Synthesis of Precursors for Medium-Ring Aromatic Lactones

Estelle Métay,[a] Eric Léonel,*[a] Christine Sulpice-Gaillet,[b] Jean-Yves Nédélec[a]

[a] Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582, Institut des Sciences Chimiques Seine-Amont, IFR 1780, CNRS – Université Paris XII, 2, Rue Henri Dunant, B.P. 28, 94320 Thiais, France
Fax +33(1)49781148; E-mail: leonel@glvt-cnrs.fr

[b] Laboratoire de Recherche sur les Polymères, UMR 7581, Institut des Sciences Chimiques Seine-Amont, IFR 1780, CNRS – Université Paris XII, 2, Rue Henri Dunant, B.P. 28, 94320 Thiais, France

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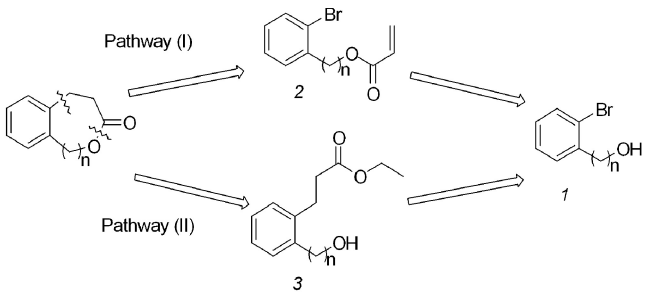
Abstract: Hydroxyacids have been prepared via the nickel-catalysed electrochemical arylation of ethyl acrylate from an *ortho*-substituted aryl bromide. Protection and deprotection steps have been selected in terms of suitability and efficiency. The lactonisation was performed according to an already reported method. Two-dimensional NMR analysis has been used to ascertain the structure of the lactones formed.

Key words: electrochemical arylation, nickel catalysis, medium ring lactones

Lactones are basic structures in many bioactive molecules from plants, insects or bacteria.[1] They are also intermediates in many synthetic applications. Lactones containing up to a six-membered ring are easily prepared, either by lactonisation or by Baeyer–Villiger oxidation of cycloalkanones.[2] Also, macrocyclic lactones larger than 11-membered rings can be efficiently obtained when high dilution reaction conditions are used. On the contrary, medium-sized ring lactones, like other medium-size ring compounds, are reported to be the most difficult to prepare by cyclisation.[3] In his extended review on the synthesis of medium-sized ring lactones, Rousseau[4] has pointed out that in addition to the classical Pitzer or torsional strain, and the Baeyer or angle strain, transannular interactions create an extra strain which is significatively more important in medium than in small or large rings. As a result, tentative preparations of medium ring lactones frequently lead to the formation of the macrocyclic diolide.[5]

Classical routes[4] to lactones are either lactonisation from hydroxy-[5,6] or halo-acids,[7] cyclisation by C–C bond formation from a starting compound containing an ester group in the chain or the ring expansion by ionic or radical route.

Our purpose was to apply an efficient C–C bond forming electrochemical reaction, involving the nickel-catalysed arylation of activated olefins, to the formation of medium ring benzolactones. The first idea was to perform this reaction in an intramolecular manner, as illustrated in Scheme 1, pathway I. In such a simple route, the activated olefin is first tethered to the aryl moiety before the electrochemical arylation of the C–C double bond, thus leading to the expected fused benzolactone in only two steps. Unfortunately, this methodology is of low efficiency, as the main products in the electrochemical step come from reduction and cleavage of the starting compound.[8] As an alternative, the C–C bond could first be formed by a bimolecular process before closing the ring by lactonisation. Though the starting reagent is similar in these two pathways, pathway II, however, requires additional steps, as compared to pathway I, i.e. the protection/deprotection of the hydroxy group and of the carboxylic group as well as the lactonisation step. In addition to this, we could envision some possible *ortho*-steric hindrance in the electrochemical arylation reaction.



Scheme 1

Preliminary investigations on pathway II, revealed that the bimolecular electrochemical arylation reaction is feasible. This encouraged us to optimise this reaction for any length of side-chain *ortho* to the halogen. In addition, we studied more deeply the protecting groups with regard to both the ease of formation and removal, as well as their compatibility with the reaction conditions. Finally, we had to not only carry out the lactonisation as efficiently as possible, but also, as detailed below, to ascertain the structure of the benzolactone and, more precisely, the carboxyl connection.

The various steps of the synthesis via pathway II are indicated in Scheme 2.

Our aim has been to have access to a series of benzolactones from seven through to ten-membered rings, some of which having not being described so far. Of the required *ortho*-bromophenyl alkanols necessary as starting materials, only **1a** and **1b** are commercially available. The others were prepared (Scheme 3) according to the method reported by Gibson for **1c** and by Jordis for **1d**,[9] i.e. by per-

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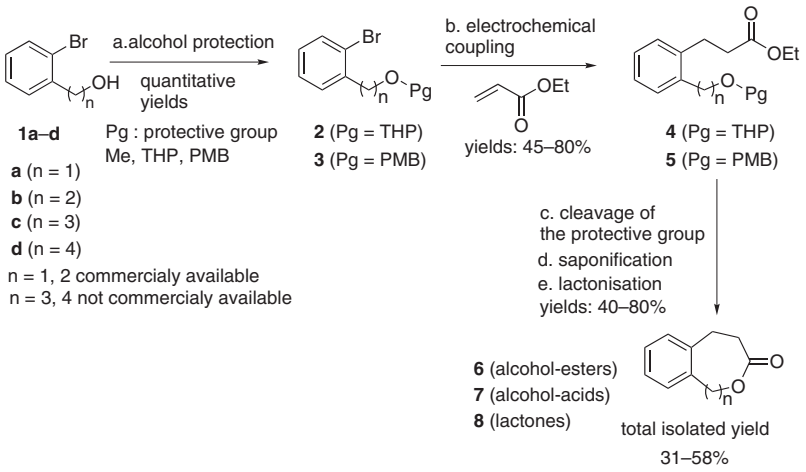
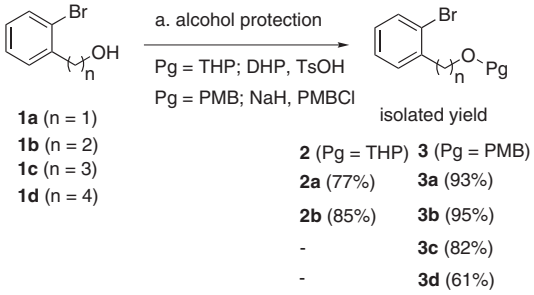


Scheme 2

forming a Wadsworth–Emmons condensation on a suitable carbonyl compound, then the reduction of the C–C double bond and ester group by super hydride ($LiBEt_3H$).

The choice of the OH-protecting group is a key parameter in this synthetic methodology. Notably, the electrochemical step requires a protecting group which is not easily reduced, nor sensitive to Lewis acids. THP derivatives are easily prepared, but this was not a good general protection method since the THP group is partially cleaved during the electrolysis, and the overall yields are only moderate.[8] The most convenient OH-protecting group for our purpose is *para*-methoxybenzyl group (PMB),[10] which is easily introduced, and can be cleaved efficiently by CAN.[11] The isolated yields for the two methods are good to excellent. The results are presented in Scheme 4.

The electrochemical step[12] has been conducted with ethyl acrylate as the Michael acceptor. The reaction conditions are similar to those previously reported, i.e. DMF containing 10% pyridine, and with $NiBr_2$ as the catalyst precursor. A higher temperature (100 °C) was found to be more efficient with these models, whereas 60 °C is usually

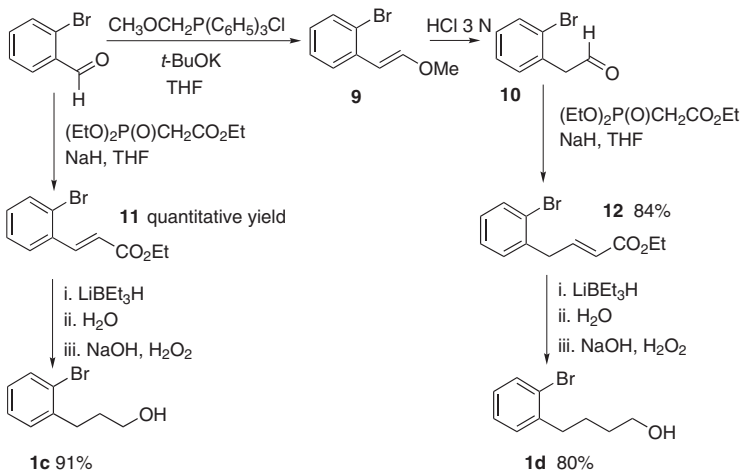


Scheme 4

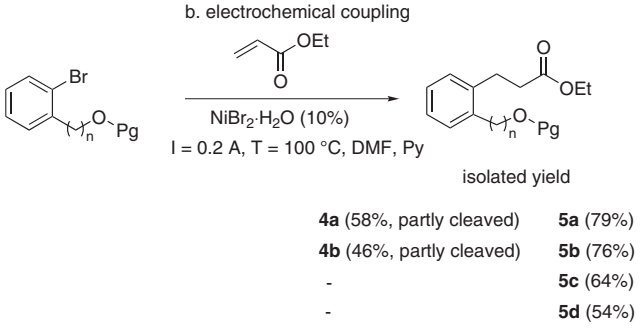
enough with the more simple structures. We can see (Scheme 5) that yields are good and higher with PMB than with THP as the protecting group. Also, the yields decrease slightly with increasing side chain length; there is no major steric effect due to the *ortho* substitution.

The next step is the cleavage of the PMB protecting group using the methodology described in the literature[11] (Scheme 6).

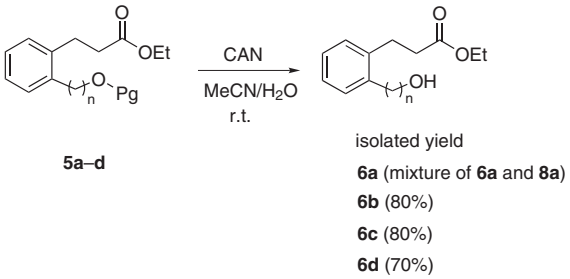
This reaction is easily and efficiently performed with CAN in an acetonitrile–water mixture at room tempera-



Scheme 3



Scheme 5

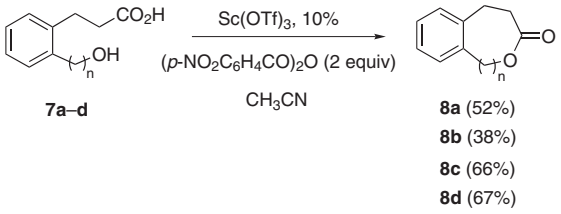


Scheme 6

ture in one hour. From **6a**, we have obtained, by purification of the crude product on silica gel, the lactone along with the expected hydroxyester. Based on this, we tried to increase the amount of lactone obtained by simply using acid catalysis, TsOH in toluene with a Dean–Stark apparatus. This attempt, however, did not produce the expected lactone, but only the corresponding diolide. No lactone was formed, either, in basic conditions. Similar results were obtained with all substrates.

The best method for generating the hydroxyacid is the saponification of the ethyl ester in dioxane.[13] This, however, was the turning point in the characterisation of the products, we obtained odd spectroscopic data for the hydroxyacid. Indeed, the IR spectrum shows a C=O band at ca. 1730 cm^{-1}, while the O–H bands of both the acid and the alcohol are of lower intensity than expected. The typical signals of the corresponding protons of these groups are also absent in the ^1H NMR spectrum in acetone-d_6. Finally, the high resolution mass spectrum (EI) gave as the mass of the parent ion, the one corresponding to the loss of H_2O, which is also the mass of the lactone. These observations were indeed misleading and we could neither confirm nor rule out the formation of the lactone during the saponification. Actually, we could only notably characterise each one unequivocally by 2D NMR spectroscopy as detailed below, and thus confirm that the product obtained by saponification followed by neutralisation is the hydroxyacid.

For preparing the lactone from the hydroxy acid, we tried some reported methods and found that the method described by Yamamoto[14] scandium triflate catalysis in acetonitrile under high dilution conditions afforded the expected ring compound in good yields (Scheme 7).



Scheme 7

As mentioned above, the characterisation of the hydroxyacid by spectroscopy is not simple. We could only definitely ascertain the structure of the lactones by 2D NMR spectroscopy using the HMBC program, which is based on the ^2J and ^3J ^1H–^{13}C couplings. Thus, each lactone spectrum displays the coupling between the carbon of the carbonyl and the protons of the methylene on the alcohol side through the C–O bond (Figure 1). Such a coupling is obviously not observed in the spectra of the hydroxyacids.

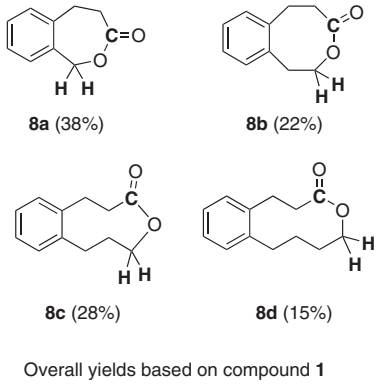


Figure 1

In conclusion, we have described in this paper a methodology to prepare precursors of medium-sized ring aromatic lactones. The key step is the nickel-catalysed electrochemical arylation of acrylic ester. Most of the lactones prepared, as well as some intermediates, are new products. This methodology can now be applied to the preparation of new types of lactones having various substituents on the aryl ring or containing a heteroaryl moiety.

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.

^1H, ^{13}C NMR spectra were recorded on a Brucker AC-200 (200 MHz) or AVANCE 300 (300 MHz) spectrometer at r.t., except for **8d**. Regarding the ^{13}C NMR data, some of the aromatic signals are missing, which may be a consequence of the overlapping of certain signals. 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 spectral and elemental analyses were performed by Service Central d'Analyses du CNRS, Lyon.

3-(2-Bromophenyl)propan-1-ol (1c)

Triethyl phosphonoacetate (11.9 mL, 60 mmol) was added to a stirred suspension of NaH (2.5 g, 65 mmol) in THF (70 mL) at 0 °C to give a white foam. The mixture was allowed to warm to r.t. and after 30 min was re-cooled in an ice bath and 2-bromobenzaldehyde (5.83 mL, 50 mmol) was added as a solution in THF (70 mL). After 20 min the reaction mixture was allowed to warm to r.t. and stirred for 1 h. Sat. aq NH_4Cl (50 mL) was then added to the mixture. Et_2O (30 mL) was added and the organic phases were combined and washed with H_2O (3 × 25 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give ethyl (*E*)-3-(2-bromophenyl)prop-2-enoate (**11**) as a pale yellow oil (12.7 g, quantitative yield).

11[15]

IR ($CHCl_3$): 3025, 2985, 2874, 1708, 1637, 1586, 1562 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.87 (d, *J* = 15.9 Hz, 1 H, CH), 7.75–7.17 (m, 4 H, ArH), 6.4 (d, *J* = 15.9 Hz, 1 H, CH), 4.1 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.16 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, acetone-d_6): δ = 166.4, 143.0, 142.7, 135.0, 134.1, 132.4, 129.0, 125.6, 122.1, 61.0, 14.2.

EIMS: *m*/*z* (%) = 256 (3), 254 (3), 211 (12), 209 (12), 176 (11), 175 (75), 148 (11), 147 (100), 103 (35), 102 (30).

To a solution of **11** (2.55 g, 10 mmol) in THF (14 mL) at –78 °C under argon was added $LiBEt_3H$ (1 M soln in THF; 40 mL, 40 mmol) dropwise over 1 h. The reaction mixture was then stirred for a further hour at –78 °C and then allowed to warm to r.t. After stirring at r.t. for 18 h, H_2O (11 mL) was added carefully and the reaction mixture was refluxed for 2 h. After cooling to r.t., aq NaOH (3 M, 26 mL) was added. Finally, after chilling to 0 °C, 27% aq H_2O_2 (30 mL) was added dropwise. When the reactivity had lessened, the ice bath was removed and the reaction allowed to warm to r.t., the reaction mixture was stirred for a further hour and then diluted with H_2O (30 mL). After extraction with Et_2O (3 × 30 mL), the organic layers were combined, washed with H_2O (3 × 40 mL), dried ($MgSO_4$) and evaporated in vacuo to give, 3-(2-bromophenyl)propan-1-ol (**1c**), as a pale yellow oil (2.13 g, 91%).

1c[16]

IR ($CHCl_3$): 3435, 3062, 2940, 2880, 1053 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.43–6.92 (m, 4 H, ArH), 3.47 (t, *J* = 6.4 Hz, 2 H, CH_2), 3.45 (br s, 1 H, OH), 2.68 (t, *J* = 7.7 Hz, 2 H, CH_2), 1.75–1.60 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 142.4, 133.6, 131.5, 128.6, 124.8, 61.8, 33.8, 33.2.

EIMS: *m*/*z* (%) = 216 (<1), 214 (<1), 171 (10), 169 (11), 135 (45), 134 (13), 117 (100), 115 (29), 107 (14), 91 (20), 90 (13).

3-(2-Bromophenyl)butan-1-ol (1d)

To a stirred suspension of $CH_3OCH_2P(C_6H_5)_3Cl$ (2.2 equiv, 44 mmol, 15 g) in anhyd THF (75 mL), *t*-BuOK (2 equiv, 40 mmol, 4.5 g) was added at 0 °C within 30 min and stirred for 30 min at this temperature. *o*-Bromobenzaldehyde (20 mmol, 2.3 mL) was added within 30 min, the resulting mixture was stirred for 5 h at r.t. and then hydrolysed with H_2O (20 mL). The solvent was removed in vacuo, and the residue was acidified with HCl (2 N; 20 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel; pentane–EtOAc, 20:1). The product was diluted in THF (30 mL) and HCl (2 N; 10 mL) and this solution was stirred under reflux for 2.5 h. H_2O (20 mL) was added, and the solution was concentrated in vacuo to a volume of 45 mL. The residue was extracted with EtOAc (3 × 25 mL), the combined organic layers were washed with H_2O (15 mL), sat. $NaHCO_3$ (15 mL) and brine, dried, filtered and evaporated in vacuo. At the same time, triethyl phosphonoacetate (24 mmol, 5.3 mL) was added to a stirred suspension of NaH (22 mmol, 0.848 g) in THF (50 mL) at 0 °C to give a white foam. The mixture was allowed to warm r.t. and after 30 min was re-cooled in an ice bath and the aldehyde in THF (50 mL) added slowly. After 4 h, the reaction mixture was allowed to warm to r.t. and stirred for 1 h. Sat. aq NH_4Cl (20 mL) was then added to the mixture. Et_2O (30 mL) was added and the organic layers were combined and washed with H_2O (3 × 25 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by column chromatography (silica gel; pentane–EtOAc, 40:1) to give ethyl (*E*)-3-(2-bromophenyl)but-2-enoate (**12**) as a pale yellow oil (4.5 g, 84%; *E*/*Z*, 3:1).

***E*-12**[17]

IR ($CHCl_3$): 3072, 2980, 2906, 1714, 1654, 1568, 1468 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.73–7.63 (m, 1 H, CH), 7.44–7.03 (m, 4 H, ArH), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1 H, CH), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.76 (dd, *J* = 6.6, 1.6 Hz, 2 H, CH_2), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 166.3, 146.2, 138.5, 133.6, 132.0, 129.6, 128.8, 126.8, 123.6, 60.6, 38.9, 14.5.

EIMS: *m*/*z* (%) = 270 (32), 268 (31), 224 (11), 195 (11), 190 (14), 189 (100), 161 (49), 144 (74), 143 (35), 133 (23), 117 (14), 116 (60), 115 (75).

The reduction of **12** (15 mmol) was carried out as for the reduction of **11** to yield 3-(2-bromophenyl)butan-1-ol (**1d**) (2.74 g, 80%).

1d[16]

IR ($CHCl_3$): 3472, 3043, 2939, 2865, 1045 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.7–7.1 (m, 4 H, ArH), 3.63–3.53 (m, 2 H, CH_2), 2.93–2.75 (m, 2 H, CH_2), 1.84–1.62 (m, 4 H, 2 × CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 142.7, 133.7, 133.5, 131.6, 128.6, 124.9, 62.4, 36.6, 33.4, 27.3.

EIMS: *m*/*z* (%) = 230 (<1), 228 (<1), 184 (53), 182 (55), 171 (24), 169 (27), 150 (11), 149 (100), 131 (77), 116 (26), 115 (18), 107 (21), 103 (34), 91 (34), 90 (23), 89 (22).

Protection of Alcohols 1; General Procedure

To a suspension of NaH (1.73 g, 45 mmol) in THF (30 mL) was added alcohol (30 mmol) in THF (50 mL) at r.t. After the mixture was stirred for 10 min, *p*-methoxybenzyl choride (4.6 mL, 36 mmol) and TBAI (1.6 g, 4.2 mmol) were added. The resulting mixture was stirred for 4 h at 50 °C, and then H_2O (20 mL) was added. The mixture was extracted with Et_2O several times (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and evaporated to leave a crude product, which was purified by column chromatography (silica gel; pentane–Et_2O, 95:5).

3a[18]

Yield: 8.9 g (93%); colourless oil.

IR ($CHCl_3$): 3027, 2958, 2863, 1613, 1587, 1514, 1087, 1035 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.55–6.85 (m, 8 H, ArH), 4.59 (s, 2 H, CH_2), 4.56 (s, 2 H, CH_2), 3.80 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.1, 137.6, 130.0, 129.2, 128.7, 127.2, 122.6, 113.7, 72.3, 71.1, 55.1.

EIMS: *m*/*z* (%) = 308 (7), 306 (9), 150 (12), 137 (100), 122 (42), 121 (43), 119 (19), 91 (24), 77 (11).

Anal. Calcd for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92; O, 10.42; Br, 26.01; Found: C, 58.83; H, 4.98; O, 10.80; Br, 26.11.

3b

Yield: 9.12 g (95%); colourless oil.

IR ($CHCl_3$): 3027, 2960, 2862, 1613, 1586, 1514, 1090, 1037 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.73–7.09 (m, 8 H, ArH), 4.67 (s, 2 H, CH_2), 4.0 (s, 3 H, CH_3), 3.91–3.87 (m, 2 H, CH_2), 3.29–3.24 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 138.1, 132.7, 130.3, 129.1, 128.9, 127.1, 124.5, 113.6, 72.4, 68.9, 55.1, 36.3.

EIMS: *m/z* (%) = 322 (5), 320 (4), 241 (26), 121 (100), 105 (9), 91(7), 77 (9).

Anal. Calcd for $C_{16}H_{17}BrO_2$: C, 59.83; H, 5.33; O, 9.96; Br, 24.88. Found: C, 60.09; H, 5.46; O, 10.21; Br, 24.97.

3c

Yield: 8.2 g (82%); colourless oil.

IR ($CHCl_3$): 3027, 2937, 2839, 1613, 1586, 1512, 1104.

^1H NMR (200 MHz, acetone-d_6): δ = 7.49–6.81 (m, 8 H, ArH), 4.36 (s, 2 H, CH_2), 3.69 (s, 3 H, CH_3), 3.40 (t, *J* = 6.2 Hz, 2 H, CH_2), 2.75 (t, *J* = 7.7 Hz, 2 H, CH_2), 1.85–1.77 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 160.0, 142.1, 133.6, 133.4, 131.8, 131.5, 130.0, 129.8, 128.6, 124.8, 114.4, 72.9, 69.5, 55.4, 33.4, 30.6.

EIMS: *m/z* (%) = 336 (2), 334 (2), 256 (17), 255 (86), 137 (21), 122 (15), 121 (100), 119 (11), 91 (24), 77 (15).

HRMS (ESI): *m/z* calcd for $C_{17}H_{19}BrO_4Na$ (M + Na): 389.0364; found: 389.0343.

3d

Yield: 6.43 g (61%); colourless oil.

IR ($CHCl_3$): 3047, 2938, 2863, 1611, 1513, 1098 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.91–6.92 (m, 8 H, ArH), 4.50 (s, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 3.60–3.55 (m, 2 H, CH_2), 2.84–2.78 (m, 2 H, CH_2), 1.81–1.67 (m, 4 H, 2 × CH_2).

^{13}C NMR (75 MHz, acetone-d_6): δ = 159.2, 141.7, 132.8, 130.7, 130.4, 129.3, 127.6, 127.5, 126.3, 114.4, 113.8, 74.4, 69.9, 55.3, 35.9, 29.5, 26.6.

EIMS: *m/z* (%) = 350 (2), 348 (2), 122 (33), 121 (100).

HRMS (ESI): *m/z* calcd for $C_{18}H_{21}BrO_2Na$ (M + Na): 371.0623; found: 371.0603.

Arylation of Electron-Deficient Olefins; General Procedure

Under argon, in an undivided cell equipped with nickel foam (area 40 cm^2) as the cathode and an iron rod as the anode, TBAB (0.34 mmol) and TBAI (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·dm^{-2}) at r.t. over 15 min a small amount of iron ions resulted. The activated olefin (25 mmol), $NiBr_2·3H_2O$ (1 mmol) and aryl bromide (10 mmol) was added, and the reaction mixture was heated at 100 °C. The electrosynthesis was run at current density 0.2 A·dm^{-2}. The reaction was monitored by GC and stopped after the aryl bromide was consumed. The mixture was then hydrolysed with HCl (1 N; 30 mL) and diluted with Et_2O (2 × 50 mL) and the combined organic layers were washed with H_2O (15 mL) and sat. NaCl soln, then dried with $MgSO_4$. The oil thus obtained was purified by column chromatography (silica gel; pentane–Et_2O, 90:10) to give the desired compound.

5a

Yield: 2.6 g (79%); colourless oil.

IR ($CHCl_3$): 3025, 1726, 1612, 1586, 1514 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.55–7.09 (m, 8 H, ArH), 4.74 (s, 2 H, CH_2), 4.70 (s, 2 H, CH_2), 4.32 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.98 (s, 3 H, CH_3), 3.23–3.15 (m, 2 H, CH_2), 2.84–2.75 (m, 2 H, CH_2), 1.43 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.9, 159.1, 139.5, 135.8, 130.1, 129.5, 129.1, 128.1, 126.3, 113.7, 72.0, 70.0, 60.3, 55.1, 35.5, 27.5, 14.1.

EIMS: *m/z* (%) = 328 (<1), 192 (14), 161 (12), 146 (21), 137 (100), 133 (29), 122 (10), 121 (78), 118 (17), 117 (19), 115 (14), 109 (19), 105 (13), 91 (17), 77 (15).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.17; H, 7.52; O, 19.38.

5b

Yield: 2.6 g (76%); colourless oil.

IR ($CHCl_3$): 3025, 2960, 2862, 1726, 1613, 1586, 1514, 1076 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.02 (m, 8 H, ArH), 4.64 (s, 2 H, CH_2), 4.31 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.96 (s, 3 H, CH_3), 3.83 (t, *J* = 7.4 Hz, 2 H, CH_2), 3.15 (m, 4 H, 2 CH_2), 2.79–2.71 (m, 2 H, CH_2), 1.42 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.7, 159.0, 138.6, 136.5, 130.3, 129.7, 129.0, 126.4, 113.6, 72.5, 70.4, 60.3, 55.1, 35.3, 32.7, 27.6, 14.0.

EIMS: *m/z* (%) = 342 (<1), 254 (18), 137 (15), 122 (13), 121 (100).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65; O, 18.69. Found: C, 73.67; H, 7.64; O, 18.91.

5c

Yield: 1.59 g (64%); colourless oil.

IR ($CHCl_3$: 3027, 2939, 2863, 1727, 1612, 1586, 1513, 1096 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.12–6.70 (m, 8 H, ArH), 4.25 (s, 2 H, CH_2), 3.89 (q, *J* = 7.0 Hz, 2 H, CH_2), 3.59 (s, 3 H, CH_3), 3.29 (t, *J* = 5.9 Hz, 2 H, CH_2), 2.77 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.60–2.52 (m, 2 H, CH_2), 2.42–2.34 (m, 2 H, CH_2), 1.73–1.63 (m, 2 H, CH_2), 1.0 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, acetone-d_6): δ = 172.8, 160.0, 140.7, 139.3, 131.8, 129.9, 127.1, 114.3, 72.8, 69.7, 60.1, 55.4, 35.8, 31.9, 29.6, 28.1, 14.3.

EIMS: *m/z* (%) = 268 (27), 205 (13), 171 (10), 137 (21), 129 (11), 122 (18), 121 (100), 117 (11), 91 (14).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.32; H, 8.09; O, 18.00.

5d

Yield: 1.99 g (54%); colourless oil.

IR ($CHCl_3$): 3027, 2939, 2863, 1727, 1612, 1586, 1513, 1096 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.31–6.89 (m, 8 H, ArH), 4.41 (s, 2 H, CH_2), 4.07 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.78 (s, 3 H, CH_3), 3.48–3.44 (m, 2 H, CH_2), 2.98–2.92 (m, 2 H, CH_2), 2.68–2.55 (m, 4 H, 2 CH_2), 1.69–1.65 (m, 4 H, 2 × CH_2), 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, acetone-d_6): δ = 172.8, 159.8, 141.1, 139.1, 131.8, 129.9, 126.9, 114.2, 72.8, 70.3, 60.5, 55.4, 35.8, 32.8, 28.1, 14.5.

EIMS: *m/z* (%) = 268 (27), 205 (13), 171 (10), 137 (21), 129 (11), 122 (18), 121 (100), 117 (11), 91 (14).

HRMS (ESI): *m/z* calcd for $C_{23}H_{30}O_4Na$ (M + Na): 393.2042; found: 393.2005.

Deprotection of Alcohols 5; Typical Procedure

A solution of product **5a** (2.6 g, 7.88 mmol) and CAN (8.64 g, 15.3 mmol) in MeCN–H_2O (9:1, 37 mL) was stirred for 30 min at r.t. The reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic

phase was washed with sat. aq $NaHCO_3$ (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (silica gel; pentane–EtOAc, ratio).

6a[14]

Isolated as a mixture of **6a** and **8a**.

EIMS: *m*/*z* (%) = 208 (5), 190 (54), 175 (12), 163 (17), 162 (30), 147 (10), 145 (50), 144 (53), 134 (17), 133 (100), 119 (32), 118 (14), 117 (84), 116 (93), 115 (72), 107 (20), 105 (27), 103 (11), 91 (48), 79 (27), 77 (20).

6b

Due to the instability of **6b**, it was characterized by IR, NMR and MS only.

Yield: 1.52 g (80%); colourless oil.

IR ($CHCl_3$): 3462, 3032, 1727 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.21–7.00 (m, 4 H, ArH), 4.05 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.8 (br s, 1 H, OH under the next signal) 3.74 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.00–2.92 (m, 2 H, CH_2), 2.87 (t, *J* = 7.2 Hz, 2 H, CH_2), 2.60–2.52 (m, 2 H, CH_2), 1.16 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, acetone-d_6): δ = 173.1, 139.9, 138.0, 130.8, 129.7, 128.8, 127.1, 63.6, 60.7, 36.8, 35.9, 28.4, 14.5.

EIMS: *m*/*z* (%) = 222 (<1), 192 (51), 160 (40), 159 (51), 147 (18), 146 (100), 133 (18), 131 (47), 130 (38), 129 (28), 121 (13), 119 (21), 118 (88), 117 (78), 116 (16), 115 (53), 105 (29), 104 (25), 103 (11), 93 (11), 91 (37).

6c

Yield: 1.03 g (80%); colourless oil.

IR ($CHCl_3$): 3474, 3034, 1723 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.11–6.98 (m, 4 H, ArH), 3.98 (q, *J* = 7.2 Hz, 2 H, CH_2), 3.50 (br s, 1 H, OH under the signal), 3.50 (t, *J* = 6.3 Hz, 2 H, CH_2), 2.90–2.82 (m, 2 H, CH_2), 2.63 (t, *J* = 6.3 Hz, 2 H, CH_2), 2.51–2.43 (m, 2 H, CH_2), 1.76–1.62 (m, 2 H, CH_2), 1.09 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, acetone-d_6): δ = 172.7, 140.9, 139.1, 129.7, 126.6, 61.7, 60.4, 35.7, 35.0, 30.0, 27.9, 14.3.

EIMS: *m*/*z* (%) = 236 (9), 218 (54), 190 (15), 173 (26), 172 (92), 147 (10), 146 (37), 145 (46), 144 (92), 143 (17), 131 (34), 130 (47), 129 (100), 119 (11), 118 (22), 117 (79), 116 (23), 115 (54), 103 (12), 105 (38), 91 (39), 77 (12).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{20}O_3Na$ (M + Na): 259.1310; found: 259.1321.

6d

Yield: 0.75 g (70%); colourless oil.

IR ($CHCl_3$): 3474, 3034, 1723 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.20–7.09 (m, 4 H, ArH), 4.09 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.59 (t, *J* = 6.1 Hz, 2 H, CH_2), 3.56 (br s, 1 H, OH), 2.98–2.93 (m, 2 H, CH_2), 2.65 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.61–2.55 (m, 2 H, CH_2), 1.67–1.61 (m, 4 H, 2 × CH_2), 1.20 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, acetone-d_6): δ = 172.2, 140.5, 138.4, 129.2, 128.8, 126.2, 125.9, 61.3, 59.8, 35.1, 32.7, 32.1, 27.6, 27.4, 13.6.

EIMS: *m*/*z* (%) = 250 (<1), 204 (16), 187 (15), 186 (100), 159 (13), 158 (49), 145 (28), 144 (27), 143 (23), 133 (12), 132 (11), 131 (27), 130 (34), 129 (33), 128 (13), 118 (11), 117 (38), 116 (15), 115 (28), 105 (11), 91 (17).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{23}O_3$ (M + H): 251.1647; found: 251.1664.

Saponification; Typical Procedure

To a solution of **6a** (1.46 g, 7 mmol) in dioxane–H_2O (1:1, 70 mL) was added a 20% soln of KOH in H_2O (1.56 g, 24 mmol). The reaction mixture was refluxed for 16 h, cooled to r.t., then H_2SO_4 was added until pH = 1 was reached. The mixture was extracted with Et_2O (3 × 25 mL). The combined extracts were dried ($MgSO_4$) and evaporated to leave the crude product.

7a[19]

Yield: 1.26 g (quantitative).

IR (KBr): 3346, 1694 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.27–6.98 (m, 4 H, ArH), 4.56 (s, 2 H, CH_2), 2.88–2.80 (m, 2 H, CH_2), 2.53–2.45 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 174.3, 140.5, 139.7, 129.7, 129.1, 128.2, 126.8, 62.6, 35.4, 27.7.

7b

Yield: 1.36 g (quantitative).

IR (KBr): 3392, 2918, 2865, 1702 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.09–6.94 (m, 4 H, ArH), 3.62 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.87–2.79 (m, 2 H, CH_2), 2.76 (t, *J* = 7.3 Hz, 2 H, CH_2), 2.49–2.41 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 174.1, 139.9, 137.8, 130.6, 126.9, 126.6, 63.4, 36.5, 35.4, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{11}H_{14}O_3Na$ (M + Na): 217.0841; found: 217.0840.

7c

Yield: 1.46 g (quantitative).

IR (KBr): 3300, 2936, 2865, 1720 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 7.09–6.93 (m, 4 H, ArH), 3.49 (t, *J* = 6.3 Hz, 2 H, CH_2), 2.87–2.79 (m, 2 H, CH_2), 2.61 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.49–2.41 (m, 2 H, CH_2), 1.73–1.59 (m, 2 H, CH_2).

^{13}C NMR (50 MHz, acetone-d_6): δ = 174.0, 140.9, 139.4, 129.8, 126.9, 126.6, 61.8, 35.4, 35.0, 34.8, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}O_3Na$ (M + Na): 231.0997; found: 231.0976.

7d

Yield: 1.55 g (quantitative).

IR (KBr): 3300, 2937, 2868, 1711 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.21–7.01 (m, 4 H, ArH), 3.60 (t, *J* = 6.2 Hz, 2 H, CH_2), 2.98–2.93 (m, 2 H, CH_2), 2.69 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.62–2.56 (m, 2 H, CH_2), 1.65–1.62 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, acetone-d_6): δ = 174.7, 141.4, 139.6, 127.0, 126.9, 62.5, 35.8, 33.6, 33.1, 32.8, 28.5, 28.3.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M + Na): 245.1154; found: 245.0871.

***p*-Nitrobenzoic Anhydride**

To a mixture of *p*-nitrobenzoic acid (3.34 g, 20 mmol) and *p*-nitrobenzoic chloride (3.71g, 20 mmol) in CH_2Cl_2 (50 mL) was added pyridine (2.02 mL, 25 mmol) dropwise at 0 °C. The reaction mixture was stirred for 15 h at r.t. and then quenched with cold H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the organic phases were dried with $MgSO_4$ and evaporated. The crude product was purified by recrystallisation from CH_2Cl_2–hexane to afford *p*-nitrobenzoic anhydride (5.4 g, 85% yied).

Lactonisation; Typical Procedure

p-Nitrobenzoic anhydride (506 mg, 1.6 mmol) was dissolved in anhyd MeCN (340 mL), and a cloudy solution of $Sc(OTf)_3$ (1.6 mL,

0.16 mmol, 0.1 M) in MeCN was added to the solution at r.t. under argon. A solution of hydroxycarboxylic acid (20 mL, 0.8 mmol, 0.08 M) in THF was added slowly from a mechanically driven syringe over 15 h to the mixed solution at reflux under argon, and the reaction mixture was stirred for a further 5 h at reflux. After cooling to r.t., the solution was quenched with aq sat. $NaHCO_3$ (8 mL). The resulting mixture was concentrated under reduced pressure and extracted with Et_2O (2 × 25 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (silica gel; pentane–EtOAc) gave the desired lactone.

8a[8,20]

Yield: 0.067 g (52%); colourless oil.

IR ($CHCl_3$): 3060, 2927, 1733, 1606, 1530 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.05 (m, 4 H, ArH), 5.18 (s, 2 H, CH_2), 3.18–3.13 (m, 2 H, CH_2), 3.01–2.96 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 137.0, 133.2, 130.0, 129.2, 126.6, 70.2, 31.5, 28.4.

EIMS: *m*/*z* (%) = 162 (26), 144 (27), 133 (19), 118 (19), 117 (100), 116 (50), 115 (50), 105 (17), 91 (42), 77 (12).

8b[8]

Yield: 0.053 g (38%); colourless oil.

IR ($CHCl_3$): 3022, 2928, 1732, 1604, 1492 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.23–7.18 (m, 4 H, ArH), 4.29 (t, *J* = 5.5 Hz, 2 H, CH_2), 3.07 (t, *J* = 6.5 Hz, 2 H, CH_2), 2.98 (t, *J* = 5.5 Hz, 2 H, CH_2), 2.61 (t, *J* = 6.5 Hz, 2 H, CH_2).

^{13}C NMR (75 MHz, acetone-d_6): δ = 176.5, 139.9, 137.7, 130.9, 130.3, 127.2, 127.1, 67.2, 39.1, 35.8, 30.9.

EIMS: *m*/*z* (%) = 176 (57), 161 (11), 147 (13), 146 (36), 131 (52), 130 (40), 117 (31), 116 (11), 115 (29), 105 (10), 104 (100), 103 (14), 78 (27).

8c

Yield: 0.100 g (66%); colourless oil.

IR ($CHCl_3$): 3016, 2937, 2868, 1736, 1603, 1491 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.2–7.08 (m, 4 H, ArH), 4.21–4.16 (m, 2 H, CH_2), 3.05–2.98 (m, 2 H, CH_2), 2.89–2.70 (m, 2 H, CH_2), 2.52–2.45 (m, 2 H, CH_2), 2.19–2.05 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, acetone-d_6): δ = 173.7, 142.6, 138.1, 130.4, 130.2, 126.8, 126.1, 62.3, 36.7, 31.1, 30.7, 26.7.

EIMS: *m*/*z* (%) = 191 (11), 190 (60), 173 (16), 172 (100), 157 (20), 146 (20), 145 (20), 144 (50), 133 (12), 131 (26), 130 (22), 129 (59), 128 (21), 118 (22), 117 (87), 116 (26), 115 (58), 105 (18), 91 (40).

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}O_2$ (M + H):191.1072; found: 191.1085.

8d

Yield: 0.109 g (67%); colourless oil.

IR ($CHCl_3$): 3056, 2957, 2860, 1732, 1530, 1491 cm^{-1}.

^1H NMR (300 MHz, DMF-d_7, 343 K): δ = 7.27–7.10 (m, 4 H, ArH), 4.23–4.18 (m, 2 H, CH_2), 3.05–2.91 (m, 4 H, 2 × CH_2), 2.64–2.59 (m, 2 H, CH_2), 2.08–1.99 (m, 2 H, CH_2), 1.43–1.35 (m, 2 H, CH_2).

^{13}C NMR (75 MHz, DMF-d_7, 343 K): δ = 171.1, 139.6, 138.7, 130.3, 128.5, 126.4, 125.8, 65.5, 37.2, 28.5, 28.4, 27.2, 24.4.

EIMS: *m*/*z* (%) = 204 (59), 187 (13), 186 (100), 171 (26), 158 (83), 157 (15), 145 (12), 143 (25), 142 (13), 131 (30), 130 (53), 129 (46), 128 (17), 117 (51), 116 (19), 115 (55), 105 (12), 91 (26).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{17}O_2$ (M + H): 205.1229; found: 205.1232.

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