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Synthesis of 4-hydroxy- and 2,4-dihydroxy-homophthalates by [4+2] cycloaddition of 1,3-bis(silyloxy)-1,3-butadienes with dimethyl allene-1,3-dicarboxylate

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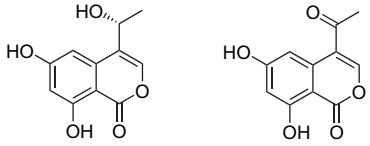
ABSTRACT

The reaction of 1,3-bis(trimethylsiloxy)-1,3-butadienes with dimethyl allene-1,3-dicarboxylate provides a convenient and regioselective approach to a variety of functionalized 4-hydroxy- and 2,4-dihydroxy-homophthalates.

1. Introduction

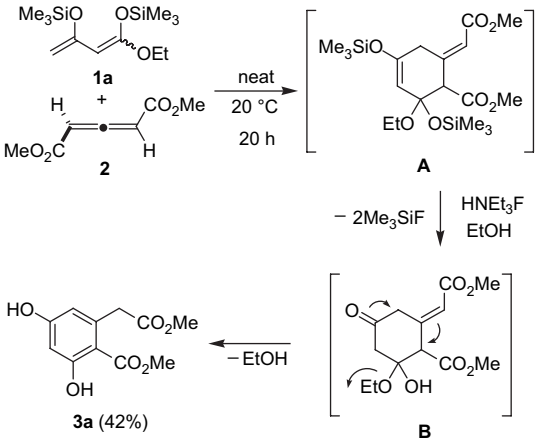
Allenes represent versatile synthetic building blocks in inter- and intramolecular [4+2] cycloadditions.[1] The [4+2] cycloaddition of 2-silyloxy-1,3-dienes with allenes has been reported to give functionalized phenols. For example, (*R*)-(+)-lasiodiplodin was prepared based on the cyclization of a cyclic allenylester with 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene.[2] The reaction of allenylphenylsulfone with Danishefsky's diene afforded 3-methyl-4-(phenylsulfonyl)-phenol.[3] Roush and Murphy were the first to report the cycloaddition of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with dimethyl allene-1,3-dicarboxylate.[4] Some years ago, we reported the synthesis of various homophthalates based on the cycloaddition of dimethyl allene-1,3-dicarboxylate with various 1,3-bis(silyl enol ethers).[5] Later on, this methodology was successfully applied to the synthesis of an analogue of lactonamycin,[6] of the N_7–C_{25} fragment of psymberin,[7] and of the 4-acetylisocoumarins AGI-7 and sescandelin (Scheme 1).[8] Herein, we report full details of the methodology and a study related to the preparative scope.



Scheme 1. Structure of (−)-sescandelin and AGI-7.

2. Results and discussion

The reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**1a**), prepared from ethyl acetoacetate in two steps,[9,10] with dimethyl allene-1,3-dicarboxylate (**2**), available from dimethyl acetone-1,3-dicarboxylate,[11] afforded the homophthalate **3a** in up to 75% yield (Scheme 2). The best yield was obtained when a mixture of the starting materials (neat) was stirred for 20 h at 20 °C. Subsequently, to the mixture was added an ethanol solution of triethylammonium fluoride.[12] The formation of **3a** can be explained



Scheme 2. Possible mechanism for the formation of **3a**.

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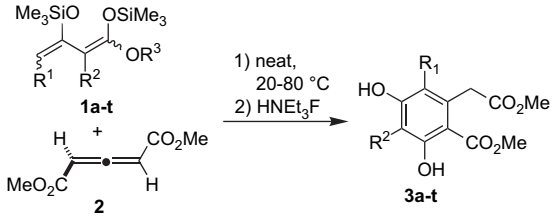
by [4+2] cycloaddition to give intermediate **A**, cleavage of the Si–O bonds upon addition of triethylammonium fluoride, and subsequent aromatization by extrusion of ethanol, enolization and migration of the exocyclic double bond. The yield decreased when the reaction was carried out at elevated temperature (40 or 80 °C), or when the reaction was carried in a toluene solution (room temperature or reflux). The yield also decreased when the reaction time was decreased (no complete conversion) or increased (decomposition). The stoichiometry also played an important role. The use of an excess of the dienophile did not result in an increase of the yield.

It should be worthwhile mentioning that the selective elimination of ethanol (formation of a 3-hydroxyphenol) rather than water (formation of a 3-ethoxyphenol) was observed. The relatively low yield can be explained by partial decomposition of the quite sensitive diene, due to the long reaction time.

The cycloaddition of **2** with 1-alkoxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes **1a–t**, prepared in two steps from the corresponding β-ketoesters, afforded the 2,4-dihydroxy-homophthalates **3a–t** (Scheme 3, Table 1). A wide range of products, including fluoro-, chloro-, alkyl-, methoxy-, benzyloxy-, aryloxy-, arylthio-substituted derivatives, were successfully prepared. Moderate to good yields were obtained for all products (except for **3s**). The reaction conditions had to be optimized for each individual experiment (reaction time and temperature, see Section 4). The yield increases with the scale of the reaction. For example, Roush and Murphy reported[4] the synthesis of **3a** in 70% yield on large scale. Floreancig and Rech reported[7] a 70% yield for **3f** on large scale. The yield of **3s** was increased from 16% (1.4 mmol scale) to 44% (50 mmol scale). Notably, the reaction of **1a** with allenes other than **2** proved to be unsuccessful in our hands. The reaction of **1a** with methyl buta-



Scheme 3. Synthesis of 2,4-dihydroxyhomophthalates **3a–t**.

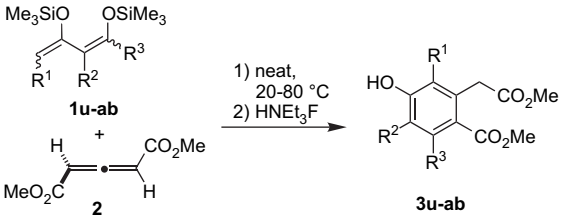
Table 1
Synthesis of 2,4-dihydroxy-homophthalates **3a–t**

3	R^1	R^2	R^3	Yield % (3)[a]
a	H	H	Et	75 (70)[b]
b	H	Et	Et	52
c	H	Cl	Et	64
d	H	F	Et	70
e	H	SPh	Me	50
f	Me	H	Me	55 (70)[c]
g	Me	Cl	Me	47
h	Et	H	Et	43
i	Allyl	H	Et	60
j	*n*-Bu	H	Et	38
k	*n*-Hex	H	Me	52
l	*n*-Oct	H	Me	56
m	Bn	H	Et	42
n	OMe	H	Me	40
o	OPh	H	Et	58
p	O(2-MeC_6H_4)	H	Et	48
q	O(3-MeC_6H_4)	H	Et	50
r	O(4-MeC_6H_4)	H	Et	54
s	OBn	H	Et	16 (44)[d]
t	SPh	H	Et	41

[a] Yields of isolated products on a scale of approximately 1 mmol.
[b] Ref. 4 (102 mmol scale).
[c] Ref. 7 (77 mmol scale).
[d] On large scale.

2,3-dienoate (containing only one ester group) and methoxyallene (containing a π-donating substituent) resulted in the formation of complex mixtures.

The cycloaddition of **2** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **1u–ab**, available from the corresponding 1,3-diketones, afforded the 4-hydroxy-homophthalates **3u–ab** (Scheme 4, Table 2). The conditions had again to be individually optimized. Interestingly, the yields again increased when the reactions were carried out on large scale. Danishefsky co-workers isolated **3x** in 75% yield on a large scale.[6]



Scheme 4. Synthesis of 4-hydroxy-homophthalates **3u–ab**.

Table 2
Synthesis of **3u–ab**

3	R^1	R^2	R^3	Yield % (3)[a]
u	H	H	Me	55
v	H	H	Ph	46
w	H	Me	Me	44
x	H	CO_2Me	Me	20 (75)[b]
y	H	Cl	Me	42
z	H	O[4-(EtO)C_6H_4]	Me	48
aa	H	O(4-ClC_6H_4)	Me	45
ab	H	O[4-(CN)C_6H_4]	Me	56

[a] Yields of isolated products.
[b] Ref. 8 (large scale).

Products **3o–r** and **3z–ab** represent functionalized diaryl ethers. It should be worthwhile mentioning that diaryl ethers occur in various natural products (e.g., geodinhydrate methylester, methyl chloroasterrate,[13a,b] 1-desgalloylsanguiin,[13c] dehydrotrigallic acid,[13d] epiphorellic acid,[13e] jolkianin,[13f] remurin A[13g] and micareic acid[13h]) and have been shown to possess a wide range of pharmacological activities.

The structures of all products were established by spectroscopic methods. The structure of **3b** was independently confirmed by X-ray crystal structure analysis (Fig. 1).[14]

3. Conclusions

In conclusion, a variety of functionalized 4-hydroxy- and 2,4-dihydroxy-homophthalates, which are not readily available by other methods, were prepared by reaction of 1,3-bis(trimethylsiloxy)-1,3-butadienes with dimethyl allene-1,3-dicarboxylate. Many

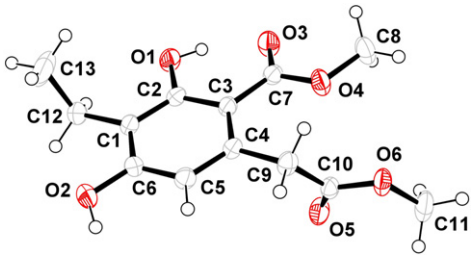


Figure 1. Crystal structure of **3b**.

functional groups were tolerated in the cycloadditions. This includes fluoro-, chloro-, alkyl-, methoxy- and benzyloxy-groups, and diarylether- and diaryl sulfide moieties.

4. Experimental section

4.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

4.2. General procedure for the synthesis of homophthalates

To neat allene **2** (1.0 mmol) was added neat diene **1** (1.25 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and then the solution was stirred at 20−75 °C for several hours. To the mixture was added an ethanol solution (96%, 2 mL) of triethylammonium fluoride, which was prepared from $NEt_3{\cdot}(HF)_3$ as previously reported.[12] The solution was diluted with water and repeatedly extracted with diethyl ether or dichloromethane. The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, heptanes/EtOAc=1:1 or petroleum ether/diethyl ether=1:1) to give product **3**.

4.2.1. Methyl 2,4-dihydroxy-6-(methoxycarbonylmethyl)-benzoate (**3a**)

Starting with **1a** (0.242 g, 0.88 mmol), **2** (0.132 g, 0.85 mmol) and $NEt_3{\cdot}(HF)_3$ (0.272 g, 1.69 mmol), **3a** was isolated as a yellow solid (0.152 g 75%). Reaction time: 20 h (20 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=3.68 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2), 6.21–6.25 (m, 2H, Ar–H). The spectroscopic data were identical with those reported.[4]

4.2.2. Methyl 3-ethyl-2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)-benzoate (**3b**)

Starting with **1b** (0.361 g, 1.25 mmol), **2** (0.156 g, 1.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.242 g, 1.5 mmol), **3b** was isolated as a yellow viscous oil (0.139 g, 52%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=0.98 (t, ^{3}J=7.4 Hz, 3H, CH_2CH_3), 2.53 (q, ^{3}J=7.4 Hz, 2H, CH_2CH_3), 3.58 (s, 3H, $COOCH_3$), 3.67 (s, 2H, CH_2COOCH_3), 3.71 (s, 3H, CH_2COOCH_3), 6.13 (s, 1H, CH_{Ar}). ^{13}C NMR (62 MHz, CD_3OD): δ=13.4 (CH_2CH_3), 16.8 (CH_2CH_3), 43.2 (CH_2COOCH_3), 52.6 ($COOCH_3$), 52.7 (CH_2COOCH_3), 104.6 (C_{Ar}), 113.1 (CH_{Ar}), 117.8, 136.0 (C_{Ar}), 161.1, 163.9 (COH_{Ar}), 172.6 ($COOCH_3$), 174.2 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3285 (w), 2961 (w), 1699 (s), 1646 (m), 1604 (m), 1439 (m), 1275 (s), 1193 (s), 1156 (s), 1051 (m), 984 (m), 839 (m), 746 (m). GC–MS (EI, 70 eV): m/z (%)=268 ([M^+], 33), 250 (5), 236 (30), 222 (10), 208 (19), 189 (22), 176 (100), 148 (8), 91 (6), 77 (6).

4.2.3. Methyl 3-chloro-2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)-benzoate (**3c**)

Starting with **1c** (0.386 g, 1.25 mmol), **2** (0.156 g, 1.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.242 g, 1.5 mmol), **3c** was isolated as a yellow viscous oil (0.177 g, 64%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=3.67 (s, 3H, $COOCH_3$), 3.82 (s, 2H, CH_2COOCH_3), 3.85 (s, 3H, CH_2COOCH_3), 6.38 (s, 1H, CH_{Ar}). ^{13}C NMR (62 MHz, CD_3OD): δ=43.0 (CH_2COOCH_3), 52.4 ($COOCH_3$), 52.4 (CH_2COOCH_3), 106.2 (C_{Ar}), 113.5 (CH_{Ar}), 137.6 ($2C_{Ar}$), 159.6, 161.6 (COH_{Ar}), 172.3 ($COOCH_3$), 173.8 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3226 (w), 2958 (w), 1698 (m), 1654 (m), 1435 (m), 1319 (m), 1235 (s), 1189 (s), 1076 (m), 959 (m), 800 (m), 687 (m). GC–MS (EI, 70 eV): m/z (%)=276 ([M^+], ^{37}Cl, 16), 274 ([M^+], ^{35}Cl, 48), 244 (^{37}Cl, 20), 242 (^{35}Cl, 42), 216 (^{37}Cl, 37), 214 (^{35}Cl, 100), 201 (^{37}Cl, 24), 199 (^{35}Cl, 76), 185 (13), 171 (8), 155 (33). HRMS (EI): calcd for $C_{11}H_{11}O_6Cl$ ([M^+], ^{35}Cl): 274.02387; found: 274.02379.

4.2.4. Methyl 3-fluoro-2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)-benzoate (**3d**)

Starting with **1d** (0.920 g, 2.5 mmol), **2** (0.312 g, 2.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.483 g, 3.0 mmol), **3d** was isolated as a red solid (0.361 g, 70%), mp=148−156 °C. Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=2.36 (s, 3H, $COOCH_3$), 2.47 (s, 2H, CH_2COOCH_3), 2.54 (s, 3H, CH_2COOCH_3), 5.04 (d, ^{4}J=7.6 Hz, 1H, CH_{Ar}). ^{13}C NMR (62 MHz, CD_3OD): δ=42.6 (CH_2COOCH_3), 52.4 ($COOCH_3$), 52.5 (CH_2COOCH_3), 106.7 (C_{Ar}), 114.2 (d, ^{3}J=1.3 Hz, CH_{Ar}), 126.3 (C_{Ar}), 133.8 (d, ^{3}J=4.1 Hz, C_{Ar}), 140.6 (d, ^{1}J=234.3 Hz, CF_{Ar}), 150.8 (d, ^{2}J=9.6 Hz, COH_{Ar}), 153.6 (d, ^{2}J=10.3 Hz, COH_{Ar}), 171.9 ($COOCH_3$), 174.0 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3231 (w), 2956 (w), 1706 (s), 1657 (m), 1597 (m), 1437 (s), 1324 (m), 1249 (s), 1199 (s), 1105 (m), 1059 (m), 979 (s), 844 (m), 743 (s). GC–MS (EI, 70 eV): m/z (%)=258 ([M^+], 49), 226 (63), 198 (90), 183 (100), 169 (13), 155 (8), 139 (39), 110 (5), 83 (11). HRMS (EI): calcd for $C_{11}H_{11}FO_6$: 258.05342; found: 258.05382.

4.2.5. Methyl 2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)-3-(phenylsulfanyl)benzoate (**3e**)

Starting with **1e** (0.920 g, 2.5 mmol), **2** (0.312 g, 2.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.483 g, 3.0 mmol), **3e** was isolated as a red viscous oil (0.341 g, 50%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.63 (s, 3H, $COOCH_3$), 3.77 (s, 3H, CH_2COOCH_3), 3.80 (s, 2H, CH_2COOCH_3), 6.74 (br s, 1H, OH_{Ar}), 7.04–7.07 (m, 2H, CH_{Ph}), 7.10 (m, 1H, CH_{SPh}), 7.13 (s, 1H, CH_{SPh}), 7.15–7.18 (m, 1H, CH_{SPh}), 7.28 (s, 1H, CH_{Ar}), 12.37 (br s, 1H, OH_{Ar}). ^{13}C NMR (62 MHz, $CDCl_3$): δ=42.9 (CH_2COOCH_3), 52.0 ($COOCH_3$), 52.1 (CH_2COOCH_3), 105.4 (C_{Ar}), 111.5 (CH_{SPh}), 126.3 (C_{Ar}), 126.4 (CH_{Ar}), 126.8 ($2CH_{SPh}$), 129.1 ($2CH_{SPh}$), 129.3 (C_{Ar}), 140.7 (C_{SPh}), 162.2, 166.0 (COH_{Ar}), 171.1 ($COOCH_3$), 171.3 (CH_2COOCH_3). MS (EI, 70 eV): m/z (%)=348 ([M^+], 1), 238 (4), 284 (32), 150 (6), 123 (27), 110 (100), 84 (12), 66 (21), 44 (25).

4.2.6. Methyl 2,4-dihydroxy-5-methyl-6-(methoxycarbonyl-methyl)benzoate (**3f**)

Starting with **1f** (0.399 g, 1.45 mmol), **2** (0.170 g, 1.09 mmol) and $NEt_3{\cdot}(HF)_3$ (0.351 g, 2.18 mmol), **3f** was isolated as a white solid (0.153 g, 55%). Reaction time: 18 h (20 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=2.08 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.96 (s, 2H, CH_2), 6.33 (s, 1H, Ar–H). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=11.3 (Ar–CH_3), 36.7 (Ar–$CH_2CO_2CH_3$), 52.5, 56.3 ($2\times OCH_3$), 98.9 (Ar), 116.6 (C–CH_3), 117.7 (C–$CH_2CO_2CH_3$), 134.1 (C–CO_2CH_3), 157.4, 159.1 (2×C–OH), 170.7 (Ar–CO_2CH_3), 173.1 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3410 (br), 3335 (m), 3002 (m), 2955 (m), 2851 (m), 2480 (w), 1710 (s, C=O), 1439 (s), 1337 (s), 1002 (m), 850 (m), 806 (m), 772 (m), 643 (w). MS (EI, 70 eV): 254 (M^+, 64), 222 (77), 194 (100), 179 (68), 162 (19), 154 (18). Anal. Calcd for $C_{12}H_{14}O_6$ (254.4): C, 56.69; H, 5.55. Found: C, 56.58; H, 5.57.

4.2.7. Methyl 3-chloro-2,4-dihydroxy-6-(2-methoxy-2-oxoethyl)-5-methylbenzoate (**3g**)

Starting with **1g** (0.386 g, 1.25 mmol), **2** (0.156 g, 1.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.242 g, 1.5 mmol), **3g** was isolated as a yellow solid (0.135 g, 47%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.13 (s, 3H, CH_3), 3.64 (s, 3H, $COOCH_3$), 3.83 (s, 3H, CH_2COOCH_3), 3.88 (s, 2H, CH_2COOCH_3), 6.21 (br, 1H, OH), 11.88 (br, 1H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ=12.2 (CH_3), 37.2 (CH_2COOCH_3), 52.0 ($COOCH_3$), 52.4 (CH_2COOCH_3), 106.4, 107.1, 117.1, 134.4, 154.7, 157.4 (C_{Ar}), 171.1 ($COOCH_3$), 171.2 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3256 (w), 2956 (w), 1716 (s), 1648 (m), 1577 (m), 1436 (m), 1326 (s), 1216 (s), 1165 (s), 1001 (m), 962 (m), 808 (m).

GC–MS (EI, 70 eV): m/z (%)=290 ([M^+], ^{37}Cl, 16), 288 ([M^+], ^{35}Cl, 49), 258 (^{37}Cl, 18), 256 (^{35}Cl, 48), 230 (^{37}Cl, 37), 228 (^{35}Cl, 100), 215 (^{37}Cl, 29), 213 (^{35}Cl, 90), 196 (17), 105 (6), 77 (20). HRMS (EI): calcd for $C_{12}H_{13}O_6Cl$ ([M^+], ^{35}Cl): 288.03952; found: 288.03964.

4.2.8. Methyl 2,4-dihydroxy-5-ethyl-6-(methoxycarbonylmethyl)benzoate (**3h**)

Starting with **1h** (0.437 g, 1.44 mmol), **2** (0.174 mg, 1.11 mmol) and $NEt_3\cdot(HF)_3$ (0.358 mg, 2.22 mmol), **3h** was isolated as a white solid (0.125 g, 43%). Reaction time: 20 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=1.04 (t, ^3J=7.4 Hz, 3H, CH_3), 2.52 (q, ^3J=7.4 Hz, 2H, CH_2CH_3), 3.63 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.97 (s, 2H, $CH_2CO_2CH_3$), 6.50 (s, 1H, Ar–H). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=14.3 (CH_2CH_3), 19.7 (CH_2CH_3), 37.0 ($CH_2CO_2CH_3$), 51.8, 52.1 (2×OCH_3), 102.5 (Ar), 106.1 (C–CH_2CH_3), 124.9 (C–$CH_2CO_2CH_3$), 136.9 (C–CO_2CH_3), 161.5, 163.3 (2×C–OH), 172.2 (Ar–CO_2CH_3), 172.3 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3351 (br), 3309 (s), 2957 (m), 1706 (s, C=O), 1656 (s), 1597 (s), 1487 (m), 1440 (m), 1347 (s), 1224 (s), 1080 (s), 970 (m), 849 (m), 792 (m), 639 (w). MS (EI, 70 eV): 268 (M^+, 37), 236 (58), 208 (100), 193 (65), 176 (62), 121 (13). Anal. calcd for $C_{13}H_{16}O_6$: C, 58.21; H 6.01. Found: C, 58.38; H 5.89.

4.2.9. Methyl 5-allyl-2,4-dihydroxy-6-(methoxycarbonylmethyl)benzoate (**3i**)

Starting with **1i** (0.413 mg, 1.31 mmol), **2** (0.195 mg, 1.25 mmol) and $NEt_3\cdot(HF)_3$ (0.402 mg, 2.50 mmol), **3i** was isolated as a deep yellow solid (0.208 g, 60%). Reaction time: 16 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=3.25 (br, 1H, OH), 3.39 (m, 2H, CH_2CH=CH_2), 3.62 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.92 (s, 2H, $CH_2CO_2CH_3$), 4.91 (m, 2H, CH=CH_2), 5.84 (m, 1H, CH=CH_2), 6.42 (s, 1H, Ar–H). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=29.5 ($CH_2CO_2CH_3$), 36.5 (CH_2CH=CH_2), 51.0, 51.4 (CO_2CH_3), 101.5 (Ar), 105.5 (C–CO_2CH_3), 114.0 (C=CH_2), 119.5, 119.5 (C–$CH_2CO_2CH_3$, C–CH=CH_2), 136.4 (C–CH=CH_2), 137.3 (Ar–CO_2CH_3), 160.8, 162.8 (2×C–OH), 169.2 (Ar–CO_2CH_3), 171.3 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3348 (s), 3290 (br), 2987 (w), 2952 (w), 1729 (s, C=O), 1706 (s), 1656 (m), 1601 (s), 1498 (w), 1431 (s), 1325 (s), 1262 (s), 1205 (s), 1153 (s), 1092 (m), 1022 (w), 850 (w), 756 (w), 614 (w). MS (CI, 70 eV): 298 ([M+NH_4]$^+$), 281 ([M+H]$^+$).

4.2.10. Methyl 2,4-dihydroxy-5-(n-butyl)-6-(methoxycarbonylmethyl)benzoate (**3j**)

Starting with **1j** (0.397 mg, 1.20 mmol), **2** (0.174 mg, 1.11 mmol) and $NEt_3\cdot(HF)_3$ (0.359 g, 2.23 mmol), **3j** was isolated as a white solid (0.108 g, 38%). Reaction time: 26 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=0.83 (m, 3H, CH_3), 1.38 (m, 4H, 2×CH_2), 2.60 (m, 2H, Ar–CH_2), 3.62 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.96 (s, 2H, $CH_2CO_2CH_3$), 5.62 (s, 1H, Ar–H), 6.41 (s, 2H, OH). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=14.2 (CH_2CH_3), 23.4, 26.3 ($CH_2CH_2CH_3$, $CH_2CH_2CH_3$), 32.7 (Ar–CH_2), 37.2 ($CH_2CO_2CH_3$), 51.8, 52.1 (2×CO_2CH_3), 102.5 (C–CH_2CH_2), 106.8 (Ar), 123.6 (C–$CH_2CO_2CH_3$), 137.0 (C–CO_2CH_3), 161.7, 163.3 (2×C–OH), 172.2 (Ar–CO_2CH_3), 172.3 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3319 (s), 2957 (m), 2927 (m), 2852 (m), 2469 (w), 1708 (s, C=O), 1651 (s), 1604 (s), 1443 (m), 1423 (m), 1347 (s), 1259 (s), 1155 (m), 1083 (m), 976 (w), 948 (m), 771 (w), 637 (w). MS (EI, 70 eV): 296 (M^+, 63), 265 (23), 264 (49), 253 (23), 236 (31), 221 (100), 204 (27), 189 (71). HRMS: calcd for $C_{15}H_{20}O_6$: 296.1259; found: 296.1259±2 ppm.

4.2.11. Methyl 3-hexyl-4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-benzoate (**3k**)

Starting with **1k** (0.557 g, 1.5 mmol), **2** (0.187 g, 1.2 mmol) and $NEt_3\cdot(HF)_3$ (0.290 g, 1.8 mmol), **3k** was isolated as a colourless solid (0.170 g, 52%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.80 (t, ^3J=6.8 Hz, 3H, $CH_2(CH_2)_4CH_3$), 1.20–1.26 (m, 8H, $CH_2(CH_2)_4CH_3$), 2.43 (t, ^3J=6.8 Hz, 2H, $CH_2(CH_2)_4CH_3$), 3.69 (s, 3H, $COOCH_3$), 3.80 (s, 3H, CH_2COOCH_3), 3.87 (s, 2H, CH_2COOCH_3), 6.10 (s, 1H, CH_{Ar}), 6.56 (s, 1H, OH_{Ar}), 11.16 (br s, 1H, OH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 ($(CH_2)_5CH_3$), 22.6, 26.1, 29.5, 29.8, 31.7 ($(CH_2)_5CH_3$), 36.8 (CH_2COOCH_3), 51.8 ($COOCH_3$), 52.2 (CH_2COOCH_3), 102.9 (CH_{Ar}), 105.5, 128.3, 134.8 (C_{Ar}), 159.9, 162.4 (COH_{Ar}), 171.1 ($COOCH_3$), 173.4 (CH_2COOCH_3). GC–MS (EI, 70 eV): m/z (%)=324 ([M^+], 33), 292 (24), 253 (25), 221 (100), 189 (80), 163 (20), 134 (5), 105 (5), 69 (12). HRMS (EI): calcd for $C_{17}H_{24}O_6$: 324.15674; found: 324.15600.

4.2.12. Methyl 3-hexyl-4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-benzoate (**3l**)

Starting with **1l** (0.465 g, 1.25 mmol), **2** (0.156 g, 1.0 mmol) and $NEt_3\cdot(HF)_3$ (0.242 g, 1.5 mmol), **3l** was isolated as a colourless viscous oil (0.197 g, 56%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.82 (t, ^3J=6.3 Hz, 3H, $CH_2(CH_2)_6CH_3$), 1.18 (m, 12H, $CH_2(CH_2)_6CH_3$), 3.63 (t, ^3J=5.8 Hz, 2H, $CH_2(CH_2)_6CH_3$), 3.69 (s, 3H, $COOCH_3$), 3.79 (s, 3H, CH_2COOCH_3), 3.86 (s, 2H, CH_2COOCH_3), 6.08 (s, 1H, CH_{Ar}), 6.92 (s, 1H, OH_{Ar}), 11.16 (s, 1H, OH_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 ($(CH_2)_7CH_3$), 22.5, 26.0, 29.2, 29.4, 29.7, 29.8, 31.8 ($(CH_2)_5CH_3$), 36.7 (CH_2COOCH_3), 51.7 ($COOCH_3$), 52.1 (CH_2COOCH_3), 102.8 (CH_{Ar}), 105.2, 123.3, 134.6 (C_{Ar}), 160.1, 162.3 (COH_{Ar}), 171.0 ($COOCH_3$), 173.5 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3281 (w), 2923 (w), 2847 (w), 1701 (m), 1651 (m), 1592 (m), 1438 (w), 1329 (m), 1253 (s), 1194 (s), 1152 (s), 1096 (w), 971 (m), 841 (m), 673 (m). GC–MS (EI, 70 eV): m/z (%)=352 ([M^+], 43), 321 (15), 279 (5), 253 (98), 221 (100), 189 (14), 163 (13). HRMS (EI): calcd for $C_{19}H_{28}O_6$: 352.18804; found: 352.18813.

4.2.13. Methyl 5-benzyl-2,4-dihydroxy-6-(methoxycarbonylmethyl)benzoate (**3m**)

Starting with **1m** (0.435 g, 1.19 mmol), **2** (0.107 mg, 0.69 mmol) and $NEt_3\cdot(HF)_3$ (0.221 g, 1.37 mmol), **3m** was isolated as a yellow solid (0.095 g, 42%). Reaction time: 10 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=3.52 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.94 (s, 2H, $CH_2CO_2CH_3$), 4.18 (s, 2H, CH_2Ph), 6.51 (s, 1H, Ar–H), 7.24 (m, 5H, Ph–H), 9.52 (br s, 2H, 2×OH). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=31.6 (Ph–CH_2), 37.6 ($CH_2CO_2CH_3$), 51.8, 52.2 (2×CO_2CH_3), 102.7 (C–CH_2Ph), 106.6 (Ar), 121.5 (C–$CH_2CO_2CH_3$), 126.5, 128.8, 129.0 (5×Ph–CH), 138.5 (C–CO_2CH_3), 141.4 (Ph–C), 161.9, 163.7 (C–OH), 171.8 (Ar–CO_2CH_3), 172.1 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3353 (s), 3310 (br), 3085 (w), 3062 (w), 2956 (w), 1704 (s, C=O), 1651 (s), 1606 (s), 1594 (s), 1492 (m), 1439 (m), 1424 (m), 1386 (s), 1333 (s), 1253 (s), 1188 (s), 1153 (m), 1008 (w), 845 (m), 735 (m), 698 (m), 522 (w). MS (EI, 70 eV): 330 (M^+, 42), 329 (9), 298 (43), 270 (21), 238 (100), 237 (48).

4.2.14. Methyl 4,6-dihydroxy-3-methoxy-6-(methoxycarbonylmethyl)benzoate (**3n**)

Starting with **1n** (0.342 g, 1.18 mmol), **2** (0.166 g, 0.90 mmol) and $NEt_3\cdot(HF)_3$ (0.292 mg, 1.81 mmol), **3n** was isolated as a yellow solid (0.087 g, 40%). Reaction time: 18 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=3.58 (s, 3H, OCH_3), 3.64 (s, 2H, $CH_2CO_2CH_3$), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 6.58 (s, 1H, Ar–H), 8.58 (s, 1H, OH). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=33.1 ($CH_2CO_2CH_3$), 51.9, 51.9 (2×CO_2CH_3), 56.4 ($COCH_3$), 61.0 ($COCH_3$), 100.7 (Ar–C), 116.1 (C–$CH_2CO_2CH_3$), 128.6 (C–CO_2CH_3), 140.8 (C–OH), 152.9 ($COCH_3$), 155.0 ($COCH_3$), 167.8 (Ar–CO_2CH_3), 171.5 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3341 (m), 3290 (br), 3007 (w), 3958 (w), 2851 (w), 1741 (m, C=O), 1655 (w), 1618 (w), 1440 (m), 1336 (br), 1079 (s), 801 (m), 573 (w), 470 (m). MS (EI, 70 eV): 284 (M^+, 100), 270 (1), 253 (55), 237 (96), 225 (39), 209 (61), 195 (12), 181 (36). HRMS (EI): calcd for $C_{13}H_{16}O_7$: 284.0896; found: 284.0896±2 ppm.

4.2.15. Methyl 4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-3-phenoxy-benzoate (**3o**)

Starting with **1o** (0.630 g, 1.8 mmol), **2** (0.225 g, 1.4 mmol) and $NEt_3\cdot(HF)_3$ (0.348 g, 2.2 mmol), **3o** was isolated as a yellow viscous

oil (0.278 g, 58%). Reaction time: 18 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.48 (s, 3H, COO*CH*$_3$), 3.78 (s, 2H, *CH*$_2$COOCH$_3$), 3.79 (s, 3H, CH$_2$COO*CH*$_3$), 6.54 (br s, 1H, CH$_{Ar}$), 6.78–6.82 (m, 3H, CH$_{Ph}$), 6.97–7.00 (m, 1H, CH$_{Ph}$), 7.17–7.20 (m, 1H, CH$_{Ph}$), 7.24 (br s, 1H, OH$_{Ar}$), 11.45 (br s, 1H, OH$_{Ar}$). ^{13}C NMR (62 MHz, $CDCl_3$): δ=34.2 (*CH*$_2$COOCH$_3$), 51.8 (COO*CH*$_3$), 51.9 (CH$_2$COO*CH*$_3$), 103.9 (CH$_{Ar}$), 105.4 (C$_{Ar}$), 114.9 (2CH$_{Ph}$), 123.1 (CH$_{Ph}$), 129.9 (2CH$_{Ph}$), 130.4, 133.9 (C$_{Ar}$), 154.8 (C$_{Ph}$), 157.1, 162.4 (COH$_{Ar}$), 170.7 (*C*OOCH$_3$), 171.2 (CH$_2$*C*OOCH$_3$). IR (neat, cm^{-1}): $\tilde{\nu}$=3350 (w), 2952 (w), 1734 (m), 1658 (m), 1589 (m), 1489 (m), 1436 (m), 1329 (m), 1154 (s), 1022 (m), 978 (m), 750 (s), 688 (s), 540 (m). MS (EI, 70 eV): *m*/*z* (%)=332 ([M$^+$], 100), 300 (70), 268 (43), 240 (84), 212 (32), 191 (16), 171 (13), 109 (12), 77 (17), 69 (33). HRMS (EI): calcd for $C_{17}H_{16}O_7$: 332.08905; found: 332.08918.

4.2.16. Methyl 4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-3-(2-methylphenoxy)benzoate (**3p**)

Starting with **1p** (0.657 g, 1.8 mmol), **2** (0.225 g, 1.4 mmol) and $NEt_3\cdot(HF)_3$ (0.348 g, 2.2 mmol), **3p** was isolated as a yellow viscous oil (0.249 g, 50%). Reaction time: 17 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.28 (s, 3H, CH$_{3Tol}$), 3.42 (s, 3H, COO*CH*$_3$), 3.71 (s, 2H, *CH*$_2$COOCH$_3$), 3.72 (s, 2H, CH$_2$COO*CH*$_3$), 6.02 (br s, 1H, OH$_{Ar}$), 6.32 (d, ^3J=6.8 Hz, 1H, CH$_{Tol}$), 6.49 (s, 1H, CH$_{Ar}$), 6.80–6.86 (m, 1H, CH$_{Tol}$), 7.06–7.09 (m, 2H, CH$_{Tol}$), 11.38 (br s, 1H, OH$_{Ar}$). ^{13}C NMR (62 MHz, $CDCl_3$): δ=16.1 (CH$_{3Tol}$), 34.1 (*CH*$_2$COOCH$_3$), 51.7 (COO*CH*$_3$), 51.9 (CH$_2$COO*CH*$_3$), 103.8 (CH$_{Ar}$), 105.3 (C$_{Ar}$), 112.4, 122.6 (CH$_{Tol}$), 126.0 (C$_{Ar}$), 127.1 (C$_{Tol}$), 130.1, 131.4 (CH$_{Tol}$), 134.2 (C$_{Tol}$), 154.8 (C$_{Ar}$), 155.2, 162.2 (COH$_{Ar}$), 170.7 (*C*OOCH$_3$), 171.2 (CH$_2$*C*OOCH$_3$). IR (neat, cm^{-1}): $\tilde{\nu}$=3368 (w), 2952 (w), 1735 (s), 1658 (m), 1592 (m), 1489 (m), 1435 (m), 1329 (m), 1222 (s), 1187 (s), 1018 (m), 983 (m), 844 (m), 750 (s). MS (EI, 70 eV): *m*/*z* (%)=346 ([M$^+$], 100), 314 (56), 282 (22), 271 (44), 254 (42), 226 (13), 193 (29), 105 (8), 91 (21). HRMS (EI): calcd for $C_{18}H_{18}O_7$: 346.10470; found: 346.10437.

4.2.17. Methyl 4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-3-(3-methylphenoxy)benzoate (**3q**)

Starting with **1q** (0.951 g, 2.5 mmol), **2** (0.312 g, 2.0 mmol) and $NEt_3\cdot(HF)_3$ (0.242 g, 3.0 mmol), **3q** was isolated as a slightly yellow solid (0.336 g, 48%), mp=130–133 °C. Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.15 (s, 3H, CH$_{3Tol}$), 3.43 (s, 3H, COO*CH*$_3$), 3.71 (s, 3H, CH$_3$COO*CH*), 3.73 (s, 2H, *CH*$_2$COOCH$_3$), 6.14 (br s, 1H, OH$_{Ar}$), 6.47 (s, 1H, CH$_{Ar}$), 6.50–6.54 (m, 2H, CH$_{Tol}$), 6.72 (d, ^3J=7.6 Hz, 1H, CH$_{Tol}$), 7.01 (d, ^3J=8.4 Hz, 1H, CH$_{Tol}$), 11.39 (br s, 1H, OH$_{Ar}$). ^{13}C NMR (62 MHz, $CDCl_3$): δ=21.3 (CH$_{3Tol}$), 34.1 (*CH*$_2$COOCH$_3$), 51.7 (COO*CH*$_3$), 51.8 (CH$_2$COO*CH*$_3$), 103.8 (CH$_{Ar}$), 105.1 (C$_{Ar}$), 111.8, 115.4, 123.7, 129.5 (CH$_{Tol}$), 130.3 (*C*CH$_{3Tol}$), 134.1, 140.1 (C$_{Ar}$), 154.9 (C$_{Tol}$), 157.1, 162.2 (COH$_{Ar}$), 170.7 (*C*OOCH$_3$), 171.4 (CH$_2$*C*OOCH$_3$). IR (neat, cm^{-1}): $\tilde{\nu}$=3239 (w), 2948 (w), 1700 (s), 1655 (m), 1595 (m), 1438 (m), 1328 (m), 1228 (s), 1180 (s), 1105 (m), 983 (m), 844 (m), 770 (s). GC–MS (EI, 70 eV): *m*/*z* (%)=346 ([M$^+$], 100), 314 (51), 282 (35), 271 (51), 254 (39), 226 (19), 191 (18), 157 (4), 129 (8), 91 (18). HRMS (EI): calcd for $C_{18}H_{18}O_7$: 346.10470; found: 346.10525.

4.2.18. Methyl 4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-3-(4-methylphenoxy)benzoate (**3r**)

Starting with **1r** (0.951 g, 2.5 mmol), **2** (0.312 g, 2.0 mmol) and $NEt_3\cdot(HF)_3$ (0.483 g, 3.0 mmol), **3r** was as a brown solid (0.380 g, 54%), mp=116–124 °C. Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=2.15 (s, 3H, CH$_{3Tol}$), 3.46 (s, 3H, COO*CH*$_3$), 3.73 (s, 3H, CH$_2$COO*CH*$_3$), 3.78 (s, 2H, *CH*$_2$COOCH$_3$), 4.77 (br s, 1H, OH$_{Ar}$), 6.37 (s, 1H, CH$_{Ar}$), 6.59 (d, ^3J=8.5 Hz, 2H, CH$_{Tol}$), 6.93 (d, ^3J=8.4 Hz, 2H, CH$_{Tol}$). ^{13}C NMR (62 MHz, CD_3OD): δ=20.5 (CH$_{3Tol}$), 34.6 (*CH*$_2$COOCH$_3$), 52.3 (COO*CH*$_3$), 52.5 (CH$_2$COO*CH*$_3$), 104.4 (CH$_{Ar}$), 105.1 (C$_{Ar}$), 115.7 (2CH$_{Tol}$), 130.7 (2CH$_{Tol}$), 132.0 (C$_{Ar}$), 132.2 (*C*CH$_{3Tol}$), 136.4 (C$_{Ar}$), 157.3 (COH$_{Ar}$), 157.8 (C$_{Tol}$), 162.8 (COH$_{Ar}$), 172.1 (*C*OOCH$_3$), 173.5 (CH$_2$*C*OOCH$_3$). IR (neat, cm^{-1}): $\tilde{\nu}$=3268 (w), 2434 (w), 1702 (m), 1645 (m), 1610 (m), 1507 (m), 1440 (m), 1341 (m), 1217 (s), 1102 (m), 990 (m), 821 (s), 773 (m). GC–MS (EI, 70 eV): *m*/*z* (%)=346 ([M$^+$], 100), 314 (30), 282 (32), 271 (49), 254 (43), 239 (35), 239 (35), 191 (15), 157 (5), 129 (9), 91 (16), 69 (21). HRMS (EI): calcd for $C_{18}H_{18}O_7$: 346.10470; found: 346.10523.

4.2.19. Methyl 2,4-dihydroxy-5-benzyloxy-6-(methoxycarbonylmethyl)benzoate (**3s**)

Starting with **1s** (0.676 g, 1.78 mmol), **2** (0.213 mg, 1.37 mmol) and $NEt_3\cdot(HF)_3$ (0.440 mg, 2.82 mmol), **3s** was isolated as a yellow solid (0.073 g, 16%). On a 50 mmol scale, the yield was increased to 44%. Reaction time: 21 h (20 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.63 (s, 3H, OCH$_3$), 3.89 (s, 3H, OCH$_3$), 4.03 (s, 2H, C*H*$_2$CO$_2$CH$_3$), 4.84 (s, 2H, COCH$_2$Ph), 6.08 (br s, 1H, OH), 6.44 (s, 1H, Ar–H), 7.41 (m, 5H, Ph–H), 11.48 (s, 1H, OH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=34.5 (*CH*$_2$CO$_2$CH$_3$), 51.9, 52.0 (2×OCH$_3$), 77.0 (COCH$_2$Ph), 103.2 (Ar), 104.6 (*C*–CH$_2$CO$_2$CH$_3$), 128.3, 128.9, 128.9 (5×PhC), 129.5 (ArC–OCH$_2$), 136.1 (Ph–*C*CH$_2$), 138.8 (*C*–CO$_2$CH$_3$), 155.2, 161.7 (2×C–OH), 170.8 (C–*C*O$_2$CH$_3$), 172.2 (CH$_2$*C*O$_2$CH$_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3267 (s, OH), 3071 (w), 2956 (m), 2875 (w), 1716 (s, C=O), 1657 (s), 1618 (w), 1592 (w), 1504 (m), 1441 (m), 1336 (s), 1258 (s), 1225 (s), 1201 (s), 1101 (s), 996 (s), 984 (s), 945 (m), 856 (w), 806 (w), 769 (m), 696 (m), 602 (w), 508 (w). MS (EI, 70 eV): 346 (M$^+$, 24), 255 (34), 223 (42), 191 (47), 91 (100).

4.2.20. Methyl 4,6-dihydroxy-2-(2-methoxy-2-oxoethyl)-3-(phenylsulfanyl)benzoate (**3t**)

Starting with **1t** (0.955 g, 2.5 mmol), **2** (0.312 g, 2.0 mmol) and $NEt_3\cdot(HF)_3$ (0.483 g, 3.0 mmol), **3t** was isolated as a reddish viscous oil (0.290 g, 41%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.47 (s, 3H, COO*CH*$_3$), 3.80 (s, 3H, CH$_2$COO*CH*$_3$), 4.27 (s, 2H, *CH*$_2$COOCH$_3$), 6.61 (s, 1H, CH$_{Ar}$), 6.91–6.95 (m, 2H, CH$_{Ph}$), 7.07–7.11 (m, 1H, CH$_{SPh}$), 7.11–7.16 (m, 2H, CH$_{SPh}$), 7.18 (br s, 1H, OH$_{Ar}$), 11.69 (br s, 1H, OH$_{Ar}$). ^{13}C NMR (62 MHz, $CDCl_3$): δ=39.9 (*CH*$_2$COOCH$_3$), 51.8 (COO*CH*$_3$), 52.2 (CH$_2$COO*CH*$_3$), 102.8 (CH$_{Ar}$), 107.6, 111.2 (C$_{Ar}$), 126.2 (2CH$_{SPh}$), 126.3 (CH$_{SPh}$), 129.3 (2CH$_{SPh}$), 134.4 (C$_{SPh}$), 143.9 (C$_{Ar}$), 162.2, 166.1 (COH$_{Ar}$), 170.6 (*C*OOCH$_3$), 171.1 (CH$_2$*C*OOCH$_3$). GC–MS (EI, 70 eV): *m*/*z* (%)=348 ([M$^+$], 100), 316 (25), 284 (32), 256 (82), 228 (11), 207 (8), 171 (10), 128 (16), 69 (16). HRMS (EI): calcd for $C_{17}H_{16}O_6S$: 348.0662; found: 348.06559.

4.2.21. Methyl 4-hydroxy-6-methyl-2-(methoxycarbonylmethyl)benzoate (**3u**)

Starting with **1u** (0.323 g, 1.32 mmol), **2** (0.163 mg, 1.04 mmol) and $NEt_3\cdot(HF)_3$ (0.337 g, 2.09 mmol), **3u** was isolated as a white solid (0.130 g, 55%). Reaction time: 18 h (20 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.34 (s, 3H, CH$_3$), 3.68 (s, 3H, OCH$_3$), 3.71 (s, 3H, OCH$_3$), 3.92 (s, 2H, C*H*$_2$CO$_2$CH$_3$), 5.53 (s, 1H, OH), 6.53–6.61 (m, 2H, 2×Ar–H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT): δ=21.0 (CH$_3$), 39.9 (*CH*$_2$CO$_2$CH$_3$), 51.7, 52.1 (2×OCH$_3$), 115.8, 116.7 (2×Ar), 125.1 (*C*–CH$_3$), 134.9 (*C*–CH$_2$CO$_2$CH$_3$), 139.8 (*C*–CO$_2$CH$_3$), 156.8 (C–OH), 169.3 (Ar–*C*O$_2$CH$_3$), 171.9 (CH$_2$*C*O$_2$CH$_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3340 (br), 3332 (s), 2954 (w), 2932 (w), 1711 (s, C=O), 1616 (s), 1440 (m), 1365 (m), 1322 (s), 1291 (s), 1257 (s), 1217 (s), 1165 (s), 1103 (m), 1003 (w), 909 (w), 855 (w), 748 (w). MS (EI, 70 eV): 238 (M$^+$, 60), 207 (75), 206 (100), 179 (94), 163 (90).

4.2.22. Methyl 4-hydroxy-2-methoxycarbonylmethyl-6-phenylbenzoate (**3v**)

Starting with **1v** (0.277 mg, 0.90 mmol), **2** (0.100 g, 0.64 mmol) and $NEt_3\cdot(HF)_3$ (0.207 g, 1.28 mmol), **3v** was isolated as a yellow oil (0.087 g, 46%). Reaction time: 28 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=3.37 (s, 3H, OCH$_3$), 3.49 (s, 3H, OCH$_3$), 3.78 (s, 2H, C*H*$_2$CO$_2$CH$_3$), 6.78 (d, ^4J=1.5 Hz, 1H, Ar–H), 6.82 (d, ^4J=1.5 Hz, 1H,

Ar–H), 7.31 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, acetone-d_6): δ=38.6 ($CH_2CO_2CH_3$), 50.8, 51.2 (2×OCH_3), 115.5, 116.9 (2×Ar), 123.7, 127.3, 127.9, 128.2, 135.3 (5×Ph–C), 141.2 (*C*–$CH_2CO_2CH_3$), 142.7 (*C*–CO_2CH_3), 158.2 (*C*–Ph), 169.1 (Ar–CO_2CH_3), 171.8 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3378 (s), 3310 (br), 2977 (w), 2952 (m), 1737 (s, C=O), 1716 (s), 1605 (s), 1589 (s), 1454 (s), 1431 (s), 1327 (s), 1281 (s), 1195 (s), 1121 (s), 1081 (m), 1019 (m), 962 (m), 868 (w), 797 (m), 771 (m), 702 (m). MS (CI, 70 eV): 300 (M^+, 7), 255 (17), 225 (12), 147 (11), 115 (9), 105 (100), 77 (52), 43 (24).

4.2.23. Methyl 5,6-dimethyl-4-hydroxy-2-(methoxycarbonylmethyl)benzoate (**3w**)

Starting with **1w** (0.249 g, 0.96 mmol), **2** (0.104 g, 0.70 mmol) and $NEt_3{\cdot}(HF)_3$ (0.292 g, 1.81 mmol), **3w** was isolated as a white solid (0.078 g, 44%). Reaction time: 22 h (20 °C). ^{1}H NMR (250 MHz, acetone-d_6): δ=2.08 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.51 (s, 2H, $CH_2CO_2CH_3$), 3.62 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.71 (s, 1H, Ar–H), 8.64 (s, 1H, OH). ^{13}C NMR (62.9 MHz, acetone-d_6, APT): δ=10.8 (CH_3), 16.6 (CH_3), 38.8 ($CH_2CO_2CH_3$), 50.9, 51.1 (2×CO_2CH_3), 114.8 (Ar), 122.3 (*C*–$CH_2CO_2CH_3$), 126.0 (*C*–CO_2CH_3), 130.6 (*C*CH_3), 136.1 (*C*CH_3), 155.8 (C–OH), 169.6 (Ar–CO_2–CH_3), 171.0 (CH_2–CO_2–CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$=3352 (s), 3024 (w), 2993 (w), 2950 (m), 1717 (s, C=O), 1598 (s), 1437 (s), 1418 (s), 1360 (s), 1317 (s), 1291 (s), 1232 (s), 1178 (s), 1154 (s), 1096 (m), 1060 (m), 999 (w), 959 (w), 866 (w), 779 (w), 731 (w), 684 (w), 558 (w). MS (EI, 70 eV): 252 (M^+, 63), 220 (99), 292 (97), 177 (100), 167 (30).

4.2.24. Methyl 4-hydroxy-2-methyl-3-methoxycarbonyl-6-(methoxycarbonylmethyl)benzoate (**3x**)

Starting with **1x** (0.327 g, 1.08 mmol), **2** (0.133 g, 0.85 mmol) and $NEt_3{\cdot}(HF)_3$ (0.274 g, 1.70 mmol), **3x** was isolated as a white solid (0.045 g, 20%). Reaction time: 18 h (20 °C). ^{1}H NMR (250 MHz, CD_3OD): δ=2.43 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.64 (s, 2H, $CH_2CO_2CH_3$), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.76 (s, 1H, Ar–H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=20.6 (CH_3), 28.9, 29.7 (2×Ar–CO_2CH_3), 39.6 ($CH_2CO_2CH_3$), 112.2 ($CH_2CO_2CH_3$), 118.1 (Ar), 125.3, 127.6 (2×*C*–CO_2CH_3), 138.0 (*C*–CH_3), 139.4 (*C*–$CH_2CO_2CH_3$), 162.8 (C–OH), 169.4, 170.4 (2×Ar–CO_2CH_3), 171.4 ($CH_2CO_2CH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$=3307 (s), 3043 (w), 3002 (m), 2956 (s), 2934 (w), 2855 (m), 1705 (s, C=O), 1607 (s), 1435 (s), 1365 (s), 1321 (s), 1235 (s), 1117 (s), 1051 (s), 946 (m), 866 (m), 752 (m), 649 (m). MS (EI, 70 eV): 296 (M^+, 60), 264 (100), 239 (14), 236 (19), 232 (53), 204 (66). HRMS (EI): calcd for $C_{14}H_{16}O_7$: 296.0896; found: 296.0896±2 ppm.

4.2.25. Methyl 3-chloro-4-hydroxy-6-(2-methoxy-2-oxoethyl)-2-methylbenzoate (**3y**)

Starting with **1y** (0.349 g, 1.25 mmol), **2** (0.156 g, 1.0 mmol) and $NEt_3{\cdot}(HF)_3$ (0.242 g, 1.5 mmol), **3y** was isolated as a reddish viscous oil (0.114 g, 42%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.31 (s, 3H, CH_3), 3.59 (s, 2H, CH_2COOCH_3), 3.61 (s, 3H, $COOCH_3$), 3.62 (s, 1H, OH_{Ar}), 3.66 (s, 3H, CH_2COOCH_3), 6.32 (s, 1H, CH_{Ar}). ^{13}C NMR (62 MHz, $CDCl_3$): δ=26.3 (CH_3), 35.6 (CH_2COOCH_3), 51.7 ($COOCH_3$), 51.8 (CH_2COOCH_3), 82.7 (C_{Ar}), 124.3 (CH_{Ar}), 144.4, 165.2, 165.2 (C_{Ar}), 170.1 (COH_{Ar}), 198.9 (2CO). IR (neat, cm^{-1}): $\tilde{\nu}$=3002 (w), 2954 (w), 1731 (s), 1649 (w), 1435 (m), 1356 (m), 1327 (m), 1252 (m), 1166 (s), 1012 (m), 859 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=274 ([M^+], ^{37}Cl, 9), 272 ([M^+], ^{35}Cl, 25), 242 (^{37}Cl, 40), 240 (^{35}Cl, 100), 211 (^{37}Cl, 15), 209 (^{35}Cl, 46), 197 (5), 180 (6), 154 (4), 125 (5), 89 (11), 77 (6). HRMS (EI): calcd for $C_{12}H_{13}ClO_5$ ([M^+], ^{35}Cl): 272.04460; found: 272.04423.

4.2.26. Methyl 3-(4-ethoxyphenoxy)-4-hydroxy-6-(3-methoxy-2-oxoethyl-2-methyl)benzoate (**3z**)

Starting with **1z** (0.761 g, 2.0 mmol), **2** (0.251 g, 1.6 mmol) and $NEt_3{\cdot}(HF)_3$ (0.241 g, 1.5 mmol), **3z** was isolated as a red viscous oil (0.359 g, 48%). Reaction time: 14 h (40 °C). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.27 (t, ^3J=6.9 Hz, 3H, OCH_2CH_3), 2.07 (s, 3H, CH_{3Ar}), 3.57 (s, 3H, $COOCH_3$), 3.61 (s, 3H, CH_2COOCH_3), 3.71 (s, 2H, CH_2COOCH_3), 3.86 (q, ^3J=6.9 Hz, 2H, OCH_2CH_3), 6.38 (s, 1H, CH_{Ar}), 6.68 (m, 2H, CH_{Ph}), 6.70 (m, 2H, CH_{Ph}), 6.78 (s, 1H, OH_{Ar}). ^{13}C NMR (62 MHz, $CDCl_3$): δ=14.7 (CH_{3Ar}), 25.9 (OCH_2CH_3), 34.2 (CH_2COOCH_3), 51.5 ($COOCH_3$), 51.9 (CH_2COOCH_3), 63.7 (OCH_2CH_3), 95.2 (C_{Ar}), 115.3 (2CH_{Ph}), 115.8 (C_{Ar}), 117.3 (2CH_{Ph}), 127.5 (CH_{Ar}), 145.1, 147.8 (C_{Ar}), 150.3, 154.5 (C_{Ph}), 165.5 (COH_{Ar}), 170.4 ($COOCH_3$), 201.5 (CH_2COOCH_3). IR (neat, cm^{-1}): $\tilde{\nu}$=3434 (w), 2953 (w), 1735 (s), 1502 (s), 1435 (m), 1194 (s), 1140 (m), 1044 (m), 825 (m), 774 (w). GC–MS (EI, 70 eV): *m*/*z* (%)=374 ([M^+], 46), 342 (81), 313 (100), 299 (3), 271 (7), 253 (6). HRMS (EI): calcd for $C_{20}H_{22}O_7$: 374.13600; found: 374.13532.

4.2.27. Methyl 3-(4-chlorophenoxy)-4-hydroxy-6-(2-methoxy-2-oxoethyl)-2-methylbenzoate (**3aa**)

Starting with **1aa** (0.560 g, 1.60 mmol) and **2** (0.200 g, 1.28 mmol), **3aa** was isolated as a white solid (0.210 g, 45%). Reaction time: 18 h (20 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.09 (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 3.70 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.92 (s, 1H, OH), 6.78 (d, 2H, *J*=9.0 Hz, ArH), 6.81 (s, 1H, ArH), 7.22 (d, 2H, *J*=9.0 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9 (CH_3), 29.4 (CH_2), 51.9, 52.1 (OCH_3), 116.1 (2CAr), 116.8 (C_{Ar}), 126.4, 127.5 (C), 129.7 (2C_{Ar}), 131.2, 131.7, 138.6, 150.1, 155.4, 168.6, 171.4 (C). IR (KBr): $\tilde{\nu}$=3309 (s), 2945 (m), 1707 (s), 1612 (m), 1487 (s), 1337 (s), 1092 (w), 1009 (m), 956 (w), 828 (s), 760 (w). GC–MS (EI, 70 eV): *m*/*z* (%): 366 (M^+, ^{37}Cl, 13), 364 (M^+, ^{35}Cl, 35), 332 (42), 305 (65), 289 (100). Anal. Calcd for $C_{18}H_{17}ClO_6$ (364.78): C, 59.27; H, 4.70. Found: C, 58.82; H, 4.61.

4.2.28. Methyl 3-(4-cyanophenoxy)-4-hydroxy-6-(2-methoxy-2-oxoethyl)-2-methylbenzoate (**3ab**)

Starting with **1ab** (0.380 g, 1.07 mmol) and **2** (0.110 g, 0.85 mmol), **3ab** was isolated as a white solid (0.180 g, 56%). Reaction time: 18 h (20 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.04 (s, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.67 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 6.83 (s, 1H, ArH), 6.91 (d, 2H, *J*=8.9 Hz, ArH), 7.75 (d, 2H, *J*=8.9 Hz, ArH), 10.31 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.3 (CH_3), 38.7 (CH_2), 51.6, 51.7 (OCH_3), 105.1 (C), 116.6, 118.5 (CH_{Ar}), 119.8, 125.7, 131.8, 132.4 (C), 135.2 (CH_{Ar}), 138.7, 151.8, 161.7, 168.8, 171.9 (C). IR (KBr): $\tilde{\nu}$=3435 (m), 2949 (w), 1743 (s), 1709 (s), 1601 (m), 1426 (w), 1328 (s), 1235 (s), 1162 (s), 1057 (w), 842 (m), 759 (w), 546 (m). MS (CI): 356 ([M+1]$^+$). Anal. Calcd for $C_{19}H_{17}NO_6$ (355.34): C, 64.22; H, 4.82; N, 3.94. Found: C, 64.48; H, 5.00; N, 3.98.

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References and notes

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