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Efficient and versatile synthesis of 5-*O*-acylquinic acids with a direct esterification using a *p*-methoxybenzyl quinate as a key intermediate

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ABSTRACT

An efficient and versatile synthesis of 5-*O*-acylquinic acids from commercially available (−)-quinic acid was accomplished. We designed *p*-methoxybenzyl quinate as a key intermediate, and two problems, the esterification of the sterically hindered 5-OH group for the concise divergent synthesis and the low yield of the final deprotection step, were solved. For the first problem, we improved Tanabe's method, TsCl/NMI-mediated esterification using free carboxylic acids, by the addition of *i*-Pr_2NEt. For the second problem, we established a TFA- or BCl_3/C_6HMe_5-catalyzed deprotection reaction for the final deprotection step. 5-*O*-Acylquinic acids were synthesized in seven steps with 45–60% overall yield.

1. Introduction

Acylquinic acids are widely distributed in nature as plant-derived (poly)phenols.[1] They have attracted considerable attention because they exhibit a wide range of biological activities, including antioxidation,[2] anti-HIV-1 activity,[3] antitumor activity,[4] hepatoprotective activity,[5] antifungal activity,[6] collagenase inhibition,[7] flower color development,[8] and plant disease prevention.[9] Interestingly, chlorogenic acid (3-*O*-caffeoylquinic acid) has been detected as a fermentation product of wine by *Saccharomyces cerevisiae* although grapes lack acylquinic acids.[10] Thus, 5-*O*-acylquinic acids and the related compounds will probably be discovered in a wine during fermentation. Furthermore, acylquinic acid (i.e., chlorogenic acid) has been used to comprehend the formation mechanism of glutathion-substituted dihydroxyphenyl compounds formed during the oxidation of white wine because the caffeic acid plays an important role in wine oxidation.[11] Di- and triacylquinic acid derivatives, in particular, possess remarkable and interesting biological activity. For example, 3,4,5-tri-*O*-caffeoylquinic acid[3a] and 3,5-tri-*O*-caffeoylquinic acid[3c] are recognized to exhibit high potential as anti-HIV-1 inhibitors. Of the monoacylquinic acid derivatives, Cisneros-Zevallos et al. reported that chlorogenic acid and 5-*O*-caffeoylquinic acid (**1**) exhibited anti-breast cancer activity.[4b] It is well known that **1** and/or 5-*O*-*p*-coumaroylquinic acid (**2**) work as essential co-pigments to produce the blue color of hydrangeas.[8] Recently, chlorogenic acid and **1** were reportedly linked to the increased resistance of peaches to brown rot infection.[9]

To investigate these unique biological properties of acylquinic acid derivatives, especially those of 5-*O*-acylquinic acids, an efficient and reliable synthetic methodology can be applied not only for natural ones but also for molecular designed analogs. Until now, a number of synthetic routes toward 3-*O*-acylquinic acids have been reported.[12] However, only two examples for 5-*O*-acylquinic acids exist (Scheme 1).[8b,c,13,14] In these syntheses, there are two problems. One is the esterification of the sterically hindered axial 5-OH group. To achieve this reaction, unstable acyl chloride is required.[8b,c,13] The other problem is the low yield of the final deprotection step. Under acidic conditions, the competitive deacylation[8b,c] between the 5-acyl group and the 1-methyl group and the acyl transfer occurs

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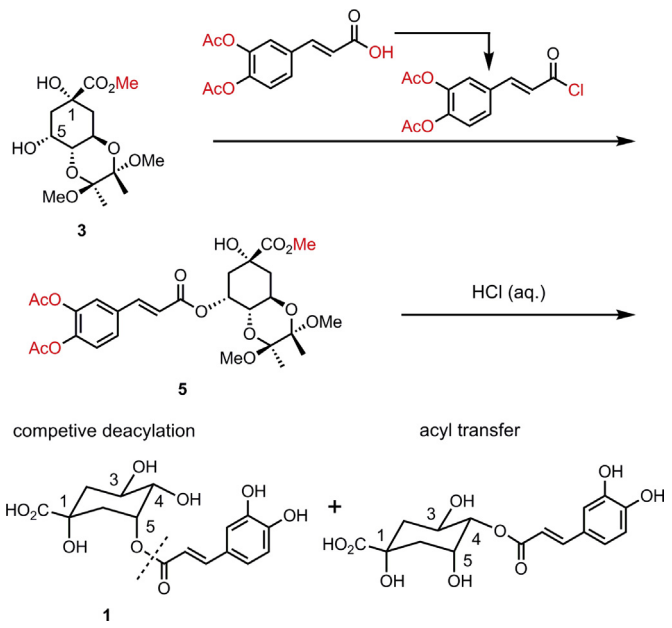
(Scheme 1).[8b,c,13] Thus, the choice of protecting group is crucial. We overcame these two problems and achieved an efficient and versatile synthesis of 5-*O*-acylquinic acids from (−)-quinic acid using *p*-methoxybenzyl (PMB) quinate **4** as a key intermediate.



Scheme 1. Previously reported route for 5-*O*-acylquinic acids using methyl quinate **3**.

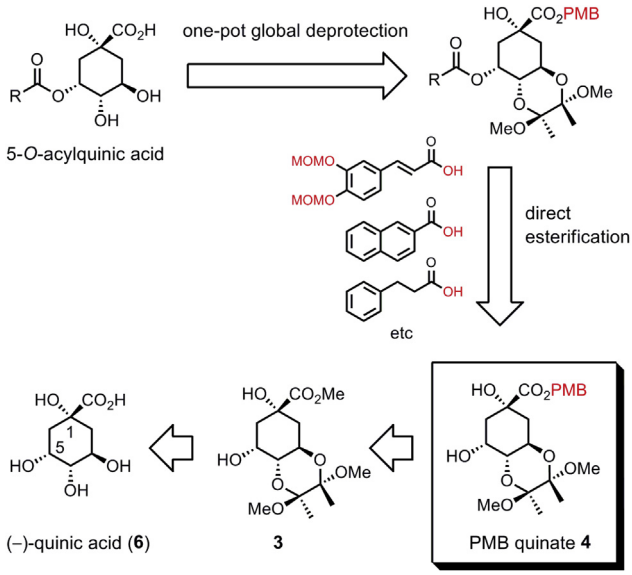
2. Results and discussion

2.1. Re-examination of the deprotection reaction of methyl 5-*O*-caffeoylquinate (5) under hydrochloric acid

Initially, we re-examined the deprotection reaction of methyl 5-*O*-caffeoylquinate (**5**) under hydrochloric acid. Sefkow et al. reported that the treatment of **5** in 1 M HCl/THF at 23 °C for 7 days gave 5-*O*-caffeoylquinic acid (**1**) in 81% yield (Scheme 1).[13] However, our re-examination only gave a yield of less than 30%. To investigate the cause of such a low yield, the stability of **1** was studied under Sefkow's deprotection condition.[13] More than 40% of **1** was decomposed after 7 days. Because hydrochloric acid obviously decomposes **1** gradually, we reasoned that a mild acidic condition and short reaction time should be required to solve the low yield of the final deprotection step.

2.2. Synthetic strategy for 5-*O*-acylquinic acids

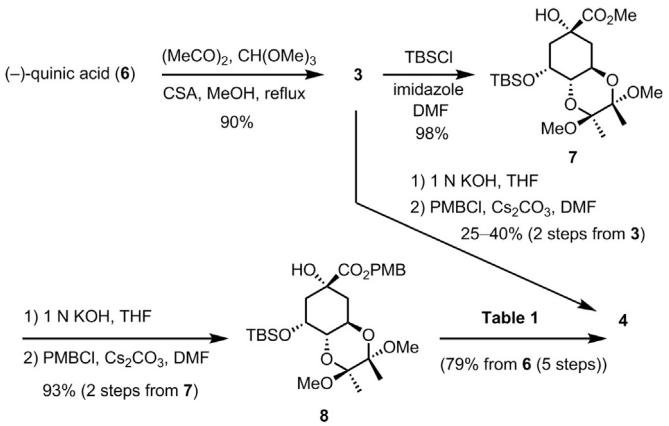
Our retrosynthetic analysis of 5-*O*-acylquinic acids is shown in Scheme 2. Because the demethylation of 1-carboxylic acid might require a hard acidic condition and/or a long reaction time, we decided to replace the methyl group of the 1-carboxylic acid with a PMB group, which can be easily deprotected by using mild acidic conditions.[15–20] Furthermore, we selected the MOM (methoxymethyl) group as the protecting group of the hydroxycinnamic moiety for the synthesis of 5-*O*-caffeoylquinic acid (**1**) and 5-*O*-*p*-coumaroylquinic acid (**2**) due to the rapid and mild deprotection under acidic conditions.[21] 5-*O*-Acylquinic acids would be obtained by one-pot global deprotection from the corresponding 5-*O*-acyl PMB quinates. 5-*O*-Acyl PMB quinates could be synthesized by direct esterification using free carboxylic acids. The key intermediate **4** could be prepared from (−)-quinic acid (**6**).



Scheme 2. Retrosynthetic analysis of 5-*O*-acylquinic acids using PMB quinate **4**.

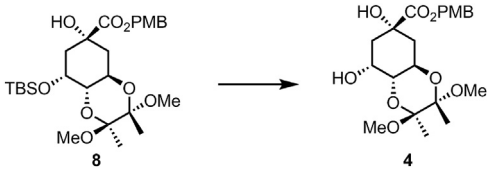
2.3. Preparation of PMB quinate 4

Methyl quinate **3** was prepared based on a previous report[14] in 90% yield (Scheme 3). After the alkaline hydrolysis of **3**, the PMB group was introduced by regioselective esterification according to Frost's report (Scheme 3).[22] However, the yield of this protection step was quite low (25–40%). Thus, **4** was instead prepared using protection–deprotection techniques, as shown in Scheme 3. The protection of **3** by TBSCl produced the TBS ether **7** in 98% yield. Subsequent alkaline hydrolysis followed by protection with PMBCl generated the PMB ester **8** in 93% yield. However, desilylation of **8** by TBAF produced PMB quinate **4** in modest yield (55%) (Table 1, entry 1). A $Sc(OTf)_3$-catalyzed desilylation[23] increased the yield (73%) (Table 1, entry 2). Finally, TBAF/AcOH gave **4** in 96% yield[24] (79% overall yield from **6**) (Table 1, entry 3); its structure was unambiguously proven by X-ray crystallographic analysis (Fig. 1).



Scheme 3. Synthesis of PMB quinate **4**.

Table 1
Conditions for optimizing the desilylation of **8**



Entry	Reagents	Yield[a] (%)
1	TBAF, THF	55
2	5 mol % $Sc(OTf)_3$, CH_3CN, H_2O	73
3	TBAF, AcOH, THF	96

[a] Isolated yield.

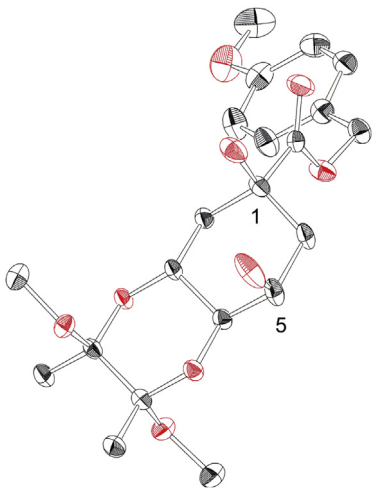


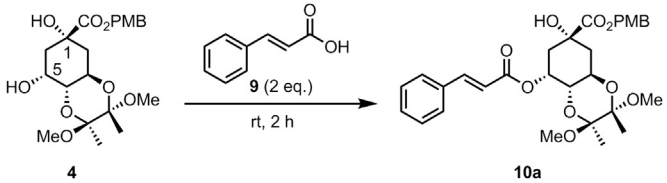
Fig. 1. X-ray crystal structure of PMB quinate **4**.

2.4. Esterification of 5-OH of PMB quinate 4

With the key building block **4** in hand, various direct esterifications to the sterically hindered axial 5-OH group were examined (Table 2).[25,26] Tanabe's esterification[25] was carried out using 2 equiv of cinnamic acid (**9**). The yield of the desired ester **10a** was low (31%) (Table 2, entry 1). To enhance the nucleophilicity of alcohol **4**, *i*-Pr_2NEt was added to give a yield of 60%.[27,28] As a further optimization, we found that the use of 4 equiv of TsCl at 40 °C in $C_2H_4Cl_2$ in the presence of MS 4 Å gave **10a** in 81% yield (Table 2, entry 3, method A). Other esterification methods were examined,[26] but the yields were lower than our improved TsCl/NMI/*i*-Pr_2NEt-mediated esterification (Table 2, entries 4–8).

Next, 2-naphthoic acid (**11**) was tested (Table 3, entry 1, method A). As expected, the desired ester **14a** was obtained in high yield (86%). However, 2-acylimidazole **15**, unexpectedly was obtained as a byproduct of the reaction in 35% yield (based on **11**) due to Friedel–Crafts-type C-acylation.[29] In the absence of *i*-Pr_2NEt, **15** was not observed. To prevent the generation of an acceptor of C-acylation, NMI was added at the final step. As a result, the reaction using 1.5 equiv of **11** at room temperature was carried out to give the combined yield of 91% without **15** (Table 3, entry 2, method B). The esterification of cinnamic acid (**9**) was re-examined using method B (Table 3, entry 3), and it was found that method B was superior to method A (Table 2, entry 3 vs Table 3, entry 3).

Table 2
Direct esterification of PMB quinate **4** with cinnamic acid (**9**)

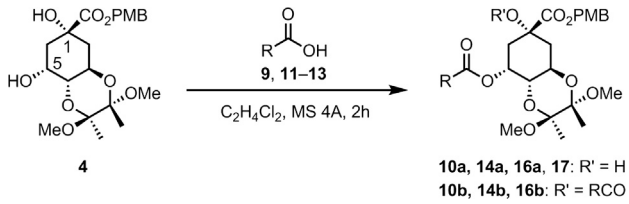


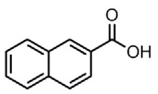
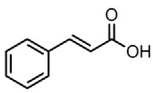
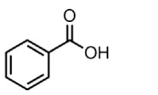
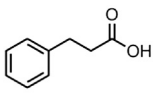
Entry	Reagents (equiv)	Temp (°C)	Solvent	Yield[a] (%)
1[25]	TsCl (2), NMI (6)	rt	CH_2Cl_2	31
2	TsCl (2), NMI (6), *i*-Pr_2NEt (6)	rt	CH_2Cl_2	60
3	TsCl (4), NMI (6), *i*-Pr_2NEt (6), MS 4 Å	40	$C_2H_4Cl_2$	81[b,c]
4[26a]	EDCI (2), DMAP (0.5)	rt	CH_2Cl_2	55
5[26b]	DCC (2), DMAP (2), HOBt (2)	rt	CH_2Cl_2	29
6[26c]	EDCI (2), *i*-Pr_2NEt (4), HOBt (1)	rt	DMF	4
7[26d]	EDCI (2), *i*-Pe_2NEt (4), HOAt (1)	rt	DMF	5
8[26e]	TBTU (2), DBU (4)	rt	DMF	19

NMI=*N*-methylimidazole; EDCI=1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; DCC=*N*,*N*′-dicyclohexylcarbodiimide; HOBt=1-hydroxybenzotriazole; HOAt=1-hydroxy-7-azabenzotriazole; TBTU=2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

[a] Isolated yield.
[b] Method A: (1) RCO_2H/TsCl/NMI/*i*-Pr_2NEt=1:2:3:;, (2) **4**.
[c] The corresponding 1,5-*O*-diacylquinate **10b** was obtained in 4% yield.

Table 3
TsCl/NMI-mediated esterification between PMB quinate **4** and carboxylic acids (**9** and **11**–**13**)



Entry	RCO_2H (equiv)	Method	Temp (°C)	yield[a] (%)
1	 **11** (2.0)	A	40	**14a** (86), **15** (35)[b]
2	**11** (1.5)	B	rt	**14a** (84), **14b** (7)
3	 **9** (2.0)	B	rt	**10a** (87), **10b** (5)
4	 **12** (1.1)	B	40	**16a** (94), **16b** (3)
5	 **13** (2.0)	B	40	**17** (65)
6	**13** (2.0)	C	40	**17** (72)

Method A: (1) RCO_2H/TsCl/NMI/*i*-Pr_2NEt=1:2:3:3; (2) **4**.
Method B: (1) RCO_2H/TsCl/*i*-Pr_2NEt=1:2:3; (2) **4**; (3) NMI (6 equiv).
Method C: (1) RCO_2H/TsCl/NMI=1:2:3; (2) **4**.

[a] Isolated yield.
[b] Compound **15** is 1-methyl-2-naphthoylimidazole. Yield is based on **11**.

With the reaction condition of method B in hand, the esterification of **12** and **13** was examined (Table 3, entries 4–6). In the case of **12** (1.1 equiv), the yield was 94%. However, the esterification of the aliphatic carboxylic acid **13** gave a moderate yield of **17** (65%) (Table 3, entry 5), whereas the corresponding esterification in the absence of *i*-Pr_2NEt afforded a higher yield (72%) (Table 3, entry 6). Based on these observations, *i*-Pr_2NEt was effective only for the esterification of aromatic carboxylic acids.

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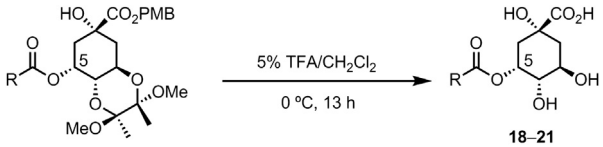
2.5. Deprotection of 5-*O*-acylquinic acids (10a, 14a, 16a, and 17)

With PMB-protected 5-acylquinates (**10a**, **14a**, **16a**, and **17**) in hand, we examined mild deprotection reactions (TFA/PhOH,[16] TfOH/*p*-TolSO$_2$NH$_2$/dioxane,[17] CBr$_4$/MeOH,[18] CeCl$_3$·7H$_2$O/NaI/CH$_3$CN,[19] and CAN/H$_2$O/CH$_3$CN[20]). However, the desired deprotection products were not obtained cleanly in any case. Then, TFA-catalyzed deprotection was examined. According to the literature,[15] the treatment of **10a** with 10% TFA in CH_2Cl_2 at 25 °C for 2 h was conducted. This deprotection afforded mainly **18** as observed by HPLC analysis. Furthermore, this reaction proceeded cleanly even using 5% TFA in CH_2Cl_2 at 25 °C for 2 h. As a further optimization, the treatment of **10a** with 5% TFA in CH_2Cl_2 at 0 °C for 13 h afforded **18** in 87% yield (Table 4, entry 1). The deprotection of **14a**, **16a**, and **17** under the same TFA-catalyzed conditions gave the corresponding 5-*O*-acylquinates (**19**, **20**, and **21**) in high yields (Table 4, entries 2–4). These deprotection yields were quite improved compared to our previous results.[8b,c]

Table 4
Global deprotection of 5-*O*-acyl PMB quinate (**10a**, **14a**, **16a**, and **17**) using TFA



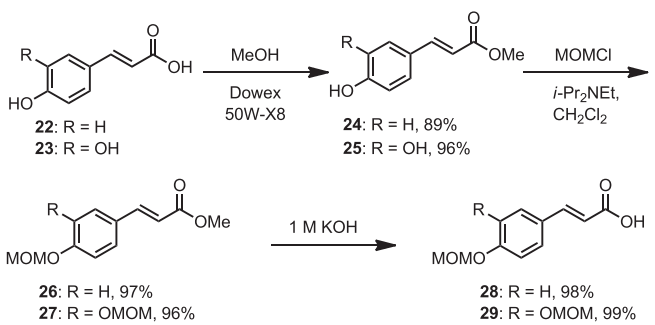
10a, 14a, 16a, 17 **18–21**

Entry	5-Acyl PMB quinate	Product	Yield[a] (%)
1	**10a**	**18**	87
2	**14a**	**19**	80
3	**16a**	**20**	80
4	**17**	**21**	79

[a] Isolated yield.

2.6. Synthesis of 5-*O*-caffeoylquinic acid (1) and 5-*O*-*p*-coumaroylquinic acid (2)

Having established both the esterification for the sterically hindered 5-OH group and the condition for the final deprotection step, the synthesis of 5-*O*-caffeoylquinic acid (**1**) and 5-*O*-*p*-coumaroylquinic acid (**2**) was carried out. The MOM group is well known to be removed easily by TFA.[21a,c,f] Therefore, the MOM group was used for the protection of the phenolic hydroxyl group. MOM-protected carboxylic acids **28** and **29** were prepared from commercially available **22** and **23**, respectively (Scheme 4). Formation of the methyl ester of **24** in the presence of Dowex H$^+$ in MeOH followed by MOM etherification yielded **26**. Subsequent hydrolysis by KOH furnished the desired **28** in high yield. Additionally, carboxylic acid **29** was prepared in a similar manner (Scheme 4).

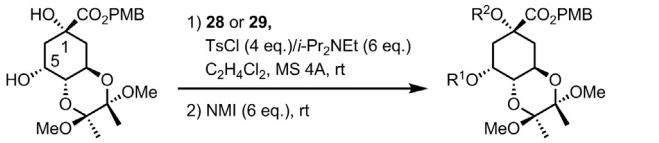


22: R = H
23: R = OH
24: R = H, 89%
25: R = OH, 96%
26: R = H, 97%
27: R = OMOM, 96%
28: R = H, 98%
29: R = OMOM, 99%

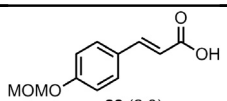
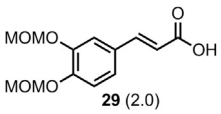
Scheme 4. Synthesis of carboxylic acids **28** and **29**.

The esterifications of PMB quinate **4** with carboxylic acids **28** and **29** were performed (Table 5) by using our method B. Although the esterification of **29** needed 6 h, both reactions at room temperature gave **30a** and **31a** in 86% and 83% yields, respectively.

Table 5
TsCl/NMI/*i*-PrNEt$_2$-mediated esterification between PMB quinate **4** and carboxylic acids (**28** and **29**)



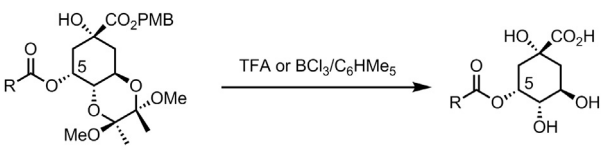
4
30a, 31a: R^1 = RCO, R^2 = H
30b, 31b: R^1 = H, R^2 = RCO

Entry	RCO$_2$H (equiv)	Time (h)	Yield[a] (%)
1	 **28** (2.0)	2	**30a** (86), **30b** (<9)
2	 **29** (2.0)	6	**31a** (83), **31b** (<4)

[a] Isolated yield.

The deprotection of **30a** and **31a** using the above optimized conditions (5% TFA in CH_2Cl_2 for 13 h at 0 °C) was conducted. Unexpectedly, these deprotections gave only trace amounts of the desired products. Even increasing the concentration of TFA to 10% afforded **1** and **2** in 39% and 34% yields, respectively (Table 6, entries 1 and 2). To clarify the low yield of the deprotection, the reactions of **30a** and **31a** were analyzed by NMR, HPLC, and ESI-Q-TOF-MS. The NMR and HPLC profiles of the crude reaction mixtures of **30a** and **31a** were sluggish due to having many unidentified byproducts compared to that of **10a**. ESI-Q-TOF-MS analysis revealed that the MOM groups remained at the last stage accompanied with undesired decomposition. This might have arisen from the formaldehyde derived from the MOM group.[30] To overcome these problems, several protecting groups for the phenolic hydroxyl moiety, such as PMB[31] and 3,4-DMB (3,4-dimethoxybenzyl), were examined using TFA-catalyzed deprotection conditions (10% TFA in CH_2Cl_2 at 0 °C). However, the yield of these reactions could not be improved.

Table 6
Global deprotection of 5-*O*-acyl PMB quinates (**30a** and **31a**)



30a, 31a **1, 2**

Entry	5-Acyl PMB quinate	Reaction conditions	Product	Yield[a] (%)
1	**30a**	10% TFA, 0 °C, 13 h	**2**	34
2	**31a**	10% TFA, 0 °C, 13 h	**1**	39
3[b]	**30a**	BCl$_3$/C$_6$HMe$_5$, −40 to 0°C, 5 h	**2**	73
4[b]	**31a**	BCl$_3$/C$_6$HMe$_5$, −40 to 0°C, 3 h	**1**	69

[a] Isolated yield.
[b] BCl$_3$ of 10 equiv was used. C$_6$HMe$_5$ (12.5 equiv).

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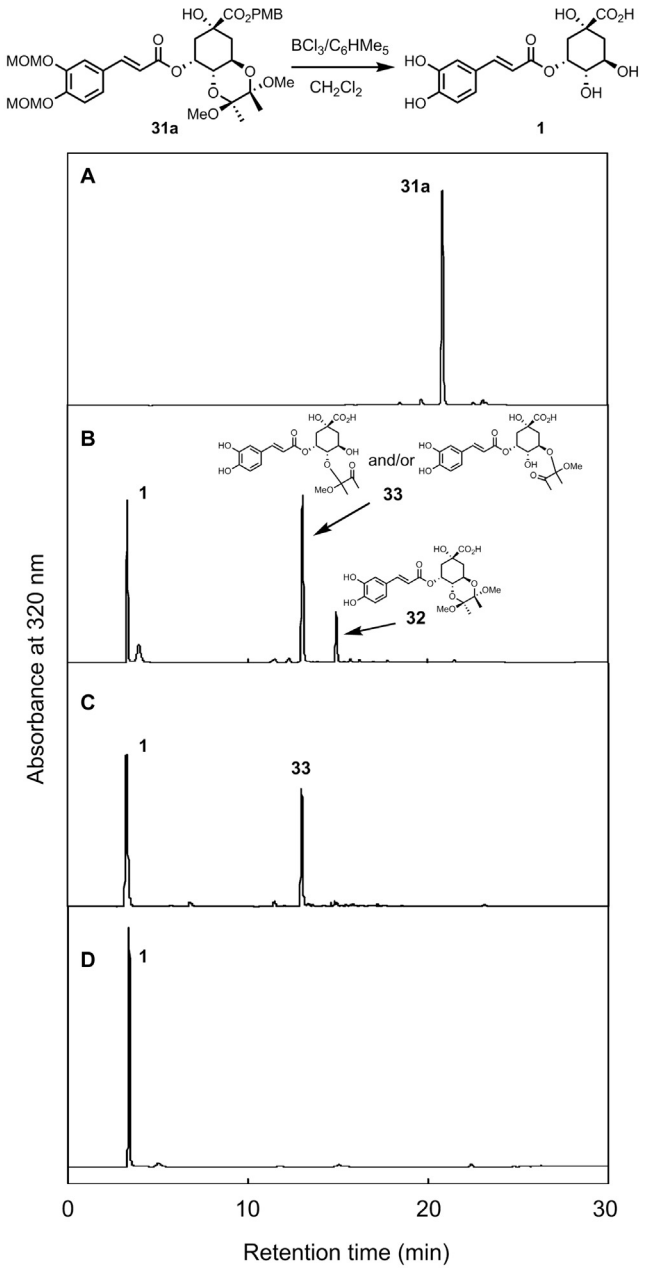
Our attention turned to Lewis acid deprotection conditions. BCl_3 is a promising deprotection reagent for MOM[32] and benzyl[33,34] groups. Thus, the deprotection reaction of **31a** using BCl_3 in CH_2Cl_2 was monitored by HPLC. This gave a simple chromatogram in which **1** was a major peak with some unidentified peaks. To prevent the side reactions by scavenging electrophiles derived from the protecting groups, pentamethylbenzene (C_6HMe_5) as a cation scavenger was added.[34]

In this reaction at −78 °C, the MOM and PMB groups were removed immediately, and the bisacetal group was cleaved gradually (Fig. 2B). During the deprotection, the intermediates **32** and **33** were detected by the negative ESI-Q-TOF-MS (for **32**: calcd for $C_{22}H_{27}O_{11}$ $[M-H]^-$ 467.16, found 467.15, for **33**: calcd for $C_{21}H_{25}O_{11}$ $[M-H]^-$ 453.14, found 453.15). When the reaction temperature was increased from −40 to 0 °C for 1 h, **33** and the desired **1** were detected (Fig. 2C). Eventually, this reaction was completed after 3 h (Fig. 2D). To our delight, the deprotection of **31a** with BCl_3/C_6HMe_5 in CH_2Cl_2 gave pure 5-*O*-caffeoylquinic acid (**1**) in 69% yield by ODS HPLC (Table 6, entry 4). The deprotection of **30a** under the same BCl_3/C_6HMe_5-catalyzed conditions gave 5-*O*-*p*-coumaroylquinic acid (**2**) in 73% yield (Table 6, entry 3).



(A) The starting material **31a**. (B) The reaction mixture at -78 ºC for 3 h. (C) The reaction mixture at –40 to 0 ºC for 1 h. (D) The reaction mixture at –40 to 0 ºC for 3 h.

Fig. 2. HPLC chromatogram of the global deprotection reaction of **31a** using a combination of BCl_3 and C_6HMe_5 in CH_2Cl_2.

3. Conclusion

In summary, an efficient and versatile synthesis of 5-*O*-acylquinic acids was developed using PMB quinate **4** as a key intermediate. The overall yields were 45–60% in seven steps from (−)-quinic acid (**6**). The key to the success of these syntheses was the introduction of PMB and MOM groups, and their deprotection by TFA and BCl_3/C_6HMe_5. In addition, the use of *i*-Pr_2NEt was found to accelerate the TsCl/NMI-mediated esterification between the sterically hindered axial alcohol **4** and the aromatic carboxylic acids. Further applications of our novel synthetic route using PMB quinate **4** for the synthesis of quinic acid derivatives are being developed in our group.

4. Experimental section

4.1. General

Melting points (mp) were determined on a Yanaco MP-3 instrument and are uncorrected. Optical rotations were recorded on a JASCO P-1010-GT polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR 6100 spectrometer. UV/VIS spectra were recorded on a JASCO V560 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM A400, a JNM ECA-600, and a JNM A600 spectrometer. Chemical shifts for ^1H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) and are referenced to residual solvent signals ($CDCl_3$: δ 7.26 ppm, CD_3OD: δ 3.31 ppm, DMSO-d_6: δ 2.49 ppm) or TMS (δ 0.00 ppm) as an internal reference. Chemical shifts for ^{13}C NMR were reported in the scale relative to the NMR solvent ($CDCl_3$: δ 77.0 ppm, CD_3OD: δ 49.0 ppm, DMSO-d_6: δ 39.5 ppm) as an internal reference. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 (FAB) and Bruker micrOTOF-QII (ESI) spectrometer. Analytical HPLC was conducted by our method[8b,35] with an ODS column (Develosil ODS-HG-5, 4.6 mm $\phi\times$250 mm, Nomura Chemical) with some modifications. The chromatography was performed by eluting at 1.0 mL/min with a linear gradient from 10% to 90% CH_3CN in H_2O containing 0.5% TFA for 30 min at 40 °C. Preparative ODS-HPLC was performed by using a column (Develosil ODS-HG-5 20 mm $\phi\times$250 mm, Nomura Chemical) with isocratic elution with 5% CH_3CN in H_2O containing 0.5% TFA at 40 °C.[8b,35] Flash column chromatography was performed on Fuji Silysia silica gel (PSQ 60B). Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{254}. Preparative TLC separations were performed on Merck analytical plates (0.50 mm thick) precoated with silica gel 60 F_{254}. All commercially available reagents and solvents were used directly without further purification. All nonaqueous reactions were carried out under an argon atmosphere.

4.2. Methyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (3)

To a solution of (−)-quinic acid (**6**) (1.0 g, 5.2 mmol), methyl orthoformate (2.8 mL, 26.0 mmol), and 2,3-butandione (0.9 mL, 10.4 mmol) in MeOH (15 mL) was added CSA (12 mg, 5.2 mmol) at room temperature and the resulting mixture was stirred for 45 h at

85 °C. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/AcOEt=1:4) to give **3** as a white solid (1.495 g, 90%). Mp: 137–138 °C; $[\alpha]_D^{24}$ +136.0 (*c* 1.0, $CHCl_3$); IR (KBr) 3442, 2952, 1727, 1451, 1279, 1243, 1133, 1042, 911 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.33 (s, 3H), 1.91 (t, *J*=12.5 Hz, 1H), 2.03 (dd, *J*=15.0, 3.0 Hz, 1H), 2.09 (ddd, *J*=12.5, 4.8, 3.0 Hz, 1H), 2.18 (td, *J*=14.8, 3.0 Hz, 1H), 3.25 (s, 3H), 3.26 (s, 3H), 3.59 (dd, *J*=10.5, 3.0, Hz, 1H), 3.78 (s, 3H), 4.18 (q, *J*=3.0 Hz, 1H), 4.30 (ddd, *J*=12.5, 10.5 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 17.8, 37.4, 38.7, 47.9, 52.9, 62.4, 69.2, 72.8, 75.8, 99.8, 100.4, 174.3; HRMS (FAB) calcd for $C_{14}H_{24}O_8Na$ $[M+Na]^+$ 343.1369, found 343.1364.

4.3. Methyl (2′*S*,3′*S*)-5-*O*-*tert*-butyldimethylsilyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (7)

To a solution of methyl ester **3** (5.125 g, 16.0 mmol) and imidazole (2.178 g, 32.0 mmol) in DMF (40 mL) was added TBSCl (4.823 g, 32.0 mmol) at room temperature. After stirring for 25 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% AcOEt in hexane) to give **7** as a white solid (6.842 g, 98%). Mp: 110–111 °C; $[\alpha]_D^{22}$ +102.0 (*c* 0.5, $CHCl_3$); IR (KBr) 3458, 2956, 1736, 1450, 1378, 1248, 1132, 1040, 978, 890, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.18 (s, 3H), 0.91 (s, 9H), 1.27 (s, 3H), 1.29 (s, 3H), 1.87 (t, *J*=12.5 Hz, 1H), 2.04–2.11 (m, 2H), 2.19 (ddd, *J*=12.5, 4.8, 2.5 Hz, 1H), 3.22 (s, 3H), 3.24 (s, 3H), 3.49 (dd, *J*=10.5, 2.5 Hz, 1H), 3.76 (s, 3H), 4.24–4.29 (m, 2H), 4.95 (s, H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 17.8, 18.1, 25.7, 38.4, 39.4, 47.6, 47.8, 52.6, 62.4, 70.9, 72.8, 76.2, 99.4, 99.9, 173.7; HRMS (FAB) calcd for $C_{20}H_{38}O_8SiNa$ $[M+Na]^+$ 457.2234, found 457.2223.

4.4. 4-Methoxybenzyl (2′*S*,3′*S*)-5-*O*-*tert*-butyldimethylsilyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (8)

To a solution of **7** (3.872 g, 8.9 mmol) in THF (12 mL) was added aqueous KOH (12 mL, 1.0 M) at room temperature. After stirring for 75 min at this temperature, the reaction mixture was neutralized with 0.5 M $NaHSO_4$ and then the crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude carboxylic acid. The crude product was used in the next step without further purification. To a solution of the crude carboxylic acid and Cs_2CO_3 (4.354 g, 13.4 mmol) in DMF (20 mL) was added PMBCl (1.8 mL, 13.4 mmol) at room temperature. After stirring for 2 h at 80 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% AcOEt in hexane) to give **8** as a white solid (4.473 mg, 93%). Mp: 71–72 °C; $[\alpha]_D^{22}$ +95.6 (*c* 0.2, $CHCl_3$); IR (KBr) 3437, 2955, 1748, 1610, 1515, 1376, 1262, 1131, 984, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 1.26 (s, 3H), 1.28 (s, 3H), 1.83 (t, *J*=12.5 Hz, 1H), 2.02–2.09 (m, 2H), 2.17 (ddd, *J*=12.5, 4.5, 3.0 Hz, 1H), 3.20 (s, 3H), 3.22 (s, 3H), 3.46 (dd, *J*=10.0, 3.0 Hz, 1H), 3.81 (s, 3H), 4.23 (q, *J*=3.0 Hz, 1H), 4.26 (ddd, *J*=12.5, 10.0, 4.5 Hz, 1H), 4.91 (s, 1H, OH), 5.08 (d, *J*=12.0 Hz, 1H), 5.15 (d, *J*=12.0 Hz, 1H), 6.87 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 17.8, 18.1, 25.7, 38.3, 39.3, 47.6, 47.7, 55.3, 62.5, 66.8, 70.9, 72.8, 76.1, 99.4, 99.9, 113.9, 127.8, 130.1, 159.7, 172.9; HRMS (FAB) calcd for $C_{27}H_{44}O_9SiNa$ $[M+Na]^+$ 563.2652, found 563.2648.

4.5. 4-Methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (4)

To a solution of **8** (8.057 g, 14.9 mmol) in a mixture of THF (35 mL) and AcOH (3.4 mL) was added TBAF (14.9 mL, 1.0 M in THF) at room temperature. After stirring for 13 h at this temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% AcOEt in hexane) to give **4** as a white solid (6.108 g, 96%). Using EtOAc/hexane as solvent, alcohol **4** could be crystallized to afford crystal suitable for X-ray analysis. Mp: 91–92 °C; $[\alpha]_D^{23}$ +96.6 (*c* 1.0, $CHCl_3$); IR (KBr) 3492, 2956, 1740, 1613, 1515, 1383, 1249, 1130, 1032 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.33 (s, 3H), 1.91 (t, *J*=12.5 Hz, 1H), 2.02 (dd, *J*=14.5, 3.0 Hz, 1H), 2.06 (ddd, *J*=12.5, 4.8, 3.0 Hz, 1H), 2.15 (dt, *J*=14.5, 3.0 Hz, 1H), 3.24 (s, 3H), 3.25 (s, 3H), 3.56 (dd, *J*=10.2, 3.0 Hz, 1H), 3.81 (s, 3H), 4.15 (q, *J*=3.0 Hz, 1H), 4.30 (ddd, *J*=12.5, 10.2, 4.8 Hz, 1H), 5.11 (d, *J*=12.0 Hz, 1H), 5.16 (d, *J*=12.0 Hz, 1H), 6.88 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 17.8, 37.5, 38.5, 47.9, 55.3, 62.5, 67.5, 69.1, 72.8, 75.7, 99.7, 100.3, 114.0, 127.2, 130.1, 159.9, 173.9; HRMS (FAB) calcd for $C_{21}H_{30}O_9Na$ $[M+Na]^+$ 449.1788, found 449.1778.

4.6. 4-Methoxybenzyl (2′*S*,3′*S*)-5-*O*-cinnamoyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (10a) and 4-methoxybenzyl (2′*S*,3′*S*)-1,5-*O*-dicinnamoyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (10b) (method A, Table 2, entry 3)

To a solution of carboxylic acid **9** (207 mg, 1.4 mmol), TsCl (534 mg, 2.8 mmol), *i*-Pr_2NEt (0.73 mL, 4.2 mmol), and MS 4 Å (ca. 2.1 g) in dichloroethane (5 mL) was added NMI (0.33 mL, 4.2 mmol) at room temperature and the resulting mixture was stirred for 30 min at this temperature. To the reaction mixture was added a solution of alcohol **4** (300 mg, 0.7 mmol) in dichloroethane (5 mL) at room temperature. After stirring for 2 h at 40 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% AcOEt in hexane) to give **10a** (318 mg, 81%) and **10b** (19 mg, 4%).

*4.6.1. Compound **10a**.* White solid; mp: 69–70 °C; $[\alpha]_D^{27}$ +59.6 (*c* 0.5, $CHCl_3$); IR (KBr) 3359, 3260, 2951, 2835, 1714, 1515, 1308, 1249, 1131, 1036 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 281 (17,000); ^1H NMR (600 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (s, 3H), 1.97–2.03 (m, 2H), 2.09 (dd, *J*=15.0, 3.0 Hz, 1H), 2.24 (td, *J*=15.0, 3.0 Hz, 1H), 3.25 (s, 3H), 3.30 (s, 3H), 3.69 (dd, *J*=10.0, 3.0 Hz, 1H), 3.82 (s, 3H), 4.43 (td, *J*=10.0, 5.8 Hz, 1H), 5.10 (d, *J*=12.0 Hz, 1H), 5.15 (d, *J*=12.0 Hz, 1H), 5.33 (q, *J*=3.0 Hz, 1H), 6.50 (d, *J*=16.2 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.37–7.40 (m, 3H), 7.53–7.54 (m, 2H), 7.71 (d, *J*=16.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.9, 36.5, 38.7, 47.9, 48.0, 55.3, 62.9, 67.9, 69.8, 71.2, 74.5, 99.6, 100.1, 114.1, 118.5, 127.0, 128.2, 128.8, 130.2, 130.3, 134.6, 145.1, 160.0, 166.6, 175.0; HRMS (FAB) calcd for $C_{30}H_{36}O_{10}Na$ $[M+Na]^+$ 579.2206, found 576.2216.

*4.6.2. Compound **10b**.* Colorless amorphous; $[\alpha]_D^{24}$ +45.9 (*c* 0.27, $CHCl_3$); IR (KBr) 2948, 2836, 1716, 1637, 1517, 1450, 1246, 1170, 1108, 1036, 768 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 276 (32,000); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.30 (s, 3H), 1.92 (dd, *J*=13.0, 12.0 Hz, 1H), 2.24 (dd, *J*=16.0, 3.0 Hz, 1H), 2.50 (ddd, *J*=13.0, 4.0, 3.0 Hz, 1H), 2.97 (td, *J*=16.0, 3.0 Hz, 1H), 3.26 (s, 3H), 3.34 (s, 3H),

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3.72 (dd, J=10.0, 3.0 Hz, 1H), 3.79 (s, 3H), 4.43 (ddd, J=12.0, 10.0, 4.0 Hz, 1H), 5.09 (d, J=12.0 Hz, 1H), 5.14 (d, J=12.0 Hz, 1H), 5.44 (q, J=3.0 Hz, 1H), 6.32 (d, J=16.5 Hz, 1H), 6.36 (d, J=16.5 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 7.12 (t, J=7.5 Hz, 2H), 7.20–7.26 (m, 5H), 7.25 (d, J=8.5 Hz, 2H), 7.31–7.36 (m, 3H), 7.63 (d, J=16.0 Hz, 1H), 7.64 (d, J=16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.8, 32.6, 36.7, 47.9, 48.0, 55.2, 62.8, 67.4, 68.8, 70.9, 79.7, 99.8, 100.1, 114.0, 117.6, 118.3, 127.4, 127.9, 128.1, 128.7, 128.9, 130.0, 130.2, 130.4, 133.9, 134.2, 145.0, 145.8, 159.7, 165.1, 166.2, 170.5; HRMS (FAB) calcd for $C_{39}H_{42}O_{11}Na$ $[M+Na]^+$ 709.2625, found 709.2623.

4.7. Compounds 10a and 10b (method B, Table 3, entry 3)

To a solution of cinnamic acid **9** (74 mg, 0.5 mmol), TsCl (191 mg, 1.0 mmol), and MS 4 Å (ca. 0.8 g) in dichloroethane (1.5 mL) was added *i*-Pr_2NEt (262 μL, 1.5 mmol) at room temperature and the resulting mixture was stirred for 30 min at this temperature. To the reaction mixture was added a solution of alcohol **4** (107 mg, 0.25 mmol) in dichloroethane (1.8 mL) and subsequently NMI (120 μL, 1.5 mmol) was added at room temperature. After stirring for 2 h at 40 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% AcOEt in hexane) to give **10a** (122 mg, 87%) and **10b** (9 mg, 5%), respectively.

4.8. 4-Methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-5-*O*-naphthoylquinate (14a) and 1-methyl-2-naphthoylimidazole (15)

According to the procedure described for **10a** (method A, Table 2, entry 3), **11** (241 mg, 1.41 mmol) was esterified with **4** (300 mg, 0.7 mmol) to afford **14a** (352 mg, 86%) and **15** (115 mg, 35% based on **11**), respectively (solvent used for flash column chromatography: 20–30% AcOEt in hexane).

*4.8.1. Compound **14a**.* Colorless amorphous; $[\alpha]_D^{23}$ +62.1 (*c* 1.0, $CHCl_3$); IR (KBr) 3487, 2952, 2837, 1715, 1515, 1284, 1233, 1131 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 246 (27,000); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.30 (s, 3H), 2.06 (d, J=8.5 Hz, 2H), 2.19 (dd, J=15.4, 3.0 Hz, 1H), 2.32 (brd, J=15.4 Hz, 1H), 3.27 (s, 3H), 3.35 (s, 3H), 3.76 (dd, J=10.0, 3.0 Hz, 1H), 3.82 (s, 3H), 4.63 (td, J=10.0, 8.5 Hz, 1H), 5.11 (d, J=12.0 Hz, 1H), 5.16 (d, J=12.0 Hz, 1H), 5.51 (q, J=3.0 Hz, 1H), 6.89 (d, J=7.0 Hz, 2H), 7.27 (d, J=7.0 Hz, 2H), 7.53 (t, J=8.0 Hz, 1H), 7.58 (t, J=8.0 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.95 (d, J=8.0 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.8, 36.7, 38.8, 48.0, 55.3, 62.9, 68.0, 70.3, 71.5, 74.5, 99.6, 100.0, 114.1, 125.5, 126.4, 127.0, 127.7, 128.0, 128.1, 129.4, 130.2, 131.5, 132.6, 135.5, 160.0, 166.4, 175.1; HRMS (FAB) calcd for $C_{32}H_{36}O_{10}Na$ $[M+Na]^+$ 603.2206, found 603.2198.

*4.8.2. Compound **15**.* Pale yellow oil; IR (neat) 3058, 2957, 1638, 1466, 1401, 1274, 1236, 1162, 1118, 903, 781 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 3H), 7.14 (s, 1H), 7.28 (s, 1H), 7.53 (ddd, J=8.3, 7.0, 1.0 Hz, 1H), 7.59 (ddd, J=8.3, 7.0, 1.0 Hz, 1H), 7.88 (d, J=8.5 Hz, 1H), 7.92 (d, J=8.5 Hz, 1H), 8.01 (d, J=8.5 Hz, 1H), 8.27 (dd, J=8.5, 1.5 Hz, 1H), 8.99 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.4, 125.9, 126.4, 126.7, 127.6, 127.8, 128.3, 129.3, 129.9, 132.4, 133.3, 134.5, 135.4, 143.3, 183.9; HRMS (ESI) calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$ 237.1022, found 237.1034.

4.9. Compound 14a and 4-methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-*O*-naphthoylquinate (14b)

According to the procedure described for **10a** (method B, Table 3, entry 3), **11** (65 mg, 0.376 mmol) was esterified with **4** (107 mg, 0.25 mmol) to afford **14a** (122 mg, 84%) and **14b** (13 mg, 7%), respectively (solvent used for flash column chromatography: 20–30% AcOEt in hexane).

*4.9.1. Compound **14b**.* White solid; mp: 152–154 °C; $[\alpha]_D^{22}$ +97.0 (*c* 0.2, $CHCl_3$); IR (KBr) 2961, 2834, 1715, 1614, 1516, 1466, 1305, 1198, 1112, 930, 825 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 247 (26,000); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.34 (s, 3H), 2.13 (dd, J=13.5, 12.0 Hz, 1H), 2.37 (dd, J=16.5, 3.5 Hz, 1H), 2.71 (td, J=13.5, 3.5 Hz, 1H), 3.21 (td, J=16.5, 3.5 Hz, 1H), 3.28 (s, 3H), 3.40 (s, 3H), 3.76 (s, 3H), 3.82 (dd, J=10.5, 3.5 Hz, 1H), 4.72 (ddd, J=12.0, 10.5, 3.5 Hz, 1H), 5.11 (d, J=12.0 Hz, 1H), 5.16 (d, J=12.0 Hz, 1H), 5.56 (q, J=3.5 Hz, 1H), 6.80 (d, J=8.5 Hz, 2H), 7.11–7.15 (m, 2H), 7.22 (d, J=8.5 Hz, 1H), 7.26–7.29 (m, 3H), 7.27 (d, J=8.5 Hz, 2H), 7.34 (d, J=8.5 Hz, 1H), 7.37 (ddd, J=8.0, 6.3, 1.5 Hz, 1H), 7.26–7.29 (m, 3H), 7.42 (td, J=8.0, 1.0 Hz, 1H), 7.47 (t, J=8.5 Hz, 1H), 7.55 (d, J=8.0 Hz, 1H), 7.70 (dd, J=8.5, 1.5 Hz, 1H), 7.75 (dd, J=8.5, 1.5 Hz, 1H), 8.24 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 17.8, 33.3, 36.5, 47.9, 48.1, 55.2, 62.7, 67.4, 70.0, 71.3, 80.3, 99.8, 100.0, 113.9, 124.7, 125.0, 126.1, 126.5, 127.3, 127.4, 127.6, 127.7, 127.8, 128.0, 128.9, 130.1, 131.0, 131.1, 131.9, 132.1, 135.1, 135.2, 159.7, 165.2, 166.4, 170.5; HRMS (FAB) calcd for $C_{43}H_{42}O_{11}Na$ $[M+Na]^+$ 757.2625, found 757.2601.

4.10. 4-Methoxybenzyl (2′*S*,3′*S*)-5-*O*-benzoyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (16a) and 4-methoxybenzyl (2′*S*,3′*S*)-1,5-*O*-dibenzoyl-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)quinate (16b)

According to the procedure described for **10a** (method B, Table 3, entry 3), **12** (60 mg, 0.495 mmol) was esterified with **4** (192 mg, 0.45 mmol) to afford **16a** (225 mg, 94%) and **16b** (9 mg, 3%), respectively (solvent used for flash column chromatography: 20–30% AcOEt in hexane).

*4.10.1. Compound **16a**.* Colorless amorphous; $[\alpha]_D^{25}$ +31.2 (*c* 0.5, $CHCl_3$); IR (KBr) 3507, 2951, 2834, 1717, 1612, 1516, 1452, 1374, 1282, 1127, 714 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 241 (9400); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.28 (s, 3H), 2.02 (d, J=8.5 Hz, 2H), 2.14 (dd, J=15.4, 3.2 Hz, 1H), 2.25 (td, J=15.4, 1.2 Hz, 1H), 3.20 (br s, 1H, OH), 3.25 (s, 3H), 3.30 (s, 3H), 3.72 (dd, J=10.2, 3.2 Hz, 1H), 3.82 (s, 3H), 4.54 (td, J=10.2, 8.5 Hz, 1H), 5.09 (d, J=12.0 Hz, 1H), 5.15 (d, J=12.0 Hz, 1H), 5.46 (q, J=3.2 Hz, 1H), 6.89 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.41–7.46 (m, 2H), 7.52–7.57 (m, 1H), 8.08 (dd, J=8.6, 1.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.8, 36.7, 38.7, 47.9, 48.0, 55.3, 62.8, 67.9, 70.1, 71.4, 74.5, 99.5, 100.0, 114.1, 127.0, 128.3, 129.9, 130.2, 130.8, 132.8, 160.0, 166.2, 175.1; HRMS (FAB) calcd for $C_{28}H_{34}O_{10}Na$ $[M+Na]^+$ 553.2050, found 553.2039.

*4.10.2. Compound **16b**.* Colorless amorphous; $[\alpha]_D^{25}$ +56.3 (*c* 0.5, $CHCl_3$); IR (KBr) 2949, 2835, 1719, 1517, 1282, 1126, 710 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 241 (7400); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.30 (s, 3H), 2.07 (dd, J=13.0, 12.5 Hz, 1H), 2.31 (dd, J=16.0, 3.5 Hz, 1H), 2.63 (td, J=13.0, 3.5 Hz, 1H), 3.04 (td, J=16.0, 3.5 Hz, 1H), 3.26 (s, 3H), 3.28 (s, 3H), 3.79 (s, 3H), 3.76 (dd, J=10.0, 3.5 Hz, 1H), 4.54 (ddd, J=13.0, 10.0, 3.5 Hz, 1H), 5.09 (d, J=12.0 Hz, 1H), 5.13 (d, J=12.0 Hz, 1H), 5.54 (q, J=3.5 Hz, 1H), 6.82 (d, J=8.8 Hz, 2H), 7.11 (t, J=8.0 Hz, 2H), 7.18 (t, J=8.0 Hz, 2H), 7.21 (d, J=8.8 Hz, 2H), 7.39–7.43 (m, 2H), 7.78 (dd, J=8.0, 1.0 Hz, 2H), 7.84 (dd, J=8.0, 1.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.5, 17.7, 33.6, 36.3, 47.8, 48.0, 55.2, 62.6, 67.4, 69.6, 71.2, 80.3, 99.7, 100.0, 100.6, 113.9, 127.3, 128.0, 128.1,

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129.4, 129.7, 130.1, 130.4, 132.5, 133.0, 159.7, 165.0, 166.1, 170.4; HRMS (FAB) calcd for $C_{35}H_{38}O_{11}Na$ $[M+Na]^+$ 657.2312, found 657.2312.

4.11. 4-Methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-5-*O*-phenylethylcarbonylquinate (17) (method C, Table 3, entry 6)

To a solution of carboxylic acid **13** (75 mg, 0.5 mmol), TsCl (191 mg, 1.0 mmol), and MS 4 Å (ca. 0.8 g) in dichloroethane (1.5 mL) was added NMI (0.12 mL, 1.5 mmol) at room temperature and the resulting mixture was stirred for 30 min at this temperature. To the reaction mixture was added a solution of alcohol **4** (107 mg, 0.25 mmol) in dichloroethane (1.5 mL) at room temperature. After stirring for 2 h at 40 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure and the residue was purified by flash column chromatography (25% AcOEt in hexane) to give **17** (100 mg, 72%) as a colorless amorphous. $[\alpha]_D^{26}$ +66.5 (*c* 0.5, $CHCl_3$); IR (KBr) 3523, 2952, 2835, 1732, 1615, 1518, 1452, 1376, 1245, 1131, 1032 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 240 (6000); ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.28 (s, 3H), 1.92–1.99 (m, 2H), 2.03 (dd, *J*=15.4, 3.0 Hz, 1H), 2.09 (td, *J*=15.4, 3.0 Hz, 1H), 2.64 (ddd, *J*=15.5, 8.5, 7.5 Hz, 1H), 2.72 (ddd, *J*=15.5, 8.5, 6.5 Hz, 1H), 2.97–3.00 (m, 2H), 3.24 (s, 3H), 3.25 (s, 3H), 3.63 (dd, *J*=10.3, 3.0 Hz, 1H), 3.81 (s, 3H), 4.34 (td, *J*=10.3, 5.5 Hz, 1H), 5.09 (d, *J*=12.0 Hz, 1H), 5.14 (d, *J*=12.0, 1H), 5.25 (q, *J*=3.0 Hz, 1H), 6.89 (d, *J*=8.4 Hz, 2H), 7.16–7.29 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.8, 30.9, 36.3, 36.4, 38.5, 47.9, 55.3, 62.6, 67.8, 69.5, 71.1, 74.4, 99.5, 100.0, 114.1, 126.1, 127.0, 128.3, 128.4, 130.2, 140.8, 159.9, 172.5, 174.9; HRMS (FAB) calcd for $C_{30}H_{38}O_{10}Na$ $[M+Na]^+$ 581.2363, found 581.2351.

4.12. Methyl (*E*)-*p*-coumarate (24)

To a solution of *p*-coumaric acid **22** (3.0 g, 18.3 mmol) in MeOH (40 mL) was added Dowex 50W-X8 (2.4 g) at room temperature and the resulting mixture was refluxed for 90 h. After the Dowex 50W-X8 was filtered, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (30% AcOEt in hexane) to give a methyl ester with trace impurities. Recrystallization from $CHCl_3$ gave **24** (2.91 g, 89%) as a white solid in a pure form. Mp: 130–132 °C; IR (KBr) 3384, 2952, 1689, 1634, 1602, 1517, 1435, 1284, 1200, 986, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.33 (s, 1H; OH), 6.30 (d, *J*=16.0 Hz, 1H), 6.85 (d, *J*=8.5 Hz, 2H), 7.43 (d, *J*=8.5 Hz, 2H), 7.64 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.7, 115.1, 115.9, 127.1, 130.0, 144.8, 157.8, 168.1; HRMS (FAB) calcd for $C_{10}H_{11}O_3$ $[M+H]^+$ 179.0708, found 179.0700.

4.13. Methyl (*E*)-caffeate (25)

To a solution of caffeic acid **23** (3.00 g, 16.7 mmol) in MeOH (40 mL) was added Dowex 50W-X8 (2.4 g) at room temperature and the resulting mixture was refluxed for 52 h. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (50% AcOEt in hexane) to give **25** as a white solid (3.09 g, 96%). Mp: 148–150 °C; IR (KBr) 3477, 3091, 2952, 1677, 1606, 1445, 1308, 1281, 1243, 1191, 1113, 1045, 971, 864 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 3.68 (s, 3H), 6.26 (d, *J*=16.0 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 6.99 (dd, *J*=8.4, 2.1 Hz, 1H), 7.04 (d, *J*=2.1 Hz, 1H), 7.47 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 51.2, 113.7, 114.8, 115.7, 121.4, 125.4, 145.1, 145.5, 148.4, 166.9; HRMS (FAB) calcd for $C_{10}H_{10}O_4$ $[M+H]^+$ 194.0579, found 194.0578.

4.14. Methyl (*E*)-4-*O*-methoxymethyl-*p*-coumarate (26)

To a solution of methyl ester **24** (2.91 g, 16.3 mmol) and *i*-Pr_2NEt (5.7 mL, 49.0 mmol) in CH_2Cl_2 (60 mL) was added MOMCl (3.7 mL, 49.0 mmol) at room temperature and the mixture was stirred for 21 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% AcOEt in hexane) to give **26** as a colorless oil (3.52 g, 97%). IR (neat) 2952, 2828, 1791, 1636, 1604, 1510, 1436, 1315, 1242, 1170, 1081, 992, 831 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.79 (s, 3H), 5.20 (s, 2H), 6.32 (d, *J*=16.0 Hz, 1H), 7.04 (d, *J*=8.5 Hz, 2H), 7.47 (d, *J*=8.5 Hz, 2H), 7.65 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.6, 56.1, 94.2, 115.8, 116.5, 128.2, 129.6, 144.4, 159.0, 167.7; HRMS (FAB) calcd for $C_{12}H_{15}O_4$ $[M+H]^+$ 223.0970, found 223.0978.

4.15. Methyl (*E*)-3,4-di-*O*-methoxymethylcaffeate (27)

To a solution of methyl ester **25** (3.09 g, 15.9 mmol) and *i*-Pr_2NEt (13.9 mL, 79.6 mmol) in CH_2Cl_2 (60 mL) was added MOMCl (6.1 mL, 79.6 mmol) at room temperature and the mixture was stirred for 79 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl. The crude products were extracted with AcOEt. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% AcOEt in hexane) to give **27** as a white solid (4.3 g, 96%). Mp: 40–41 °C; IR (KBr) 2952, 2837, 1715, 1635, 1599, 1509, 1435, 1315, 1257, 1173, 1130, 1080, 1011, 981 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.51 (s, 3H), 3.53 (s, 3H), 3.79 (s, 3H), 5.25 (s, 2H), 5.26 (s, 2H), 6.32 (d, *J*=16.0, 1H), 7.13–7.16 (m, 2H), 7.36 (d, *J*=1.2 Hz, 1H), 7.61 (d, *J*=16.0, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.6, 56.2, 56.3, 95.1, 95.6, 115.7, 116.2, 116.4, 123.4, 128.9, 144.4, 147.4, 149.2, 167.5; HRMS (FAB) calcd for $C_{14}H_{18}O_6$ $[M+H]^+$ 282.1103, found 282.1100.

4.16. (*E*)-4-*O*-Methoxymethyl-*p*-coumaric acid (28)

To a solution of methyl ester **26** (3.49 g, 15.7 mmol) in THF (20 mL) was added aqueous KOH (37.5 mL, 1.0 M) at room temperature. After stirring for 21 h at room temperature, the reaction mixture was neutralized with aqueous $NaHSO_4$ (0.5 M) and then the product was extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was a pure form of **28** (3.21 g, 98%) as a white solid. Mp: 149–150 °C; IR (KBr) 2955, 2825, 2590, 1687, 1623, 1603, 1511, 1430, 1315, 1238, 1176, 1156, 1077, 1004, 829 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.49 (s, 3H), 5.21 (s, 2H), 6.34 (d, *J*=16.0 Hz, 1H), 7.06 (d, *J*=8.5 Hz, 2H), 7.50 (d, *J*=8.5 Hz, 2H), 7.75 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 94.2, 115.0, 116.5, 127.8, 130.0, 146.6, 159.3, 171.7; HRMS (FAB) calcd for $C_{11}H_{13}O_4$ $[M+H]^+$ 209.0814, found 209.0807.

4.17. (*E*)-3,4-Di-*O*-methoxymethylcaffeic acid (29)

To a solution of methyl ester methyl ester **27** (4.30 g, 15.2 mmol) in THF (20 mL) was added aqueous KOH (40 mL, 1.0 M) at room temperature. After stirring for 21 h at room temperature, the reaction mixture was neutralized with aqueous $NaHSO_4$ (0.5 M) and then the product was extracted with AcOEt. The combined extracts were dried over anhydrous $MgSO_4$. After removal of the solvent in vacuo, the residue was a pure form of **29** (4.09 g, 99%) as a white

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solid. Mp: 120–121.5 °C; IR (KBr) 2961, 2825, 2600, 1669, 1623, 1598, 1510, 1434, 1313, 1253, 1158, 1134, 1081, 1024, 992, 915 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.52 (s, 3H), 3.54 (s, 3H), 5.27 (s, 2H), 5.28 (s, 2H), 6.34 (d, J=15.6, 1H), 7.17 (s, 2H), 7.39 (s, 1H), 7.71 (d, J=15.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.3, 56.4, 95.1, 95.5, 115.6, 115.9, 116.2, 123.8, 128.5, 146.6, 147.4, 149.6, 171.5; HRMS (FAB) calcd for $C_{13}H_{16}O_6$ $[M+H]^+$ 268.0947, found 268.0948.

4.18. 4-Methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-5-*O*-(4″-*O*-methoxymethyl-*p*-coumaroyl) quinate (30a) and 4-methoxybenzyl (2′*S*,3′*S*) -3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-*O*-(4″-*O*-methoxymethyl-*p*-coumaroyl)quinate (30b)

According to the procedure described for **10a** (method B, Table 3, entry 3), **28** (187 mg, 0.9 mmol) was esterified with **4** (192 mg, 0.45 mmol) to afford **30a** (240 mg, 86%) and **30b** (24 mg, 9%) with inseparable impurities, respectively (solvent used for flash column chromatography: 35% AcOEt in hexane).

*4.18.1. Compound **30a**.* Colorless amorphous; $[\alpha]_D^{27}$ +64.6 (c 0.5, $CHCl_3$); IR (KBr) 3504, 2952, 2833, 1711, 1602, 1511, 1377, 1243, 1131, 992, 831 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 299 (23,000); ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.29 (s, 3H), 1.96–2.04 (m, 2H), 2.09 (dd, J=15.4, 3.0 Hz, 1H), 2.23 (td, J=15.4, 3.0 Hz, 1H), 3.25 (s, 3H), 3.30 (s, 3H), 3.48 (s, 3H), 3.68 (dd, J=10.5, 3.0 Hz, 1H), 3.82 (s, 3H), 4.42 (td, J=10.5, 5.5 Hz, 1H), 5.10 (d, J=11.7 Hz, 1H), 5.15 (d, J=11.7 Hz, 1H), 5.20 (s, 2H), 5.33 (q, J=3.0 Hz, 1H), 6.38 (d, J=15.8 Hz, 1H), 6.89 (d, J=8.5 Hz, 2H), 7.03 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 7.66 (d, J=15.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.9, 36.6, 38.6, 48.0, 55.3, 56.1, 62.9, 67.9, 69.6, 71.2, 74.5, 94.2, 99.5, 100.1, 114.1, 116.4, 116.5, 127.0, 128.4, 129.8, 130.3, 144.7, 158.9, 159.9, 166.8, 174.9; HRMS (FAB) calcd for $C_{32}H_{40}O_{12}Na$ $[M+Na]^+$ 639.2417, found 639.2394.

*4.18.2. Compound **30b**.* ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.32 (s, 3H), 1.86 (dd, J=13.3, 12.5 Hz, 1H), 2.11 (dd, J=16.0, 3.0 Hz, 1H), 2.45 (td, J=13.3, 3.0 Hz, 1H), 2.84 (td, J=16.0, 3.0 Hz, 1H), 3.25 (s, 3H), 3.27 (s, 3H), 3.48 (s, 3H), 3.56 (dd, J=10.0, 3.0 Hz, 1H), 3.78 (s, 3H), 4.15 (q, J=3.0 Hz, 1H), 4.33 (ddd, J=12.5, 10.0, 3.0 Hz, 1H), 5.10 (s, 1H), 5.11 (s, 1H), 5.20 (s, 2H), 6.31 (d, J=15.8 Hz, 1H), 6.84 (d, J=8.8 Hz, 2H), 7.03 (d, J=8.8 Hz, 2H), 7.25 (d, J=8.8 Hz, 2H), 7.45 (d, J=8.8 Hz, 2H), 7.63 (d, J=15.8 Hz, 1H); HRMS (FAB) calcd for $C_{32}H_{40}O_{12}Na$ $[M+Na]^+$ 639.2417, found 639.2421.

4.19. 4-Methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-5-*O*-(3″,4″-di-*O*-methoxymethylcaffeoyl) quinate (31a) and 4-methoxybenzyl (2′*S*,3′*S*)-3-*O*,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-*O*-(3″,4″-di-*O*-methoxymethylcaffeoyl)quinate (31b)

According to the procedure described for **10a** (method B, Table 3, entry 3), **29** (135 mg, 0.5 mmol) was esterified with **4** (107 mg, 0.25 mmol) to afford **31a** (141 mg, 83%) and **31b** (7 mg, 4%) with inseparable impurities, respectively (solvent used for flash column chromatography: 40% AcOEt in hexane).

*4.19.1. Compound **31a**.* Colorless amorphous; $[\alpha]_D^{27}$ +60.9 (c 0.5, $CHCl_3$); IR (KBr) 3507, 2955, 2833, 1710, 1513, 1252, 1132, 989, 819 cm^{-1}; UV ($CHCl_3$) λ_{max}/nm (ε), 315 (16,000); ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (s, 3H), 1.97–2.05 (m, 2H), 2.09 (dd, J=15.3, 3.0 Hz, 1H), 2.23 (td, J=15.3, 3.0 Hz, 1H), 3.25 (s, 3H), 3.31 (s, 3H), 3.52 (s, 3H), 3.53 (s, 3H), 3.69 (dd, J=10.5, 3.0 Hz, 1H), 3.82 (s, 3H), 4.43 (td, J=10.5, 5.5 Hz, 1H), 5.10 (d, J=12.0 Hz, 1H), 5.15 (d, J=12.0, 1H), 5.26 (s, 2H), 5.27 (s, 2H), 5.34 (q, J=3.0 Hz, 1H), 6.38 (d, J=16.0 Hz, 1H), 6.89 (d, J=8.5 Hz, 2H), 7.15 (s, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.37 (s, 1H), 7.63 (d, J=16.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 17.8, 36.6, 38.6, 47.9, 48.0, 55.3, 56.2, 56.3, 62.9, 67.9, 69.7, 71.2, 74.5, 95.1, 95.5, 99.5, 100.1, 114.1, 115.8, 116.1, 117.0, 123.6, 127.0, 129.1, 130.2, 144.8, 147.3, 149.1, 159.9, 166.7, 174.9; HRMS (FAB) calcd for $C_{34}H_{44}O_{14}Na$ $[M+Na]^+$ 699.2629, found 699.2604.

*4.19.2. Compound **31b**.* ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.33 (s, 3H), 1.86 (t, J=13.0 Hz, 1H), 2.11 (dd, J=16.0, 3.0 Hz, 1H), 2.44 (td, J=13.0, 3.0 Hz, 1H), 2.84 (td, J=16.0, 3.0 Hz, 1H), 3.25 (s, 3H), 3.27 (s, 3H), 3.52 (s, 3H), 3.53 (s, 3H), 3.79 (s, 3H), 4.15 (q, J=3.0 Hz, 1H), 4.33 (ddd, J=13.0, 10.0, 3.0 Hz, 1H), 5.09 (s, 1H), 5.10 (s, 1H), 5.25 (s, 2H), 5.27 (s, 2H), 6.31 (d, J=16.0 Hz, 1H), 6.85 (d, J=8.5 Hz, 2H), 7.12–7.14 (m, 2H), 7.25 (d, J=8.5 Hz, 2H), 7.34 (d, J=2.0 Hz, 1H), 7.60 (d, J=16.0 Hz, 1H); HRMS (FAB) calcd for $C_{34}H_{44}O_{14}Na$ $[M+Na]^+$ 699.2629, found 699.2625.

4.20. 5-*O*-(*E*)-Cinnamoylquinic acid (18)

To a solution of **10a** (111 mg, 0.2 mmol) in CH_2Cl_2 (24 mL) was added TFA (1.2 mL) at 0 °C and the resulting mixture was stirred for 13 h at this temperature. H_2O (40 mL) was added to the reaction mixture and then CH_2Cl_2 was removed under reduced pressure at 30 °C. The residual aqueous solution was purified by ODS open column chromatography (COSMOSIL 75C_{18}-OPN: 5–10% CH_3CN in H_2O) to give an aqueous CH_3CN solution of **18** containing TFA. A few times of azeotropic removal of TFA by using 50% aqueous CH_3CN under reduced pressure at 55 °C gave **18** (56 mg, 87%) as a white solid. Mp: 190–191 °C; $[\alpha]_D^{22}$ −6.6 (c 0.5, CH_3OH); IR (KBr) 3465, 3344, 2955, 1706, 1677, 1290, 1126, 978 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.96 (dd, J=13.5, 3.5 Hz, 1H), 2.12–2.24 (m, 3H), 3.65 (dd, J=9.0, 3.5 Hz, 1H), 4.16 (td, J=9.0, 3.5 Hz, 1H), 5.38 (q, J=3.5 Hz, 1H), 6.57 (d, J=16.0 Hz, 1H), 7.39–7.41 (m, 3H), 7.59–7.61 (m, 2H), 7.73 (d, J=16.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 36.7, 41.6, 68.2, 73.3, 74.8, 75.4, 119.6, 129.2, 130.0, 131.4, 136.0, 146.1, 168.4, 178.3; HRMS (FAB) calcd for $C_{16}H_{17}O_7Na_2$ $[M-H+2Na]^+$ 367.0770, found 367.0769.

4.21. 5-*O*-Naphthoylquinic acid (19)

According to the procedure described for **18**, **14a** (116 mg, 0.2 mmol) was deprotected by TFA (1.6 mL) in CH_2Cl_2 (32 mL) to afford **19** (55.3 mg, 80%) as a white solid (solvent used for ODS open column chromatography: 5–20% CH_3CN in H_2O). Mp: 171–172 °C; $[\alpha]_D^{22}$ −9.5 (c 0.2, CH_3OH); IR (KBr) 3422, 1691, 1291, 1231, 1199, 1131, 1066 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.00 (dd, J=13.0, 9.5, 1H), 2.20–2.33 (m, 3H), 3.73 (dd, J=9.5, 3.5 Hz, 1H), 4.32 (td, J=9.5, 3.5 Hz, 1H), 5.58 (q, J=3.5 Hz, 1H), 7.56 (t, J=8.0 Hz, 1H), 7.61 (t, J=8.0 Hz, 1H), 7.92 (d, J=8.0 Hz, 2H), 8.00 (d, J=8.0, 1H), 8.10 (d, J=8.0 Hz, 1H), 8.69 (s, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 36.8, 41.9, 68.2, 73.9, 75.2, 75.5, 126.5, 127.7, 128.8, 129.0, 129.3, 130.3, 132.3, 133.9, 137.0, 168.0, 178.4; HRMS (FAB) calcd for $C_{18}H_{17}O_7Na_2$ $[M-H+2Na]^+$ 391.0770, found 391.0765.

4.22. 5-*O*-Benzoylquinic acid (20)

According to the procedure described for **18**, **16a** (106 mg, 0.2 mmol) was deprotected by TFA (1.6 mL) in CH_2Cl_2 (32 mL) to afford **20** (47.3 mg, 80%) as a white solid (Solvent used for ODS open column chromatography: 0–5% CH_3CN in H_2O). Mp: 200–201 °C; $[\alpha]_D^{24}$ −36.2 (c 0.2, CH_3OH); IR (KBr) 3484, 3277, 2972, 1731, 1696, 1363, 1289, 1123, 1066, 711 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.97 (dd, J=13.5, 9.0, 1H), 2.16–2.28 (m, 3H), 3.69 (dd, J=9.0, 3.5 Hz, 1H), 4.24 (td, J=9.0, 3.5 Hz, 1H), 5.51 (q, J=3.5 Hz, 1H), 7.45 (t, J=8.0 Hz, 2H), 7.58 (t, J=8.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 8.09 (d, J=8.0, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 36.8, 41.9, 68.2, 73.8, 75.2, 75.5,

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129.3, 130.9, 132.1, 134.0, 167.9, 178.4; HRMS (FAB) calcd for $C_{14}H_{15}O_7Na_2$ $[M-H+2Na]^+$ 341.0613, found 341.0619.

4.23. 5-*O*-Phenylethylcarbonylquinic acid (21)

According to the procedure described for **18**, **17** (112 mg, 0.2 mmol) was deprotected by TFA (1.6 mL) in CH_2Cl_2 (32 mL) to afford **21** (51.2 mg, 79%) as a white solid (solvent used for ODS open column chromatography: 5–10% CH_3CN in H_2O). Mp: 154–155 °C; $[\alpha]_D^{24}$ −38.2 (*c* 0.2, CH_3OH); IR (KBr) 3420, 3198, 1729, 1687, 1354, 1298, 1198, 1128, 1086 cm^{-1}; UV (CH_3OH) λ_{max}/nm (ε), 209 (7300); ^1H NMR (500 MHz, CD_3OD) δ 1.92 (dd, *J*=13.0, 9.0 Hz, 1H), 2.07–2.15 (m, 3H), 2.66 (t, *J*=8.0, 1H), 2.67 (t, *J*=8.0 Hz, 1H), 2.94 (t, *J*=8.0 Hz, 2H), 3.58 (dd, *J*=9.0, 3.5 Hz, 1H), 4.08 (td, *J*=9.0, 3.5 Hz, 1H), 5.24 (q, *J*=3.5 Hz, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR (150 MHz, CD_3OD) δ 31.8, 36.5, 37.1, 41.5, 68.2, 73.3, 74.7, 75.3, 127.1, 129.4, 129.5, 142.3, 174.5, 178.3; HRMS (FAB) calcd for $C_{16}H_{19}O_7Na_2$ $[M-H+2Na]^+$ 369.0926, found 369.0926.

4.24. 5-*O*-(*E*)-Caffeoylquinic acid (1)

To a solution of **31a** (40 mg, 0.06 mmol) and pentamethylbenzene (C_6HMe_5) (111.2 mg, 0.75 mmol) in CH_2Cl_2 (2 mL) was added BCl_3 (0.6 mL, 0.60 mmol, 1 M in CH_2Cl_2) at −40 °C. After stirring for 10 min at −40 °C, the reaction mixture was allowed to warm to 0 °C for 3 h and quenched by H_2O (2 mL). The crude products were washed with CH_2Cl_2 in order to remove C_6HMe_5. The residual aqueous solution was purified by ODS HPLC (Develosil ODS-HG-5, Nomura Chemicals) with 5% CH_3CN aqueous solution containing 0.5% TFA. A few times of azeotropic evaporation by addition of CH_3CN under reduced pressure at 30 °C gave **1** (14.7 mg, 69%) as a white solid. Mp: 187–188 °C; $[\alpha]_D^{24}$ +6.6 (*c* 0.2, CH_3OH); IR (KBr) 3448, 1712, 1686, 1631, 1601, 1291, 1205, 1126, 1077, 813 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.96 (dd, *J*=13.5, 9.0 Hz, 1H), 2.11–2.23 (m, 3H), 3.64 (dd, *J*=9.0, 3.5 Hz, 1H), 4.15 (td, *J*=9.0, 3.5 Hz, 1H), 5.35 (q, *J*=3.5 Hz, 1H), 6.31 (d, *J*=16.0 Hz, 1H), 6.77 (d, *J*=8.5 Hz, 1H), 6.94 (d, *J*=8.5 Hz, 1H), 7.04 (s, 1H), 7.59 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 36.7, 41.5, 68.3, 73.0, 74.8, 75.4, 115.1, 115.8, 116.5, 122.9, 128.0, 146.8, 146.8, 149.4, 169.0, 178.3; HRMS (FAB) calcd for $C_{16}H_{19}O_9$ $[M+H]^+$ 355.1029, found 355.1040.

4.25. 5-*O*-(*E*)-*p*-Coumaroylquinic acid (2)

According to the procedure described for **1**, **30a** (123.3 mg, 0.2 mmol) was deprotected by BCl_3 (2.0 mL, 2.0 mmol, 1 M in CH_2Cl_2) and pentamethylbenzene (C_6HMe_5) (370.6 mg, 2.5 mmol) in CH_2Cl_2 (7 mL) to afford **2** (49.4 mg, 73%) as a white solid (-Develosil ODS-HG-5, Nomura Chemicals: 5% CH_3CN aqueous solution containing 0.5% TFA). Mp: 169.5–170.5 °C; $[\alpha]_D^{24}$ +10.3 (*c* 0.2, CH_3OH); IR (KBr) 3409, 1692, 1606, 1515, 1278, 1176, 980, 828 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.96 (dd, *J*=13.5, 9.5 Hz, 1H), 2.11–2.23 (m, 3H), 3.64 (dd, *J*=9.0, 3.5 Hz, 1H), 4.15 (td, *J*=9.0, 3.5 Hz, 1H), 5.36 (q, *J*=3.5 Hz, 1H), 6.37 (d, *J*=15.0 Hz, 1H), 6.80 (d, *J*=8.5 Hz, 2H), 7.46 (d, *J*=8.5 Hz, 2H), 7.65 (d, *J*=15.0 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 36.8, 41.2, 68.5, 72.9, 74.6, 75.5, 115.9, 116.8, 127.4, 131.1, 146.4, 161.1, 169.0, 178.8; HRMS (FAB) calcd for $C_{16}H_{19}O_8$ $[M+H]^+$ 339.1080, found 339.1071.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR data of products. Crystallographic data for **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 996730. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.08.064.

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