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Paper

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Enantioselective synthesis of a new styryl lactone 9-deoxygoniopypyrone derivative and its antiproliferative activity

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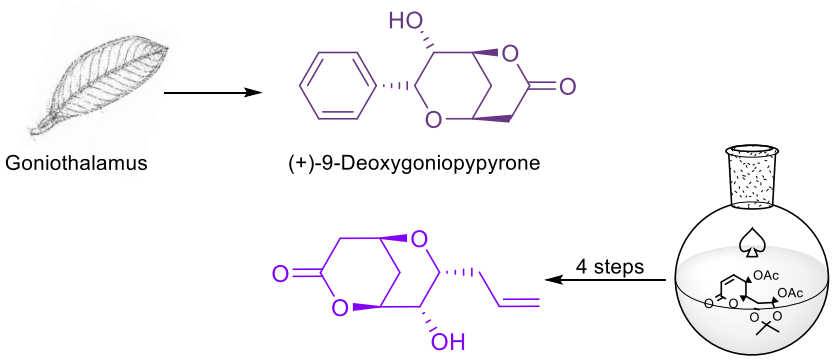
Abstract

We report the enantioselective synthesis of a novel styryl lactone using a versatile Chiron derived from D-glucose under mild conditions. The synthesis is carried out in four steps with an overall yield of 57%. The change of the phenyl functional group by an allyl group was performed to analyze the effects that this modification causes on cytotoxicity in mouse breast cancer cell lines (Ep-H4-EV, 67NR,66cl4 and 4T1) in comparison with 9-deoxygoniopipyrone from a natural source, observing an increase in selectivity. The findings suggest potential pathways for further structural modifications to enhance the anticancer properties of these compounds. The results pave the way for developing new derivatives of 9-deoxygoniopypyrone for in vitro cancer research.



Keywords: Styryl lactone; α,β-unsaturated lactone, Antiproliferative; Chiron; Cytotoxicity

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Introduction

Designing new compounds by modifying the structure of nature's products is interesting. The Goniothalamus genus is a source of secondary metabolites that include bioactive linear and cyclic styryl lactone derivatives,[1-3] many of these compounds have showed cytotoxicity to P-388, KB, MCF-7, A549, Hek 293 and ASK cell lines. For example (+)-goniothalamin **1**,[4] (+)-5-hydroxygoniothalamin **2**,[5] (+)-goniotriol **3**,[6] (+)-goniopypyrone **4**.[7] The activity presented by these compounds is due to their structures including a delta lactone α,β-unsaturated with C6 having an ***R*** configuration, a hydroxy group at C5, and an aromatic ring at C8. Changes in its structure such as inverting the configuration of C6 from *R* to *S*, protecting the hydroxy group at C5 or eliminating it, as in the following compounds (-)-goniotalamin **5**,[7] (+)-5-acetoxygoniotalamin **6**,[5] (+)-goniodiol **7** and (+)-9-deoxygoniopypyrone **7**,[8] respectively, cause an increase in its cytotoxic activity. De Fatima et al., report that the lactone ring is essential in cytotoxic activity, as well as the *S* configuration at C6 (Figure 1).

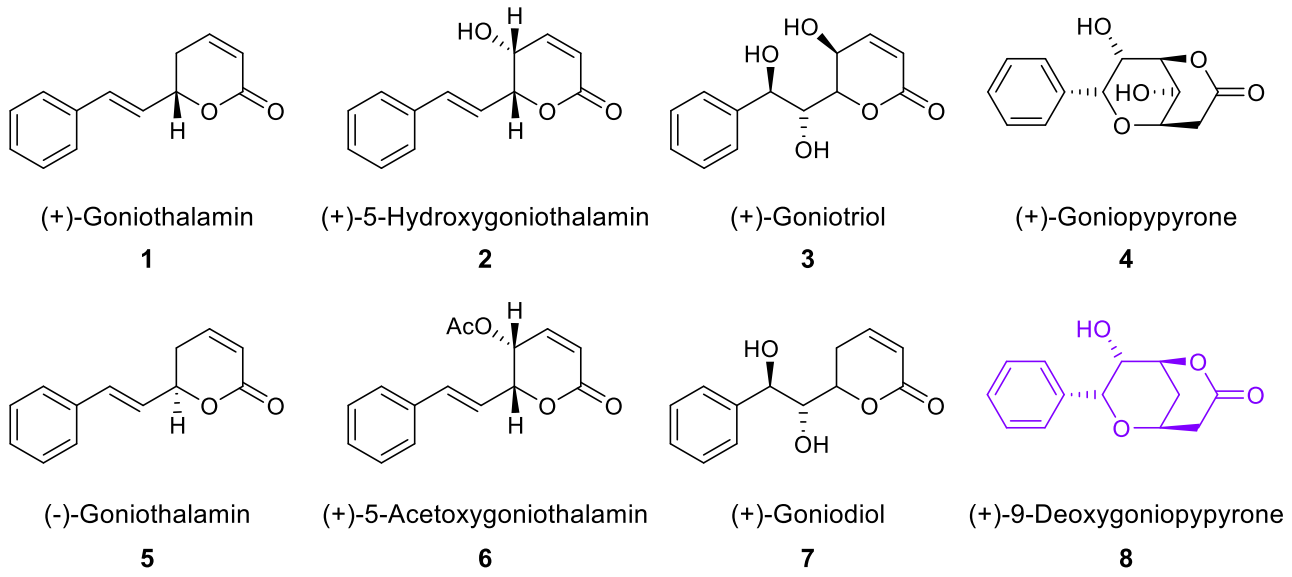


Figure 1. Compounds **1-8** isolated from the goniothalamus species.

The study of goniopypyrone sheds light on the diverse chemical composition of natural products from plants and their potential pharmacological applications. Further research on goniopypyrone and its derivatives may lead to the development of novel therapeutic agents with cytotoxic properties against specific types of cancer cells.

Goniopypyrone is the target of synthesis, such as that proposed by Prasad and Gholap[9] whose key building block was synthesized in a facile stereoselective route of 5 steps from the dimethyl amide of tartaric acid. The goniopypyrone was obtained after 9 steps. Yuki Miyazawa and colleagues[10] proposed a synthesis of goniopypyrone that was accomplished through a 14-step process, resulting in an 8.5% overall yield. The key reaction involved the Pd-catalyzed carbonylation to form the lactone ring. With this background, we asked ourselves how the change of the hydrophobic tail, from a phenyl to an allyl group, would affect the cytotoxicity of styryl lactones. To have the answer, we chose (+)-9-deoxygoniopypyrone **8** as a model to synthesize the analogue **9** (Figure 2) that would have an allyl group instead of the phenyl group and test its cytotoxic activity with cancer cells.

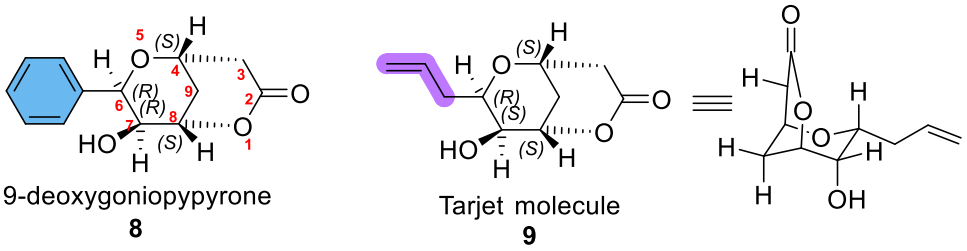
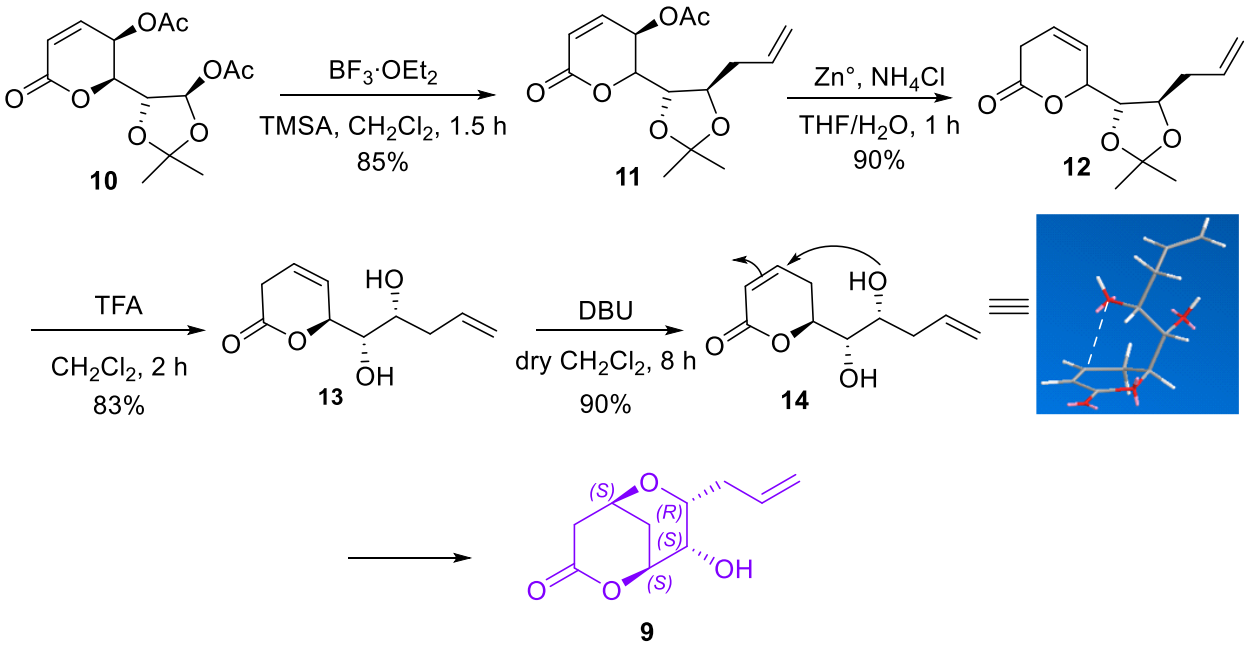


Figure 2. 9-deoxygoniopypyrone **8** and its allylated analogue **9**.

Results and Discussion

We use the glucose-derived Chiron **10**,[11a] which has shown high selectivity in nucleophilic addition at C8. This has been a short but efficient synthesis of the expected analogue **9** (Scheme 1).

We performed the allylation of **10** with allyl trimethyl silane and the $BF_3{\cdot}OEt_2$ as Lewis acid,[11b] obtaining **11** in a stereospecific manner with good yields. Deacetoxylation was carried out with Zn and NH_4Cl in a THF/H_2O mixture (1:1) with quantitative yields of **12**.[11b] We hydrolyzed **12** with TFA in dichloromethane and obtained **13**, the isomerization of the β,γ double bond to an α,β double bond of the lactone ring was carried out with DBU in dichloromethane, simultaneously producing a Michael addition of the OH to the double bond of *α,β*-unsaturated ester **14** on the *Si* face, this interaction is the result of the pseudoaxial conformation adopted by the side chain due to the C6 configuration (blue box) resulting in the formation of **9** with very good yields. The enantiopure product is a crystalline solid with a specific rotation of $[\alpha]^{25}_D$ +40.3° (*c* = 1, $CHCl_3$), allowing the single crystal structure determination of **9**. According to the X-ray structure, the new chiral center originating from the Michael cyclization configured (*S*) forming the bicyclic ring, other chiral centers in **9** are (*S)* for the center bonded to the hydroxy group, and (*R)* for the center bonded to the allyl group (Scheme 1).



Scheme 1. Synthesis of allyl analogue **9**.

Unexpectedly, two solid-state polymorphs were crystallized for **9**, in space groups $P2_1$ and $P2_12_12_1$ (Table S1, supporting information). Molecular structures are identical (see Fig. 3a), as evidenced through a molecule overlay (rms deviation: 0.09 Å, Fig. 3b). In particular, the allyl group displays the same conformation in both crystal structures, with a torsion angle C8–C9–C10–C11 of -135.0(3)° or -139.0(2)° for the $P2_12_12_1$ and $P2_1$ crystals, respectively. Moreover, both crystals have different melting points: 366 K ($P2_1$ form) and 357 K ($P2_12_12_1$ form). As seen in Fig. 3b, the polymorphism is a consequence of different orientations for the OH group. A rotation of *ca*. 50° around the C8–O8 bond modifies the crystal structure, as the supramolecular structure based on O–H…O hydrogen bonds depend on the OH group orientation: in the monoclinic $P2_1$ crystal, the hydroxy group is bonded to O6 [H8…O6 separation: 1.97(3) Å], to form supramolecular $C_1^1(5)$ chains running in the [010] direction. The hydrogen bonding scheme in the orthorhombic form involves the same hydroxy group in a bifurcated bond with O6 and O8 atoms as acceptors [H8…O6 and H8…O8 separations: 2.44(3) and 2.35(4) Å]. Although the supramolecular structure remains essentially 1D, molecules now form zigzag chains with graph-set $C_1^1(2)$ and $C_1^1(5)$, running in the [100] direction.

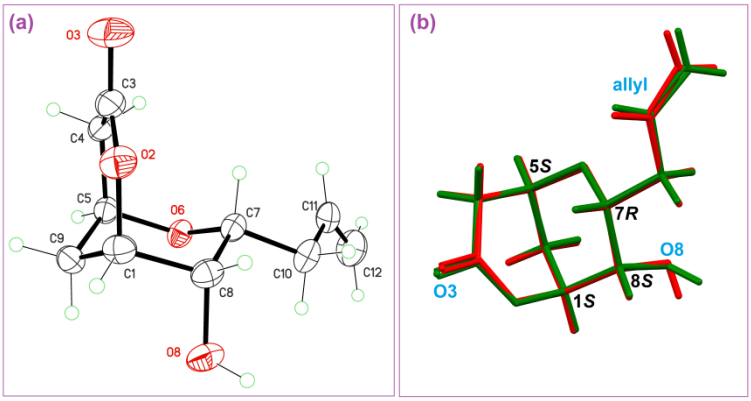


Figure 3. (a) ORTEP view of the molecular structure of **9** (polymorph $P2_1$), with displacement ellipsoids at the 30% probability level. (b) Molecule overlay between $P2_1$ (green) and $P2_12_12_1$ (red) polymorphs crystallized for compound **9**.

The reaction was scaled up to produce 0.5 g of the compound, providing sufficient material to perform cytotoxicity tests. Initially, a cytotoxicity study was conducted against five mouse mammary epithelial cell lines: EpH4-Ev and mouse tumor lines 67NR, 66cl4, and 4T1, using the propidium iodide protocol. Cell proliferation was evaluated as the percentage of confluence over time, varying the concentration of compound **9** from 10 to 40 µM, with each untreated cell group serving as control. Positive results were predominantly observed for EpH4-Ev at a concentration of 40 µM of compound **9**, where proliferation was not affected and even increased. In contrast, 4T1 cells exhibited significant inhibition at the same concentration. This difference indicates that compound **9** selectively targets highly metastatic 4T1 cells while having no adverse effects on normal cells. For the 67NR line, the inhibition observed was low, and no alterations were noted for the 66cl4 line (Figure 4).

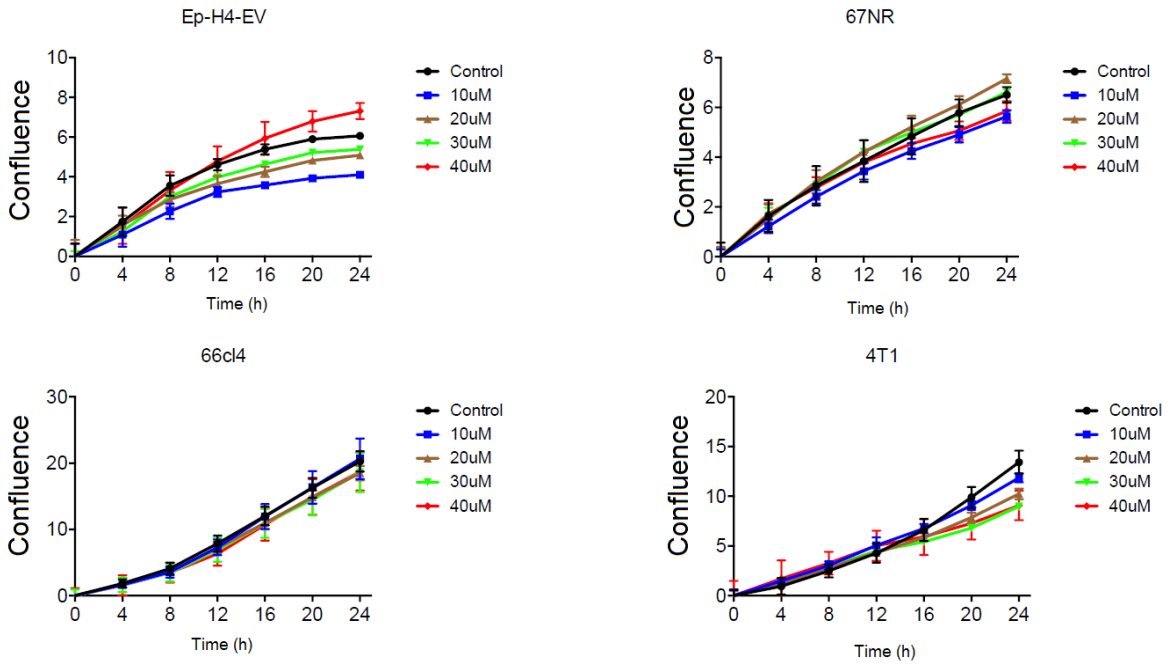


Figure 4. Cell confluence (%) *vs* incubation time with **9** at different concentrations, in the Ep-H4-EV, 67NR,66cl4, and 4T1 cells; only results of six wells are plotted for clarity.

We also did cytotoxicity tests of **9** with human cells U251 = central nervous system glia, PC-3 = prostate, K562 = leukemia, HCT-15 = colon, MCF-7 = breast, SKLU = lung. COS-7: monkey kidney cell line (non-cancerous), in ethanol at concentrations of 10 μg (blue) and 25 μg (gray). In this case, although a slight activity is seen with the MCF-7 cell line and K562 cell line, it was not relevant compared to the control (5-FU) (Table S2) (supporting Information).

Conclusions

The concise synthesis of an allylated analogue of 9-deoxygoniopypyrone resulted in an enantiomerically pure compound with good yields and escalated to grams. Its characteristics as a polymorphic solid highlight the possible interactions with active sites of the cell. Cytotoxicity studies indicated that substituting the phenyl group with an allyl group decreased cytotoxicity but increased selectivity. This is attributed to the allylic double bond being further away from the chiral center compared to the phenyl derivative, which is directly bonded with it. Future modifications to this structure could involve introducing substituted aromatic rings with electron-withdrawing groups, electron-donating groups, or other groups to enhance anticancer efficacy, suggesting potential pathways for developing new derivatives for in vitro cancer research.

Experimental Section

General. Dichloromethane (CH_2Cl_2) was freshly distilled over CaH_2 before use. Tetrahydrofuran (THF) was newly distilled over sodium/benzophenone before use. Thin Layer Chromatography (TLC) was performed on aluminum plates pre-coated with silica gel (MERCK, $60F_{254}$), which were visualized by UV fluorescence (λ_{max} 254 nm) and/or by staining with 10% w/v $(NH_4)_2MoO_4$ in 1.8M aqueous H_2SO_4; or 1% v/v *p*-anisaldehyde in

EtOH/AcOH/H_2SO_4 (85:10:5). Nuclear Magnetic Resonance (NMR) spectra were acquired on a BRUKER 500 spectrometer 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively. Unequivocal ^{1}H and ^{13}C assignments were made using two-dimensional HH-COSY and CH-HSQC experiments. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals at 7.26 ppm ($CDCl_3$), All ^{13}C NMR spectra were reported in ppm relative to 77.16 ppm ($CDCl_3$) and were obtained with ^{1}H-decoupling. Data for ^{1}H NMR are described as follows: chemical shift (δ in ppm), multiplicity (σ, singlet; d, doublet; t, triplet; m, multiple; br, broad signal), coupling constant *J* (Hz), integration. Data for ^{13}C NMR spectra are described in terms of chemical shift (δ in ppm).

(2*S*,3*R*)-2-[(4*S*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl]-6-oxo-3,6-dihydro-2*H*-pyran-3-yl acetate (11). To a stirred solution of diacetoxylated **10** (1.0 g, 3.2 mmol) in anhydrous CH_2Cl_2 (12 mL), allyltrimethylsilane (1.01 mL, 6.4 mmol) was added, the mixture was cooled to -40 °C, then $BF_3{\cdot}OEt_2$ (0.79 mL, 6.4 mmol) was added dropwise, after 10 min the reaction mixture was stirred at room temperature for 1.5 h. Finally, it was neutralized with $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction was purified by flash chromatography (EtOAc/Hexane, 2:8), obtaining the allylated **11**, (0.8 g, 85%) as a colorless oil: R_f 0.64 (Hexane/EtOAc, 1:1); FT-IR (cm^{-1}) ν: 3057, 2992, 1740, 1375, 1265, 1224; $[\alpha]_D^{22}$ -99.2° (*c* 1.0, $CHCl_3$); HRMS-FAB (*m/z*): [M+1] $^+$ calculated to $C_{15}H_{20}O_6$ 297.1338 found 297.1332; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 6.85 (dd, *J* 10.0, 5.0, 1H), 6.20 (dd, *J* 9.5, 0.5, 1H), 5.88-5.79 (m, 1H), 5.54-5.52 (m, 1H), 5.16-5.12 (m, 1H), 4.24 (dt, *J* 12.0, 6.0, 2.0, 1H), 3.96 (dd, *J* 8.5, 3.5, 1H), 2.37 (t, *J* 6.3, 6.1, 2H), 2.10 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 170.1, 162.0, 140.1, 133.1, 124.6, 118.2, 109.7, 78.1, 75.9, 75.4, 62.4, 37.0, 27.2, 26.6, 20.7.

(*S*)-6-[(4*S*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl]-3,6-dihydro-2*H*-pyran-2-one (12). To a stirred solution of the allylated **11** (0.7 g, 2.2 mmol) in THF (10 mL) was added Zn powder (0.77 g, 11.82 mmol), followed by a supersaturated solution of NH_4Cl (10 mL) and the mixture was allowed to stir for 1 h. In the end, the solids were decanted, and the phases were separated by extractions with EtOAc (3 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (Hexane/EtOAc, 4:1) obtaining the deacetoxylated compound **12** (0.51 g, 90%) as a colorless oil: R_f 0.65 (Hexane/EtOAc, 1:1); FT-IR (cm^{-1}) ν: 3327, 2856, 1720, 1644, 1528, 1452, 1377; $[\alpha]_D^{22}$ -44.43 (*c* 1.0, $CHCl_3$), FAB-HRMS: [M+1]$^+$ *m/z* calculated to $C_{13}H_{18}O_4$ 239.1287, found 239.1283; ^{1}H NMR (500 MHz, CDC_{l3}): δ_H 5.92-5.88 (m, 1H), 5.84-5.77 (m, 2H), 5.13-5.07 (m, 2H), 4.87 (s, 1H), 4.25 (dd, *J* 14.2, 6.2, 1H), 3.70 (d, *J* 8.4, 1H), 3.02-3.12 (m, 2H), 2.36 (dtd, *J* 20.9, 14.1, 6.5, 2H), 1.34 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 168.8, 133.1, 123.5, 123.0, 118.1, 109.3, 81.7, 76.5, 74.4, 36.9, 30.4, 27.4, 26.2.

(*S*)-6-[(1*S*,2*R*)-1,2-Dihydroxypent-4-en-1-yl]-3,6-dihydro-2*H*-pyran-2-one (13). Trifluoroacetic acid (0.38 mL, 5 mmol) was added to a solution of **12** (0.3 g, 1.25 mmol) in dichloromethane (4 mL). The mixture was kept stirring at room temperature for 2 h. The reaction was treated with a saturated $NaHCO_3$ solution until pH 7. The layers were separated, and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (Hexanes/EtOAc, 7:3) of the raw product yielded **13** (207 mg, 83%) as a colorless oil as the only isolable product: R_f 0.15 (Hexane/EtOAc, 1:2 ratio); FT-IR (cm^{-1}) ν: 3418, 3057, 2924, 1728, 1642, 1381, 1365, 1225; $[\alpha]_D^{20}$ -49.3 (*c* 1.0, $CHCl_3$). FAB-HRMS: [M+1]$^+$ *m/z* calculated to $C_{10}H_{14}O_4$ 199.0985, found 199.0970; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.98-5.88 (m, 1H), 5.84 (ddd, *J* 10.5, 5.2, 3.2, 2H), 5.17-5.12 (m, 2H), 5.05 (s, 1H), 3.87 (dt, *J* 5.35, 5.2, 4.9 1H), 3.57 (dd, *J* 3.5, 3.6, 1H), 3.14 (dd, *J* 48.6, 22.0, 2H), 2.31-2.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 169.7, 133.9, 123.3, 123.0, 118.2, 81.1, 74.7, 70.4, 38.1, 30.1.

(1*S*,5*S*,7*S*,8*S*)-7-Allyl-8-hydroxy-2,6-dioxabicyclo[3.3.1]nonan-3-one (9). To a solution of **13** (0.3 g, 1.51 mmol) in anhydrous dichloromethane (4 mL), the temperature was lowered to 0 °C, and DBU (0.537 mL, 3.6 mmol) was added slowly. After stirring for 8 h, the mixture was neutralized with a 10% HCl solution. The layers were separated, and the aqueous layer was extracted (EtOAc, 3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue (Hexanes/EtOAc, 7:3) yielded compound **9** (0.27 g, 90%) as a colorless crystals, which was the only isolable product: R_f 0.27 (Hexane/EtOAc, 1:2), mp: 93-94 °C; FT-IR (cm^{-1}) ν: 2925, 2854, 3469, 1733, 1642, 1388, 1348, 1333, 1195, 1070; $[\alpha]_D^{20}$ +40.3(*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 5.78 (ddt, *J* 11.7, 7.1, 4.1, 1H), 5.17 (dq, *J* 17.2, 3.3, 1.7, 1.65, 1H), 5.11 (dq, *J* 10.2, 3.2, 1.7, 1.4, 1H), 4.72-4.75 (m, 1H), 4.35-4.33 (m, 1H), 3.79-3.75 (m, 2H), 2.87 (dt, *J* 19.4, 2.1, 2.0, 1H), 2.81 (d, *J* 5.2, 1H), 2.77 (d, *J* 5.1, 1H), 2.73 (d, 6.5, 1H) 2.49 -2.32 (m, 3H), 1.79 (dd, *J* 14.2, 4.2, 4.1, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.8 (C-2), 133.4 (C-4′), 118.1 (C-5′), 75.1 (C-6), 68.0 (C-2′), 66.4 (C-1′), 65.8 (C-4), 36.4 (C-3), 35.3 (C-3′), 24.3 (C-5).

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Supplementary Material

Supporting Information File 1: Compound characterization data (IR, ^{1}H, ^{13}C NMR, MS, melting point, X-ray crystallography) of new compounds.
Supporting Information File 2: Crystallographic file for compound **9**.

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