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Efficient lipase-catalyzed synthesis of new lipid antioxidants based on a catechol structure

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Abstract—Lipid antioxidants phenolic saturated fatty acid esters were synthesized in high yields and short reaction times using the corresponding ethyl fatty acid esters, lipase from Candida Antarctica, vacuum and no solvent. Phenolic esters with mono- and polyunsaturated fatty acids (EPA and DHA) were also prepared.

1. Introduction

Oxygen is necessary for life of most biological systems. Paradoxically, the exposition to oxygen leads to oxidative stress by the formation of free radicals that react easily with other molecules in the cell, and may alter cellular mechanisms, being a possible cause of some inflammatory or cardiovascular diseases or even cancer and aging.[1–3] Similarly, oxidation affects deterioration of food, specially items with a high lipid fraction in their composition. Antioxidants are used by nature to counteract the effect of oxidation,[4] and new synthetic antioxidants are also been developed against the effects of oxidative stress.

Phenols are a large family of natural compounds that are able to donate the hydrogen atom of the phenolic OH to the free radicals, thus stopping the propagation chain during the oxidation process. Phenolic antioxidants have been studied due to their biological relevance. Hydroxytyrosol, a component of olive oil phenols, has been shown to inhibit human low-density lipoprotein (LDL) oxidation (a critical step in atherosclerosis),[5,6] to inhibit platelet aggregation[7] and to possess anti-inflammatory,[8] anticancer[9] and cell protection properties.[10] Lipid antioxidants have been prepared from natural antioxidants, since they would be able to prevent lipid peroxidation of cell membranes[11,12] and may also prevent oxidation of biologically important polyunsaturated fatty acids. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were covalently attached to ascorbic acid to protect them from oxidation.[13] Moreover, most of the phenolic derivatives posses high solubility in aqueous solutions and it is very desirable for the food industry to be able to make them soluble in fats and oils.[14]

The use of lipases in non-aqueous solvents has been previously described for the preparation of phenolic acid esters. Guyot et al.[15] and Stamatis et al.[16] reported enzymatic esterification of phenolic acids and fatty alcohols with lipase CAL-B from Candida Antarctica, but in both cases very long reaction times were needed to obtain reasonable yields. Twu et al.[17] partially solved this problem for the esterification of hydroxyphenylpropionic acid and octanol, where high yields were obtained after 58 h. Buisman et al.[18] first investigated the esterification of phenols with carboxylic fatty acids and reported the synthesis of hydroxytyrosol with octanoic acid in hexane. They obtained acylation at the primary hydroxyl group of hydroxytyrosol with moderate yield after long reaction time. González-Alcudia et al.[19] reported the synthesis of hydroxytyrosol acetate in presence of pancreatic lipase in ethyl acetate after 48 h of reaction with 86% yield.

We present the enzymatic esterification of a series of di-*ortho*-phenolic compounds, including hydroxytyrosol, with several fatty acids using Novozym 435® (Fig. 1). High yields were obtained in short reaction times for all the phenolic esters prepared with saturated fatty acids by using no solvent and applying vacuum during the reaction (Fig. 2). Moderate to good yields were obtained for esters containing

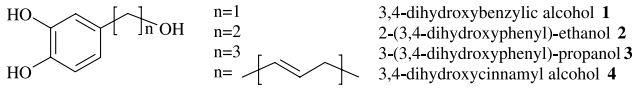

Figure 1. Structures of phenol antioxidants under study.

Keywords: Lipid antioxidants; Phenols; Fatty acid ester; Hydroxytyrosol.
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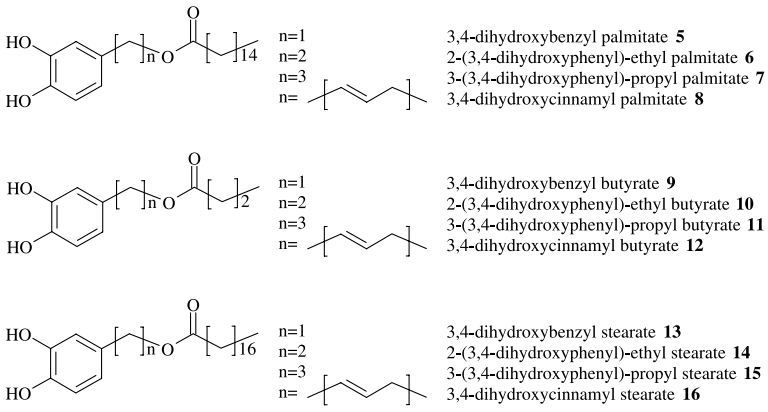

Figure 2. Structures of phenolic saturated fatty acid esters synthesized.

monounsaturated and polyunsaturated fatty acids under the same reaction conditions (Fig. 3).

2. Results and discussion

We prepared the phenolic alcohols (**1**–**4**) by reduction from their corresponding carboxylic acids as reported by Capasso et al.[20] Acylation of these phenols was carried out with palmitic acid and lipase Novozym 435® following conditions reported by Buisman et al.[18] except that acetonitrile was used as solvent instead of hexane, due to solubility problems. We obtained the corresponding esters (**5**–**8**) in moderate yields (Table 1).

In order to improve the yields of the acylations obtained in acetonitrile, we tried ethyl esters as the acylating agents and also as the solvent. When 3,4-dihydroxybenzylic alcohol **1** was reacted with ethyl palmitate as the solvent using Novozym 435® at 37 °C, the reaction went almost to completion after 14 h and the corresponding ester was obtained with 98% yield after column purification. Work-up of the reaction was quite simple. The reaction mixture was dissolved in acetonitrile, the lipase filtered, and the acetonitrile phase washed with hexane to eliminate excess of ethyl palmitate. Finally, it was concentrated and purified on a short silica column. When these new reaction conditions were extended to the other phenols in the series, high yields were obtained except for compound **8**, similarly to what happened under the previous reaction conditions (see Table 1).

Next, we extended the study to other saturated fatty acids to probe the influence of the length of the fatty acid in the esterification reaction using the conditions with ethyl fatty ester, no solvent and vacuum. We observed lower yields of ester formation for a short chain fatty acid, such as butyrate, than for palmitate, except for phenols **3** and **4**, where similar or better yields were obtained. High yields were obtained when ethyl stearate was used as the acylating agent in the reaction, similar to those for ethyl palmitate, except for compound **1**, possibly due to its low solubility in the reaction media. The effect of the length of the saturated carboxylic acid is not very clear. Actually, contradictory

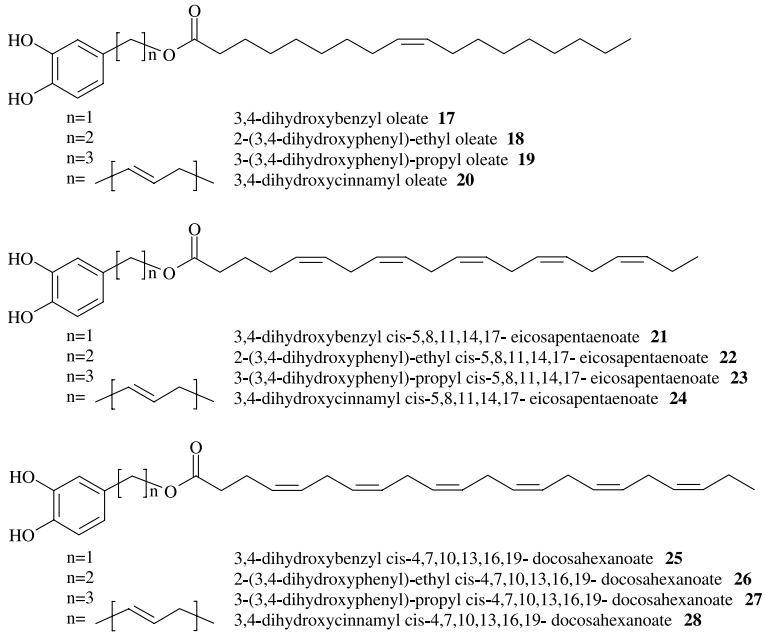

Figure 3. Structures of phenolic unsaturated and polyunsaturated fatty acid esters synthesized.

Table 1. Reaction yields for phenolic saturated fatty acid esters

Phenol	Acylating agent	Product	Yield (%)
3,4-Dihydrobenzylic alcohol **1**	Palmitic acid[a]	**5**	75
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Palmitic acid[a]	**6**	81
3-(3,4-Dihydroxyphenyl)-propanol **3**	Palmitic acid[a]	**7**	85
3,4-Dihydroxycinnamylic alcohol **4**	Palmitic acid[a]	**8**	69
3,4-Dihydrobenzylic alcohol **1**	Ethyl palmitate[b]	**5**	98
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl palmitate[b]	**6**	98
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl palmitate[b]	**7**	97
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl palmitate[b]	**8**	71
3,4-Dihydrobenzylic alcohol **1**	Ethyl butyrate[b]	**9**	75
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl butyrate[b]	**10**	59
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl butyrate[b]	**11**	97
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl butyrate[b]	**12**	96
3,4-Dihydrobenzylic alcohol **1**	Ethyl stearate[b]	**13**	74
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl stearate[b]	**14**	94
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl stearate[b]	**15**	97
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl stearate[b]	**16**	72

[a] Reaction conditions: phenol-fatty acid ratio, 1:2, Novozym 435®, acetonitrile, 37 °C, 16 h.
[b] Reaction conditions: phenol/ethyl fatty acid ester ratio, 1:30, Novozym 435®, no solvent, 37 °C, 6–16 h.

results are also found in the literature when Candida Antarctica lipase is used to esterify ascorbic acid with saturated fatty acids. Stamatis et al.[16] found a decrease in yields for ester formation with increasing chain length, whereas Yan et al.[21] found just the opposite effect. It is important to note that, in both cases, acetone or *tert*-butanol were used as the solvent and that long reaction times were needed to obtain reasonable yields.

Finally, we studied the phenolic ester formation with the ethyl esters of the biologically relevant oleic, eicosapentaenoic (EPA), and docosahexaenoic (DHA) acids. Lower yields were obtained for oleic than for stearic ethyl ester for all four phenolic compounds in the series, except for compound **4** that maintained the same yields for both (see Table 2). A more dramatic decrease in yields (29–51%) was obtained for EPA and DHA ethyl esters when reacted with phenols **1**, **2**, and **4**. Actually, the side reaction of hydrolysis of the corresponding fatty acid ethyl esters to the carboxylic acid was quite fast in these cases as observed by TLC. Surprinsingly, reaction with compound **3** resulted in 67 and 97% of the ester formation with DHA and EPA, respectively. Probably, the fact that the primary alcohol is at three-carbon distance from the phenolic structure in compound **3** helps the ester reaction to compete with the hydrolysis reaction of the polyunsaturated ethyl esters.

3. Experimental

Chemicals were purchased from Sigma-Aldrich and used without further purification. The immobilized lipase from Candida Antarctica (Novozym 435®) was a gift from Novozymes A/S Spain. Thin-layer chromatography (TLC) was performed on precoated silica gel 60 Alugram SIL/UV_{254} from Macherey Nagel. FAB Mass spectra were collected on a Hewlett-Packard 5988 spectrometer, using a Fisons VG platform or a Fisons VG Autospec-Q. NMR experiments were performed on a Bruker AM-300 and a Bruker AMX-300, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, and on a Bruker AMX-400, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. $CDCl_3$ was used as solvent. Chemical shifts are expressed in δ (parts per million) using the solvent as internal reference.

3.1. Synthetic procedure

A suspension of the alcohol (0.4 mmol), Novozym 435® (40 mg) in ethyl fatty acid ester (12 mmol) was stirred vigorously under vacuum (5–10 mmHg) at 37 °C for 4–16 h. Then, acetonitrile (75 mL) was added, lipase filtered, and the crude washed with hexane (3×25 mL). The acetonitrile phase was concentrated to dryness under reduced pressure and finally purified in a short silica column using flash chromatography (hexane/diethyl ether 10:1, 2:1

Table 2. Reaction yields for phenolic mono- and polyunsaturated fatty acid esters

Phenol	Acylating agent	Product	Yield (%)
3,4-Dihydrobenzylic alcohol **1**	Ethyl oleate	**17**	64
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl oleate	**18**	81
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl oleate	**19**	87
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl oleate	**20**	72
3,4-Dihydrobenzylic alcohol **1**	Ethyl eicosapentaenoate	**21**	33
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl eicosapentaenoate	**22**	51
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl eicosapentaenoate	**23**	97
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl eicosapentaenoate	**24**	32
3,4-Dihydrobenzylic alcohol **1**	Ethyl docosahexaenoate	**25**	32
2-(3,4-Dihydroxyphenyl)-ethanol **2**	Ethyl docosahexaenoate	**26**	43
3-(3,4-Dihydroxyphenyl)-propanol **3**	Ethyl docosahexaenoate	**27**	67
3,4-Dihydroxycinnamylic alcohol **4**	Ethyl docosahexaenoate	**28**	29

Reaction conditions: phenol-carboxylic ethyl ester ratio, 1:30, Novozym 435®, no solvent, 37 °C, 4–16 h.

or 1:1 depending on the polarity of final compound) to yield the phenolic fatty acid ester. In the case of the reactions with butyrate ethyl ester, no final chromatography was needed. All compounds were >95% pure as observed by ^{1}H NMR spectroscopy.

3.2. HPLC procedure

Monitoring by HPLC was carried out using 2695 Alliance Waters separation system and a 2996 photodiode array detector. The column was a Symmetry C18, 250×4.0 mm, 5 μm particle size, protected with a C18 precolumn. The mobile phase A was acetonitrile and B was 1% acetic acid in water. Gradient started on 92% A for 4 min, then linear ramp to 100% A in 6 more min, maintaining 100% A for 8 min, and returning to starting conditions in 2 min. Flow rate was 1 mL/min and detection was achieved at 280 nM.

3.2.1. 3,4-Dihydroxybenzylic palmitate 5. 98%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (d, J=1.5 Hz, 1H, ar), 6.84 (d, J=8.1 Hz, 1H, ar), 6.79 (dd, J=8.0, 1.7 Hz, 1H, ar), 4.99 (s, 2H, PhCH_2OOC–), 2.32 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.61 (q, J=6.0 Hz, 2H, OOC–CH_2–CH_2), 1.25 (m, 24H, –CH_2–), 0.87 (t, J=6.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7 (–COO–), 145.2, 144.9, 130.3, 122.9, 117.2, 116.7 (Ar), 67.5 (Ph*C*H_2OCO–), 35.9 (–OOC–*C*H_2–), 33.3, 31.1, 31.0, 30.8, 30.7, 30.6, 30.5, 26.3, 24.1 (–CH_2–), 15.5 (–CH_3); HRMS FAB+ calcd 401.2668 for $C_{23}H_{38}O_4Na$ $[M+Na]^+$, found 401.2672.

3.2.2. 2-(3,4-Dihydroxyphenyl) ethyl palmitate 6. 98%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J=8.1 Hz, 1H, ar), 6.73 (d, J=1.5 Hz, 1H, ar), 6.63 (dd, J=8.0, 1.5 Hz, 1H, ar), 4.23 (t, J=7.1 Hz, 2H, –CH_2OOC–), 2.80 (t, J=7.1 Hz, 2H, ar-CH_2–), 2.28 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.58 (q, J=6.1 Hz, 2H, –OOC–CH_2–CH_2), 1.25 (m, 24H, –CH_2–), 0.87 (t, J=6.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (–COO–), 143.7, 142.4, 130.7, 121.4, 116.0, 115.5 (Ar), 65.1 (–CH_2OCO–), 34.6, 34.5, 32.0, 29.8, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 25.0, 24.8, 22.8 (–CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 415.2824 for $C_{24}H_{40}O_4Na$ $[M+Na]^+$, found 415.2819.

3.2.3. 3-(3,4-Dihydroxyphenyl) propyl palmitate 7. 97%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J=8.0 Hz, 1H, ar), 6.68 (d, J=1.8 Hz, 1H, ar), 6.58 (dd, J=8.0, 1.8 Hz, 1H, ar), 4.06 (t, J=6.6 Hz, 2H, –CH_2OOC–), 2.55 (t, J=7.4 Hz, 2H, ar-CH_2–), 2.30 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.88 (q, J=6.7 Hz, 2H, –CH_2–), 1.65 (q, J=7.2 Hz, 2H, –OOC–CH_2–CH_2), 1.24; ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (–COO–), 143.7, 141.8, 134.3, 120.8, 115.6, 115.5 (Ar), 63.8 (–CH_2OCO–), 34.5, 32.0, 31.5, 30.4, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.1, 22.8 (–CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 429.2981 for $C_{25}H_{42}O_4Na$ $[M+Na]^+$, found 429.2977.

3.2.4. 3,4-Dihydroxycinnamyl palmitate 8. 71%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H, ar), 6.81 (s, 2H, ar), 6.51 (d, J=15.8 Hz, 1H, Ph-C*H*=CH–CH_2–), 6.09 (dt, J=15.8, 6.6 Hz, 1H, Ph-CH=C*H*–CH_2–), 4.69 (d, J=6.5 Hz, Ph-CH=CH–CH_2–), 2.33 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.63 (q, J=7.0 Hz, 2H, –OOC–CH_2–CH_2), 1.25 (m, 24H, –CH_2–), 0.87 (t, J=6.3 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (–COO–), 134.0 (Ph-*C*H=CH–), 121.3 (Ph-CH=*C*H–), 143.9, 143.8, 129.9, 120.2, 115.5, 113.3 (Ar), 65.2 (–CH_2OCO–), 34.4, 32.0, 30.4, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 25.1, 22.8 (–CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 427.2824 for $C_{25}H_{40}O_4Na$ $[M+Na]^+$, found 427.2819.

3.2.5. 3,4-Dihydroxybenzylic butyrate 9. 75%. Transparent syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, J=1.8 Hz, 1H, ar), 6.83 (d, J=8.0 Hz, 1H, ar), 6.79 (dd, J=8.0, 1.7 Hz, 1H, aro), 4.99 (s, 2H, PhCH_2OOC–), 2.31 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.65 (h, J=7.4 Hz, 2H, OOC–CH_2–CH_2), 0.92 (t, J=7.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (–COO–), 144.0, 143.7, 128.9, 121.5, 115.9, 115.4 (Ar), 66.3 (Ph*C*H_2OCO–), 36.4 (–OOC–*C*H_2–), 18.5 (–OOC–CH_2–*C*H_2), 13.7 (–CH_3); HRMS FAB+ calcd 222.0892 for $C_{12}H_{14}O_4Na$ $[M+Na]^+$, found 222.0892.

3.2.6. 2-(3,4-Dihydroxyphenyl) ethyl butyrate 10. 59%. Transparent syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J=8.1 Hz, 1H, ar), 6.73 (d, J=1.5 Hz, 1H, ar), 6.63 (dd, J=8.0, 1.5 Hz, 1H, ar), 6.19 (1s (w), 1H, Ph-OH), 6.0 (1s (w), 1H, Ph-OH), 4.23 (t, J=7.1 Hz, 2H, –CH_2OOC–), 2.79 (t, J=7.1 Hz, 2H, Ph-CH_2–), 2.27 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.65 (h, J=7.4 Hz, 2H, –OOC–CH_2–CH_2), 0.92 (t, J=7.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9 (–COO–), 143.9, 142.6, 130.5, 121.3, 115.9, 115.5 (Ar), 65.3 (–CH_2OCO–), 36.4 (–OOC–*C*H_2–), 34.5 (Ph-CH_2–), 18.5 (–OOC–CH_2–*C*H_2), 13.7 (–CH_3); HRMS FAB+ calcd 247.0946 for $C_{12}H_{16}O_4Na$ $[M+Na]^+$, found 247.0947.

3.2.7. 3-(3,4-Dihydroxyphenyl) propyl butyrate 11. 97%. Transparent syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, J=8.0 Hz, 1H, ar), 6.68 (d, J=1.5 Hz, 1H, ar), 6.58 (dd, J=8.0, 1.6 Hz, 1H, ar), 4.07 (t, J=6.6 Hz, 2H, –CH_2OOC–), 2.55 (t, J=7.4 Hz, 2H, ar-CH_2–), 2.30 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.89 (q, J=6.7 Hz, 2H, –CH_2–), 1.65 (h, J=7.5 Hz, 2H, –OOC–CH_2–CH_2), 0.95 (t, J=7.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (–COO–), 143.8, 141.9, 134.2, 120.8, 115.6, 115.4 (Ar), 63.9 (–CH_2OCO–), 36.4 (–OOC–*C*H_2–), 31.5, 30.3, 18.6 (–CH_2–), 13.7 (–CH_3); HRMS FAB+ calcd 261.1103 for $C_{13}H_{18}O_4Na$ $[M+Na]^+$, found 261.1107.

3.2.8. 3,4-Dihydroxycinnamyl butyrate 12. 96%. Transparent syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H, ar), 6.80 (s, 2H, ar), 6.51 (d, J=15.8 Hz, 1H, Ph-C*H*=CH–CH_2–), 6.09 (dt, J=15.8, 6.6 Hz, 1H, Ph-CH=C*H*–CH_2–), 4.69 (d, J=6.5 Hz, Ph-CH=CH–CH_2–), 2.32 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.66 (h, J=7.4 Hz, 2H, –OOC–CH_2–CH_2), 0.95 (t, J=7.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (–COO–), 134.1 (Ph-*C*H=CH–), 121.4 (Ph-CH=*C*H–), 144.0, 143.8, 129.8, 120.2, 115.5, 113.3 (Ar), 65.3 (–CH_2OCO–), 36.4 (–OOC–*C*H_2–), 18.6 (–CH_2–), 13.7 (–CH_3); HRMS FAB+ calcd 259.1105 for $C_{13}H_{16}O_4Na$ $[M+Na]^+$, found 259.1109.

3.2.9. 3,4-Dihydroxybenzylic stearate 13. 74%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, J=1.8 Hz, 1H, ar), 6.83 (d, J=8.1 Hz, 1H, ar), 6.78 (dd, J=8.0,

1.7 Hz, 1H, ar), 4.99 (s, 2H, $PhCH_2OOC$–), 2.33 (t, J= 7.7 Hz, 2H, –OOC–CH_2–), 1.61 (q, J=7.2 Hz, 2H, OOC–CH_2–CH_2), 1.25 (m, 28H, –CH_2–), 0.87 (t, J=6.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7 (–COO–), 144.1, 143.7, 128.8, 121.5, 115.8, 115.3 (Ar), 66.3 (PhCH_2-OCO–), 34.6 (–OOC–CH_2–), 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 22.7 (–CH_2–), 14.1 (–CH_3); HRMS FAB+ calcd 429.2981 for $C_{25}H_{42}O_4Na$ $[M+Na]^+$, found 429.2987.

3.2.10. 2-(3,4-Dihydroxyphenyl) ethyl stearate 14. 94%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79 (d, J=8.1 Hz, 1H, ar), 6.72 (d, J=2.0 Hz, 1H, ar), 6.63 (dd, J=8.0, 2.0 Hz, 1H, ar), 4.23 (t, J=7.1 Hz, 2H, –CH_2OOC–), 2.80 (t, J=7.1 Hz, 2H, ar-CH_2–), 2.28 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.58 (m, 2H, –OOC–CH_2–CH_2–), 1.24 (m, 28H, –CH_2–), 0.87 (t, J=6.9 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (–COO–), 143.8, 142.5, 130.6, 121.4, 116.0, 115.4 (Ar), 65.1 (–CH_2OCO–), 34.6, 34.5, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 25.0, 24.8, 22.7 (–CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 443.3137 for $C_{26}H_{44}O_4Na$ $[M+Na]^+$, found 443.3141.

3.2.11. 3-(3,4-Dihydroxyphenyl) propyl stearate 15. 97%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J=8.1 Hz, 1H, ar), 6.69 (d, J=1.9 Hz, 1H, ar), 6.59 (dd, J=8.1, 2.0 Hz, 1H, ar), 4.07 (t, J=6.6 Hz, 2H, –CH_2OOC–), 2.56 (t, J=7.6 Hz, 2H, ar-CH_2–), 2.30 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.89 (q, J=6.8 Hz, 2H, –CH_2–), 1.61 (q, J= 7.0 Hz, 2H, –OOC–CH_2–CH_2), 1.27 (m, 28H, –CH_2–), 0.87 (t, J=6.9 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (–COO–), 143.7, 141.8, 134.3, 120.8, 115.5, 115.4 (Ar), 63.7 (–CH_2OCO–), 34.5, 31.9, 31.5, 30.3, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 25.1, 22.7 (–CH_2–), 14.1 (–CH_3); HRMS FAB+ calcd 457.3294 for $C_{27}H_{46}O_4Na$ $[M+Na]^+$, found 457.3301.

3.2.12. 3,4-Dihydroxycinnamyl stearate 16. 72%. White solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (s, 1H, ar), 6.81 (s, 2H, ar), 6.51 (d, J=15.8 Hz, 1H, Ph-CH=CH–CH_2–), 6.09 (dt, J=15.8, 6.6 Hz, 1H, Ph-CH=CH–CH_2–), 4.69 (d, J=6.5 Hz, Ph-CH=CH–CH_2–), 2.33 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.63 (q, J=7.1 Hz, 2H, –OOC–CH_2–CH_2), 1.24 (m, 28H, –CH_2–), 0.87 (t, J=6.4 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (–COO–), 134.0 (Ph-CH=CH–), 121.3 (Ph-CH=CH–), 143.9, 143.7, 129.9, 120.3, 115.5, 113.3 (Ar), 65.2 (–CH_2OCO–), 34.5, 32.0, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 25.1, 22.8 (–CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 455.3137 for $C_{27}H_{44}O_4Na$ $[M+Na]^+$, found 455.3136.

3.2.13. 3,4-Dihydroxybenzylic oleate 17. 63%. Light yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (s, 1H, ar), 6.83 (d, AB system, J=8.0 Hz, 1H, ar), 6.79 (d, AB system, J=8.4, 1.7 Hz, 1H, ar), 5.34 (m, 2H, HC=CH), 4.99 (s, 2H, $PhCH_2OOC$–), 2.32 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 1.99 (m, 4H, –CH_2–HC=CH–CH_2–), 1.61 (q, J= 6.8 Hz, 2H, –OOC–CH_2–CH_2–), 1.26 (m, 26H, –CH_2–), 0.87 (t, J=6.7 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (–COO–), 130.1, 129.8 (–HC=CH–) 143.9, 143.7, 129.0, 121.6, 115.9, 115.4 (Ar), 66.2 (PhCH_2OCO–), 34.5, 31.9, 29.8, 29.7, 29.6, 29.4, 29.2, 29.1, 27.3, 27.2, 25.0, 22.7 (–CH_2–HC=CH–CH_2–, –CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 427.2824 for $C_{25}H_{40}O_4Na$ $[M+Na]^+$, found 427.2822.

3.2.14. 2-(3,4-Dihydroxyphenyl) ethyl oleate 18. 93%. Light yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (d, J=8.1 Hz, 1H, ar), 6.72 (d, J=2.0 Hz, 1H, ar), 6.63 (dd, J=8.0, 2.0 Hz, 1H, ar), 5.34 (m, 2H, HC=CH), 4.23 (t, J= 7.1 Hz, 2H, –CH_2OOC–), 2.80 (t, J=7.1 Hz, 2H, ar-CH_2–), 2.28 (t, J=7.6 Hz, 2H, –OOC–CH_2–), 1.99 (m, 4H, –CH_2–HC=CH–CH_2–), 1.58 (m, 2H, –OOC–CH_2–CH_2–), 1.26 (m, 20H, –CH_2–), 0.87 (t, J=6.9 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8 (–COO–), 130.1, 129.8 (–HC=CH–) 143.8, 142.5, 130.5, 121.3, 115.9, 115.4 (Ar), 65.3 (–CH_2OCO–), 34.5, 31.9, 31.3, 29.7, 29.6, 29.4, 29.2, 29.1, 27.3, 27.2, 25.0, 22.7 (–CH$_2$–HC=CH–CH$_2$–, –CH_2–), 14.2 (–CH_3); HRMS FAB+ calcd 441.2981 for $C_{26}H_{42}O_4Na$ $[M+Na]^+$, found 441.2979.

3.2.15. 3-(3,4-Dihydroxyphenyl) propyl oleate 19. 87%. Light yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (d, J=8.1 Hz, 1H, ar), 6.69 (d, J=2.0 Hz, 1H, ar), 6.58 (dd, J=8.0, 2.0 Hz, 1H, ar), 5.33 (m, 2H, HC=CH), 4.07 (t, J= 6.6 Hz, 2H, –CH_2OOC–), 2.55 (t, J=7.3 Hz, 2H, ar-CH_2–), 2.30 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 1.99 (m, 4H, –CH_2–HC=CH–CH_2–), 1.89 (q, J=6.8 Hz, 2H, –CH_2–), 1.61 (m, 2H, –OOC–CH_2–CH_2–), 1.26 (m, 20H, –CH_2–), 0.87 (t, J= 6.9 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (–COO–), 130.1, 129.8 (–HC=CH–) 143.7, 141.9, 134.2, 120.7, 115.5, 115.4 (Ar), 63.8 (–CH_2OCO–), 34.5, 31.9, 31.4, 30.3, 29.8, 29.7, 29.6, 29.4, 29.2, 29.1, 27.3, 27.2, 25.0, 22.7 (–CH$_2$–HC=CH–CH$_2$–, –CH_2–), 14.1 (–CH_3); HRMS FAB+ calcd 455.3137 for $C_{27}H_{44}O_4Na$ $[M+Na]^+$, found 455.3138.

3.2.16. 3,4-Dihydroxycinnamyl oleate 20. 72%. Light yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (s, 1H, ar), 6.81 (s, 2H, ar), 6.51 (d, J=15.8 Hz, 1H, Ph-CH=CH–CH_2–), 6.08 (dt, J=15.8, 6.6 Hz, 1H, Ph-CH=CH–CH_2–), 5.34 (m, 2H, HC=CH), 4.69 (d, J=6.6 Hz, Ph-CH=CH–CH_2–), 2.33 (t, J=7.5 Hz, 2H, –OOC–CH_2–), 2.0 (m, 4H, –CH_2–HC=CH–CH_2–), 1.63 (q, J=7.1 Hz, 2H, –OOC–CH_2–CH_2–), 1.26 (m, 26H, –CH_2–), 0.87 (t, J=7.0 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (–COO–), 130.1, 129.8 (–HC=CH–), 134.1 (Ph-CH=CH–), 121.2 (Ph-CH=CH–), 144.0, 143.8, 129.7, 120.1, 115.4, 113.2 (Ar), 65.3 (–CH_2OCO–), 34.5, 33.9, 31.9, 29.8, 29.7, 29.6, 29.3, 29.2, 29.1, 27.3, 27.2, 25.0, 24.7, 22.7 (–CH$_2$–HC=CH–CH$_2$–, –CH_2–), 14.1 (–CH_3); HRMS FAB+ calcd 430.3239 for $C_{27}H_{42}O_4$ $[M]^+$, found 430.3240.

3.2.17. 3,4-Dihydroxybenzylic *cis*-5,8,11,14,17-eicosapentanoate 21. 33%. Light yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (s, 1H, ar), 6.81 (dd, AB system, J=8.1 Hz, 2H ar), 5.35 (m, 10H, HC=CH), 4.99 (s, 2H, $PhCH_2OOC$–), 2.80 (m, 8H, –HC=CH–CH_2–HC=CH–), 2.34 (t, J=7.4 Hz, 2H, –OOC–CH_2–), 2.06 (m, 4H, –HC=CH–CH_2–CH_3, –HC=CH–CH_2–CH_2–) 1.69 (m, 2H, –CH_2–CH_2–COO–), 0.96 (t, J=7.5 Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (–COO–), 144.0, 143.7, 132.1, 129.1, 128.9, 128.8, 128.6, 128.3, 128.2, 128.1, 127.9, 127.1, 121.6, 115.9, 115.3 (Ar, HC=CH–), 66.2 (PhCH_2OCO–), 33.9, 33.3, 26.6, 26.5, 25.7, 25.6, 28.8, 24.6, 20.6 (–CH_2–, –HC=CH–CH$_2$–HC=CH–), 14.3

(–CH_3); HRMS FAB+ calcd 447.5963 for $C_{27}H_{36}O_4Na$ $[M+Na]^+$, found 447.5961.

3.2.18. 2-(3,4-Dihydroxyphenyl) ethyl *cis*-5,8,11,14,17-eicosapentanoate 22. 51%. Light yellow syrup; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, $J=8.1$ Hz, 1H, ar), 6.72 (d, $J=2.0$ Hz, 1H, ar), 6.63 (dd, $J=8.0$, 2.0 Hz, 1H, ar), 5.35 (m, 10H, HC=CH), 4.25 (t, $J=7.1$ Hz, 2H, –CH_2OOC–), 2.81 (m, 8H, –HC=CH–CH_2–HC=CH–), 2.80 (t, $J=7.1$ Hz, 2H, ar-CH_2–), 2.29 (t, $J=7.6$ Hz, 2H, –OOC–CH_2–), 2.07 (m, 4H, HC=CH–CH_2–CH_3, –HC=CH–CH_2–CH_2–) 1.67 (t, $J=7.4$ Hz, 2H, –CH_2–CH_2–COO–), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1 (–COO–), 144.0, 142.7, 132.1, 129.1, 128.9, 128.7, 128.6, 128.3, 128.2, 128.0, 127.9, 127.1, 121.6, 115.9, 115.3 (Ar, HC=CH–), 66.2 (–CH_2OCO–), 34.5, 33.9, 33.4, 26.6, 26.5, 25.7, 25.6, 24.6, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 461.6120 for $C_{28}H_{38}O_4Na$ $[M+Na]^+$, found 461.6115.

3.2.19. 3-(3,4-Dihydroxyphenyl) propyl *cis*-5,8,11,14,17-eicosapentanoate 23. 97%. Light yellow syrup; ^1H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, $J=8.1$ Hz, 1H, ar), 6.72 (d, $J=1.8$ Hz, 1H, ar), 6.57 (dd, $J=8.0$, 1.8 Hz, 1H, ar), 5.37 (m, 10H, HC=CH), 4.07 (t, $J=6.6$ Hz, 2H, –CH_2OOC–), 2.82 (m, 8H, –HC=CH–CH_2–HC=CH–), 2.55 (t, $J=7.1$ Hz, 2H, ar-CH_2–), 2.33 (t, $J=7.5$ Hz, 2H, –OOC–CH_2–), 2.09 (m, 4H, HC=CH–CH_2–CH_3, –HC=CH–CH_2–CH_2–), 1.89 (q, $J=6.8$ Hz, 2H, –CH_2–), 1.67 (t, $J=7.4$ Hz, 2H, –CH_2–CH_2–COO–), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6 (–COO–), 143.8, 142.0, 134.1, 132.2, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 127.9, 127.1, 120.7, 115.6, 115.4 (Ar, HC=CH–), 64.1 (–CH_2OCO–), 33.9, 31.5, 30.3, 26.7, 25.7, 25.6, 24.9, 20.7 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 475.6277 for $C_{29}H_{40}O_4Na$ $[M+Na]^+$, found 475.6269.

3.2.20. 3,4-Dihydroxycinnamyl *cis*-5,8,11,14,17-eicosapentanoate 24. 32%. Light yellow syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H, ar), 6.80 (s, 2H, ar), 6.51 (d, $J=15.8$ Hz, 1H, Ph-C*H*=CH–CH_2–), 6.09 (dt, $J=15.8$, 6.6 Hz, 1H, Ph-CH=C*H*–CH_2–), 5.36 (m, 10H, HC=CH), 4.69 (d, $J=6.6$ Hz, Ph-CH=CH–CH_2–), 2.82 (m, 8H, –HC=CH–CH_2–HC=CH–), 2.36 (t, $J=7.4$ Hz, 2H, –OOC–CH_2–), 2.06 (m, 4H, –HC=CH–CH_2–CH_3, –HC=CH–CH_2–CH_2–) 1.72 (q, $J=7.4$ Hz, 2H, –CH_2–CH_2–COO–), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0 (–COO–), 144.0, 143.8, 134.1, 132.2, 129.0, 128.9, 128.7, 128.4, 128.3, 128.2, 127.9, 127.1, 121.1, 120.7, 115.6, 115.4 (Ar, HC=CH–), 65.4 (–CH_2OCO–), 33.8, 26.6, 25.7, 25.6, 24.8, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 473.6265 for $C_{29}H_{38}O_4Na$ $[M+Na]^+$, found 473.6254.

3.2.21. 3,4-Dihydroxybenzylic *cis*-4,7,10,13,16,19-docosahexanoate 25. 32%. Light yellow syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (d, $J=1.6$ Hz, 1H, ar), 6.83 (d, $J=8.0$ Hz, 1H, ar), 6.78 (dd, $J=8.0$, 1.7 Hz, 1H, ar), 5.38 (m, 12H, HC=CH), 4.99 (s, 2H, –CH_2OOC–), 2.83 (m, 10H, –HC=CH–CH_2–HC=CH–), 2.40 (m, 2H, –OOC–CH_2–), 2.39 (m, 2H, –HC=CH–CH_2–CH_2–COO–) 2.06 (q, $J=7.4$ Hz, 2H, –HC=CH–CH_2–CH_3), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (–COO–), 144.0, 143.7, 132.2, 129.7, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 121.6, 115.9, 115.4 (Ar, HC=CH–), 66.4 (Ph*C*H_2OCO–), 34.5, 33.8, 25.7, 25.7, 25.6, 22.9, 22.6, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 473.6215 for $C_{29}H_{38}O_4Na$ $[M+Na]^+$, found 473.6208.

3.2.22. 2-(3,4-Dihydroxyphenyl) ethyl *cis*-4,7,10,13,16,19-docosahexanoate 26. 43%. Light yellow syrup; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, $J=8.1$ Hz, 1H, ar), 6.72 (d, $J=2.0$ Hz, 1H, ar), 6.58 (dd, $J=8.0$, 2.0 Hz, 1H, ar), 5.38 (m, 12H, HC=CH), 4.23 (t, $J=7.1$ Hz, 2H, –CH_2OOC–), 2.81 (m, 10H, –HC=CH–CH_2–HC=CH–), 2.80 (t, $J=7.1$ Hz, 2H, ar-CH_2–), 2.35 (m, 2H, –OOC–CH_2–), 2.35 (m, 2H, –HC=CH–CH_2–CH_2–COO–) 2.06 (m, $J=7.6$ Hz, 2H, –HC=CH–CH_2–CH_3), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.3 (–COO–), 144.0, 143.7, 132.2, 129.7, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 121.6, 115.9, 115.4 (Ar, HC=CH–), 66.4 (–CH_2OCO–), 34.5, 33.8, 25.7, 25.7, 25.6, 22.9, 22.6, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 487.6572 for $C_{30}H_{40}O_4Na$ $[M+Na]^+$, found 487.6562.

3.2.23. 3-(3,4-Dihydroxyphenyl) propyl *cis*-4,7,10,13,16,19-docosahexanoate 27. 67%. Light yellow syrup; ^1H NMR (400 MHz, $CDCl_3$): δ 6.76 (d, $J=8.1$ Hz, 1H, ar), 6.68 (d, $J=1.8$ Hz, 1H, ar), 6.58 (dd, $J=8.0$, 1.8 Hz, 1H, ar), 5.38 (m, 12H, HC=CH), 4.08 (t, $J=6.7$ Hz, 2H, –CH_2OOC–), 2.84 (m, 10H, –HC=CH–CH_2–HC=CH–), 2.56 (t, $J=7.4$ Hz, 2H, ar-CH_2–), 2.38 (m, 2H, –OOC–CH_2–), 2.38 (m, 2H, –HC=CH–CH_2–CH_2–COO–) 2.08 (q, $J=7.3$ Hz, 2H, –HC=CH–CH_2–CH_3), 1.89 (q, $J=6.9$ Hz, 2H, –CH_2–), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7 (–COO–), 144.0, 143.7, 132.2, 129.7, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.1, 121.6, 115.9, 115.4 (Ar, HC=CH–), 66.4 (–CH_2OCO–), 34.3, 31.4, 30.3, 25.7, 25.6, 25.6, 22.9, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 501.6729 for $C_{31}H_{42}O_4Na$ $[M+Na]^+$, found 501.6716.

3.2.24. 3,4-Dihydroxycinnamyl *cis*-4,7,10,13,16,19-docosahexanoate 28. 29%. Light yellow syrup; ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H, ar), 6.80 (s, 2H, ar), 6.51 (d, $J=15.8$ Hz, 1H, Ph-C*H*=CH–CH_2–), 6.09 (dt, $J=15.8$, 6.6 Hz, 1H, Ph-CH=C*H*–CH_2–), 5.36 (m, 12H, HC=CH), 4.69 (d, $J=6.6$ Hz, Ph-CH=CH–CH_2–), 2.83 (m, 10H, –HC=CH–CH_2–HC=CH–), 2.41 (m, 2H, –OOC–CH_2–), 2.39 (m, 2H, –HC=CH–CH_2–CH_2–COO–) 2.07 (q, $J=7.1$ Hz, 2H, –HC=CH–CH_2–CH_3), 0.96 (t, $J=7.5$ Hz, 3H, –CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (–COO–), 144.0, 143.8, 134.2, 132.1, 129.7, 129.5, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.1, 121.1, 120.2, 115.4, 113.2 (Ar, HC=CH–), 65.5 (–CH_2OCO–), 34.4, 25.7, 25.6, 22.9, 20.6 (–CH_2–, –HC=CH–*C*H_2–HC=CH–), 14.3 (–CH_3); HRMS FAB+ calcd 499.6705 for $C_{31}H_{40}O_4Na$ $[M+Na]^+$, found 499.6710.

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