Application of Organolithium and Related Reagents in Synthesis, Part 24.[1] Synthetic Strategies Based on Aromatic Metallation. A Concise Regiospecific Conversion of Benzoic Acids into 2-(1-Aryl-2-methoxycarbonylethyl)benzoic Acids

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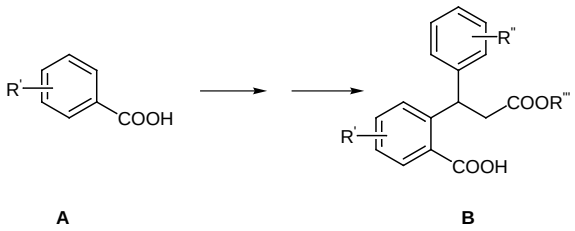
Abstract: The synthesis of the 3-arylphthalides **3** via metallation (BuLi) of the benzanilides **1** and subsequent reaction of the generated bis-lithiated anilides **2** with aromatic aldehydes is described. Conversion of **3** into the corresponding 2-(1-aryl-2-methoxycarbonylethyl)benzoic acids **4** by treatment with 1-methoxy-1-trimethylosiloxyethene in the presence of titanium tetrachloride, as a way of regiospecific transformation of benzoic acids, is also described.

Key words: lithiation, anilides, phthalides, silyl enol ethers, benzoic acids

The current interest in *ortho*-alkylated (by secondary substituent with the carbomethoxy group at the end of alkyl chain) aromatic carboxylic acids **B** as key starting materials for preparation of numerous poly-aromatic compounds including important physiologically active products[2] has led us to examine methods for the synthesis of these systems.

Available methods for the preparation of *ortho*-alkylated aromatic carboxylic acids generally require one of the following techniques. The most common approach involves the lateral lithiation of *ortho*-toluic acids derivatives[3,4] followed by the reaction with appropriate alkyl halides. It appears that, this method, in the case of carboxylic acids substituted by tertiary carbon atom, is laborious and first requires preparation of *ortho*-benzylated derivatives.[5,6,8c] The most attractive route so far reported for the preparation of the *ortho*-substituted carboxylic acids type **B** is the transformation of readily available 3-arylphthalides via reaction with the trimethylsilyl ketene acetal of ethyl propionate in the presence of $ZnCl_2$.[2b,7] However, it is still mostly related only to specific instances.



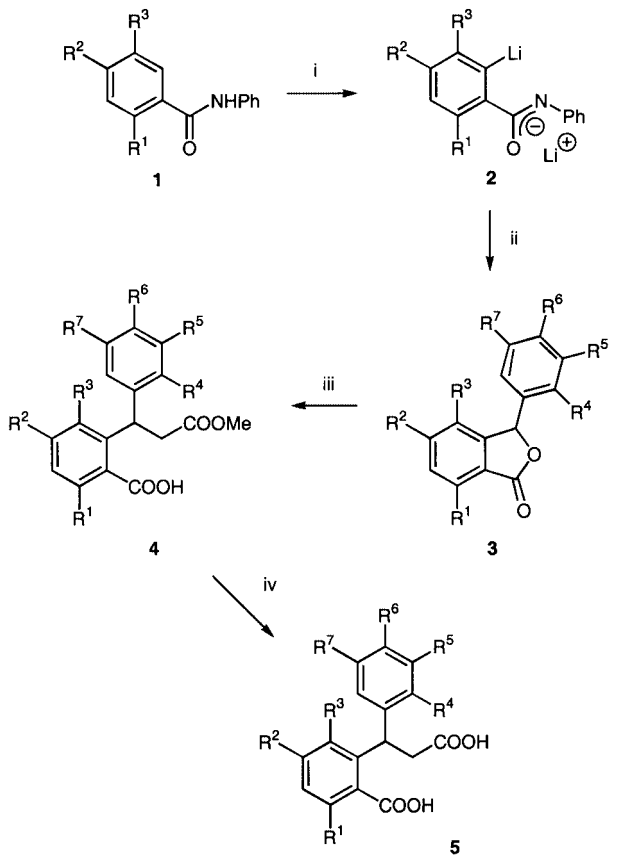
Scheme 1

Our aim was to extend the scope of this idea, as a general procedure, for the synthesis of new *ortho*-substituted benzoic acids **B** and we report here the results obtained starting with a series of 3-arylphthalides. This method provides access to an efficient synthetic sequence as a general strategy for transformation of aromatic carboxylic acids **A** into *ortho*-alkylated benzoic acids **B** in a two-step protocol starting from benzoic acids anilides **1**.

In a series of recent studies, we have reported[8] that the secondary carboxamide moiety provides an excellent possibility for the regiospecific synthesis of 3-arylphthalides, which are key starting materials here. Therefore, 3-arylphthalides **3** were obtained by the lithiation of benzoic acids anilides **1**, using BuLi in THF,[8] followed by the reaction of the generated bis(*N*- and *C*-*ortho*) lithiated anilides **2** with aromatic aldehydes. Thus, the formed *ortho* hydroxy-arylmethyl products, without isolation upon acid-driven cyclization, yielded the corresponding phthalides **3**.

In the next step, the Mukaiyama procedure[9] was used for the synthesis of desired *ortho* substituted benzoic acids **4** by treatment of phthalides **3** with the corresponding methylotrimethylosilyl ketene acetal. The Mukaiyama procedure,[9] which was initially known in the literature as reaction of *O*-silyl enol ethers in the specific aldol condensation, alkylation, or Michael addition, has recently been used for alkylation of acetylated benzyl- and allyl alcohols[2b,7] in the presence of Lewis acid such as $ZnCl_2$. It was expected that the reaction of phthalides **3** with 1-methoxy-1-trimethylsilyloxyethene would provide effectively the desired *ortho* substituted benzoic acids **4** as products of reductive alkylation. In reality, phthalide **3a** when reacted with 1-methoxy-1-trimethylsilyloxyethene in the presence of titanium tetrachloride in methylene chloride furnished the corresponding 2-[2-methoxycarbonyl-1-(4-methoxyphenyl)ethyl]benzoic acid **4a**.

Therefore, a question appeared to what extent fixation of substituents in the close neighbourhood to the centre of the reaction would affect the process. The results of the reaction of 1-methoxy-1-trimethylsilyloxyethylene with phthalides **3** are reported in the Table. Examination of the data reveals that the only products obtained from the reaction were the corresponding monoester of the dicarboxylic acid **4** together with recovered phthalides. In the cases



i: BuLi/THF, -78 °C (0.5 h) → 20 °C (1 h) → -78 °C;
ii: Ar-CHO;
iii: 1-methoxy-1-trimethyl-silyloxyethene / $TiCl_4$ / CH_2Cl_2;
iv: 5 % solution of NaOH

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7
a	H	H	H	H	H	OMe	H
b	H	Cl	H	H	H	OMe	H
c	H	OMe	H	H	H	OMe	H
d	OMe	H	H	H	H	OMe	H
e	H	H	H	OMe	H	H	OMe
f	H	H	OMe	OMe	H	H	H
g	H	H	OMe	OMe	H	H	OMe
h	H	H	OMe	OMe	OMe	H	H

Scheme 2

of the phthalides **3c** and **3d**, the formed monoesters of dicarboxylic acids **4c** and **4d** were isolated after basic hydrolysis to the dicarboxylic acids **5c** and **5d**, respectively.

The observed yields indicated that the tested reductive alkylation is significantly affected by the substituents surrounding the reaction centre. In the cases of phthalides **3a**–**d**, in which the substituent at position 4 of the phthalide nucleus ("*peri*" to the reaction centre) is no higher than a hydrogen atom, the reductive alkylation gave good and comparable results. The presence of the *ortho* methoxy group at the 3-phenyl ring of phthalide **3e** did not produce a change in the reaction yield. On the other hand, when the hydrogen atom at position 4 of the phthalide nucleus was replaced by the methoxy group (compounds **3f**,**g**), the output of the process decreased by more than a half. This may be attributed to the steric hindrance caused

Table Reaction of Phthalides **3** with 1-Methoxy-1-trimethylsiloxyethene

Phtalide	Product	Yield [%]
3a	**4a**	69
3b	**4b**	67
3c	**4c**[a]	66
3d	**4d**	66
3e	**4e**	64
3f	**4f**	34
3g	**4g**	32
3h	**4h**	22

[a] Part of product **4c** was isolated as diacid **5c**. The given yield is the sum of products **4c** and **5c**.

by the methoxy group at the C-4 for the S_{N2}-type nucleophilic attack by 1-methoxy-1-trimethylsilyloxyethene, which would be in good agreement with the behaviour of lactones in the reaction with hard acids and soft nucleophilic systems.[10] This is especially distinct in the case of phthalide **3h**, since the steric repulsion of the 2-methoxy and 3-methoxy groups of the phenyl ring attached at position 3 of the phthalide nuclei causes deformation of valency angles of benzene nucleus (Streitweiser's bond rehybridization model[11]), which brings about an additional increase of the steric hindrance around of the reaction centre.

In summary, we have shown a versatile synthetic method for the preparation of *ortho*-substituted benzoic acids type **B** with an economy of steps. The synthesis involves: (i) successive conversion of benzoic acids anilides **1** via the direct lithiation–electrophilic substitution (aromatic aldehydes) sequence, into phthalides **3**, and (ii) their transformation via reductive alkylation into the desired *ortho*-substituted benzoic acids **4**.

Mps were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Zeiss–Jena Specord 71-IR (KBr pellets). ^{1}H NMR spectra were determined on a Varian-Gemini-200 (200 MHz) using TMS as an internal standard. Compounds were purified until observed as single spots on TLC (Kieselgel GF-254, type 60). Anilides **1** and phthalide (**3b**) were obtained by known methods.[8b] 2-Methoxybenzaldehyde, 4-methoxybenzaldehyde, 2,3-dimethoxybenzaldehyde and 2,5-dimethoxybenzaldehyde (Aldrich) were used without purification. *n*-BuLi (Aldrich) was titrated before use. 1-Methoxy-1-trimethylsiloxyethene was obtained according to a known procedure[12] from methyl acetate anion and chlorotrimethylsilane and it was used as a mixture with methyl(trimethylsilyl) acetate as impurity. The composition of the isomeric ratios were determined by ^{1}H NMR ($CDCl_3$; internal reference TMS) spectroscopy utilising the ratio of the peak areas of the $-OCH_3$ protons of an *O*-silylated (δ = 3.54 ppm) to *C*-silylated species (δ = 3.62 ppm).

Phthalides 3; General Procedure

To the anilide (0.01 mol) in anhyd THF (25 mL) at −78 °C was added BuLi (0.021 mol) dropwise, and the solution was maintained at −78 °C for 0.5 h. The mixture was warmed up to r.t., kept at this temperature for 1 h, and then cooled to −78 °C. To the solution of the lithiated species at −78 °C was added an aldehyde (0.011 mol). After 1 h at −78°C, the mixture was allowed to reach r.t., stirred for

1 h, then HCl (50 mL, 1:1) was added, and the mixture stirred overnight. After partial evaporation of THF, the mixture was extracted with $CHCl_3$ (3 × 50 mL), the layers were separated, and the organic one was dried ($MgSO_4$). The solvent was removed and solid residue was crystallised to give phthalides **3**.

3-(4-Methoxyphenyl)-3*H*-isobenzofuran-1-one (3a)
Yield: 61%, mp: 114−116 °C (needles from EtOH), (Lit.[13] mp: 113−114 °C).

IR (KBr): ν = 1760 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.96 (d, 1H, *J* = 7.3 Hz, Ar-H), 7.72−7.30 (m, 2H, Ar-H), 7.36−7.25 (m, 1H, Ar-H), 7.18 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.89 (d, 2H, *J* = 8.6 Hz, Ar-H), 6.37 (s, 1H, CH), 3.89 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.3, 160.1, 149.5, 134.1, 129.0, 128.5, 128.0, 125.5, 125.1, 122.8, 114.0, 82.5, 55.0.

3-(4-Methoxyphenyl)-5-methoxy-3*H*-isobenzofuran-1-one (3c)
Yield: 54%, mp: 114−116 °C (plates from EtOH).

IR (KBr): ν = 1750 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.85 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.21−7.14 (m, 2H, Ar-H), 7.05 (dd, 1H, *J* = 8.1, 2.1 Hz, Ar-H), 6.94−6.85 (m, 2H, Ar-H), 6.70 (d, 1H, *J* = 1.8 Hz, Ar-H), 6.27 (s, 1H, CH), 3.83 (s, 3H, OMe), 3.81 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.3, 164.9, 160.4, 152.6, 128.8, 128.4, 127.0, 118.2, 116.9, 114.3, 106.6, 82.1, 55.8, 55.3.

Anal. Calcd for $C_{16}H_{14}O_4$:.C, 71.10; H, 5.22. Found: C, 70.97; H, 5.18.

3-(4-Methoxyphenyl)- 7-methoxy-3*H*-isobenzofuran-1-one (3d)
Yield: 68%, mp: 127−129 °C (needles from EtOH).

IR (KBr): ν = 1750 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.60−7.50 (m, 1H, Ar-H), 7.20−7.11 (m, 2H, Ar-H), 6.96−6.76 (m, 4H, Ar-H), 6.25 (s, 1H, CH), 4.00 (s, 3H, OMe), 3.78 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 168.5, 160.2, 158.4, 152.6, 136.4, 128.6, 128.5, 114.6, 114.2, 113.3, 110.7, 81.6, 56.1, 55.3.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.22; H, 5.30.

3-(2,5-Dimethoxyphenyl)-3*H*-isobenzofuran-1-one (3e)
Yield: 77%, mp: 93−95 °C (needles from EtOH/H_2O, 8:2), (Lit.[14] mp: 80 °C).

IR (KBr): ν = 1750 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.89 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.65−7.40 (m, 3H, Ar-H), 6.97−6.60 (m, 4H, Ar-H), 3.86 (s, 3H, OMe), 3.65 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.9, 153.6, 150.9, 150.3, 134.3, 129.0, 126.0, 125.3, 123.0, 114.4, 112.5, 112.1, 77.86, 56.1, 55.6.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.32; H, 5.41.

3-(2-Methoxyphenyl)-4-methoxy-3*H*-isobenzofuran-1-one (3f),
Yield: 60%, mp: 188−190 °C (plates from EtOH).

IR (KBr): ν = 1750 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.58−7.46 (m, 2H, Ar-H), 7.38−7.25 (m, 1H, Ar-H), 7.09 (dd, 1H, *J* = 7.0, 2.5 Hz, Ar-H), 6.93 (d, 1H, *J* = 8.2 Hz), 6.87−6.79 (m, 3H, Ar-H and CH) 3.84 (s, 3H, OMe), 3.73 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.8, 158.1, 154.5, 136.9, 131.0, 130.5, 128.7, 128.4, 123.5, 120.4, 117.0, 115.3, 111.2, 55.8, 55.7.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.26; H, 5.23.

3-(2,5-Dimethoxyphenyl)-4-methoxy-3*H*-isobenzofuran-1-one (3g)
Yield: 55%, mp: 142−144 °C (plates from EtOH), (Lit.[14] mp: 133−135 °C).

IR (KBr): ν = 1760 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.56−7.44 (m, 2H, Ar-H), 7.14−7.02 (m, 1H, Ar-H), 6.92−6.74 (m, 3H, Ar-H), 6.39 (s, 1H, CH), 3.80 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.65 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.8, 158.1, 154.5, 153.4, 152.4, 131.1, 130.5, 128.4, 120.4, 117.0, 115.3, 114.7, 112.6, 111.2, 56.5, 55.7.

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 68.11; H, 5.28.

3-(2,3-Dimethoxyphenyl)-4-methoxy-3*H*-isobenzofuran-1-one (3h)
Yield: 40%, mp: 193−195 °C (needles from EtOH).

IR (KBr): ν = 1770 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.60−7.44 (m, 2H, Ar-H), 7.08 (dd, 1H, *J* = 8.0, 3.6 Hz, Ar-H), 7.02−6.88 (m, 2H, Ar-H), 6.78 (s, 1H, CH), 6.45 (dd, 1H, J_2 = 8.0, 2.2 Hz, Ar-H), 3.88 (s, 6H, 2 × OMe), 3.72 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 170.8, 154.4, 152.8, 148.2, 137.1, 131.1, 129.2, 128.3, 124.0, 119.9, 117.0, 115.4, 113.2, 61.3, 55.8, 55.6.

Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.85; H, 5.34.

Reaction of 1-Methoxy-1-trimethylsilyloxyetene with 3-Arylphthalides
To stirred solution of phthalide (0.01 mol) and 1-methoxy-1-trimethylsilyloxyethene (0.03 mol) in 10 mL of CH_2Cl_2, a solution of $TiCl_4$ (2.0 mL) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. The mixture was stirred overnight at r.t.. Next, 5% $KHSO_4$ (50 mL) was added, and after 1 h the mixture was extracted with $CHCl_3$ (3 × 25 mL). To the combined extracts, after removal of the solvent till dryness, 5% Na_2CO_3 (100 mL) was added. After filtering same solids, the aqueous layer was acidified with 5% HCl. The precipitated product **4a**−**h** were filtered and purified by crystallisation. In the case of phthalide **3c**, the residue after extraction with Na_2CO_3 was extracted with 5% NaOH (100 mL). In this case, the product was isolated as dicarboxylic acid **5c** after acidification of the alkaline solution with 5% HCl. The corresponding product was filtered and purified by crystallisation. The monoacid **4d** was formed as an oil, therefore basic hydrolysis at r.t. with 5% NaOH furnished dicarboxylic acid **5d**.

2-[2-Methoxycarbonyl-1-(4-methoxyphenyl)ethyl]benzoic Acid (4a)
Yield: 69%, mp: 148−150 °C (plates from MeOH/H_2O, 1:1).

IR (KBr): ν = 1710, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.94 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.55−7.40 (m, 1H, Ar-H), 7.38−7.20 (m, 4H, Ar-H), 6.88−6.78 (m, 2H, Ar-H), 5.53 (m, 1H, CH), 3.76 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.08 (d, 2H, *J* = 7.8 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 172.6, 172.4, 158.1, 145.4, 135.1, 132.7, 131.2, 129.2, 128.9, 128.4, 126.4, 113.8, 55,2, 51.8, 40.8, 40.7.

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.85; H, 5.70.

4-Chloro-2-[2-methoxycarbonyl-1-(4-methoxyphenyl)ethyl]benzoic Acid (4b)
Yield: 67%, mp: 160−162 °C (needles from benzene/hexane, 10:15).

IR (KBr): ν = 1730, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.91 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.37−7.15 (m, 4H, Ar-H), 6.90−6.78 (m, 2H, Ar-H), 5.66 (m, 1H, CH), 3.77 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.02 (d, 2H, *J* = 8.1 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 172.1, 171.9, 158.3, 148.0, 139.2, 134.2, 132.8, 128.8, 127.3, 126.7, 114.0, 55.3, 55.2, 51.9, 40.5.

Anal. Calcd for $C_{18}H_{17}ClO_5$: C, 61.99; H, 4.91; Cl, 10.16. Found: C, 62.05; H, 4.96; Cl, 10.08.

4-Methoxy-2-[2-methoxycarbonyl-1-(4-methoxyphenyl)-ethyl]benzoic Acid (4c)
Yield: 23%, mp: 125−127 °C (needles from benzene/hexane, 85:15).

IR (KBr): ν = 1740, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 11.59 (s, 1H, COOH), 8.08−7.99 (m, 1H, Ar-H), 7.27−7.16 (m, 2H, Ar-H), 6.87−6.69 (m, 4H, Ar-H), 5.81 (m, 1H, CH), 3.76 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.04 (d, 2H, *J* = 5.5 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 172.2, 163.0, 158.04, 148.9, 135.0, 134.3, 129.0, 128.9, 120.6, 114.95, 113.8, 110.7, 55.3, 55.2, 51.7, 40.9, 40.8, 30.9.

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C; 66.30; H, 5.70.

3-(2-Carboxy-5-methoxyphenyl)-3-(4-methoxyphenyl)propanoic Acid (5c)
Yield: 43%, mp: 183−185 °C (needles from toluene).

IR (KBr): ν = 1710, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 12.33 (s, 2H, COOH), 7.78 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.28−7.18 (m, 2H, Ar-H), 6.92−6.77 (m, 4H, Ar-H), 5.64 (t, 1H, *J* = 7.7 Hz, CH), 3.76 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.94 (d, 2H, *J* = 7.7 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 172.2, 163.0, 158.0, 148.9, 135.0, 134.3, 129.1, 128.9, 120.6, 115.0, 113.8, 110.7, 55.3, 55.2, 51.8, 40.8, 30.9.

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.36; H, 5.43.

2-Methoxy-6-[2-methoxycarbonyl-1-(4-methoxyphenyl)ethyl]benzoic Acid (4d)
Yield: (66%), oil.

IR (KBr): ν = 1720, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.35−7.12 (m, 3H, Ar-H), 6.88−6.72 (m, 4H, Ar-H), 4.76 (m, 1H, CH), 3.80 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.09 (d, 2H, *J* = 8.1 Hz, CH_2).

3-(2-Carboxy-3-methoxyphenyl)-3-(4-methoxyphenyl)propanoic Acid (5d)

Yield: 90%, mp 165−167 °C (plates from toluene).

IR (KBr): ν = 1710, 1680 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 9.00 (s, 2H, COOH), 7.30−7.16 (m, 4H, Ar-H), 6.84−6.74 (m, 3H, Ar-H), 4.78 (t, 1H, *J* = 7.8 Hz, CH), 3.82 (s, 3H, OMe), 3.74 (s, 3H OMe), 3.11 (d, 2H, *J* = 8.0, CH_2).

^{13}C NMR ($CDCl_3$): δ = 177.9, 173.5, 158.3, 156.4, 142.7, 134.0, 131.1, 128.7, 122.6, 119.5, 114.0, 109.3, 76.4, 56.0, 55.1, 42.1, 40.5.

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.80; H, 5.47.

2-[1-(2,5-Dimethoxyphenyl)-2-methoxycarbonylethyl]benzoic Acid (4e)
Yield: 64%, mp 193−195 °C (plates from PrOH).

IR (KBr): ν = 1720, 1700 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.78−7.70 (m, 1H, Ar-H), 7.44−7.16 (m, 3H, Ar-H), 6.80−6.65 (m, 3H, Ar-H), 5.67 (m, 1H, CH), 3.71 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.55 (s, 3H, OMe) 3.10−2.90 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$): δ = 176.9, 170.4, 153.4, 132.2, 131.6, 130.2, 127.8, 126.5, 113.8, 113.7, 111.2, 110.8, 55.7, 55.5, 52.4, 39.0, 35.6.

Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C,65.30; H, 65.92.

3-Methoxy-2-[2-methoxycarbonyl-1-(2-methoxyphenyl)ethyl]benzoic Acid (4f)
Yield: 34%, mp: 204−206 °C (plates from EtOH).

IR (KBr): ν = 1740, 1690 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.39 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.31−7.11 (m, 3H, Ar-H), 6.98−6.82 (m, 2H, Ar-H), 6.74 (d, 1H, *J* = 7.8 Hz, Ar-H), 5.22 (dd, 1H, *J* = 12.0, 3.8 Hz, CH), 4.11 (dd, 1H, *J* = 17.9, 12.0 Hz, CH_2), 3.08 (dd, 1H, *J* = 17.5, 5.1 Hz, CH_2), 3.69 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe).

^{13}C NMR ($CDCl_3$): δ = 176.8, 170.5, 158.2, 156.9, 136.6, 128.6, 128.0, 127.6, 126.9, 122.2, 119.3, 114.4, 110.0, 55.4, 54.6, 52.7, 35.3, 34.2.

Anal. Calcd for $C_{18}H_{18}O_6$: C, 66.27; H, 5.87. Found: C, 66.13; H, 5.90.

3-Methoxy-2-[-1-(2,5-dimethoxyphenyl)-2-methoxycarbonylethyl]benzoic Acid (4g)
Yield: 32%, mp: 186−188 °C (plates from EtOAc).

IR (KBr): ν = 1740, 1710 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.31−7.12 (m, 2H, Ar-H), 7.00 (d, 1H, *J* = 2.3 Hz, Ar-H), 6.88 (dd, 1H, *J* = 7.7, 4.2 Hz, Ar-H), 6.73−6.60 (m, 1H, Ar-H), 5.21 (dd, 1H, *J* = 11.5, 4.6 Hz, CH), 3.91 (dd, 1H, *J* = 17.8, 11.5 Hz, CH_2), 3.78 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.65 (s, 3H, COOMe), 3.08 (dd, 1H, *J* = 17.6, 4.6 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 176.4, 170.6, 158.2, 152.7, 151.4, 136.4, 129.9, 128.1, 126.8, 122.3, 115.6, 114.4, 111.1, 110.4, 55.8, 55.4, 55.1, 52.6, 35.4, 34.4, 29.7.

Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.40; H, 5.74.

3-Methoxy-2-[-1-(2,3-dimethoxyphenyl)-2-methoxycarbonylethyl]benzoic Acid (4h)
Yield: 22%, mp: 77−79 °C (needles from Et_2O/heptane, 1:1).

IR (KBr): ν = 1720, 1710 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 7.40−7.18 (m, 3H, Ar-H), 7.02−6.83 (m, 3H, Ar-H), 5.36 (t, 1H, *J* = 6.6 Hz, CH), 3.78 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.61 (s,3H, OMe), 3.51 (s, 3H, OMe), 3.33 (d, 2H, *J* = 6.6 Hz, CH_2).

^{13}C NMR ($CDCl_3$): δ = 174.6, 171.2, 158.3, 152.3, 146.9, 134.8, 129.3, 128.0, 122.7, 122.5, 120.2, 114.9, 110.8, 59.8, 55.6, 55.5, 52.2, 36.1, 35.3.

Anal. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.84; H, 6.15.

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