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First total synthesis and absolute stereochemical assignment of vittarilide-A, an antioxidant extractive component isolated from *Vittaria anguste-elongata* Hayata

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ABSTRACT

The first stereocontrolled synthesis of vittarilide-A and its C5-epimer was completed from D-glucuronolactone. Comparison with the spectroscopic properties reported for authentic material has given a clear indication as to the absolute stereochemistry of the natural vittarilide-A.

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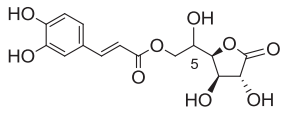
1. Introduction



vittarilide-A

Vittaria anguste-elongata Hayata, family Vittariaceae, is a very rare linear grass-like fern distributed in Taiwan, Philippines, and Pacific Islands.[1] In 2005, Wu and co-workers have identified 12 new and 20 known compounds in a crude methanol extract from this plant and have shown one of the components can exhibit significant cytotoxic activity against human cancer cell lines.[2] Vittarilide-A serves as one constituent of the new extractive components with potent antioxidant property (IC_{50} value of 91 μM, α,α-diphenyl-β-picrylhydrazyl free radical (DPPH) scavenging assay), whose structure consisting of *trans*-caffeoyl (3,4-dihydroxycinnamoyl) moiety and D-gluconate skeleton has been established on the basis of spectroscopic studies.[2] As a promising candidate for potential biological applications, vittarilide-A can be an appealing synthetic target due to the fact that the low abundance of the natural source has limited its availability, impeding a more detailed investigation of its unique biological properties. Nevertheless, to our knowledge, no synthetic challenges associated with this natural product have been reported previously, and hence its absolute stereochemistry at C5 has remained unspecified. Accordingly, total synthesis is expected to offer beneficial opportunities to gain complete understanding of the chemical structure as well as to address the supply problem leading to broader exploration of its biological function and further development of clinically superior analogs. From this basis, we set out to develop a stereocontrolled route to access this new natural product from commercially available D-glucuronolactone as an inexpensive chiral pool material.[3,4] In this publication, we report the success in the first total synthesis and absolute stereochemical assignment of vittarilide-A.

2. Results and discussion

We commenced our synthetic approach with protection of D-glucuronolactone (Scheme 1). As reported in our previous work, this substrate was readily protected through treatment with acetone and concd H_2SO_4 at room temperature and the resulting acetonide **1a** could be further converted to the corresponding benzyl ether **1b** (95% for two steps).[4] Subsequently, we attempted the stepwise reduction of the remaining lactone moiety with DIBAL–H and $NaBH_4$ to furnish the corresponding diol, whose primary and secondary hydroxyl groups were then chemoselectively protected as the TBS and MOM ethers, respectively, to obtain **2** in 87% (for four steps). At this stage, we replaced the TBS group in **2** with benzyl substituent from the viewpoint of functional group tolerance. As a matter of fact, the benzyl functionality

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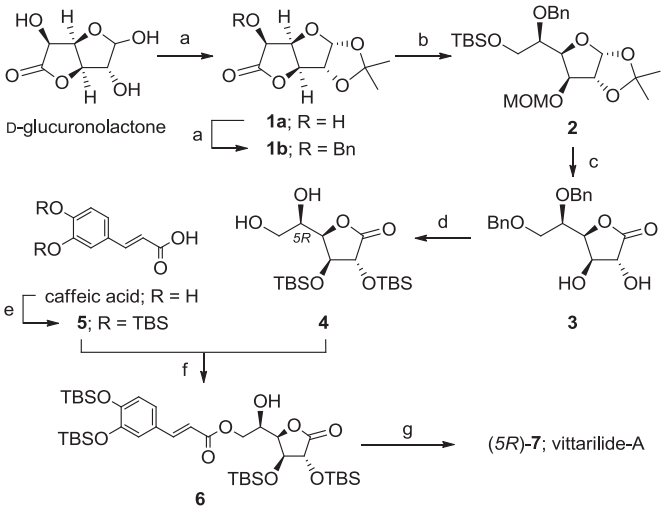
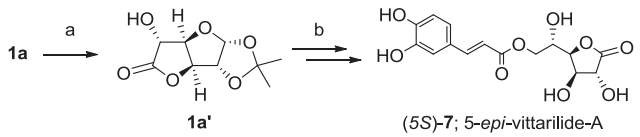
introduced through the desilylation–benzylation sequence was tolerant to acidic treatment with methanolic HCl_{aq}, allowing for removal of the acetonide and MOM groups to the corresponding methyl glycoside. Further acidic hydrolysis of this product employing HCl_{aq} in 1,4-dioxane at 90 °C led to efficient production of the corresponding lactol (75% for four steps), which underwent chemoselective Fetizon oxidation[5] to give the expected lactone **3** in 83% yield. Protection of all the hydroxyl groups in **3** with TBSCl and subsequent deprotective hydrogenolysis of all the benzyl groups in the presence of palladium hydroxide on carbon afforded the desired gluconate segment **4** in 77% for two steps, which can be considered to have *R*-configuration at the C5 stereocenter. Having the gluconate intermediate in hand, our next objective was introduction of *trans*-caffeoyl moiety onto the hydroxyl group located at the terminal position of the gluconate structure. The site-selective introduction was successfully achieved by EDCI coupling of **4** with a TBS-protected substrate **5**, which was readily derived from caffeic acid (71% yield), to give **6** in 56%. Removal of all the TBS groups, although challenging for the polyhydroxylated system and initially problematic,[6] was finally accomplished through treatment with $BF_3{\cdot}OEt_2$ in acetonitrile at 0 °C,[7] giving rise to the synthetic target (5*R*)-**7** in 50% yield, which could be purified by silica gel column chromatography.

In order to obtain precise determination of the absolute configuration of the naturally occurring vittarilide-A, we decided to



Scheme 1. Reagents and conditions: (a) see Ref. 4; (b) (i) DIBAL–H, CH_2Cl_2, −40 °C, (ii) $NaBH_4$, MeOH, rt, (iii) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt; 91% (three steps), (iv) MOMCl, DIPEA, CH_2Cl_2, rt; 87% (four steps), (c) (i) TBAF, THF, rt, (ii) BnBr, NaH, THF, rt, (iii) HCl_{aq}, MeOH, 50 °C, (iv) HCl_{aq}, 1,4-dioxane, 90 °C; 75% (four steps), (v) Ag_2CO_3, Celite, toluene, 80 °C; 83%; (d) (i) TBSCl, imidazole, DMF, rt, (ii) H_2, $Pd(OH)_2/C$, EtOH, rt; 77% (two steps); (e) (i) TBSCl, imidazole, DMF, rt, (ii) K_2CO_3, MeOH/H_2O (1:1), rt; 71% (two steps); (f) EDCI, DMAP, CH_2Cl_2, 0 °C; 56%; (g) $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C; 50%.

pursue synthesis of C5-epimeric counterpart of (5*R*)-**7**. The requisite chiral substrate for the synthesis could be prepared by inversion of the stereogenic center at α-position of the lactone ring in **1a** (Scheme 2). Indeed, **1a** was treated with triflic anhydride in the presence of pyridine to give triflate, which was subjected to reaction with potassium acetate in the presence of 18-crown-6, providing the corresponding acetate with complete inversion of the relevant stereochemistry in 99% yield for two steps. Hydrolysis of this compound under basic conditions resulted in removal of the acetyl moiety and concomitant lactone ring opening to generate hydroxyl acid, which was readily cyclized to **1a**′ (71% yield for two steps) by treatment with pyridinium *p*-toluenesulfonate (PPTS). As expected, transformation of **1a**′ into (5*S*)-**7** was achieved by following the established above strategy for (5*R*)-**7**, allowing for the preparation of substantial quantities of the reference compound in analytically pure form (see Supplementary data)[8].



Scheme 2. Reagents and conditions: (a) (i) Tf_2O, pyridine, CH_2Cl_2, 0 °C, (ii) AcOK, 18-crown-6, DMF, 0 °C; 99% (two steps), (iii) K_2CO_3, MeOH, 0 °C, (iv) PPTS, $(CH_2Cl)_2$, 80 °C; 71% (two steps); (b) see Supplementary data.

The structural identity of the synthetic and natural products was confirmed by comparison of ^1H and ^{13}C NMR spectral data with those in the literature.[2,9] Fig. 1 depicts the ^1H NMR spectra of (5*R*)- and (5*S*)-**7**. As can be seen in this figure, these two compounds showed remarkably different patterns for resonances attributed to the gluconate segments in the higher magnetic fields, whereas similar spectral shapes were given for resonances attributed to the *trans*-caffeoyl moieties in the lower magnetic fields. Additionally, chemical shift deviations estimated from the root-mean-square (rms) of δ value differences between the reported and observed data (Δδ values) are shown in Table 1. From inspection of these data, it appears that δ values of (5*R*)-**7** closely match those for vittarilide-A, giving 0.064 ppm of the rms for the gluconate segment much less than 0.396 ppm for that of (5*S*)-**7**, while no impressive differences in the δ value deviations were observed for the *trans*-caffeoyl moieties of these two compounds (0.040 ppm for (5*R*)-**7** and 0.020 ppm for (5*S*)-**7**). From these observations along with identity of all coupling constants (*J* values) for (5*R*)-**7** with those reported in the literature, it is evident that (5*R*)-**7** can be assigned as the naturally occurring vittarilide-A and (5*S*)-**7** should be its C5-epimer.

Furthermore, the ^{13}C NMR spectra of (5*R*)- and (5*S*)-**7** showed similar trends observed in the ^1H NMR spectra, which gave significant difference in resonance patterns attributed to the gluconate segments in the higher magnetic fields as well as similarity of resonance patterns attributed to the *trans*-caffeoyl moieties in the lower magnetic fields (Fig. 2). In view of Table 2 that lists chemical shift deviations estimated from the rms of δ value differences between the reported and observed data (Δδ values), one can clearly see that δ values of (5*R*)-**7** closely match those for vittarilide-A, giving 0.173 ppm of the rms for the gluconate segment much less than 2.52 ppm for that of (5*S*)-**7** besides 0.224 ppm for the *trans*-caffeoyl moieties of (5*R*)-**7** significantly less than 1.15 ppm for (5*S*)-**7**. From these observations, it is evident that (5*R*)-**7** can be assigned as the naturally occurring vittarilide-A and (5*S*)-**7** should be its C5-epimer, in agreement with the conclusion drawn from the data analysis of the ^1H NMR. Therefore, the obvious conclusion that can be drawn from the comparison of the NMR data is that the unspecified C5

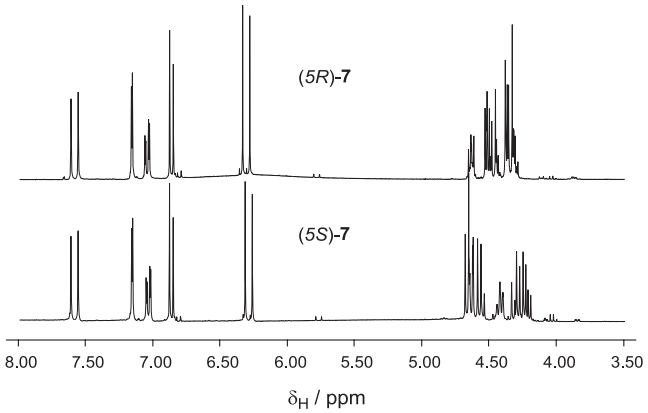


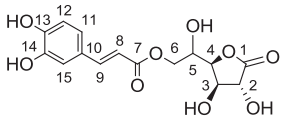
Fig. 1. Comparison of ^1H NMR spectra of (5*R*)- and (5*S*)-**7** in acetone-d_6.

Table 1
Observed chemical shifts (δ_H) and their deviations from the reported data

	H9[c]	H15[c]	H11[c]	H12[c]	H8[c]	rms[b]
Natural[a]	7.58	7.15	7.03	6.86	6.30	—
(5*R*)-**7**	7.59	7.17	7.05	6.87	6.31	—
$\Delta\delta_H$	+0.01	+0.02	+0.03	+0.01	+0.01	0.040
(5*S*)-**7**	7.59	7.16	7.05	6.87	6.30	—
$\Delta\delta_H$	+0.01	+0.01	+0.02	+0.01	0	0.020

	H4[c]	H3[c]	H6[c]	H6′[c]	H2[c]	H5[c]	rms[b]
Natural[a]	4.63	4.49	4.46	4.34	4.33	4.30	—
(5*R*)-**7**	4.64	4.52	4.48	4.35	4.38	4.31	—
$\Delta\delta_H$	+0.01	+0.03	+0.02	+0.01	+0.05	+0.01	0.064
(5*S*)-**7**	4.62	4.54	4.30	4.22	4.65	4.41	—
$\Delta\delta_H$	−0.01	+0.05	−0.16	−0.12	+0.32	+0.11	0.396

[a] Spectral data for the natural vittarilide-A are reported in Ref. 2.
[b] Root-mean-square of $\Delta\delta_H$ values.
[c] For the numbering scheme, see below.



(5*R*)- or (5*S*)-**7**

stereocenter in the naturally occurring vittarilide-A should have *R*-configuration. Unexpectedly, we noted that (5*R*)-**7** gave a much greater optical rotation of $[\alpha]_D$ +49.8 (*c* 1.80, MeOH) than the reported value of $[\alpha]_D$ +5.1 (*c* 1.075, MeOH),[10] besides a comparable optical rotation of $[\alpha]_D$ +45.3 (*c* 0.830, MeOH) was given for (5*S*)-**7**. Considering the chemical integrity of the synthetic products ensured by a range of analytical experiments, this pronounced difference in absolute value of the optical rotation observed for (5*R*)-**7** can hardly be explained otherwise than that the extractive sample of natural vittarilide-A would contain several impurities.[11]

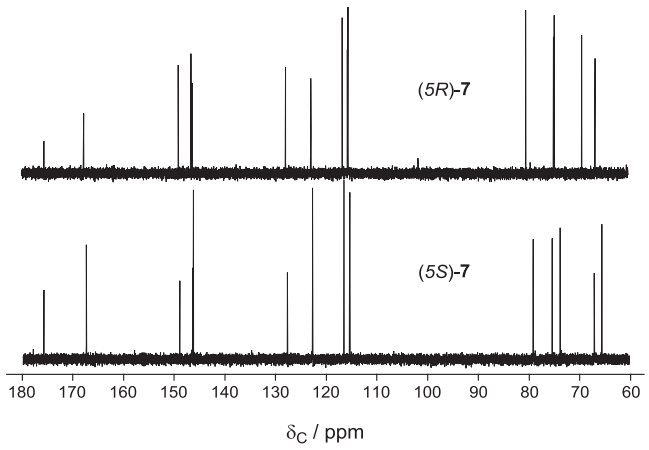


Fig. 2. Comparison of ^{13}C NMR spectra of (5*R*)- and (5*S*)-**7** in acetone-d_6.

3. Conclusions

In conclusion, we have achieved the stereocontrolled synthesis of vittarilide-A and its C5-epimer. The stereochemistry of this natural product has been unequivocally established, with the convincing spectroscopic evidence demonstrated by comparison with the two possible synthetic candidates. To the best of our knowledge, this report represents the first example of synthetic elaboration of vittarilide-A, providing an indication of a need for revision in the optical rotation value, as well as the initial disclosure of the complete absolute stereochemistry of this natural product.

4. Experimental section

4.1. General

All solvents and reagents were of reagent grade quality from Wako Pure Chemicals and Tokyo Chemical Industry (TCI), and used without further purification. The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded on a JEOL JNM-AL300 spectrometer in chloroform-*d* ($CDCl_3$) and acetone-d_6 unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP-1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Column chromatography was performed on Kanto Chemical silica gel 60N eluting with the indicated solvent system. Fourier transform infrared (FTIR) spectra were recorded on a JASCO FT/IR-550 spectrometer. Elemental analyses were performed by JSL Model JM 10 instruments. Samples of D-glucuronolactone derivatives **1a** and **1b** were prepared by the procedures reported in the literature.[4] Their physical properties and spectroscopic data were in full agreement with those reported earlier.

4.2. Preparation and characterization of new compounds

*4.2.1. Synthesis and characterization of **2** and all the related compounds.* To a solution of **1b** (3.43 g, 11.2 mmol) in anhydrous CH_2Cl_2 (37.3 mL) was added diisobutylaluminum hydride (DIBAL–H,

Table 2
Observed chemical shifts (δ_C) and their deviations from the reported data

	C1[c]	C7[c]	C13[c]	C12[c]	C9[c]	C10[c]	C15[c]	C14[c]	C8[c]	C11[c]	rms[b]
Natural[a]	175.3	167.5	148.7	146.4	146.0	127.5	122.5	116.3	115.3	115.1	—
(5*R*)-**7**	175.3	167.4	148.8	146.3	146.0	127.6	122.5	116.3	115.3	115.2	—
$\Delta\delta_C$	0	0	+0.1	−0.1	0	+0.1	0	0	0	+0.1	0.040
(5*S*)-**7**	176.0	167.6	149.1	146.6	146.4	127.8	122.8	116.6	115.5	115.5	—
$\Delta\delta_C$	−0.7	+0.1	+0.4	+0.2	+0.4	+0.3	+0.3	+0.3	+0.2	+0.4	0.020

	C4[c]	C2[c]	C3[c]	C5[c]	C6[c]	rms[b]
Natural[a]	80.1	74.5	74.5	69.0	66.4	
(5*R*)-**7**	80.1	74.5	74.4	68.9	66.3	
$\Delta\delta_C$	0	0	−0.1	−0.1	−0.1	0.173
(5*S*)-**7**	79.2	75.4	73.8	67.1	65.6	
$\Delta\delta_C$	−0.9	+0.9	−0.7	−1.9	−0.8	2.52

[a] Spectral data for the natural vittarilide-A are reported in Ref 2.
[b] Root-mean-square of $\Delta\delta_C$ values.
[c] For the numbering scheme, see Table 1.

21.5 mL, 22.4 mmol, 1.04 M *n*-hexane solution) at −78 °C. The reaction mixture was warmed to −40 °C, stirred at this temperature for additional 2 h, quenched by addition of saturated aqueous Rochelle salt (potassium sodium tartarate, 30 mL), and warmed to room temperature. After stirring for 17 h, the resulting mixture was extracted with CH_2Cl_2 (70 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide crude hemiacetal intermediate. To a solution of the hemiacetal (3.53 g) in methanol (37.3 mL) was added sodium borohydride ($NaBH_4$, 508 mg, 13.4 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, quenched by addition of water (15 mL), extracted with AcOEt (70 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude diol intermediate. To a solution of the diol (3.58 g) in anhydrous CH_2Cl_2 (11.2 mL) were added triethylamine (Et_3N, 2.83 g, 28.0 mmol), *N*,*N*-dimethyl-4-aminopyridine (DMAP, 684 mg, 5.60 mmol), and *tert*-butyldimethylsilyl chloride (TBSCl, 3.38 g, 22.4 mmol) at room temperature. The reaction mixture was stirred for 45 min, quenched by addition of water (20 mL) at room temperature, extracted with CH_2Cl_2 (40 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 9:1 to 4:1) gave the TBS ether (4.33 g, 10.2 mmol, 91% for three steps) as colorless oil: R_f=0.34 (silica gel, hexane/AcOEt=3:1); $[\alpha]_D^{23}$ −10.1 (*c* 1.31, $CHCl_3$); IR (NaCl): ν_{max} 3450 (O−H), 3018 (C−H), 2955 (C−H), 2930 (C−H), 2858 (C−H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49−7.40 (m, 5H, Ar*H*), 6.11 (d, *J*=3.6 Hz, 1H, C*H*), 4.93 (d, *J*=11.7 Hz, 1H, CH_2), 4.87 (d, *J*=11.7 Hz, 1H, CH_2), 4.63 (d, *J*=3.6 Hz, 1H, C*H*), 4.45 (t, *J*=2.7 Hz, 1H, C*H*), 4.37 (dd, *J*=2.7, 5.1 Hz, 1H, C*H*), 4.17 (q, *J*=5.1 Hz, 1H, C*H*), 4.05 (d, *J*=2.7 Hz, 1H, O*H*), 3.99 (dd, *J*=5.1, 10.5 Hz, 1H, CH_2), 3.91 (dd, *J*=5.1, 10.5 Hz, 1H, CH_2), 1.61 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.04 (s, 9H, CH_3), 0.21 (s, 3H, CH_3), 0.20 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0 (*C*), 128.7 (*C*H), 128.20 (*C*H), 128.19 (*C*H), 111.6 (*C*), 104.7 (*C*H), 85.4 (*C*H), 79.3 (*C*H), 78.7 (*C*H), 75.7 (*C*H), 74.0 (*C*H_2), 63.3 (*C*H_2), 26.8 (*C*H_3), 26.2 (*C*H_3), 25.9 (*C*H_3), 18.2 (*C*), −5.46 (*C*H_3), −5.53 (*C*H_3). Anal. Calcd for $C_{22}H_{36}O_6Si$: C, 62.23; H, 8.55. Found: C, 62.25; H, 8.20.

To a solution of the TBS ether (1.44 g, 3.39 mmol) in anhydrous CH_2Cl_2 (2.30 mL) were added methoxymethyl chloride (MOMCl, 2.73 g, 33.9 mmol) and *N*,*N*-diisopropylethylamine (DIPEA, 4.38 g, 33.9 mmol) at 0 °C. After warming to room temperature, the reaction mixture was stirred for 23 h, quenched by addition of water (20 mL), extracted with CH_2Cl_2 (40 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide an orange oily residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 10:1) gave **2** (1.53 g, 3.26 mmol, 96%) as colorless oil: R_f=0.43 (silica gel, hexane/AcOEt=3:1); $[\alpha]_D^{20}$ +1.12 (*c* 1.37, $CHCl_3$); IR (NaCl): ν_{max} 3019 (C−H), 2954 (C−H), 2931 (C−H), 2894 (C−H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45−7.35 (m, 5H, Ar*H*), 6.00 (d, *J*=3.6 Hz, 1H, C*H*), 5.02 (d, *J*=11.4 Hz, 1H, CH_2), 4.73 (d, *J*=3.6 Hz, 1H, C*H*), 4.72 (s, 2H, CH_2), 4.65 (d, *J*=11.4 Hz, 1H, CH_2), 4.35 (dd, *J*=3.0, 8.4 Hz, 1H, C*H*), 4.28 (d, *J*=3.0 Hz, 1H, C*H*), 4.19 (m, 1H, C*H*), 3.98−3.90 (m, 2H, CH_2), 3.45 (s, 3H, OCH_3), 1.58 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.04 (s, 9H, CH_3), 0.20 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1 (*C*), 128.5 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 111.9 (*C*), 105.2 (*C*H), 97.4 (*C*H_2), 83.3 (*C*H), 81.4 (*C*H), 78.6 (*C*H), 77.0 (*C*H), 72.5 (*C*H_2), 64.1 (*C*H_2), 56.0 (*C*H_3), 26.8 (*C*H_3), 26.4 (*C*H_3), 26.0 (*C*H_3), 18.3 (*C*), −5.36 (*C*H_3), −5.42 (*C*H_3). Anal. Calcd for $C_{24}H_{40}O_7Si$: C, 61.51; H, 8.60. Found: C, 61.14; H, 8.25.

4.2.2. Synthesis and characterization of ***3*** *and all the related compounds.* To a solution of **2** (1.53 g, 3.26 mmol) in anhydrous THF (11.0 mL) was added tetra(*n*-butyl)ammonium fluoride (TBAF, 1 M THF solution, 8.20 mL, 8.20 mmol) at room temperature. The reaction mixture was stirred for 4.5 h, quenched by addition of water (15 mL), extracted with AcOEt (50 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude alcohol intermediate. To a solution of the alcohol (1.56 g) in anhydrous THF (4.10 mL) were added in small portions sodium hydride (NaH, 711 mg, ca. 16.3 mmol, 55−56% dispersion in mineral oil), benzyl bromide (BnBr, 5.58 g, 32.6 mmol) at 0 °C over a period of 10 min. After warming to room temperature, the reaction mixture was stirred for 17 h, quenched by addition of saturated aqueous NH_4Cl (20 mL), extracted with AcOEt (40 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/acetone, 50:1 to 8:1) gave the benzyl ether (1.36 g, 3.06 mmol, 94% for two steps) as colorless oil: R_f=0.54 (silica gel, hexane/AcOEt=2:1); $[\alpha]_D^{22}$ −9.08 (*c* 1.18, $CHCl_3$); IR (NaCl): ν_{max} 3018 (C−H), 2935 (C−H), 2896 (C−H), 2867 (C−H), 757 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.24 (m, 10H, Ar*H*), 5.89 (d, *J*=3.6 Hz, 1H, C*H*), 4.86 (d, *J*=11.4 Hz, 1H, CH_2), 4.61 (d, *J*=3.6 Hz, 1H, C*H*), 4.60 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 4.52 (d, *J*=11.4 Hz, 1H, CH_2), 4.30 (dd, *J*=3.0, 9.0 Hz, 1H, C*H*), 4.18 (d, *J*=3.0 Hz, 1H, C*H*), 3.97 (ddd, *J*=1.8, 5.7, 9.0 Hz, 1H, C*H*), 3.94 (dd, *J*=1.8, 10.8 Hz, 1H, CH_2), 3.70 (dd, *J*=5.7, 10.8 Hz, 1H, CH_2), 3.34 (s, 3H, OCH_3), 1.48 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7 (*C*), 138.6 (*C*), 128.40 (*C*H), 128.39 (*C*H), 127.73 (*C*H), 127.66 (*C*H), 127.62 (*C*H), 127.5 (*C*H), 111.9 (*C*), 105.0 (*C*H), 97.2 (*C*H_2), 83.2 (*C*H), 81.1 (*C*H), 78.7 (*C*H), 75.3 (*C*H), 73.4 (*C*H_2), 72.1 (*C*H_2), 70.9 (*C*H_2), 55.9 (*C*H_3), 26.7 (*C*H_3), 26.3 (*C*H_3). Anal. Calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.16; H, 7.11.

To a solution of the benzyl ether (1.16 g, 2.61 mmol) in methanol (17.4 mL) was added concd HCl_{aq} (1.28 g, 13.1 mmol) at 0 °C. After warming to 50 °C, the reaction mixture was stirred for 3 h, cooled to 0 °C, quenched by addition of saturated aqueous $NaHCO_3$ (25 mL), extracted with AcOEt (20 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude methyl glycoside (1.01 g) as colorless oil. A solution of the crude methyl glycoside (1.01 g) in a 1:1 mixture of 3% w/w HCl_{aq} and 1,4-dioxane (12.3 mL) was heated at 90 °C. This reaction mixture was stirred for 5 h, cooled to 0 °C, quenched by addition of saturated aqueous $NaHCO_3$ (15 mL), extracted with AcOEt (20 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 1:1) gave the lactol (756 mg, 2.10 mmol, 80% for two steps) as colorless oil: R_f=0.23 (silica gel, hexane/AcOEt=1:2); $[\alpha]_D^{17}$ −13.8 (*c* 0.490, $CHCl_3$); IR (NaCl): ν_{max} 3408 (O−H), 3019 (C−H), 2927 (C−H), 2870 (C−H), 758 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33−7.22 (m, 20H, Ar*H*), 5.44 (m, 1H, C*H*), 5.12 (m, 1H, C*H*), 4.72−4.40 (m, 8H, CH_2), 4.26−4.14 (m, 2H, C*H*), 4.04−3.94 (m, 4H, C*H*), 3.84−3.76 (m, 2H, C*H*), 3.72−3.57 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (*C*), 138.0 (*C*), 137.96 (*C*), 137.94 (*C*), 128.7 (*C*H), 128.6 (*C*H), 128.19 (*C*H), 128.18 (*C*H), 128.15 (*C*H), 128.11 (*C*H), 128.0 (*C*H), 127.96 (*C*H), 127.93 (*C*H), 127.90 (*C*H), 103.2 (*C*H), 96.8 (*C*H), 81.2 (*C*H), 80.0 (*C*H), 78.0 (*C*H), 77.5 (*C*H), 77.43 (*C*H), 77.41 (*C*H), 77.37 (*C*H), 76.6 (*C*H), 76.2 (*C*H), 73.6 (*C*H_2), 73.5 (*C*H_2), 73.4 (*C*H_2), 73.1 (*C*H_2), 70.1 (*C*H_2), 69.9 (*C*H_2). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.96; H, 7.01.

To a solution of the lactol (25.3 mg, 0.0702 mmol) in toluene (0.7 mL) were added silver carbonate (Ag_2CO_3, 38.6 mg, 0.140 mmol) and Celite (40 mg) at room temperature. After warming to 80 °C, the reaction mixture was stirred for 6 h, cooled to room temperature, filtered through a pad of Celite followed by successive washings with AcOEt (40 mL), and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 2:1) gave **3** (21.0 mg, 0.0586 mmol, 83%) as colorless oil: R_f=0.49 (silica gel, hexane/AcOEt=1:2); $[\alpha]_D^{22}$ +18.1 (*c* 0.790, $CHCl_3$); IR (NaCl):

ν_{max} 3434 (O–H), 3019 (C–H), 2926 (C–H), 2871 (C–H), 1782 (C=O), 758 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.23 (m, 10H, Ar*H*), 4.68 (d, *J*=11.4 Hz, 1H, CH_2), 4.62 (dd, *J*=3.6, 6.0 Hz, 1H, C*H*), 4.54 (d, *J*=11.4 Hz, 1H, CH_2), 4.51 (s, 2H, CH_2), 4.44 (q, *J*=6.0 Hz, 1H, C*H*), 4.44 (br s, 1H, O*H*), 4.11 (br s, 1H, O*H*), 4.04 (dd, *J*=3.6, 5.1 Hz, 1H, C*H*), 3.89 (d, *J*=6.0 Hz, 1H, C*H*), 3.75 (dd, *J*=5.1, 10.5 Hz, 1H, CH_2), 3.68 (dd, *J*=5.1, 10.5 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5 (*C*=O), 137.6 (*C*), 137.4 (*C*), 128.83 (*C*H), 128.76 (*C*H), 128.42 (*C*H), 128.39 (*C*H), 128.2 (*C*H), 128.0 (*C*H), 79.4 (*C*H), 78.1 (*C*H), 74.7 (*C*H), 73.8 (*C*H), 73.7 (*C*H_2), 73.6 (*C*H_2), 69.0 (*C*H_2). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.11; H, 6.25.

4.2.3. Synthesis and characterization of ***4****.* To a solution of **3** (406 mg, 1.13 mmol) in DMF (0.380 mL) were added *tert*-butyldimethylsilyl chloride (TBSCl, 1.70 g, 11.3 mmol) and imidazole (846 mg, 12.4 mmol) at room temperature. The reaction mixture was stirred for 17 h, quenched by addition of water (10 mL), extracted with AcOEt (40 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude TBS ether. To a solution of the TBS ether (1.26 g) in ethanol (2.30 mL) was added palladium hydroxide on carbon ($Pd(OH)_2$/C, 94.5 mg), and the resulting mixture was hydrogenated at room temperature. After 1 h, the reaction mixture was filtrated through a pad of Celite followed by successive washings with AcOEt (100 mL). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt, 5:1) to give **4** (355 mg, 0.873 mmol, 77% for two steps) as a white solid: R_f=0.17 (silica gel, hexane/AcOEt=4:1); mp 71–72 °C; $[\alpha]_D^{20}$ +34.6 (*c* 1.31, $CHCl_3$); IR (KBr): ν_{max} 3494 (O–H), 3397 (O–H), 2953 (C–H), 2930 (C–H), 2887 (C–H), 2858 (C–H), 1786 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.52 (dd, *J*=4.2, 8.4 Hz, 1H, C*H*), 4.31 (dd, *J*=3.0, 4.2 Hz, 1H, C*H*), 4.10 (d, *J*=3.0 Hz, 1H, C*H*), 4.01 (dddd, *J*=3.6, 4.5, 5.4, 8.4 Hz, 1H, C*H*OH), 3.90 (dt, *J*=3.6, 11.1 Hz, 1H, CH_2), 3.79 (dt, *J*=4.5, 11.1 Hz, 1H, CH_2), 2.78 (d, *J*=5.4 Hz, 1H, O*H*), 2.18 (dd, *J*=3.6, 4.5 Hz, 1H, O*H*), 0.91 (s, 18H, CH_3), 0.17 (s, 6H, CH_3), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (*C*=O), 80.5 (*C*H), 75.0 (*C*H), 74.9 (*C*H), 68.6 (*C*H), 63.9 (*C*H_2), 25.71 (*C*H_3), 25.67 (*C*H_3), 18.1 (*C*), 18.0 (*C*), −4.69 (*C*H_3), −4.71 (*C*H_3), −5.0 (*C*H_3). Anal. Calcd for $C_{18}H_{38}O_6Si_2$: C, 53.16; H, 9.42. Found: C, 52.93; H, 9.29.

4.2.4. Synthesis and characterization of ***5****.* To a solution of caffeic acid (585 mg, 3.25 mmol) in DMF (1.10 mL) were added *tert*-butyldimethylsilyl chloride (TBSCl, 1.62 g, 10.7 mmol) and imidazole (1.46 g, 21.5 mmol) at room temperature. The reaction mixture was stirred for 6 h, quenched by addition of water (10 mL), extracted with AcOEt (40 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude mixture. To a solution of this mixture in 50% v/v aqueous methanol (11.0 mL) was added potassium carbonate (K_2CO_3, 449 mg, 3.25 mmol) at room temperature. The reaction mixture was stirred for 1 h, quenched by addition of 3% w/w HCl_{aq} (35 mL), extracted with AcOEt (40 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 4:1) gave **5** (948 mg, 2.32 mmol, 71% for two steps) as a white solid: R_f=0.43 (silica gel, hexane/AcOEt=2:1); mp 158–159 °C; IR (KBr): ν_{max} 3422 (O–H), 2962 (C–H), 2930 (C–H), 2859 (C–H), 1685 (C=O), 1629 (C=C), 1508 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J*=15.9 Hz, 1H, C*H*=CH), 7.05 (dd, *J*=2.1, 8.4 Hz, 1H, Ar*H*), 7.05 (d, *J*=2.1 Hz, 1H, Ar*H*), 6.84 (d, *J*=8.4 Hz, 1H, Ar*H*), 6.25 (d, *J*=15.9 Hz, 1H, CH=C*H*), 1.00 (s, 9H, CH_3), 0.99 (s, 9H, CH_3), 0.23 (s, 3H, CH_3), 0.23 (s, 3H, CH_3), 0.22 (s, 3H, CH_3), 0.22 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2 (*C*=O), 150.3 (*C*), 147.6 (*C*), 147.3 (*C*), 128.0 (*C*H), 123.0 (*C*H), 121.5 (*C*H), 120.9 (*C*H), 114.9 (*C*H), 26.05 (*C*H_3), 26.02 (*C*H_3), 18.64 (*C*), 18.59 (*C*), −3.95 (*C*H_3), −4.00 (*C*H_3). Anal. Calcd for $C_{21}H_{36}O_4Si_2$: C, 61.72; H, 8.88. Found: C, 62.11; H, 9.05.

4.2.5. Synthesis and characterization of ***6****.* To a solution containing **4** (355 mg, 0.873 mmol) and **5** (392 mg, 0.960 mmol) in anhydrous CH_2Cl_2 (8.80 mL) were successively added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 201 mg, 1.05 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP, 138 mg, 1.13 mmol) at 0 °C. The reaction mixture was stirred for 4 h, quenched by addition of water (15 mL), extracted with AcOEt (40 mL), washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 20:1) gave **6** (391 mg, 0.490 mmol, 56%) as colorless oil: R_f=0.51 (silica gel, hexane/AcOEt=4:1); $[\alpha]_D^{23}$ +31.0 (*c* 0.875, $CHCl_3$); IR (NaCl): ν_{max} 3465 (O–H), 3020 (C–H), 2956 (C–H), 2931 (C–H), 2897 (C–H), 2886 (C–H), 2859 (C–H), 1789 (C=O), 1705 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J*=15.9 Hz, 1H, C*H*=CH), 7.03 (dd, *J*=2.1, 8.7 Hz, 1H, Ar*H*), 7.03 (d, *J*=2.1 Hz, 1H, Ar*H*), 6.83 (d, *J*=8.7 Hz, 1H, Ar*H*), 6.29 (d, *J*=15.9 Hz, 1H, CH=C*H*), 4.62 (dd, *J*=2.4, 12.0 Hz, 1H, CH_2), 4.54 (dd, *J*=3.9, 8.4 Hz, 1H, C*H*), 4.37 (dd, *J*=5.7, 12.0 Hz, 1H, CH_2), 4.32 (dd, *J*=2.4, 3.9 Hz, 1H, C*H*), 4.21 (dddd, *J*=2.4, 5.1, 5.7, 8.4 Hz, 1H, C*H*OH), 4.10 (d, *J*=2.4 Hz, 1H, C*H*), 2.97 (d, *J*=5.1 Hz, 1H, O*H*), 1.00 (s, 9H, CH_3), 0.99 (s, 9H, CH_3), 0.91 (s, 9H, CH_3), 0.91 (s, 9H, CH_3), 0.23 (s, 6H, CH_3), 0.22 (s, 6H, CH_3), 0.17 (s, 6H, CH_3), 0.16 (s, 3H, CH_3), 0.15 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (*C*=O), 168.6 (*C*=O), 150.1 (*C*), 147.6 (*C*), 146.4 (*C*), 128.0 (*C*H), 122.8 (*C*H), 121.4 (*C*H), 120.8 (*C*H), 114.9 (*C*H), 80.5 (*C*H), 75.1 (*C*H), 74.9 (*C*H), 67.8 (*C*H), 66.6 (*C*H_2), 26.02 (*C*H_3), 25.99 (*C*H_3), 25.77 (*C*H_3), 25.72 (*C*H_3), 18.61 (*C*), 18.56 (*C*), 18.21 (*C*), 18.09 (*C*), −3.97 (*C*H_3), −4.01 (*C*H_3), −4.65 (*C*H_3), −4.94 (*C*H_3), −4.96 (*C*H_3). Anal. Calcd for $C_{39}H_{72}O_9Si_4$: C, 58.75; H, 9.10. Found: C, 58.48; H, 9.41.

*4.2.6. Synthesis and characterization of (5R)-****7****.* To a solution of **6** (383 mg, 0.480 mmol) in anhydrous CH_3CN (2.40 mL) was added boron trifluoride ethyl ether complex ($BF_3{\cdot}OEt_2$, 300 mg, 2.11 mmol) at 0 °C. After stirring for 20 min at this temperature, the reaction mixture was quenched by addition of water (0.5 mL) and powders of $NaHCO_3$ (1 g), dried over Na_2SO_4, filtered through cotton followed by successive washings with AcOEt (100 mL), and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 1:3) gave (5*R*)-**7** (81.0 mg, 0.238 mmol, 50%) as pale yellow oil: R_f=0.42 (silica gel, AcOEt); $[\alpha]_D^{25}$ +49.8 (*c* 1.80, MeOH); IR (KBr): ν_{max} 3359 (O–H), 2964 (C–H), 1698 (C=O), 1632 (C=C), 1601 (C=C), 1523 (C=C) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.59 (d, *J*=15.9 Hz, 1H, C*H*=CH), 7.17 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.05 (dd, *J*=2.1, 8.4 Hz, 1H, Ar*H*), 6.87 (d, *J*=8.4 Hz, 1H, Ar*H*), 6.31 (d, *J*=15.9 Hz, 1H, CH=C*H*), 4.64 (dd, *J*=5.4, 6.6 Hz, 1H, C*H*), 4.52 (dd, *J*=4.5, 5.4 Hz, 1H, C*H*), 4.48 (dd, *J*=2.7, 10.8 Hz, 1H, CH_2), 4.38 (d, *J*=4.5 Hz, 1H, C*H*), 4.35 (dd, *J*=2.7, 10.8 Hz, 1H, CH_2), 4.31 (dd, *J*=2.7, 6.6 Hz, 1H, C*H*); ^{13}C NMR (75 MHz, acetone-d_6): δ 175.3 (*C*=O), 167.4 (*C*=O), 148.8 (*C*), 146.3 (*C*H), 146.0 (*C*H), 127.6 (*C*), 122.5 (*C*H), 116.3 (*C*), 115.3 (*C*H), 115.2 (*C*H), 80.1 (*C*H), 74.5 (*C*H), 74.4 (*C*H), 68.9 (*C*H), 66.3 (*C*H_2). Anal. Calcd for $C_{15}H_{16}O_9$: C, 52.94; H, 4.74. Found: C, 53.18; H, 5.07.

4.2.7. Synthesis and characterization of ***1a′*** *and all the related compounds.* To a solution of **1a** (1.77 g, 8.19 mmol) in anhydrous CH_2Cl_2 (8.20 mL) were added pyridine (842 mg, 10.6 mmol) and triflic anhydride (Tf_2O, 2.77 g, 9.83 mmol) at 0 °C. After stirring at this temperature for 10 min, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (100 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude triflate (7.46 g). To a solution of the crude triflate (7.46 g) in DMF (8.20 mL) were added 18-crown-6 (216 mg, 0.819 mmol) and potassium

acetate (AcOK, 965 mg, 9.83 mmol) at 0 °C. After stirring at this temperature for 1 h, the reaction mixture was quenched by addition of water (10 mL), extracted with AcOEt (100 mL), washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue. Purification of the residue by column chromatography on silica gel (eluent: hexane/AcOEt, 6:1) gave acetate (2.09 g, 8.09 mmol, 99% for two steps) as colorless oil: R_f=0.57 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{19}$ +104 (*c* 1.17, $CHCl_3$); IR (NaCl): ν_{max} 2992 (C–H), 2940 (C–H), 1800 (C=O), 1759 (C=O), 1376 (C–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.98 (d, *J*=3.6 Hz, 1H, C*H*), 5.09 (d, *J*=3.6 Hz, 1H, C*H*), 4.95 (d, *J*=0.3 Hz, 1H, C*H*), 4.86 (d, *J*=3.6 Hz, 1H, C*H*), 4.82 (dd, *J*=0.3, 3.6 Hz, 1H, C*H*), 2.16 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9 (*C*=O), 169.6 (*C*=O), 113.0 (*C*H_3), 106.1 (*C*H), 85.2 (*C*H), 82.0 (*C*H), 81.3 (*C*H), 72.5 (*C*H), 26.9 (*C*H_3), 26.4 (*C*H_3), 19.9 (*C*). Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16; H, 5.46. Found: 51.17; H, 5.75.

To a solution of the acetate (4.77 g, 18.5 mmol) in methanol (37.0 mL) was added potassium carbonate (K_2CO_3, 256 mg, 1.85 mmol) at −10 °C. After stirring at this temperature for 2 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL), extracted with AcOEt (150 mL), washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude ester (4.49 g). To a solution of the ester (4.49 g) in 1,2-dichloroethane ($(CH_2Cl)_2$, 18.5 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 4.65 g, 18.5 mmol) at 80 °C. After stirring at this temperature for 6 h, the reaction mixture was cooled to room temperature, quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (150 mL), washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a crude residue (3.74 g). Purification of the residue by recrystallization from toluene gave **1a**′ (2.81 g, 13.0 mmol, 71% for two steps) as a white solid: R_f=0.29 (silica gel, hexane/AcOEt=2:1); mp 134–135 °C; $[\alpha]_D^{26}$ +109 (*c* 1.07, $CHCl_3$); IR (KBr): ν_{max} 3406 (O–H), 2987 (C–H), 2944 (C–H), 2859 (C–H), 1767 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (d, *J*=3.6 Hz, 1H, C*H*), 5.06 (d, *J*=3.0 Hz, 1H, C*H*), 4.84 (d, *J*=3.6 Hz, 1H, C*H*), 4.80 (dd, *J*=0.3, 3.0 Hz, 1H, C*H*), 4.33 (d, *J*=0.3 Hz, 1H, C*H*), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1 (*C*=O), 113.5 (*C*), 106.4 (*C*H), 85.3 (*C*H), 82.6 (*C*H), 82.2 (*C*H), 71.9 (*C*H), 27.1 (*C*H_3), 26.9 (*C*H_3). Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: 49.62; H, 5.33.

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Supplementary data

Details of the transformation of **1a**′ into (5*S*)-**7**, experimental details and characterization data for all the new compounds related to this transformation. Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tet.2012.06.105.

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8. Characterization data for (5*S*)-**7** (5-*epi*-vittarilide-A): R_f=0.14 (silica gel, AcOEt); $[\alpha]_D^{20}$ +45.3 (*c* 0.830, MeOH); IR (KBr): ν_{max} 3393 (O–H), 2961(C–H), 1722 (C=O), 1602 (C=C) cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.59 (d, *J*=15.9 Hz, 1H, CH=CH), 7.16 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.05 (dd, *J*=2.1, 7.8 Hz, 1H, ArH), 6.87 (d, *J*=7.8 Hz, 1H, Ar*H*), 6.30 (d, *J*=15.9 Hz, 1H, CH=C*H*), 4.65 (d, *J*=7.5 Hz, 1H, C*H*), 4.62 (dd, *J*=1.8, 7.5 Hz, 1H, C*H*), 4.54 (t, *J*=7.5 Hz, 1H, C*H*), 4.41 (ddd, *J*=1.8, 6.3, 6.9 Hz, 1H, C*H*OH), 4.30 (dd, *J*=6.9, 10.5 Hz, 1H, CH_2), 4.22 (dd, *J*=6.3, 10.5 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, acetone-d_6): δ 176.0 (*C*=O), 167.6 (*C*=O), 149.1 (*C*), 146.6 (*C*), 146.4 (*C*H), 127.8 (*C*), 122.8 (*C*H), 116.6 (*C*H), 115.58 (*C*H), 115.54 (*C*H), 79.2 (*C*H), 75.4 (*C*H), 73.8 (*C*H), 67.1 (*C*H), 65.6 (*C*H_2). Anal. Calcd for $C_{15}H_{16}O_9$: C, 52.94; H, 4.74. Found: C, 53.29; H, 5.12.
9. High purities of the synthetic samples were secured on the basis of the integrities of the spectral shapes and well-resolved sets of ^1H NMR signals, allowing for complete understanding of all coupling interactions encountered with the molecular systems as well as for precise analyses of the coupling constants rather than those of the natural sample (see Ref. 2).
10. In fact, we observed that the optical rotation value of (5*R*)-**7** fell off seriously after a period of an hour ($[\alpha]_D$ +33.6) probably due to occurrence of undesirable ring-opening reaction with methanol yielding acyclic ester.
11. In our experiments, we found that (5*R*)- and (5*S*)-**7** were unstable and degraded upon long-term exposure to air at ambient temperature, making them very difficult to isolate. Considering this, it cannot be excluded that the optical rotation value reported for the natural sample would be much lower than that of the intrinsic property due to unexpected decomposition of the extract during experimental treatment.