 MHz) δ 24.5 (CH_3), 26.4 (CH_3), 44.6 (CH_2), 79.6 (CH), 84.0 (CH), 110.7 (C), 118.6 (CH_2), 126.6 (CH × 2), 128.4 (CH × 3), 129.5 (CH), 135.8 (C), 206.5 (CO); MS (CI) m/z 247 $[M + H]^+$, 231, 189, 177, 141, 119, 89 (base); HRMS (CI) Found m/z 247.1313 $[M + H]^+$ $C_{15}H_{19}O_3$ requires 247.1334.

Reduction of 1-(2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl)-3-buten-1-one (17). Entry 1: A solution of ketone **17** (51.0 mg, 0.207 mmol) in THF (17 mL) was treated with L-selectride (1 M THF soln., 0.42 mL, 0.415 mmol, 2.0 equiv) at −78 °C for 2.5 h. Water was added and the mixture was stirred for 2.5 h before concentration in vacuo. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give a residue. The residue was purified with silica-gel column chromatography (hexane–EtOAc, in gradient) to afford **16a**[9] and **16b**[9] (60:40, 39.0 mg, 77%). Entry 2: Similarly, ketone **17** (47.5 mg, 0.193 mmol) in THF (3 mL) was treated with DIBAL (1 M in toluene, 0.39 mL, 0.386 mmol, 2.0 equiv) to yield **16a** and **16b** (42:58, 55.9 mg, quant.). Entry 3: Ketone **17** (63.5 mg, 0.258 mmol) in Et_2O (4 mL) gave **16a**, **16b**, and **17** (21:17:58, 21.4 mg) with $Zn(BH_4)_2$ (4.65 mL, 2.32 mmol, 9.0 equiv). Entry 4: Ketone **17** (19.1 mg, 0.0776 mmol) was reduced with $LiAlH_4$ (12.0 mg, 0.311 mmol, 4.0 equiv) to give **16a** and **16b** (72:28, 9.7 mg, 50%). Entry 5: Ketone **17** (20.8 mg, 0.0846 mmol) in Et_2O (4 mL) was treated with $NaBH_4$ (13.0 mg, 0.338 mmol, 4.0 equiv) to give **16a** and **16b** (52:48, 15.8 mg, 75%). Entry 6: Ketone **17** (28.7 mg, 0.117 mmol) in THF (2 mL) was reduced with $LiBHEt_3$ (1 M THF soln., 0.02 mL, 0.175 mmol, 1.5 equiv) to give **16a** and **16b** (73:27, 24.8 mg, 85%). Entry 7: Ketone **17** (25.4 mg, 0.103 mmol) afforded **16a** and **16b** (73:27, 19.6 mg, 77%) with $LiBH_4$ (10.0 mg, 0.413 mmol, 4.0 equiv) in Et_2O (2 mL). Entry 8: Ketone **17** (7.5 mg, 0.0305 mmol) in THF (2 mL) was treated with $LiBH_4$ (2.6 mg, 0.122 mmol, 4.0 equiv) and LiBr (3.9 mg, 0.0457 mmol, 1.5 equiv) in THF (2 mL) to give **16a** and **16b** (70:30, 6.4 mg, 84%).

(1*R*)-1-[(4*S*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-enyl Acrylate (18a) and (1*S*)-1-[(4*S*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]but-3-enyl Acrylate (18b). To a solution of alcohol **16** (1.0 g, 4.0 mmol) in CH_2Cl_2 (50 mL) were added *N*,*N*-diisopropylethylamine (2.8 mL, 16.0 mmol), acryloyl chloride (0.8 mL, 9.8 mmol), and DMAP (100 mg) at 0 °C. The mixture was stirred for 5 h at 0 °C. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and was evaporated to afford a residue, which was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–20%) to yield **18a**[9] (254 mg, 21%) and **18b**[9] (424 mg, 35%). **18a**: $[\alpha]_D^{23}$ −65.8 (*c* 1.00, $CHCl_3$); **18b**: $[\alpha]_D^{30}$ +0.93 (*c* 2.00, $CHCl_3$). *ent*-**18a**; $[\alpha]_D^{19}$ +98.1 (*c* 0.48, $CHCl_3$); *ent*-**18b**; $[\alpha]_D^{18}$ −7.7 (*c* 0.53, $CHCl_3$).

(6*R*)-6-[(4*S*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5,6-dihydro-2*H*-pyran-2-one (19a). A solution of Grubbs' reagent (**3**, 92.2 mg, 0.11 mmol) in degassed CH_2Cl_2 (10 mL) was added to a solution of diene **18a**[9] (170 mg, 0.56 mmol) in degassed CH_2Cl_2 (100 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with CH_2Cl_2) to yield lactone **19a**[9] (134 mg, 87%). $[\alpha]_D^{20}$ −65.8 (*c* 1.40, $CHCl_3$). *ent*-**19a**; $[\alpha]_D^{17}$ +79.2 (*c* 1.30, $CHCl_3$).

(6*S*)-6-[(4*S*,5*R*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-yl]-5,6-dihydro-2*H*-pyran-2-one (19b). A solution of Grubbs' reagent (**3**, 187.6 mg, 0.23 mmol) in degassed CH_2Cl_2 (30 mL) was added to a solution of diene **18b**[9] (344 mg, 1.14 mmol) in degassed CH_2Cl_2 (200 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with CH_2Cl_2) to yield lactone **19b**[9] (261 mg, 84%). $[\alpha]_D^{20}$ −16.4 (*c* 2.00, $CHCl_3$). *ent*-**19b**; $[\alpha]_D^{20}$ +26.5 (*c* 0.45, $CHCl_3$).

(+)-Goniodiol (1). To a solution of lactone **19a**[9] (13.7 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added Montmorillonite KSF (68.5 mg), and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with hexane–EtOAc; 0–50%) to yield goniodiol (**1**)[7,9] (6.8 mg, 58%); Oil; $[\alpha]_D$ +72.4 (*c* 0.68, $CHCl_3$); FT-IR 3460, 1730 cm^{-1}; ^1H NMR (200 MHz) δ 2.18 (1H, ddd, $J = 18.5$, 6.4, 3.8 Hz), 2.49 (1H, d, $J = 8.4$ Hz), 2.79 (1H, ddt, $J = 18.5$, 12.9, 2.7 Hz), 2.92 (1H, s), 3.72 (1H, br t, $J = 7.0$ Hz), 4.80 (1H, ddd, $J = 12.9$, 3.8, 2.3 Hz), 4.94 (1H, dd, $J = 7.1$, 3.4 Hz), 5.99 (1H, dd, $J = 9.8$, 2.7 Hz), 6.93 (1H, ddd, $J = 9.8$, 6.4, 2.3 Hz), 7.30–7.43 (5H, m); ^{13}C NMR (50 MHz) δ 26.1 (CH_2), 73.7 (CH), 75.1 (CH), 76.8 (CH), 120.6 (CH), 126.6 (CH), 128.3 (CH), 128.8 (CH), 140.8 (C), 146.2 (CH), 163.8 (CO); MS (CI) m/z 235 $[M + H]^+$, 217 (base), 199, 171, 128, 107, 97, 41; HRMS (CI): Found m/z 235.0968 $[M + H]^+$ $C_{13}H_{15}O_4$ requires 235.0970. *ent*-goniodiol (**1e**); $[\alpha]_D^{18}$ −80.5 (*c* 1.18, $CHCl_3$).

(−)-6-*epi*-Goniodiol (2). To a solution of lactone **19b**[9] (79.1 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) was added Montmorillonite KSF (395.5 mg), and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with hexane–EtOAc; 0–50%) to yield 6-*epi*-goniodiol (**2**)[9,12] (56.7 mg, 84%); $[\alpha]_D$ −40.1 (*c* 2.8, $CHCl_3$); FT-IR: 3400, 1700 cm^{-1}; ^1H NMR (400 MHz) δ 2.43–2.58 (3H, m), 2.71 (1H, ddt, $J = 20.2$, 11.4, 2.8 Hz), 4.18 (1H, td, $J = 5.7$, 3.6 Hz), 4.38 (1H, dt, $J = 11.4$, 5.7 Hz), 4.93 (1H, dd, $J = 5.7$, 2.8 Hz), 6.00 (1H, ddd, $J = 9.7$, 2.8, 1.1 Hz), 6.93 (1H, ddd, $J = 9.7$, 6.2, 2.8 Hz), 7.33–7.43 (5H, m); ^{13}C NMR (100 MHz) δ 24.5 (CH_2), 73.9 (CH), 74.8 (CH), 78.0 (CH), 120.8 (CH), 126.8 (CH), 128.5 (CH), 128.7 (CH), 139.6 (C), 145.9 (CH), 163.8 (CO); MS (CI) m/z 235 $[M + H]^+$, 217 (base), 173, 171, 128, 107, 97, 82; HRMS (CI): Found m/z 235.0974 $[M + H]^+$ $C_{13}H_{15}O_4$ requires 235.0970. *ent*-6-*epi*-goniodiol (**2e**); $[\alpha]_D^{18}$ +43.0 (*c* 0.64, $CHCl_3$).

(5*S*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5*H*-furan-2-one (22) and (5*R*)-5-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5*H*-furan-2-one (23). To a solution of aldehyde **20** (3.9 g, 30 mmol) in THF (150 mL) was added vinylmagnesium bromide (1.0 M in THF, 62 mL, 62 mmol) at −78 °C, and the mixture was warmed to room temperature overnight. Saturated NH_4Cl was added, and the solvent was removed. The residue was extracted with ether, and the organic layer was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was pu-

rified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–50%) to yield alcohol (3.2 g, 68%). To a solution of alcohol (3.2 g, 20 mmol) in CH_2Cl_2 (320 mL) was added triethylamine (8.4 mL, 60 mmol), DMAP (320 mg), and acryloyl chloride (3.25 mL, 40 mmol) at 0 °C, and the mixture was stirred for 4 h. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–20%) to yield ester **21** (3.0 g, 47%). A solution of catalyst **4** (2.4 g, 2.83 mmol) in degassed CH_2Cl_2 (20 mL) was added to a solution of ester **21** (3.0 g, 14.2 mmol) in degassed CH_2Cl_2 (1.4 L). The mixture was stirred for 2 days at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–50%) to yields lactone **22** (1.1 g, 41%) and lactone **23** (1.3 g, 50%); **22**: FT-IR: 1765 cm^{-1}; ^1H NMR (400 MHz) δ 1.35 (3H, s), 1.47 (3H, s), 3.92 (1H, ddd, $J = 8.1$, 6.2, 4.0 Hz), 4.10 (1H, dd, $J = 9.2$, 4.0 Hz), 4.16 (1H, dd, $J = 9.2$, 6.2 Hz), 4.86 (1H, dd, $J = 8.1$, 1.8 Hz), 6.21 (1H, dd, $J = 5.9$, 1.8 Hz), 7.64 (1H, dd, $J = 5.9$, 1.8 Hz); ^{13}C NMR (100 MHz) δ 24.6 (CH_3), 26.4 (CH_3), 66.6 (CH_2), 75.9 (CH), 82.9 (CH), 110.2 (C), 122.3 (CH), 154.8 (CH), 172.4 (C); MS (CI) m/z 185 $[M + H]^+$ (base), 169, 127, 101; HRMS (CI) Found m/z 185.0785 $[M + H]^+$ $C_9H_{13}O_4$ requires 185.0814; **23**: FT-IR: 1765 cm^{-1}; ^1H NMR (400 MHz) δ 1.30 (3H, s), 1.37 (3H, s), 3.80 (1H, dd, $J = 8.8$, 5.5 Hz), 4.06 (1H, dd, $J = 8.8$, 6.6 Hz), 4.37 (1H, ddd, $J = 6.6$, 5.5, 3.7 Hz), 5.05 (1H, dt, $J = 3.7$, 1.8 Hz), 6.18 (1H, dd, $J = 5.9$, 1.8 Hz), 7.43 (1H, dd, $J = 5.9$, 1.8 Hz); ^{13}C NMR (100 MHz) δ 24.8 (CH_3), 25.7 (CH_3), 64.6 (CH_2), 74.0 (CH), 82.0 (CH), 110.2 (C), 123.0 (CH), 152.9 (CH), 172.5 (C); MS (CI) m/z 185 $[M + H]^+$ (base), 169, 127, 101; HRMS (CI) Found m/z 185.0783 $[M + H]^+$ $C_9H_{13}O_4$ requires 185.0813.

(6*S*)-6-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5,6-dihydropyran-2-one (25) and (6*R*)-6-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5,6-dihydropyran-2-one (26). To a solution of aldehyde **20** (2.0 g, 15 mmol) in THF (20 mL) was added allylmagnesium bromide (2.0 M in THF, 26 mL, 52 mmol) at −15 °C, and the mixture was warmed to room temperature overnight. Saturated NH_4Cl was added, and the solvent was removed. The residue was extracted with ether, and the organic layer was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–50%) to yield alcohol (1.9 g, 71%). To a solution of alcohol (1.9 g, 11 mmol) in CH_2Cl_2 (190 mL) was added triethylamine (3.0 mL, 22 mmol), DMAP (190 mg), and acryloyl chloride (2.7 mL, 22 mmol) at 0 °C, and the mixture was stirred overnight at room temperature. Water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, water and brine, dried ($MgSO_4$), and evaporated to afford a residue, which was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–20%) to yield ester **24** (673 mg, 27%). A solution of catalyst **4** (751 mg, 0.88 mmol) in degassed CH_2Cl_2 (5 mL) was added to a solution of ester **24** (1.0 g, 4.42 mmol) in degassed CH_2Cl_2 (445 mL). The mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure, and the residue was purified by silica-gel column chromatography (elution with hexane–EtOAc in gradient; 0–50%) to yields lactone **25** (420 mg, 42%) and lactone **26** (430 mg, 49%); **25**: $[\alpha]_D^{21}$ −71.0 (*c* 1.01, $CHCl_3$); FT-IR: 1730 cm^{-1}; ^1H NMR (600 MHz) δ 1.36 (3H, s), 1.42 (3H, s), 2.46 (1H, ddt, $J = 18.7$, 11.0, 2.75 Hz), 2.62 (1H, dddd, $J = 18.7$, 6.04, 4.12, 1.10 Hz), 4.05 (1H, td, $J = 7.14$, 3.85 Hz), 4.15–4.20 (2H, m), 4.29 (1H, ddd, $J = 11.0$, 7.97, 4.12 Hz), 6.04 (1H, ddd, $J = 9.76$, 2.74, 1.10 Hz), 6.93 (1H, ddd, $J = 9.76$, 6.04, 2.74 Hz); ^{13}C NMR (50 MHz) δ 24.9 (CH_3), 26.1 (CH_2), 26.6 (CH_3), 66.9 (CH_2), 76.0 (CH), 77.9 (CH), 109.9 (C), 121.3 (CH), 145.0 (CH), 163.1 (C); MS (CI) m/z 199 $[M + H]^+$ (base), 141, 123, 89; HRMS (CI) Found m/z 199.0977 $[M + H]^+$ $C_{10}H_{15}O_4$ requires 199.0970; **26**: $[\alpha]_D^{22}$ +131.9 (*c* 1.01, $CHCl_3$); FT-IR: 1730 cm^{-1}, ^1H NMR (600 MHz) δ 1.38 (3H, s), 1.46 (3H, s), 2.36 (1H, dddd, $J = 18.4$, 6.04, 4.12, 1.10 Hz), 2.54 (1H, ddt, $J = 18.4$, 12.1, 2.47 Hz), 4.05 (1H, dd, $J = 8.79$, 6.59 Hz), 4.09 (1H, dd, $J = 8.79$, 6.59 Hz), 4.33 (1H, td, $J = 6.59$, 4.12 Hz), 4.54 (1H, dt, $J = 12.1$, 4.12 Hz), 6.04 (1H, ddd, $J = 9.89$, 2.47, 1.10 Hz), 6.93 (1H, ddd, $J = 9.89$, 6.04, 2.47 Hz); ^{13}C NMR (50 MHz) δ 24.9 (CH_3), 25.0 (CH_3), 26.0 (CH_2), 64.7 (CH_2), 75.6 (CH), 77.7 (CH), 110.1 (C), 121.2 (CH), 145.0 (CH), 163.5(C); MS (CI) m/z 199 $[M + H]^+$ (base), 183, 123, 101; HRMS (CI) Found m/z 199.0970 $[M + H]^+$ $C_{10}H_{15}O_4$ requires 199.0970.

Evalution of in vitro Cytotoxicity.[21] Cytotoxicity against HL-60 cells was assessed as follows: 1×10^4 cells seeded onto 96-well plate were incubated with the chemicals at the indicated concentrations at 37 °C for 24 h. Then, viability of the cells were determined by WST-8 assay using cell counting kit-8 according to the manufacturer's instruction (Wako Pure Chemicals, Ltd., Osaka, Japan).

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