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Expedient Synthesis of Alphitolic Acid and Its Naturally Occurring 2-*O*-Ester Derivatives

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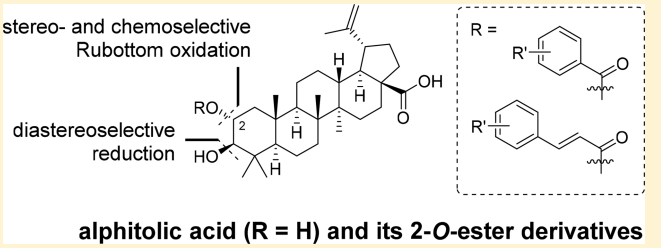
Supporting Information

ABSTRACT: The expedient synthesis of alphitolic acid (**1**) as well as its natural C-3-epimer and 2-*O*-ester derivatives was accomplished in a few steps from the readily commercially available betulin (**9**). A Rubottom oxidation delivered an α-hydroxy group in a stereo- and chemoselective manner. The diastereoselective reduction of the α-hydroxy ketone was key to accessing the 1,2-diol moiety of this class of natural products. Our concise and stereoselective synthetic protocol allowed the gram-scale synthesis of these natural products, which will facilitate future biological evaluations.



Alphitolic acid (**1**, Figure 1) is a pentacyclic triterpenoid with a lupane skeleton. This triterpene has been found in various plant species and was first isolated from *Alphitonia whitei* Braid (Rhamnaceae).[1] Since alphitolic acid displays a broad spectrum of interesting biological effects, including anti-inflammatory,[2] antiparasitic,[3] antimicrobial,[4] and cytotoxic activities,[5] there has been a growing interest in this compound as a lead compound. Recently, a number of its 2-*O*-ester derivatives including **2**−**7** have been isolated by our colleague, the late Prof. S. H. Sung[6] and others.[7] These compounds showed interesting biological activities including antiplasmodial,[8] anti-inflammatory,[7b,9] and cytotoxic activities.[6,7] To facilitate further biological investigation[10] and the evaluation of preliminary structure−activity relationships, we developed an efficient and scalable synthetic route to alphitolic acid and its natural *O*-ester derivatives as well as their structural analogues. In this article, we report our synthetic studies on these triterpenoids.

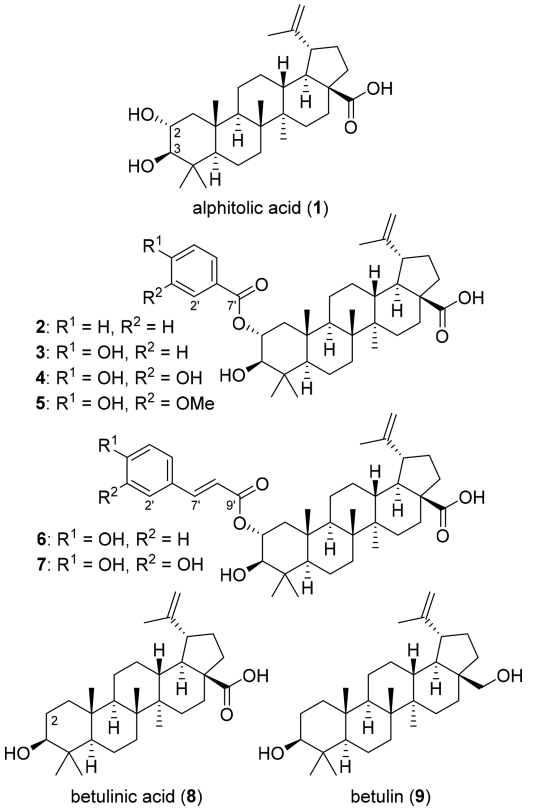


Figure 1. Structures of alphitolic acid (**1**), its 2-*O*-ester natural derivatives **2**−**7**, and congeners **8** and **9**.

RESULTS AND DISCUSSION

Structurally, alphitolic acid (**1**) is a 2-hydroxylated derivative of betulinic acid (**8**), which is a natural triterpenoid generally found in the bark of the white birch tree and several other plants.[4,11] On the one hand, however, betulinic acid (**8**) is isolated in low yield[12] and is thus rather expensive. On the other hand, its reduced congener betulin (**9**) is inexpensive and commercially available in large quantities. Therefore, betulin was considered as a suitable starting material for the synthesis of alphitolic acid (**1**) and its derivatives. In fact, alphitolic acid has been previously synthesized from betulin, but the process was quite lengthy at 13 steps.[13] Since the high number of steps limits the application of this synthetic method to the preparation of alphitolic acid derivatives, we sought to design a more concise and efficient method.

The retrosynthetic plan used is depicted in Scheme 1. It was planned to synthesize alphitolic acid (**1**) and its *O*-ester

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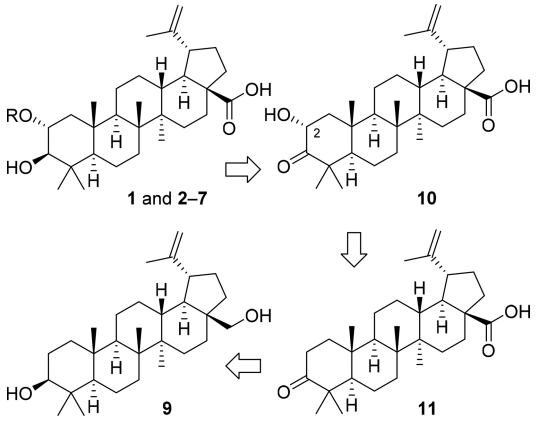
Scheme 1. Retrosynthetic Route toward Alphitolic Acid (1) and its 2-*O*-Ester Derivatives 2−7

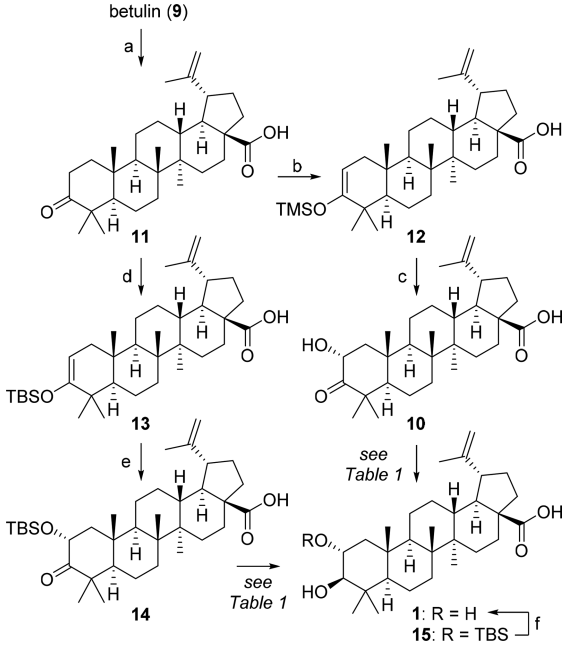


derivatives **2**−**7** from **10** via diastereoselective reduction. Compound **10** was envisioned to be synthesized from the triterpene natural product betulonic acid (**11**) via 2α-hydroxylation. Previously, the introduction of the 2-hydroxy group in structurally related triterpenoids was accomplished by a α-bromination-hydroxylation sequence from the corresponding 3-ketones[14] and an oxidative hydroxylation of 3-ketones or their enol acetate.[15] However, the application of these methods to betulin-type triterpenoids is hindered by the presence of an oxidatively vulnerable isopropylene group.[16] To overcome this problem, it was decided to utilize a Rubottom-type oxidation for the 2α-hydroxylation of **11**. Betulonic acid (**11**) was reported to be readily accessible from betulin (**9**) through oxidation.[17]

The synthesis began with Jones oxidation of betulin (**9**) to give betulonic acid (**11**) in high yield (Scheme 2).[17b] For the formation of electron-rich silyl enol ethers, **11** was treated with 2 equiv of trimethylsilyl trifluoromethanesulfonate at low temperature. A Rubottom oxidation[18,19] of crude silyl enol ether **12** with *m*-chloroperoxybenzoic acid at 0 °C followed by removal of the trimethylsilyl group using oxalic acid yielded α-hydroxyketone **10** in 62% overall yield (three steps). Only the desired α-isomer was formed possibly through epoxidation from the less hindered α-face. In this transformation, an additional step for the protection of the carboxylic acid functional group was not necessary.

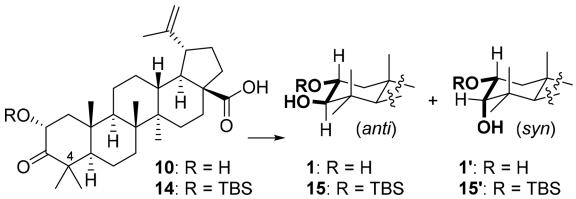
To obtain alphitolic acid (**1**) by conversion of the ketone group of **10** to an equatorial alcohol, compound **10** was reduced using various reducing agents. Under the most reductive conditions examined, regardless of the bulkiness of the hydride donor, the desired equatorial alcohol *anti*-diol **1** was obtained as the major isomer but in only a slight excess (Table 1). For example, the small hydride donor $NaBH_4$ led to a mixture of the diastereomers in only a 2.5:1 ratio (entry 1).[20] It was reasoned that the low diastereoselectivity in the $NaBH_4$ reduction of **10** might result from boron chelation to the α-hydroxy ketone moiety, which hinders the axial approach of $NaBH_4$ to some extent. This assumption was strengthened by the results of the reduction with $Zn(BH_4)_2$, which is well-known to reduce α-hydroxy ketones stereoselectively through a chelation-controlled reduction.[21] The reduction of **10** with $Zn(BH_4)_2$ resulted in a mixture of diastereomers in a ratio (2.6:1) similar to that achieved with $NaBH_4$ (entry 2). The bulky hydride donor $LiAlH(Ot\text{-}Bu)_3$ also provided the equatorial alcohol **1** as the major isomer with similarly low

Scheme 2. Synthesis of 2-Hydroxy Ketones 10 and 14 as Substrates for Diastereoselective Reduction[a]



[a]Reagents and conditions: (a) Jones reagent, acetone, 0 °C, 2 h, 72%; (b) trimethylsilyl trifluoromethanesulfonate, Et_3N, CH_2Cl_2, −78 °C, 1 h; (c) (i) *m*-chloroperoxybenzoic acid, $NaHCO_3$, CH_2Cl_2, 0 °C, 3 h; (ii) oxalic acid, MeOH, room temperature (rt), 10 min, 62% (3 steps); (d) *tert*-butyldimethylsilyl trifluoromethanesulfonate, Et_3N, CH_2Cl_2, −78 °C, 1.5 h, 89%; (e) *m*-chloroperoxybenzoic acid, Na_2HPO_4, CH_2Cl_2, rt, 5 h, 83%; (f) tetrabutylammonium fluoride, THF, reflux, 3 h, 83%.

Table 1. Diastereoselective Reduction of α-Hydroxy Ketones 10 and 14



entry	SM[a]	reducing agent	solvent	yield[b]	dr[c] (*anti*/*syn*)
1	**10**	$NaBH_4$	THF/EtOH	88	2.5:1
2	**10**	$Zn(BH_4)_2$[d]	THF/EtOH	93	2.6:1
3	**10**	$LiAlH(Ot\text{-}Bu)_3$	THF	71	2.3:1
4	**10**	$NaBH(OAc)_3$	THF/AcOH	76	1:10
5	**14**	$NaBH_4$	THF/EtOH	73	10:1
6	**14**	$LiAlH(Ot\text{-}Bu)_3$	THF	84	10:1

[a]Starting material. [b]Combined yield of the *anti* and *syn* products. [c]The diastereomeric ratio was determined by ^1H NMR analysis. [d]Zinc borohydride was freshly prepared from $ZnCl_2$ and $NaBH_4$ in ether.

selectivity, even though bulky hydride donors generally prefer equatorial attack for steric reasons (entry 3). The low selectivity was attributed to the C-4-*gem*-dimethyl group adjacent to the ketone, which adds additional steric bulk to the upper face of the ring.

Surprisingly, when the reduction was performed with $NaBH(OAc)_3$ in the presence of AcOH (entry 4), a switch in the diastereoselectivity was observed, and *syn*-diol **1′** was generated as the major isomer with high selectivity (1:10). *Syn*-

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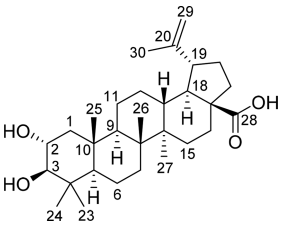
diol **1′**, C-3-*epi*-alphitolic acid, is also a natural triterpenoid and has been synthesized once by Sun and co-workers from betulin (**9**) in a nine-step route.[13] In general, $NaBH(OAc)_3$-mediated reductions of cyclohexanones possessing axial α-hydroxy groups provide *anti*-diols via hydroxy-directing effects.[22,23] However, there are few reports on the $NaBH(OAc)_3$ reductions of ketones with an equatorial α-hydroxy group.[24] Although the exact mechanism in the case of equatorial α-hydroxy cyclohexanones remains to be elucidated, it appears that the equatorial 2-hydroxy group first reacted with $NaBH(OAc)_3$ and delivered the hydride equatorially in an intramolecular manner to give *syn*-diol **1′**.

It was envisioned that the protection of the 2-hydroxy group would enable the diastereoselective reduction of the ketone group to equatorial alcohol by eliminating the chelation effect and/or increasing the torsional strain that develops during the formation of the axial alcohol. Instead of protecting the 2-hydroxy group in **10** with a bulky silyl group, the 2-hydroxy-protected ketone **14** was prepared directly from **11** in two steps (Scheme 1). Treatment of **11** with *tert*-butyldimethylsilyl trifluoromethanesulfonate led to the formation of silyl enol ether **13** after basic workup. A Rubottom oxidation with *m*-CPBA gave **14** in good overall yield. With a small hydride donor $NaBH_4$, ketone **14** furnished predominantly the equatorial alcohol **15** via an axial attack (10:1, Table 1, entry 5). Bulky $LiAlH(Ot\text{-}Bu)_3$ also provided **15** with the same level of diastereoselectivity in higher yield (entry 6). TBS deprotection with TBAF afforded alphitolic acid (**1**) in good yield. The ^1H and ^{13}C NMR spectra of synthetic **1** were in good agreement with those of natural **1** (Table 2).[6]

After the development of a concise and diastereoselective synthetic pathway to alphitolic acid (**1**) and its C-3-epimer **1′**, the route was extended to furnish natural 2-*O*-ester derivatives **2**–**7**. Hydroxy ketone **10** was an excellent precursor for preparing **2**–**7**. Most natural 2-*O*-ester alphitolic acid derivatives possess one or two phenolic hydroxy groups in their ester moieties. These phenolic hydroxy groups needed to be protected for successful esterification with **10**. The phenol groups of commercial acids **16a**–**e** were protected with a TBS group to give **17a**–**e**, and the acid groups in **17a**–**e** were activated as the *N*-succinimidyl esters to give **18a**–**e** (Scheme 3). Chemoselective coupling of **10** with **18a**–**e** in the presence of LiHMDS at low temperature yielded **19a**–**e** (Scheme 4). The diastereoselective reduction with $LiAlH(Ot\text{-}Bu)_3$ followed by silyl deprotection afforded desired 2-*O*-ester derivatives **3**–**7** with high diastereoselectivity (10:1). For the synthesis of natural 2-*O*-benzoate alphitolic acid (**2**), **10** was reacted with benzoic anhydride in the presence of 4-(dimethylamino)-pyridine to give benzoate **20**. The subsequent reduction of **20** with $LiAlH(t\text{-}BuO)_3$ afforded desired natural product **2** with high diastereoselectivity (10:1). The spectral data of the obtained natural derivatives of alphitolic acid were all in good agreement with those of the natural products,[6,7] and this is the first synthesis of natural 2-*O*-ester derivatives **2**–**7**.

In conclusion, a concise and stereoselective synthesis of alphitolic acid (**1**) and its natural 2-*O*-ester derivatives **2**–**7** was accomplished in five–seven steps starting from the commercially available and inexpensive betulin (**9**). In addition, natural C-3-*epi*-alphitolic acid (**1′**) was synthesized stereoselectively starting from the same material in five steps. A key step in the synthesis was the Rubottom oxidation of a silyl enol ether in the presence of an oxidizable isopropylene group, which allowed facile access to 2α-hydroxy betulonic acid.

Table 2. NMR Spectroscopic Data of Natural[a] and Synthetic[b] Alphitolic Acid (1) in Pyridine-d_5



	δ_H, mult (J in Hz)		δ_C	
position	natural	synthetic	natural	synthetic
1a	2.34, dd (12.5, 4.5)	2.29, dd (12.4, 4.4)	48.6	48.2
1b	1.29, m	1.35, m		
2	4.14, m	4.08, td (10.3, 4.0)	69.2	68.8
3	3.42, d (9.4)	3.38, d (9.2)	84.1	83.8
4			40.3	39.9
5	1.01, m	0.96, m	56.4	56
6a	1.56, m	1.54, m	19.2	18.8
6b	1.43, m	1.46, m		
7a	1.47, m	1.46, m	35.1	34.7
7b	1.39, m	1.35, m		
8			41.5	41.1
9	1.50, m	1.46, m	50.1	50.9
10			37.9	37.6
11a	1.52, m	1.54, m	21.7	21.3
11b	1.22, m	1.15, m		
12a	1.95, m	1.85, m	26.4	26
12b	1.18, m	1.15, m		
13	2.74, dt (12.1, 3.4)	2.70, td (11.6, 3.2)	39	38.7
14			43.2	42.8
15a	1.88, m	1.85, m	30.6	30.2
15b	1.25, m	1.15, m		
16a	2.65, m	2.60, dt (12.4, 2.8)	33.2	32.8
16b	1.56, m	1.54, m		
17			56.9	56.6
18	1.75, dd (11.3, 11.3)	1.72, dd (11.3, 11.3)	50.1	49.7
19	3.55, dt (4.8, 11.2)	3.50, td (10.3, 5.3)	48.6	47.7
20			151.6	151.2
21a	2.24, m	2.20, m	31.5	31.1
21b	1.54, m	1.46, m		
22a	2.27, m	2.20, m	38.9	38.5
22b	1.59, m	1.54, m		
23	1.28, s	1.23, s	29.6	29.2
24	1.08, s	1.033, s	17.8	17.4
25	0.92, s	0.88, s	18	17.7
26	1.06, s	1.026, s[c]	16.8	16.4
27	1.06, s	1.020, s[c]	15.2	14.9
28			179.2	178.8
29a	4.95, s	4.91, d (2.3)	110.4	110
29b	4.79, s	4.75, m		
30	1.80, s	1.76, s	19.8	19.4

[a]Measured at 600 MHz (^1H NMR) and 150 MHz (^{13}C NMR). [b]Measured at 400 MHz (^1H NMR) and 125 MHz (^{13}C NMR). [c]Interchangeable assignments.

Substrate-controlled diastereoselective reduction provided a viable synthetic route to both C-3-epimers of alphitolic acid. This concise and efficient synthesis allowed the gram-scale synthesis of alphitolic acid (**1**), its natural C-3-epimer (**1′**), and its 2-*O*-ester derivatives **2**–**7** for further evaluation in various biological tests, including in vivo assays.

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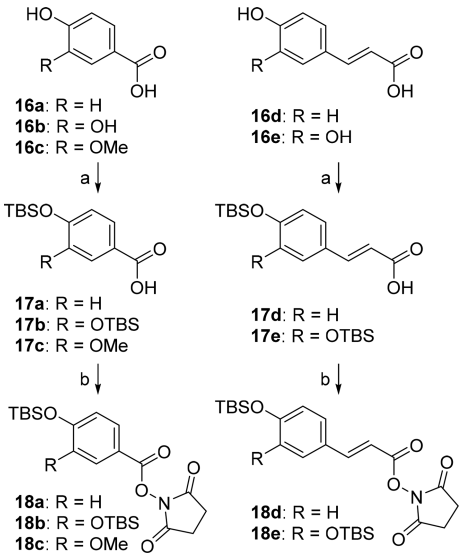
Scheme 3. Preparation of *N*-Succinimidyl Esters 18a−e[a]



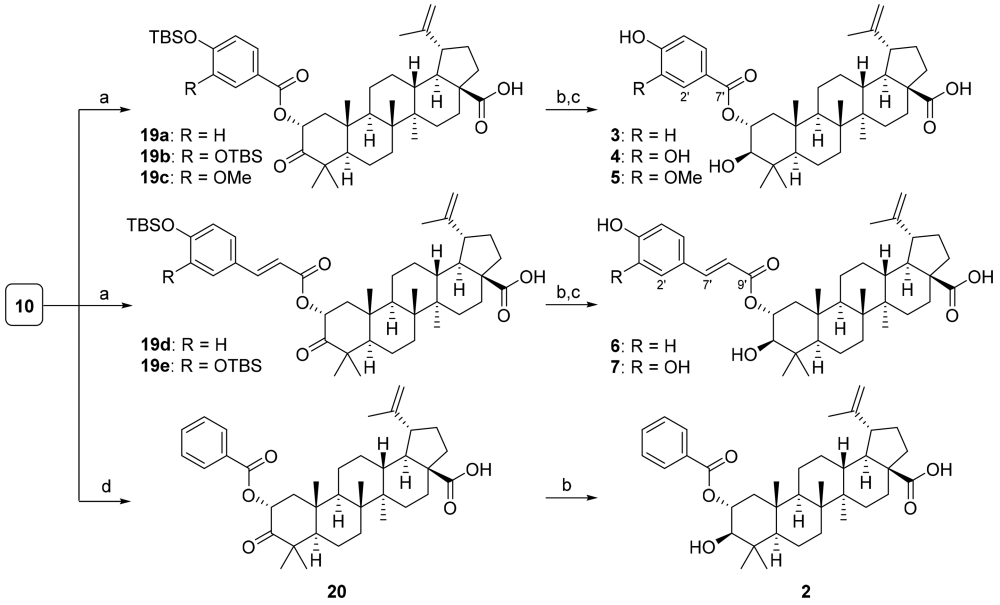
[a]Reagents and conditions: (a) *tert*-butyldimethylsilyl chloride, imidazole, dimethylformamide (DMF), rt, 0.5 h, 53−98%; (b) *N*-hydroxysuccinimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, CH_2Cl_2, rt, 16 h, 36−56%.

EXPERIMENTAL SECTION

General Experimental Procedures. All the chemicals used herein were of reagent grade and were used as received. Betulin (**9**) was purchased from Jilin Tely Imp. & Exp.Co., Ltd. (Jilin). The reactions were monitored by thin-layer chromatography (TLC) performed on silica gel 60 F_{254} TLC plates. The synthesized products were purified by flash column chromatography on silica gel 60 (40−63 μm, 230−400 mesh, Merck). Melting points were measured on a Büchi B-545 apparatus (Büchi Labortechnik AG). Optical rotations were measured on a JASCO P-2000 polarimeter (Hachioji) using a 10 cm cell, and IR spectra were acquired using an Agilent 5500a FTIR (Agilent). NMR spectra were obtained on a JNM-ECZ400S/L1 (JEOL), a Bruker AVANCE 500 (Bruker), a JEOL JNM-ECA600 (JEOL), or an 800-MHz Bruker Avance III HD spectrometer with a 5 mm triple resonance inverse (TCI) CryoProbe (Bruker BioSpin). High-resolution fast-atom bombardment mass spectrometry (HRFABMS) spectra were obtained on a JEOL JMS-700 spectrometer (JEOL).

*2α-Hydroxybetulonic Acid (**10**).* To a solution of betulonic acid (**11**, 1.0 equiv, 25.0 g, 55.0 mmol) in CH_2Cl_2 (500 mL) were added triethylamine (5.0 equiv, 38.3 mL, 275 mmol) and trimethylsilyl trifluoromethanesulfonate (2.0 equiv, 19.9 mL, 110 mmol) at −78 °C. The reaction mixture was stirred at the same temperature. After 2.5 h, the mixture was warmed to 0 °C, and water was added. The mixture was washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude silyl enol ether **12**. The crude product was dissolved in CH_2Cl_2 (500 mL), and the solution was cooled to 0 °C. Solid $NaHCO_3$ (10 equiv, 46.2 g, 550 mmol) was added, and then *m*-chloroperbenzoic acid (≤77%, 1.6 equiv, 19.7 g, 88.0 mmol) dissolved in CH_2Cl_2 (120 mL) was added in three portions at 0 °C. After 2 h, the reaction was quenched with 10% aqueous Na_2SO_3 solution (100 mL) at 0 °C, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was dissolved in MeOH (180 mL), and oxalic acid (0.4 equiv, 2.0 g, 22.0 mmol) was added. This solution was stirred for 15 min at room temperature, and then water was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc−AcOH, 82:17:1) to give 2α-hydroxybetulonic acid (**10**, 16.1 g, 34.1 mmol, 62% for three steps) as a white solid: mp 173 °C; $[\alpha]_D^{20}$ + 5.7 (*c* 0.50, MeOH); IR (neat) υ_{max} 2944, 1701, 1457, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.73 (1H, d, *J* = 1.8 Hz), 4.60 (1H, s), 4.51 (1H, dd, *J* = 12.6, 6.6 Hz), 2.98 (1H, td, *J* = 10.6, 4.4 Hz), 2.45 (1H, dd, *J* = 12.6, 6.6 Hz), 2.27 (1H, m), 2.20 (1H, m), 1.97 (2H, m), 1.71 (1H, d, *J* = 15.6 Hz), 1.66 (3H, s), 1.44 (12H, m), 1.18 (1H, m), 1.15 (3H, s), 1.12 (3H, s), 1.08 (1H, m), 1.07 (3H, s), 1.02 (2H, m), 0.97 (3H, s), 0.93 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.7, 181.5, 150.1, 109.9, 69.4, 57.9, 56.3, 50.1, 49.2, 47.7, 46.9, 42.6, 40.8, 38.3, 38.0, 37.0, 34.1, 32.1, 30.5, 29.6, 25.2, 24.6, 21.3, 21.1, 19.3,

Scheme 4. Synthesis of 2-*O*-Ester Derivatives of Alphitolic Acid 2−7[a]



[a]Reagents and conditions: (a) lithium bis(trimethylsilyl)amide, **18a−e**, THF, −40 °C, 24 h, 63−76%; (b) $LiAlH(Ot\text{-}Bu)_3$, THF, 0 °C, 3 h, 50−79%; (c) tetrabutylammonium fluoride trihydrate, acetic acid, THF, 0 °C, 10 min, 70−100%; (d) benzoic anhydride, 4-(dimethylamino)pyridine, pyridine, rt, 2 h, 53%.

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19.1, 16.7, 16.2, 14.6; HRFABMS m/z 471.3478 $[M + H]^+$ (calcd for $C_{30}H_{47}O_4$, 471.3474).

General Procedure of the Diastereoselective Reduction of 10. To a solution of compound **10** (1 equiv) in solvent (0.1 M) was added reducing agent (2 equiv) at 0 °C. The reaction was allowed to stir at 0 °C for 1 h. The reaction mixture was quenched with 1 N HCl, poured into water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH–AcOH, 94:5:1) to give alphitolic acid (**1**) and C-3-*epi*-alphitolic acid (**1′**).

Alphitolic Acid (1). A white solid: decomposed and melted at 292 °C; $[\alpha]_D^{20}$ + 29.0 (*c* 0.10, MeOH); IR (neat) υ_{max} 2942, 2869, 1723, 1687, 1048 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 4.91 (1H, d, *J* = 2.3 Hz), 4.75 (1H, m), 4.08 (1H, td, *J* = 10.3, 4.0 Hz), 3.50 (1H, td, *J* = 10.3, 5.3 Hz), 3.38 (1H, d, *J* = 9.2 Hz), 2.70 (1H, td, *J* = 11.6, 3.2 Hz), 2.60 (1H, dt, *J* = 12.4, 2.8 Hz), 2.29 (1H, dd, *J* = 12.4, 4.4 Hz), 2.20 (2H, m), 1.85 (2H, m), 1.76 (3H, s), 1.72 (1H, dd, *J* = 11.3, 11.3 Hz), 1.54 (4H, m), 1.46 (4H, m), 1.35 (2H, m), 1.23 (3H, s), 1.15 (3H, m), 1.03 (3H, s), 1.026 (3H, s), 1.020 (3H, s), 0.96 (1H, m), 0.88 (3H, s); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 178.8, 151.2, 110.0, 83.7, 68.8, 56.6, 56.0, 50.9, 49.7, 48.2, 47.7, 42.8, 41.1, 39.9, 38.7, 38.5, 37.6, 34.7, 32.8, 31.2, 30.2, 29.2, 26.0, 21.3, 19.4, 18.8, 17.6, 17.4, 16.4, 14.9; HRFABMS m/z 473.3642 $[M + H]^+$ (calcd for $C_{30}H_{49}O_4$, 473.3631).

C-3-epi-Alphitolic Acid (1′). A white solid: decomposed and melted at 280 °C; $[\alpha]_D^{20}$ − 3.1 (*c* 0.10, MeOH); IR (neat) υ_{max} 2941, 2871, 1725, 1696, 1274 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 4.90 (1H, d, *J* = 2.3 Hz), 4.73 (1H, s), 4.28 (1H, dt, *J* = 11.5, 3.5 Hz), 3.74 (1H, d, *J* = 2.4 Hz), 3.49 (1H, td, *J* = 11.8, 5.1 Hz), 2.67 (1H, td, *J* = 11.9, 3.1 Hz), 2.58 (1H, app d, *J* = 12.8 Hz), 2.19 (2H, m), 1.96 (1H, dd, *J* = 11.9, 4.1 Hz), 1.84 (2H, m), 1.74 (3H, s), 1.68 (2H, td, *J* = 11.5, 4.0 Hz), 1.49 (8H, m), 1.33 (2H, m), 1.23 (3H, s), 1.13 (3H, m), 1.02 (3H, s), 0.91 (3H, s), 0.85 (6H, s); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 178.8, 151.3, 109.9, 79.4, 66.3, 56.6, 50.8, 49.7, 48.7, 47.8, 43.2, 42.9, 41.3, 38.9, 38.8, 38.5, 37.5, 34.7, 32.8, 31.2, 30.2, 29.4, 26.0, 22.1, 21.2, 19.4, 18.4, 17.4, 16.4, 14.8; HRFABMS m/z 473.3628 $[M + H]^+$ (calcd for $C_{30}H_{49}O_4$, 473.3631).

Silyl Enol Ether 13. To a solution of betulonic acid (**11**, 1.0 equiv, 5.0 g, 11.0 mmol) in CH_2Cl_2 (110 mL) were added *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 equiv, 12.6 mL, 55.0 mmol) and triethylamine (10 equiv, 15.3 mL, 110 mmol) at −78 °C. After 1.5 h, 1 N NaOH (70 mL) was added, and the reaction mixture was allowed to stir at room temperature for 12 h. The resulting solution was quenched with 3 N HCl, diluted with diethyl ether, and washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc–AcOH, 93:6:1) to give compound **13** (5.6 g, 9.8 mmol, 89%) as a white solid: decomposed and melted at 245 °C; $[\alpha]_D^{20}$ + 38.7 (*c* 0.10, MeOH); IR (neat) υ_{max} 2924, 2855, 1685, 833, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.73 (1H, d, *J* = 1.4 Hz), 4.59 (1H, s), 4.50 (1H, d, *J* = 5.0 Hz), 3.01 (1H, td, *J* = 10.7, 4.6 Hz), 2.26 (1H, app d, *J* = 12.8 Hz), 2.17 (1H, td, *J* = 12.0, 3.2 Hz), 1.96 (3H, m), 1.68 (3H, s), 1.35 (15H, m), 1.06 (2H, m), 1.00 (3H, s), 0.96 (3H, s), 0.94 (3H, s), 0.91 (10H, s), 0.86 (3H, s), 0.84 (3H, s), 0.13 (3H, s), 0.09 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.5, 155.9, 150.5, 109.6, 98.5, 56.5, 53.0, 49.3, 49.1, 47.0, 42.4, 40.5, 40.3, 38.7, 38.2, 37.0, 36.2, 33.5, 32.1, 30.6, 29.8, 28.2, 25.9, 25.6, 21.3, 19.7, 19.5, 19.4, 18.3, 16.1, 15.8, 14.7, −3.9, −4.8; HRFABMS m/z 568.4317 $[M]^+$ (calcd for $C_{33}H_{60}O_3Si$, 568.4312).

2α-Silyloxybetulonic Acid 14. To a solution of compound **13** (1 equiv, 4.0 g, 7.0 mmol) in CH_2Cl_2 (70 mL) was added sodium phosphate dibasic (20 equiv, 20.0 g, 141 mmol) at 0 °C. The reaction mixture was stirred for 0.5 h, and *m*-chloroperbenzoic acid (≤77%, 1.1 equiv, 1.7 g, 7.7 mmol) dissolved in CH_2Cl_2 (30 mL) was added in three portions. The reaction was allowed to stir at room temperature for 5 h. The solution was washed with water, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc–AcOH, 87:12:1) to give compound **14** (3.3 g, 5.08 mmol, 83%) as a white solid: decomposed and melted at 218 °C; $[\alpha]_D^{20}$ + 5.5 (*c* 0.10, MeOH); IR (neat) υ_{max} 2927, 1721, 1694, 837, 779 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.72 (1H, d, *J* = 1.4 Hz), 4.59 (1H, s), 4.53 (1H, dd, *J* = 12.0, 6.4 Hz), 2.99 (1H, td, *J* = 10.9, 4.4 Hz), 2.21 (3H, m), 1.97 (2H, m), 1.73 (1H, d, *J* = 13.3 Hz), 1.67 (3H, s), 1.58 (1H, dd, *J* = 11.5, 11.5 Hz), 1.38 (14H, m), 1.16 (1H, app d, *J* = 13.3 Hz), 1.11 (3H, s), 1.08 (3H, s), 1.02 (3H, s), 0.96 (3H, s), 0.91 (3H, s), 0.88 (9H, s), 0.10 (3H, s), −0.01 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.2, 181.7, 150.2, 109.9, 71.3, 56.7, 56.3, 50.4, 50.2, 49.2, 48.3, 46.9, 42.5, 40.8, 38.4, 38.0, 37.1, 34.1, 32.1, 30.5, 29.6, 25.8, 25.6, 25.1, 21.6, 21.1, 19.2, 19.1, 18.5, 16.8, 16.1, 14.6, −4.6, −5.6; HRFABMS m/z 585.4343 $[M + H]^+$ (calcd for $C_{36}H_{61}O_4Si$, 585.4339).

General Procedure of the Diastereoselective Reduction of 14. To a solution of compound **14** (1 equiv) in solvent (0.1 M) was added reducing agent (5 equiv) at 0 °C. The reaction was allowed to stir at room temperature for 24–36 h. The reaction mixture was quenched with 1 N HCl, poured into water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane–EtOAc–AcOH, 90:9:1) to give compound **15** and compound **15′**.

2-O-tert-Butyldimethylsilylalphitolic Acid (15). A white solid: decomposed and melted at 269 °C; $[\alpha]_D^{20}$ − 15.0 (*c* 0.10, MeOH); IR (neat) υ_{max} 2947, 1696, 1456, 1085, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.72 (1H, d, *J* = 1.8 Hz), 4.60 (1H, s), 3.66 (1H, td, *J* = 10.3, 4.0 Hz), 2.98 (2H, m), 2.26 (1H, app d, *J* = 12.8 Hz), 2.17 (1H, td, *J* = 12.1, 3.0 Hz), 1.97 (2H, m), 1.85 (1H, dd, *J* = 12.6, 4.8 Hz), 1.70 (1H, m), 1.67 (3H, s), 1.57 (1H, dd, *J* = 11.4, 11.4 Hz), 1.27 (11H, m), 1.18 (1H, m), 1.00 (3H, s), 0.95 (3H, s), 0.90 (3H, s), 0.87 (9H, s), 0.85 (3H, s), 0.81 (2H, m), 0.77 (3H, s), 0.72 (1H, m), 0.08 (3H, s), −0.01 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.9, 150.4, 109.7, 83.1, 71.0, 56.4 55.4, 50.3, 49.2, 47.3, 46.9, 42.5, 40.8, 38.75, 38.66, 38.3, 37.1, 34.2, 32.1, 30.6, 29.6, 28.6, 25.9, 25.4, 20.9, 19.3, 18.1, 18.0, 17.3, 16.6, 16.1, 14.6, −3.9, −4.6; HRFABMS m/z 587.4488 $[M + H]^+$ (calcd for $C_{36}H_{63}O_4Si$, 587.4496).

2-O-tert-Butyldimethylsilyl-C-3-epi-alphitolic Acid (15′). A white solid: decomposed and melted at 255 °C; $[\alpha]_D^{20}$ + 204.7 (*c* 0.10, MeOH); IR (neat) υ_{max} 2947, 1696, 1456, 1085, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.72 (1H, d, *J* = 1.8 Hz), 4.58 (1H, s), 3.97 (1H, dt, *J* = 10.7, 3.8 Hz), 3.25 (1H, d, *J* = 2.8 Hz), 2.98 (1H, td, *J* = 10.8, 4.6 Hz), 2.24 (1H, app d, *J* = 11.9 Hz), 2.17 (1H, td, *J* = 12.2, 3.3 Hz), 1.95 (2H, m), 1.71 (1H, m), 1.66 (3H, s), 1.58 (1H, dd, *J* = 11.3, 11.3 Hz), 1.31 (15H, m), 0.99 (3H, s), 0.94 (3H, s), 0.90 (3H, s), 0.86 (9H, s), 0.82 (3H, s), 0.79 (3H, s), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 179.8, 150.4, 109.7, 79.1, 68.0, 56.3, 50.1, 49.2, 47.8, 46.9, 42.5, 42.2, 40.9, 38.4, 38.3, 37.8, 37.0, 34.0, 32.1, 30.5, 29.6, 28.4, 25.8, 25.4, 21.8, 20.8, 19.3, 18.0, 17.9, 17.2, 16.0, 14.7, −4.5, −4.8; HRFABMS m/z 587.4488 $[M + H]^+$ (calcd for $C_{36}H_{63}O_4Si$, 587.4496).

Experimental Procedure for the TBS-Deprotection of 15. To a solution of compound **15** (1 equiv, 2.0 g, 3.4 mmol) in tetrahydrofuran (THF) was added 1 M tetrabutylammonium fluoride in THF (2.5 equiv, 8.5 mL, 8.5 mmol) at room temperature. The reaction was refluxed for 3 h, cooled to room temperature, quenched with saturated aqueous NH_4Cl, and poured into water. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH–AcOH, 94:5:1) to give alphitolic acid (**1**, 1.67 g, 2.9 mmol, 83%).

Experimental Procedure for the Esterification of 10 with 18. To a solution of compound **10** (1 equiv, 6.4 mmol) in anhydrous THF (32 mL) was added 1 M lithium bis(trimethylsilyl)amide in THF (2 equiv, 12.8 mmol) at −40 °C. After 10 min, a solution of **18** (1.1 equiv, 7.0 mmol) in anhydrous THF (20 mL) was added to the reaction mixture. The reaction was stirred for 20 h at −40 °C, quenched with aqueous NH_4Cl, poured into water, and extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried

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over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc−AcOH, 90:9:1) to give compound **19**.

*2α-Hydroxy-O-p-(tert-butyldimethylsilyloxy)benzoylbetulonic Acid (**19a**).* A white solid (63%): mp 188 °C; $[\alpha]_D^{20}$ + 17.2 (*c* 0.50, MeOH); IR (neat) υ_{max} 2946, 2860, 1716, 1266, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.94 (2H, m), 6.82 (2H, m), 5.80 (1H, dd, *J* = 13.2, 6.4 Hz), 4.72 (1H, s), 4.59 (1H, s), 2.99 (1H, td, *J* = 10.7, 4.7 Hz), 2.39 (1H, m), 2.27 (1H, m), 2.21 (1H, td, *J* = 12.3, 3.2 Hz), 1.98 (2H, m), 1.73 (1H, app d, *J* = 13.3 Hz), 1.67 (3H, s), 1.49 (14H, m), 1.23 (3H, s), 1.19 (1H, m), 1.16 (3H, s), 1.11 (3H, s), 1.06 (1H, m), 1.00 (3H, s), 0.96 (12H, s), 0.20 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.3, 181.3, 165.6, 160.2, 150.2, 131.8, 122.9, 119.8, 109.9, 72.1, 57.3, 56.3, 50.3, 49.2, 48.8, 46.9, 46.2, 42.6, 40.9, 38.31, 38.29, 37.0, 34.1, 32.1, 30.5, 29.6, 25.6, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 18.2, 16.6, 16.2, 14.6, −4.4; HRFABMS *m/z* 705.4549 $[M + H]^+$ (calcd for $C_{43}H_{65}O_6Si$, 705.4550).

*2α-Hydroxy-O-m,p-bis(tert-butyldimethylsilyloxy)-benzoylbetulonic Acid (**19b**).* A white solid (64%): mp 164 °C;$[\alpha]_D^{20}$ + 10.0 (*c* 0.50, MeOH); IR (neat) υ_{max} 2950, 2860, 1714, 1510, 1301, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54 (2H, m), 6.81 (1H, d, *J* = 8.7 Hz), 5.78 (1H, dd, *J* = 13.0, 6.2 Hz), 4.72 (1H, s), 4.59 (1H, s), 2.99 (1H, td, *J* = 10.7, 4.6 Hz), 2.38 (1H, dd, *J* = 12.4, 6.4 Hz), 2.28 (1H, app d, *J* = 12.8 Hz), 2.20 (1H, td, *J* = 12.3, 3.4 Hz), 1.98 (2H, m), 1.73 (1H, m), 1.67 (3H, s), 1.47 (14H, m), 1.23(4H, s), 1.18 (2H, m), 1.15 (3H, s), 1.10 (3H, s), 0.965 (11H, s), 0.960 (10H, s), 0.20 (6H, s), 0.19 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.3, 181.9, 165.6, 151.8, 150.2, 146.7, 123.8, 123.0, 122.5, 120.5, 109.9, 72.1, 57.3, 56.3, 50.3, 49.2, 48.8, 46.9, 46.1, 42.6, 40.9, 38.3, 37.0, 34.0, 32.1, 30.5, 29.6, 25.91, 25.86, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 18.5, 18.4, 16.6, 16.2, 14.6, −4.08, −4.11, −4.13; HRFABMS *m/z* 835.5356 $[M + H]^+$ (calcd for $C_{49}H_{79}O_7Si_2$, 835.5364).

*2α-Hydroxy-O-p-tert-butyldimethylsilyloxy-m-methoxy-benzoylbetulonic Acid (**19c**).* A white solid (69%): mp 163 °C;$[\alpha]_D^{20}$ + 10.9 (*c* 0.5, MeOH); IR (neat) υ_{max} 2949, 2868, 1714, 1288, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (1H, dd, *J* = 8.3, 1.7 Hz), 7.53 (1H, d, *J* = 1.8 Hz), 6.83 (1H, d, *J* = 8.2 Hz), 5.79 (1H, dd, *J* = 13.2, 6.4 Hz), 4.72 (1H, s), 4.59 (1H, s), 3.82 (3H, s), 2.99 (1H, td, *J* = 10.6, 4.7 Hz), 2.40 (1H, dd, *J* = 12.4, 6.0 Hz), 2.28 (1H, m), 2.21 (1H, td, *J* = 12.2, 3.0 Hz), 1.99 (2H, m), 1.73 (1H, m), 1.66 (3H, s), 1.47 (14H, m), 1.23 (3H, s), 1.20 (1H, m), 1.16 (3H, s), 1.12 (3H, s), 1.06 (1H, m), 1.01 (3H, s), 0.97 (9H, s), 0.96 (3H, s), 0.15 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.3, 181.8, 165.7, 150.6, 150.2, 149.8, 123.6, 123.2, 120.5, 113.1, 109.9, 72.2, 57.3, 56.3, 55.4, 50.3, 49.2, 48.8, 46.9, 46.2, 42.6, 40.9, 38.3, 37.0, 34.1, 32.1, 30.5, 29.6, 25.6, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 18.5, 16.6, 16.2, 14.6, −4.6; HRFABMS *m/z* 735.4660 $[M + H]^+$ (calcd for $C_{44}H_{67}O_7Si$, 735.4656).

*2α-Hydroxy-O-p-tert-butyldimethylsilyloxycinnamoylbetulonic Acid (**19d**).* A white solid (70%): mp 191 °C;$[\alpha]_D^{20}$ + 22.0 (*c* 0.10, MeOH); IR (neat) υ_{max} 2944, 1702, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (1H, d, *J* = 15.9 Hz), 7.40 (2H, d, *J* = 8.5 Hz), 6.81 (2H, d, *J* = 8.5 Hz), 6.35 (1H, d, *J* = 15.9 Hz), 5.72 (1H, dd, *J* = 13.1, 6.1 Hz), 4.72 (1H, s), 4.59 (1H, s), 2.99 (1H, td, *J* = 10.5, 4.6 Hz), 2.34 (1H, dd, *J* = 12.3, 6.1 Hz), 2.28 (1H, app d, *J* = 12.8 Hz), 2.21 (1H, app t, *J* = 10.6 Hz), 1.96 (2H, m), 1.72 (2H, m), 1.67 (3H, s), 1.58 (3H, m), 1.48 (3H, m), 1.41 (7H, m), 1.22 (3H, s), 1.17 (1H, m), 1.14 (3H, s), 1.10 (3H, s), 1.05 (1H, m), 0.99 (3H, s), 0.963 (9H, s), 0.956 (3H, s), 0.20 (6H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.5, 182.0, 166.4, 157.9, 150.2, 145.2, 129.8, 127.7, 120.4, 115.2, 109.9, 71.8, 57.3, 56.3, 50.3, 49.2, 48.7, 46.9, 46.2, 42.6, 40.8, 38.33, 38.27, 37.0, 34.0, 32.1, 30.5, 29.6, 25.6, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 18.2, 16.6, 16.2, 14.6, −4.4; HRFABMS *m/z* 730.4637 $[M]^+$ (calcd for $C_{45}H_{66}O_6Si$, 730.4629).

*2α-Hydroxy-O-m,p-bis(tert-butyldimethylsilyloxy)-cinnamoylbetulonic Acid (**19e**).* A white solid (76%): mp 163 °C; $[\alpha]_D^{20}$ + 10.9 (*c* 0.50, MeOH); IR (neat) υ_{max} 2952, 2859, 1714, 1509, 1290, 1255, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (1H, d, *J* = 16.0 Hz), 6.98 (2H, dd, *J* = 6.6, 2.1 Hz), 6.79 (2H, dd, *J* = 6.6, 2.5 Hz), 6.28 (1H, d, *J* = 15.6 Hz), 5.72 (1H, dd, *J* = 13.2, 6.4 Hz), 4.72 (1H, s), 4.59 (1H, s), 2.99 (1H, td, *J* = 10.7, 4.9 Hz), 2.35 (1H, dd, *J* = 12.2, 5.8 Hz) 2.27 (1H, app d, *J* = 12.8 Hz), 2.20 (1H, td, *J* = 12.2, 3.2 Hz), 1.97 (2H, m), 1.77 (1H, m), 1.67 (3H, s), 1.47 (13H, m), 1.22 (3H, s), 1.18 (2H, m), 1.14 (3H, s), 1.10 (3H, s), 0.99 (3H, s), 0.97 (9H, s), 0.96 (9H, s), 0.95 (3H, s), 0.20 (6H, s), 0.19 (6H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 209.5, 181.0, 166.4, 150.2, 149.5, 147.1, 145.4, 128.0, 122.4, 121.1, 120.4, 115.1, 109.9, 71.8, 57.3, 56.2, 50.3, 49.2, 48.7, 46.9, 46.2, 42.6, 40.8, 38.31, 38.27, 37.0, 34.1, 32.1, 30.5, 29.6, 25.90, 25.86, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 18.5, 18.4, 16.6, 16.2, 14.6, −4.07, −4.08, −4.10; HRFABMS *m/z* 860.5457 $[M]^+$ (calcd for $C_{51}H_{80}O_7Si_2$, 860.5443).

Synthesis of Natural 2-O-Ester Derivatives 3−7 from 19. To a solution of compound **19** (1 equiv, 3.0 mmol) in THF (30 mL) was added lithium tri-*tert*-butoxyaluminum hydride (1 M in THF, 2 equiv, 6.0 mmol) at 0 °C. The reaction was stirred at room temperature for 3 h, quenched with 1 N HCl, and diluted with water. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−acetone−AcOH, 83:16:1) to give the corresponding alcohol. To a solution of the alcohol (1 equiv, 1.8 mmol) in THF (9 mL) were added acetic acid (1.1 equiv, 2.0 mmol) and tetrabutylammonium fluoride trihydrate (1.1 equiv, 2.0 mmol) at 0 °C. After 10 min, the reaction mixture was poured into water and extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc/AcOH, 66:33:1) to give natural derivatives **3**−**7**.

*2-O-p-Hydroxybenzoylalphitolic Acid (**3**).* A white solid (77% for two steps): decomposed and melted at 221 °C; $[\alpha]_D^{20}$ −10.7 (*c* 0.10, MeOH); IR (neat) υ_{max} 2952, 1699, 1276 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 8.30 (2H, m), 7.16 (2H, m), 5.70 (1H, td, *J* = 10.6, 4.3 Hz), 4.93 (1H, d, *J* = 2.3 Hz), 4.78 (1H, s), 3.68 (1H, d, *J* = 10.1 Hz), 3.52 (1H, td, *J* = 11.4, 5.5 Hz), 2.70 (1H, m), 2.62 (1H, app d, *J* = 12.8 Hz), 2.32 (1H, dd, *J* = 12.4, 4.6 Hz), 2.18 (2H, m), 1.85 (2H, m), 1.79 (3H, s), 1.74 (1H, dd, *J* = 11.3, 11.3 Hz), 1.57 (4H, m), 1.46 (1H, m), 1.37 (3H, m), 1.28 (3H, s), 1.18 (5H, m), 1.09 (3H, s), 1.06 (3H, s), 1.03 (1H, m), 1.00 (3H, s), 0.98 (3H, s); ^{13}C NMR (pyridine-d_5, 150 MHz) δ 178.8, 166.7, 163.4, 151.4, 132.4, 122.6, 116.0, 110.0, 79.8, 74.1, 56.6, 55.7, 50.8, 49.8, 47.8, 45.0, 42.9, 41.1, 40.6, 38.6, 37.6, 34.7, 32.9, 31.1, 30.2, 29.1, 26.0, 21.3, 19.4, 18.8, 17.42, 17.40, 16.3, 14.9; HRFABMS *m/z* 593.3850 $[M + H]^+$ (calcd for $C_{37}H_{53}O_6$, 593.3842).

*2-O-Protocatechuoylalphitolic Acid (**4**).* A white solid (71% for two steps): decomposed and melted at 246 °C;$[\alpha]_D^{20}$ − 8.7 (*c* 0.10, MeOH); IR (neat) υ_{max} 3340, 2943, 1693, 1448, 1291, 1218 cm^{-1}; ^1H NMR (pyridine-d_5, 400 MHz) δ 8.24 (1H, d, *J* = 1.8 Hz), 7.93 (1H, dd, *J* = 8.0, 2.1 Hz), 7.25 (1H, d, *J* = 8.3 Hz), 6.56 (1H, s), 5.68 (1H, td, *J* = 10.6, 4.1 Hz), 4.93 (1H, d, *J* = 1.8 Hz), 4.79 (1H, s), 3.65 (1H, d, *J* = 9.7 Hz), 3.52 (1H, m), 2.69 (1H, m), 2.61 (1H, app d, *J* = 12.4 Hz), 2.30 (1H, dd, *J* = 12.4, 4.6 Hz), 2.20 (2H, m), 1.88 (1H, m), 1.86 (1H, m), 1.79 (3H, s), 1.74 (1H, dd, *J* = 11.3, 11.3 Hz), 1.47 (18H, m), 1.27 (3H, s), 1.17 (5H, m), 1.08 (3H, s), 1.05 (3H, s), 0.99 (3H, s), 0.97 (3H, s); ^{13}C NMR (pyridine-d_5, 200 MHz) δ 178.8, 167.0, 152.3, 151.4, 147.0, 123.1, 123.0, 118.0, 116.0, 110.0, 79.8, 74.0, 56.5, 55.7, 50.8, 49.8, 47.7, 45.0, 42.9, 41.1, 40.5, 38.7, 38.6, 37.6, 34.6, 32.9, 31.1, 30.2, 29.1, 26.0, 21.2, 19.4, 18.8, 17.41, 17.37, 16.3, 14.8; HRFABMS *m/z* 609.3795 $[M + H]^+$ (calcd for $C_{37}H_{53}O_7$, 609.3791).

*2-O-Vanilloylalphitolic Acid (**5**).* A white solid (56% for two steps): decomposed and melted at 211 °C; $[\alpha]_D^{20}$ + 25.1 (*c* 0.10, MeOH); IR (neat) υ_{max} 2936, 1701, 1282, 1218 cm^{-1}; ^1H NMR (pyridine-d_5, 800 MHz) δ 8.02 (1H, dd, *J* = 8.2, 1.9 Hz), 7.96 (1H, d, *J* = 1.8 Hz), 7.23 (1H, d, *J* = 8.2 Hz), 6.61 (1H, s), 5.74 (1H, td, *J* = 10.7, 4.7 Hz), 4.94 (1H, d, *J* = 1.8 Hz), 4.79 (1H, s), 3.69 (3H, s), 3.68 (1H, m), 3.52 (1H, td, *J* = 10.8, 4.9 Hz), 2.70 (1H, td, *J* = 11.9, 3.3 Hz), 2.62 (1H, dt, *J* = 12.8, 3.2 Hz), 2.33 (1H, dd, *J* = 12.3, 4.8 Hz), 2.23 (2H, m), 1.88 (1H, m), 1.85 (1H, m), 1.79 (3H, s), 1.74 (1H, dd, *J* = 11.3, 11.3 Hz), 1.54 (4H, m), 1.40 (4H, m), 1.27 (3H, s), 1.25 (1H, m), 1.24 (1H, m), 1.23 (1H, m), 1.16 (1H, m), 1.12 (1H, m), 1.10 (3H, s), 1.06 (3H, s), 1.01 (3H, s), 0.99 (3H, s), 0.97

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(1H, m); ^{13}C NMR (pyridine-d_5, 200 MHz) δ 178.8, 166.7, 153.0, 151.4, 148.3, 124.7, 122.7, 116.1, 113.5, 110.0, 79.7, 74.1, 56.5, 55.8, 55.7, 50.8, 49.8, 47.7, 45.0, 42.9, 41.1, 40.5, 38.7, 38.6, 37.6, 34.7, 32.9, 31.1, 30.2, 29.1, 26.0, 21.2, 19.4, 18.8, 17.41, 17.39, 16.3, 14.8; HRFABMS m/z 623.3946 $[M + H]^+$ (calcd for $C_{38}H_{55}O_7$, 623.3948).

*2-O-trans-p-Coumaroylalphitolic Acid (**6**).* A white solid (50% for two steps): decomposed and melted at 252 °C;$[\alpha]_D^{20}$ + 29.0 (c 0.10, MeOH); IR (neat) υ_{max} 2947, 1703, 1688, 1605, 1253, 1169, 832 cm^{-1}; ^{1}H NMR (pyridine-d_5, 800 MHz) δ 8.01 (1H, d, J = 15.8 Hz), 7.54 (2H, d, J = 11.4 Hz), 7.13 (2H, d, J = 8.5 Hz), 6.61 (1H, d, J = 15.9 Hz), 5.62 (1H, td, J = 10.7, 4.4 Hz), 4.94 (1H, s), 4.78 (1H, s), 3.64 (1H, d, J = 9.9 Hz), 3.52 (1H, td, J = 10.7, 4.9 Hz), 2.71 (1H, td, J = 12.0, 3.4 Hz), 2.62 (1H, app d, J = 12.9 Hz), 2.31 (1H, dd, J = 12.3, 4.7 Hz), 2.23 (2H, m), 1.90 (1H, m), 1.85 (1H, td, J = 13.5, 3.6 Hz), 1.79 (3H, s), 1.74 (1H, dd, J = 11.3, 11.3 Hz), 1.54 (4H, m), 1.42 (3H, m), 1.36 (2H, m), 1.27 (3H, s), 1.23 (2H, m), 1.16 (1H, m), 1.12 (1H, m), 1.09 (3H, s), 1.06 (3H, s), 1.01 (3H, s), 0.98 (3H, s), 0.97 (1H, m); ^{13}C NMR (pyridine-d_5, 200 MHz) δ 178.8, 167.5, 161.4, 151.4, 144.7, 130.6, 126.2, 116.8, 116.0, 110.0, 79.8, 73.8, 56.5, 55.7, 50.8, 49.8, 47.7, 45.0, 42.9, 41.1, 40.5, 38.8, 38.6, 37.6, 34.7, 32.9, 31.1, 30.2, 29.1, 26.0, 21.3, 19.4, 18.7, 17.42, 17.39, 16.3, 14.8; HRFABMS m/z 619.3997 $[M + H]^+$ (calcd for $C_{39}H_{55}O_6$, 619.3999).

*2-O-trans-Caffeoylalphitolic Acid (**7**).* A white solid (57% for two steps): decomposed and melted at 246 °C;$[\alpha]_D^{20}$ − 361.1 (c 0.10, MeOH); IR (neat) υ_{max} 2946, 1696, 1603, 1275, 1179 cm^{-1}; ^{1}H NMR (CD_3OD, 800 MHz) δ 7.54 (1H, d, J = 15.8 Hz), 7.03 (1H, d, J = 2.0 Hz), 6.93 (1H, dd, J = 8.2, 2.0 Hz), 6.76 (1H, d, J = 8.1 Hz), 6.27 (1H, d, J = 15.8 Hz), 5.04 (1H, td, J = 10.8, 4.4 Hz), 4.69 (1H, d, J = 1.3 Hz), 4.56 (1H, s), 3.21 (1H, d, J = 10.1 Hz), 3.01 (1H, td, J = 10.9, 4.8 Hz), 2.32 (1H, td, J = 11.8, 2.3 Hz), 2.23 (1H, app d, J = 13.0 Hz), 2.08 (1H, dd, J = 12.3, 4.6 Hz), 1.92 (2H, m), 1.71 (1H, m), 1.67 (3H, s), 1.60 (1H, dd, J = 11.3, 11.3 Hz), 1.55 (2H, m), 1.48 (2H, m), 1.40 (5H, m), 1.28 (2H, m), 1.17 (1H, m), 1.07 (1H, td, J = 13.2, 4.5 Hz), 1.03 (3H, s), 1.01 (3H, s), 1.00 (3H, s), 0.97 (3H, s), 0.94 (1H, dd, J = 11.9, 11.9 Hz), 0.89 (1H, m), 0.85 (3H, s) ^{13}C NMR (CD_3OD, 200 MHz) δ 181.1, 170.1, 152.8, 150.3, 147.6, 147.4, 128.7, 123.6, 117.3, 116.6, 115.9, 111.0, 81.9, 74.8, 58.4, 57.5, 52.6, 51.2, 49.3, 46.2, 44.4, 42.8, 41.8, 40.5, 40.4, 39.0, 36.2, 34.2, 32.6, 31.6, 29.9, 27.6, 23.0, 20.4, 20.3, 18.5, 18.0, 17.4, 15.9; HRFABMS m/z 635.3958 $[M + H]^+$ (calcd for $C_{39}H_{55}O_7$, 635.3948).

*2α-Hydroxy-O-benzoylbetulonic Acid (**20**).* To a solution of compound **10** (1 equiv, 3.4 g, 7.2 mmol) in pyridine (36 mL) was added DMAP (0.05 equiv, 44 mg, 0.36 mmol) and benzoic anhydride (3 equiv, 5.2 g, 21.6 mmol) at room temperature. The reaction was stirred at the same temperature for 2 h. The mixture was quenched with saturated aqueous NH_4Cl, poured into water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−acetone−AcOH, 94:5:1) to give compound **20** (2.2 g, 3.9 mmol, 53%) as a white solid: mp 165 °C; $[\alpha]_D^{20}$ − 26.6 (c 0.50, MeOH); IR (neat) υ_{max} 2946, 1717, 1273, 1119, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (2H, m), 7.54 (1H, t, J = 7.6 Hz), 7.41 (2H, t, J = 7.8 Hz), 5.83 (1H, dd, J = 13.2, 6.4 Hz), 4.72 (1H, s), 4.59 (1H, s), 2.98 (1H, td, J = 12.7, 4.8 Hz), 2.42 (1H, dd, J = 12.4, 6.4 Hz), 2.24 (2H, m), 1.95 (2H, m), 1.74 (1H, m), 1.68 (3H, s), 1.49 (14H, m), 1.25 (3H, s), 1.21 (1H, m), 1.17 (3H, s), 1.13 (3H, s), 1.06 (1H, m), 1.00 (3H, s), 0.97 (3H, s); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 209.1, 179.8, 165.8, 150.1, 133.0, 129.9, 129.8, 128.3, 109.9, 72.4, 57.3, 56.2, 50.3, 49.2, 48.8, 46.8, 46.2, 42.6, 40.9, 38.29, 38.27, 37.0, 34.0, 32.1, 30.4, 29.6, 25.3, 24.7, 21.2, 21.1, 19.3, 19.0, 16.7, 16.2, 14.6; HRFABMS m/z 575.3735 $[M + H]^+$ (calcd for $C_{37}H_{51}O_5$, 575.3737).

*2-O-Benzoylalphitolic Acid (**2**).* To a solution of compound **20** (1 equiv, 2.0 g, 3.4 mmol) in THF (17 mL) was added lithium tri-*tert*-butoxyaluminum hydride (1 M in THF, 2 equiv, 6.8 mL, 6.8 mmol) at 0 °C. The reaction was stirred at room temperature for 24 h, quenched with 1 N HCl, and diluted with water. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane−EtOAc−AcOH, 87:12:1) to give compound **2** (1.0 g, 1.7 mmol, 50%) as a white solid: decomposed and melted at 210 °C; $[\alpha]_D^{20}$ −16.6 (c 0.10, MeOH); IR (neat) υ_{max} 2944, 1713, 1451, 1275, 1115, 711 cm^{-1}; ^{1}H NMR (pyridine-d_5, 400 MHz) δ 8.26 (2H, m), 7.49 (1H, app t, J = 7.4 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.38 (3H, t, J = 7.4 Hz), 6.64 (1H, s), 5.70 (1H, td, J = 10.6, 4.3 Hz), 4.93 (1H, s), 4.77 (1H, s), 3.66 (1H, d, J = 9.7 Hz), 3.52 (1H, td, J = 11.0, 4.4 Hz), 2.71 (1H, m), 2.63 (1H, app d, J = 12.9 Hz), 2.29 (1H, dd, J = 12.4, 4.6 Hz), 2.19 (2H, m), 1.87 (2H, m), 1.78 (3H, s), 1.74 (1H, dd, J = 11.3, 11.3 Hz), 1.55 (4H, m), 1.40 (4H, m), 1.27 (3H, s), 1.22 (2H, m), 1.15 (3H, m), 1.08 (3H, s), 1.07 (3H, s), 1.02 (1H, m), 0.99 (3H, s), 0.98 (3H, s); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 178.9, 166.6, 151.4, 133.1, 131.8, 130.0, 128.7, 110.0, 79.7, 74.7, 56.6, 55.7, 50.9, 49.8, 47.8, 44.9, 42.9, 41.1, 40.6, 38.8, 38.6, 37.6, 34.7, 32.9, 31.2, 30.2, 29.1, 26.0, 21.3, 19.4, 18.8, 17.4, 16.3, 14.9; HRFABMS m/z 577.3905 $[M + H]^+$ (calcd for $C_{37}H_{53}O_5$, 577.3893).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00986.

Experimental procedures and spectroscopic data of compounds including **11**, **17a−e**, and **18a−e**; fully assigned ^{1}H and ^{13}C NMR spectroscopic data of **2−7**; ^{1}H and ^{13}C NMR copies of novel compounds and natural compounds **1−7** and **1′** (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This work is dedicated to the late Prof. Sang Hyun Sung, who passed away in July 2018 at the early age of 50.

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