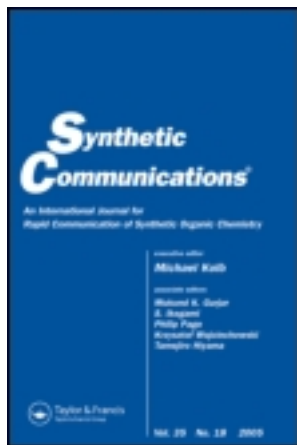


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An Alternative Method for the Synthesis of γ -Lactones by Using Cesium Fluoride-Celite/Acetonitrile Combination

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An Alternative Method for the Synthesis of γ -Lactones by Using Cesium Fluoride-Celite/Acetonitrile Combination

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ABSTRACT

A variety of 2-(1-bromoalkyl) benzoic acids **4** undergo intramolecular nucleophilic substitution reaction when treated with a CsF-Celite as solid base in acetonitrile under reflux condition to give the corresponding cyclized phthalides in moderate to very good yield. These

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†This communication is the result of a joint research program with Late Prof. Dr. Ernst Bayer, Institut für Organische Chemie der Universität Tübingen, Tübingen, Germany.

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2-(1-bromoalkyl) benzoic acids **4** are formed by the α -bromination of 2-alkylbenzoic acids **3** using *N*-bromosuccinimide and a catalytic amount of α,α' -azoisobutyronitrile in carbon tetrachloride under reflux.

Key Words: Cesium fluoride; Celite 521, 2-(1-Bromoalkyl) benzoic acids; Intramolecular nucleophilic substitution; Phthalide and derivatives.

INTRODUCTION

Many natural products have γ -lactones skeletons^[1] most of which display a wide variety of significant biological activity.^[2] They have also been employed as key intermediates for the synthesis of natural products.^[3] Therefore, the synthesis of γ -lactones is a very important and useful in organic chemistry. Although a number of articles^[4-6] and reviews^[7] have been published to achieve this goal, some of these require expensive reagents and tedious reaction work-up. Other methods involve the direct preparation of γ -lactones from the corresponding *o*-alkyl aromatic carboxylic acids and the use of $\text{Na}_2\text{S}_2\text{O}_8/\text{AgNO}_3$ and CuX_2 at 80°C ,^[8] [*bis*(trifluoroacetoxy)iodo]benzene and iodine^[9,10] and organohypervalent iodine compounds in the Suarez system^[11] as reagent. More recently, we have reported the conversion of *o*-alkyl benzoic acids into its corresponding γ -lactones by using the $\text{NaBrO}_3/\text{NaHSO}_3$ reagent under a two-phase system.^[12] In extension of our work for the synthesis of these important phthalides, we developed a new moderate to high yielding methodology. In this article we describe the conversion of 2-(1-bromoalkyl) aromatic carboxylic acids into its corresponding γ -lactones by using the CsF-Celite as a solid base in acetonitrile.

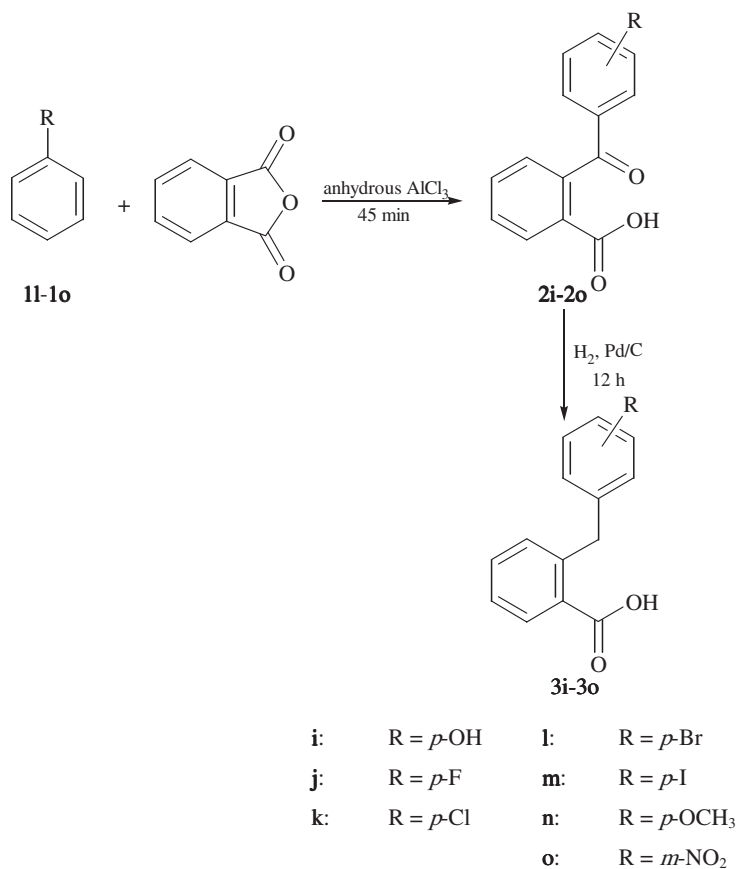
The chemistry of the CsF-Celite has been studied because it can serve as an excellent base for converting carboxylic acid into their corresponding esters with alkyl halides.^[13] Alkylation of cesium carboxylate salts with alkyl halides is also very useful tool for the preparation of carboxylic esters.^[14,15] In the course of our study to extend the scope of the CsF-Celite in organic chemistry, we have found that 2-(1-bromoalkyl) aromatic carboxylic acids are converted in the presence of CH_3CN under reflux conditions to the corresponding γ -lactones. In previous reports, no single example has appeared for the intramolecular reaction of this type by the same reagent.



RESULTS AND DISCUSSION

Preparation of Substrate 4 for Phthalides

The 2-(1-bromoalkyl) benzoic acids **4** were prepared by the α -bromination of 2-alkylbenzoic acids **3**. Few of the 2-alkylbenzoic acid **3** are commercially available. Those not available such as 2-ethylbenzoic acid (**3e**), 2-*n*-propylbenzoic acid (**3f**), and 2-*n*-butylbenzoic acid (**3g**) were prepared by the lithiation-alkylation of *o*-methyl benzoic acid^[16] whereas substituted 2-benzylbenzoic acids **3i–o** were prepared using the procedures described in Sch. 1. Substituted phenyl **11–o** were



Scheme 1.



Table 1. Spectral data of compound 2l–2o and 3i–3o.

Compound	¹ H NMR ^{a,b,c,d} δ, J (Hz)	¹³ C NMR ^{a,e,f,g} δ	IR ν (cm ⁻¹)
2l	11.05 (br, s, 1H, -OH), 8.01–7.11 (m, 4H, Ar-H), 7.96 (d, 2H, J=7.6, H-2'/H-6'), 7.44 (d, 2H, J=7.6, H-3'/H-5')	194.5, 172.2, 142.2, 137.8, 132.1, 132.1, 130.6, 130.2, 129.6, 129.2, 128.8, 128.4, 125.6	(KBr) 2912, 1725, 1675, 1431, 1145, 1081, 836, 664
2m	10.14 (br, s, 1H, -OH), 8.06–7.86 (m, 4H, Ar-H), 7.54 (d, 2H, J=7.6, H-3'/H-5'), 7.16 (d, 2H, J=7.6, H-2'/H-6')	193.1, 171.5, 141.5, 137.6, 136.4, 136.4, 131.4, 131.4, 131.2, 130.8, 129.4, 128.9, 128.6, 96.4	(KBr) 2956, 1742, 1668, 1434, 1146, 1075, 741, 643
2n	11.04 (br, s, 1H, -OH), 8.11–7.82 (m, 4H, Ar-H), 7.32 (d, 2H, J=8.6, H-2'/H-6'), 6.88 (d, 2H, J=8.6, H-3'/H-5'), 3.82 (s, 3H, OCH ₃)	192.3, 171.5, 163.2, 143.2, 134.6, 132.1, 131.6, 131.6, 130.4, 129.6, 128.1, 127.9, 113.8, 113.8, 55.7	(KBr) 2856, 1748, 1667, 1572, 1302, 1156, 1025, 938, 742
2o	11.06 (br, s, 1H, -OH), 8.17–7.71 (m, 4H, Ar-H), 7.65–7.41 (m, 4H, Ar-H)	192.4, 172.3, 149.5, 142.6, 137.6, 134.1, 132.4, 131.6, 129.8, 129.3, 128.7, 128.1, 126.4, 123.8	(KBr) 2916, 1738, 1674, 1543, 1184, 1054, 845, 762
3i	7.95–7.08 (m, 4H, Ar-H), 7.16 (d, 2H, J=8.7, H-2'/H-6'), 6.86 (d, 2H, J=8.7, H-3'/H-5'), 4.54 (s, 2H, -CH ₂)	173.8, 158.6, 138.5, 136.4, 131.4, 130.4, 129.6, 129.6, 129.4, 128.6, 128.2, 116.5, 116.5, 42.5	(KBr) 3312, 2904, 1684, 1154, 1046, 842, 736
3j	8.04–7.16 (m, 4H, Ar-H), 7.45 (d, 2H, J=8.9, H-2'/H-6'), 6.94 (d, 2H, J=8.9, H-3'/H-5'), 4.38 (s, 2H, -CH ₂)	172.5, 163.7, 137.4, 134.5, 132.4, 131.4, 131.4, 130.4, 129.6, 128.9, 128.4, 113.6, 113.6, 44.3	(KBr) 2887, 1682, 1136, 1083, 811, 738, 684

Synthesis of γ -Lactones

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3k	8.11–7.18 (m, 4H, Ar-H), 7.48 (d, 2H, $J=8.5$, H-3'/H-5'), 7.22 (d, 2H, $J=8.5$, H-2'/H-6'), 4.36 (s, 2H, -CH ₂)	172.1, 136.4, 133.4, 132.6, 132.4, 131.8, 131.8, 130.2, 129.8, 129.6, 128.4, 128.4, 127.9, 46.5	(KBr) 2896, 1663, 1138, 1082, 734, 674
3l	8.08–7.18 (m, 4H, Ar-H), 7.49 (d, 2H, $J=7.9$, H-3'/H-5'), 7.24 (d, 2H, $J=7.9$, H-2'/H-6'), 4.46 (s, 2H, -CH ₂)	173.6, 137.4, 134.2, 131.8, 131.8, 131.3, 130.2, 129.4, 129.1, 128.6, 128.2, 128.2, 127.6, 45.6	(KBr) 2894, 1668, 1148, 1084, 836, 746, 664
3m	8.11–7.16 (m, 4H, Ar-H), 7.49 (d, 2H, $J=7.8$, H-3'/H-5'), 7.08 (d, 2H, $J=7.8$, H-2'/H-6'), 4.41 (s, 2H, -CH ₂)	173.8, 137.2, 137.2, 136.4, 133.4, 131.6, 130.8, 130.8, 130.4, 129.5, 128.8, 127.6, 95.8, 43.4	(KBr) 2914, 1676, 1211, 1056, 741, 647
3n	8.04–7.16 (m, 4H, Ar-H), 7.41 (d, 2H, $J=8.5$, H-2'/H-6'), 6.62 (d, 2H, $J=8.5$, H-3'/H-5'), 4.35 (s, 2H, -CH ₂), 3.72 (s, 3H, -OCH ₃)	173.4, 161.6, 136.1, 133.2, 131.6, 130.6, 130.6, 130.2, 129.4, 129.2, 127.8, 114.6, 114.6, 56.4, 42.6	(KBr) 2894, 1682, 1142, 1028, 816, 736
3o	8.11–7.58 (m, 4H, Ar-H), 7.51–7.09 (m, 4H, Ar-H), 4.32 (s, 2H, -CH ₂)	173.7, 150.3, 138.4, 136.6, 132.3, 132.2, 130.3, 129.5, 129.4, 128.6, 127.8, 125.8, 124.3, 45.2	(KBr) 2908, 1674, 1545, 1182, 1054, 841, 768

^aChemical shift δ (ppm), coupling constant J (Hz).^b2l: 250 MHz, MeOH-*d*₆.^c2m, 2n, 2o: 250 MHz, acetone-*d*₆.^d3i, 3j, 3k, 3l, 3m, 3n, 3o: 250 MHz, CDCl₃.^e2l: 63 MHz, MeOH-*d*₆.^f2m, 2n, 2o: 63 MHz, acetone-*d*₆.^g3i, 3j, 3k, 3l, 3m, 3n, 3o: 63 MHz, CDCl₃.



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reacted with phthalic anhydride in the presence of anhydrous AlCl_3 to yield the corresponding substituted 2-benzoylbenzoic acids **2i–o**,^[17] while **2i**, **2j**, and **2k** were commercially available. The ketonic group from **2i–o** was reduced by high pressure hydrogenation at 70°C to yield substituted 2-benzylbenzoic acids **3i–o**.^[18] The spectroscopic data of the following compounds were collected in Table 1.

The 2-alkyl benzoic acids **3** were then subjected to 2-(1-bromoalkyl) benzoic acids **4** by using *N*-bromosuccinimide and carbon tetrachloride (CCl_4) as a solvent in the presence of α,α' -azoisobutyronitrile under stirring at reflux for 6 h^[19] (Sch. 2). The following compounds were obtained in 35–65% yields and characterized by spectroscopic data collected in Table 2.

Synthesis of γ -Lactones

The reaction of **4** (1 mmol) with cesium fluoride-celite (1.5 mmol) in acetonitrile under reflux for 10 h, led to the formation of the corresponding phthalides **5** in moderate to excellent yields (Sch. 2). The yields of γ -lactones are shown in Table 3. This methodology shows that the α -bromobenzoic acid undergoes intramolecular nucleophilic substitution reaction to afford the corresponding γ -lactones. The versatility of the reaction was demonstrated by its application to a wide range of structurally different α -bromobenzoic acids **4a–o**. The spectroscopic data of the all synthesized compounds were collected in Table 4.

CONCLUSION

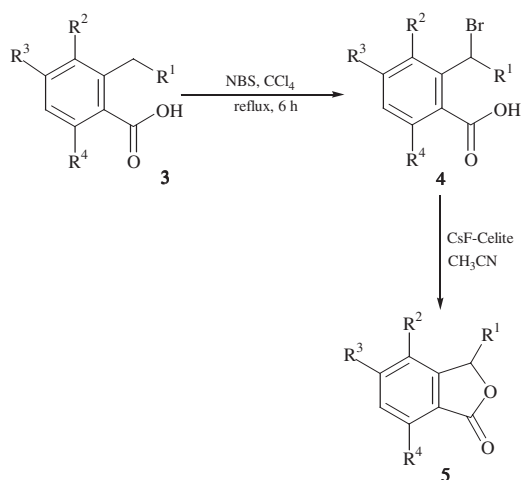
The convenient, efficient, simple, and moderate to high yielding phthalides were prepared from the substituted α -brominated benzoic acids using CsF-Celite as a solid base in acetonitrile, presented in this article, serves as a useful synthetic entry to valuable 3-alkyl and 3-arylphthalides.

EXPERIMENTAL

Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. The ultraviolet spectra were measured in chloroform on a Lambda 5 UV/VIS spectrometer (Perkin-Elmer). Infrared spectra (KBr discs) were recorded on a Bruker FT-IR IFS 48 spectrometer. EI mass spectral data were recorded with Varian MAT 711 (70 eV) spectrometer

Synthesis of γ -Lactones

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- | | | | |
|----|-------------------------------------|----|--|
| a: | $R^1 = R^2 = R^3 = R^4 = H$ | h: | $R^2 = R^3 = R^4 = H, R^1 = C_6H_5$ |
| b: | $R^1 = R^3 = R^4 = H, R^2 = NO_2$ | i: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-OH-C}_6\text{H}_5$ |
| c: | $R^1 = R^2 = R^4 = H, R^3 = Br$ | j: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-F-C}_6\text{H}_5$ |
| d: | $R^1 = R^2 = R^3 = H, R^4 = NH_2$ | k: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-Cl-C}_6\text{H}_5$ |
| e: | $R^2 = R^3 = R^4 = H, R^1 = CH_3$ | l: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-Br-C}_6\text{H}_5$ |
| f: | $R^2 = R^3 = R^4 = H, R^1 = C_2H_5$ | m: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-I-C}_6\text{H}_5$ |
| g: | $R^2 = R^3 = R^4 = H, R^1 = C_3H_7$ | n: | $R^2 = R^3 = R^4 = H, R^1 = p\text{-OCH}_3\text{-C}_6\text{H}_5$ |
| | | o: | $R^2 = R^3 = R^4 = H, R^1 = m\text{-NO}_2\text{-C}_6\text{H}_5$ |

Scheme 2.

and data are tabulated as m/z . 3-Nitrobenzyl alcohol was used in the matrix of mass spectra. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 , $\text{MeOH-}d_6$ and $\text{acetone-}d_6$ containing ca. 1% tetramethylsilane as an internal standard with Bruker AC 250 (250 MHz and 62.9 MHz) spectrometer, respectively. Splitting patterns were as follows: *s*, singlet; *d*, doublet; *dd*, double doublet; *t*, triplet; *q*, quartet; *m*, multiplet; *br*, broad. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz. The progress of all reactions was monitored by TLC, which was performed on 2.0×5.0 cm aluminum sheets precoated with silica gel 60F₂₅₄ to a thickness of 0.25 mm (Merck). The chromatograms were visualized under ultraviolet light (254–366 nm).

N-Bromosuccinimide, α,α' -azoisobutyronitrile, phthalic anhydride, and substituted phenyl **11–o** are commercially available (Fluka, Aldrich). The **2i**, **2j**, **3a–d**, and **3h** were used as obtained from Fluka and Aldrich chemical companies. All reagents palladium on carbon (5% Pd), CsF, celite, and anhydrous AlCl_3 are also available from Fluka and Aldrich. The CsF-Celite was adsorbed on Celite 521 using water



Table 2. Spectral data of compound 4a–o.

Compound	$^1\text{H NMR}^{\text{a,b,c}}$ δ , J (Hz)	$^{13}\text{C NMR}^{\text{a,d,e}}$ δ	IR ν (cm^{-1})
4a	10.72 (br, s, 1H, -OH), 8.11–7.35 (m, 4H, Ar-H), 4.57 (s, 2H, -CH ₂ Br)	171.6, 138.4, 134.2, 130.4, 129.2, 128.9, 128.5, 33.8	(KBr) 2911, 1668, 1516, 1134, 1083, 764, 662
4b	10.63 (br, s, 1H, -OH), 8.21–7.51 (m, 3H, Ar-H), 4.49 (s, 2H, -CH ₂ Br)	171.8, 154.2, 138.4, 131.9, 130.1, 126.4, 123.2, 33.4	(KBr) 2906, 1672, 1582, 1526, 1182, 1052, 735, 656
4c	11.01 (br, s, 1H, -OH), 8.11–7.58 (m, 3H, Ar-H), 4.65 (s, 2H, -CH ₂ Br)	172.4, 137.5, 132.4, 131.9, 129.4, 128.7, 127.4, 34.6	(KBr) 2895, 1684, 1582, 1145, 1072, 805, 704, 674
4d	10.94 (br, s, 1H, -OH), 7.16–6.56 (m, 3H, Ar-H), 4.84 (s, 2H, -NH ₂), 4.38 (s, 2H, -CH ₂ Br)	174.2, 148.2, 135.8, 129.6, 128.9, 127.8, 117.4, 38.5	(KBr) 3425, 2904, 1672, 1506, 1145, 1062, 814, 658
4e	8.12–7.19 (m, 4H, Ar-H), 5.39 (q, 1H, $J=7.2$, -CHBr), 2.06 (d, 3H, $J=7.2$, CH ₃)	173.4, 139.8, 132.4, 130.4, 129.8, 129.3, 127.6, 48.9, 25.7	(KBr) 2926, 1684, 1591, 1148, 1032, 807, 746, 668
4f	8.14–7.21 (m, 4H, Ar-H), 5.49 (t, 1H, $J=7.0$, -CHBr), 2.12 (m, 2H, CH ₂), 1.04 (t, 3H, $J=7.3$, CH ₃)	173.4, 140.2, 133.2, 131.2, 129.8, 129.3, 127.9, 52.3, 33.5, 12.8	(KBr) 2915, 1682, 1572, 1143, 1072, 812, 735, 652
4g	8.13–7.18 (m, 4H, Ar-H), 5.64 (t, 1H, $J=7.0$, -CHBr), 2.13 (m, 2H, CH ₂), 1.56 (m, 2H, CH ₂), 0.99 (t, 3H, $J=7.3$, CH ₃)	172.2, 142.1, 133.6, 130.2, 129.8, 129.3, 127.8, 54.3, 31.2, 19.8, 13.2	(KBr) 2921, 1678, 1572, 1408, 1148, 1072, 842, 735, 658
4h	8.12–7.54 (m, 4H, Ar-H), 7.48–7.08 (m, 5H, Ar-H), 5.64 (s, 1H, -CHBr)	172.6, 142.4, 140.1, 132.2, 131.6, 131.6, 130.7, 129.8, 129.1, 128.8, 128.8, 128.4, 127.8, 62.6	(KBr) 2916, 1672, 1583, 1282, 1148, 1064, 974, 745, 652
4i	8.10–7.22 (m, 4H, Ar-H), 7.18 (d, 2H, $J=8.6$, H-2'/H-6'), 6.87 (d, 2H, $J=8.6$, H-3'/H-5'), 5.74 (s, 1H, -CHBr)	173.2, 157.8, 142.2, 141.5, 132.2, 131.4, 129.8, 129.4, 129.4, 128.7, 128.1, 115.8, 115.8, 63.8	(KBr) 3308, 2917, 1674, 1526, 1152, 1042, 848, 736, 662

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4j	7.98–7.16 (m, 4H, Ar-H), 7.42 (d, 2H, $J=8.8$, H-2'/H-6'), 6.92 (d, 2H, $J=8.8$, H-3'/H-5'), 5.73 (s, 1H, -CHBr)	172.6, 164.8, 141.6, 140.8, 132.3, 131.6, 131.6, 129.9, 129.8, 128.7, 127.9, 114.8, 114.8, 62.3	(KBr) 2925, 1678, 1506, 1264, 1142, 1082, 815, 736, 682, 658
4k	8.06–7.19 (m, 4H, Ar-H), 7.42 (d, 2H, $J=9.1$, H-3'/H-5'), 7.23 (d, 2H, $J=9.1$, H-2'/H-6'), 5.68 (s, 1H, -CHBr)	172.5, 142.3, 140.3, 133.2, 132.1, 131.6, 131.6, 130.2, 129.6, 128.9, 128.2, 128.2, 127.8, 63.2	(KBr) 2886, 1668, 1524, 1273, 1134, 1078, 734, 672, 662
4l	8.04–7.15 (m, 4H, Ar-H), 7.42 (d, 2H, $J=8.6$, H-3'/H-5'), 7.23 (d, 2H, $J=8.6$, H-2'/H-6'), 5.63 (s, 1H, -CHBr)	173.1, 141.8, 140.6, 132.5, 131.6, 131.6, 129.9, 129.4, 129.2, 128.6, 128.3, 128.3, 127.8, 61.4	(KBr) 2925, 1673, 1516, 1258, 1149, 1082, 836, 745, 658
4m	7.98–7.17 (m, 4H, Ar-H), 7.45 (d, 2H, $J=8.7$, H-3'/H-5'), 7.11 (d, 2H, $J=8.7$, H-2'/H-6'), 5.76 (s, 1H, -CHBr)	172.7, 142.5, 141.6, 137.5, 137.5, 132.1, 131.4, 131.4, 130.2, 129.9, 128.8, 127.8, 96.4, 62.4	(KBr) 2932, 1678, 1541, 1306, 1178, 1056, 741, 662, 645
4n	7.99–7.18 (m, 4H, Ar-H), 7.38 (d, 2H, $J=8.7$, H-2'/H-6'), 6.68 (d, 2H, $J=8.7$, H-3'/H-5'), 5.73 (s, 1H, -CHBr), 3.76 (s, 3H, -OCH ₃)	171.8, 162.3, 141.3, 140.6, 131.8, 130.6, 130.4, 130.4, 129.6, 128.5, 127.9, 115.3, 115.3, 63.1, 56.2	(KBr) 2935, 1676, 1528, 1284, 1145, 1032, 816, 732, 667
4o	8.21–7.54 (m, 4H, Ar-H), 7.61–7.12 (m, 4H, Ar-H), 5.68 (s, 1H, -CHBr)	173.6, 152.3, 141.5, 139.8, 131.9, 131.5, 129.8, 129.6, 129.5, 128.8, 127.8, 126.1, 123.7, 62.3	(KBr) 2936, 1678, 1548, 1406, 1184, 1056, 843, 768, 663

^aChemical shift δ (ppm), coupling constant J (Hz).^b4a, 4b, 4c, 4d, 4e, 4f, 4g: 250 MHz, MeOH-*d*₆.^c4h, 4i, 4j, 4k, 4l, 4m, 4n, 4o: 400 MHz, MeOH-*d*₆.^d4a, 4b, 4c, 4d, 4e, 4f, 4g: 63 MHz, MeOH-*d*₆.^e4h, 4i, 4j, 4k, 4l, 4m, 4n, 4o: 100 MHz, MeOH-*d*₆.



Table 3. Conversion of 2-(1-bromoalkyl) benzoic acids **4** into γ -lactones using a CsF-celite/CH₃CN system.

Substrate	γ -Lactone	Yield ^a (%)
4a	5a	80
4b	5b	60
4c	5c	65
4d	5d	84
4e	5e	68
4f	5f	65
4g	5g	64
4h	5h	70
4i	5i	86
4j	5j	77
4k	5k	80
4l	5l	80
4m	5m	82
4n	5n	85
4o	5o	75

^aIsolated yield of pure products.

under stirring at room temperature for 20 min.^[13] The carbon tetrachloride (CCl₄) dried with potassium hydroxide and stored over 5 Å° molecular sieves,^[20] while anhydrous acetonitrile and methanol were purchased from Merck and used without purification.

General Procedure for the Preparation of **2l–o**

A mixture of substituted phenyl substrate **1l–o** (20 mmol), phthalic anhydride (2.36 g, 16 mmol), and anhydrous AlCl₃ (4.36 g, 32 mmol) was thoroughly ground in an agate mortar and pestle for 45 min. The reaction mixture was mixed with crushed ice and extracted with ether. The ethereal extract was washed with brine, dried over anhydrous MgSO₄, and filtered. The filtrate was evaporated in vacuo; the residue was purified by column chromatography on silica gel (hexane/EtOAc, 8:2, v/v) to afford the corresponding products **2l–o**.

2-(4'-Bromobenzoyl) benzoic acid (2l). Yield: 3.66 g (60%); colorless compound. M.p.: 86–89°C. *R_f* = 0.43 (hexane:ethyl acetate, 5:2). EI MS: *m/z* (%) = 305 [M⁺] (51), 260 (17), 225 (100), 149 (22), 121 (44), 104 (15), 76 (79). Anal. calcd. for C₁₄H₉BrO₃: C 55.11, H 2.97. Found: C 55.19, H 2.89.

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2-(4'-Iodobenzoyl) benzoic acid (2m). Yield: 3.87 g (55%); colorless compound. M.p.: 83–85°C (Lit. m.p. 86–96°C).^[21] $R_f=0.45$ (hexane: ethyl acetate, 5:2); EI MS: m/z (%) = 352 [M^+] (39), 324 (831), 307 (14), 225 (49), 149 (100), 127 (7), 121 (17), 104 (23), 77 (63). Anal. calcd. for $C_{14}H_9IO_3$: C 47.75, H 2.58. Found: C 47.81, H 2.49.

2-(4'-Methoxybenzoyl) benzoic acid (2n). Yield: 3.69 g (72%); colorless prisms. M.p.: 120–123°C (Lit. m.p. 122–123°C).^[22] $R_f=0.38$ (hexane: ethyl acetate, 5:2). EI MS: m/z (%) = 256 [M^+] (27), 241 (19), 225 (42), 211 (36), 149 (100), 121 (74), 104 (33), 76 (56). Anal. calcd. for $C_{15}H_{12}O_4$: C 70.31, H 4.72. Found: C 70.25, H 4.78.

2-(3'-Nitrobenzoyl) benzoic acid (2o). Yield: 2.98 g (55%); colorless plates. M.p.: 79–82°C. $R_f=0.35$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 271 [M^+] (54), 226 (34), 197 (42), 149 (27), 121 (100), 104 (13), 77 (52), 46 (17). Anal. calcd. for $C_{14}H_9NO_5$: C 62.00, H 3.34, N 5.16. Found: C 62.09, H 3.28, N 5.19.

General Procedure for the Preparation of 3i–o

The above keto-acids **2i–o** (10 mmol) was dissolved in 20 mL of methanol along with 5% palladium on carbon (0.59 g). The solution was maintained under 20 atm of hydrogen at 70°C for 12 h. The reaction mixture was filtered through celite. The celite was washed well with methanol. The combined methanol was evaporated to dryness. The material was then chromatographed on silica gel using 20–40% ethyl acetate in hexane to give corresponding products **3i–o**.

2-(4'-Hydroxybenzyl) benzoic acid (3i). Yield: 1.85 g (81%); colorless needles. M.p.: 149–151°C (Lit. m.p. 151°C).^[23] $R_f=0.56$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 228 [M^+] (48), 211 (43), 183 (64), 135 (51), 121 (100), 76 (25). Anal. calcd. for $C_{14}H_{12}O_3$: C 73.67, H 5.30. Found: C 73.59, H 5.37.

2-(4'-Fluorobenzyl) benzoic acid (3j). Yield: 1.91 g (83%); colorless compound. M.p.: 121–123°C (Lit. m.p. 122–124°C).^[24] $R_f=0.66$ (hexane: ethyl acetate, 5:2). EI MS: m/z (%) = 230 [M^+] (38), 211 (34), 185 (15), 135 (100), 121 (69), 104 (44), 77 (21). Anal. calcd. for $C_{14}H_{11}FO_2$: C 73.03, H 4.82. Found: C 72.95, H 4.89.

2-(4'-Chlorobenzyl) benzoic acid (3k). Yield: 2.12 g (86%); colorless needles. M.p.: 123–126°C (Lit. m.p. 125–128°C).^[18b] $R_f=0.67$ (hexane: ethyl acetate, 5:2). EI MS: m/z (%) = 246 [M^+] (46), 229 (17), 211 (37), 201 (24), 135 (100), 121 (58), 104 (33), 76 (43). Anal. calcd. for $C_{14}H_{11}ClO_2$: C 68.16, H 4.49. Found: C 68.24, H 4.41.



Table 4. Spectral data of compound 5a–o.

Compound	¹ H NMR ^{a,b,c} δ, J (Hz)	¹³ C NMR ^{a,d,e} δ	IR ν (cm ⁻¹)
5a	7.92–7.49 (m, 4H, Ar-H), 5.33 (s, 2H, CH ₂)	171.1, 146.6, 134.0, 129.1, 129.0, 125.7, 122.2, 69.7	(KBr) 2912, 1720, 1135, 1083, 760
5b	7.91–7.51 (m, 3H, Ar-H), 5.29 (s, 2H, CH ₂)	171.1, 152.1, 146.5, 134.1, 129.1, 125.7, 122.2, 69.7	(KBr) 2905, 1740, 1586, 1525, 1210, 1055, 735
5c	7.78–7.66 (m, 3H, Ar-H), 5.31 (s, 2H, CH ₂)	172.2, 149.5, 132.7, 132.7, 128.7, 127.1, 125.6, 68.9	(KBr) 2892, 1736, 1145, 1079, 764
5d	6.94–6.43 (m, 3H, Ar-H), 4.91 (s, 2H, CH ₂), 4.89 (s, 2H, NH ₂)	172.2, 149.5, 141.0, 132.6, 121.7, 116.5, 116.1, 69.4	(KBr) 3435, 2906, 1732, 1141, 1068, 816, 745
5e	7.78–7.65 (m, 4H, Ar-H), 5.71 (q, 1H, J=6.7, CH), 1.69 (d, 3H, J=6.7, CH ₃)	167.4, 146.5, 131.7, 131.6, 130.5, 129.9, 125.6, 77.8, 21.6	(neat) 2924, 1718, 1592, 1145, 1030, 806, 751
5f	8.06–7.38 (m, 4H, Ar-H), 5.33 (t, 1H, J=7.3, CH), 1.46 (m, 2H, CH ₂), 0.94 (t, 3H, J=7.3, CH ₃)	163.5, 141.0, 131.7, 130.8, 129.2, 128.1, 127.7, 77.1, 19.3, 13.7	(neat) 2915, 1736, 1574, 1144, 1076, 882, 735
5g	7.76–7.03 (m, 4H, Ar-H), 5.33 (t, 1H, J=7.5, CH), 1.57 (m, 2H, CH ₂), 1.34 (m, 2H, CH ₂), 0.84 (t, 3H, J=7.5, CH ₃)	167.4, 148.1, 131.7, 131.6, 130.5, 129.9, 125.6, 72.6, 21.6, 19.3, 13.7	(neat) 2923, 1736, 1578, 1406, 1273, 1145, 1074, 842, 733
5h	8.01–7.84 (m, 4H, Ar-H), 7.72–7.12 (m, 5H, Ar-H), 6.58 (s, 1H, CH)	166.5, 151.3, 137.0, 132.3, 131.8, 131.8, 130.9, 130.8, 129.1, 129.0, 128.8, 128.8, 128.6, 83.3	(neat) 2918, 1746, 1581, 1457, 1283, 1138, 1064, 975, 745
5i	8.06–7.36 (m, 4H, Ar-H), 7.32 (d, 2H, J=7.9, H-2'/H-6'), 6.91 (d, 2H, J=7.9, H-3'/H-5'), 6.06 (s, 1H, CH)	169.8, 161.8, 137.1, 135.8, 132.4, 131.0, 129.9, 129.9, 129.3, 128.4, 128.1, 117.7, 117.7, 83.7	(KBr) 3310, 2906, 1732, 1675, 1233, 1156, 1047, 834, 732

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5j	8.06–7.37 (m, 4H, Ar-H), 7.52 (d, 2H, $J=8.1$, H-2'/H-6'), 6.91 (d, 2H, $J=8.1$, H-3'/H-5'), 6.07 (s, 1H, CH)	165.9, 163.5, 138.0, 132.3, 131.7, 131.7, 130.8, 129.3, 128.1, 127.7, 122.5, 113.7, 113.7, 83.7	(KBr) 2892, 1738, 1664, 1254, 1134, 1084, 804, 734, 687
5k	8.01–7.36 (m, 4H, Ar-H), 7.94 (d, 2H, $J=7.6$, H-2'/H-6'), 7.47 (d, 2H, $J=7.6$, H-3'/H-5'), 6.22 (s, 1H, CH)	166.9, 137.4, 132.3, 132.1, 131.8, 131.8, 131.2, 131.2, 130.9, 129.3, 129.0, 128.2, 127.9, 83.7	(KBr) 2895, 1741, 1663, 1408, 1264, 1134, 1081, 732, 678
5l	8.01–7.37 (m, 4H, Ar-H), 7.96 (d, 2H, $J=7.8$, H-2'/H-6'), 7.49 (d, 2H, $J=7.8$, H-3'/H-5'), 6.31 (s, 1H, CH)	167.0, 137.4, 132.3, 131.8, 131.8, 131.3, 131.3, 130.9, 129.4, 129.1, 128.4, 128.2, 127.9, 83.7	(KBr) 2898, 1743, 1665, 1248, 1145, 1081, 836, 745, 663
5m	8.06–7.34 (m, 4H, Ar-H), 7.51 (d, 2H, $J=7.9$, H-3'/H-5'), 6.93 (d, 2H, $J=7.9$, H-2'/H-6'), 6.05 (s, 1H, CH)	166.8, 136.8, 136.8, 135.6, 132.4, 131.0, 130.8, 130.8, 129.4, 128.7, 128.2, 123.6, 97.8, 83.3	(KBr) 2910, 1735, 1675, 1406, 1292, 1110, 1053, 741, 646
5n	8.05–7.35 (m, 4H, Ar-H), 7.41 (d, 2H, $J=7.9$, H-2'/H-6'), 6.95 (d, 2H, $J=7.9$, H-3'/H-5'), 6.10 (s, 1H, CH), 3.85 (s, 3H, -OCH ₃)	167.1, 163.5, 138.0, 132.2, 131.8, 131.8, 130.8, 129.2, 128.1, 127.7, 122.6, 113.7, 113.7, 83.7, 55.4	(KBr) 2892, 1732, 1656, 1411, 1272, 1144, 1026, 818, 742
5o	8.24–7.60 (m, 4H, Ar-H), 7.56–7.41 (m, 4H, Ar-H), 6.11 (s, 1H, CH)	166.7, 148.3, 136.4, 132.8, 132.3, 131.7, 130.8, 130.0, 129.2, 128.8, 128.1, 127.5, 123.9, 83.4	(KBr) 2912, 1736, 1675 1542, 1268, 1186, 1058, 842, 764

^aChemical shift δ (ppm), coupling constant J (Hz).^b5a, 5b, 5c, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l, 5m, 5n, 5o: 250 MHz, CDCl₃.^c5d: 250 MHz, MeOH-*d*₆.^d5a, 5b, 5c, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l, 5m, 5n, 5o: 63 MHz, CDCl₃.^e5d: 63 MHz, MeOH-*d*₆.



2-(4'-Bromobenzyl) benzoic acid (3l). Yield: 2.44 g (84%); colorless compound. M.p.: 131–134°C (Lit. m.p. 136–137°C).^[18b] $R_f=0.68$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 291 [M^+] (62), 274 (21), 246 (74), 211 (44), 135 (100), 121 (51), 104 (42), 77 (31). Anal. calcd. for $C_{14}H_{11}BrO_2$: C 57.76, H 3.81. Found: C 57.69, H 3.75.

2-(4'-Iodobenzyl) benzoic acid (3m). Yield: 2.77 g (82%); colorless compound. M.p.: 127–130°C. $R_f=0.70$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 338 [M^+] (27), 321 (16), 293 (42), 211 (53), 135 (71), 127 (9), 121 (100), 103 (28), 77 (36). Anal. calcd. for $C_{14}H_{11}IO_2$: C 49.73, H 3.28. Found: C 49.81, H 3.21.

2-(4'-Methoxybenzyl) benzoic acid (3n). Yield: 2.05 g (85%); colorless compound. M.p.: 114–116°C (Lit. m.p. 117–119°C).^[18b,22] $R_f=0.58$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 242 [M^+] (49), 227 (41), 225 (17), 211 (37), 197 (9), 135 (100), 121 (61), 104 (53), 77 (34). Anal. calcd. for $C_{15}H_{14}O_3$: C 74.36, H 5.82. Found: C 74.29, H 5.89.

2-(3'-Nitrobenzyl) benzoic acid (3o). Yield: 2.11 g (82%); colorless compound. M.p.: 113–116°C. $R_f=0.47$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 257 [M^+] (64), 240 (48), 212 (36), 211 (19), 135 (62), 121 (100), 104 (56), 77 (32), 47 (15). Anal. calcd. for $C_{14}H_{11}NO_4$: C 65.37, H 4.31, N 5.44. Found: C 65.46, H 4.38, N 5.36.

General Procedure for the Preparation of 4a–o

The substituted *o*-alkyl benzoic acids **3a–o** (8 mmol) was dissolved in dry CCl_4 (20 mL), *N*-bromosuccinimide (1.42 g, 8 mmol) and α,α' -azoisobutyronitrile (0.05 g) were added and the mixture was heated to reflux temperature for 6 h. The solution was cooled, succinimide was filtered off, and the solvent was removed in vacuo to leave a crude solid. The solid was chromatographed on silica gel using 20–40% ethyl acetate in hexane to give corresponding products **4a–o**.

2-(Bromomethyl) benzoic acid (4a). Yield: 1.12 g (65%); colorless compound. M.p.: 134–137°C. $R_f=0.58$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 215 [M^+] (37), 170 (32), 135 (78), 121 (100), 80 (21), 76 (16). Anal. calcd. for $C_8H_7BrO_2$: C 44.68, H 3.28. Found: C 44.59, H 3.36.

2-Bromomethyl-3-nitro-benzoic acid (4b). Yield: 1.10 g (53%); colorless compound. M.p.: 209–211°C. $R_f=0.53$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 260 [M^+] (51), 211 (21), 180 (62), 166 (56), 120 (100), 80 (35), 76 (11), 50 (9). Anal. calcd. for $C_8H_6BrNO_4$: C 36.95, H 2.33, N 5.39. Found: C 36.87, H 2.41, N 5.48.

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2-Bromomethyl-4-nitro-benzoic acid (4c). Yield: 1.20 g (51%); colorless compound. M.p.: 211–214°C. $R_f=0.53$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 294 [M^+] (19), 277 (35), 249 (42), 214 (45), 200 (19), 120 (100), 80 (38), 77 (14), 49 (8). Anal. calcd. for $C_8H_6Br_2O_2$: C 32.69, H 2.06. Found: C 32.76, H 2.13.

2-Bromomethyl-6-amino-benzoic acid (4d). Yield: 0.87 g (47%); colorless compound. M.p.: 156–159°C. $R_f=0.43$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 230 [M^+] (27), 214 (56), 185 (38), 150 (62), 136 (48), 120 (100), 80 (42), 76 (11), 50 (8). Anal. calcd. for $C_8H_8BrNO_2$: C 41.77, H 3.51, N 6.09. Found: C 41.85, H 3.59, N 6.01.

2-(1-Bromoethyl) benzoic acid (4e). Yield: 0.96 g (52%); colorless compound. M.p.: 179–181°C. $R_f=0.55$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 229 [M^+] (26), 214 (63), 184 (56), 134 (100), 121 (72), 80 (32), 76 (18), 49 (7). Anal. calcd. for $C_9H_9BrO_2$: C 47.19, H 3.96. Found: C 47.26, H 3.88.

2-(1-Bromopropyl) benzoic acid (4f). Yield: 0.97 g (50%); colorless compound. M.p.: 163–165°C. $R_f=0.65$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 243 [M^+] (23), 228 (63), 214 (71), 198 (48), 134 (100), 121 (58), 80 (45), 77 (13), 50 (8). Anal. calcd. for $C_{10}H_{11}BrO_2$: C 49.41, H 4.56. Found: C 49.49, H 4.49.

2-(1-Bromobutyl) benzoic acid (4g). Yield: 0.98 g (48%); colorless compound. M.p.: 153–156°C. $R_f=0.72$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 257 [M^+] (33), 242 (56), 226 (62), 212 (48), 177 (42), 134 (100), 121 (72), 80 (38), 77 (12), 50 (6). Anal. calcd. for $C_{11}H_{13}BrO_2$: C 51.38, H 5.10. Found: C 51.46, H 5.15.

2-(Bromobenzyl) benzoic acid (4h). Yield: 1.28 g (55%); colorless compound. M.p.: 192–194°C. $R_f=0.53$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 291 [M^+] (36), 246 (32), 214 (48), 211 (66), 134 (58), 121 (100), 80 (44), 76 (15), 50 (7). Anal. calcd. for $C_{14}H_{11}BrO_2$: C 57.76, H 3.81. Found: C 57.69, H 3.88.

2-[4'-Hydroxy(bromobenzyl)] benzoic acid (4i). Yield: 1.03 g (42%); colorless compound. M.p.: 196–199°C. $R_f=0.51$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 307 [M^+] (25), 290 (71), 262 (32), 227 (48), 214 (62), 134 (58), 121 (100), 80 (28), 76 (15), 50 (11). Anal. calcd. for $C_{14}H_{11}BrO_3$: C 54.75, H 3.61. Found: C 54.81, H 3.56.

2-[4'-Fluoro(bromobenzyl)] benzoic acid (4j). Yield: 0.98 g (40%); colorless compound. M.p.: 161–163°C. $R_f=0.61$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 309 [M^+] (31), 290 (42), 264 (62), 229 (38), 214 (54), 134 (68), 121 (100), 80 (35), 76 (11), 49 (5). Anal. calcd. for $C_{14}H_{10}BrFO_2$: C 54.40, H 3.26. Found: C 54.49, H 3.18.

2-[4'-Chloro(bromobenzyl)] benzoic acid (4k). Yield: 1.07 g (41%); colorless compound. M.p.: 168–171°C. $R_f=0.62$ (hexane:ethyl acetate,



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5:2). EI MS: m/z (%) = 325 [M^+] (22), 290 (56), 280 (51), 245 (18), 214 (42), 134 (11), 121 (100), 80 (37), 77 (19), 50 (7). Anal. calcd. for $C_{14}H_{10}BrClO_2$: C 51.65, H 3.10. Found: C 51.71, H 3.17.

2-[4'-Bromo(bromobenzyl)] benzoic acid (4l). Yield: 1.11 g (38%); colorless compound. M.p.: 193–195°C. R_f = 0.63 (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 370 [M^+] (27), 325 (38), 290 (52), 214 (48), 134 (100), 121 (62), 80 (21), 76 (14), 50 (5). Anal. calcd. for $C_{14}H_{10}Br_2O_2$: C 45.44, H 2.72. Found: C 45.52, H 2.64.

2-[4'-Iodo(bromobenzyl)] benzoic acid (4m). Yield: 1.17 g (35%); colorless compound. M.p.: 158–161°C. R_f = 0.65 (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 417 [M^+] (18), 372 (36), 337 (46), 290 (51), 214 (62), 134 (100), 127 (26), 121 (58), 80 (31), 76 (11), 50 (5). Anal. calcd. for $C_{14}H_{10}BrIO_2$: C 40.32, H 2.42. Found: C 40.41, H 2.51.

2-[4'-Methoxy(bromobenzyl)] benzoic acid (4n). Yield: 1.36 g (53%); colorless compound. M.p.: 175–177°C. R_f = 0.53 (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 321 [M^+] (28), 306 (65), 290 (55), 276 (42), 241 (32), 214 (62), 134 (72), 121 (100), 80 (45), 76 (13), 50 (9). Anal. calcd. for $C_{15}H_{13}BrO_3$: C 56.10, H 4.08. Found: C 56.17, H 4.15.

2-[3'-Nitro(bromobenzyl)] benzoic acid (4o). Yield: 1.14 g (42%); colorless compound. M.p.: 167–170°C. R_f = 0.42 (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 336 [M^+] (36), 319 (19), 290 (53), 256 (47), 214 (61), 134 (72), 121 (100), 80 (43), 76 (16), 49 (9). Anal. calcd. for $C_{14}H_{10}BrNO_4$: C 50.03, H 3.00, N 4.17. Found: C 50.11, H 3.09, N 4.09.

General Procedure for the Synthesis of γ -Lactones

To a suspension of substituted 2-(1-bromoalkyl) benzoic acid **4a–o** (1.0 mmol) and CsF-Celite (0.318 g, 1.5 mmol) in 100 mL of dry acetonitrile were stirred. The reaction mixture was heated to reflux temperature for 10 h. The solution was cooled, solvent was evaporated, and the residue was dissolved in EtOAc. The precipitates were filtered off, washed with EtOAc (20 mL), and the filtrate was evaporated. The residue was chromatographed on silica gel column using a mixture of hexane and ethyl acetate (7:3, v/v) as eluent to give corresponding products **5a–o**.

Phthalide (5a). Yield: 0.11 g (80%); colorless compound. M.p.: 73–75°C (Lit. m.p. 74–75°C).^[9] R_f = 0.43 (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 134 [M^+] (48), 105 (100), 89 (15), 77 (38), 50 (20). Anal. calcd. for $C_8H_6O_2$: C 71.64, H 4.51. Found: C 71.72, H 4.44.

4-Nitrophthalide (5b). Yield: 0.11 g (60%); colorless compound. M.p.: 151–154°C. R_f = 0.27 (hexane:ethyl acetate, 5:1). EI MS: m/z (%) = 179 [M^+] (31), 164 (100), 146 (41), 132 (38), 117 (31), 105 (28), 91 (45), 77 (14),

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51 (9). Anal. calcd. for $C_8H_5NO_4$: C 53.64, H 2.81, N 7.82. Found: C 53.71, H 2.72, N 7.91.

5-Bromophthalide (5c). Yield: 0.14 g (65%); colorless compound. M.p.: 153–155°C. $R_f=0.38$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 214 [$M^+ - H$] (35), 185 (100), 155 (38), 133 (23), 104 (21), 76 (12), 50 (9). Anal. calcd. for $C_8H_5BrO_2$: C 45.11, H 2.37. Found: C 45.19, H 2.28.

7-Aminophthalide (5d). Yield: 0.07 g (48%); yellow compound. M.p.: 97–99°C. $R_f=0.25$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 150 [$M^+ - H$] (65), 132 (56), 121 (100), 104 (43), 88 (6), 74 (34), 56 (12), 42 (8). Anal. calcd. for $C_8H_7NO_2$: C 64.42, H 4.73, N 9.39. Found: C 64.49, H 4.67, N 9.47.

3-Methylphthalide (5e). Yield: 0.10 g (68%); oily compound. $R_f=0.33$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 148 [M^+] (73), 133 (41), 104 (62), 76 (36), 61 (11), 50 (100), 38 (7). Anal. calcd. for $C_9H_8O_2$: C 72.96, H 5.44. Found: C 73.06, H 5.35.

3-Ethylphthalide (5f). Yield: 0.10 g (65%); oily compound. $R_f=0.53$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 162 [M^+] (33), 135 (11), 120 (21), 105 (63), 95 (18), 68 (58), 41 (100). Anal. calcd. for $C_{10}H_{10}O_2$: C 74.06, H 6.21. Found: C 74.14, H 6.15.

3-*n*-Propylphthalide (5g). Yield: 0.11 g (64%); oily compound. $R_f=0.58$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 177 [$M^+ - H$] (31), 160 (7), 147 (100), 130 (11), 104 (48), 90 (5), 76 (62), 50 (43). Anal. calcd. for $C_{11}H_{12}O_2$: C 74.98, H 6.86. Found: C 75.09, H 6.78.

3-Phenylphthalide (5h). Yield: 0.15 g (70%); colorless compound. M.p.: 111–113°C (lit. m.p. 113–114°C).^[11] $R_f=0.49$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 210 [M^+] (29), 182 (6), 121 (11), 105 (100), 77 (37), 50 (23). Anal. calcd. for $C_{14}H_{10}O_2$: C 79.98, H 4.79. Found: C 79.91, H 4.86.

3-(4'-Hydroxyphenyl)phthalide (5i). Yield: 0.19 g (86%); colorless compound. M.p.: 162–165°C. $R_f=0.36$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 225 [$M^+ - H$] (51), 209 (11), 198 (18), 182 (43), 134 (24), 105 (28), 91 (100), 77 (32), 65 (14). Anal. calcd. for $C_{14}H_{10}O_3$: C 74.33, H 4.46. Found: C 74.24, H 4.52.

3-(4'-Fluorophenyl)phthalide (5j). Yield: 0.17 g (77%); colorless compound. M.p.: 102–104°C (Lit. m.p. 100–101°C).^[24] $R_f=0.49$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 228 [M^+] (35), 181 (11), 167 (10), 149 (24), 133 (21), 125 (9), 105 (56), 91 (100), 76 (41), 57 (14). Anal. calcd. for $C_{14}H_9FO_2$: C 73.68, H 3.97. Found: C 73.75, H 3.89.

3-(4'-Chlorophenyl)phthalide (5k). Yield: 0.19 g (80%); colorless compound. M.p.: 111–113°C. $R_f=0.53$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 244 [M^+] (29), 209 (16), 181 (28), 162 (23), 134 (100), 121



(42), 105 (63), 83 (56), 76 (43), 55 (32). Anal. calcd. for $C_{14}H_9ClO_2$: C 68.73, H 3.71. Found: C 68.81, H 3.64.

3-(4'-Bromophenyl)phthalide (5l). Yield: 0.23 g (80%); colorless compound. M.p.: 138–141°C (Lit. m.p. 139–140°C).^[18b] $R_f=0.54$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 289 [M^+] (43), 261 (18), 209 (32), 161 (23), 149 (15), 133 (100), 105 (48), 91 (35), 76 (56), 57 (25). Anal. calcd. for $C_{14}H_9BrO_2$: C 58.16, H 3.14. Found: C 58.22, H 3.07.

3-(4'-Iodophenyl)phthalide (5m). Yield: 0.27 g (82%); colorless compound. M.p.: 102–105°C. $R_f=0.56$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 336 [M^+] (38), 308 (31), 293 (16), 279 (22), 209 (56), 134 (62), 127 (48), 105 (100), 76 (28), 57 (18). Anal. calcd. for $C_{14}H_9IO_2$: C 50.03, H 2.70. Found: C 50.11, H 2.62.

3-(4'-Methoxyphenyl)phthalide (5n). Yield: 0.20 g (85%); colorless compound. M.p.: 117–119°C (Lit. m.p. 118–119°C).^[5c] $R_f=0.41$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 240 [M^+] (45), 225 (21), 212 (31), 209 (48), 133 (65), 105 (100), 90 (23), 76 (19), 50 (34). Anal. calcd. for $C_{15}H_{12}O_3$: C 74.99, H 5.03. Found: C 74.91, H 5.11.

3-(3'-Nitrophenyl)phthalide (5o). Yield: 0.19 g (75%); colorless compound. M.p.: 113–116°C. $R_f=0.28$ (hexane:ethyl acetate, 5:2). EI MS: m/z (%) = 256 [M^+-H] (41), 228 (42), 209 (38), 179 (28), 162 (16), 133 (58), 119 (31), 105 (100), 91 (24), 77 (45), 50 (21). Anal. calcd. for $C_{14}H_9NO_4$: C 65.88, H 3.55, N 5.49. Found: C 65.79, H 3.61, N 5.42.

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