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Access to a new family of medium ring aromatic lactones

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Abstract—We report a new method for preparation of hydroxyacids as precursors of benzolactones using a simple and an efficient electrochemical step. This gives in only four steps six- to eleven-membered lactones with high isolated yields from conveniently substituted aryl bromides. The lactonisation was performed according to the Yamamoto's process.

1. Introduction

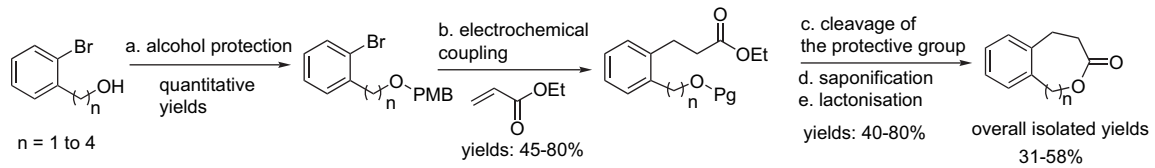
The development of new methods for the construction of hetero- and carbo-cyclic medium ring systems has been a long standing goal to organic chemists. Among the targeted structures, medium ring lactones are of interest as backbones of many bioactive compounds like antibiotics.[1] Their access is staying difficult despite number of cyclisation methods.[2] Our current investigations have focused on the preparation of medium ring benzolactones, which are core structures of compounds like Salicylihalamide A, a potential anticancer drug.[3] As a general feature, these benzolactones have a non-conjugated carbonyl, and therefore, are not obtainable through conventional methods. We have already reported a method for preparation of the precursor hydroxyacid, using an efficient electrochemical C–C bond forming step (Scheme 1).[4]

2. Results and discussion

In this approach, the starting material bears the alcohol function, while the carboxylic group is introduced through the electrochemical step. This method was used to prepare seven- to ten-membered benzolactones in good yields. However, this strategy requires five steps from the alcohol, which may also be eventually commercially unavailable, and including the protection–deprotection of the alcohol (respectively, steps **a** and **c** in Scheme 1).

To improve the efficiency of the synthesis, we thought of avoiding the alcohol protection step. This can be done by having a carbonyl group as an alcohol precursor. Based on this, the carbonyl group should be first introduced, that requires it being compatible with the electrochemical step, or, alternatively, introduced through the electrochemical step conducted on a starting compound bearing a carboxylic group. These two pathways have been explored and compared in this study. The first run involved 2-bromophenylacetone as the starting material in the electrochemical coupling with ethyl acrylate. As shown in Scheme 2, the unexpected bicyclic compound **1** was only formed as a result of a tandem reaction involving the favoured nucleophilic addition to the carbonyl (Scheme 2). Such a ring forming tandem reaction has already been observed,[5] and cannot be avoided whatever the reaction parameters are.

In view of this result, we chose to reverse the order of insertion of the functional groups, i.e., first the carboxylic group by a chemical step if the starting compound is not commercially available, then the carbonyl in the electrochemical coupling. We checked this route with the ester **2** and methylvinylketone (MVK) (Scheme 3). We obtained the formation of the products **3** and **4**. However, the reduction product **4** is



Scheme 1.

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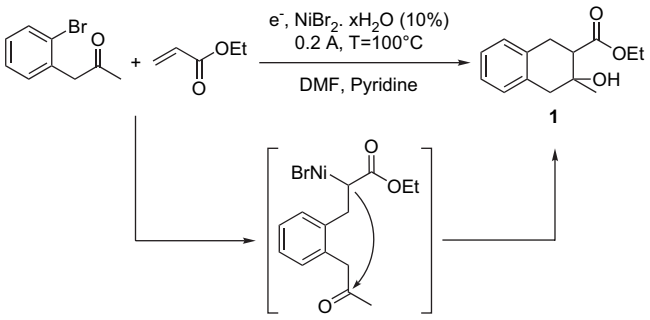


Scheme 2.

the major isolated compound (43%). Interestingly, no cyclisation has occurred.

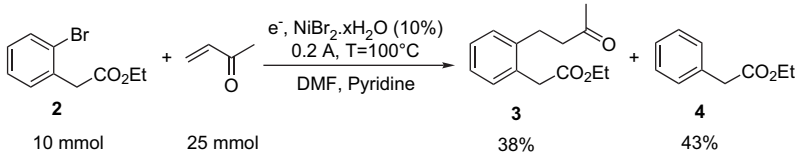
Compound **5**, which was prepared by a Wittig reaction, was next involved in the electrochemical coupling with MVK. The purpose for this study was to check whether the conjugated double bond would react or not in the reaction conditions, for the reason that, it could be necessary to keep it as such to have it in the final compound, or simply not to have it reduced in the early stage, but later along with the ketone group (see below). Actually, this reaction ended with the formation of a 1/1 mixture (GC) of **6** and **7** (not isolated), as reported in Scheme 4.

To obtain **6** selectively, and without **7**, we tuned several reaction parameters (solvent DMF–ACN instead of DMF–Pyridine, temperature, etc.) and notably found that the use of a large amount of MVK (ca. 10 equiv instead of 2.5 vs ArX) as well as of a higher amount of nickel catalyst by generating nickel salts from the anode, either stainless steel or (64/36) iron/nickel rod, can quite favourably improve the yield and the selectivity. The effect of these parameters can be understood on the basis of the mechanism given in Scheme 5.

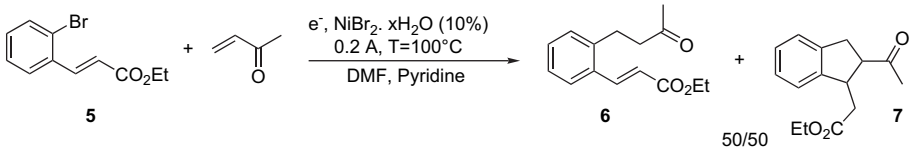
The formation of **7** along with **6** indicates that, as shown in Scheme 5, the key intermediate (I) can reversibly evolve into intermediate (II) by addition to the C–C double bond. In addition, (II) can be assumed to be at least as stable as (I). This would account for the formation of **7** in significant amount, and for the need for some more nickel catalysts than usually required in order to improve the yield of **6**. Similar effects have already been mentioned.[6] So, having a large excess of MVK as both reagent and ligand to shift the equilibrium back to (I) enabled to obtain **6** in 63% isolated yield, and without even traces of compound **7**.

According to this procedure, we could develop a new approach to the aimed benzolactones in a shorter sequence than the one in the previous method.[4] This is summarised in Scheme 6.

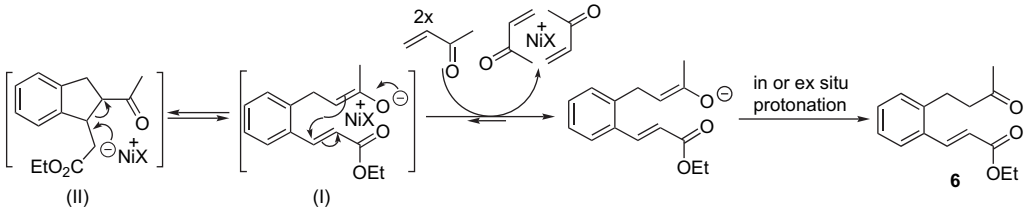
We first prepared a series of commercially unavailable *ortho*-bromoesters (ethyl *ortho*-bromophenylalkenoates) from either *ortho*-bromo-2-phenylacetic acid (for n=1 and n'=0) or *ortho*-bromobenzaldehyde (for n=0, 1 and n'=0–2). Thus, compound **2** was prepared by esterification of the corresponding acid.[7] Compounds corresponding to n=0, 1 and n'=0–2 were prepared by Wittig or Wadsworth–Emmons methods as described by Gibson[8] (**5** and **10**), Jordis[9] (**9**) and Touchard[10] (**8**). Also, to examine the possibility of having medium ring lactones with double C–C bonds, we have prepared the (*E*)-(**5**) and (*Z*)-(**8**) isomers of ethyl 3-(2-bromophenyl)prop-2-enoate.



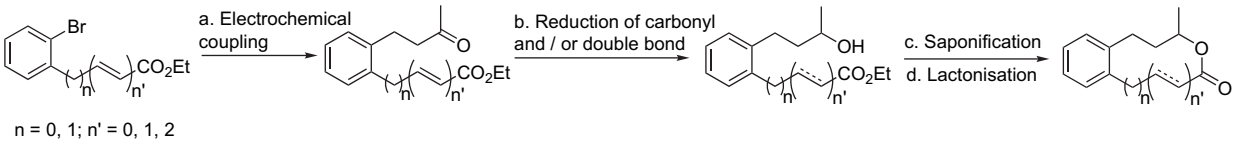
Scheme 3.



Scheme 4.

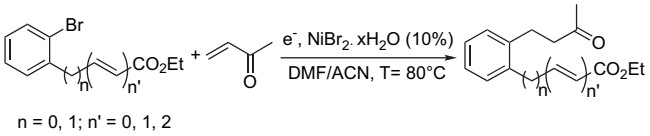


Scheme 5.



Scheme 6.

The next step was the electrochemical coupling with MVK (Scheme 7) using reaction conditions described above. Yields are given in Table 1.



Scheme 7.

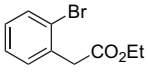
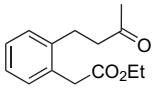
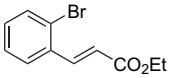
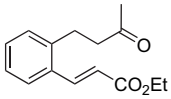
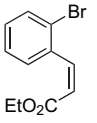
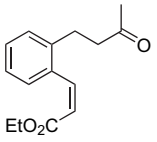
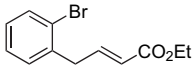
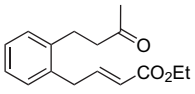
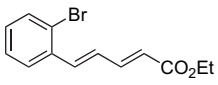
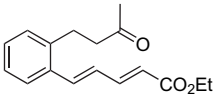
Isolated yields are good and show that the steric *ortho* effect has only a slight influence on the results in agreement with our previous results.[5] No internal tandem addition was observed whatever the starting ester was. Of the two stereoisomers **5** and **8** (see Table 1, entries 2 and 3) the *Z*-isomer gives a lower yield along with the formation of more of the reduced product of the C-halogen bond (ArH). Access to primary alcohols would require acrolein as substrate. However, previous investigations have shown that reactions involving acrolein are unsuccessful, and that its diethyl acetal can be used instead.[11] This gives the expected aldehyde **14**, after hydrolysis of the adduct, with a yield in agreement with our previous investigations[11] (Scheme 8).

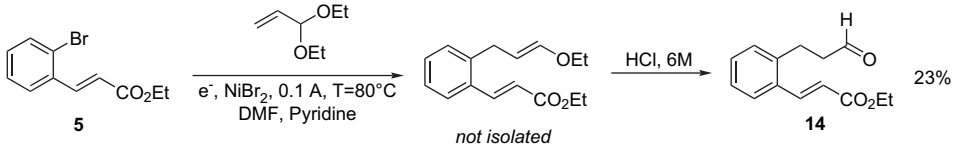
Hydroxyesters were obtained by reduction of the carbonyl. The keto-esters containing a C–C double bond can also be reduced selectively either at the carbonyl of the ketone (reduction by $NaBH_4$)[12] or at both the carbonyl and the C–C double bond by reaction of $NiCl_2/NaBH_4$ in MeOH, at 0 °C to room temperature, as described by Narisada.[13] Results are shown in Table 2.

The two final steps were conducted (Scheme 9) as in our previous paper.[4] Hydroxyesters were converted to the corresponding hydroxyacids by saponification in KOH–dioxane at reflux (quantitative yields).[14] Lactones were obtained from hydroxyacids by the efficient Yamamoto's process[15] using $Sc(OTf)_3$ (10%) and *p*-$(NO_2C_6H_4CO)_2O$ (2 equiv) in acetonitrile.

Yields for the lactonisation step are given in Table 3.

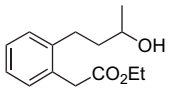
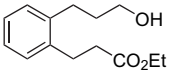
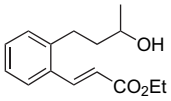
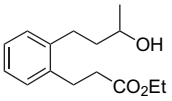
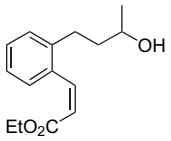
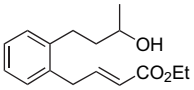
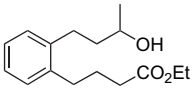
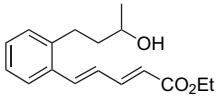
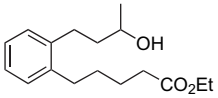
Table 1. Nickel-catalysed arylation of methylvinylketone with *ortho*-bromoarylester

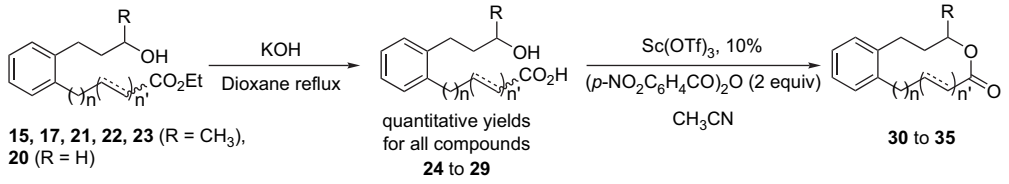
Entry	*ortho*-Bromoarylester	Compound number	Product	Compound number	Isolated yield (%)
1		**2**		**3**	65
2		**5**		**6**	63
3		**8**		**11**	50
4		**9**		**12**	84
5		**10**		**13**	63



Scheme 8.

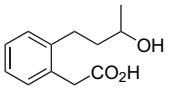
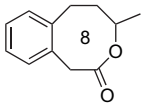
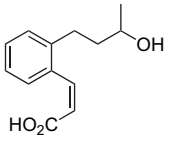
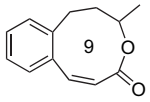
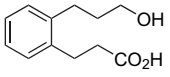
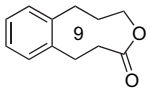
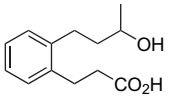
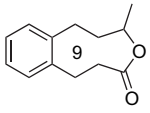
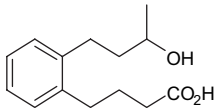
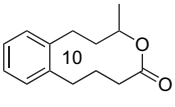
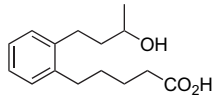
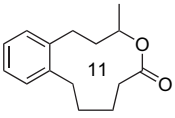
Table 2. Reductions of keto-esters by $NaBH_4$ or $NaBH_4/NiCl_2$

Entry	Hydroxyester obtained by $NaBH_4$ reduction in methanol at 0 °C			Hydroxyester obtained by $NiCl_2/NaBH_4$ reduction in methanol at 0 °C		
	Compound		Isolated yield (%)	Compound		Isolated yield (%)
1		**15**	70		**20**	75
2		**16**	95		**21**	Quantitative
3		**17**	Quantitative	—		—
4		**18**	Quantitative		**22**	Quantitative
5		**19**	93		**23**	90



Scheme 9.

Table 3. Lactonisation of hydroxyacids

Entry	Hydroxyacid	Compound number	Benzolactone	Compound number	Isolated yield (%)
1		**24**		**30**	53
2		**25**		**31**	66
3		**26**		**32**	66
4		**27**		**33**	74
5		**28**		**34**	65
6		**29**		**35**	60

Thus, we prepared six benzolactones with ring size from 8 to 11. Regarding the possible presence of a C–C double bond in the medium-size lactone ring, it comes out that the cyclisation was only observed from the *Z*-isomer (**25**) leading to a nine-membered lactone, whereas no cyclisation has occurred from the corresponding *E*-isomer. These benzolactones, which have methyl group on lactone ring, are racemic. No attempt to perform enantioselective reduction was made so far. The obtained yields range from 53 to 74%, and no trend can be found to explain the observed differences in yields, though the lowest yield is obtained in the formation of a eight-membered lactone, as mentioned in our previous study.[4] Most of the prepared compounds, either precursors or lactones are new compounds.

3. Experimental

3.1. General

All reagents and supporting electrolytes were used as obtained commercially. All reactions were performed under an inert atmosphere (argon) unless otherwise indicated. An iron rod was used as the anode. The cathode was made of nickel foam.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) or AVANCE 300 (300 MHz) spectrometer at room temperature, except for **33** and **34** at 70 °C. Regarding the ^{13}C data, some of aromatic signal are missing. This might be a consequence of the overlapping of certain signal. Infrared spectra were recorded on a Perkin Elmer Spectrum BX II spectrometer. Mass spectra (electron impact) were obtained on a Thermoquest GCQ spectrometer coupled to a Finnigan-GCQ chromatograph with a CPSIL5CB/MS capillary column. High-resolution mass spectra and elemental analyses were performed by 'Service Central d'Analyses du CNRS, Lyon'.

3.1.1. Ethyl 2-(2-bromophenyl)ethanoate (2). RN: [2178-24-7].[16]

3.1.2. Ethyl (*E*)-3-(2-bromophenyl)prop-2-enoate (5) and ethyl (*E*)-4-(2-bromophenyl)but-2-enoate (9). See in Ref. 4, respectively, for compounds **11** and **12**.

3.1.3. Ethyl (*E*,*E*)-5-(2-bromophenyl)penta-2,4-dienoate (10). Triethyl phosphonocrotonate (9.31 mL, 42 mmol) was added to a stirred suspension of sodium hydride (1.5 g, 39 mmol) in THF (50 mL) at 0 °C to give a white foam. The mixture was allowed to warm to room temperature for 30 min then recooled in an ice bath and 2-bromobenzaldehyde (5.55 mL, 30 mmol) was added as a solution in THF (70 mL). After 20 min the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous ammonium chloride (50 mL) was then added to the mixture. Diethyl ether was added and the combined layers were washed with water (3×25 mL), dried ($MgSO_4$) and the solvent removed under vacuum to give **10**. Colorless oil, 5.71 g, 68%, purification by column chromatography (silica gel, pentane–Et_2O, 90/10). ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.63–7.57 (m, 2H, ArH), 7.51 (dd, J=11.1 and J=15.3 Hz, 1H), 7.35–7.26 (m, 2H, ArH), 7.19–7.09 (m, 1H, ArH), 6.82 (dd, J=11.1 Hz and J=15.4 Hz, 1H), 6.05 (d, J=15.4 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 166.7, 144.1, 138.5, 135.7, 133.3, 130.1, 128.7, 127.6, 127.0, 124.6, 122.5, 60.5, 14.4. EIMS *m*/*z* (% relative abundance): 282 (19), 280 (21), 209 (23), 208 (17), 207 (26), 206 (16), 156 (20), 129 (31), 128 (100), 127 (13). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3065, 2979, 1707, 1627. HRMS (ESI) *m*/*z* Calcd for $C_{13}H_{14}BrO_2$ (M+H): 281.0177; Found: 281.0192.

3.1.4. Ethyl (*Z*)-3-(2-bromophenyl)prop-2-enoate (8). In a 500-mL flask were added under argon K_2CO_3 (4 g, 29 mmol), 18-crown-6 (18C6) (0.76 g, 1.44 mmol) and 300 mL of chlorobenzene. The mixture was stirred at room temperature for 3 h before being cooled to 0 °C. The phosphonate (5.06 g, 15.24 mmol) and the aldehyde (3.4 mL, 14.5 mmol) were then added. The mixture was maintained at 0 °C until the work-up. The reaction mixture was quenched with 50 mL saturated NH_4Cl and the organic phase washed by saturated NH_4Cl and water until neutrality. It was then dried over Na_2SO_4 and the solvent removed under vacuum. The *Z*/*E*-mixture was purified by gel chromatography (pentane–Et_2O, 95/5). Colorless oil, 3.27 g, 98%; RN: [99134-35-7]. ^{1}H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.63–7.19 (m, 4H, ArH), 7.13 (d, J=12.2 Hz, 1H), 6.05 (d, J=12.2 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 165.5, 142.5, 135.9, 132.2, 130.8, 129.9, 126.6, 123.1, 121.8, 60.3, 14.0. EIMS *m*/*z* (% relative abundance): 257 (<10), 255 (<10), 175 (57), 147 (100), 103 (34), 102 (24). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3029, 3021, 2925, 2940, 1719, 1637.

3.2. General procedure for the arylation of electron-deficient olefins

Under argon, in an undivided cell equipped with a nickel grid (area 40 cm^2) as the cathode and a Fe/Ni (64/36) rod as the anode, tetrabutylammonium bromide (0.34 mmol) and tetrabutylammonium iodide (0.21 mmol) as supporting electrolytes were dissolved in a mixture of DMF (25 mL) and ACN (25 mL). 1,2-Dibromoethane (0.1 mmol) was introduced. After a short electrolysis run at constant current density (0.2 A) and at room temperature over 15 min, the activated olefin (100 mmol), $NiBr_2 \cdot 3H_2O$ (1 mmol) was added and the reaction mixture was heated at 80 °C. The electrosynthesis was run at current density (0.2 A) 10 min after, the aryl bromide (10 mmol) was added. The reaction was monitored by GC and stopped after the aryl bromide was consumed. The mixture was then hydrolysed with hydrochloric acid (1 N, 30 mL) and diluted with diethyl ether (2×50 mL) and the combined organic layers were washed with water and saturated NaCl solution, then dried over $MgSO_4$. The oil thus obtained was purified by column chromatography (silica gel, pentane–ether, 90/10 eluent) to give the desired compound.

3.2.1. Ethyl 2-[2-(3-oxobutyl)phenyl]ethanoate (3). Colorless oil, 1.52 g, 65%. ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.27–7.17 (m, 4H, ArH), 4.18 (q, J=7.2 Hz, 2H), 3.70 (s, 2H), 2.97–2.92 (m, 2H), 2.81–2.76 (m, 2H), 2.18 (s, 3H), 1.29 (t, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz,

δ ppm): 207.8, 171.7, 139.7, 132.5, 130.7, 129.2, 127.6, 126.5, 60.9, 44.5, 38.6, 30.0, 26.6, 14.2. EIMS *m/z* (% relative abundance): 234 (2), 216 (21), 189 (12), 188 (78), 170 (25), 161 (15), 146 (17), 145 (100), 144 (36), 143 (50), 142 (26), 131 (11), 129 (11), 128 (10), 117 (63), 116 (12), 115 (32), 91 (17). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3036, 2941, 1719, 1604, 1493. HRMS (ESI) *m/z* Calcd for $C_{14}H_{19}O_3$ (M+H): 235.1334; Found: 235.1329.

3.2.2. Ethyl (*E*)-3-[2-(3-oxobutyl)phenyl]prop-2-enoate (6). Colorless oil, 1.55 g, 63%. ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 8.00 (d, *J*=15.8 Hz, 1H), 7.71–7.24 (m, 4H, ArH), 6.45 (d, *J*=15.8 Hz, 1H), 4.23 (q, *J*=7.0 Hz, 2H), 3.03–2.98 (m, 2H), 2.80–2.74 (m, 2H), 2.12 (s, 3H), 1.30 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 206.8, 166.1, 141.4, 141.0, 132.9, 130.1, 129.8, 126.7, 126.6, 119.8, 59.9, 44.1, 28.9, 26.6, 13.7. EIMS *m/z* (% relative abundance): 246 (3), 201 (17), 200 (18), 172 (30), 158 (16), 157 (100), 131 (11), 130 (17), 129 (60), 128 (15), 115 (17). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3068, 2985, 2940, 2905, 2876, 1704, 1634, 1601, 1368. HRMS (ESI) *m/z* Calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334; Found: 247.1335.

3.2.3. Ethyl (*Z*)-3-[2-(3-oxobutyl)phenyl]prop-2-enoate (11). Colorless oil, 1.23 g, 50%. ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.57–7.19 (m, 5H, ArH), 6.09 (d, *J*=12.0 Hz, 1H), 4.11 (q, *J*=7.1 Hz, 2H), 2.93–2.88 (m, 2H), 2.77–2.71 (m, 2H), 2.16 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 207.9, 165.9, 142.8, 138.5, 129.2, 128.6, 126.7, 125.8, 122.0, 60.2, 44.2, 30.1, 27.5, 14.0. EIMS *m/z* (% relative abundance): 201 (16), 200 (20), 172 (17), 158 (17), 157 (100), 131 (10), 130 (12), 129 (62), 128 (19), 115 (20). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3032, 2987, 2962, 1713, 1634. HRMS (ESI) *m/z* Calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334; Found: 247.1347.

3.2.4. Ethyl (*E*)-4-[2-(3-oxobutyl)phenyl]but-2-enoate (12). Colorless oil, 2.19 g, 84% mixture of *E*/*Z* (80/20). ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.25–7.17 (m, 4H, ArH), 7.09 (dt, J_{trans}=15.6 Hz, *J*=6.4 Hz, 1H), 5.75 (dt, J_{trans}=15.6 Hz, *J*=1.7 Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 3.62 (dd, *J*=6.4 Hz, *J*=1.7 Hz, 2H), 2.92–2.75 (m, 4H), 2.11 (s, 3H), 1.24 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 206.3, 165.6, 147.5, 139.7, 135.8, 129.9, 129.3, 127.0, 126.4, 121.9, 59.7, 43.8, 35.0, 29.0, 26.1, 13.7. EIMS *m/z* (% relative abundance): 260, 215 (14), 214 (88), 196 (10), 181 (14), 173 (11), 171 (17), 169 (14), 157 (49), 156 (100), 145 (11), 144 (13), 143 (22), 129 (83), 128 (83), 127 (10), 115 (24). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3072, 2983, 1715, 1603, 1491. HRMS (ESI) *m/z* Calcd for $C_{16}H_{20}O_3Na$ (M+Na) 283.1310; Found: 283.1311.

3.2.5. Ethyl (*E*,*E*)-5-[2-(3-oxobutyl)phenyl]penta-2,4-dienoate (13). Colorless oil, 1.72 g, 63%. ^1H NMR (Acetone-d_6, 200 MHz, δ ppm): 7.62–7.14 (m, 6H, ArH), 6.95 (dd, *J*=15.4 and 10.9 Hz, 1H), 6.00 (d, J_{trans}=15.3 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 2.97–2.89 (m, 2H), 2.79–2.69 (m, 2H), 2.04 (s, 3H), 1.21 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (Acetone-d_6, 50 MHz, δ ppm): 207.1, 167.6, 145.8, 141.2, 138.5, 135.6, 130.9, 129.9, 128.7, 127.6, 126.9, 122.2, 60.7, 45.2, 29.9, 27.8, 14.7. EIMS *m/z* (% relative abundance): 272 (15), 229 (16), 214 (39), 198 (23), 186 (10), 185 (23), 183 (25), 181 (33), 180 (24), 169 (23), 168 (47), 165 (16), 155 (40), 153 (16), 142 (17), 141 (100), 129 (20), 128 (18), 115 (28). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3032, 2984, 2875, 1708, 1610. HRMS (ESI) *m/z* Calcd for $C_{17}H_{20}O_3Na$ (M+Na): 295.1310; Found: 295.1299.

3.2.6. Ethyl (*E*)-3-[2-(3-oxopropyl)phenyl]prop-2-enoate (14). Under argon, in an undivided cell equipped with a nickel grid (area 40 cm^2) as the cathode and a Fe/Ni (64/36) rod as the anode, tetrabutylammonium bromide (0.34 mmol) and tetrabutylammonium iodide (0.21 mmol) as supporting electrolytes were dissolved in a mixture of DMF (50 mL) and pyridine (5 mL). 1,2-Dibromoethane (0.1 mmol) was introduced after a short electrolysis run at constant current density (0.2 A) and at room temperature over 15 min, the olefin (30 mmol), $NiBr_2 \cdot 3H_2O$ (0.75 mmol) and the aryl bromide (10 mmol) were added, and the reaction mixture heated at 80 °C. The electrosynthesis was run at current density (0.1 A). The reaction was monitored by GC and stopped after the aryl bromide was consumed. The mixture was then hydrolysed with hydrochloric acid (6 N, 30 mL) and diluted with diethyl ether (2×50 mL) and the combined organic layers were washed with water and saturated NaCl solution, then dried over $MgSO_4$. The oil thus obtained was purified by column chromatography (silica gel, pentane–ether, 70/30 eluent) to give **14**. Colorless oil, 0.54 g, 23%. ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 9.77 (s, 1H), 7.98 (d, *J*=15.8 Hz, 1H), 7.56–7.20 (m, 4H, ArH), 6.37 (d, *J*=15.8 Hz, 1H), 4.25 (q, *J*=7.1 Hz, 2H), 3.10–3.04 (m, 2H), 2.75–2.69 (m, 2H), 1.32 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 200.8, 166.8, 141.4, 139.9, 133.0, 130.2, 129.9, 127.0, 126.8, 120.2, 60.4, 44.9, 25.4, 14.3. EIMS *m/z* (% relative abundance): 231 (27), 204 (19), 203 (100), 202 (34), 178 (17). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3068, 2979, 2828, 1711. HRMS (ESI) *m/z* Calcd for $C_{14}H_{17}O_3$ (M+H): 233.1178; Found: 233.1175.

3.3. Reduction of carbonyl function only

To a solution of product (1 equiv, 7 mmol, 1.64 g) in methanol (30 mL) was added $NaBH_4$ (1 equiv, 0.27 g) portion by portion at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then quenched with aqueous saturated sodium hydrogen carbonate (10 mL). The mixture was extracted with ethyl acetate (3×20 mL). The organic layers were dried over $MgSO_4$ and evaporated. Purification was done by column chromatography on silica gel (eluent: pentane–ethyl acetate system) to give the desired hydroxyesters.

3.3.1. Ethyl 2-[2-(3-hydroxybutyl)phenyl]ethanoate (15). Colorless oil, 1.14 g, 70%, purification by column chromatography (silica gel, pentane–ethyl acetate, 70/30). ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.28–7.17 (m, 4H, ArH), 4.18 (q, *J*=7.1 Hz, 2H), 3.87–3.83 (m, 1H), 3.72 (s, 2H), 2.84–2.68 (m, 3H), 1.79–1.72 (m, 2H), 1.29 (t, *J*=7.1 Hz, 3H), 1.26 (d, *J*=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 172.1, 140.8, 132.4, 130.6, 129.4, 127.5, 126.2, 67.2, 61.0, 40.1, 38.7, 28.9, 23.5, 14.2. EIMS *m/z* (% relative abundance): 237 (<10), 218 (29), 192 (16), 190 (23), 175

(12), 172 (22), 149 (10), 147 (14), 146 (28), 145 (100), 144 (93), 143 (50), 131 (27), 130 (24), 129 (82), 128 (12), 119 (21), 118 (29), 117 (49), 116 (13), 115 (20), 105 (31), 104 (14), 103 (10), 91 (26). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3474, 3037, 2970, 2875, 1727, 1603, 1493. HRMS (ESI) *m/z* Calcd for $C_{14}H_{21}O_3$ (M+H): 237.1491; Found: 237.1496.

3.3.2. Ethyl (*E*)-3-[2-(3-hydroxybutyl)phenyl]prop-2-enoate (16). Colorless oil, 0.94 g, 95%, purification by column chromatography (silica gel, pentane–ethyl acetate, 70/30). ^{1}H NMR (Acetone-d_6, 200 MHz, δ ppm): 8.15 (d, J=15.8 Hz, 1H), 7.84–7.34 (m, 4H), 6.57 (d, J=15.8 Hz, 1H), 4.35 (q, J=7.1 Hz, 2H), 3.94–3.83 (m, 1H), 3.11–2.90 (m, 2H), 2.1 (br s, 1H, H_{OH}), 1.84–1.73 (m, 2H), 1.42 (t, J=7.1 Hz, 3H), 1.31 (d, J=5.9 Hz, 3H). ^{13}C NMR (Acetone-d_6, 50 MHz, δ ppm): 167.0, 143.2, 142.6, 142.4, 133.6, 130.8, 127.4, 127.2, 120.1, 67.0, 60.7, 42.0, 24.0, 23.8, 14.5. EIMS *m/z* (% relative abundance): 248 (<5), 230 (8), 203 (12), 185 (14), 169 (12), 160 (14), 159 (31), 158 (19), 157 (52), 156 (52), 155 (15), 147 (12), 145 (15), 144 (26), 143 (34), 142 (88), 141 (21), 132 (11), 131 (40), 130 (47), 129 (100), 128 (23), 117 (33), 116 (33), 115 (37). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3462, 3036, 2932, 2876, 1694, 1600, 1484. HRMS (ESI) *m/z* Calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310; Found: 271.1303.

3.3.3. Ethyl (*Z*)-3-[2-(3-hydroxybutyl)phenyl]prop-2-enoate (17). Colorless oil, 1.08 g, quantitative yield, purification by column chromatography (silica gel, pentane–ethyl acetate, 70/30). ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.59–7.17 (m, 5H, ArH and olefinic H), 6.06 (d, J=12.0 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.83–3.76 (m, 1H), 2.77–2.65 (m, 2H), 2.56 (br s, 1H, H_{OH}), 1.75–1.68 (m, 2H), 1.21 (d, J=6.2 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 166.2, 143.1, 139.8, 134.9, 129.2, 128.8, 128.6, 125.4, 121.1, 67.1, 60.2, 39.8, 29.8, 23.6, 13.9. EIMS *m/z* (% relative abundance): 185 (25), 169 (12), 159 (13), 158 (20), 157 (45), 156 (43), 155 (12), 147 (14), 144 (22), 143 (13), 142 (34), 141 (21), 131 (26), 130 (21), 129 (100), 128 (27), 117 (17), 116 (20), 115 (40). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3474, 2970, 2931, 1713, 1633. HRMS (ESI) *m/z* Calcd for $C_{15}H_{21}O_3$ (M+H): 249.1491; Found: 249.1492.

3.3.4. Ethyl (*E*)-4-[2-(3-hydroxybutyl)phenyl]but-2-enoate (18). Colorless oil, 1.04 g, quantitative yield, *E*/*Z* (80/20) purification by column chromatography (silica gel, pentane–ethyl acetate, 70/30). ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.50–7.11 (m, 5H), 5.77 (dt, J_{trans}=15.6 Hz, J=1.7 Hz, 1H), 4.21 (q, J=7.1 Hz, 2H), 3.93–3.80 (m, 1H), 3.60 (dd, J=6.4 Hz, J=1.7 Hz, 2H), 2.92–2.61 (m, 2H), 2.03 (br s, 1H, H_{OH}), 1.83–1.70 (m, 2H), 1.33–1.25 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 166.7, 147.6, 140.4, 135.5, 130.0, 129.5, 127.1, 126.3, 122.2, 67.6, 60.3, 40.4, 35.5, 28.9, 23.6, 14.2. EIMS *m/z* (% relative abundance): 262, 216 (18), 215 (12), 198 (11), 183 (18), 173 (11), 171 (16), 170 (39), 169 (38), 157 (26), 156 (29), 155 (16), 145 (15), 144 (11), 143 (18), 141 (29), 131 (13), 130 (23), 129 (100), 128 (61), 127 (12), 117 (19), 115 (27), 91 (11). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3608, 3504, 3020, 2970, 2874, 1712, 1602, 1490. HRMS (ESI) *m/z* Calcd for $C_{16}H_{22}O_3Na$ (M+Na): 285.1467; Found: 285.1470.

3.3.5. Ethyl (*E*,*E*)-5-[2-(3-hydroxybutyl)phenyl]penta-2,4-dienoate (19). Colorless oil, 0.79 g, 93%, purification by column chromatography (silica gel, pentane–ether, 70/30). ^{1}H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.51 (dd, J=15.3 Hz, J=11.1 Hz, 1H), 7.45 (d, J_{trans}=15.3 Hz, 1H), 7.69–7.22 (m, 4H), 7.03 (dd, J=15.3 Hz, J=11.1 Hz, 1H), 6.00 (d, J_{trans}=15.3 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.84–3.76 (m, 1H), 3.02–2.76 (m, 3H), 1.71–1.63 (m, 2H), 1.27 (t, J=7.2 Hz, 3H), 1.18 (d, J=6.1 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 167.2, 145.9, 142.4, 138.7, 135.2, 130.8, 129.7, 128.2, 127.1, 126.5, 121.8, 67.1, 60.6, 41.9, 29.9, 24.2, 14.6. EIMS *m/z* (% relative abundance): 274 (10), 228 (20), 200 (14), 185 (14), 183 (26), 182 (22), 181 (21), 170 (40), 169 (27), 168 (25), 167 (46), 157 (18), 156 (16), 155 (25), 153 (28), 144 (16), 143 (58), 142 (66), 141 (100), 132 (13), 129 (43), 128 (43), 117 (12), 116 (12), 115 (44). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3510, 2971, 2875, 1707, 1600. HRMS (ESI) *m/z* Calcd for $C_{17}H_{23}O_3$ (M+H): 275.1647; Found: 275,1641.

3.4. Typical procedure for reduction

To a solution of product (1 equiv, 5.7 mmol) and $NiCl_2$ (5.7 mmol) in methanol (50 mL) was added $NaBH_4$ (7 equiv, 39.9 mmol) portionwise at 0 °C. The reaction mixture was stirred for 3 h at room temperature and then quenched with aqueous saturated sodium hydrogen carbonate (20 mL). The mixture was extracted with ethyl acetate (3×20 mL). The organic layers were dried over $MgSO_4$ and evaporated. Purification was done by column chromatography on silica gel (pentane–ethyl acetate system, eluent) to give the desired hydroxyl-esters.

3.4.1. Ethyl 3-[2-(3-hydroxypropyl)phenyl]propanoate (20). See Ref. 4 (compound **6c**), 0.97 g, 75%. RN: [136416-11-0].[4]

3.4.2. Ethyl 3-[2-(3-hydroxybutyl)phenyl]propanoate (21). Colorless oil, 1.42 g, quantitative yield, purification by column chromatography (silica gel, pentane–ethyl acetate, 50/50). ^{1}H NMR (Acetone-d_6, 200 MHz, δ ppm): 7.31–7.20 (m, 4H, ArH), 4.20 (q, J=7.0 Hz, 2H), 3.94–3.86 (m, 1H), 3.75 (br s, 1H, H_{OH}), 3.12–2.66 (m, 6H), 1.85–1.74 (m, 2H), 1.35–1.28 (m, 6H). ^{13}C NMR (Acetone-d_6, 50 MHz, δ ppm): 173.0, 141.3, 139.2, 130.0, 129.6, 127.1, 126.6, 67.1, 60.6, 41.7, 35.8, 28.2, 24.1, 23.9, 14.4. EIMS *m/z* (% relative abundance): 250 (3), 232 (55), 187 (24), 186 (78), 185 (10), 179 (11), 171 (23), 160 (12), 159 (18), 158 (63), 157 (15), 156 (11), 146 (14), 145 (40), 144 (56), 143 (75), 142 (21), 133 (24), 131 (37), 130 (27), 129 (100), 128 (53), 118 (20), 117 (79), 116 (31), 115 (52), 105 (21), 104 (10), 91 (28). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3473, 3034, 2980, 2875, 1724, 1603, 1491. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.77; H, 8.84; O, 19.30.

3.4.3. Ethyl 4-[2-(3-hydroxybutyl)phenyl]butanoate (22). Colorless oil, 0.575 g, quantitative yield, purification by column chromatography (silica gel, pentane–ethyl acetate, 50/50). ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.31–7.16 (m, 4H, ArH), 4.19 (q, J=7.1 Hz, 2H), 3.97–3.86 (m, 1H), 2.92–2.61 (m, 4H), 2.43 (t, J=7.1 Hz, 2H), 2.01–1.90

(m, 3H, H_{OH}), 1.81–1.71 (m, 2H), 1.33–1.28 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 173.8, 140.1, 139.3, 129.4, 129.3, 126.6, 126.0, 67.7, 60.5, 40.9, 33.9, 32.0, 28.7, 26.4, 23.7, 14.3. EIMS *m/z* (% relative abundance): 264, 246 (49), 201 (42), 200 (72), 199 (14), 185 (17), 182 (17), 177 (12), 172 (16), 160 (21), 159 (47), 158 (65), 157 (27), 156 (12), 147 (22), 146 (26), 145 (60), 144 (19), 143 (54), 142 (15), 132 (14), 131 (90), 130 (54), 129 (100), 128 (17), 118 (20), 117 (82), 116 (17), 115 (37), 105 (22), 91 (36). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3055, 2968, 1727, 1603, 1491. HRMS (ESI) *m/z* Calcd for $C_{16}H_{25}O_3$ (M+H): 265.1804; Found: 265.1802.

3.4.4. Ethyl 5-[2-(3-hydroxybutyl)phenyl]pentanoate (23). Colorless oil, 1.61 g, 90%, purification by column chromatography (silica gel, pentane–ethyl acetate, 50/50). ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.31–7.15 (m, 4H, ArH), 4.17 (q, J=7.1 Hz, 2H), 3.96–3.86 (m, 1H), 2.89–2.64 (m, 4H), 2.43–2.38 (m, 2H), 2.16 (br s, 1H, H_{OH}), 1.83–1.62 (m, 6H), 1.30 (d, J=6.2 Hz, 3H), 1.30 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 173.9, 140.0, 139.9, 129.3, 129.2, 126.1, 126.0, 67.7, 60.4, 40.8, 34.2, 32.3, 30.7, 28.8, 25.0, 23.7, 14.3. EIMS *m/z* (% relative abundance): 278, 260 (47), 215 (17), 214 (28), 186 (19), 185 (11), 173 (14), 171 (18), 158 (11), 146 (15), 145 (100), 144 (34), 143 (26), 131 (54), 130 (20), 129 (59), 128 (20), 117 (48), 115 (21), 105 (22), 91 (22). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3517, 3017, 2937, 2869, 1728, 1602, 1490. HRMS (ESI) *m/z* Calcd for $C_{17}H_{26}O_3Na$ (M+Na): 301.1780; Found: 301.1780.

3.5. Typical procedure for saponification

To a solution of product (7 mmol) in dioxane–water (1:1, v:v, 70 mL) was added a 20% solution of potassium hydroxide in water (24 mmol). The reaction mixture was refluxed for 16 h and cooled to room temperature, then H_2SO_4 was added until pH=1 was reached. The mixture was extracted with ether (3×25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to leave a crude product.

3.5.1. 2-[2-(3-Hydroxybutyl)phenyl]ethanoic acid (24). Colorless oil, 0.73 g, quantitative yield. ^1H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.26–7.13 (m, 4H, ArH), 3.83–3.71 (m, 1H), 3.71 (s, 2H), 2.86–2.65 (m, 2H), 1.73–1.66 (m, 2H), 1.19 (d, J=6.2 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 172.4, 141.3, 133.1, 130.6, 129.2, 127.1, 125.7, 66.4, 40.4, 37.7, 28.9, 23.1. IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3406, 3200–2800, 2968, 2646, 1712, 1603, 1493. HRMS (ESI) *m/z* Calcd for $C_{12}H_{17}O_3$ (M+H): 209.1178; Found: 209.1190.

3.5.2. (*Z*)-3-[2-(3-Hydroxybutyl)phenyl]prop-2-enoic acid (25). Colorless oil, 0.884 g, 91%. ^1H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.35–7.10 (m, 5H, ArH), 6.07 (d, J=12.2 Hz, 1H), 3.80–3.70 (m, 1H), 2.98–2.62 (m, 2H), 1.70–1.62 (m, 2H), 1.15 (d, J=6.2 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 166.4, 142.2, 140.5, 134.9, 129.2, 128.7, 128.2, 125.1, 121.3, 66.2, 40.2, 29.7, 23.1. IR pellet of KBr (ν cm^{-1}): 3200–2800, 1703, 1364. HRMS (ESI) *m/z* Calcd for $C_{13}H_{17}O_3$ (M+H): 221.1178; Found: 221.1174.

3.5.3. 3-[2-(3-Hydroxypropyl)phenyl]propanoic acid (26). See Ref. 4 (compound **7c**).

3.5.4. 3-[2-(3-Hydroxybutyl)phenyl]propanoic acid (27). Colorless oil, 0.475 g, 97%. ^1H NMR (Acetone-d_6, 200 MHz, δ ppm): 7.06–6.92 (m, 4H, ArH), 3.73–3.64 (m, 1H), 2.85–2.40 (m, 6H), 1.61–1.49 (m, 2H), 1.06 (d, J=6.2 Hz, 3H). ^{13}C NMR (Acetone-d_6, 50 MHz, δ ppm): 174.7, 141.2, 139.4, 130.0, 129.6, 127.1, 126.7, 67.4, 41.5, 35.6, 28.2, 23.9, 23.8. IR pellet of KBr (ν cm^{-1}): 3387, 3040, 2968, 2875, 1711, 1604, 1491. HRMS (ESI) *m/z* Calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154; Found: 245.1141.

3.5.5. 4-[2-(3-Hydroxybutyl)phenyl]butanoic acid (28). Colorless oil, 0.45 g, quantitative yield. ^1H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.99–6.96 (m, 4H, ArH), 3.82–3.76 (m, 1H), 2.99–2.62 (m, 4H), 2.39 (t, J=7.3 Hz, 2H), 1.92–1.82 (m, 2H), 1.71–1.63 (m, 2H), 1.19 (d, J=6.2 Hz, 3H). ^{13}C NMR (Acetone-d_6, 300 MHz, δ ppm): 173.9, 140.5, 139.5, 129.2, 126.0, 125.8, 66.5, 41.1, 33.0, 31.6, 28.6, 26.5, 23.1. IR pellet of KBr (ν cm^{-1}): 3200–2800, 3018, 2967, 1710, 1604, 1491. HRMS (ESI) *m/z* Calcd for $C_{14}H_{21}O_3$ (M+H): 237.1491; Found: 237.1496.

3.5.6. 5-[2-(3-Hydroxybutyl)phenyl]pentanoic acid (29). Colorless oil, 1.61 g, 90%. ^1H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.19–7.08 (m, 4H, ArH), 3.89–3.83 (m, 1H), 2.89–2.67 (m, 4H), 2.38–2.33 (m, 2H), 1.75–1.63 (m, 6H), 1.23 (d, J=6.0 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 174.6, 140.3, 140.0, 129.2, 129.17, 125.9, 125.8, 66.8, 40.9, 33.3, 32.1, 30.7, 28.6, 24.8, 23.1. IR pellet of KBr (ν cm^{-1}): 3200–2800, 3018, 2937, 2870, 1705, 1604, 1490. HRMS (ESI) *m/z* Calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467; Found: 273.1458.

3.6. Preparation of *p*-nitrobenzoic anhydride

To a mixture of *p*-nitrobenzoic acid (3.34 g, 20 mmol) and *p*-nitrobenzoic chloride (3.71 g, 20 mmol) in dichloromethane (50 mL) was added pyridine (2.02 mL, 25 mmol) dropwise at 0 °C. The reaction mixture was stirred for 15 h at room temperature and then quenched with cold water (20 mL). The mixture was extracted with dichloromethane several times. The organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by recrystallisation from dichloromethane–hexane to afford *p*-nitrobenzoic anhydride (5.4 g, 85% yield).

3.7. Typical procedure for lactonisation

p-Nitrobenzoic anhydride (506 mg, 1.6 mmol) was dissolved in dry acetonitrile (340 mL), and a cloudy solution of scandium triflate (1.6 mL, 0.16 mmol, 0.1 M) in acetonitrile was added to the solution at room temperature under argon. A solution of hydroxycarboxylic acid (20 mL, 0.8 mmol, 0.08 M) in THF was slowly added with a syringe pump over 15 h to the mixed solution at reflux under argon, and the reaction mixture was stirred for an additional 5 h at reflux. After being cooled to room temperature, the solution was quenched with aqueous saturated sodium hydrogen carbonate (8 mL). The resulting mixture was concentrated under reduced

pressure and extracted with diethyl ether twice. The organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. Purification was done by flash column chromatography on silica gel to give the desired lactone.

3.7.1. 2-[2-(3-Hydroxybutyl)phenyl]ethanoic acid, ζ lactone (30). Colorless oil, 0.08 g, 53%, purification by flash column chromatography (silica gel, pentane–Et_2O, 90/10). ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.30–7.14 (m, 4H, ArH), 4.84–4.79 (m, 1H), 4.12 (d, AB system $\Delta\nu$/J=7.2 Hz, J=14.4 Hz, 1H), 3.78 (d, AB system $\Delta\nu$/J=7.2 Hz, J=14.4 Hz, 1H), 2.97–2.90 (m, 2H), 2.05–1.86 (m, 2H), 1.40 (d, J=6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 173.1, 139.3, 133.3, 130.3, 129.8, 127.9, 127.2, 77.1, 39.7, 38.6, 33.0, 22.4. EIMS *m*/*z* (% relative abundance): 190 (<10), 148 (17), 146 (31), 131 (79), 118 (11), 117 (41), 115 (30), 105 (14), 104 (100), 103 (17), 91 (25), 78 (37). IR ν_{max} in $CHCl_3$ solution (cm^{-1}): 3024, 2971, 2931, 1728, 1603, 1493. HRMS (ESI) *m*/*z* Calcd for $C_{12}H_{15}O_2$ (M+H): 191.1072; Found: 191.1064.

3.7.2. (*Z*)-3-[2-(3-Hydroxybutyl)phenyl]prop-2-enoic acid, η lactone (31). Colorless oil, 0.097 g, 0.66%, purification by flash column chromatography (silica gel, pentane–Et_2O, 90/10). ^1H NMR (DMF-d_7, 300 MHz, δ ppm): 7.38–7.20 (m, 5H, ArH), 6.15 (d, J=12.2 Hz, 1H), 5.24–5.13 (m, 1H), 2.79–2.72 (m, 1H), 2.47–2.35 (m, 2H), 1.90–1.78 (m, 1H), 1.10 (d, J=6.5 Hz, 3H). ^{13}C NMR (DMF-d_7, 75 MHz, δ ppm): 168.1, 142.8, 142.3, 134.6, 131.0, 130.6, 128.9, 125.5, 121.7, 71.0, 34.7, 29.75, 21.8. EIMS *m*/*z* (% relative abundance): 202 (31), 174 (24), 161 (11), 160 (37), 159 (40), 158 (16), 157 (31), 156 (100), 147 (15), 146 (25), 145 (12), 143 (13), 142 (62), 141 (18), 133 (12), 132 (46), 131 (52), 130 (27), 129 (58), 128 (41), 127 (13), 118 (34), 117 (16), 116 (24), 115 (60), 104 (10), 103 (13), 91 (12), 89 (12). IR ν_{max} in CH_2Cl_2 solution (cm^{-1}): 3058, 2984, 2935, 1705. HRMS (ESI) *m*/*z* Calcd for $C_{13}H_{15}O_2$ (M+H): 203.1072; Found: 203.1068.

3.7.3. 3-[2-(3-Hydroxypropyl)phenyl]propanoic acid, η lactone (32). See Ref. 4 (compound **8c**).

3.7.4. 3-[2-(3-Hydroxybutyl)phenyl]propanoic acid, η lactone (33). Colorless oil, 0.121 g, 74%, purification by flash column chromatography (silica gel, pentane–Et_2O, 90/10). ^1H NMR (DMF-d_7 70 °C, 300 MHz, δ ppm): 7.39–7.20 (m, 4H, ArH), 4.93–4.85 (m, 1H), 3.41–3.32 (m, 1H), 2.99–3.12 (m, 2H), 2.66–2.78 (m, 2H), 2.54–2.63 (m, 1H), 2.34–2.42 (m, 1H), 2.07–2.14 (m, 1H), 1.38 (d, J=6.4 Hz, 3H). ^{13}C NMR (DMF-d_7, 70 °C, 75 MHz, δ ppm): 173.9, 142.5, 138.7, 130.8, 130.6, 126.9, 126.2, 70.9, 38.9, 37.3, 30.6, 27.1, 20.7. EIMS *m*/*z* (% relative abundance): 205 (13), 204 (10), 187 (12), 186 (66), 171 (13), 158 (11), 157 (15), 146 (13), 145 (29), 144 (100), 143 (29), 142 (12), 133 (15), 131 (44), 130 (13), 129 (55), 128 (33), 118 (42), 117 (99), 116 (22), 115 (73), 104 (15), 91 (34), 77 (11). IR ν_{max} in CH_2Cl_2 solution (cm^{-1}): 3058, 2929, 2856, 1728, 1604, 1492. HRMS (ESI) *m*/*z* Calcd for $C_{13}H_{17}O_2$ (M+H): 205.1229; Found: 205.1233.

3.7.5. 4-[2-(3-Hydroxybutyl)phenyl]butanoic acid, θ lactone (34). Colorless oil, 0.113 g, 65%, purification by flash column chromatography (silica gel, pentane–Et_2O, 90/10). ^1H NMR (DMF-d_7 70 °C, 300 MHz, δ ppm): 7.25–7.11 (m, 4H, ArH), 4.68–4.52 (m, 1H), 2.98–2.65 (m, 4H), 2.32–2.02 (m, 5H), 1.94–1.82 (m, 1H), 1.18 (d, J=6.2 Hz, 3H). ^{13}C NMR (DMF-d_7, 70 °C, 75 MHz, δ ppm): 172.8, 140.7, 139.2, 129.4, 128.8, 125.7, 125.6, 70.8, 36.8, 33.5, 28.3, 27.5, 26.7, 20.3. EIMS *m*/*z* (% relative abundance): 218 (21), 201 (17), 200 (100), 185 (16), 160 (11), 159 (10), 158 (50), 157 (21), 146 (17), 145 (68), 144 (18), 143 (79), 132 (11), 131 (88), 130 (62), 129 (59), 128 (16), 118 (27), 117 (81), 116 (16), 115 (45), 105 (12), 104 (10), 91 (33), 78 (15). IR ν_{max} in CH_2Cl_2 solution (cm^{-1}): 3017, 2977, 2932, 2867, 1725, 1492. HRMS (ESI) *m*/*z* Calcd for $C_{14}H_{19}O_2$ (M+H): 219.1385; Found: 219.1393.

3.7.6. 5-[2-(3-Hydroxybutyl)phenyl]pentanoic acid, ι lactone (35). Colorless oil, 0.11 g, 60%, purification by flash column chromatography (silica gel, pentane–Et_2O, 90/10). ^1H NMR (Acetone-d_6, 300 MHz, δ ppm): 7.18–7.07 (m, 4H, ArH), 5.11–5.02 (m, 1H), 3.03–2.96 (m, 2H), 2.62–2.47 (m, 3H), 2.33–2.25 (m, 1H), 1.92–1.75 (m, 5H), 1.53–1.35 (m, 1H), 1.27 (d, J=6.5 Hz, 3H). ^{13}C NMR (Acetone-d_6, 75 MHz, δ ppm): 172.8, 140.6, 139.9, 129.8, 129.3, 125.9, 125.8, 69.5, 36.4, 33.1, 29.9, 29.2, 25.5, 23.7, 18.1. EIMS *m*/*z* (% relative abundance): 232 (37), 214 (17), 185 (10), 157 (12), 156 (14), 146 (14), 145 (100), 144 (16), 143 (30), 132 (10), 131 (78), 130 (32), 129 (48), 128 (18), 117 (51), 116 (12), 115 (33), 105 (13), 91 (31). IR ν_{max} in CH_2Cl_2 solution (cm^{-1}): 3061, 2871, 1723, 1603, 1492. HRMS (ESI) *m*/*z* Calcd for $C_{15}H_{21}O_2$ (M+H): 233.1542; Found: 233.1554.

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