

Graphical Abstract

One-Pot Esterification and Amidation of Phenolic Acids

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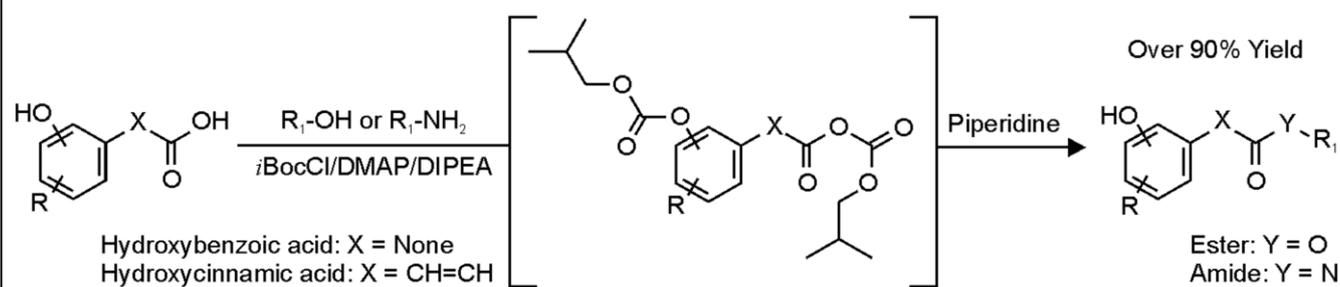
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ABSTRACT

We developed a new one-pot reaction of phenolic acids to afford the corresponding esters and amides through acyl-protected and activated phenolic acid intermediates. The simultaneous protection/activation of phenolic acids with alkylchloroformates proceeded readily in the presence of DMAP at room temperature; subsequent addition of alcohols or amines afforded the corresponding esters or amides. The use of *iso*-butyloxycarbonyl as the protecting and activating group in the one-pot reactions afforded phenolic esters or amides in 91% average yield. As a practical example of this convenient synthesis, caffeic acid phenethyl ester (CAPE) was readily synthesized from commercially available caffeic acid and phenethyl alcohol in 95% yield, and an isotopomer of CAPE, [3,10-¹³C₂]CAPE, was synthesized in 91% yield from [3-¹³C]caffeic acid and 2-[1-¹³C]phenethyl alcohol. This method may be useful for the convenient esterification and amidation of diverse phenolic acids.

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1. Introduction

Phenolic acids including hydroxycinnamic acids and hydroxybenzoic acids are ubiquitous in the plant kingdom. Phenolics readily scavenge radical species by forming resonance-stabilized phenoxy radicals, which are responsible for their potent antioxidant^{1,2} and radical-scavenging capabilities.^{3,4} Recently, phenolic acids and their derivatives are shown to reduce the risk of chronic diseases.⁵⁻⁹ The esterification and amidation of phenolic acids are practical techniques to improve their solubility and emulsification properties as well as enhance their antioxidant and antidiabetic activities.¹⁰⁻¹⁶ The amidation of selected hydroxycinnamic acids and hydroxybenzoic acids improved their antioxidant activities.¹⁴ The serine esters of phenolic acids exhibited superior antioxidative activity in heterogeneous systems.¹⁵ The amides of ferulic acid with alkyl or cyclic alkyl amines promoted insulin release in *in vitro* experiments.¹⁶ The conversions of phenolic acids to the corresponding esters or amides are generally carried out by three or four synthetic steps:

(i) protection of the phenolic hydroxyl group(s), (ii) activation of the carboxylic acid group, (iii) condensation with alcohols or amines, and (iv) deprotection of the phenolic hydroxyl group(s).^{15,16} More convenient alternative methods have also been reported. For example, thermally stable phenolic acid esters have been synthesized in one step using an acidic catalyst such as thionyl chloride (SOCl₂) under reflux.^{17,18} One-step low-temperature (−78 °C) esterification using boron trichloride has been reported.¹⁹ However, these methods suffered from low yields of phenolic acid esters. In a short-step amidation without protecting phenolic hydroxyl groups, the yields were mostly <60%.^{17,20} Phenolic acids can also be enzymatically esterified or amidated in one step.^{20,21} However, these methods are effective for specific phenolic acids only, particularly when a longtime reaction can be allowed. Thus, a widely applicable, convenient, and high-yield alternative method is still needed for the synthesis of phenolic acid esters and amides. In this paper, we report a new one-pot convenient method for the esterification/amidation of phenolic acids to their esters or amides.

Caffeic acid phenethyl ester (CAPE), which is one of the most effective natural phenolic acid derivatives, exhibits significant anticancer²² and anti-β-amyloid activities²³ *in vitro* caused by the inhibition of transcription factor NF-κB.^{24,25} CAPE was first isolated from propolis, which is a mixture of gathered leaf buds and secretions of honey bees, as a defensive barrier for beehive.²⁶ The *in vivo* dynamics of CAPE after the oral administration have

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been studied for practical use.²⁷ Recently, the accurate mass spectrometric determination of a phenolic compound *in vivo* has been reported using the corresponding isotopomer as the internal standard.²⁸ An isotopomer was also used as the labeled compound for the *in vivo* dynamics analysis.²⁹ An isotopomer of CAPE is an ideal internal standard and a metabolic tracer. In general, an isotopomer is chemically synthesized and labeled with a stable isotope of ¹³C. A high-yield method is needed for the synthesis of ¹³C-labeled compounds because of the expensiveness of the labeled compounds. As a practical example of our convenient developed method, the isotopomers of CAPE were synthesized from ¹³C-labeled caffeic acid and 2-phenethyl alcohol in excellent yields.

2. Results and discussion

To develop a convenient method to obtain phenolic acid esters and amides, we initially protected the phenolic hydroxyl group by Boc, which has been used extensively as a protecting group in peptide chemistry.³⁰ Di-*tert*-butyl dicarbonate ((Boc)₂O, 1.2 equiv) was reacted with ferulic acid in the presence of 0.1 equiv of DMAP as the catalyst and 1.0 equiv of triethylamine (TEA) as the base. After reacting for 2 h at 0 °C, the Boc-protected ferulate, (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxycinnamic acid (**1**, Fig. 1), was obtained in 60-70% yields in several synthetic experiments. In these reactions, a by-product was formed in 10-20% yields. From the ¹H and ¹³C NMR analyses, the structure of the by-product was established to be *tert*-butyl (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxy-cinnamate (**2**, Fig. 1). The carboxylic acid group of **1** may have reacted with (Boc)₂O to form a mixed anhydride followed by the reaction of the mixed anhydride with *tert*-butyl alcohol liberated from (Boc)₂O to afford *tert*-butyl ester **2**. Therefore, we synthesized the mixed anhydride of ferulic acid with Boc. Ferulic acid was reacted with 2.2 equiv of (Boc)₂O in the presence of 0.05 equiv of DMAP and 1.0 equiv of TEA at -15 °C for 2 h, and (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxycinnamic mono-*tert*-butyl carbonic anhydride (**3a**) was obtained as a white crystal in 82% yield. The reaction of **3a** with *tert*-butyl alcohol afforded **2**.

The simultaneous protection/activation of ferulic acid to form **3a** can be utilized for a high-yield convenient synthesis of phenolic acid derivatives by reducing a synthetic step. Therefore, selected protected ferulic acid mixed anhydrides were prepared to optimize the protection/activation condition. Table 1 shows the results of the preparations of protected ferulic acid monoalkyl carbonate mixed anhydride and their conversions to the corresponding piperidine amides. Compounds **3b-h** were synthesized using monoalkyl chloroformates or acid chlorides under the similar conditions as for **3a**. The protected ferulic acid mixed anhydrides were obtained in excellent yields, except unstable **3h**. No by-product such as **2** was formed in the reaction using the monoalkyl chloroformates or acid chlorides. After the reaction, the mixed anhydrides were obtained as almost pure products simply by filtration to remove triethylamine hydrochloride precipitate and evaporation to remove the solvent. All the obtained products except **3c** and **3e** were recrystallized. Usually, the isolation and crystallization of anhydrides are difficult because of the instability at room temperature. The phenolic acid mixed anhydrides are easy to use because of their stable nature.

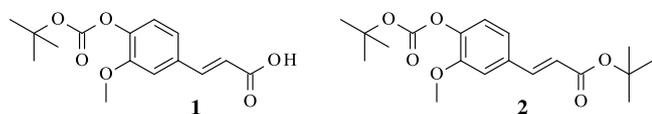


Fig. 1. Structures of compound **1** and **2**

Table 1

Syntheses of protected-activated ferulic acids^a and subsequent amide formation with piperidine

| R | Yield % | |
|---|-------------------------------|-----------------------|
| | 3 | 4 ^b |
| -OC(CH ₃) ₃ | 82 ^b (3a) | 98 |
| -OCH ₂ CH(CH ₃) ₂ | 99 ^b (3b) | 97 |
| -OCH ₂ CH ₂ CH ₂ CH ₃ | 99 (3c) | 94 |
| -OCH ₂ CH ₂ CH ₃ | 97 ^b (3d) | 90 |
| -OCH ₂ CH ₃ | 96 (3e) | 73 |
| -OCH ₃ | 90 ^b (3f) | 64 |
| -C(CH ₃) ₃ | 99 ^b (3g) | 0 |
| -CH ₃ | 20 ^b (3h) | 0 |

^aReactant **3a**: (Boc)₂O, **3b-f**: alkyl chloroformates, **3g-h**: acid chlorides.

^bCrystallized compounds.

Table 1 also shows the yields of (*E*)-*N*-feruloyl piperidine (**4**) obtained from the reaction of **3a-h** with piperidine. Urethane-type protecting groups on the phenolic hydroxyl group of **3a-f** are cleaved with nucleophilic bases as reported previously.³⁰ Therefore, the amidation and deprotection could be carried out at once using excessive amounts of piperidine, and **4** was obtained in excellent yields from **3a-c**. The yield of **4** from **3d-f** improved when the bulkiness of the acyl side chain was increased, even though the reactions of **3g** and **3h** with piperidine did not afford **4**. In the reaction of **3h** with the smallest acyl group, only ferulic acid was obtained. The bulkiness of the acyl group on the protected ferulic acid mixed anhydrides was important to afford **4**. In the reaction of **3g**, the amidation occurred quantitatively; however, the deprotection of the pivaloyl group with piperidine did not proceed. Collectively, (Boc)₂O and *iso*-butyl chloroform-

Table 2

Synthesis of *O*-protected phenolic mono-*tert* or *iso*-butyl carbonic anhydrides using (Boc)₂O or *i*BocCl^{a,b}

| | R ₁ | R ₂ | R ₃ | Yield (%) |
|------------------------|--------------------|--------------------|-----------------|-----------|
| 5a ^c | -H | -H | -O- <i>t</i> Bu | 81 |
| 5b ^c | -H | -H | -O- <i>i</i> Bu | 99 |
| 6a ^c | -OMe | -OMe | -O- <i>t</i> Bu | 70 |
| 6b ^c | -OMe | -OMe | -O- <i>i</i> Bu | 99 |
| 7a | -H | -OCOO- <i>t</i> Bu | -O- <i>t</i> Bu | 72 |
| 7b | -H | -OCOO- <i>i</i> Bu | -O- <i>i</i> Bu | 96 |
| 8 | -H | -H | -O- <i>i</i> Bu | 97 |
| 9 | -H | -OMe | -O- <i>i</i> Bu | 97 |
| 10 ^c | -OMe | -OMe | -O- <i>i</i> Bu | 96 |
| 11 | -OCOO- <i>i</i> Bu | -OCOO- <i>i</i> Bu | -O- <i>i</i> Bu | 90 |

^aReactants of **5a**, **6a**, **7a**: (Boc)₂O, **5b**, **6b**, **7b**, **8-11**: *i*BocCl.

^bBoc: *tert*-butoxycarbonyl, *i*Boc: *iso*-butoxycarbonyl, *t*Bu: *tert*-butyl, *i*Bu: *iso*-butyl

^cCrystallized compounds.

ate (*i*BocCl) were concluded to be favorable protecting/activating reactants to synthesize the phenolic acid piperidine amides.

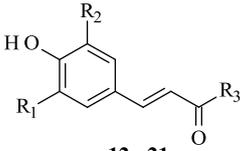
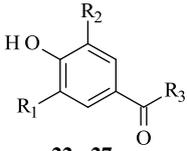
Based on the results shown in Table 1, *tert*- and *iso*-butyl carbonate mixed anhydrides were synthesized from selected phenolic acids (Table 2). The protected mixed anhydrides of hydroxy cinnamates, *p*-coumaric acid (**5b**), sinapinic acid (**6b**), and caffeic acid (**7b**) were obtained in high yields, and the products except those from caffeic acid were crystallized. The compounds, **5b**, **6b**, and **7b**, containing *i*Boc groups were obtained in higher yields than **5a**, **6a**, and **7a** containing Boc groups, where the lower yields can be attributed to the side reactions to afford each *tert*-butyl ester as described before. Therefore, the mixed anhydrides of hydroxy benzoates, *p*-hydroxy benzoic acid (**8**), vanillic acid (**9**), syringic acid (**10**), and gallic acid (**11**) were synthesized using *i*BocCl in high yields. The simultaneous protection/activation using various types of phenolic acids by *i*BocCl was conveniently demonstrated to undergo subsequent esterification and amidation.

Next, we examined the conversions of phenolic acids to their corresponding esters and amides in one-pot reactions using *i*BocCl. The results are shown in Table 3. Diverse phenolic acids were converted to the corresponding esters and amides in good yields in one-pot reactions. Primary and secondary amines including cyclic amines readily reacted with the phenolic acids to afford the corresponding amides (**12**, **18**, **20**, and **26**). The esters of primary alcohols (**13**, **14**, **21**, **23**, and **27**), secondary alcohols (**19** and **24**), tertiary alcohols (**15** and **22**), and phenols (**16**, **17**, and **25**) with the phenolic acids were obtained. The average yield was 91%, and all the products were obtained in one day. Thus, a convenient conversion of phenolic acids to their esters and amides was achieved using *i*BocCl in one-pot reactions. However, the esterification and amidation of gallic acid failed, even though the protected anhydride of gallic acid (**11**) was readily obtained. To obtain the esters and amides of gallic acid, more rigid protection of the hydroxyl groups such as with pivaloyl group may be necessary allowing lower yield. In fact, we synthesized epigallocatechin gallate using pivaloyl-protected gallic acid.³¹

Using the developed convenient method, CAPE (**21**) was readily synthesized from commercially available caffeic acid and phenethyl alcohol in a high yield. CAPE has distinguished biological activities as described previously.²²⁻²⁵ For further investigations to elucidate the detailed *in vivo* dynamics of CAPE, its isotopomer can be utilized as a metabolic tracer and an internal standard for the dynamics analysis. In this study, two types of isotopomers of CAPE, [3,10-¹³C₂]CAPE (**28**) and [10-

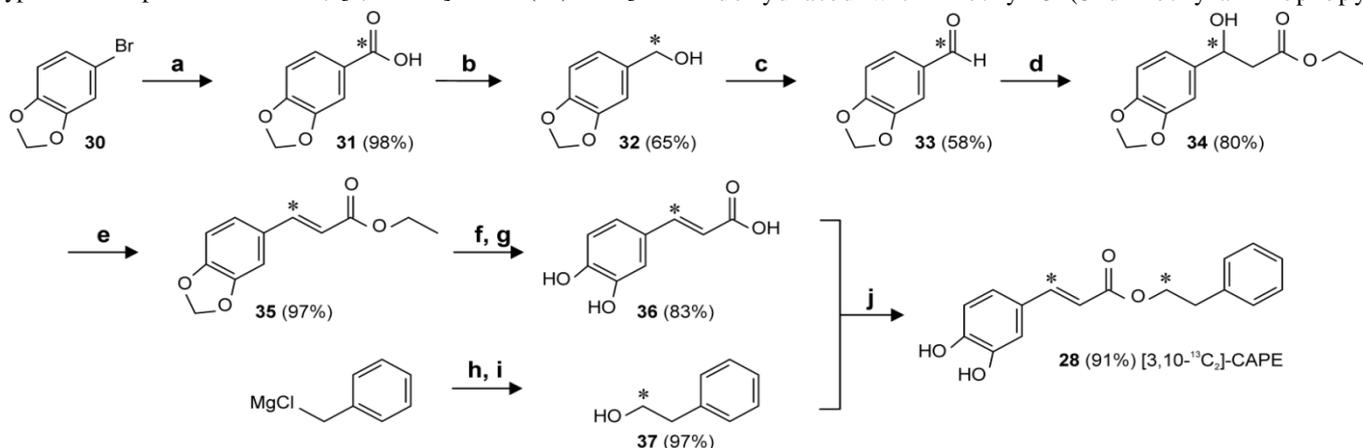
Table 3

Synthesis of phenolic acid derivatives through the protected mixed acid anhydrides

| |  | |  | |
|------------------------|--|----------------|---|-----------|
| | R ₁ | R ₂ | R ₃ | Yield (%) |
| 12 ^a | -H | -OMe | -NH <i>i</i> Pr | 95 |
| 13 | -H | -OMe | -OMe | 90 |
| 14 | -H | -OMe | -OEt | 90 |
| 15 | -H | -OMe | -O <i>t</i> Bu | 91 |
| 16 | -H | -OMe | -OPh | 96 |
| 17 ^a | -H | -OMe | -ONAPH ^b | 89 |
| 18 ^a | -H | -H | -N(<i>i</i> Pr) ₂ | 89 |
| 19 | -H | -H | -O <i>i</i> Pr | 82 |
| 20 ^a | -OMe | -OMe | -NEt ₂ | 96 |
| 21 ^a | -H | -OH | -O(CH ₂) ₂ Ph | 95 |
| 22 | -H | -H | -O <i>t</i> Bu | 100 |
| 23 ^a | -H | -OMe | -OMe | 93 |
| 24 ^a | -H | -OMe | -O <i>i</i> Pr | 83 |
| 25 ^a | -H | -OMe | -OPh | 85 |
| 26 ^a | -OMe | -OMe | -NEt ₂ | 89 |
| 27 ^a | -H | -OH | -O(CH ₂) ₂ Ph | 92 |

^aCrystallized compounds. ^bNAPH: β-naphthol

¹³C]CAPE (**29**) were conveniently synthesized in high yields by using our method at the final condensation step. The isotopomer of CAPE (**28**) was synthesized as shown in Scheme 1. First, the hydroxyl groups of catechol moiety were protected with methylene acetal to avoid decomposition during the synthetic process. Therefore, 1-bromo-3,4-(methylenedioxy)benzene (**30**) was used as the starting material. The bromine-lithium exchange of compound **30** using aeriform carbon-¹³C dioxide as the electrophile afforded carboxylic acid **31** in a good yield. The reduction of the ¹³C-labeled carboxylic acid **31** with LAH to alcohol **32** and the subsequent oxidation of alcohol **32** with NaClO afforded aldehyde **33**. The aldol product of **34** produced by the aldol condensation of aldehyde **33** with ethyl acetate was dehydrated with 1-ethyl-3-(3-dimethylaminopropyl)



Scheme 1. Synthesis of isotopomer of CAPE: Reagent and conditions: (a) ¹³CO₂, BuLi, -78 °C, 30 min; (b) LAH, rt, 2 h; (c) TEMPO, NaClO, rt, 30 min; (d) ethyl acetate, LDA, -78 °C, 2 h; (e) EDC·HCl, CuCl (I), rt, 12 h; (f) LiOH, 4 h; (g) BBr₃, DCM, -78 °C, 2 h; (h) ¹³CO₂, -10 °C, 30 min; (i) LAH, 2 h; (j) 2-[1-¹³C]phenethyl alcohol, *i*BocCl/DMAP/TEA/piperidine (9.5% over eight steps of a-g, j to synthesize **28**).

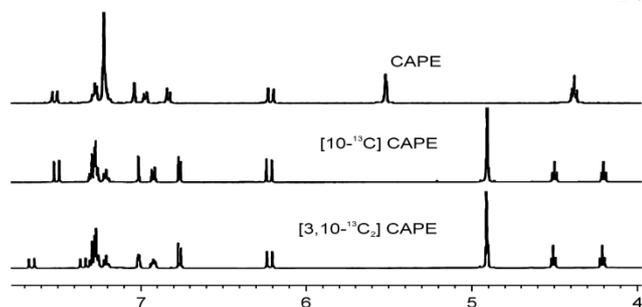


Fig. 2. Comparison of the ^1H NMR Spectrum of CAPE, $[10\text{-}^{13}\text{C}]$ CAPE and $[3,10\text{-}^{13}\text{C}_2]$ CAPE. The 2-H triplet signal of CAPE at δ 4.35 ppm is split into two triplets on $[10\text{-}^{13}\text{C}]$ and $[3,10\text{-}^{13}\text{C}_2]$ CAPE. The olefin H doublet signal at δ 7.47 ppm of CAPE is split into two doublets on $[3,10\text{-}^{13}\text{C}_2]$ CAPE. The full spectra for compounds are available in the Supplementary Data.

carbodiimide hydrochloride (EDC·HCl) in the presence of copper (I) chloride (CuCl(I)) to obtain protected $[3\text{-}^{13}\text{C}]$ caffeic acid ethyl ester **35**. After the de-esterification with lithium hydroxide (LiOH) and the deprotection with boron tribromide (BBr_3), (*E*)- $[3\text{-}^{13}\text{C}]$ caffeic acid (**36**) was obtained in seven steps and 11.9% yield. Another part of the isotopomer of CAPE, 2- $[1\text{-}^{13}\text{C}]$ phenethyl alcohol (**37**) was readily obtained in one step by the reduction using LAH of phenyl $[1\text{-}^{13}\text{C}]$ acetic acid, which was synthesized from commercially available benzyl magnesium chloride and aeriform carbon- ^{13}C dioxide by Grignard reaction.³² As a result of the condensation of (*E*)- $[3\text{-}^{13}\text{C}]$ caffeic acid (**36**) with 2- $[1\text{-}^{13}\text{C}]$ phenethyl alcohol (**37**) by our esterification, $[3,10\text{-}^{13}\text{C}_2]$ CAPE (**28**) was obtained in 91% yield. Based on the starting material of **30**, the total yield was 9.5% in eight steps. $[10\text{-}^{13}\text{C}]$ CAPE (**29**) was also synthesized by the reaction of nonlabeled caffeic acid with 2- $[1\text{-}^{13}\text{C}]$ phenethyl alcohol (**37**) in a good yield. The structure and purity of the synthesized compounds were confirmed by NMR and MALDI-TOF-MS analyses. The HPLC purity of $[3,10\text{-}^{13}\text{C}_2]$ CAPE and $[10\text{-}^{13}\text{C}]$ CAPE were 99.7% and 99.2%, respectively. Specific ^{13}C - ^1H heteronuclear spin couplings were observed on the ^1H -NMR spectrum of compounds **28** and **29** as shown in Figure 2. CAPE and the isotopomers were selectively determined by the LC-MS analysis using the selected ion monitoring (SIM) mode as shown in Figure 3, and the isotopomers were applicable as the internal standards for the *in vivo* dynamic analysis of CAPE.

The chemical synthesis of CAPE from caffeic acid and 2-phenethyl alcohol was reported by Chen et al. DCC was used as the condensation agent, and the yield of CAPE was 38% in three

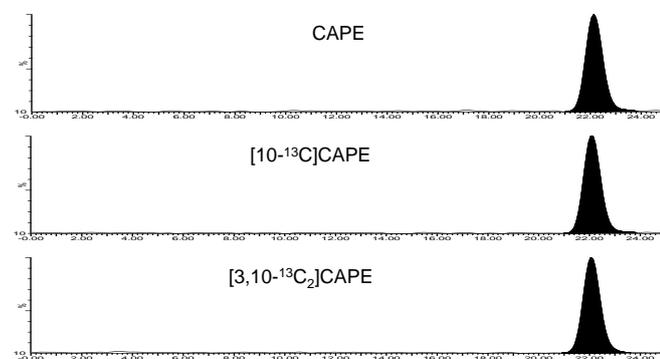


Fig. 3. Selective determination of CAPE, $[10\text{-}^{13}\text{C}]$ CAPE and $[3,10\text{-}^{13}\text{C}_2]$ CAPE by LC-MS. MS detection was performed with ESI positive ion mode and selected ion monitoring mode at m/z 283.1 $[\text{M} - \text{H}]^-$ for CAPE, m/z 284.1 $[\text{M} - \text{H}]^-$ for $[10\text{-}^{13}\text{C}]$ CAPE, and m/z 285.1 $[\text{M} - \text{H}]^-$ for $[3,10\text{-}^{13}\text{C}_2]$ CAPE.

steps.³³ Chen et al. reported the one-step enzymatic synthesis of CAPE by immobilized lipase at a conversion rate of 91.9% after 59 h at 60 °C reaction.²¹ Using our method, CAPE was synthesized in 95% yield in 2 h reaction from unprotected caffeic acid and 2-phenethyl alcohol in a one-pot reaction. Furthermore, the isotopomers of CAPE, **28** and **29**, were synthesized in 91% and 88% yields, respectively, from the corresponding isotopomers of caffeic acid and 2-phenethyl alcohol, in one-pot reactions.

Our esterification and amidation of phenolic acids was a modified method of mixed anhydride method for peptide synthesis using *i*BocCl³⁴ and esterification using mixed carboxylic-carbonic anhydrides and DMAP.³⁵ The advantage of our method is simultaneous protection of phenolic hydroxyl group(s) on phenolic acid in the esterification and amidation. A one-pot esterification of N-protected amino acids using isopropenyl chloroformate has been reported by Jouin et al.³⁶ In the report, the esterification is described as being inadaptable to preparation of esters with free hydroxyl group on amino acid side chain. Using *i*BocCl and optimum condition setting for the simultaneous protection/activation could achieve our convenient esterification and amidation of diverse phenolic acids.

3. Conclusion

In this study, the developed method could convert phenolic acids to the corresponding esters and amides in one-pot reactions using *i*BocCl. Sixteen types of esters and amides as shown in Table 3 were synthesized in one-pot reactions in 91% average yield and over 82% yields from eight types of phenolic acids. Using the method, we obtained CAPE in 95% yield in a one-pot reaction for 2 h. This result afforded the highest yield and shortest reaction time ever reported for CAPE synthesis. This protocol was then applied to the preparation of isotopically labeled CAPE. Hence, it may be a versatile method to obtain the phenolic acid derivatives in better yields.

4. Materials and methods

4.1. Chemicals

All the chemicals and solvents were purchased from commercial suppliers and used as received without further purification. NaCl, NaClO, NaHCO_3 , KHSO_4 , H_2SO_4 , Na_2SO_4 (anhydrous), LiOH, DCM, methanol, ethanol, *n*-hexane, ethyl acetate, THF, TEA, acetonitrile (HPLC grade), diethyl amine, 1.0 M BBr_3 in DCM, and *p*-hydroxy benzoic acid were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Piperidine, TFA, DMF, and DMAP were purchased from Watanabe Chemical Industries, Ltd. (Hiroshima, Japan). Phenol, isopropanol, *tert*-butanol, β -naphthol, 1,4-dioxane, 0.10 M HCl, sodium dihydrogen phosphate, CuCl(I) , 1.6 M butyllithium (BuLi)/hexane, ferulic acid, vanillic acid, syringic acid, gallic acid, *p*-coumaric acid, sinapinic acid, caffeic acid, *iso*-propyl amine, *N,N*-di-*iso*-propylamine, acetyl chloride, ethyl chloroformate, methyl chloroformate, *n*-propyl chloroformate, *n*-butyl chloroformate, (Boc) $_2$ O, *i*BocCl, EDC·HCl, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), and 1-bromo-3,4-(methylenedioxy)benzene were purchased from Wako Pure Chemical Industries (Osaka, Japan). Pivaloyl chloride, LAH, benzyl magnesium chloride, chloroform-*d* (CDCl_3), methanol-*d*₄ (CD_3OD), dimethyl sulfoxide-*d*₆ ($\text{DMSO-}d_6$), and 2 M LDA in THF/heptane/ethylbenzene were purchased from Sigma-Aldrich (St. Louis, MO, USA). Carbon dioxide- ^{13}C ($^{13}\text{CO}_2$) was from SI Science Co., Ltd. (Saitama, Japan). Purified water was obtained from a Sartorius purification system (Sartorius AG, Gottingen, Germany).

4.2. General techniques

All the reactions were monitored by TLC on aluminum silica gel plates (TLC silica gel 60F-254, Merck Millipore, Germany) with UV light. Preparative TLC and flash column chromatography were carried out with preparative TLC silica gel plate (60F-254, 20 × 20 cm², 2 mm, Merck Millipore) and silica gel (40-100 μm, Fuji Silysia, Aichi, Japan) with the indicated solvent system. NMR, LC-MS, and FT-IR analyses were performed at the CREFAS (Collaborated Research Center for Food Functions, Faculty of Agriculture, Shinshu University). NMR spectra in the indicated solvents were recorded using a Bruker DRX500 spectrometer (Bruker BioSpin Corp., Billerica, MA) at 500 MHz for ¹H and 126 MHz for ¹³C NMR or a Varian UNITY plus-400 (Varian Inc., Palo Alto, CA) at 400 MHz for ¹H and 100 MHz for ¹³C NMR at 25 °C. Chemical shifts were referenced to the signal of TMS as the internal standard. The LC-MS analytical system was a Quattro micro API (MS) with an ACQUITY UPLC (Waters Co., USA). The HPLC separation analyses were performed at 35 °C using a Cadenza HS C-18 reversed-phase column (4.6 × 150 mm²; Imtakt Co., Kyoto, Japan). The elution was performed at a flow rate of 0.8 mL/min using water with 0.5% formic acid and acetonitrile with 0.5% formic acid (3:1 v/v). The UV detection was performed at 215 nm with an injection volume of 20 μL. The mass spectra were acquired in the ESI mode using 3500 V capillary voltage, 50 V cone voltage, 350 L/h N₂ gas flow (desolvation), 50 L/h N₂ gas flow (cone), 100 °C source temperature, and 350 °C desolvation temperature. The mass spectrometer was operated in the negative mode and SIM mode at *m/z* 283.1 [M-H]⁻ for CAPE, *m/z* 284.1 [M-H]⁻ for [10-¹³C]CAPE, and *m/z* 285.1 [M-H]⁻ for [3,10-¹³C₂]CAPE. LC2010CHT HPLC system (Shimadzu, Co., Kyoto, Japan) was used for the HPLC analyses. One milligram of each of the reaction mixture was dissolved in 1.0 mL of CH₃CN/H₂O (1:1 v/v) containing 0.1% TFA. The chromatography was performed at 40 °C at a flow rate of 0.8 mL/min and an injection volume of 10 μL, and the chromatograms were acquired at 215 nm. The separation was performed at 30 °C using a CHEMCOBOND 5-ODS-W reversed-phase column (4.6 × 150 mm²; ChemcoPlus Scientific Co., Ltd.). The gradient elution was performed using a mobile phase of acetonitrile with 0.1% TFA (Solvent B) and 0.1% TFA in purified water (Solvent A) as per the following gradient program: 0-10 min, 0-5% Solvent B; 10-15 min, 5-5% Solvent B; 15-20 min, 5-10% Solvent B; 20-40 min, 10-20% Solvent B; and 40-50 min, 20-100% Solvent B. IR spectra were recorded on a Jasco FT/IR-480 Plus spectrometer (Jasco Co., Tokyo, Japan). Melting points were determined using a Yanaco MP-S3 micro melting point apparatus (Yanagimoto Co., Kyoto, Japan). The high-resolution MALDI-TOF-MS analyses were performed on an AB SCIEX TOF/TOF 5800 equipped with a 1 kHz a neodymium: yttrium-aluminum-garnet laser (AB SCIEX, Framingham, MA, USA) at the Research Center for Human and Environmental Science at Shinshu University.

4.3. Reaction of ferulic acid with (Boc)₂O

4.3.1 (E)-4-tert-Butoxycarbonyloxy-3-methoxycinnamic acid (1) (Boc)₂O (0.24 g, 1.1 mmol) was added to a solution of ferulic acid (0.19 g, 1.0 mmol), DMAP (1.2 mg, 0.010 mmol), and TEA (0.14 mL, 1.0 mmol) in DCM (2.0 mL) at 0 °C. After stirring for 2 h, 5% KHSO₄ (10 mL) was added, and the product was extracted three times with ethyl acetate (20 mL). The combined organic layer was washed with saturated brine (60 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residual crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:5-1:1 v/v) to afford **1** (0.32 g, 0.76 mmol, 76% yield) as a white crystal; mp 148-

150 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.73 (1H, d, *J* = 15.6 Hz, ArCH=), 7.15-7.11 (3H, m, ArH), 6.37 (1H, d, *J* = 16.0 Hz, =CH-), 3.87 (3H, s, OCH₃), 1.54 (9H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 172.0 (C), 151.6 (C), 151.0 (C), 146.3 (CH), 142.2 (C), 132.8 (C), 123.0 (CH), 121.6 (CH), 117.5 (CH), 111.6 (CH), 83.8 (C), 56.0 (CH₃), 27.6 (CH₃). IR (film, *v*_{max}): 2979, 1760, 1715, 1628, 1508, 1457, 1418, 1370, 1253, 1145, 1123, 1074, 888, 778, 744 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 333.0486, required *m/z* 333.0735.

4.3.2 tert-Butyl (E)-4-tert-butoxycarbonyloxy-3-methoxycinnamate (2) To a solution of (E)-4-tert-butoxycarbonyloxy-3-methoxycinnamic mono-tert-butyl carbonic anhydride (**3a**, 59.0 mg, 0.15 mmol) in tert-butanol/DCM (1:1 v/v, 0.60 mL) was added DMAP (1.8 mg, 0.015 mmol) in DCM (10 μL) at room temperature. The crude product was purified by preparative TLC (ethyl acetate/hexane, 1:3 v/v) to afford compound **2** (28 mg, 0.135 mmol, 93% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.50 (1H, d, *J* = 16.0 Hz, ArCH=), 7.08-7.06 (3H, m, ArH), 6.28 (1H, d, *J* = 15.6 Hz, =CH-), 3.85 (3H, s, OCH₃), 1.53 (9H, s, CH₃), 1.51 (9H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 166.1 (C), 151.5 (C), 151.2 (C), 142.8 (CH), 141.6 (C), 133.5 (C), 122.8 (CH), 121.1 (CH), 120.4 (CH), 111.2 (CH), 83.6 (C), 80.6 (C), 55.9 (CH₃), 28.2 (CH₃), 27.6 (CH₃). IR (film, *v*_{max}): 2979, 2935, 1763, 1705, 1638, 1603, 1508, 1458, 1417, 1393, 1369, 1256, 1145, 1125, 1036, 983, 890, 851, 779, 744 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 389.1264, required *m/z* 389.1361.

4.4. Typical procedure for protected ferulate monoalkyl carbonate mixed anhydrides 3a-3h.

To a solution of ferulic acid (0.19 g, 1.0 mmol) and TEA (0.30 mL, 2.2 mmol) in DCM (2.0 mL) was slowly added alkyl chloroformate (2.2 mmol) or (Boc)₂O (0.48 g, 2.2 mmol) at -15 °C. After stirring for 5 min- 2 h, hexane (10-40 mL) was added to the reaction mixture. The precipitate was filtered, and the filtrate was evaporated under reduced pressure.

4.4.1 (E)-4-tert-Butoxycarbonyloxy-3-methoxycinnamic mono-tert-butyl carbonic anhydride (3a) Obtained 82% yield after silica gel column chromatography (ethyl acetate/hexane, 1:9-1:5 v/v), white crystal; mp 86-88 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.72 (1H, d, *J* = 16.0 Hz, ArCH=), 7.14-7.07 (3H, m, ArH), 6.32 (1H, d, *J* = 16.0 Hz, =CH-), 3.86 (3H, s, OCH₃), 1.54 (9H, s, CH₃), 1.53 (9H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 161.3 (C), 151.6 (C), 150.9 (C), 147.6 (CH), 147.0 (C), 142.4 (C), 132.4 (C), 123.0 (CH), 121.7 (CH), 116.0 (CH), 111.5 (CH), 85.4 (C), 83.9 (C), 55.9 (CH₃), 27.5 (CH₃), 27.4 (CH₃). IR (film, *v*_{max}): 2981, 2936, 1796, 1762, 1633, 1602, 1509, 1458, 1419, 1396, 1371, 1243, 1146, 1120, 1082, 995, 890, 847, 779, 745 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 433.1224, required *m/z* 433.1259.

4.4.2 (E)-4-iso-Butoxycarbonyloxy-3-methoxycinnamic mono-iso-butyl carbonic anhydride (3b) Obtained 99% yield using *i*BocCl, white crystal; mp 49-51 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.77 (1H, d, *J* = 16.0 Hz, ArCH=), 7.16-7.10 (3H, m, ArH), 6.36 (1H, d, *J* = 16.0 Hz, =CH-), 4.08 (2H, d, *J* = 6.8 Hz, OCH₂-), 4.03 (2H, d, *J* = 6.8 Hz, OCH₂-), 3.87 (3H, s, OCH₃), 2.09-1.99 (2H, m, CH), 0.98 (12H, d, *J* = 6.4 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 160.8 (C), 152.9 (C), 151.6 (C), 149.3 (C), 148.1 (CH), 142.5 (C), 132.6 (C), 123.0 (CH), 121.8 (CH), 115.8 (CH), 111.7 (CH), 75.5 (CH₂), 75.1 (CH₂), 56.0 (CH₃), 27.8 (CH), 27.6 (CH), 18.8 (CH₃). IR (film, *v*_{max}): 2965, 2876, 1801, 1767, 1633, 1602, 1510, 1470, 1419, 1397, 1379, 1244, 1141, 1092, 1050, 960, 846, 775, 756 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found *m/z* 417.1595, required *m/z* 417.1520.

4.4.3 (E)-4-n-Butoxycarbonyloxy-3-methoxycinnamic mono-n-butyl carbonic anhydride (3c) Obtained 99% yield using n-butyl chloroformate, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.78 (1H, d, *J* = 15.9 Hz, ArCH=), 7.19-7.12 (3H, m, ArH), 6.37 (1H, d, *J* = 15.9 Hz, =CH-), 4.32 (2H, t, *J* = 6.6 Hz, OCH₂-), 4.27 (2H, t, *J* = 6.6 Hz, OCH₂-), 3.89 (3H, s, OCH₃), 1.76-1.71 (4H, m, CH₂), 1.49-1.42 (4H, m, CH₂), 0.97 (6H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.8 (C), 152.9 (C), 151.7 (C), 149.3 (C), 148.1 (CH), 142.6 (C), 132.7 (C), 123.1 (CH), 121.8 (CH), 115.9 (CH), 111.8 (CH), 69.6 (CH₂), 69.1 (CH₂), 56.1 (CH₃), 30.6 (CH₂), 30.4 (CH₂), 18.9 (CH₂), 13.6 (2 × CH₃). IR (film, ν_{max}): 2962, 2874, 1801, 1766, 1633, 1602, 1510, 1466, 1419, 1390, 1248, 1141, 1093, 1065, 984, 924, 847, 775 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found *m/z* 417.1568, required *m/z* 417.1520.

4.4.4 (E)-4-n-Propyloxycarbonyloxy-3-methoxycinnamic mono-n-propyl carbonic anhydride (3d) Obtained 97% yield using n-propyl chloroformate, white crystal; mp 34-36 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.78 (1H, d, *J* = 15.9 Hz, ArCH=), 7.19-7.12 (3H, m, ArH), 6.38 (1H, d, *J* = 15.9 Hz, =CH-), 4.27 (2H, t, *J* = 6.7 Hz, OCH₂-), 4.23 (2H, t, *J* = 6.7 Hz, OCH₂-), 3.89 (3H, s, OCH₃), 1.82-1.75 (4H, m, CH₂), 1.01 (6H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.8 (C), 152.9 (C), 151.7 (C), 149.3 (C), 148.1 (CH), 142.6 (C), 132.7 (C), 123.1 (CH), 121.8 (CH), 115.9 (CH), 111.8 (CH), 71.2 (CH₂), 70.8 (CH₂), 56.1 (CH₃), 22.0 (CH₂), 21.8 (CH₂), 10.1 (CH₃). IR (film, ν_{max}): 2972, 1801, 1766, 1633, 1602, 1510, 1466, 1419, 1392, 1244, 1141, 1093, 1061, 1032, 982, 939, 848, 776 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 405.1257, required *m/z* 405.0946.

4.4.5 (E)-4-Ethyloxycarbonyloxy-3-methoxycinnamic monoethyl carbonic anhydride (3e) Obtained 96% yield using ethyl chloroformate, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.78 (1H, d, *J* = 15.9 Hz, ArCH=), 7.19-7.12 (3H, m, ArH), 6.37 (1H, d, *J* = 15.9 Hz, =CH-), 4.37 (2H, q, *J* = 7.2 Hz, OCH₂-), 4.33 (2H, q, *J* = 7.5 Hz, OCH₂-), 3.90 (3H, s, OCH₃), 1.41-1.38 (6H, m, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.8 (C), 152.8 (C), 151.7 (C), 149.2 (C), 148.1 (CH), 142.6 (C), 132.7 (C), 123.1 (CH), 121.8 (CH), 115.9 (CH), 111.8 (CH), 65.7 (CH₂), 65.3 (CH₂), 56.1 (CH₃), 14.2 (CH₃), 14.0 (CH₃). IR (film, ν_{max}): 2985, 1800, 1764, 1633, 1601, 1509, 1467, 1419, 1369, 1251, 1143, 1089, 1053, 981, 850, 776 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found *m/z* 361.0804, required *m/z* 361.0894.

4.4.6 (E)-4-Methyloxycarbonyloxy-3-methoxycinnamic monomethyl carbonic anhydride (3f) Obtained 90% yield using methyl chloroformate, white crystal; mp 113-115 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.79 (1H, d, *J* = 15.9 Hz, ArCH=), 7.19-7.13 (3H, m, ArH), 6.38 (1H, d, *J* = 15.9 Hz, =CH-), 3.95 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 3.90 (3H, s, OCH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.6 (C), 153.4 (C), 151.7 (C), 149.9 (C), 148.3 (CH), 142.5 (C), 132.7 (C), 123.1 (CH), 121.8 (CH), 115.8 (CH), 111.9 (CH), 56.1 (CH₃), 55.9 (CH₃), 55.7 (CH₃). IR (film, ν_{max}): 2961, 1805, 1767, 1735, 1633, 1601, 1510, 1441, 1419, 1262, 1212, 1142, 1093, 1057, 1031, 981, 932, 851, 777 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 349.0056, required *m/z* 349.0320.

4.4.7 (E)-4-Pivaloyloxy-3-methoxycinnamic pivalic anhydride (3g) Obtained 99% yield using pivaloyl chloride, white crystal; mp 75-77 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (1H, d, *J* = 15.9 Hz, ArCH=), 7.16-7.04 (3H, m, ArH), 6.38 (1H, d, *J* = 15.9 Hz, =CH-), 3.86 (3H, s, OCH₃), 1.37 (9H, s, CH₃), 1.33 (9H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 176.4 (C), 174.0 (C), 162.6 (C), 151.8 (C), 147.8 (CH), 142.9 (C), 132.4 (C), 123.4 (CH), 121.9 (CH), 116.9 (CH), 111.6 (CH), 56.1 (CH₃), 40.1 (C), 39.2 (C), 27.2 (CH₃), 26.6 (CH₃). IR (film, ν_{max}): 2976,

2937, 2874, 1797, 1755, 1726, 1631, 1600, 1588, 1509, 1480, 1464, 1419, 1397, 1367, 1326, 1257, 1208, 1159, 1111, 1052, 1017, 942, 890, 840, 804, 748 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 401.1195, required *m/z* 401.1361.

4.4.8 (E)-4-Acetyloxy-3-methoxycinnamic acetylic anhydride (3h) Obtained 20% yield using acetyl chloride, white crystal; mp 92-94 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.75 (1H, d, *J* = 16.0 Hz, ArCH=), 7.17-7.08 (3H, m, ArH), 6.38 (1H, d, *J* = 16.0 Hz, =CH-), 3.88 (3H, s, OCH₃), 2.33 (3H, s, CH₃), 2.32 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 168.7 (C), 166.6 (C), 162.1 (C), 151.6 (C), 148.0 (CH), 142.3 (C), 132.6 (C), 123.5 (CH), 121.9 (CH), 116.7 (CH), 111.6 (CH), 56.0 (CH₃), 22.4 (CH₃), 20.7 (CH₃). IR (film, ν_{max}): 2942, 1804, 1766, 1725, 1631, 1600, 1509, 1467, 1419, 1370, 1333, 1303, 1260, 1199, 1158, 1125, 1084, 1032, 1006, 927, 905, 834 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 317.0281, required *m/z* 317.0422.

4.5. Procedure for *N*-feruloyl piperidine (4) from 3a-3h.

To a solution of each compound **3a-3h** (100 μmol) in DCM (100 μL) was added 10 equiv of piperidine (100 μL, 1.0 mmol) at room temperature. After stirring for 3 h, the reaction mixture was extracted thrice with ethyl acetate (30 mL) and washed with 4% KHSO₄ aq. solution (30 mL), followed by deionized water (30 mL) and then with saturated brine (30 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:1-3:1 v/v)

4.5.1 (E)-*N*-feruloyl piperidine (4) Obtained yield from **3a**-98%, **3b**-97%, **3c**-94%, **3d**-90%, **3e**-73%, **3f**-64%, **3g**-0%, and **3h**-0%, white crystal; mp 138-140 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.56 (1H, d, *J* = 15.2 Hz, ArCH=), 7.06 (1H, dd, *J* = 8.4, 1.6 Hz, ArH), 6.96 (1H, d, *J* = 2.0 Hz, ArH), 6.89 (1H, d, *J* = 8.4 Hz, ArH), 6.72 (1H, d, *J* = 15.2 Hz, =CH-), 3.90 (3H, s, OCH₃), 3.60 (4H, s, NCH₂), 1.66-1.57 (6H, m, CH₂); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 165.6 (C), 147.2 (C), 146.7 (C), 142.5 (CH), 128.0 (C), 121.7 (CH), 115.0 (CH), 114.7 (CH), 109.9 (CH), 55.9 (CH₃), 26.2 (CH₂), 24.6 (CH₂), -0.1 (CH₂). IR (film, ν_{max}): 3165, 2938, 2855, 1708, 1639, 1589, 1515, 1457, 1364, 1269, 1252, 1219, 1162, 1138, 1124, 1021, 979, 817, 728 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 300.0666, required *m/z* 300.0997.

4.6. Typical procedure for *tert*- and *iso*-butyl carbonate mixed anhydrides 5a-11

Compounds with *tert*-butyl groups and *iso*-butyl groups were synthesized following the procedure as **3a** and **3b**, respectively.

4.6.1 (E)-4-*tert*-Butoxycarbonyloxy-3-methoxycinnamic mono-*tert*-butyl carbonic anhydride (5a) Obtained 81% yield using *p*-coumaric acid, white crystal; mp 80-82 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.78 (1H, d, *J* = 16.0 Hz, ArCH=), 7.57-7.55 (2H, m, ArH), 7.24-7.22 (2H, m, ArH), 6.36 (1H, d, *J* = 16.0 Hz, =CH-), 1.58 (9H, s, CH₃), 1.57 (9H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 161.4 (C), 153.1 (C), 151.3 (C), 147.2 (CH), 147.1 (C), 131.2 (C), 129.6 (CH), 121.9 (CH), 115.9 (CH), 85.4 (C), 84.1 (C), 27.6 (CH₃), 27.5 (CH₃). IR (film, ν_{max}): 2982, 2936, 1797, 1759, 1634, 1603, 1508, 1474, 1458, 1417, 1396, 1371, 1275, 1227, 1147, 1120, 1082, 993, 894, 837, 780 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 403.0746, required *m/z* 403.1154.

4.6.2 (E)-4-*iso*-Butoxycarbonyloxy-3-methoxycinnamic mono-*iso*-butyl carbonic anhydride (5b) Obtained 99% yield using *p*-coumaric acid, white crystal; mp 29-31 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.81 (1H, d, *J* = 16.0 Hz, ArCH=), 7.58 (2H, d, *J* = 8.6 Hz, ArH), 7.26 (2H, d, *J* = 8.5 Hz, ArH), 6.39 (1H, d, *J* = 16.0 Hz, =CH-), 4.10 (2H, d, *J* = 6.7 Hz, CH₂), 4.06 (2H, d, *J* = 6.7 Hz,

CH₂), 2.06 (2H, sep, *J* = 6.7 Hz, CH), 1.02-0.99 (12H, m, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.9 (C), 153.2 (C), 149.4 (C), 147.7 (CH), 131.3 (C), 131.1 (C), 129.8 (CH), 122.0 (CH), 115.7 (CH), 75.5 (CH₂), 75.0 (CH₂), 27.8 (CH), 27.5 (CH), 18.9 (CH₃), 18.7 (CH₃). IR (film, ν_{max}): 2965, 2877, 1803, 1764, 1633, 1603, 1585, 1509, 1471, 1418, 1397, 1379, 1344, 1222, 1172, 1141, 1092, 1053, 1015, 961, 864, 838, 777, 749 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 403.1013, required *m/z* 403.1154.

4.6.3 (E)-4-tert-Butoxycarbonyloxy-3,5-dimethoxycinnamic mono-tert-butyl carbonic anhydride (**6a**) Obtained 70% yield using sinapinic acid, white crystal; mp 158-160 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (1H, d, *J* = 15.9 Hz, ArCH=), 6.77 (2H, s, ArH), 6.34 (1H, d, *J* = 15.9 Hz, =CH-), 3.87 (6H, s, OCH₃), 1.58 (9H, s, CH₃), 1.55 (9H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 161.3 (C), 152.7 (C), 150.8 (C), 148.1 (CH), 147.1 (C), 131.9 (C), 131.7 (C), 116.2 (CH), 105.2 (CH), 85.5 (C), 83.8 (C), 56.3 (CH₃), 27.6 (CH₃), 27.5 (CH₃). IR (film, ν_{max}): 2981, 1794, 1759, 1633, 1597, 1508, 1458, 1421, 1371, 1348, 1246, 1133, 1080, 994, 824 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 463.1128, required *m/z* 463.1365.

4.6.4 (E)-4-iso-Butoxycarbonyloxy-3,5-dimethoxycinnamic mono-iso-butyl carbonic anhydride (**6b**) Obtained 99% yield using sinapinic acid, white crystal; mp 71-73 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.76 (1H, d, *J* = 15.9 Hz, ArCH=), 6.79 (2H, s, ArH), 6.38 (1H, d, *J* = 15.9 Hz, =CH-), 4.10 (2H, d, *J* = 6.7 Hz, CH₂), 4.06 (2H, d, *J* = 6.7 Hz, CH₂), 3.88 (6H, s, OCH₃), 2.11-2.03 (2H, m, CH), 1.00 (12H, d, *J* = 6.7 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.8 (C), 152.8 (C), 152.7 (C), 149.4 (C), 148.6 (CH), 132.0 (C), 131.7 (C), 116.0 (CH), 105.3 (CH), 75.6 (CH₂), 75.1 (CH₂), 56.3 (CH₃), 27.9 (CH), 27.7 (CH), 18.8 (CH₃). IR (film, ν_{max}): 2963, 2875, 1766, 1713, 1638, 1599, 1509, 1465, 1420, 1396, 1378, 1346, 1323, 1277, 1247, 1216, 1173, 1155, 1131, 1053, 976, 826, 776 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 463.1049, required *m/z* 463.1365.

4.6.5 (E)-3,4-Di-tert-butoxycarbonyloxy-cinnamic mono-tert-butyl carbonic anhydride (**7a**) Obtained 72% yield using caffeic acid, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.74 (1H, d, *J* = 16.0 Hz, ArCH=), 7.46 (1H, d, *J* = 2.4 Hz, ArH), 7.41 (1H, dd, *J* = 8.4, 2.4 Hz, ArH), 7.32 (1H, d, *J* = 8.4 Hz, ArH), 6.35 (1H, d, *J* = 16.0 Hz, =CH-), 1.57 (9H, s, CH₃), 1.56 (9H, s, CH₃), 1.55 (9H, s, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 161.2 (C), 150.5 (C), 150.3 (C), 147.0 (C), 146.4 (CH), 144.6 (C), 143.0 (C), 132.3 (C), 126.6 (CH), 123.7 (CH), 122.8 (CH), 117.0 (CH), 85.5 (C), 84.3 (2 × C), 27.6 (CH₃), 27.5 (CH₃). IR (film, ν_{max}): 2981, 1769, 1709, 1508, 1370, 1252, 1150, 1116, 772 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 519.1566, required *m/z* 519.1627.

4.6.6 (E)-3,4-Di-iso-butoxycarbonyloxy-cinnamic mono-iso-butyl carbonic anhydride (**7b**) Obtained 96% yield using caffeic acid, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.77 (1H, d, *J* = 16.0 Hz, ArCH=), 7.49 (1H, d, *J* = 2.4 Hz, ArH), 7.45 (1H, dd, *J* = 8.6, 2.0 Hz, ArH), 7.36 (1H, d, *J* = 8.4 Hz, ArH), 6.39 (1H, d, *J* = 16.0 Hz, =CH-), 4.10 (2H, d, *J* = 6.8 Hz, CH₂), 4.06 (2H, d, *J* = 6.8 Hz, CH₂), 4.06 (2H, d, *J* = 6.4 Hz, CH₂), 2.12-2.00 (3H, m, CH), 1.01-0.98 (18H, m, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 160.6 (C), 152.6 (C), 152.4 (C), 149.3 (C), 146.8 (CH), 144.6 (C), 143.0 (C), 132.5 (C), 127.0 (CH), 123.8 (CH), 122.8 (CH), 116.9 (CH), 75.6 (CH₂), 75.4 (CH₂), 27.8 (CH), 27.7 (CH), 18.8 (CH₃). IR (film, ν_{max}): 2964, 1772, 1635, 1508, 1471, 1379, 1245, 1197, 1141, 1092, 960, 772 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 519.1465, required *m/z* 519.1627.

4.6.7 4-iso-Butoxycarbonyloxybenzoic mono-iso-butyl carbonic anhydride (**8**) Obtained 97% yield using *p*-hydroxy benzoic acid, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 8.12 (2H, d, *J*

= 8.7 Hz, ArH), 7.33 (2H, d, *J* = 8.7 Hz, ArH), 4.13 (2H, d, *J* = 6.7 Hz, CH₂), 4.07 (2H, d, *J* = 6.6 Hz, CH₂), 2.11-2.04 (2H, m, CH), 1.01 (12H, d, *J* = 6.7 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.4 (C), 155.9 (C), 152.8 (C), 149.4 (C), 132.3 (CH), 125.4 (C), 121.4 (CH), 75.9 (CH₂), 75.2 (CH₂), 27.8 (CH), 27.7 (CH), 18.9 (CH₃), 18.8 (CH₃). IR (film, ν_{max}): 2965, 1806, 1766, 1605, 1507, 1471, 1379, 1217, 1195, 1159, 1063, 991, 767 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 377.0819, required *m/z* 377.0997.

4.6.8 4-iso-Butoxycarbonyloxy-3-methoxybenzoic mono-iso-butyl carbonic anhydride (**9**) Obtained 97% yield using vanillic acid, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.72 (1H, d, *J* = 10.0 Hz, ArH), 7.66 (1H, s, ArH), 7.25 (1H, d, *J* = 9.9 Hz, ArH), 4.14 (2H, d, *J* = 6.7 Hz, CH₂), 4.06 (2H, d, *J* = 6.6 Hz, CH₂), 3.92 (3H, s, OCH₃), 2.11-2.03 (2H, m, CH), 1.01 (6H, d, *J* = 6.9 Hz, CH₃), 1.00 (6H, d, *J* = 7.1 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.6 (C), 152.6 (C), 151.5 (C), 149.4 (C), 145.2 (C), 126.5 (C), 123.8 (CH), 122.7 (CH), 114.3 (CH), 75.9 (CH₂), 75.3 (CH₂), 56.3 (CH₃), 27.9 (CH), 27.7 (CH), 18.8 (CH₃). IR (film, ν_{max}): 2965, 2877, 1805, 1769, 1606, 1509, 1470, 1416, 1397, 1379, 1328, 1249, 1208, 1191, 1157, 1126, 1074, 1033, 1008, 943, 834, 807, 760, 740 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 407.0797, required *m/z* 407.1103.

4.6.9 4-iso-Butoxycarbonyloxy-3,5-dimethoxybenzoic mono-iso-butyl carbonic anhydride (**10**) Obtained 96% yield using syringic acid, white crystal; mp 40-42 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.34 (2H, s, ArH), 4.15 (2H, d, *J* = 6.7 Hz, CH₂), 4.06 (2H, d, *J* = 6.7 Hz, CH₂), 3.91 (6H, s, OCH₃), 2.08 (2H, sep, *J* = 6.8 Hz, CH), 1.02 (6H, d, *J* = 6.7 Hz, CH₃), 1.00 (6H, d, *J* = 6.8 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 160.8 (C), 152.5 (C), 152.4 (C), 149.4 (C), 134.3 (C), 125.9 (C), 125.7 (C), 107.3 (CH), 76.0 (CH₂), 75.2 (CH₂), 56.5 (CH₃), 27.9 (CH), 27.7 (CH), 18.8 (2 × CH₃). IR (film, ν_{max}): 2965, 2877, 1805, 1770, 1607, 1506, 1466, 1419, 1397, 1372, 1347, 1250, 1215, 1190, 1148, 1086, 1050, 1017, 952, 862, 813, 749 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found *m/z* 421.1012, required *m/z* 421.1469.

4.6.10 3,4,5-Tri-iso-butoxycarbonyloxybenzoic mono-iso-butyl carbonic anhydride (**11**) Obtained 90% yield using gallic acid, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.95 (2H, s, ArH), 4.13 (2H, d, *J* = 6.7 Hz, CH₂), 4.06 (6H, d, *J* = 6.6 Hz, CH₂), 2.09-2.01 (4H, m, CH), 1.01-0.97 (24H, m, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 159.1 (C), 152.1 (C), 150.9 (C), 148.7 (C), 144.2 (C), 140.1 (C), 126.0 (C), 125.9 (C), 122.8 (CH), 76.1 (CH₂), 75.9 (CH₂), 75.8 (CH₂), 75.7 (CH₂), 27.8 (CH), 27.7 (CH), 18.8 (CH₃), 18.7 (CH₃). IR (film, ν_{max}): 2965, 1781, 1506, 1471, 1436, 1397, 1379, 1342, 1230, 1214, 1145, 1080, 986, 948, 770 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 609.1719, required *m/z* 609.1944.

4.7. Typical procedure for phenolic acids amides in one-pot reaction

To a solution of phenolic acid (1.0 mmol), 0.050 equiv of DMAP (6.1 mg, 0.050 mmol), and 1.0 equiv of TEA (0.14 mL, 1.0 mmol) in DCM (2.0 mL) was added 2.2 equiv of *i*BocCl (0.29 mL, 2.2 mmol) at -15 °C. After stirring for 5 min, 10 equiv of amine (10 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. The crude product was purified by preparative TLC (ethyl acetate/hexane, 5:1 v/v).

4.7.1 (E)-N-iso-propylferuloylamide (**12**) Obtained 95% yield using ferulic acid and iso-propyl amine, white crystal; mp 178-180 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.50 (1H, d, *J* = 15.6 Hz, ArCH=), 7.02-6.86 (3H, m, ArH), 6.21 (1H, d, *J* = 15.6 Hz, =CH-), 4.24-4.15 (1H, m, CH), 3.86 (3H, s, OCH₃), 1.19 (6H, d, *J* = 6.4 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 165.4 (C),

147.3 (C), 146.7 (C), 140.7 (CH), 127.4 (C), 121.9 (CH), 118.5 (CH), 114.7 (CH), 109.6 (CH), 55.8 (CH₃), 41.5 (CH), 22.8 (CH₃). IR (film, ν_{max}): 3273, 2973, 1706, 1654, 1590, 1516, 1458, 1428, 1364, 1271, 1211, 1160, 1126, 1033, 980, 848, 817 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 274.0834, required m/z 274.0840.

4.7.2. (E)-N,N-Di-iso-propyl-p-coumaroylamide (**18**) Obtained 89% yield using *p*-coumaric acid and N,N-di-iso-propylamine, white crystal; mp 205-207 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.47 (1H, d, J = 15.6 Hz, ArCH=), 7.29-7.26 (2H, m, ArH), 6.88-6.85 (2H, m, ArH), 6.63 (1H, d, J = 15.6 Hz, =CH-), 4.10 (1H, m, CH), 3.86 (1H, m, CH), 1.38-1.29 (12H, m, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.5 (C), 158.7 (C), 141.9 (CH), 129.3 (CH), 126.9 (C), 116.6 (CH), 116.1 (CH), 116.0 (CH), 48.3 (CH), 46.1 (CH), 21.5 (CH₃), 20.7 (CH₃). IR (film, ν_{max}): 3155, 2971, 2935, 1711, 1638, 1608, 1574, 1514, 1451, 1372, 1345, 1282, 1260, 1208, 1170, 1152, 1045, 981, 905, 828 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 286.1312, required m/z 286.1204.

4.7.3. (E)-N,N-Diethylsinapoylamide (**20**) Obtained 96% yield using sinapic acid and diethyl amine, white crystal; mp 149-151 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.62 (1H, d, J = 15.3 Hz, ArCH=), 6.76 (2H, s, ArH), 6.66 (1H, d, J = 15.3 Hz, =CH-), 3.93 (6H, s, OCH₃), 3.50-3.49 (4H, m, CH₂), 1.27-1.19 (6H, m, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 165.9 (C), 147.2 (C), 142.7 (CH), 136.6 (C), 127.1 (C), 115.7 (CH), 105.0 (CH), 56.5 (CH₃), 56.3 (CH₃), 42.3 (CH₂), 41.0 (CH₂), 15.1 (CH₃), 13.3 (CH₃). IR (film, ν_{max}): 3389, 2974, 2936, 1708, 1644, 1602, 1515, 1461, 1425, 1339, 1282, 1218, 1140, 1116, 980, 913, 829 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 318.1144, required m/z 318.1102.

4.7.4. (E)-N,N-Diethylsyringoylamide (**26**) Obtained 89% yield using syringic acid and diethyl amine, white crystal; mp 116-118 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 6.64 (2H, s, ArH), 3.90 (6H, s, OCH₃), 3.50-3.42 (4H, m, CH₂), 1.22-1.19 (6H, m, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 171.2 (C), 146.9 (C), 135.8 (C), 128.2 (C), 103.8 (CH), 65.9 (CH₂), 56.5 (CH₃), 15.3 (CH₃). IR (film, ν_{max}): 3249, 2971, 1593, 1519, 1461, 1421, 1332, 1280, 1247, 1216, 1166, 1117, 829, 763 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 292.0933, required m/z 292.0946.

4.8. Typical procedure for phenolic acids esters in one-pot reaction

To a solution of phenolic acid (0.19 g, 1.0 mmol), 0.050 equiv of DMAP (6.1 mg, 0.050 mmol), and 1.0 equiv of TEA (0.14 mL, 1.0 mmol) in DCM (2.0 mL) was added 2.2 equiv of *i*BocCl (0.29 mL, 2.2 mmol) at -15 °C. After stirring for 5 min, 3.0 equiv of alcohol (0.12 mL, 3.0 mmol) and 0.1 equiv of DMAP (12 mg, 0.10 mmol) were added, and the reaction mixture was stirred at room temperature. After stirring for 3 h, 10 equiv of piperidine (1.0 mL, 10.0 mmol) was added at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The crude product was purified by preparative TLC (ethyl acetate/hexane, 1:2 v/v).

4.8.1. Methyl (E)-ferulate (**13**) Obtained 90% yield using ferulic acid and methanol, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.60 (1H, d, J = 16.0 Hz, ArCH=), 7.06-6.88 (3H, m, ArH), 6.27 (1H, d, J = 15.6 Hz, =CH-), 3.89 (3H, s, OCH₃), 3.77 (3H, s, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.7 (C), 148.0 (C), 146.7 (C), 145.0 (CH), 126.9 (C), 123.0 (CH), 115.1 (CH), 114.8 (CH), 109.3 (CH), 55.9 (CH₃), 51.6 (CH₃). IR (film, ν_{max}): 3394, 2951, 1699, 1635, 1592, 1515, 1435, 1375, 1324, 1270, 1173, 1123, 1033, 981, 847, 819 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 247.0359, required m/z 247.0367.

4.8.2. Ethyl (E)-ferulate (**14**) Obtained 90% yield using ferulic acid and ethanol, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.59 (1H, d, J = 16.0 Hz, ArCH=), 7.06-6.88 (3H, m, ArH), 6.27 (1H, d, J = 16.0 Hz, =CH-), 4.23 (2H, q, J = 7.2 Hz, CH₂), 3.90 (3H, s, OCH₃), 1.31 (3H, t, J = 7.2 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.3 (C), 147.9 (C), 146.7 (C), 144.7 (CH), 127.0 (C), 123.0 (CH), 115.6 (CH), 114.7 (CH), 109.3 (CH), 60.4 (CH₂), 55.9 (CH₃), 14.4 (CH₃). IR (film, ν_{max}): 3393, 2980, 1698, 1633, 1591, 1514, 1465, 1429, 1369, 1268, 1157, 1122, 1033, 980, 846, 816 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 261.0509, required m/z 261.0524.

4.8.3. tert-Butyl (E)-ferulate (**15**) Obtained 91% yield using ferulic acid and tert-butanol as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.43 (1H, d, J = 16.0 Hz, ArCH=), 7.27 (1H, s, ArH), 7.05 (1H, d, J = 8.0 Hz, ArH), 6.77 (1H, d, J = 8.0 Hz, ArH), 6.34 (1H, d, J = 15.6 Hz, =CH-), 3.80 (3H, s, OCH₃), 1.46 (9H, s, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm: 166.1 (C), 149.3 (C), 148.1 (C), 144.2 (CH), 125.9 (C), 123.0 (CH), 116.5 (CH), 115.6 (CH), 111.2 (CH), 79.5 (C), 55.8 (CH₃), 28.1 (CH₃). IR (film, ν_{max}): 3393, 2961, 1699, 1633, 1591, 1514, 1466, 1429, 1377, 1269, 1157, 1032, 980, 846, 816 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 289.0881, required m/z 289.0837.

4.8.4. Phenyl (E)-ferulate (**16**) Obtained 96% yield using ferulic acid and phenol, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.79 (1H, d, J = 16.0 Hz, ArCH=), 7.41-7.37 (2H, m, ArH), 7.25-7.21 (1H, m, ArH), 7.17-7.11 (3H, m, ArH), 7.08 (1H, d, J = 2.0 Hz, ArH), 6.93 (1H, d, J = 8.0 Hz, ArH), 6.47 (1H, d, J = 16.0 Hz, =CH-), 3.93 (3H, s, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 165.7 (C), 150.9 (C), 148.3 (C), 146.8 (C), 146.6 (CH), 129.4 (CH), 126.8 (C), 125.7 (CH), 123.4 (CH), 121.7 (CH), 114.8 (CH), 114.6 (CH), 109.5 (CH), 55.9 (CH₃). IR (film, ν_{max}): 3420, 1717, 1632, 1591, 1514, 1492, 1456, 1430, 1375, 1269, 1246, 1195, 1163, 1136, 1030, 980, 846, 815, 748, 707, 688 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found m/z 293.0983, required m/z 293.0784.

4.8.5. β -Naphthyl (E)-ferulate (**17**) Obtained 89% yield using ferulic acid and β -naphthol, white crystal; mp 132-134 °C. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.88-7.80 (4H, m, ArCH=, ArH), 7.63 (1H, d, J = 2.0 Hz, ArH), 7.51-7.43 (2H, m, ArH), 7.30 (1H, dd, J = 8.8, 2.4 Hz, ArH), 7.16-7.13 (1H, m, ArH), 7.09 (1H, d, J = 2.0 Hz, ArH), 6.95 (1H, d, J = 8.0 Hz, ArH), 6.53 (1H, d, J = 16.0 Hz, =CH-), 3.92 (3H, s, OCH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 165.9 (C), 148.5 (C), 148.4 (C), 146.8 (CH), 133.8 (C), 131.4 (C), 129.4 (CH), 127.7 (CH), 127.6 (CH), 126.7 (C), 126.5 (CH), 125.6 (CH), 123.5 (CH), 121.3 (CH), 118.6 (CH), 114.9 (C), 114.8 (CH), 114.5 (CH), 109.5 (CH), 56.0 (CH₃). IR (film, ν_{max}): 3420, 3059, 1716, 1628, 1600, 1513, 1465, 1430, 1363, 1270, 1237, 1209, 1186, 1157, 1136, 1032, 981, 897, 846, 817, 789, 755 cm⁻¹. MALDI-TOF-MS: [M+H]⁺ found m/z 321.1183, required m/z 321.1121.

4.8.6. iso-Propyl (E)-p-coumarate (**19**) Obtained 82% yield using *p*-coumaric acid and isopropanol, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.60 (1H, d, J = 15.6 Hz, ArCH=), 7.39-7.37 (2H, m, ArH), 6.86-6.84 (2H, m, ArH), 6.25 (1H, d, J = 16.0 Hz, =CH-), 5.12 (1H, sep, J = 6.3 Hz, CH), 1.29 (6H, d, J = 6.4 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 167.7 (C), 158.2 (C), 144.6 (CH), 130.0 (CH), 126.8 (C), 116.0 (CH), 115.9 (CH), 115.7 (CH), 115.6 (CH), 68.1 (CH), 22.0 (CH₃), 21.9 (CH₃). IR (film, ν_{max}): 3343, 2981, 1681, 1633, 1605, 1586, 1515, 1443, 1360, 1309, 1278, 1204, 1170, 1105, 983, 914, 865, 832 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found m/z 245.0566, required m/z 245.0575.

4.8.7. *Phenethyl (E)-caffeate (21, CAPE)* Obtained 95% yield using caffeic acid and phenethyl alcohol, white crystal; mp 124–126 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.57 (1H, d, *J* = 16.0 Hz, ArCH=), 7.34–7.23 (5H, m, ArH), 7.10 (1H, d, *J* = 2.0 Hz, ArH), 7.00 (1H, dd, *J* = 8.3, 2.0 Hz, ArH), 6.88 (1H, d, *J* = 8.0 Hz, ArH), 6.25 (1H, d, *J* = 16.0 Hz, =CH-), 4.42 (2H, t, *J* = 7.0 Hz, CH₂), 3.02 (2H, t, *J* = 7.0 Hz, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 167.7 (C), 146.3 (C), 145.1 (CH), 143.7 (C), 137.8 (C), 128.9 (CH), 128.5 (CH), 127.5 (C), 126.6 (CH), 122.5 (CH), 115.5 (2 × CH), 114.4 (CH), 65.2 (CH₂), 35.2 (CH₂). IR (film, ν_{\max}): 3310, 1683, 1600, 1508, 1456, 1387, 1272, 1179, 1112, 978, 853, 813, 698 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 323.0658, required *m/z* 323.0680.

4.8.8. *tert-Butyl p-hydroxybenzoate (22)* Obtained 100% yield using *p*-hydroxy benzoic acid and *tert*-butanol, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.89 (2H, d, *J* = 8.5 Hz, ArH), 6.87 (2H, d, *J* = 9.0 Hz, ArH), 1.59 (9H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 166.6 (C), 160.2 (C), 131.8 (CH), 123.9 (C), 115.2 (CH), 81.2 (C), 28.3 (CH₃). IR (film, ν_{\max}): 3336, 2963, 1683, 1608, 1514, 1444, 1376, 1312, 1278, 1164, 1100, 980, 851, 771, 698, 618 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 233.0513, required *m/z* 233.0575.

4.8.9. *Methyl vanillate (23)* Obtained 93% yield using vanillic acid and methanol, white crystal; mp 63–65 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.64 (1H, dd, *J* = 8.0, 2.0 Hz, ArH), 7.55 (1H, d, *J* = 2.0 Hz, ArH), 6.94 (1H, d, *J* = 8.5 Hz, ArH), 3.94 (3H, s, OCH₃), 3.89 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 167.0 (C), 150.0 (C), 146.2 (C), 124.2 (CH), 122.2 (C), 114.1 (CH), 111.7 (CH), 56.1 (CH₃), 52.0 (CH₃). IR (film, ν_{\max}): 3393, 2953, 1713, 1596, 1515, 1456, 1436, 1377, 1289, 1224, 1104, 1032, 986, 878, 765, 726 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 220.9892, required *m/z* 221.0211.

4.8.10. *iso-Propyl vanillate (24)* Obtained 83% yield using vanillic acid and isopropanol, white crystal; mp 109–111 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.64 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.55 (1H, d, *J* = 2.0 Hz, ArH), 6.93 (1H, d, *J* = 8.5 Hz, ArH), 5.23 (1H, sep, *J* = 6.3 Hz, CH), 3.94 (3H, s, OCH₃), 1.36 (6H, d, *J* = 6.0 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 166.0 (C), 149.8 (C), 146.1 (C), 124.0 (CH), 123.0 (C), 114.0 (CH), 111.7 (CH), 68.2 (CH), 56.1 (CH₃), 22.0 (CH₃). IR (film, ν_{\max}): 3394, 2980, 2939, 1705, 1597, 1515, 1465, 1429, 1374, 1352, 1285, 1224, 1146, 1103, 1032, 942, 879, 836, 813, 767, 726 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 249.0523, required *m/z* 249.0524.

4.8.11. *Phenyl vanillate (25)* Obtained 85% yield using vanillic acid and phenol, white crystal; mp 93–95 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.82 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.67 (1H, d, *J* = 2.0 Hz, ArH), 7.44–7.40 (2H, m, ArH), 7.28–7.25 (1H, m, ArH), 7.21–7.19 (2H, m, ArH), 7.00 (1H, d, *J* = 8.5 Hz, ArH), 3.96 (3H, s, OCH₃); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 165.0 (C), 151.1 (C), 150.7 (C), 146.3 (C), 129.5 (CH), 125.8 (CH), 125.0 (CH), 122.0 (CH), 121.5 (C), 114.3 (CH), 112.2 (CH), 56.2 (CH₃). IR (film, ν_{\max}): 3406, 1729, 1595, 1514, 1494, 1457, 1429, 1380, 1284, 1191, 1121, 1076, 1028, 926, 904, 877, 812, 774, 757, 742, 689 cm⁻¹. MALDI-TOF-MS: [M+K]⁺ found *m/z* 283.0388, required *m/z* 283.0367.

4.8.12. *Phenethyl protocatechuate (27)* Obtained 92% yield using protocatechuic acid and phenethyl alcohol, white crystal; mp 128–130 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.66 (1H, d, *J* = 2.0 Hz, ArH), 7.54 (1H, dd, *J* = 8.5, 2.0 Hz, ArH), 7.33–7.23 (5H, m, ArH), 6.90 (1H, d, *J* = 8.5 Hz, ArH), 4.50 (2H, t, *J* = 7.0 Hz, CH₂), 3.06 (2H, t, *J* = 7.0 Hz, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 167.3 (C), 149.2 (C), 143.3 (C), 138.0 (C), 129.2

(CH), 128.8 (CH), 126.9 (CH), 124.1 (CH), 122.6 (C), 116.9 (CH), 115.1 (CH), 65.9 (CH₂), 35.4 (CH₂). IR (film, ν_{\max}): 3337, 2961, 1684, 1604, 1523, 1498, 1445, 1386, 1296, 1232, 1117, 986, 889, 828, 765, 699 cm⁻¹. MALDI-TOF-MS: [M+Na]⁺ found *m/z* 281.0743, required *m/z* 281.0784.

4.9. Synthesis of isotopomers of caffeic acid and CAPE

4.9.1. *[1-¹³C]3,4-Methylenedioxy benzoic acid (31)* To a solution of 1-bromo-3,4-(methylenedioxy)benzene (**30**, 0.72 mL, 6.0 mmol) in THF (10 mL) was added 1.0 equiv of 1.6 M butyllithium in hexane solution (3.8 mL, 6 mmol) at –78 °C in an acetone/dry ice bath under N₂ atmosphere. After stirring for 15 min, ¹³CO₂ gas was injected to the mixture by syringe, and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched by adding water (30 mL). After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to afford compound **31** in 98% yield (0.99 g, 5.9 mmol, white powder; mp 213–215 °C). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm: 12.82 (1H, s, ¹³COOH), 7.55 (1H, ddd, *J*_{HH} = 8.0, 1.5 Hz, *J*_{CH} = 4.0 Hz, ArH), 7.36 (1H, dd, *J*_{CH} = 3.8 Hz, *J*_{HH} = 1.5 Hz, ArH), 7.01 (1H, d, *J*_{HH} = 8.0 Hz, ArH), 6.13 (2H, s, CH₂); ¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm: 167.1 (¹³C), 151.6 (C), 147.9 (C), 125.5 (CH), 125.1 (C, d, *J*_{CC} = 74.3 Hz), 109.3 (CH), 108.6 (CH), 102.4 (CH₂). IR (film, ν_{\max}): 3349, 2895, 1502, 1490, 1443, 1249, 1094, 1039, 988, 934, 863, 809, 764 cm⁻¹.

4.9.2. *[1-¹³C]3,4-Methylenedioxy benzyl alcohol (32)* To a solution of compound **31** (0.99 g, 5.9 mmol) in THF (10 mL) was added dropwise 1.5 equiv of LAH (0.34 g) in THF (10 mL) with constant stirring for 2 h at room temperature under N₂ atmosphere. The reaction was quenched by adding water (30 mL). After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 3:1 v/v) to afford **32** (0.85 g, 5.5 mmol, 65%) as a white crystal; mp 40–42 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 6.80–6.73 (3H, m, ArH), 5.91 (2H, s, CH₂), 4.48 (2H, d, *J*_{CH} = 142.5 Hz, ¹³CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 147.8 (C), 147.0 (C), 134.9 (C, d, *J*_{CC} = 47.9 Hz), 120.5 (CH), 108.2 (CH), 107.9 (CH), 101.0 (CH₂), 65.0 (¹³CH₂). IR (film, ν_{\max}): 3336, 2894, 1502, 1490, 1443, 1249, 1094, 1039, 934, 864, 809, 764, 648 cm⁻¹.

4.9.3. *[1-¹³C]3,4-Methylenedioxy benzaldehyde (33)* To a solution of compound **32** (0.85 g, 5.5 mmol) and 0.1 equiv of TEMPO (85 mg, 0.56 mmol) in ethyl acetate (10 mL) was added dropwise 1.0 equiv of NaClO solution (8.2 g, 5.5 mmol) with constant stirring for 30 min at room temperature under N₂ atmosphere. The reaction was quenched by adding water (30 mL). After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 5:1 v/v) to afford **33** (0.53 g, 3.5 mmol, 58% yield) as a white crystal; mp 52–54 °C. ¹H NMR (500 MHz, CDCl₃) δ ppm: 9.80 (1H, d, *J*_{CH} = 174.0 Hz, ¹³COH), 7.41 (1H, ddd, *J*_{HH} = 8.0, 1.5 Hz, *J*_{CH} = 6.0 Hz, ArH), 7.33 (1H, dd, *J*_{CH} = 4.0 Hz, *J*_{HH} = 1.5 Hz, ArH), 6.93 (1H, d, *J*_{HH} = 8.0 Hz, ArH), 6.08 (2H, s, CH₂); ¹³C NMR (126 MHz, CDCl₃) δ ppm: 190.3 (¹³CH), 153.1 (C), 148.7 (C), 131.8 (C, d, *J*_{CC} = 55.4 Hz), 128.7 (CH), 108.4 (CH), 106.8 (CH), 102.2 (CH₂). IR

(film, ν_{\max}): 3336, 2885, 1503, 1490, 1444, 1250, 1095, 1039, 927, 864, 809, 769 cm^{-1} .

4.9.4. *[3- ^{13}C]3-(3',4'-Methylenedioxyphenyl)-3-hydroxypropionic acid ethyl ester (34)* To a solution of 3.0 equiv of 2 M LDA in THF/heptane/ethylbenzene (4.5 mL, 9.0 mmol) was added THF (8.0 mL) under N_2 atmosphere, and the solution was cooled to -78°C in an acetone/dry ice bath. The mixture was added to 3.0 equiv of ethyl acetate (0.88 mL, 9.0 mmol) and stirred for 30 min. To the reaction mixture was added dropwise compound **33** (0.45 g, 3.0 mmol) in THF (5.0 mL) with constant stirring for 2 h. The reaction was quenched by adding water (30 mL) at room temperature. After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 9:1 v/v) to afford **34** (2.4 mmol, 0.57 g, 80% yield) as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ ppm: 6.88 (1H, dd, $J_{\text{CH}} = 4.0$ Hz, $J_{\text{HH}} = 1.5$ Hz, ArH), 6.81 (1H, ddd, $J_{\text{HH}} = 8.0$, 1.5 Hz, $J_{\text{CH}} = 4.5$ Hz, ArH), 6.76 (1H, d, $J_{\text{HH}} = 8.0$ Hz, ArH), 5.94 (2H, s, CH_2), 5.03 (1H, ddt, $J_{\text{CH}} = 147.5$ Hz, $J_{\text{HH}} = 9.5$, 3.8 Hz, ^{13}CH), 4.17 (2H, q, $J_{\text{HH}} = 7.2$ Hz, CH_2), 2.74-2.61 (2H, m, CH_2), 1.26 (3H, t, $J_{\text{HH}} = 7.3$ Hz, CH_3); ^{13}C NMR (126 MHz, CDCl_3) δ ppm: 172.4 (C), 147.8 (C), 147.1 (C), 136.7 (C, d, $J_{\text{CC}} = 50.4$ Hz), 119.1 (CH), 108.2 (CH), 106.3 (CH), 101.1 (CH_2), 70.2 (^{13}CH), 60.9 (CH_2), 43.4 (CH_2 , d, $J_{\text{CC}} = 37.8$ Hz), 14.2 (CH_3). IR (film, ν_{\max}): 2915, 1677, 1622, 1601, 1498, 1489, 1449, 1417, 1357, 1265, 1116, 1096, 1036, 929, 864, 813, 785 cm^{-1} .

4.9.5. *(E)-[3- ^{13}C]3,4-Methylenedioxy cinnamic acid ethyl ester (35)* To a solution of compound **34** (2.4 mmol, 0.57 g) in 1.1 equiv of EDC·HCl (0.51 mg, 2.6 mmol) and 0.3 equiv of CuCl (I) (71 mg, 0.72 mmol) was added DCM (15 mL) under N_2 atmosphere, and the solution was stirred for 12 h. The reaction was quenched by adding water (20 mL). After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 5:1 v/v) to afford **35** (0.45 g, 2.0 mmol, 97%) as a light yellow oil. ^1H NMR (500 MHz, CDCl_3) δ ppm: 7.59 (1H, dd, $J_{\text{CH}} = 156.0$ Hz, $J_{\text{HH}} = 16.0$ Hz, $\text{Ar}^{13}\text{CH}=\text{}$), 7.03 (1H, dd, $J_{\text{CH}} = 4.0$ Hz, $J_{\text{HH}} = 2.0$ Hz, ArH), 7.00 (1H, ddd, $J_{\text{HH}} = 8.0$, 2.0 Hz, $J_{\text{CH}} = 5.8$ Hz, ArH), 6.81 (1H, d, $J_{\text{HH}} = 8.0$ Hz, ArH), 6.26 (1H, d, $J_{\text{HH}} = 16.0$ Hz, $=\text{CH}-$), 6.01 (2H, s, CH_2), 4.25 (2H, q, $J_{\text{HH}} = 7.0$ Hz, CH_2), 1.33 (3H, t, $J_{\text{HH}} = 7.3$ Hz, CH_3); ^{13}C NMR (126 MHz, CDCl_3) δ ppm: 167.2 (C), 149.6 (C), 148.3 (C), 144.3 (^{13}CH), 128.9 (C, d, $J_{\text{CC}} = 56.7$ Hz), 124.4 (CH), 116.2 (CH, d, $J_{\text{CC}} = 71.8$ Hz), 108.6 (CH), 106.5 (CH), 101.6 (CH_2), 60.4 (CH_2), 14.4 (CH_3). IR (film, ν_{\max}): 2981, 2902, 1705, 1598, 1503, 1491, 1446, 1370, 1301, 1250, 1174, 1098, 1038, 976, 930, 851, 810 cm^{-1} .

4.9.6. *(E)-[3- ^{13}C]Caffeic acid (36)* To a solution of compound **35** (0.51 g, 2.3 mmol) in DCM (5.0 mL) was added 10 equiv of 6.0 M LiOH (27 mL) and methanol (40 mL), and the solution was stirred for 4 h at room temperature. After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 3:1 v/v) to afford *(E)*-[3- ^{13}C]3,4-methylenedioxy cinnamic acid (0.42 g, 2.2 mmol) as a white powder. To a solution of the compound (0.20 mg, 1.0 mmol) in DCM (10 mL)

cooled to -90°C in a liquid nitrogen/methanol bath was added dropwise 5.0 equiv of 1.0 M BBr_3 -DCM solution (5.2 mL) with constant stirring for 2 min under N_2 atmosphere. The reaction was quenched by adding a sodium dihydrogen phosphate solution. After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (DCM/methanol, 9:1 v/v) to afford **36** (0.14 g, 0.78 mmol, 83% yield) as a brown powder; mp 228-230 $^\circ\text{C}$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm: 7.27 (1H, dd, $J_{\text{CH}} = 153.5$ Hz, $J_{\text{HH}} = 16.0$ Hz, $\text{Ar}^{13}\text{CH}=\text{}$), 7.00 (1H, dd, $J_{\text{CH}} = 4.0$ Hz, $J_{\text{HH}} = 1.5$ Hz, ArH), 6.87 (1H, ddd, $J_{\text{HH}} = 7.8$, 2.0 Hz, $J_{\text{CH}} = 5.0$ Hz, ArH), 6.75 (1H, d, $J_{\text{HH}} = 8.0$ Hz, ArH), 6.16 (1H, d, $J_{\text{HH}} = 16.0$ Hz, $=\text{CH}-$); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ ppm: 168.3 (C), 149.6 (C), 148.5 (C), 144.3 (^{13}CH), 129.1 (C, d, $J_{\text{CC}} = 56.7$ Hz), 125.1 (CH), 117.5 (CH, d, $J_{\text{CC}} = 70.6$ Hz), 108.9 (CH), 107.1 (CH). IR (film, ν_{\max}): 3412, 1655, 1598, 1294, 809 cm^{-1} . MALDI-TOF-MS: $[\text{M}+\text{K}]^+$ found m/z 220.0083, required m/z 220.0088.

4.9.7. *2-[1- ^{13}C]Phenethyl alcohol (37)* To a solution of 2.0 M benzyl magnesium chloride in THF (3.0 mL, 6.0 mmol) cooled to -10°C was injected $^{13}\text{CO}_2$ gas by syringe, and the solution was stirred for 30 min. To the mixture was added dropwise 1.0 equiv of LAH (0.23 g, 6.0 mmol) in THF (5.0 mL) with constant stirring for 2 h at room temperature. The reaction was quenched by adding water (30 mL). After adjusting the pH to 2.0 with 1.0 M HCl, the product was extracted thrice with ethyl acetate (20 mL) and washed with saturated brine (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 5:1 v/v) to afford **37** (0.72 g, 5.8 mmol, 97% yield) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ ppm: 7.33-7.22 (5H, m, ArH), 3.86 (2H, dt, $J_{\text{CH}} = 143.5$, $J_{\text{HH}} = 6.5$ Hz, $^{13}\text{CH}_2$), 2.87 (2H, q, $J_{\text{HH}} = 6.0$ Hz, CH_2); ^{13}C NMR (126 MHz, CDCl_3) δ ppm: 138.4 (C), 129.0 (CH), 128.6 (CH), 126.5 (CH), 63.7 ($^{13}\text{CH}_2$), 39.2 (CH_2 , d, $J_{\text{CC}} = 35.3$ Hz). IR (film, ν_{\max}): 3383, 2933, 1635, 1496, 1454, 1027, 744, 698 cm^{-1} . MALDI-TOF-MS: $[\text{M}+\text{Na}]^+$ found m/z 146.0796, required m/z 146.0657.

4.9.8. *[3,10- $^{13}\text{C}_2$]CAPE (28)* To a solution of *(E)*-[3- ^{13}C]caffeic acid (0.18 g, 1.0 mmol) in DCM (1.6 mL) and DMF (0.4 mL) was added 3.6 equiv of TEA (0.5 mL, 3.6 mmol) and 3.6 equiv of *i*BocCl (0.47 mL, 3.6 mmol) at -15°C . After stirring for 5 min, 2.0 equiv of phenethyl alcohol (0.24 mL, 2.0 mmol) and 0.1 equiv of DMAP (12 mg, 0.1 mmol) were added, and the mixture was stirred at room temperature. After stirring for 3 h, 10.0 equiv of piperidine (1.0 mL, 10.0 mmol) was added, and the reaction mixture was stirred at 0°C for 1 h. The product was extracted thrice with ethyl acetate and washed with 1.0 M HCl, followed by saturated NaCl aq. for twice and then with saturated brine. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:3-1:1 v/v) to afford compound **28** (263 mg, 0.92 mmol, 91% yield, white powder; mp 123-125 $^\circ\text{C}$). ^1H NMR (500 MHz, CD_3OD) δ ppm: 7.50 (1H, dd, $J_{\text{CH}} = 154.3$ Hz, $J_{\text{HH}} = 16.0$ Hz, $\text{Ar}^{13}\text{CH}=\text{}$), 7.31-7.19 (5H, m, ArH), 7.02 (1H, dd, $J_{\text{CH}} = 4.5$ Hz, $J_{\text{HH}} = 2.0$ Hz, ArH), 6.92 (1H, ddd, $J_{\text{HH}} = 8.3$, 2.0 Hz, $J_{\text{CH}} = 5.5$ Hz, ArH), 6.77 (1H, d, $J_{\text{HH}} = 8.0$ Hz, ArH), 6.22 (1H, d, $J_{\text{HH}} = 16.5$ Hz, $=\text{CH}-$), 4.36 (2H, dt, $J_{\text{CH}} = 148.5$ Hz, $J_{\text{HH}} = 7.0$ Hz, $^{13}\text{CH}_2$), 2.99 (2H, q, $J_{\text{HH}} = 6.5$ Hz, CH_2); ^{13}C NMR (126 MHz, CD_3OD) δ ppm: 169.2 (C), 149.6 (C), 147.0 (^{13}CH), 146.7 (C), 139.4 (C), 130.0 (CH), 129.5 (CH), 127.7 (C, d, $J_{\text{CC}} = 56.7$ Hz), 127.5 (CH), 123.0 (CH), 116.5 (CH), 115.1 (CH), 114.9 (CH, d,

$J_{CC} = 50.4$ Hz), 66.1 ($^{13}\text{C}_2$), 36.2 (CH_2 , d, $J_{CC} = 37.8$ Hz). IR (film, ν_{max}): 3334, 1683, 1594, 1516, 1445, 1376, 1274, 1178, 1113, 975, 852, 814, 699 cm^{-1} . MALDI-TOF-MS: $[\text{M}+\text{Na}]^+$ found m/z 309.1009, required m/z 309.1008, $[\text{M}+\text{K}]^+$ found m/z 325.0673, required m/z 325.0747.

4.9.9. $[10-^{13}\text{C}]\text{CAPE}$ (**29**) Following a similar procedure as **28**, compound **29** (252 mg, 0.88 mmol, 88% yield, white powder; mp 125–127 °C) was synthesized using non labeled caffeic acid and compound **37**. ^1H NMR (500 MHz, CD_3OD) δ ppm: 7.51 (1H, d, $J_{\text{HH}} = 16.0$ Hz, ArCH=), 7.31–7.19 (5H, m, ArH), 7.02 (1H, d, $J_{\text{HH}} = 1.5$ Hz, ArH), 6.93 (1H, dd, $J_{\text{HH}} = 8.5, 1.5$ Hz, ArH), 6.77 (1H, d, $J_{\text{HH}} = 8.5$ Hz, ArH), 6.22 (1H, d, $J_{\text{HH}} = 15.5$ Hz, =CH-), 4.36 (2H, dt, $J_{\text{CH}} = 148.5$ Hz, $J_{\text{HH}} = 7.0$ Hz, $^{13}\text{C}_2$), 2.99 (2H, q, $J_{\text{HH}} = 6.5$ Hz, CH_2); ^{13}C NMR (126 MHz CD_3OD) δ ppm: 169.2 (C), 149.7 (C), 147.0 (CH), 146.9 (C), 139.5 (C), 130.0 (CH), 129.6 (CH), 127.7 (C), 127.6 (CH), 123.0 (CH), 116.5 (CH), 115.1 (CH), 115.0 (CH), 66.2 ($^{13}\text{C}_2$), 36.2 (CH_2 , d, $J_{CC} = 37.8$ Hz). IR (film, ν_{max}): 3335, 1683, 1602, 1517, 1455, 1376, 1275, 1180, 1113, 979, 854, 814, 699 cm^{-1} . MALDI-TOF-MS: $[\text{M}+\text{Na}]^+$ found m/z 308.0973, required m/z 308.0974, $[\text{M}+\text{K}]^+$ found m/z 324.0680, required m/z 324.0714.

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Supplementary data

The data include ^1H and ^{13}C NMR and FT-IR spectra of all the products and MALDI-TOF MS spectra of all compounds except for compounds **31–35** are found in Supplementary data. Supplementary data associated with this article can be found in the online version, at <http>

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