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# Derivatives of the Lignan 7′-Hydroxymatairesinol with Antioxidant Properties and Enhanced Lipophilicity

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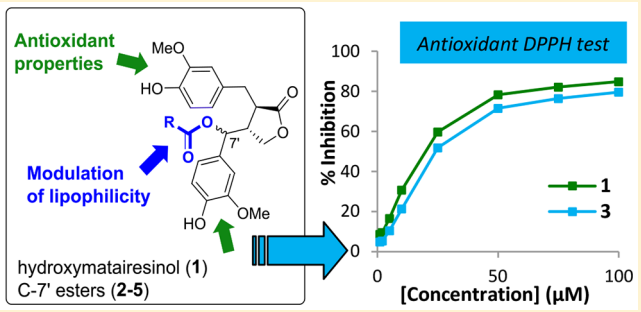
Supporting Information

**ABSTRACT:** The lignan 7′-hydroxymatairesinol (**1**), extracted from the knotwoods of fir (*Abies alba*), spruce (*Picea abies*), and Douglas fir (*Pseudotsuga menziesii*), exhibited unexpected reactivity when esterification reactions were attempted on the hydroxy group at position C-7′. To circumvent the rapid intramolecular cyclization procedure, leading quantitatively to the lignan conidendrin (**7**), a simple strategy for 7′-esterification of **1** under mild conditions (three steps, up to 80% overall yield) was developed. Compared to hydroxymatairesinol (**1**) (log $K'_w$ = 1.49), the derivatives (**2**–**5**) had increased lipophilicity with log $K'_w$ > 3.1, as determined by a UHPLC method. Compounds **1**–**5** exhibited potent antioxidant properties in the same range as the standards ascorbic acid and α-tocopherol ($IC_{50}$ = 20–25 μM) and higher than that of BHT using a DPPH radical-scavenging assay.




Wood is a renewable source of bioactive molecules such as lignans. These phenolic compounds show several biological properties such as antioxidant effects due to the presence of phenolic groups, as well as anti-inflammatory,[1,2] cardiovascular,[3,4] antiviral,[5,6] cytotoxic,[7−9] and enzyme inhibition effects.[10] The European trees Norway spruce (*Picea abies*) and fir (*Abies alba*) have shown the presence of unconjugated lignans in higher quantities in their knotwood than in the heartwood.[11−14] In this work, paper-mill wastes were used as a knotwood source, thus comprising a variable proportion of fir (*Abies alba*), spruce (*Picea abies*), and Douglas fir (*Pseudotsuga menziesii*). This wood was found to contain as major constituent the lignan 7′-hydroxymatairesinol (**1**) (30%).[11,12,14]

The presence of a benzylic hydroxy group on C-7′ is unique, providing the opportunity to produce derivatives at this position. In order to modulate the lipophilicity of compound **1**, four C-7′ ester derivatives (**2**–**5**) were designed. A consequent increase of solubility in lipophilic media was expected while retaining the antioxidant properties from the two guaiacyl groups (Figure 1). It can be assumed that natural antioxidants that originate from wood may find practical applications in medicinal chemistry, cosmetics, or food.

Previous reactivity studies on C-7′ of hydroxymatairesinol (**1**) by Eklund and associates are detailed in Scheme 1. The ether **8** was prepared in alkaline conditions after treatment of **1** with sodium methoxide. However, the treatment of **1** by methylamine resulted into the lactam **9** after rearrangement during the acidic workup. Finally, these authors suggested the role of a *para*-quinone methide (*p*QM) (**6**) formed in aqueous alkaline solution as a key intermediate in the intramolecular cyclization into conidendrin (**7**).[15]

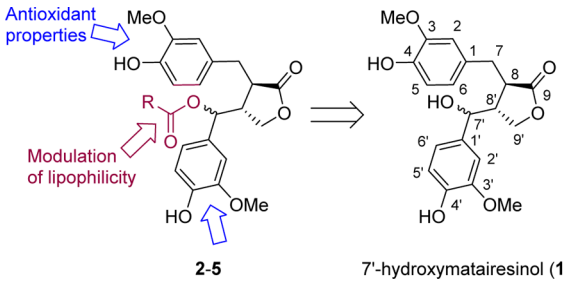



**Figure 1.** Esterification of 7′-hydroxymatairesinol (**1**) to modulate lipophilicity without altering the antioxidant guaiacyl moieties.

The work in the present investigation has explored further the reactivity of **1**, prone to cyclization or rearrangement, and, as a result, circumventing these side-reactions represented a first challenge.

## RESULTS AND DISCUSSION

**Chemistry.** The conditions of extraction from knotwoods were developed to recover **1** in large amounts.[16] Hydroxymatairesinol (**1**) was obtained in a 3:1 ratio of (7′*S*)- to (7′*R*)-hydroxymatairesinol, and all experiments were carried out on this constitutive mixture.

A first direct regioselective esterification with octanoic acid was attempted under Mitsunobu conditions but surprisingly did not provide the expected 7′-octanoate derivative **3** (Scheme

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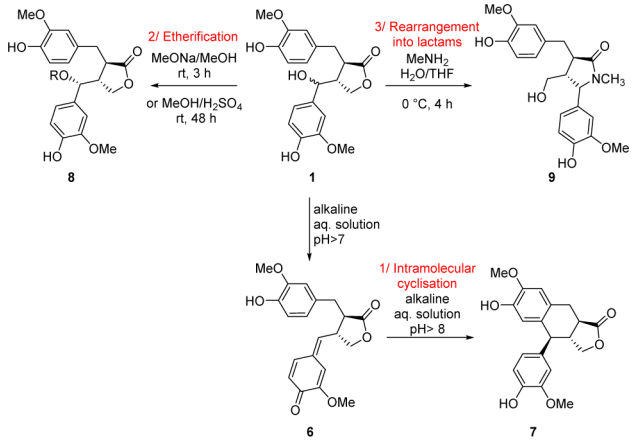
**Scheme 1. Reactivity Study on C-7′ of Compound 1 (Previous Work)**

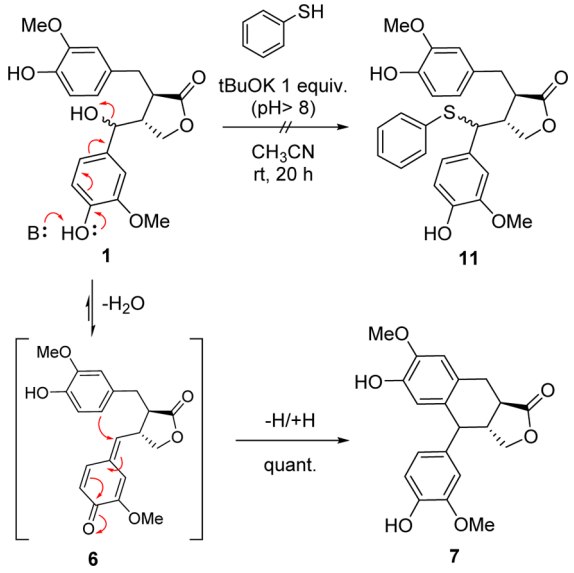



2).[17−19] The betaine resulting from the triphenylphosphine attack on diisopropyl azodicarboxylate (DIAD) was promptly formed. Nevertheless, the activation of the benzylic hydroxy group of **1** by the triphenylphosphine did not occur. The treatment of **1** with a more nucleophilic thiolate, previously formed by addition of potassium *tert*-butoxide on 1-octadecanethiol, at reflux with acetonitrile, provided the thioether **10** in moderate yield (36%). The NMR analysis confirmed the formation of **10** as the C-7′ signal shifted downfield from 75.4 ppm to 52.9 ppm in the $^{13}C$ NMR spectrum and the H-7′ signal shifted from 4.63 ppm to 3.53 ppm in the $^{1}H$ NMR spectrum. No other azodicarboxylate structures were investigated to deprotonate the nucleophiles with high p$K_a$, especially as the purification of **10** from the hydrazine side-product proved very challenging.

In the presence of a large excess (5 equiv) of a separately prepared thiophenolate, hydroxymatairesinol (**1**) rearranged into conidendrin (**7**). The reaction followed a SEAr-type (electrophilic aromatic substitution) mechanism, which may occur through a *para*-quinone methide intermediate (**6**), even though this structure has never been observed and characterized for **1**. This 1,6-conjugate addition of *p*QM with C nucleophiles clearly benefits from the rearomatization driving force to form the guaiacyl (Scheme 3). It is worth mentioning that the 1,8-conjugate addition of the enone has never been observed.

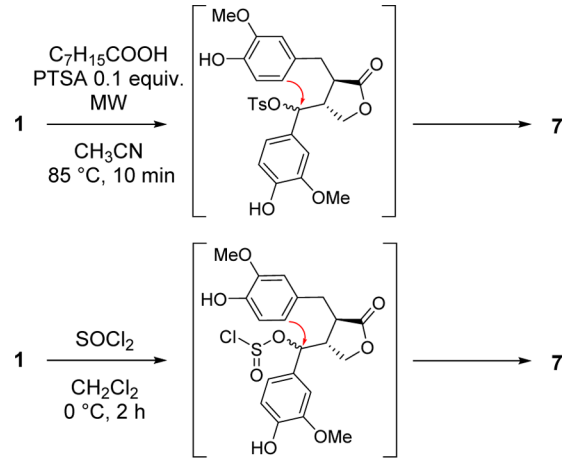
The intramolecular cyclization also occurred in acidic conditions, and treatment of **1** with formic acid in stoichiometric conditions provided compound **7** in excellent yield.[20] Activation of the benzylic hydroxy by a catalytic amount of *p*-toluenesulfonic acid (PTSA) (0.1 equiv), in the presence of octanoic acid, also resulted quantitatively in the production

**Scheme 3. Proposed Reaction Mechanism for the Formation of 7 in Alkaline Conditions**




of **7**, instead of the expected product of translactonization.[21] Microwave heating accelerated the formation of the hypothetic tosyl intermediate (10 min at 85 °C instead of 4 h at conventional reflux) (Scheme 4). Attempting to chlorinate the benzylic hydroxy group with thionyl chloride also led to conidendrin (**7**) in 2 h.[22]

**Scheme 4. Hypothetical Intermediates Leading to Conidendrin (7) in Acidic Conditions**




It appeared, therefore, that all previously described work on 4-(1-hydroxyethyl)phenol structures did not apply to **1** due to

**Scheme 2. Regioselective Hydroxy Activation under Mitsunobu Conditions**

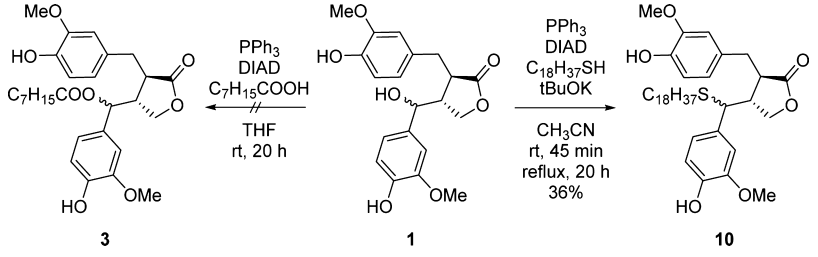





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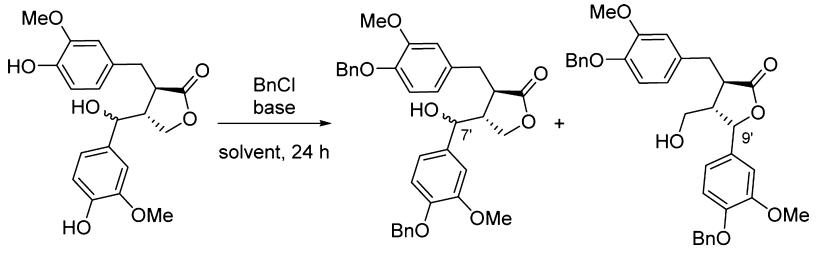
**Table 1. Optimization of the Reaction Conditions for the Dibenzylation of Hydroxymatairesinol Guaiacyl Groups**




1 12 13

| entry | base | solvent | $T$, °C | time, h | results |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | DMF | rt | 48 | no reaction |
| 2 | $K_2CO_3$ | choline chl./urea | 80 | 24 | traces |
| 3 | DMAP | acetone | rt | 24 | **12**/**13**, 1:1,[c] no completion |
| 4 | DMAP | acetone | reflux | 24 | **12**/**13**, 1:1[c] |
| 5 | $K_2CO_3$ | acetone | reflux | 24 | **12**/**13**, 1:1[c] |
| 6 | $Et_3N$/DMAP cat[a] | acetone | reflux | 24 | **12**/**13**, 1:1,[c] no completion |
| 7 | TBAB/$K_2CO_3$ | acetone | reflux | 24 | **12**, 52% |
| 8 | TBAI/$K_2CO_3$ | acetone | reflux | 24 | **12**, 60% |
| 9 | KI cat[a]/$K_2CO_3$ | acetone | reflux | 24 | **12**, 44% |
| 10 | KI/$K_2CO_3$ | acetone | reflux | 24 | **12**, 46% |
| 11 | TBAI/$Cs_2CO_3$[b] | acetone | reflux | 1 | **12**, 93% |
| 12 | TBAI/$Cs_2CO_3$[b] | acetone | rt | 4 | **12**, 96% |

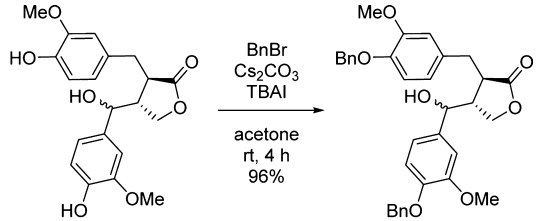
[a]0.3 equiv. [b]BnBr. [c]Yield determined by NMR spectroscopy.

the presence of the second phenolic group in the $\gamma$-position to the hydroxy group. To remedy this issue, the development of the benzyl protection of the phenolic hydroxy groups of **1** is detailed in Table 1.

Standard conditions of phenol benzylation in dimethylformamide (DMF) with $K_2CO_3$ as a base did not provide any reaction (Table 1, entry 1).[23,24] The use of a deep eutectic solvent (DES) formed by the 1:1 mixture of choline chloride and urea (Table 1, entry 2) proved not to be more efficient.[25] As shown with entries 4−6 (Table 1), the benzylation occurred at reflux in acetone for any base ($K_2CO_3$, 4-(dimethylamino)-pyridine (DMAP), or $Et_3N$ with a catalytic amount of DMAP).[26] However, the side-product **13** resulting from the translactonization rearrangement was also competitively formed. Indeed, the $^{13}C$ NMR spectrum showed a partial shift for both epimers of the *C*HOH-7′ signal to a *C*HOH-9′ signal. For example, the (*R*)-epimer of **12** exhibited a *C*HOH-7′ signal at 74.4 ppm, whereas **13** showed a *C*HOH-9′ signal at 80.9 ppm. Reaction at room temperature with DMAP did not prevent the formation of **13** (Table 1, entry 3). In either case, the reaction was not completed after 24 h. The addition of a tetrabutylammonium salt allowed increasing the yield up to 60%, and tetrabutylammonium iodide (TBAI) proved to be slightly more effective than tetrabutylammonium bromide (TBAB) (Table 1, entries 7 and 8). The reaction mechanism involves an exchange between the iodine counterion from TBAI with chlorine from benzyl chloride, as well as a better contact between the phenolate and the benzyl chloride. Indeed, assays with KI either in catalytic or stoichiometric amounts showed lower yields compared to TBAI (Table 1, entries 9 and 10). Finally, substituting $K_2CO_3$ by $Cs_2CO_3$, and benzyl chloride by benzyl bromide, allowed the completion of the reaction at reflux in acetone in only 1 h (Table 1, entry 11).

Compound **12** was obtained at room temperature in high yield (96%) after treatment of **1** with cesium carbonate associated with TBAI (Scheme 5). The IR spectrum showed the displacement of the phenol peak from 3420 $cm^{-1}$ to 3500 $cm^{-1}$.

**Scheme 5. Optimized Benzyl Protection of Compound 1**

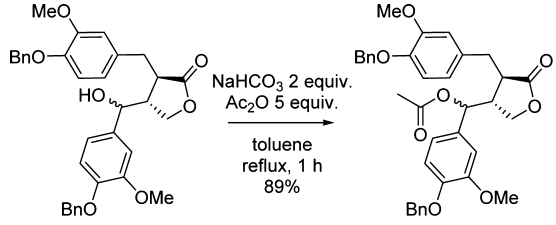



1 12

Benzylation of **1** increased its solubility in apolar solvents such as toluene. Acetate **14** was obtained in good yield (89%) after reaction of **12** with acetic anhydride in large excess (5 equiv) in the presence of $NaHCO_3$ as a base.[27] Analysis by $^{13}C$ NMR spectroscopy was consistent with a shift of the *C*HOH-7′ signal of **12** from 74.4 ppm to the *C*HOR-7′ signal of **14** at 75.4 ppm (Scheme 6). The synthesis of mixed anhydrides was not explored further on longer chains.

The reaction of acyl chlorides in the presence of DMAP in acetonitrile did not produce satisfactory results, with 52% and

**Scheme 6. Regioselective Acetylation of Compound 12**




12 14



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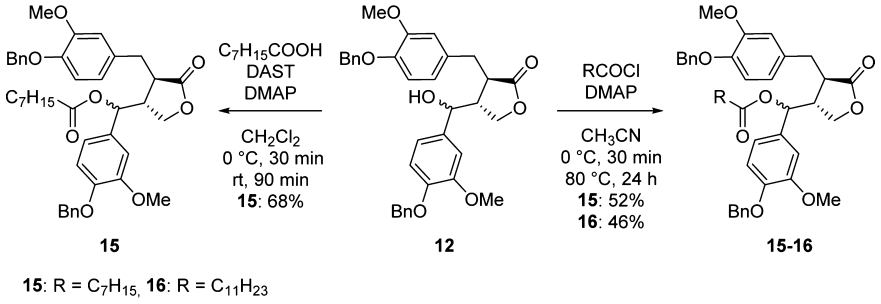
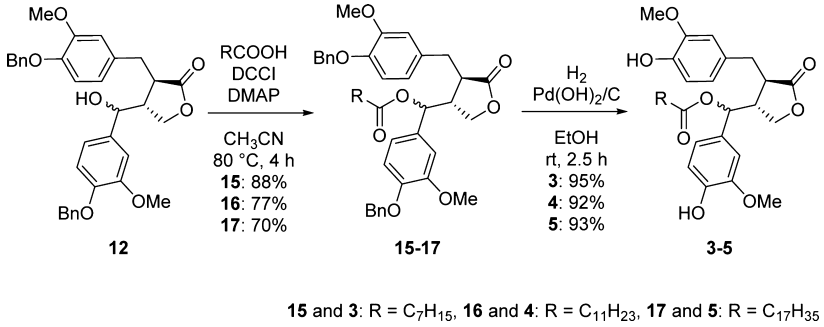
**Scheme 7. Activation Methods for Fatty Acids**




**Scheme 8. Synthetic Pathway to C-7′ Esters of Hydroxymatairesinol (1)**




46% yield for the octyl and dodecanoyl chlorides, respectively (Scheme 7).[23] Compound **12** was also reacted with extemporaneously synthesized fluorooctanoyl, prepared from octanoic acid and (diethylamino)sulfur trifluoride (DAST, 1.3 equiv), to obtain **15** with an improved yield (68%).

The use of dicyclohexylcarbodiimide (DCCI) in the presence of DMAP in stoichiometric amounts provided the esters **15** and **16** in good yields (88% and 77%, respectively) (Scheme 8). IR analysis showed the appearance of two peaks for the fatty chains at 2850 and 2920 $cm^{-1}$.

Benzylated phenols were then deprotected with hydrogen gas at atmospheric pressure (2.5 h, 92−95%) in the presence of $Pd(OH)_2$ (0.3 equiv) (Scheme 8). IR analysis confirmed the recovery of the free phenols with a broad peak at 3430 $cm^{-1}$.

The reaction pathway was scaled up from 2 g to 3 g of starting material **1**. Satisfactorily, no variations in the yields were observed at any of the steps. The pathway did not require further scale optimization, and three long-chain esters were obtained from octanoic acid, dodecanoic acid, and octadecanoic acid.

**Lipophilicity.** The behavior of bioactive molecules can be strongly affected by their lipophilicities.[28] Also influenced are absorption, metabolism, and excretion.[29] A typical example would be in drug delivery, notably transport through the blood−brain barrier, requiring further pharmacokinetic and pharmacodynamic studies.[30] It would be expected that an increase in the lipophilicity will help the solubilization of **1** in more lipophilic conditions, as, for example, when formulated in cosmetics. Additionally, recent work has shown the improvement of antioxidant activity of hydroxytyrosol derivatives after incorporating alkylcarbonate chains of various lengths.[31]

The *n*-octanol/water partition method can be replaced by chromatographic methods.[32,33] The partition coefficient in *n*-octanol/water (log *P*) is correlated to the retention time of the molecule in reversed-phase liquid chromatography (eq 1):[34,35]

$$\log P = \log K - \log \frac{V_S}{V_M} \quad (1)$$

where $V_S/V_M$ is the volume ratio of the stationary and mobile phase. The coefficient log $K'_w$ is the extrapolation of log *K* at 100% water. It is calculated with the following expression (eq 2):

$$\log K'_w = \log\left(\frac{t_R - t_0}{t_0}\right) \quad (2)$$

where $t_R$ and $t_0$ are, respectively, the retention times of the test compound and of the unretained compound (dead time). Therefore, log $K'_w$ is a representative index of lipophilicity extrapolating directly the value of log *P*.

Herein, the lipophilicities of the three synthesized esters (**3**−**5**) and of natural hydroxymatairesinol (**1**) were determined using an isocratic elution mode with acetonitrile/water as eluent, in three different proportions to cover the lipophilicity range. The two epimers (7′*R*)- and (7′*S*)- for each ester could be separated by reversed-phase UHPLC. For any length of chain, the (7′*R*)-ester was consistently calculated to have a higher value of log $K'_w$ (Table 2). Including an octyl chain on compound **1** doubled the lipophilic coefficient from 1.49 to about 3.1. The dodecanoyl and octadecanoyl chains increased the lipophilic coefficient to higher than 3.6 and 5.4, respectively.

By comparison, log *P* values for most commercially available antioxidants are very low and less than zero as for ascorbic acid (−2.15). Only a few antioxidants exhibit a higher lipophilicity, such as octyl gallate (4.1) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (5.1). Figure 2 shows the increase of lipophilicity for the (7′*S*)-ester family of hydroxymatairesinol (**1**).

**Antioxidant Activity.** The antioxidant activities of **1** and esters **3**−**5** were evaluated by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging method and compared to those of ascorbic acid, α-tocopherol, and BHT. The reaction conditions were set with equivalent volumes (1 mL) of the DPPH solution


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**Table 2. Lipophilicities and Antioxidant Activities of 1 and Ester Derivatives 3−5**

| compound | log $K'_w$ | $IC_{50}$ ($\mu$M) | $IC_{50}$ (mg·L$^{-1}$) |
|---|---|---|---|
| **1** | 1.49[a] | 20.0 ± 0.1 | 7.49 |
| **3** | 3.06/3.12[b] | 24.1 ± 0.1 | 12.06 |
| **4** | 3.63/3.68[b] | 24.5 ± 0.1 | 13.64 |
| **5** | 5.43/5.50[b] | 25.2 ± 0.1 | 16.15 |
| ascorbic acid | −2.15[c] | 20.3 ± 0.1 | 3.58 |
| | | 12.6 ± 0.2[d] | 2.22[d] |
| citric acid | −1.7[c] | nt[e] | nt[e] |
| octyl gallate | 4.1[c] | nt[e] | nt[e] |
| α-(±)-tocopherol | | 23.5 ± 0.1 | 10.12 |
| BHT | 5.1[c] | 34.0 ± 0.3 | 7.49 |

[a]A single peak was obtained under UHPLC conditions. [b](7′*S*)/(7′*R*). [c]log *P*. [d]Volume ratio of ascorbic acid solutions/DPPH solution 3:1 instead of 1:1. [e]Not tested.

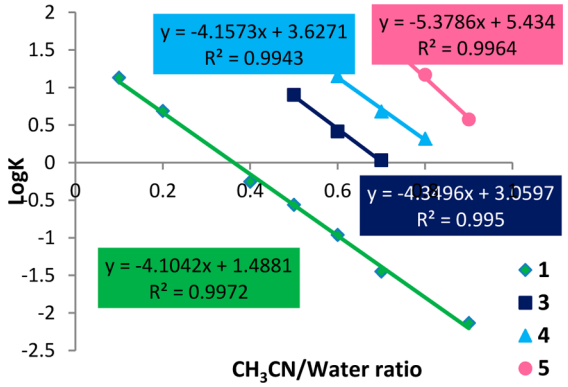


**Figure 2.** Lipophilicity determination of (7′*S*)-esters of hydroxymatairesinol (**1**).

(200 $\mu$M) and of the assayed products. A time-course study on **1** showed that an interval of 1 h was sufficient for incubation of all samples

The results for the DPPH assay are illustrated in Figure 3. All compounds exhibited good to excellent scavenging of DPPH radicals when compared to standards. The inhibition curve profiles of **1** and its derivatives **3−5** were in between those of ascorbic acid and BHT. Compound **1** reacted as instantaneously as ascorbic acid at lower concentrations, but full inhibition was not obtained until after a 1 h reaction. Esters **3−5** exhibited a slightly lower activity than **1**, with a similar inhibition profile, in a comparable manner to BHT. At lower concentrations, the DPPH radical-scavenging activities of esters **3−5** were similar to that of the lipophilic standard α-tocopherol.

The $IC_{50}$ values for each compound and standard were between 20 and 25 $\mu$M, except for BHT (34.0 $\mu$M) (Table 2). Surprisingly, the $IC_{50}$ value for **1** (20.0 $\mu$M) was slightly lower than for ascorbic acid (20.3 $\mu$M) under the conditions of the test. Ascorbic acid was tested again in literature conditions, and the result confirmed the validity of the test (12.6 $\mu$M).[36] Incorporating an ester chain on **1** increased the $IC_{50}$ value to around 4−5 $\mu$M, but the antioxidant activities of **3−5** were still kept high. Thus, the ester family exhibited close $IC_{50}$ values (24.1−25.2 $\mu$M) to that of the lipid-soluble vitamin α-tocopherol (23.5 $\mu$M).

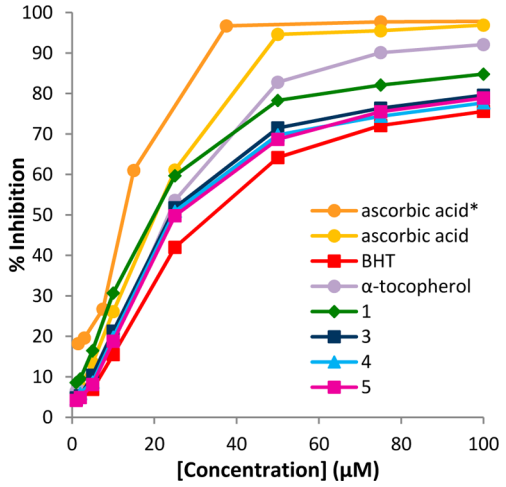


**Figure 3.** Scavenging of DPPH radicals by **1** and esters **3−5**. In a 2 mL reaction vial containing 1 mL of each assayed product (2−200 $\mu$M) in MeOH was added 1 mL of DPPH solution (200 $\mu$M) in MeOH, except ascorbic acid* (0.5 mL of DPPH solution (200 $\mu$M) in MeOH added to 1.5 mL of ascorbic acid solution (2−200 $\mu$M) in MeOH).

The inhibition profiles of **1** and derivatives **3−5** were similar to that of BHT, showing a rounded curve typical of a slow action. This was also suggested by the relatively long incubation times required for lower concentration samples to achieve stability. This slow mechanism was tempered by the presence of two guaiacyl groups that reinforced strongly the antioxidant activity.

**Concluding Remarks.** In conclusion, a simple and straightforward strategy was designed to synthesize the C-7′ ester derivatives **3−5** from hydroxymatairesinol (**1**). The benzyl protection of guaiacyls prevented side-reactions of translactonization into isohydroxymatairesinol and the intramolecular cyclization into conidendrin (**7**). Benzyl protection at room temperature with cesium carbonate and TBAI provided the dibenzylated compound **12** in high yield (96%). Once hydroxymatairesinol (**1**) was suitably protected, the intramolecular cyclization was inhibited and the molecule could undergo C-7′ esterification (70−88% depending on the chain length) by using conventional DCCI as a coupling reagent. The benzyl deprotection was catalyzed by $Pd(OH)_2$ under atmospheric $H_2$ at room temperature (92−95%). The semisynthesis of the C-7′ esters **3−5** worked efficiently under mild conditions. The three different carbon chain lengths introduced ($C_7H_{15}CO$, $C_{11}H_{23}CO$, $C_{17}H_{35}CO$) allowed the modulation of lipophilicity on **1**. The derivatives **3−5** exhibited very high antioxidant properties ($IC_{50}$: 24−25 $\mu$M) in a DPPH radical-scavenging assay when compared to the common antioxidants ascorbic acid, α-tocopherol, and BHT. Lipophilization may help solubilization of this natural hydrophilic antioxidant into lipophilic media and find industrial uses in the food, cosmetic, and pharmaceutical industries. Therefore, this work has contributed the generation of highly valuable bioactive molecules from industrial wood wastes.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** All commercially available chemicals were purchased and used as supplied by the manufacturers. Hydroxymatairesinol (**1**) was isolated from knotwood according to the method described in ref 16 and in the Supporting Information. GC-MS analysis was performed on a Clarus 680 gas chromatograph coupled to a Clarus SQ8 quadrupole mass spectrometer (PerkinElmer,


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USA). Gas chromatography was carried out on a 5% diphenyl/95% dimethyl polysiloxane fused-silica capillary column (DB-5 ms, 30 m × 0.25 mm, 0.25 μm film thickness, J&W Scientific, USA) with helium as carrier gas at a constant flow of 1 mL/min. Prior to analyses, samples were silylated by addition of 80 μL of *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide/trimethylsilyl chloride (99:1) and heating at 60 °C until complete solubilization. UHPLC analysis for determination of log $K'_w$ values was performed on a Shimadzu 8030 apparatus equipped with an SPD-M20A diode array detector. The separations were carried out in thermostated conditions at 40 °C with a reversed-phase column (Phenomenex Luna 3 μm $C_{18}$). The elution was carried out with a binary solvent system consisting of water with 0.1% formic acid and acetonitrile with 0.1% formic acid. The injection volume was fixed at 5.0 μL. Detection was carried out with a UV detector set at 254 nm and under selected ion monitoring by negative and positive mode ESIMS. The operating parameters for MS detection were as follows: nebulizing gas $N_2$, flow 3.0 L/min, drying gas flow 15 L/min, interface voltage 4.5 kV, gas pressure 230 kPa, CDL temperature 250 °C, and block heater temperature 400 °C. The DPPH assays were conducted with a methanol solution (analytical grade) of DPPH (200 μM). Methanol stock solutions of antioxidants were made at 1 mM. Solutions of antioxidants were obtained directly by dilution of aliquots from the stock solution (50 mL of each concentration, 2−200 μM). The reaction was started by adding 1 mL of DPPH (200 μM) to 1 mL of antioxidant solution. Absorbance of the reaction mixture was measured on a Shimadzu UV-2550 spectrophotometer at 517 nm. Purifications were conducted on a preparative HPLC PuriFlash 4100−250 coupled to an internal UV analyzer and a Flash-ELSD (Interchim, France). The ELSD was supplied with $N_2$ by a Parker Domnick Hunter G3110E nitrogen gas generator. The columns were prepacked high-performance silica gel with a particle size of 30 μm [Interchim PuriFlash PF-30SIHP-JP/25G or PF-30SIHP-JP/120G]. The crude mixtures were solubilized in the minimum of solvent (5−10 mL per g) and deposited on Merck Geduran silica gel SI60 0.063−0.200 mm (3 g per g of extract) before evaporation of the solvent. Dry loading used a Merck EasyVarioFlash EVF D17 5 g or EVF D24 30 g empty cartridge completed with sand when necessary. Melting points were measured on a digital melting point apparatus (Electrothermal, UK). FT-IR spectra were obtained on a Spectrum One spectrometer in ATR mode (PerkinElmer, USA). $^1$H and $^{13}$C NMR spectra were recorded with an Avance DRX 400 NMR spectrometer (Bruker, Germany) at 400 and 100 MHz, respectively, and chemical shifts are reported downfield from tetramethylsilane.

**Synthesis of Compound 12 (7′*S*-12a and 7′*R*-12b).** To a solution of **1** (7.40 mmol, 1 equiv, 2.77 g) dissolved in acetone (70 mL) were added successively TBAI (2.22 mmol, 0.3 equiv, 820 mg) and $Cs_2CO_3$ (14.80 mmol, 2 equiv, 4.82 g). Benzyl bromide (22.2 mmol, 3 equiv, 2.64 mL) was then added dropwise, and the mixture stirred at room temperature for 4 h. Excess BnBr was quenched by addition of silica gel (15 g) to the crude mixture, and the volatiles were evaporated under a vacuum. The solid load was submitted to purification over silica gel (hexane/ethyl acetate, 1:1) to provide **12** as a white solid (3.94 g, 96%): mp 54−60 °C; FTIR $\nu_{max}$ 3498br w, 1760, 1591w, 1511s sh, 1452w, 1420w, 1380w, 1259s, 1224s, 1136s, 1025s cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.43 (10H, m, H-Ar), 6.42−6.82 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.14 (2H, s, H-10), 5.11 (2H, s, H-10′), 4.60 (0.6H, d, *J* = 6.74 Hz, H-7′a), 4.36 (0.4H, d, *J* = 6.78 Hz, H-7′b), 3.87−3.94 (2H, m, H-9′), 3.84 (2H, s, $OCH_3$a), 3.82 (2H, s, $OCH_3$a), 3.81 (1H, s, $OCH_3$b), 3.80 (1H, s, $OCH_3$b), 2.85−3.09 (2H, m, H-7), 2.67−2.81 (1H, m, H-8), 2.48−2.63 (1H, m, H-8′), 1.98 (0.6H, s, OH-7′a), 1.91 (0.4H, s, OH-7′b); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 179.2 (C, C-9a), 179.0 (C, C-9b), 149.8 (C, C-3a), 149.7 (C, C-3b), 149.6 (C, C-3′b), 149.4 (C, C-3′a), 147.9 (C, C-4′a), 147.8 (C, C-4′b), 146.9 (C, C-4b), 146.8 (C, C-4a), 137.1 (C, C-11′a), 137.0 (C, C-11′b), 136.8 (C, C-11), 134.7 (C, C-1′b), 134.6 (C, C-1′a), 130.7 (C, C-1a), 130.6 (C, C-1b), 128.5 (CH, C-13′, C-15′), 128.4 (CH, C-13, C-15), 127.8 (CH, C-14), 127.7 (CH, C-14′), 127.2 (CH, C-12′a, C-16′a), 127.1 (CH, C-12′b, C-16′b), 127.1 (CH, C-12, C-16), 121.7 (CH, C-6a), 121.2 (CH, C-6b), 118.1 (CH, C-6′), 113.9 (CH, C-2b), 113.8 (CH, C-2a), 113.7 (CH, C-5a), 113.6 (CH, C-5b), 113.3 (CH, C-5′a), 112.7 (CH, C-5′b), 109.5 (CH, C-2′a), 109.4 (CH, C-2′b), 74.8 (CH, C-7′a), 73.8 (CH, C-7′b), 71.0 ($CH_2$, C-10), 70.9 ($CH_2$, C-10′a), 70.8 ($CH_2$, C-10′b), 68.4 ($CH_2$, C-9′a), 68.0 ($CH_2$, C-9′b), 55.9 ($CH_3$, $OCH_3$b), 55.8 ($CH_3$, $OCH_3$a), 46.0 (CH, C-8′b), 45.0 (CH, C-8′a), 43.4 (CH, C-8a), 43.3 (CH, C-8b), 34.8 ($CH_2$, C-7a), 34.6 ($CH_2$, C-7b); anal. C 73.63, H 6.18%, calcd for $C_{34}H_{34}O_6$, C 73.81, H 6.35%.

**General Procedures for C-7′ Esterification (Compounds 14−17).** *A. Procedure with Acetic Anhydride. Compound **14** (7′S-**14a** and 7′R-**14b**).* To a solution of **12** (216 μmol, 1 equiv, 120 mg) and $NaHCO_3$ (433 μmol, 2 equiv, 36 mg) in toluene (3 mL) was added dropwise acetic anhydride (1.08 mmol, 5 equiv, 102 μL), and the mixture heated to reflux of toluene for 1 h. After filtration, the filtrate was evaporated under vacuum and taken into $CH_2Cl_2$ (20 mL). The organic phase was washed with saturated aqueous NaCl solution (3 × 5 mL), dried over $MgSO_4$, and evaporated under a vacuum to give **14** as an off-white powder (115 mg, 89% yield) after purification over silica gel (hexane/ethyl acetate, 4:6): mp 61−63 °C; FTIR $\nu_{max}$ 2928w, 2851w, 1768s, 1739s, 1592w, 1513s sh, 1454, 1422w, 1419w, 1262s, 1228s, 1141s, 1024s cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.44 (10H, m, H-Ar), 6.43−6.90 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.76 (0.69H, d, *J* = 6.63 Hz, H-7′a), 5.55 (0.31H, d, *J* = 7.49 Hz, H-7′b), 5.12 (4H, s, H-10, H-10′), 3.83−4.18 (2H, m, H-9′), 3.81 (3H, s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 2.52−3.15 (4H, m, H-7, H-8, H-8′), 2.05 (1.9H, s, $CH_3$a), 2.04 (1.1H, s, $CH_3$b); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 178.1 (C, C-9a), 178.0 (C, C-9b), 169.7 (C, C-1″a), 169.6 (C, C-1″b), 149.7 (C, C-3b), 149.6 (C, C-3a, C-3′b), 149.5 (C, C-3′a), 148.3 (C, C-4′a), 148.2 (C, C-4′b), 147.1 (C, C-4b), 147.0 (C, C-4a), 137.0 (C, C-11′), 136.7 (C, C-11), 130.4 (C, C-1′b), 130.1 (C, C-1′a), 130.0 (C, C-1a), 129.9 (C, C-1b), 128.5 (CH, C-13′, C-15′), 128.4 (CH, C-13, C-15), 127.8 (CH, C-14), 127.7 (CH, C-14′), 127.3 (CH, C-12′a, C-16′a), 127.2 (CH, C-12′b, C-16′b), 127.1 (CH, C-12, C-16), 121.5 (CH, C-6a), 121.3 (CH, C-6b), 118.6 (CH, C-6′), 113.9 (CH, C-2), 113.7 (CH, C-5), 113.1 (CH, C-5′a), 112.7 (CH, C-5′b), 110.1 (CH, C-2′), 75.9 (CH, C-7′a), 75.4 (CH, C-7′b), 71.0 ($CH_2$, C-10), 70.8 ($CH_2$, C-10′), 67.8 ($CH_2$, C-9′b), 67.7 ($CH_2$, C-9′a), 56.0 ($CH_3$, $OCH_3$a), 55.9 ($CH_3$, $OCH_3$b), 55.8 ($CH_3$, $OCH_3$), 43.8 (CH, C-8′), 43.5 (CH, C-8b), 43.3 (CH, C-8a), 34.8 ($CH_2$, C-7a), 34.2 ($CH_2$, C-7b), 21.0 ($CH_3$, $CH_3$b), 20.9 ($CH_3$, $CH_3$a); anal. C 72.21, H, 6.34%, calcd for $C_{36}H_{36}O_8$, C 72.47, H 6.08%.

*B. Procedure with DAST (Compound **15**).* A solution of octanoic acid (216 μmol, 1.2 equiv, 34.3 μL) in $CH_2Cl_2$ (1.5 mL) was cooled to 0 °C before dropwise addition of DAST (216 μmol, 1.2 equiv, 30 μL). After 30 min, the mixture was transferred through a cannula to a solution of compound **12** (180 μmol, 1 equiv, 100 mg) and DMAP (180 μmol, 1 equiv, 22 mg) in $CH_2Cl_2$ (1.5 mL). The mixture was stirred at rt for an additional 90 min before quenching and purification over silica gel (hexane/ethyl acetate, 6:4) to provide **15** as a white solid (84 mg, 68%).

*C. Procedure with Acyl Chlorides (Compounds **15** and **16**).* To a solution of **12** (180 μmol, 1 equiv, 100 mg) in acetonitrile (4 mL) was added DMAP (216 μmol, 1.2 equiv, 26 mg), and the mixture was cooled to 0 °C before dropwise addition of acyl chloride (216 μmol, 1.2 equiv). The mixture was stirred at 80 °C for 24 h. After evaporation of the volatiles, the residue was dissolved in $CH_2Cl_2$ (20 mL) and washed with saturated aqueous NaCl solution (3 × 5 mL) to afford after evaporation under vacuum the desired compound as a white solid (**15**: 52%, **16**: 46%).

*D. General Procedure of Esterification with DCCI (Compounds **15**−**17**).* To a solution of **12** (2.70 mmol, 1 equiv, 1.5 g) in acetonitrile (35 mL) were added successively DMAP (3.52 mmol, 1.3 equiv, 430 mg), a fatty acid (3.52 mmol, 1.3 equiv), and DCCI (3.52 mmol, 1.3 equiv, 725 mg). The mixture was stirred at 80 °C for 4 h. Silica gel (20 g) was added to the crude mixture, and the solid loading was purified over silica gel (hexane/ethyl acetate, 8:2 to 4:6) to provide the esters **15**−**17** as white solids (70−88%) (**15**: 88% yield, **16**: 77% yield, **17**: 70% yield).

*Compound **15** (7′S-**15a** and 7′R-**15b**:* white solid, 88%, mp 69−71 °C; FTIR $\nu_{max}$ 3497w, 3372br w, 2920s, 2850s sh, 1739, 1610w, 1515s sh, 1468, 1370w, 1266, 1213, 1157s, 1105, 1072, 1038 cm$^{-1}$; $^1$H NMR


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($CDCl_3$, 400 MHz) $\delta$ 7.28−7.46 (10H, m, H-Ar), 6.47−6.85 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.82 (0.67H, d, $J$ = 6.22 Hz, H-7′a), 5.60 (0.33H, d, $J$ = 7.33 Hz, H-7′b), 5.11 (4H, br s, H-10, H-10′), 3.88−4.17 (2H, m, H-9′), 3.83 (2H, s, $OCH_3$a), 3.80 (4H, br s, $OCH_3$b, $OCH_3$), 2.61−3.02 (4H, m, H-7, H-8, H-8′), 2.40 (1.25H, t, $J$ = 7.36 Hz, H-2″a), 2.33 (0.75H, t, $J$ = 7.23 Hz, H-2″b), 1.64 (2H, m, H-3″), 1.30 (8H, m, 4 $CH_2$), 0.91 (3H, m, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 177.7 (C, C-9a), 177.6 (C, C-9b), 172.0 (C, C-1″a), 171.9 (C, C-1″b), 149.3 (C, C-3b, C-3′b), 149.2 (C, C-3a, C-3′a), 147.8 (C, C-4′), 146.7 (C, C-4), 136.8 (C, C-11′), 136.5 (C, C-11), 130.4 (C, C-1′b), 130.0 (C, C-1′a), 129.9 (C, C-1a), 129.8 (C, C-1b), 128.0 (CH, C-13′, C-15′), 127.9 (CH, C-13, C-15), 127.4 (CH, C-14), 127.3 (CH, C-14′), 126.9 (CH, C-12′a, C-16′a), 126.9 (CH, C-12′b, C-16′b), 126.8 (CH, C-12, C-16), 121.1 (CH, C-6a), 121.0 (CH, C-6b), 118.2 (CH, C-6′b), 118.0 (CH, C-6′a), 113.5 (CH, C-2), 113.3 (CH, C-5b), 113.2 (CH, C-5a), 112.8 (CH, C-5′a), 112.5 (CH, C-5′b), 109.7 (CH, C-2′b), 109.5 (CH, C-2′a), 75.3 (CH, C-7′a), 74.8 (CH, C-7′b), 70.5 ($CH_2$, C-10), 70.4 ($CH_2$, C-10′), 67.5 ($CH_2$, C-9′a), 67.4 ($CH_2$, C-9′b), 55.5 ($CH_3$, $OCH_3$a), 55.4 ($CH_3$, $OCH_3$b), 55.3 ($CH_3$, $OCH_3$), 43.5 (CH, C-8′b), 43.3 (CH, C-8′a), 43.1 (CH, C-8b), 43.0 (CH, C-8a), 34.4 ($CH_2$, C-7b), 33.9 ($CH_2$, C-7a), 33.8 ($CH_2$, C-2″b), 31.1 ($CH_2$, C-2″a), 28.6 ($CH_2$, C-4″a, C-5″a), 28.5 ($CH_2$, C-4″b, C-5″b), 28.4 ($CH_2$, C-6″a), 28.3 ($CH_2$, C-6″b), 24.5 ($CH_2$, C-3″b), 24.4 ($CH_2$, C-3″a), 22.1 ($CH_2$, C-7″), 13.6 ($CH_3$, C-8″); anal. C 74.13, H 7.21%, calcd for $C_{42}H_{48}O_8$, C 74.09, H 7.11%.

*Compound* ***16*** *(7′S-**16a** and 7′R-**16b**):* white solid, 77%, mp 76−78 °C; FTIR $\nu_{max}$ 2918, 2849, 1780s, 1737s, 1591w, 1518s sh, 1454, 1421w, 1365w, 1258s, 1238s, 1158s, 1137s, 1029s cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.28−7.44 (10H, m, H-Ar), 6.43−6.81 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.79 (0.69H, d, $J$ = 6.39 Hz, H-7′a), 5.57 (0.31H, d, $J$ = 7.35 Hz, H-7′b), 5.11 (4H, br s, H-10, H-10′), 3.82−4.18 (2H, m, H-9′), 3.82 (2H, s, $OCH_3$a), 3.80 (3H, br s, $OCH_3$), 3.79 (1H, s, $OCH_3$b), 2.59−3.06 (4H, m, H-7, H-8, H-8′), 2.37 (1.30H, t, $J$ = 6.99 Hz, H-2″a), 2.31 (0.70H, t, $J$ = 7.17 Hz, H-2″b), 1.61 (2H, m, H-3″), 1.27 (16H, m, 8 $CH_2$), 0.89 (3H, t, $J$ = 6.81 Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.0 (C, C-9a), 177.9 (C, C-9b), 172.4 (C, C-1″a), 172.3 (C, C-1″b), 149.6 (C, C-3′b), 149.5 (C, C-3b), 149.5 (C, C-3a), 149.4 (C, C-3′a), 148.1 (C, C-4′a), 148.0 (C, C-4′b), 147.0 (C, C-4b), 146.9 (C, C-4a), 137.0 (C, C-11′), 136.7 (C, C-11), 130.6 (C, C-1′b), 130.1 (C, C-1′a), 130.0 (C, C-1a), 129.9 (C, C-1b), 128.4 (CH, C-13′, C-15′), 128.3 (CH, C-13, C-15), 127.7 (CH, C-14), 127.6 (CH, C-14′), 127.1 (CH, C-12′a, C-16′a), 127.0 (CH, C-12′b, C-16′b), 126.9 (CH, C-12, C-16), 121.4 (CH, C-6a), 121.2 (CH, C-6b), 118.4 (CH, C-6′b), 118.3 (CH, C-6′a), 113.8 (CH, C-2), 113.6 (CH, C-5′b), 113.5 (CH, C-5′a), 113.0 (CH, C-5a), 112.7 (CH, C-5b), 109.9 (CH, C-2′b), 109.8 (CH, C-2′a), 75.5 (CH, C-7′a), 75.0 (CH, C-7′b), 70.8 ($CH_2$, C-10), 70.7 ($CH_2$, C-10′), 67.8 ($CH_2$, C-9′a), 67.7 ($CH_2$, C-9′b), 55.8 ($OCH_3$a), 55.7 ($OCH_3$b), 55.6 ($OCH_3$), 43.8 (CH, C-8′b), 43.6 (CH, C-8′a), 43.4 (CH, C-8b), 43.2 (CH, C-8a), 34.7 ($CH_2$, C-7b), 34.2 ($CH_2$, C-7a), 34.1 ($CH_2$, C-2″b), 34.0 ($CH_2$, C-2″a), 31.7 ($CH_2$, C-10″), 29.4 (2 $CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 24.7 ($CH_2$, C-3″), 22.5 ($CH_2$, C-11″), 14.0 ($CH_3$b), 13.9 ($CH_3$a); anal. C 74.64, H 7.88%, calcd for $C_{46}H_{56}O_8$, C 74.97, H 7.66%.

*Compound* ***17*** *(7′S-**17a** and 7′R-**17b**):* white solid, 70%, mp 93−95 °C; FTIR $\nu_{max}$ 2917, 2850, 1780, 1734, 1590w, 1518s sh, 1465, 1454, 1384w, 1259s, 1232s, 1156s, 1141s, 1026s cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.26−7.45 (10H, m, H-Ar), 6.45−6.82 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.81 (0.68H, d, $J$ = 6.25 Hz, H-7′a), 5.59 (0.32H, d, $J$ = 7.34 Hz, H-7′b), 5.11 (4H, br s, H-10, H-10′), 3.88−4.17 (2H, m, H-9′), 3.82 (2H, s, $OCH_3$a), 3.80 (1H, s, $OCH_3$b), 3.80 (2H, s, $OCH_3$a), 3.79 (1H, s, $OCH_3$b), 2.60−3.02 (4H, m, H-7, H-8, H-8′), 2.39 (1.30H, t, $J$ = 7.37 Hz, H-2″a), 2.32 (0.70H, t, $J$ = 7.25 Hz, H-2″b), 1.64 (2H, m, H-3″), 1.30 (28H, m, 14 $CH_2$), 0.92 (3H, t, $J$ = 6.78 Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz,) $\delta$ 177.9 (C, C-9a), 177.7 (C, C-9b), 172.1 (C, C-1″a), 172.0 (C, C-1″b), 149.5 (C, C-3′b), 149.4 (C, C-3b), 149.4 (C, C-3a), 149.3 (C, C-3′a), 147.9 (C, C-4′), 146.9 (C, C-4b), 146.8 (C, C-4a), 136.9 (C, C-11′), 136.6 (C, C-11), 130.5 (C, C-1′b), 130.0 (C, C-1′a), 129.9 (C, C-1a), 129.8 (C, C-1b), 128.2 (CH, C-13′, C-15′), 128.1 (CH, C-13, C-15), 127.5 (CH, C-14), 127.4 (CH, C-14′), 127.0 (CH, C-12′a, C-16′a), 126.9 (CH, C-12′b, C-16′b), 126.8 (CH, C-12, C-16), 121.2 (CH, C-6a), 121.1 (CH, C-6b), 118.3 (CH, C-6′b), 118.2 (CH, C-6′a), 113.6 (CH, C-2), 113.4 (CH, C-5′b), 113.3 (CH, C-5′a), 112.9 (CH, C-5a), 112.6 (CH, C-5b), 109.8 (CH, C-2′b), 109.7 (CH, C-2′a), 75.4 (CH, C-7′a), 74.9 (CH, C-7′b), 70.7 ($CH_2$, C-10), 70.5 ($CH_2$, C-10′), 67.6 ($CH_2$, C-9′), 55.6 ($CH_3$, $OCH_3$a), 55.5 ($CH_3$, $OCH_3$b), 55.4 ($CH_3$, $OCH_3$), 43.7 (CH, C-8′b), 43.4 (CH, C-8′a), 43.2 (CH, C-8b), 43.1 (CH, C-8a), 34.6 ($CH_2$, C-7b), 34.0 ($CH_2$, C-7a), 33.9 ($CH_2$, C-2″), 31.6 ($CH_2$, C-16″), 29.4 (5 $CH_2$), 29.3 (2 $CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 29.0 (2 $CH_2$), 28.8 ($CH_2$), 24.6 ($CH_2$, C-3″), 22.4 ($CH_2$, C-17″), 13.8 ($CH_3$); anal. C 75.91, H 8.48%, calcd for $C_{52}H_{68}O_8$, C 76.06, H 8.35%.

**General Procedure for Deprotection of Benzyl Groups (Compounds 3−5).** To a solution of esters **15**−**17** (∼1 mmol, 1 equiv, 750 mg) in ethanol (30 mL) was added $Pd(OH)_2$ 20% (0.3 equiv, ∼200 mg), and the mixture was vigorously stirred at rt for 2−2.5 h. After filtration over Celite, the filtrate was purified over silica gel (hexane/ethyl acetate, 8:2 to 4:6) to provide, respectively, **3**−**5** (92−95%).

*Compound* ***3*** *(7′S-**3a** and 7′R-**3b**):* colorless, viscous liquid, 95%; FTIR $\nu_{max}$ 3393br, 2956, 2937, 2857, 1740, 1613w, 1516s sh, 1457w, 1432w, 1369w, 1270, 1237, 1157, 1121, 1064, 1031 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.37−6.81 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 5.88 (2H, br s, OH-4, OH-4′), 5.77 (0.75H, d, $J$ = 6.13 Hz, H-7′a), 5.51 (0.25H, d, $J$ = 7.8 Hz, H-7′b), 3.87−4.17 (2H, m, H-9′), 3.76 (2H, s, $OCH_3$a), 3.75 (3H, br s, $OCH_3$), 3.73 (1H, s, $OCH_3$b), 2.52−2.96 (4H, m, H-7, H-8, H-8′), 2.35 (1.43H, t, $J$ = 7.52 Hz, H-2″a), 2.27 (0.57H, t, $J$ = 7.76 Hz, H-2″b), 1.57 (2H, m, H-3″), 1.24 (8H, m, 4 $CH_2$), 0.83 (3H, m, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.4 (C, C-9a), 178.2 (C, C-9b), 172.6 (C, C-1″a), 172.4 (C, C-1″b), 146.7 (C, C-3), 146.6 (C, C-3′a), 146.5 (C, C-3′b), 145.7 (C, C-4′b), 145.6 (C, C-4′a), 144.5 (C, C-4b), 144.4 (C, C-4a), 129.4 (C, C-1′b), 128.9 (C, C-1′a), 128.8 (C, C-1a), 128.7 (C, C-1b), 122.1 (CH, C-6a), 121.9 (CH, C-6b), 119.5 (CH, C-6′b), 118.8 (CH, C-6′a), 114.4 (CH, C-2a), 114.3 (CH, C-2b), 114.0 (CH, C-5′a), 113.9 (CH, C-5′b), 111.6 (CH, C-5a), 111.2 (CH, C-5b), 108.8 (CH, C-2′), 75.8 (CH, C-7′a), 75.3 (CH, C-7′b), 68.0 ($CH_2$, C-9′), 55.6 ($CH_3$, $OCH_3$a), 55.5 ($CH_3$, $OCH_3$), 55.5 ($CH_3$, $OCH_3$b), 43.8 (CH, C-8′b), 43.7 (CH, C-8′a), 43.6 (CH, C-8b), 43.3 (CH, C-8a), 34.8 ($CH_2$, C-7b), 34.3 ($CH_2$, C-7a), 34.2 ($CH_2$, C-2″a), 34.1 ($CH_2$, C-2″b), 31.41 ($CH_2$, C-6″a), 31.4 ($CH_2$, C-6″b), 28.9 ($CH_2$a), 28.8 ($CH_2$b), 28.7 ($CH_2$a), 28.6 ($CH_2$b), 24.7 ($CH_2$b), 24.6 ($CH_2$a), 22.4 ($CH_2$, H-7″), 14.0 ($CH_3$b), 13.9 ($CH_3$a); anal. C 67.11, H 7.30%, calcd for $C_{28}H_{36}O_8$, C 67.18, H 7.25.

*Compound* ***4*** *(7′S-**4a** and 7′R-**4b**):* colorless, viscous liquid, 92%; FTIR $\nu_{max}$ 3425br, 2926, 2853, 1768, 1742, 1607w, 1516s sh, 1465w, 1432w, 1376w, 1270s, 1238, 1152s, 1123, 1028s cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 6.43−6.81 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 6.01 (1H, br s, OH-4′), 5.88 (1H, br s, OH-4), 5.77 (0.84H, d, $J$ = 6.04 Hz, H-7′a), 5.51 (0.16H, d, $J$ = 7.96 Hz, H-7′b), 3.89−4.17 (2H, m, H-9′), 3.75 (3H, s, $OCH_3$), 3.74 (3H, s, $OCH_3$), 2.52−2.95 (4H, m, H-7, H-8, H-8′), 2.34 (1.64H, t, $J$ = 7.51 Hz, H-2″a), 2.27 (0.36H, t, $J$ = 7.24 Hz, H-2″b), 1.59 (2H, m, H-3″), 1.24 (16H, m, 8 $CH_2$), 0.85 (3H, t, $J$ = 6.77 Hz, $CH_3$); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.4 (C, C-9a), 178.2 (C, C-9b), 172.6 (C, C-1″a), 172.5 (C, C-1″b), 146.7 (C, C-3), 146.6 (C, C-3′a), 146.5 (C, C-3′b), 145.7 (C, C-4′b), 145.6 (C, C-4′a), 144.5 (C, C-4b), 144.4 (C, C-4a), 129.3 (C, C-1′b), 128.9 (C, C-1′a), 128.7 (C, C-1a), 128.6 (C, C-1b), 122.1 (CH, C-6a), 121.9 (CH, C-6b), 119.4 (CH, C-6′b), 118.7 (CH, C-6′a), 114.4 (CH, C-2a), 114.3 (CH, C-2b), 114.0 (CH, C-5′a), 113.9 (CH, C-5′b), 111.5 (CH, C-5a), 111.2 (CH, C-5b), 108.8 (CH, C-2′), 75.7 (CH, C-7′a), 75.3 (CH, C-7′b), 68.0 ($CH_2$, C-9′), 55.6 ($CH_3$, $OCH_3$a), 55.5 ($CH_3$, $OCH_3$, $OCH_3$b), 43.8 (CH, C-8′b), 43.7 (CH, C-8′a), 43.6 (CH, C-8b), 43.3 (CH, C-8a), 34.8 ($CH_2$, C-7b), 34.3 ($CH_2$, C-7a), 34.2 ($CH_2$, C-2″a), 34.1 ($CH_2$, C-2″b), 31.6 ($CH_2$, C-10″), 29.4 (2 $CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 24.7 ($CH_2$, C-3″), 22.5 ($CH_2$, C-11″), 13.9 ($CH_3$); anal. C 69.25, H 8.14%, calcd for $C_{32}H_{44}O_8$, C 69.04, H 7.97%.



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*Compound **5** (7′S-**5a** and 7′R-**5b**):* colorless, viscous liquid, 93%; FTIR $\nu_{max}$ 3434br, 2925, 2851, 1763, 1738, 1604w, 1516s sh, 1464, 1374w, 1237, 1272, 1154s, 1121, 1030s $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.43−6.80 (6H, m, H-2, H-5, H-6, H-2′, H-5′, H-6′), 6.03 (1H, br s, OH-4′), 5.89 (1H, br s, OH-4), 5.77 (0.86H, d, $J$ = 5.97 Hz, H-7′a), 5.51 (0.14H, d, $J$ = 7.97 Hz, H-7′b), 3.89−4.14 (2H, m, H-9′), 3.74 (3H, br s, $OCH_3$), 3.73 (3H, br s, $OCH_3$), 2.52−2.94 (4H, m, H-7, H-8, H-8′), 2.34 (1.65H, t, $J$ = 7.49 Hz, H-2″a), 2.27 (0.35H, t, $J$ = 7.69 Hz, H-2″b), 1.58 (2H, m, H-3″), 1.22 (28H, m, 14 $CH_2$), 0.85 (3H, t, $J$ = 6.73 Hz, $CH_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 178.3 (C, C-9a), 178.2 (C, C-9b), 172.6 (C, C-1″a), 172.4 (C, C-1″b), 146.7 (C, C-3), 146.6 (C, C-3′b), 146.5 (C, C-3′a), 145.7 (C, C-4′b), 145.6 (C, C-4′a), 144.5 (C, C-4b), 144.4 (C, C-4a), 129.3 (C, C-1′b), 128.9 (C, C-1′a), 128.7 (C, C-1a), 128.6 (C, C-1b), 122.0 (CH, C-6a), 121.9 (CH, C-6b), 119.4 (CH, C-6′b), 118.7 (CH, C-6′a), 114.4 (CH, C-2a), 114.3 (CH, C-2b), 114.0 (CH, C-5′a), 113.9 (CH, C-5′b), 111.5 (CH, C-5a), 111.2 (CH, C-5b), 108.8 (CH, C-2′), 75.7 (CH, C-7′a), 75.3 (CH, C-7′b), 68.0 ($CH_2$, C-9′), 55.5 ($CH_3$, $OCH_3$), 55.4 ($CH_3$, $OCH_3$), 43.8 (CH, C-8′b), 43.7 (CH, C-8′a, C-8b), 43.3 (CH, C-8a), 34.8 ($CH_2$, C-7b), 34.3 ($CH_2$, C-7a), 34.2 ($CH_2$, C-2″a), 34.1 ($CH_2$, C-2″b), 31.7 ($CH_2$, C-16″), 29.5 (5 $CH_2$), 29.4 (2 $CH_2$), 29.3 ($CH_2$), 29.2 ($CH_2$), 29.1 ($CH_2$), 29.0 ($CH_2$), 28.9 ($CH_2$), 24.7 ($CH_2$, C-3″), 22.4 ($CH_2$, C-17″), 14.0 ($CH_3$b), 13.9 ($CH_3$a); anal. C 71.39, H 8.89%, calcd for $C_{38}H_{56}O_8$, C 71.22, H 8.81%.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b01124.

Experimental for compounds **1**, **7**, **10**, and **13**; IR spectra; $^1H$ and $^{13}C$ NMR spectra; additional lipophilicity data (PDF)

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### Notes

The authors declare no competing financial interest.

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