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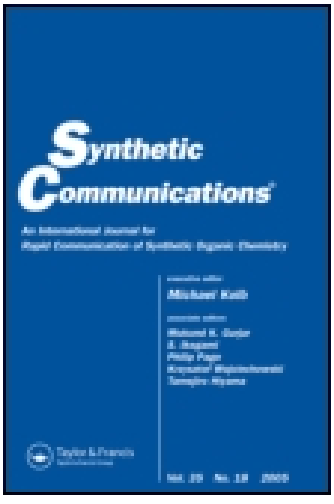

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Efficient Route to Medium-Ring Benzo- and Azabenzo-lactones

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Efficient Route to Medium-Ring Benzo- and Azabenzo-lactones

Estelle Metay, Eric Léonel, and Jean-Yves Nédélec

Institut de Chimie et des Matériaux Paris-Est, Equipe Electrochimie et Synthèse Organique, Thiais, France

Abstract: The synthesis of precursors of medium-ring benzo- and azabenzo-lactones is performed efficiently from simple *ortho*-halo aryl and heteroaryl aldehydes.

Keywords: electrochemical arylation, medium ring lactones, nickel catalysis

Medium-ring lactones are challenging targets of interest either as intermediates or as bioactive compounds.[1] Indeed, many natural products have been described with medium- to large-ring lactones.[2] However, they are hardly prepared chemically, even by the most obvious ring-forming lactonization.[3] In addition, precursors can also be difficult to prepare. We have previously reported our studies on the synthesis of $\alpha-\omega$ hydroxyacids to access to medium-ring benzolactones.[4] Lactone precursors are characterized by two carbon chains ortho to each other on the aromatic ring and ending with the carboxyl for one and the alcohol group for the other. Several features have already been investigated, such as the size of the lactone (from 7 to 11 members), the relative position of the carboxyl connection relative to the aromatic ring (excluding conjugated carbonyls), the possible presence of double bonds within the ring, and the number of steps. The study presented here refers to the aromatic side of the benzolactone, considering either the

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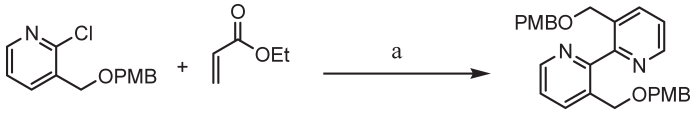

Figure 1. Reagents and conditions: (a) $NiBr_2 \cdot 3H_2O$, NBu_4Br, NBu_4I, DMF/pyridine (9/1), 100°C, 3 h.

presence of substituents on the phenyl ring or the heteroaromatic character of this moiety. Apart from considering the potential interest of the prepared structures, the purpose was to take into account the specific reactivity of the substrates in each step as a function of the aromatic ring.

Typical starting materials are aryl or heteroaryl rings featuring a C-halogen bond and a C-C bond that are *ortho* to each other. In the first experiment, we attempted to introduce a propionic chain *alpha* to the nitrogen of the OH-protected 2-chloro-3-hydroxymethylpyridine via the nickel-catalysed electrochemical coupling with ethyl acrylate. However, we only obtained the bipyridine derivative instead of the addition product to the acrylic ester (see Fig. 1). This result was both surprising, because the reaction conditions applied to the other substrates never gave such a dimer, and interesting, because *ortho*-substituted aryl halides are hardly dimerized for steric reasons.

We then shifted to another methodology, which is detailed in Scheme 1.

For this procedure, we used the commercially available precursors, *ortho*-halo aryl aldehydes or carboxylic acids, with the halogen being *alpha* to the nitrogen in pyridine and quinoline derivatives. The aldehyde carbonyl is used to introduce one carbon chain via the Wadsworth–Emmons reaction, while the C-halogen bond is involved in the electrochemical condensation with an activated olefin.

The starting compounds are listed in Scheme 2.

They are all commercial except the pyridine derivative, which was obtained from 2-chloronicotinic acid via alcohol (Scheme 3).

From these aldehydes, we started introducing a carbon chain ending with a carboxylic group via the Wadsworth–Emmons reaction[5] (Table 1). The propenoic chain was introduced efficiently (yields of 83% to 99%, Table 1, entries 1–3). The yields in the pentadienoic chain (Table 1, entries 4 and 5) were lower, between 53 and 56%, with an all (*E*)-geometry.

The next step was the introduction of the second carbon chain, ending with a precursor of the alcohol group in the form of a carbonyl. The reaction was thus the arylation of methyl-vinylketone via the electrochemical method involving nickel complexes as catalysts. Isolated yields are good to high (Table 2). It should be pointed out that this reaction is very selective, because no side reaction occurred on the unsaturated carbon chain already present on the molecule. The yield is quite medium with the fluoro derivative (Table 2, entry 1), which indeed led more importantly to mere reduction of the C-Br bond.

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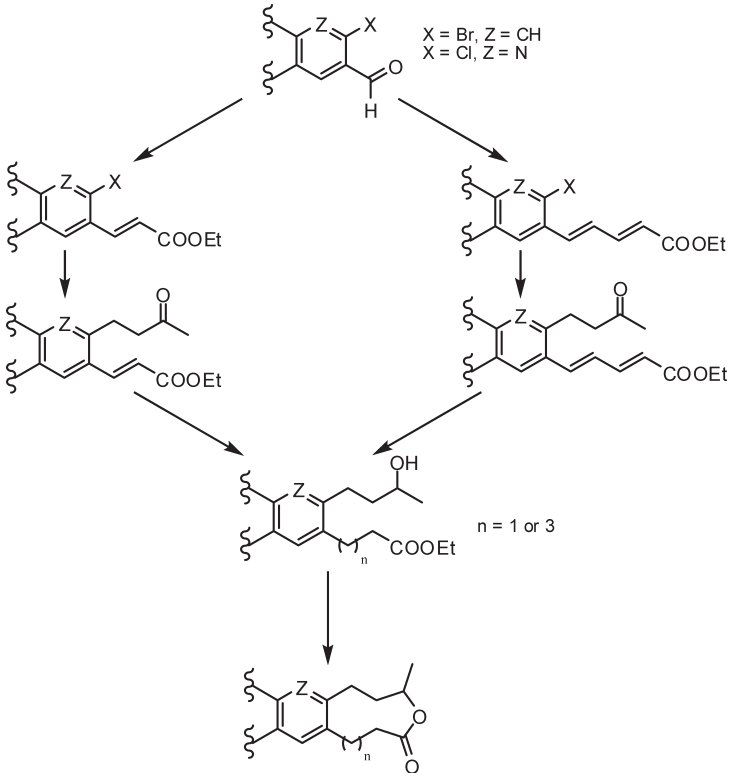
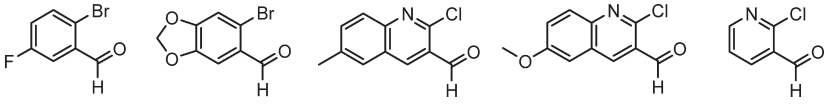


Scheme 1.

The two functional groups were then manipulated to generate the alcohol by reduction of the ketone carbonyl and the carboxylic acid by saponification.

Regarding the reduction, we selected the reagent able to reduce both the ketone carbonyl and the C═C double bond(s) without reducing the ester group. This was performed by the combination of $NaBH_4$ with $NiCl_2$, as described by Narisada.[6] The C═C double bonds had to be reduced because (*E*)-C,C double bonds preclude the hydroxy acid from lactonizing.

The carboxylic group was generated from the corresponding ester by saponification, and the hydroxy acids were obtained in high yields. The



Scheme 2.

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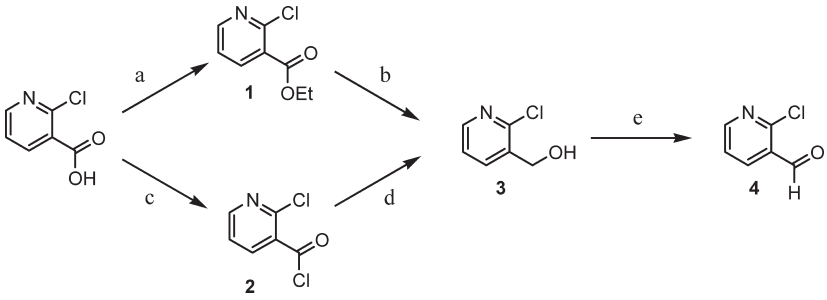
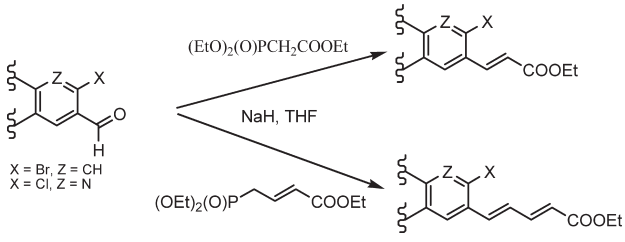
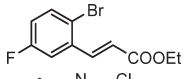
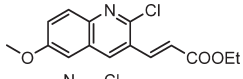
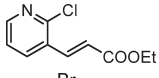
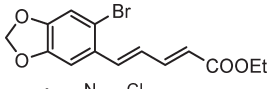
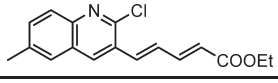


Scheme 3. Reagents and conditions: (a) 1, KOH; 2, $BrCH_2CH_3$, NBu_4Br, 30°C, 4 h; (b) $NaBH_4$, $CaCl_2$ ethanol 0°C, 2 h; (c) $SOCl_2$, reflux, 2 h; (d) $NaBH_4$, H_2O, 0°C, 30 min; (e) PCC, CH_2Cl_2, rt, 2 h.

Table 1. Wadsworth–Emmons reaction



Entry	Products	Compound number	Isolated yields (%)
1		**5**	96
2		**6**	99
3		**7**	83
4		**8**	53
5		**9**	56

reactions were conducted with KOH in water/dioxane at reflux followed by H_2SO_4 hydrolysis or with NaOH in methanol at room temperature followed by HCl treatment. The second method is more appropriate for the aza compounds with an amount of water as low as possible, thus allowing an easy recovery of the hydrochloride compounds (Table 3).

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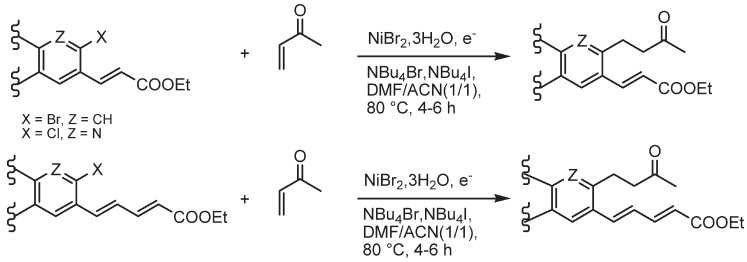
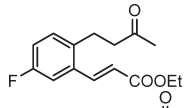
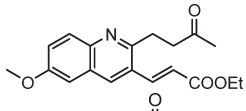
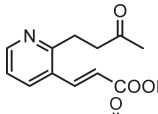
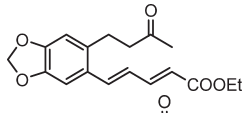
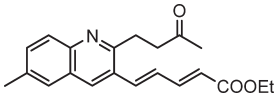
Table 2. Electrochemical arylation



Entry	Product	Compound number	Isolated yield(%)
1		**10**	43
2		**11**	82
3		**12**	66
4		**13**	65
5		**14**	63%

The final lactones were obtained by lactonization using the Yamamoto method[7] based on the use of *p*-nitrobenzoic anhydride and scandium triflate. All compounds obtained are new benzo- or azabenzo-lactones (Table 4).

EXPERIMENTAL

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 an Avance 300 (300-MHz) spectrometer at room temperature, except for benzolactone **20**, **21**, and **22** at 70°C. In the ^{13}C data, some of aromatic signals are missing. This might be a consequence of the overlapping of certain signals. Infrared spectra

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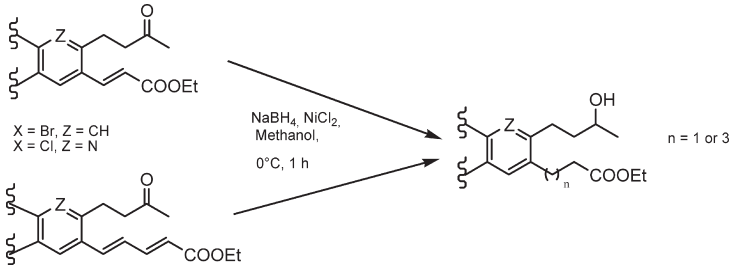
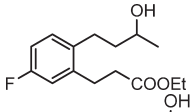
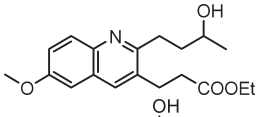
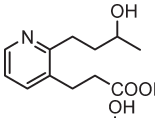
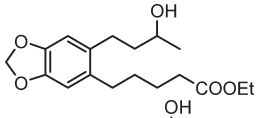
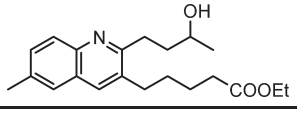
Table 3. Double bond and ketone reduction



Entry	Product	Compound number	Isolated Yield (%)
1		**15**	82
2		**16**	71
3		**17**	87
4		**18**	66
5		**19**	55%

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 were performed by Service Central d'Analyses du CNRS, Lyon, France.

Compound 1, Ethyl 2-Chloropyridine-3-carboxylate

Preparation

To a solution of chloronicotinic acid (30 mmol, 4.76 g) in methanol (50 mL), pellets of KOH (30 mmol, 1.95 g) were added. The solvent was removed

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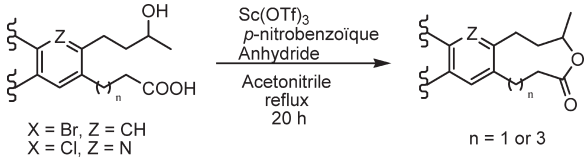
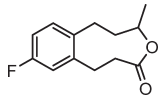
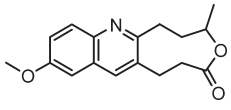
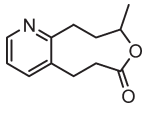
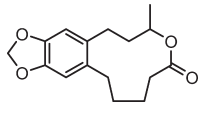
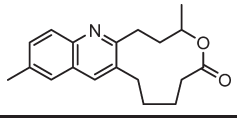
Table 4. Lactonization



Entry	Lactone	Compound number	Isolated Yields (%)
1		**20**	76
2		**21**	55
3		**22**	26
4		**23**	78
5		**24**	25

under pressure. The salt obtained was mixed in a flask with tetrabutylammonium bromide (3 mmol, 0.967 g) and bromoethane (45 mmol, 3.44 mL). After 4 h of stirring at 30°C, the reaction mixture was diluted with ether (200 mL) and filtrated over a florisil pad.

Data

RN: [1452-94-4];[8] 92%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.50 (dd, $J = 4.8$, 1.9 Hz, 1H), 8.15 (dd, $J = 7.7$, 1.9 Hz, 1H), 7.33 (dd, $J = 4.8$, 7.7 Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 164.5, 151.7, 149.9, 140.1, 127.2, 122.1, 62.1, 14.1; MS (EI) M/Z (%): 185 (18), 159 (26), 157 (78), 150 (57), 142 (35), 140 (100), 114 (11), 113 (16), 112 (31), 76 (21); IR ν_{max}: 3037, 2997, 2941, 2908, 1727, 1581, 1564.

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Compound 3, 2-Chloro-3-hydroxymethylpyridine

Method b

To a solution of ethyl-2-chloropyridine carboxylate (45 mmol, 8.4 g) in ethanol (150 mL), $NaBH_4$ (90 mmol, 3.42 g) and $CaCl_2$ (90 mmol, 9.99 g) were added portionwise at 0°C over 30 min. After 2 h of stirring at room temperature, the reaction mixture was quenched with 1 N sodium hydroxide aqueous solution (50 mL), extracted with ether, dried over $MgSO_4$, filtered, and concentrated.

Methods c and d

Chloronicotinic acid (78.9 mmol, 12.5 g) was mixed with thionyl chloride (50 mL) and heat at reflux for 2 h then concentrated. The solid obtained was added portionwise to a solution of $NaBH_4$ (78.9 mmol, 12.5 g) in water (100 mL) at 0°C. After 30 min, the reaction mixture was saturated with NaCl and extracted with ether, dried over $MgSO_4$, filtered, and concentrated.

Data

RN: [42330-59-6];[9] mp: 62–63°C; 70% (a + b); 82% (d + e); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.18 (dd, $J = 4.8$, 1.9 Hz, 1H), 7.92 (dd, $J = 7.6$, 1.9 Hz, 1H), 7.24 (dd, $J = 4.8$, 7.6 Hz, 1H), 4.73 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 148.7, 147.6, 137.0, 135.8, 122.9, 60.8; EI-MS (m/z): 145 (15), 144 (14), 143 (46), 142 (28), 116 (11), 114 (30), 108 (100), 107 (13), 106 (50), 80 (16), 79 (23), 78 (70), 76 (11), 52 (15), 51 (31); IR ($_{max}$: 3605, 3350, 1583, 1570.

Compound 4, 2-Chloro-3-formylpyridine

Preparation

To a solution of 2-chloro-3-hydroxymethylpyridine (66.5 mmol, 9.61 g) in CH_2Cl_2 (100 mL), pyridinium chlorochromate (79.8 mmol, 17.2 g) was added. After 2 h, the reaction mixture was diluted with ether, washed twice with ether, then filtered and concentrated. Purification by column chromatography (70–200 mesh; pentane/ethyle acetate 50/50) afforded 6.89 g of the title product.

Data

RN: [36404-88-3];[9] 73%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 10.24 (s, 1H), 8.62 (m, 1H), 8.25 (m, 1H), 7.46 (dd, $J = 4.5$, 7.5 Hz, 1H); EI-MS (m/z): 143 (28), 142 (37), 141 (80), 140 (100), 114 (11), 113 (11), 112 (34), 105 (69), 78 (12), 77 (28), 76 (36), 51 (19), 50 (16).

Compounds 5–9

Procedure

For general procedure, see ref. [5] for product **5** to **9**.

Ethyl (*E*)-3-(2-bromo-5-fluorophenyl)prop-2-enoate **5**

Yield 96%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.96 (d, $J = 15.9$ Hz, 1H), 7.55 (dd, $J = 8.8$ Hz, $^{4}J_{HF} = 5.2$ Hz, 1H), 7.30 (dd, $J = 3.0$ Hz, $^{3}J_{HF} = 9.4$ Hz, 1H), 6.97 (ddd, $J = 3.0$ Hz, $J = 8.8$ Hz, $^{3}J_{HF} = 7.7$ Hz, 1H), 6.37 (d, $J = 15.9$ Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.0, (d, $^{1}J_{CF} = 247.7$ Hz) 161.9, (d, $^{4}J_{CF} = 2.0$ Hz) 141.8, (d, $^{3}J_{CF} = 7.8$ Hz) 136.2, (d, $^{3}J_{CF} = 8.0$ Hz) 134.6, 122.3, (d, $^{4}J_{CF} = 3.2$ Hz) 119.4, (2d, $^{2}J_{CF} = 22.7$ Hz, 23.5 Hz) 118.4 and 114.4, 60.8, 14.3; ^{19}F NMR ($CDCl_3$, 188 MHz) δ: -113.8 (m); MS (EI) M/Z (%): 273 (9), 229 (13), 227 (13), 193 (63), 166 (10), 165 (100), 121 (23), 120 (38), 109 (13); IR ν_{max}: 3074, 2980, 2938, 1713; HRMS (ESI) m/z calcd. for $C_{11}H_{11}BrFO_2$ (M + H) 272.9926; found: 272.9940.

Ethyl (*E*)-3-(2-Chloro-6-methoxy-3-quinolyl)prop-2-enoate **6**

Mp: 109.1–111.6°C; quantitative; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.19 (s, 1H), 8.05 (d, $J = 16.0$ Hz, 1H), 7.85 (d, $J = 9.2$ Hz, 1H), 7.36 (dd, $J = 9.2$, 2.8 Hz, 1H), 7.03 (d, $J = 2.8$ Hz, 1H), 6.51 (d, $J = 16.0$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 3.92 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.9, 158.5, 147.4, 143.9, 139.3, 134.7, 129.7, 128.1, 127.4, 124.3, 122.5, 105.2, 60.9, 55.6, 14.3; MS (EI) M/Z (%): 293 (10), 291 (30), 256 (58), 229 (14), 228 (100), 200 (39), 182 (13); IR ($_{max}$: 3038, 2988, 1711, 1638, 1621. HRMS (ESI) m/z calcd. for $C_{15}H_{15}ClNO_3$ (M + H) 292.0740; found: 292.0753.

Ethyl (*E*)-3-(2-Chloro-3-pyridinyl)prop-2-enoate **7**

RN: [148247-84-1],[10] mp: 49.1–49.8°C; 83%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.40 (dd, $J = 1.8$ Hz, $J = 4.7$ Hz, 1H), 7.98 (d, $J = 15.8$ Hz, 1H), 7.94 (dd, $J = 1.8$ Hz, $J = 7.7$ Hz, 1H), 7.31 (dd, $J = 4.7$ Hz, $J = 7.7$ Hz, 1H), 6.46 (d, $J = 15.8$ Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 165.8, 151.3, 150.5, 138.8, 136.0, 129.6, (2C) 123.0, 122.9, 61.0, 14.3; MS (EI) M/Z (%): 211 (<10), 176 (72), 166 (27), 148 (100), 138 (12), 120 (24), 102 (16); IR ν_{max}: 3037, 2997, 2941, 2875, 1727, 1581, 1564.

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Ethyl (*E,E*)-5-(2-Bromo-4.5-methylenedioxyphenyl)penta-2.4-dienoate **8**

Mp: 87.3–88.9°C; 53%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.46 (dd, $J = 11.1$, $J = 15.1$ Hz, 1H), 7.18 (d. $J = 15.4$ Hz, 1H), 7.05 (s, 1H), 7.01 (s, 1H), 6.64 (dd, $J = 11.0$, $J = 15.4$ Hz, 1H), 6.00 (s, 2H), 5.98 (d, $J = 15.1$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.9, 149.0, 147.9, 144.3, 138.4, 129.1, 126.9, 121.6, 113.0, 116.6, 105.8, 102.1, 60.4, 14.4; MS (EI) M/Z (%): 326 (46), 324 (47), 253 (14), 252 (27), 251 (18), 250 (25), 223 (11), 200 (23), 199 (19), 174(10), 173 (86), 172 (100), 171 (42), 144 (10), 143 (27), 115 (33), 114 (17); IR ν_{max}: 3054, 2984, 2904, 1705, 1614, 1505, 1475.

Ethyl (*E,E*)-5-(2-Chloro-6-methyl-3-quinolyl)penta-2.4-dienoate **9**

Mp: 121–124°C; 56%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.57–7.48 (m, 3H), 7.32 (d, $J = 15.5$ Hz, 1H), 6.95 (dd, $J = 15.5$ Hz, 11.1 Hz, 1H), 6.10 (d, $J = 15.3$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 2.54 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 166.6, 149.0, 145.9, 143.5, 137.6, 134.6, 133.9, 133.2, 130.0, 128.0, 126.6, 128.6, 127.2, 123.3, 60.6, 21.6, 14.3; MS (EI) M/Z (%): 303 (15), 301 (47), 256 (13), 230 (36), 229 (21), 228 (100), 227 (23), 210 (15), 194 (12), 193 (20), 192 (53), 191 (15), 190 (12), 165 (22); IR ($_{max}$: 3025, 2992, 2928, 1707, 1629, 1602; HRMS (ESI) m/z calcd. for $C_{17}H_{17}ClNO_2$ (M + H): 302.0948; found: 302.0941.

Preparation of Compounds 10–14

Procedure

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. The reaction mixture was heated at 80°C. The electrosynthesis was run at current density (0.1 A). The reaction was monitored by gas chromatography (GC) and stopped after the aryl bromide was consumed. The mixture was then hydrolyzed 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 the desired product.

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Ethyl (*E*)-3-[5-Fluoro-2-(3-oxobutyl)phenyl]prop-2-enoate **10**

Yield 43%; ^{1}H NMR ($CDCl_3$. 300 MHz) δ: 7.94 (d, $J = 15.8$ Hz, 1H), 7.26–7.18 (m, 2H), 7.04–6.97 (m, 1H), 6.37 (d, $J = 15.8$ Hz, 1H), 4.29 (q, $J = 7.2$ Hz, 2H), 3.03–2.98 (m, 2H), 2.73–2.67 (m, 2H), 2.15 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.0, 166.5, (d, $^{1}J_{CF} = 245.1$ Hz) 161.5, (d, $^{4}J_{CF} = 2.0$ Hz) 140.4, (d, $^{4}J_{CF} = 3.0$ Hz) 136.3, (d, $^{3}J_{CF} = 7.5$ Hz) 134.7, (d, $^{3}J_{CF} = 7.9$ Hz) 131.7, 121.2, (2d, $^{2}J_{CF} = 21.2$, 22.1 Hz) 117.0 and 113.1, 60.7, 44.8, 30.0, 26.3, 14.3; MS (EI) M/Z (%): 264 (2), 190 (22), 176 (19), 175 (100), 149 (16), 148 (12), 147 (67), 146 (12), 133 (29), 127 (14); IR ν_{max}: 3068, 2987, 2940, 1715; HRMS (ESI) m/z calcd. for $C_{15}H_{18}FO_3$ (M + H): 265.1240; found: 265.1246.

Ethyl (*E*)-3-[6-Methoxy-2-(3-oxobutyl)-3-quinolyl]prop-2-enoate **11**

Mp 111.3–111.7°C; 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.15 (s, 1H), 8.09 (d, $J = 15.8$ Hz, 1H), 7.87 (d, $J = 9.1$ Hz, 1H), 7.36 (dd, $J = 9.2$, 2.8 Hz, 1H), 7.07 (d, $J = 2.8$ Hz, 1H), 6.50 (d, $J = 15.8$ Hz, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 3.95 (s, 3H), 3.39–3.35 (m, 2H), 3.11–3.06 (m, 2H), 2.36 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 208.3, 166.4, 157.7, 155.8, 144.1, 140.6, 132.6, 130.1, 127.8, 127.6, 123.0, 121.9, 105.2, 60.8, 55.6, 40.5, 30.5, 29.5, 14.3; MS (EI) M/Z (%): 327 (17), 312 (12), 285 (15), 284 (100), 256 (53), 255 (14), 254 (86), 212 (29), 211 (23), 210 (57), 168 (10), 167 (18); IR ν_{max}: 3034, 2962, 1712, 1636; HRMS (ESI) m/z calcd. for $C_{19}H_{22}NO_4$ (M + H): 328.1549; found: 328.1556.

Ethyl (*E*)-3-[2-(3-Oxobutyl)-3-pyridinyl]prop-2-enoate **12**

Yield 66%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.49 (dd, $J = 4.8$, 1.6 Hz, 1H), 7.98 (d, $J = 15.9$ Hz, 1H), 7.80 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.17 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.37 (d, $J = 15.9$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.25–3.20 (m, 2H), 3.01–2.97 (m, 2H), 2.24 (s, 3H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.9, 166.2, 158.5, 149.9, 140.1, 133.9, 128.9, 121.8, 121.6, 60.7, 40.9, 30.1, 28.6, 14.3; MS (EI) M/Z (%): 232 (57), 205 (11), 204 (100), 176 (63), 174 (86), 132 (53), 131 (29), 130 (91), 117 (11); IR ν_{max}: 3069, 2977, 2939, 1713, 1637, 1583, 1566, 1433; HRMS (ESI) m/z calcd. for $C_{14}H_{18}NO_3$ (M + H): 248.1287; found: 248.1292.

Ethyl (*E,E*)-5-[4,5-Methylenedioxy-2-(3-oxobutyl)phenyl]pent-2,4-dienoate **13**

Mp 70.5–71.3°C; 65%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.42 (dd, $J = 11.1$, $J = 15.3$ Hz, 1H), 7.05–6.64 (m, 4H), 5.95–5.90 (m, 3H), 4.20 (q, $J = 7.1$ Hz, 2H), 2.90–2.85 (m, 2H), 2.66–2.61 (m, 2H), 2.12 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 207.2, 167.0,

148.5, 146.7, 144.8, 136.8, 134.6, 127.8, 125.9, 120.6, 109.9, 105.3, 101.3, 60.3, 44.9, 30.0, 26.9, 14.3; MS (EI) M/Z (%): 317 (12), 316 (57), 258 (31), 245 (21), 229 (21), 225 (13), 213 (21), 212 (24), 201 (11), 199 (19), 186 (15), 185 (100), 183 (11), 173 (26), 169 (13), 141 (12), 115 (18); IR ν_{max}: 3054, 2984, 2900, 1708, 1614, 1504, 1484; HRMS (ESI) m/z calcd. for $C_{18}H_{20}O_5Na$ (M + Na): 339.1208; found: 339.1225.

Ethyl (*E*,*E*)-5-[6-Methyl-2-(3-oxobutyl)-3-quinolyl]penta-2.4-dienoate **14**

Yield 63%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.07 (s, 1H), 7.83 (d, $J = 8.5$ Hz, 1H), 7.55–7.45 (m, 3H), 7.23 (d, $J = 15.3$ Hz, 1H), 6.87 (dd, $J = 15.3$, 11.1 Hz, 1H), 6.05 (d, $J = 15.3$ Hz, 1H), 4.27 (q, $J = 7.1$ Hz, 2H), 3.52–3.45 (m, 2H), 3.31–3.27 (m, 2H), 2.50 (s, 3H), 2.33 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 208.3, 166.8, 157.1, 145.9, 143.5, 136.1, 135.8, 132.0, 131.8, 129.5, 128.3, 126.5, 128.9, 126.9, 122.4, 60.5, 40.5, 30.4, 29.6, 21.5, 14.3; MS (EI) M/Z (%): 337 (26), 323 (10), 322 (47), 308 (38), 295 (29), 294 (100), 280 (20), 266 (33), 264 (18), 248 (32), 222 (16), 221 (14), 220 (54), 207 (22), 206 (15), 194 (61), 181 (14); IR ν_{max}: 3041, 2979, 1723, 1628; HRMS (ESI) m/z calcd. for $C_{21}H_{24}NO_3$ (M + H): 338.1756; found: 338.1757.

Ethyl 3-[5-Fluoro-2-(3-hydroxybutyl)phenyl]propanoate **15**

Yield 82%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.14 (dd, $J = 8.2$, 6.3 Hz, 1H), 6.89–6.82 (m, 2H, H_7), 4.16 (q, $J = 7.1$ Hz, 2H), 3.92–3.81 (m, 1H), 3.00–2.95 (m, 2H), 2.83–2.58 (m, 4H), 2.44 (se, 1H), 1.76–1.68 (m, 2H), 1.29–1.24 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.9, (d, $^1J_{CF} = 243.5$ Hz) 161.2, (d, $^3J_{CF} = 7.0$ Hz, C_6) 140.3, (d. $^4J_{CF} = 3.0$ Hz) 135.7, (d, $^3J_{CF} = 7.9$ Hz) 130.6, (2d, $^2J_{CF} = 21.0$ Hz, 20.7 Hz) 115.3 and 113.2, 67.4, 60.7, 40.6, 35.0, 28.1, (d, $^4J_{CF} = 1.3$ Hz) 27.5, 23.7, 14.2; MS (EI) M/Z (%): 268 (14), 250 (38), 205 (11), 204 (44), 189 (12), 181 (11), 178 (12), 177 (21), 176 (70), 175 (17), 165 (11), 164 (14), 163 (22), 162 (55), 161 (89), 160 (16), 159 (12), 151 (32), 150 (12), 149 (76), 148 (22), 147 (100), 146 (45), 137 (17), 136 (25), 135 (83), 134 (24), 133 (33), 123 (18), 122 (12), 115 (41), 109 (22); IR ν_{max}: 3462, 3032, 1727; HRMS (ESI) m/z calcd. for $C_{15}H_{22}FO_3$ (M + H): 269.1553; found: 269.1561.

Ethyl 3-[2-(3-Hydroxybutyl)-6-methoxy-3-quinolyl]propanoate **16**

Yield 71%; ^{1}H NMR ($CDCl_3$ 300 MHz) δ: 7.93 (d, $J = 9.2$ Hz, 1H), 7.84 (s, 1H), 7.31 (dd, $J = 9.2$, 2.8 Hz, 1H), 7.02 (d, $J = 2.8$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.95–3.87 (m, 4H), 3.30–3.08 (m, 4H), 2.76–2.70 (m, 2H), 2.10–1.97 (m, 2H), 1.29 (d, $J = 6.3$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.5, 158.3, 157.8, 141.8, 134.5, 132.3, 129.4, 128.0, 121.7, 104.7, 67.6, 60.7, 55.5, 36.7, 34.4, 31.7, 27.5,

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23.7, 14.2; MS (EI) M/Z (%): 332 (2), 312 (20), 311 (100), 283 (19), 282 (13), 239 (36), 238 (73), 224 (13); IR ν_{max}: 3602, 3037, 2931, 1728, 1643; HRMS (ESI) m/z calcd. for $C_{19}H_{25}NO_4$ (M + H): 332.1862; found: 332.1848.

Ethyl 3-[2-(3-Hydroxybutyl)-3-pyridinyl]propanoate **17**

Yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.34 (dd, $J = 4.8$, 1.7 Hz, 1H), 7.47 (dd, $J = 7.7$, 1.7 Hz, 1H), 7.07 (dd, $J = 7.7$, 4.8 Hz, 1H), 4.87 (se, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.76–3.88 (m, 1H), 3.08–2.83 (m, 4H), 2.62–2.57 (m, 2H), 1.97–1.77 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.23 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 172.4, 159.6, 146.6, 137.0, 133.6, 121.4, 67.2, 60.7, 37.4, 34.5, 30.9, 27.2, 23.5, 14.2; MS (EI) M/Z (%): 250(<10), 236 (17), 234 (17), 207 (16), 206 (75), 193 (47), 190 (11), 178 (24), 164 (10), 160 (17), 144 (12), 134 (55), 132 (17), 130 (17), 122 (10), 121 (92), 120 (100), 118 (34); IR ν_{max}: 3211, 2969, 2930, 1729, 1605, 1445; HRMS (ESI) m/z calcd. for $C_{14}H_{22}NO_3$ (M + H): 252.1600; found: 252.1607.

Ethyl 5-[2-(3-Hydroxybutyl)-4.5-methylenedioxyphenyl]pentanoate **18**

Yield 66%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.68–6.65 (m, 2H), 5.90 (s, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.92–3.81 (m, 1H), 2.78–2.51 (m, 4H), 2.36 (t, $J = 7.1$ Hz, 2H), 2.10 (se, 1H), 1.75–1.58 (m, 6H), 1.30–1.25 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.8, (2C) 145.6, 132.9, 109.3, 100.6, 67.5, 60.4, 41.0, 34.1, 32.2, 31.0, 28.7, 24.9, 23.6, 14.3; MS (EI) M/Z (%): 322 (67), 304 (28), 264 (19), 205 (10), 190 (16), 189 (100), 187 (11), 175 (53), 173 (20), 161 (16), 159 (26), 149 (63), 145 (37), 131 (18); IR ν_{max}: 3608, 2937, 1727, 1504, 1486; HRMS (ESI) m/z calcd. for $C_{18}H_{26}O_5Na$ (M + Na): 345.1678; found: 345.1702.

Ethyl 3-[2-(3-Hydroxybutyl)-6-methyl-3-quinolyl]pentanoate **19**

Yield 55%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.93 (d, $J = 8.5$ Hz, 1H), 7.83 (s, 1H), 7.52 (s, 1H), 7.48 (d, $J = 8.5$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.98–3.88 (m, 1H), 3.32–3.10 (m, 2H), 2.84–2.80 (m, 2H), 2.53 (s, 3H), 2.43–2.30 (m, 2H), 2.07–1.95 (m, 2H), 1.85–1.70 (m, 5H), 1.31–1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.5, 160.1, 143.9, 136.0, 135.1, 131.3, 127.3, 125.8, 133.6, 127.2, 67.5, 60.4, 36.8, 34.1, 32.2, 31.8, 29.7, 24.8, 23.7, 21.6, 14.3; MS (EI) M/Z (%): 343 (12), 299 (19), 283 (16), 281 (22), 269 (10), 267 (16), 229 (10), 227 (43), 226 (17), 225 (84), 211 (31), 210 (22), 209 (100), 208 (16), 207 (78), 191 (12), 158 (14), 151 (13), 145 (18), 73 (12); IR ν_{max}: 3601, 3042, 2931, 1728, 1659; HRMS (ESI) m/z calcd. for $C_{21}H_{30}NO_3$ (M + H): 344.2226; found: 344.2211.

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Benzolactone 20–24

General Procedure

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-[4-Fluoro-2-(3-hydroxybutyl)phenyl]propanoic Acid, η Lactone **20**

Yield 76%; ^{1}H NMR (DMF-d_7 70°C, 300 MHz) δ: 7.28–7.23 (m, 1H), 7.06–6.95 (m, 2H), 4.88–4.65 (m, 1H), 3.27–3.15 (m, 1H), 2.96–2.84 (m, 2H), 2.73–2.62 (m, 1H), 2.59–2.41 (m, 2H), 2.27–2.18 (m, 1H), 1.98–1.87 (m, 1H), 1.25–1.23 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (DMF-d_7 70°C, 75 MHz) δ: 173.6, (d, $^1J_{CF} = 241.9$ Hz) 161.0, (d, $^3J_{CF} = 6.9$ Hz) 141.1, 138.3, (d, $^3J_{CF} = 8.0$ Hz) 132.0, (d, $^2J_{CF} = 20.5$ Hz) 116.3, (d, $^2J_{CF} = 21.0$ Hz) 113.6, 70.8, 38.5, 36.9, 30.4, 26.3, 20.6; MS (EI) M/Z (%): 222 (10), 204 (47), 189 (10), 163 (25), 162 (74), 161 (24), 151 (27), 149 (71), 148 (12), 147 (42), 146 (25), 136 (27), 135 (100), 134 (17), 133 (24), 123 (13), 122 (11), 115 (35), 109 (23); IR ν_{max}: 3065, 2987, 2934, 1731; HRMS (ESI) m/z calcd. for $C_{13}H_{15}FO_2$ (M + H): 223.1134; found: 223.1148.

3-[2-(3-Hydroxybutyl)-6-methoxy-3-quinolyl]propanoic acid, η lactone **21**

Yield 55%; mp: 123.4–124.6°C; ^{1}H NMR (DMF-d_7, 70°C, 300 MHz) δ: 8.05 (s, 1H), 7.87 (d, $J = 9.13$ Hz, 1H), 7.36 (dd, $J = 9.13$, 2.80 Hz, 1H), 7.27 (d, $J = 2.78$ Hz, 1H), 5.01–4.95 (m, 1H), 3.97 (s, 3H), 3.37–3.27 (m, 1H), 3.19–3.01 (m, 2H), 2.86–2.78 (m, 1H), 2.63–2.59 (m, 2H), 2.47–2.38 (m, 1H), 2.28–2.17 (m, 1H), 1.21–1.18 (m, 3H); ^{13}C NMR (DMF-d_7 70°C, 75 MHz) δ: 173.8, 161.1, 157.6, 143.2, 135.8, 133.5, 129.7, 128.1, 121.4, 105.3, 71.3, 55.4, 38.1, 37.6, 30.8, 30.3, 20.5; MS (EI) M/Z (%): 286 (13), 285 (69), 241 (17), 240 (12), 228 (25), 227 (11), 226 (46), 214 (51), 213 (25), 212 (100), 210 (14), 200 (10), 199 (27), 198 (44), 197 (10), 187 (13), 155 (17), 154 (13); IR ν_{max}: 3024, 2986, 2939, 1721, 1643, 1627; HRMS (ESI) m/z calcd. for $C_{17}H_{20}NO_3$ (M + H): 286.1443; found: 286.1455.

3-[2-(3-Hydroxybutyl)-3-pyridinyl]propanoic Acid, η Lactone **22**

Yield 26%; ^{1}H NMR (DMF-d_7, 70°C, 300 MHz) δ: 8.42 (dd, $J = 4.7$, 1.7 Hz, 1H), 7.60 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.15 (dd, J = 7.6, 4.7 Hz, 1H), 4.97–4.89 (m, 1H), 3.21–3.11 (m, 1H), 3.01–2.88 (m, 2H), 2.70–2.62 (m, 1H), 2.52–2.47 (m, 2H), 2.34–2.26 (m, 1H), 2.15–2.07 (m, 1H), 1.20 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (DMF-d_7 70°C, 75 MHz)δ: 173.8, 162.2, 147.6, 138.0, 133.9, 121.3, 71.4, 37.5, 36.7, 30.5, 30.1, 20.5; MS (EI) M/Z (%): 205 (<10), 161 (19), 160 (18), 148 (21), 146 (41), 144 (10), 134 (47), 133 (17), 132 (100), 130 (18), 119 (16), 118 (44), 117 (15); IR ν_{max}: 3058, 2977, 2874, 1727; HRMS (ESI) m/z calcd. for $C_{12}H_{16}NO_2$ (M + H): 206.1181; found: 206.1194.

5-[2-(3-Hydroxybutyl)-4,5-methylenedioxyphenyl]pentanoic Acid, ι Lactone **23**

Yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.66-6.64 (m, 2H), 5.92–5.90 (m, 2H), 5.15–5.07 (m, 1H), 3.02–2.89 (m, 2H), 2.58–2.35 (m, 4H), 1.95–1.73 (m, 5H), 1.56–1.45 (m, 1H), 1.28 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.9, 145.8, 145.6, 133.5, 132.9, 109.6, 109.0, 100.6, 70.0, 36.8, 33.7, 29.2, 29.1, 26.1, 23.5, 19.0; MS (EI) M/Z (%): 277 (12), 276 (66), 200 (12), 190 (16), 189 (100), 175 (33), 173 (14), 162 (22), 161 (10), 159 (29), 149 (16), 145 (27), 131 (24), 103 (10); IR ν_{max}: 3053, 2936, 1722, 1504, 1485; HRMS (ESI) m/z calcd. for $C_{16}H_{21}O_4$ (M + H): 277.1440; found: 277.1443.

5-[2-(3-Hydroxybutyl)-6-methyl-3-quinolyl]pentanoic Acid, ι Lactone **24**

Yield 25%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.92-7.90 (m, 1H), 7.82 (s, 1H), 7.50–7.46 (m, 2H), 5.21-5.16 (m, 1H), 3.37–3.28 (m, 1H), 3.14–3.06 (m, 1H), 3.03–2.96 (m, 1H), 2.82–2.71 (m, 1H), 2.53 (s, 3H), 2.52–2.46 (m, 1H), 2.42–2.33 (m, 1H), 2.25–2.14 (m, 2H), 2.08–1.66 (m, 4H), 1.32 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.7, 161.3, 145.1, 135.5, 135.2, 133.4, 131.0, 128.0, 127.2, 125.2, 70.5, 35.0, 34.0, 29.7, 29.2, 28.6, 23.4, 21.5, 19.1; MS (EI) M/Z (%): 297 (41), 282 (17), 224 (26), 210 (14), 199 (14), 198 (100), 197 (33), 196 (42), 195 (10), 194 (20), 184 (15), 183 (15), 182 (31), 181 (14), 180 (10), 171 (31), 167 (13); IR ν_{max}: 3038, 2936, 1724, 1659. HRMS (ESI) m/z Calcd for $C_{19}H_{24}NO_2$ (M + H): 298.1807; found: 298.1804.

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