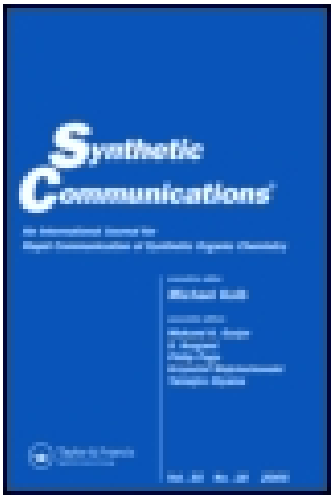


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Application of Organolithium and Related Reagents in Synthesis, Part 31: Effective Conversion of 3-Arylphthalides into 2-(1-Aryl-3-oxo-4-alkoxycarbonyl-butyl)benzoic Acids

Adam Bieniek [a] , Krystyna K. Kulikiewicz [a] & Monika M. Bartczak [a]
[a] Department of Organic Chemistry , Institute of Chemistry, University of Łódź , Łódź, Poland
Published online: 24 Nov 2006.

To cite this article: Adam Bieniek , Krystyna K. Kulikiewicz & Monika M. Bartczak (2006) Application of Organolithium and Related Reagents in Synthesis, Part 31: Effective Conversion of 3-Arylphthalides into 2-(1-Aryl-3-oxo-4-alkoxycarbonyl-butyl)benzoic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:21, 3249-3259, DOI: 10.1080/00397910600910617

To link to this article: http://dx.doi.org/10.1080/00397910600910617

Synthetic Communications®, 36: 3249–3259, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910600910617

Application of Organolithium and Related Reagents in Synthesis, Part 31: Effective Conversion of 3-Arylphthalides into 2-(1-Aryl-3-oxo-4-alkoxycarbonyl-butyl)benzoic Acids

Adam Bieniek, Krystyna K. Kulikiewicz, and Monika M. Bartczak
Department of Organic Chemistry, Institute of Chemistry, University of Łódź, Łódź, Poland

Abstract: A convenient three-step protocol preparation of the *ortho*-alkylated (long-chain substituent with terminal methylcarbonyl or acetoacetate moiety) aromatic carboxylic acids **15** or **16** from benzoic acids anilides **10** was developed, which exploited the reductive alkylation of phthalides **13** with dimethyl-6-methylene-4-(trimethoxysiloxy)-1,3-diox-4-ene (**9**) as a key step.

Keywords: Acetoacetic esters, benzoic acids, 6-methyl-1,3-dioxin-4-one, Mukaiyama reaction

The phthalide system constitutes the central core in the synthesis of a series of compounds that has important pharmacological properties. Several synthetic approaches have been reported.[1] During our work,[2] we have successfully developed an effective and regiospecific sequence of reactions for the transformation of phthalides, which upon treatment with methyl-trimethylsilyl ketene acetal in the presence of titanium tetrachloride (a modification of the Mukaiyama[3,4] procedure) furnished the desired acids **5**.[5] Most of these approaches were reported in the recent review.[6]

Received in Poland April 4, 2006
Address correspondence to Adam Bieniek, Department of Organic Chemistry, Institute of Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Łódź, Poland. E-mail: bieniek@uni.lodz.pl

Recently, a convenient route to synthesize functionalized benzoic acids, which contain a five-carbon-atom chain in the *ortho* position, by utilizing a reaction of phthalide with conjugated silyl dienolates was developed.[7] Using this protocol, functionalized *ortho*-alkylated benzoic acids **6** were synthesized from the corresponding diene, previously prepared from the commercially available crotonic ester (Scheme 1).

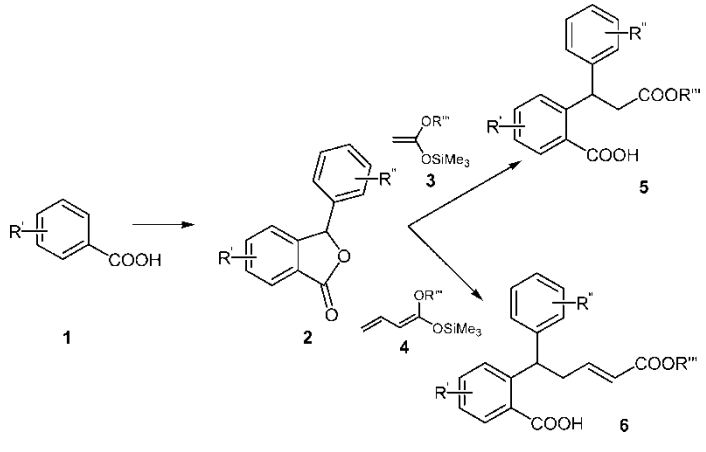
We develop this methodology for the introduction of the five-carbon-atom chain with terminally situated β-carbonyl acid system.

1,3-bis-(Trimethylsiloxy)-1-methoxybuta-1,3-diene (**7**)[8,9] as synthon of methyl acetoacetate compounds **8** was used in the reaction with phthalides (Scheme 2). Unfortunately all runs failed.

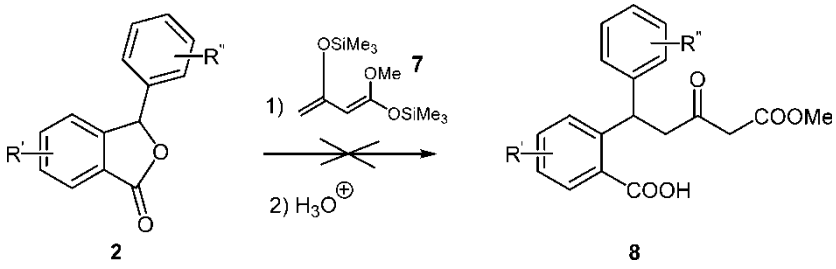
Following that, the 2,2-dimethyl-6-methylene-4-(trimethoxysiloxy)-1,3-diox-4-ene (**9**), precursor of methyl acatyloacetate terminal function, was applied. This compound is easily available from 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, by reaction with lithium diisopropyl amide (LDA) and trimethylsilyl chloride (TMS-Cl)[10] (see Scheme 3 and Experimental section).

It is known that the species **9** constitutes an interesting alternative to the classic enantioselective Mukaiyama aldol reaction with silyl enol ethers. The interest in the employment of this silyl dienolate **9** is due to the easy manipulation of the dioxinone ring in the aldol adducts to a variety of five-carbon units.[11,12] In fact, the masked acetoacetate aldol adducts serve as versatile precursors to β-keto esters and derived compounds, which are key structural subunits in biologically active natural products.[13,14]

The required 3-aryl-phthalides **13**, which are key starting materials, were obtained by the lithiation of benzoic acids anilides **10**, using BuLi in THF,[5,7,15] followed by the reaction of the generated *bis*-(*N*- and *C*-*ortho*)-lithiated anilides **11** with aromatic aldehydes. Thus, the formed *ortho*-hydroxy-arylmethyl products **12**, without isolation by acid-driven cyclization, yielded the corresponding phthalides **13** (Scheme 4).



Scheme 1.



Scheme 2.

The phthalides **13** reacted with diene **9** in the presence of $TiCl_4$ (Mukaiyama procedure[3,4]) to give compound **14**. An examination of the data reveals that the only products obtained from the reaction were the corresponding alkylated products **14** together with a small amount of recovered phthalides **13**. The high overall yields apparently show that all other possible reactions were minimized.

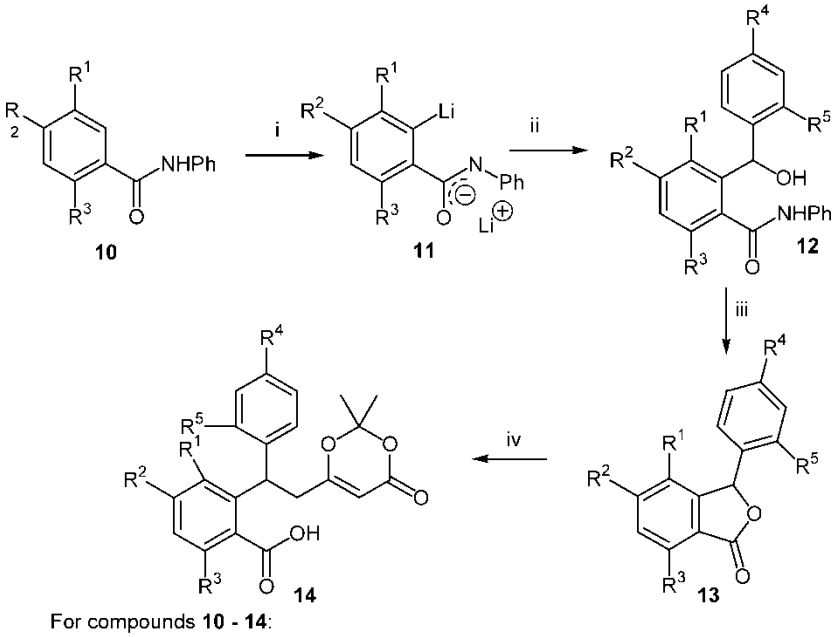
Keeping in mind that a dioxinone ring is easily manipulatable via variety of ways,[11,16] the next step was the transformation of this moiety to the acetylacetic acid ester **15** using toluene as solvent and methanol, ethanol, or propan-1-ol. The best results were obtained using propan-1-ol as reagent, probably because of its high boiling temperature.

β-Ketoesters are easily decarboxylated themselves upon hydrolysis without isolation of the acids. In the end, we tried to decarboxylate a few examples of compounds **14** with the dioxenone moiety to methyl ketones **16** using neutral conditions (reflux in a mixture of toluene and water). In this experiment, we obtained the carbonyl derivatives **16** in good yields. We previously obtained compound **16a** in the reductive alkylation reaction of phthalide **13a** with silyl enol ethers.[15] When we used phthalide with steric hindrance near the reaction center as in **13e**, only traces of product **16b** were obtained (Scheme 5).

The exact structure of compounds **16** were solved by X-ray analysis.[17]

In summary, we have shown that the conversion of benzoic acid anilides **10** into *ortho*-alkylated carboxylic acids with acetylacetic acid moiety **15** is easy and effective. The reaction of phthalide **13** with 2,2-dimethyl-6-methylene-4-trimethylsiloxy-1,3-diox-4-ene (**9**) gave the compounds with dioxenone moiety **14**. These compounds apeared to be ready for conversion into another derivative containing long chain substituent with carbonyl (**16**) or carbonyl and alkoxycarbonyl (**15**) groups.

Scheme 3.

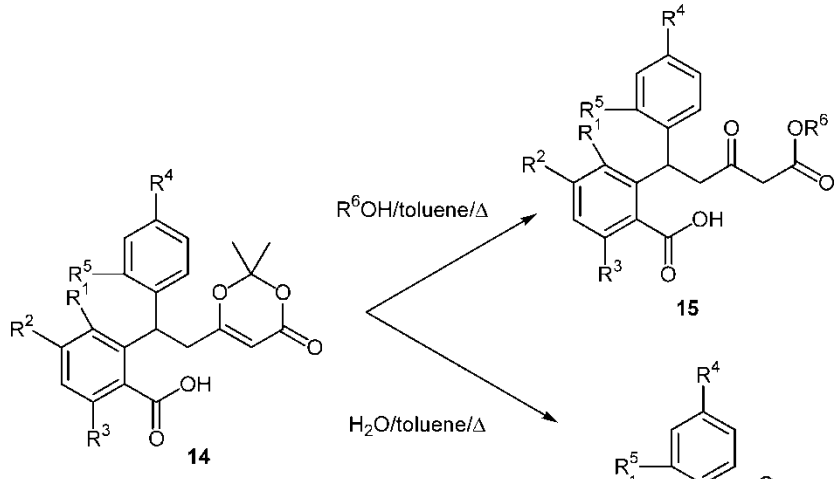


For compounds **10** - **14**:
a) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$; **b**) $R^1 = R^2 = R^5 = H$, $R^3 = R^4 = OMe$;
c) $R^2 = R^3 = R^5 = H$, $R^1 = R^4 = OMe$; **d**) $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$;
e) $R^2 = R^3 = R^4 = H$, $R^1 = R^5 = OMe$; **f**) $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$;

Scheme 4. (i) n-BuLi in THF/hexane, $-78°C/1$ h $\rightarrow 0°C$; (ii) Ar-CHO, $-78°C$; $\rightarrow 20°C/1$ h; (iii) HCl (1 : 1); (iv) 1) **9**/CH_2Cl_2/$TiCl_4$/-78deg;C; 2) $KHSO_4$ 5% aq.

EXPERIMENTAL

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR (KBr pellets). NMR analyses were performed on a Varian-Gemini-200 (200 MHz) using TMS as an internal standard in $CDCl_3$; chemical shifts are quoted in parts per million (ppm). Compounds were purified until observed as single spots with thin-layer chromatography (TLC) (Kieselgel GF-254 type 60). Tetrahydrofuran was distilled before use from sodium-benzophenone ketyl, and dichloromethane was dried from molecular sieves, 3A. Other solvents and reagents were purified according to standard procedures where appropriate. *n*-Butyllithium (*n*-BuLi) (Aldrich) was titrated before use. Reaction temperatures were recorded as bath temperatures. Elemental analysis was carried out by the Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Lodz. Phthalides **13** were obtained by known methods.[5,7,15]



For compounds **15**:
a) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$, $R^6 = Me$;
b) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$, $R^6 = Et$;
c) $R^2 = R^3 = R^5 = H$, $R^1 = R^4 = OMe$, $R^6 = n\text{-}Pr$;
d) $R^2 = R^3 = R^4 = H$, $R^1 = R^5 = OMe$, $R^6 = n\text{-}Pr$;
e) $R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$, $R^6 = n\text{-}Pr$;
f) $R^1 = R^2 = H$, $R^3 = R^4 = R^5 = OMe$, $R^6 = n\text{-}Pr$;
For compounds **16**:
a) $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = OMe$; **b**) $R^2 = R^3 = R^5 = H$, $R^1 = R^4 = OMe$;

Scheme 5.

2,2-Dimethyl-6-methylene-4-trimethylsilanyloxy-4*H*-[1,3]dioxine (9)[10]

A mixture of 9.2 cm^3 of the 2,2,6-trimethyl-[1,3]dioxin-4-one (0.07 mol) in THF (20 cm^3) was added in 20 min at −78°C to lithium diisopropylamide (0.075 mol, prepared from *n*-BuLi in hexane (0.076 mol) and diisopropylamine (0.075 mol) in 125 cm^3 of THF. A light solid precipitated in the flask. Next, after 45 min, 15 cm^3 of trimethylsilyl chloride (0.12 mol) in THF (20 cm^3) was added during 20 min. After additional 40 min, at −78°C, the whole lot was allowed to reach ambient temperature. Then the mixture was concentrated under reduced pressure and the residue filtered off. The obtained 2,2-dimethyl-6-methylene-4-trimethylsilanyloxy-4*H*-[1,3]dioxine was used without isolation and purification.

All yields of the 2,2-dimethyl-6-methylene-4-trimethylsilanyloxy-4*H*-[1,3]dioxine were determined by ^1H NMR ($CDCl_3$, internal reference $SiMe_4$) spectroscopy utilizing the peak areas of their methylene protons in

relation to the methyl protons of starting material. Yield 95%. ^{1}H NMR ($CDCl_3$) 4.58 (s, 1H, -CH═C-OSiMe$_3$), 4.01 (d, 1H, *J* 0.8 Hz, ═CH_2), 3.82 (d, 1H, *J* 0.8 Hz, ═CH_2), 1.49 (s, 6H, 2 × Me), 0.21 (s, 9H, SiMe$_3$).

Reaction of 2,2-Dimethyl-6-methylene-4-trimethylsilanyloxy-4*H*-[1,3] Dioxine (9) with 3-Arylphtalides (13)

To the stirred solution of phtalides **13** (0.011 mol) and 2,2-dimethyl-6-methylene-4-trimethylsilanyloxy-4*H*-[1,3]dioxine **(9)** (0.13 mol) in 75 cm^3 of CH_2Cl_2, a solution of $TiCl_4$ (2.0 cm^3) in CH_2Cl_2 (10 cm^3) was added dropwise at −78°C. The mixture was stirred for an additional 6 h at this temperature. Next, the whole lot was allowed to reach ambient temperature, 50 cm^3 of 5% water solution of $KHSO_4$ was added, and after 1 h the mixture was extracted with chloroform (3 × 35 cm^3). Then the combined extracts were evaporated to dryness. The solid residue was purified by column chromatography (silica gel–chloroform/hexane 1:1 and chloroform/methanol 8:2). The products **14** were purified by crystallization.

2-[2-(2,2-Dimethyl-6-oxo-6 *H*-[1,3]dioxin-4-yl)-1-(4-methoxyphenyl)-ethyl]-benzoic Acid (14a)

Yield 85%; mp 84–86°C (needles from diisopropyl ether/ethyl acetate/hexane 8:2:1); IR (KBr): 1713, 1690 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) 8.04–8.00 (m, 1H, Ar-H), 7.55–7.48 (m, 1H, Ar-H), 7.36–7.20 (m, 4H, Ar-H), 6.86–6.81 (m, 2H, Ar-H), 5.61 (t, 1H, *J* 8.2 Hz, Ar_2CH), 5.24 (s, 1H, ═CH-C═O), 3.77 (s, 3H, OMe), 3.10–2.88 (m, 2H, CH_2), 1.46 (s, 3H, Me), 1.44 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 172.6, 169.8, 161.5, 158.2, 145.2, 134.1, 132.9, 131.5, 129.0, 128.5, 128.3, 126.5, 113.8, 106.5, 94.6, 55.0, 41.0, 39.6, 24.5, 24.4. Anal. calcd. for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.01; H, 5.63.

2-[2-(2,2-Dimethyl-6-oxo-6 *H*-[1,3]dioxin-4-yl)-1-(4-methoxyphenyl)-ethyl]-6-methoxy-benzoic Acid (14b)

Yield 84%; mp 78–80°C (needles from diisopropyl ether/ethyl acetate 8:2); IR (KBr): 1723, 1700 cm^{-1} (C═O); ^{1}H NMR ($CDCl_3$) 8.11 (br s, 1H, COOH), 7.40–7.15 (m, 3H, Ar-H), 6.95–6.70 (m, 4H, Ar-H), 5.23 (s, 1H, ═CH-C═O), 4.65 (t, 1H, *J* 10.4 Hz, Ar_2CH), 3.87 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.10–2.41 (m, 2H, CH_2), 1.47 (s, 3H, Me), 1.42 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 171.6, 169.4, 161.6, 158.2, 156.3, 141.3, 133.5, 130.7, 128.7, 123.0, 119.2, 113.8, 109.3, 106.8, 94.8, 68.6, 55.8, 55.0, 42.8, 39.4, 24.5, 24.1, 22.5. Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H 5.87. Found: C, 66.73; H, 5.91.

2-[2-(2,2-Dimethyl-6-oxo-6*H*-[1,3]dioxin-4-yl)-1-(4-methoxy-phenyl)-ethyl]-3-methoxy-benzoic Acid (14c)

Yield 80%; mp 121–123°C (needles from benzene/hexane – 9:1); IR (KBr): 1720, 1710 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.45–7.41 (m, 1H, Ar-H); 7.34–7.19 (m, 3H, Ar-H); 7.01–6.95 (m, 1H, Ar-H); 6.80–6.72 (m, 2H, Ar-H); 5.38 (t, 1H, $J = 7.4$ Hz, Ar_2CH); 5.15 (s, 1H, J 7.4 Hz, ═CH-C═O); 3.73 (s, 3H, OMe); 3.69 (s, 3H, OMe); 3.36–3.06 (m, 2H, CH_2); 1.45 (s, 3H, Me); 1.34 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) 173.1, 170.9, 161.6, 158.7, 157.9, 134.0, 131.8, 131.7, 128.7, 128.1, 122.8, 115.7, 113.3, 106.5, 55.6, 55.2, 39.3, 36.3, 24.9, 24.3. Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 67.01; H, 5.94.

2-[2-(2,2-Dimethyl-6-oxo-6 *H*-[1,3]dioxin-4-yl)-1-(2-methoxy-phenyl)-ethyl]-4-methoxy-benzoic Acid (14d)

Yield 82%; mp 120–122°C (needles from diisopropyl ether/ethyl acetate/hexane 8:2:1); IR (KBr): 1724, 1710 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.45–7.19 (m, 4H, Ar-H); 7.01–6.97 (m, 1H, Ar-H); 6.78–6.73 (m, 2H, Ar-H); 5.36 (t, 1H, J 8.1 Hz, Ar_2CH); 5.15 (s, 1H, ═CH-C═O); 3.74 (s, 3H, OMe); 3.70 (s, 3H, OMe); 3.37–3.05 (m, 2H, CH_2); 1.45 (s, 3H, Me); 1.34 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) 172.2, 170.8, 161.6, 158.7, 157.8, 134.0, 131.7, 128.7, 128.1, 122.8, 115.6, 113.4, 106.4, 94.0, 55.5, 55.1, 39.3, 36.3, 24.8, 24.2. Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.83; H, 6.06.

2-[2-(2,2-Dimethyl-6-oxo-6*H*-[1,3]dioxin-4-yl)-1-(2-methoxy-phenyl)-ethyl]-3-methoxy-benzoic Acid (14e)

Yield 70%; mp 143–145°C (needles from benzene); IR (KBr): 1724, 1693 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.45–7.40 (m, 2H, Ar-H); 7.32–7.14 (m, 2H, Ar-H); 7.03–6.90 (m, 2H, Ar-H); 6.81–6.77 (m, 1H, Ar-H); 5.66 (t, 1H, J 8.4 Hz, Ar_2CH); 5.27 (s, 1H, ═CH–C═O); 3.77 (s, 3H, OMe); 3.72 (s, 3H, OMe); 3.45–3.18 (m, 2H, CH_2); 1.47 (s, 3H, Me); 1.44 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) 174.2, 171.3, 161.8, 159.1, 157.2, 133.0, 130.4, 129.0, 128.5, 128.3, 127.7, 127.5, 122.1, 119.7, 115.2, 110.3, 106.3, 55.4, 55.0, 35.0, 34.7, 24.7, 24.4. Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.93; H, 6.01.

2-[1-(2,4-Dimethoxy-phenyl)-2-(2,2-dimethyl-6-oxo-6*H*-[1,3]dioxin-4-yl)-ethyl]-6-methoxy-benzoic Acid (14f)

Yield 75%; mp 142–144°C (needles from benzene/hexane 9:1); IR (KBr): 1724, 1704 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 8.69 (br s, 1H, COOH); 7.34–

7.24 (m, 1H, Ar-H); 7.08–7.04 (m, 1H, Ar-H); 6.94–6.77 (m, 2H, Ar-H); 6.43–6.36 (m, 2H, Ar-H); 5.20 (s, 1H, =CH-C=O); 4.98 (t, 1H, *J* 8.0 Hz, Ar_2CH); 3.83 (s, 3H, OMe); 3.74 (s, 3H, OMe); 3.72 (s, 3H, OMe); 3.05–2.83 (m, 2H, CH_2); 1.43 (s, 3H, Me); 1.40 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) 172.1, 169.9, 161.6, 159.8, 157.8, 156.5, 142.1, 130.8, 128.3, 122.5, 122.3, 120.1, 109.3, 106.6, 104.0, 98.7, 94.7, 56.0, 55.2, 38.5, 36.7, 24.6, 24.5. Anal. calcd. for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.10; H, 5.96.

Reaction of 2-[2-(2,2-Dimethyl-6-oxo-6*H*-[1,3]dioxin-4-yl)-1-phenylethyl]-benzoic Acid (14) with Alcohols

A solution of 0.01 mol of adequate acid **14** in 20 cm^3 of toluene and 10 cm^3 of alcohol was heated to boiling for 5–10 h. After the solvent was evaporated in vacuo, crude products were purified by crystallization.

2-[4-Methoxycarbonyl-1-(4-methoxyphenyl)-3-oxobutyl]-benzoic Acid (15a)

Reflux time: 5 h. Yield 63%; mp 113–115°C (needles from diisopropyl ether/ethyl acetate/hexane 8:3:1); IR (KBr): 1744, 1710, 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.96–7.91 (m, 1H, Ar-H), 7.50–7.41 (m, 1H, Ar-H), 7.30–7.15 (m, 4H, Ar-H), 6.84–6.80 (m, 2H, Ar-H), 5.61 (t, 1H, *J* 7.8 Hz, CH), 3.76 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.44 (d, 2H, *J* 2.0 Hz, CO-CH_2-CO), 3.33 (d, 2H, *J* 7.8 Hz, CH_2); ^{13}C NMR ($CDCl_3$) 201.2, 170.8, 158.2 157.8, 145.5, 134.5, 132.6, 131.2, 128.9, 128.5, 126.4, 113.9, 56.4, 55.2, 52.4, 49,3, 48.8, 39.9. Anal. calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.61. Found: C, 67.44; H, 5.59.

2-[4-Ethoxycarbonyl-1-(4-methoxyphenyl)-3-oxobutyl]-benzoic Acid (15b)

Reflux time: 6 h. Yield 45%; mp 88–90°C (needles from diisopropyl ether/ethyl acetate/hexane 8:3:1); IR (KBr): 1740, 1710, 1690 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) 7.98–7.94 (m, 1H, Ar-H), 7.49–7.41 (m, 1H, Ar-H), 7.31–7.16 (m, 4H, Ar-H), 6.84–6.79 (m, 2H, Ar-H), 5.65 (t, 1H, *J* 7.7 Hz, CH), 4.15 (q, 2H, *J* 7.2 Hz, CH_2), 3.76 (s, 3H, OMe), 3.42 (s, 2H, CO-CH_2-CO), 3.34 (d, 2H, *J* 7.7 Hz, CH_2), 1.23 (t, 3H, *J* 7.2 Hz, Me); ^{13}C NMR ($CDCl_3$) 201.3, 171.7, 167.1, 158.2, 145.7, 134.7, 132.7, 131.4, 129.2, 129.0, 128.8, 128.5, 126.4, 113.9, 61.4, 55.2, 49.3, 49.1, 39.9, 30.9, 13.9. Anal. calcd. for $C_{21}H_{22}O_6$: C, 68.10; H, 5.94. Found: C, 68.07; H, 6.01.

3-Methoxy-2-[1-(4-methoxyphenyl)-3-oxo-4-propoxycarbonylbutyl]-benzoic Acid (15c)

Reflux time: 8 h. Yield 67%; light-yellow oil; IR ($CHCl_3$): 1720, 1716, 1697 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.39–7.35 (m, 1H, Ar-H), 7.28–7.24 (m, 1H, Ar-H), 7.19–7.15 (m, 2H, Ar-H), 6.96–6.91 (m, 1H, Ar-H), 6.78–6.73 (m, 2H, Ar-H), 5.35 (t, 1H, *J* 6.9 Hz, CH), 4.05 (t, 2H, *J* 6.7 Hz, CH_2), 3.73 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.54 (d, 2H, *J* 5.8 Hz, CH_2), 3.46 (d, 2H, *J* 2.1 Hz, CO-CH_2-CO), 1.70–1.52 (m, 2H, CH_2-C**H**$_2$-CH_3), 0.89 (t, 3H, *J* 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 203.7, 172.1, 167.0, 158.0, 157.6, 133.9, 133.4, 131.1, 128.7, 127.9, 122.2, 115.2, 113.2, 67.0, 55.6, 55.2, 49.3, 45.5, 39.3, 37.7, 21.8, 10.3. Anal. calcd. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.56; H, 6.34.

3-Methoxy-2-[1-(2-methoxyphenyl)-3-oxo-4-propoxycarbonylbutyl]-benzoic Acid (15d)

Reflux time: 10 h. Yield 54%; mp 129–131°C (needles from benzene/hexane 8:2); IR (KBr): 1729, 1720, 1690 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.37–7.33 (m, 1H, Ar-H), 7.27–7.10 (m, 4H, Ar-H), 6.91–6.83 (m, 1H, Ar-H), 6.74–6.70 (m, 1H, Ar-H), 5.28 (t, 1H, *J* 4.5 Hz, CH), 4.05 (t, 2H, *J* 6.6 Hz, CH_2), 3.68 (s, 3H, OMe), 3.64 (s, 3H, OMe), 3.50 (d, 2H, *J* 2.2 Hz, CH_2), 3.35 (dd, 2H, J_1 3.4 Hz, J_2 17.9 Hz, CO-CH_2-CO), 1.65–1.55 (m, 2H, CH_2-C**H**$_2$-CH_3), 0.87 (t, 3H, *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 207.1, 170.5, 158.2, 157.1, 139.1, 128.6, 128.1, 128.0, 127.6, 122.4, 119.4, 114.6, 110.2, 67.2, 55.4, 54.6, 49.2, 45.0, 33.3, 21.7, 10.1. Anal. calcd. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.87; H, 6.14.

2-[1-(2,4-Dimethoxyphenyl)-3-oxo-4-propoxycarbonylbutyl]-6-methoxy-benzoic Acid (15e)

Reflux time: 10 h. Yield 48%; light-yellow oil; IR (KBr): 1737, 1713 cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.29–7.21 (m, 1H, Ar-H), 7.16–7.06 (m, 1H, Ar-H), 6.82–6.74 (m, 2H, Ar-H), 6.44–6.35 (m, 2H, Ar-H), 5.06 (t, 1H, *J* 7.7 Hz, *J* 6.8 Hz, CH), 4.04 (t, 2H, $J = 6.8$ Hz, CH_2), 3.83 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.45 (s, 2H, CH_2), 3.32 (dd, 2H, J_1 2.3 Hz, J_2 7.5 Hz, CO-CH_2-CO), 1.70–1.52 (m, 2H, CH_2-C**H**$_2$-CH_3), 0.89 (t, 3H *J* 7.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 202.3, 170.7, 167.1, 159.6, 157.3, 156.3, 142.4, 130.7, 127.4, 122.6, 119.6, 113.0, 109.0, 103.7, 66.9, 55.9, 55.2, 55.0, 48.8, 48.4, 35.4, 21.7, 10.2. Anal. calcd. for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.90; H, 6.11.

4-Methoxy-2-[1-(2-methoxyphenyl)-3-oxo-4-propoxycarbonylbutyl]-benzoic Acid (15f)

Reflux time: 10 h. Yield 47%; light-yellow oil; IR (KBr): 1716, 1685, cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.26–7.10 (m, 2H, Ar-H), 6.92–6.69 (m, 4H, Ar-H), 5.92 (t, 1H, *J* 7.6 Hz, *J* 6.7 Hz, CH), 4.05 (t, 2H, *J* = 6.7 Hz, CH_2), 3.76 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.50 (d, 2H, *J* 4.1 Hz, CO-CH_2-CO), 3.29 (d, 2H, *J* 7.7 Hz, CH_2), 1.70–1.55 (m, 2H, CH_2-C**H**$_2$-CH_3), 0.89 (t, 3H, *J* 7.5 Hz, CH_3); ^{13}C NMR ($CDCl_3$) 201.8, 172.0, 167.4, 162.8, 157.1, 147.9, 133.9, 131.1, 127.9, 127.2, 120.5, 115.0, 110.8, 110.7, 66.9, 55.3, 55.2, 48.6, 48.2, 35.5, 21.7, 10.2. Anal. calcd. for $C_{23}H_{26}O_7$: C, 66.65; H, 6.32. Found: C, 66.55; H, 6.40.

2-[1-(4-Methoxyphenyl)-3-oxobutyl]-benzoic Acid (16a)

Reflux time: 10 h. Yield 50%; mp 153–154°C (white needles from benzene/hexane 9:1) lit.[15] mp 92–94°C; IR ($CHCl_3$): 1728, 1707, cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.45–7.35 (m, 2H, Ar-H), 7.25–7.15 (m, 4H, Ar-H), 6.83–6.78 (m, 2H, Ar-H), 5.58 (t, 1H, *J* 8.0 Hz, CH), 3.74 (s, 3H, OMe), 3.20 (dd, 2H, J_1 4.5 Hz, J_2 7.6 Hz, CH_2), 2.13 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 208.0, 172.2, 158.2, 145.8, 134.9, 132.7, 131.2, 128.9, 128.5, 126.4, 113.9, 55.2, 50.2, 40.2, 29.8. Anal. calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.33; H, 6.10.

3-Methoxy-2-[1-(2-methoxyphenyl)-3-oxobutyl]-benzoic Acid (16b)

Reflux time: 10 h. Yield 47%; mp 162–164°C (white needles from benzene/hexane 9:1); IR ($CHCl_3$): 1710, 1689, cm^{-1} (C═O); ^1H NMR ($CDCl_3$) 7.30–7.23 (m, 3H, Ar-H), 7.15–7.11 (m, 2H, Ar-H), 6.90–6.86 (m, 2H, Ar-H), 5.39 (t, 1H, *J* 7.1 Hz, CH), 3.74 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.28 (dd, 2H, J_1 4.7 Hz, J_2 18.3 Hz, CH_2), 2.21 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) 212.3, 170.9, 157.8, 157.7, 135.1, 133.5, 128.6, 128.2, 121.9, 114.8, 113.3, 55.6, 55.1, 45.7, 38.6, 30.2. Anal. calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.20; H, 6.10.

REFERENCES

1. Merck Index, 11th ed., Rahway, New Jersey, U.S.A., 1989.
2. Part 30: Jóźwiak, A.; Brzeziński, J. Z.; Płotka, M. W.; Szcześniak, A. K.; Malinowski, Z.; Epsztajn, J. Behaviour of N-pyridylbenzamides versus benzanilides in the *ortho*-directed lithiation of masked aromatic carboxylic acids. *Eur. J. Org. Chem.* **2004**, 3254–3261.

3. Mukaiyama, T. Titanium tetrachloride in organic synthesis [new synthetic methods (21)]. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817–826.
4. Mukaiyama, T.; Banno, K.; Narasaka, K. New cross-aldol reactions: Reactions of silyl enol ethers with carbonyl compounds activated by titanium tetrachloride. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.
5. Epsztajn, J.; Bieniek, A.; Kowalska, J. A.; Kulikiewicz, K. K. Application of organolithium and related reagents in synthesis, part 24: Synthetic strategies based on aromatic metallation: A concise regiospecific conversion of benzoic acid into 2-(1-aryl-2-methoxycarbonylethyl) benzoic acids. *Synthesis* **2000**, *11*, 1603–1607.
6. Bieniek, A.; Epsztajn, J.; Kulikiewicz, K. K. Reduction and reductive alkylation of 3*H*-isobenzofuran-1-ones. *Polish J. Chem.* **2003**, *77*, 1385–1410.
7. Bieniek, A.; Epsztajn, J.; Kulikiewicz, K. K. Application of organolithium and related reagents in synthesis, part 29: A concise regiospecific conversion of benzoic acids into 5-(2-carboxyphenyl)-5-phenylpent-2-enoic acids. *Monatsh. Chem.* **2004**, *135*, 69–77.
8. Chan, T.-H.; Brownbridge, P. Chemistry of enol silyl ethers, 5: A novel cyclo-aromatization reaction: Regiocontrolled synthesis of substituted methyl salicylates. *J. Am. Chem. Soc.* **1980**, *102*, 3534–3538.
9. Molander, G. A.; Cameron, K. O. Neighboring group participation in Lewis acid–promoted [3 + 4] and [3 + 5] annulations: The synthesis of oxabicyclo[3.n.1]-alkan-3-ones. *J. Am. Chem. Soc.* **1993**, *115*, 830–846.
10. Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. The formal oxidative addition of electron-rich transoid dienes to bromonaphthoquinones. *J. Org. Chem.* **1991**, *56*, 91–95.
11. Kaneko, C.; Sato, M.; Sakaki, J.-I.; Abe, Y. 1,3-dioxin-4-ones as versatile intermediates for organic synthesis. *J. Heterocycl. Chem.* **1990**, *27*, 25–30.
12. Clemens, R. J.; Witzeman, J. S. Kinetic and spectroscopic studies on the thermal decomposition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one: Generation of acetylketene. *J. Am. Chem. Soc.* **1989**, *111*, 2186–2193.
13. Singer, R. A.; Carreira, E. M. Catalytic, enantioselective dienolate additions to aldehydes: Preparation of optically active acetoacetate aldol adducts. *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361.
14. Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. Use of 1,3-dioxin-4-ones and related compounds in synthesis, XLIX: Asymmetric aldol reaction of 4-trimethylsiloxy-6-methylene-1,3-dioxines: Use of tartaric acid-derived (acyloxy)borane complex as the catalyst. *Chem. Pharm. Bull.* **1994**, *42*, 839–845.
15. Bieniek, A.; Epsztajn, J.; Kulikiewicz, K. K. Application of organolithium and related reagents in synthesis, XXVII: Effect of the nucleophilic character of silyl enol ethers upon the conversion of 3-arylphthalides into 2-(1-aryl-2-methoxycarbonyl) benzoic acids. *Synth. Commun.* **2003**, *33*, 667–677.
16. Bulman Page, P. C.; Lund, A. 1,3-Dioxins, oxathiins, dithiins, and their benzo derivatives. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science, 1996; Vol. 6.
17. Bieniek, A.; Epsztajn, J.; Grabowski, S.; Małecka, M. In preparation.