Monatshefte für Chemie 135, 69–77 (2004)
DOI 10.1007/s00706-003-0076-3

**Monatshefte für Chemie**
**Chemical Monthly**
Printed in Austria

# Application of Organolithium and Related Reagents in Synthesis, Part 29 [1]. A Concise Regiospecific Conversion of Benzoic Acids into 5-(2-Carboxyphenyl)-5-phenylpent-2-enoic Acids

**Adam Bieniek***, **Jan Epsztajn***, and **Krystyna K. Kulikiewicz**

Department of Organic Chemistry, Institute of Chemistry, University of Łódź, PL-90-136 Łódź, Poland

Received May 30, 2003; accepted (revised) June 5, 2003
Published online November 10, 2003 

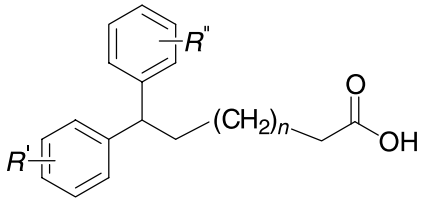
**Summary.** A convenient two-step protocol preparation of *ortho*-alkylated (substituent with the carbomethoxy group at the end of five carbon atoms alkyl chain) aromatic carboxylic acids from benzoic acids anilides is described. *Ortho*-lithiation of benzanilides and subsequent reaction of the generated bis(*N*- and *C-ortho*-)-lithiated anilides with aromatic aldehydes provided 3-arylphthalides. In the next step, these phthalides were converted into 5-(2-carboxyphenyl)-5-phenylpent-2-enoic acids by treatment with 1-methoxy-1-trimethylsilyloxybuta-1,3-diene.

**Keywords.** Anilides; Carboxylic acids; Lithiation; Phthalides; Silyl enol ethers.

## Introduction

The observed tromboxane $A_2$ receptor antagonist [2] represented by compounds of type **A** has promoted a widespread interest in their synthesis. One compound of this group (seratrodast) was launched in the market as an anti-asthmatic drug [3]. We were particularly interested in developing a general and efficient synthetic methodology for *ortho*-alkylated (by secondary substituent with carbomethoxy group at the end of alkyl chain) aromatic carboxylic acids **C** as useful starting materials for species **A** starting from carboxylic acids **B** (Scheme 1).

* Corresponding authors. E-mail: epsztajn@uni.lodz.pl



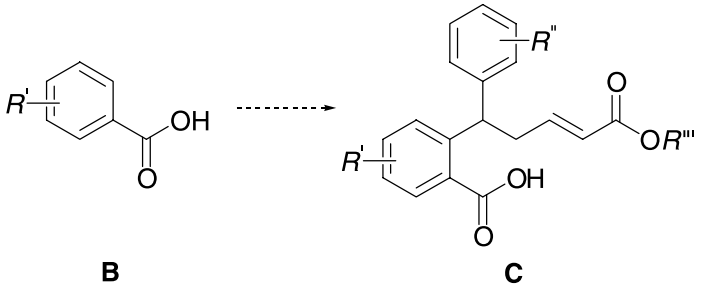

**A**

The classical methods involving the construction of *ortho*-alkylated carboxylic acids are based in most cases on lateral lithiation of *ortho* toluic acid derivatives [4, 5] followed by their reaction with appropriate alkyl halides. It appears that this method in the case of aromatic carboxylic acids *ortho*-substituted by a tertiary carbon atom is laborious, and first requires preparation of corresponding benzylated derivatives [6–8]. The most attractive route reported so far for the preparation of *ortho*-substituted carboxylic acids of type **C** is the transformation of readily available 3-arylphthalides *via* reaction with silyl enol ethers in the presence of *Lewis* acids such as $ZnCl_2$ [9, 10], or even more effectively with $TiCl_4$ [11, 12].

## Results and Discussions

Our aim was to extend the scope of reductive alkylation of phthalides as an effective procedure for the synthesis of new *ortho*-substituted benzoic acids of type **C** and we report here the results obtained starting with a series of 3-arylphthalides **4** and 1-alkoxy-1-trialkylsilyloxybuta-1,3-diene (**5**), vinylogous analog [13] of silyl enol ethers, as a source of a four-carbon atom building block. This method provides access to a new and effective synthetic sequence as a general strategy for the transformation of aromatic carboxylic acids **B** into *ortho*-alkylated benzoic acids **C**, in a two-step protocol starting from benzoic acids anilides **1** (Scheme 1).

In a series of recent studies we have reported [8, 11, 14, 15] that the secondary carboxyamide moiety provides an excellent possibility for the regioselective synthesis of 3-arylphthalides **4**, which are the key starting materials here. Therefore, 3-arylphthalides **4** were obtained by lithiation of benzoic acid anilides **1** using *n-Bu*Li in *THF* [8, 11, 12, 14, 15] followed by the reaction of the generated bis-(*N*- and *C-ortho*-)-lithiated anilides **2** with aromatic aldehydes. Thus, the

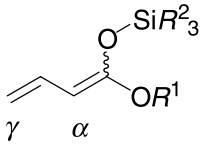



**B** **C**

**Scheme 1**

*ortho*-hydroxyarylmethyl anilides **3** without isolation upon acid-driven cyclization yielded the corresponding phthalides **4**.

In the next step the reductive alkylation of phthalides **4** [10–12] as an extension of the *Mukaiyama* process [16–20] was used for the synthesis of the desired *ortho*-substituted benzoic acids **7**. They were obtained upon treatment of **4** with 1-methoxy-1-trimethylsilyloxybuta-1,3-diene (**5a**).



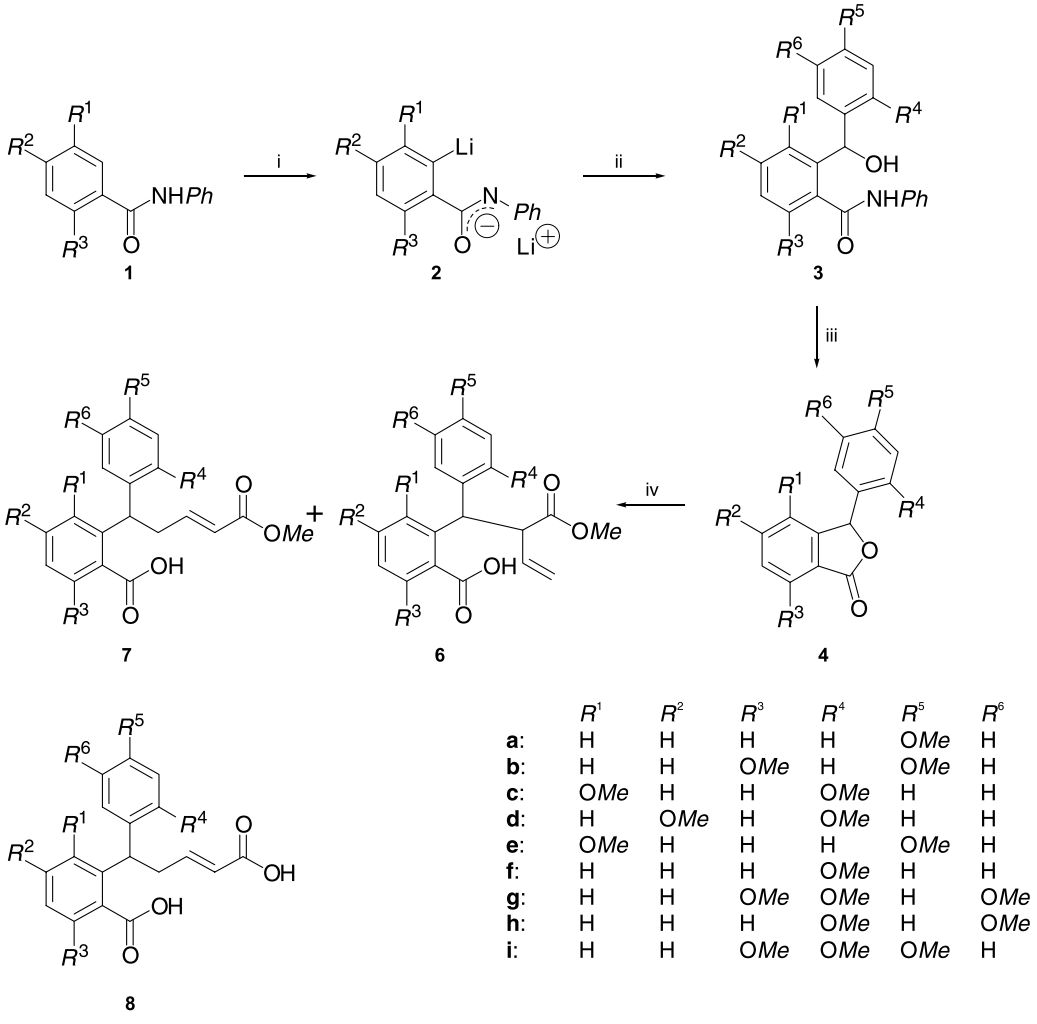

| | $R^1$ | $R^2$ |
|---|---|---|
| **5a**: | *Me* | $SiMe_3$ |
| **5b**: | *tert-Bu* | $SiMe_2$*tert-Bu* |

It has been demonstrated [13] that the conjugated silyl dienolates **5** can be alkylated at the $\alpha$- or $\gamma$-position, behaving as $d^2$ or $d^4$ – reagents [21]. From a number of reports [22–26] suggestion comes that the $\gamma$-selectivity could be enhanced by an increased dimension of the alkoxy groups as well as from relatively well-stabilised cationic electrophiles. Therefore, it was expected that the reaction of **4** with **5** would provide the desired *ortho*-substituted benzoic acids **7** as predominant product. In reality, when reacted with **5a** phthalide **4a** in the presence of titanium tetrachloride accomplished the corresponding alkylated compounds **6a** and **7a** in ratio 15:85.

To obtain more insight into this problem we decided to investigate to what extent the fixation of a substituent in close neighbourhood to the centre of the reaction would affect the transformation of **4** upon treatment with **5** into **7**. The detailed results of the reaction of 1-methoxy-1-trimethylsilyloxybuta-1,3-diene (**5a**) with phthalides **4** are reported in Table 1. An examination of the data reveals that the only products obtained from the reaction were the monoesters of the dicarboxylic acids **6** and **7** together with recovered phthalides. The monoesters of the dicarboxylic acids **7c**, **7d**, **7e**, and **7i** were partially isolated, and a basic hydrolysis provided the dicarboxylic acids **8c**, **8d**, **8e**, and **8i**.

The observed yields suggest that the reductive alkylation is significantly affected by the size of substituents surrounding the reaction centre and that two of them are of great importance. The first one is the substituent at the position 4 of the phthalide nucleus (''*peri*'' to the reaction centre). The other one is the substituent attached to the 2′ position (*ortho* at the 3-phenyl ring). Phthalides **4a** and **4b**, with substituents no larger than a hydrogen atom at the pivotal positions, reacted with **5a** to the desired $\gamma$-adducts **7a** and **7b**, but they were accompanied by the $\alpha$-adducts **6a** and **6b** with overall quantitative yields. The ratios of the formed products were found to amount: **6a**:**7a** = 15:85 and **6b**:**7b** = 43:57. The following test aimed to improve the degree of $\gamma$-selectivity. Variation of temperature and reaction time, and also replacing $TiCl_4$ with other *Lewis* acids – $SnCl_4$, $ZnCl_2$, $Ti(OPr)_4$, $TiCl_4$–$Ti(OPr)_4$, $BF_3OEt_2$ – did not affect the ratio of **6**:**7**. If in the place of **5a** the more sterically hindered diene **5b** was used no change in the course of the reaction was observed.

The phthalides in which one or two methoxy groups are attached at close positions to the centre of the reaction caused a basic change in the course of the




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ |
|---|---|---|---|---|---|---|
| **a**: | H | H | H | H | OMe | H |
| **b**: | H | H | OMe | H | OMe | H |
| **c**: | OMe | H | H | OMe | H | H |
| **d**: | H | OMe | H | OMe | H | H |
| **e**: | OMe | H | H | H | OMe | H |
| **f**: | H | H | H | OMe | H | H |
| **g**: | H | H | OMe | OMe | H | OMe |
| **h**: | H | H | H | OMe | H | OMe |
| **i**: | H | H | OMe | OMe | OMe | H |

**Scheme 2.** i) *n-Bu*Li in *THF*/hexane, −78°C/1 h → 0°C; ii) *Ar*-CHO, −78°C → 20°C/1 h; iii) HCl (1:1); iv) **5a**/$CH_2Cl_2$/$TiCl_4$/0°C

process. Thus, solely $\gamma$-selectivity was observed, but with some decrease of yields. This may be attributed to the steric hindrance caused by the pivotal methoxy groups for the $S_{N2}$ – type nucleophilic attack by **5a**, which would be in good agreement with the behaviour of lactones in the reaction with hard acids and soft nucleophilic systems [27]. Thus, phthalides **4d**, **4e**, **4f**, **4g**, and **4h**, in which one of the hydrogen atoms at the pivotal position was replaced with a methoxy group gave exclusively the $\gamma$-adducts **7d**, **7e**, **7f**, **7g**, and **7h** upon reaction with **5a**. The presence of the two methoxy groups in **4c** at positions 4 and 2′ decreased the yield to half, but at the same time with preservation of the $\gamma$-selectivity. On the other hand, introducing a methoxy group (phthalides **4g** and **4h**) at the position 5′ drastically decreased the output of the process.

Although the observed behaviour of phthalides **4g** and **4h** cannot be unequivocally explained the following should be taken into account: (i) *Angle et al.* [28, 29]

**Table 1.** Reaction of phthalides **4** with 1-methoxy-1-trimethyl-silyloxybuta-1,3-diene (**5a**)

| Phthalides | Yield/%[a] | | |
|---|---|---|---|
| | $\alpha$-Adducts | $\gamma$-Adducts | |
| **4** | **6** | **7** | **8** |
| **4a** | 15 | 85 | – |
| **4b** | 43 | 51 | – |
| **4c** | – | trace | 52 |
| **4d** | – | trace | 85 |
| **4e** | – | 60 | 32 |
| **4f** | – | 82 | – |
| **4g** | – | 15 | – |
| **4h** | – | 33 | – |
| **4i** | – | trace | 87 |

[a] All yields represent isolated pure materials

testing nucleophilic substitution of the hydroxy or alkoxy groups at the benzyl species in the presence of hard *Lewis* acids such as $TiCl_4$ have shown that the presence of the electron-donating substituent at the *para* position efficiently enhances the reaction; (ii) in the reductive alkylation of phthalides **4a**, **4b**, and **4e** in which the methoxy group is attached to the 4′ position (*para* to the reacting centre) the highest yield of the process was observed. This suggested that the shifting of the methoxy group from position 5′ (phthalide **4g**) into 4′ should improve the reaction yield. Therefore, 2′,4′,7-trimethoxyphthalide **4i** was prepared and reacted with **5a**. Thus, the $\gamma$-adduct **7i** was obtained in excellent yield. This translocation of the methoxy group (**4g** → **4i**) increased the yield by a factor about 6.

In conclusion, we have developed a versatile synthesis method for the preparation of *ortho*-substituted benzoic acids of type **C**. The synthesis involves: (i) successive conversion of benzoic acids anilides **1** *via* the directed lithiation – electrophilic substitution (aromatic aldehydes) sequence into the phthalides **4**, and (ii) their transformation upon treatment with 1-methoxy-1-trimethylsilyloxybuta-1,3-diene **5a** into the desired *ortho*-substituted benzoic acids **7**. This reaction sequence displays a general strategy for the introduction of a five-carbon atoms chain at the *ortho* position into aromatic carboxylic acids.

## Experimental

Melting points were determined using a *Boetius* hot-stage apparatus and they were uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR using 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). Silicagel 60 was from Merck. *n*-Butyllithium (Aldrich) was titrated before use. 1-Trimethylsilyloxy-1-methoxybuta-1,3-diene (**5a**) [26] and 1-(*tert*-butyldimethylsilyloxy)-1-*tert*-butoxybuta-1,3-diene (**5b**) [30] were obtained by known methods and used as crude compounds. Anilides **1**, phthalides **4a**–**4d**, and **4f**–**4h** were obtained by known methods [11]. The phthalides **4e** and **4i** were prepared in analogy to Ref. [11].

*4-Methoxy-3-(4-methoxyphenyl)-3H-isobenzofuran-1-one* (**4e**, $C_{16}H_{14}O_4$)

Yield 60%; mp 153–155°C (*Et*OH); IR (KBr): $\bar{\nu} = 1750\,cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 7.60–7.52$ (m, 2Ar-H), 7.24–7.08 (m, 3Ar-H), 6.94–6.84 (m, 2Ar-H), 6.40 (s, CH), 3.83 (s, OMe), 3.78 (s, OMe) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 159.9$, 154.4, 137.0, 131.1, 128.6, 127.6, 127.5, 116.9, 115.4, 113.7, 81.4, 55.5, 55.1 ppm.

*3-(2,4-Dimethoxyphenyl)-7-methoxy-3H-isobenzofuran-1-one* (**4i**, $C_{17}H_{16}O_5$)

Yield 61%; mp 131–133°C (*Et*OH); IR (KBr): $\bar{\nu} = 1759\,cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 7.58–7.50$ (m, 1Ar-H), 6.97–6.89 (m, 3Ar-H), 6.69 (s, CH), 6.51–6.50 (m, 1Ar-H), 6.43–6.38 (m, 1Ar-H), 4.01 (s, OMe), 3.86 (s, OMe), 3.79 (s, OMe) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 162.2$, 159.2, 159.1, 136.9, 128.9, 118.2, 115.3, 111.2, 105.2, 99.5, 77.6, 56.7, 56.3, 56.1 ppm.

*Reaction of 1-Trimethylsilyloxy-1-methoxy buta-1,3-diene (**5a**) with 3-Arylphtalides (**4**)*

To a stirred solution of 0.01 mol of **4** and 0.02 mol of **5a** in 50 $cm^3$ of $CH_2Cl_2$, a solution of 2.0 $cm^3$ of $TiCl_4$ in 10 $cm^3$ of $CH_2Cl_2$ was added dropwise at 0°C. The mixture was stirred for 20–30 min (in the case of phtalide **4h** for additional 1.5 h at the appropriate temperature and overnight at room temperature). Next, 50 $cm^3$ of 5% aqu. $KHSO_4$ was added, and after 1 h the mixture was extracted with $3\times40$ $cm^3$ of $CHCl_3$. Then, the combined extracts were evaporated to dryness. The oily reaction mixture was washed with 50 $cm^3$ of hot *n*-hexane. After cooling to room temperature, to the residue which had not dissolved in *n*-hexane 100 $cm^3$ of 10% aqu. $Na_2CO_3$ were added and stirred for 2 h. After filtering, the aqueous layer was acidified with 10% HCl. In the cases of **4a**–**4b**, the acidic solutions were extracted with 50 $cm^3$ of $CHCl_3$, the organic layer was dried over $MgSO_4$, evaporated, and the obtained oil was purified by column chromatography to give **6a**–**6b** and **7a**–**7b**. In the cases of **4e**–**4h**, the crude solid products **7e**–**7h** were filtered off and purified by crystallization. In the case of the products from **4c**–**4e** and **4i**, the residue which was left after extraction with $Na_2CO_3$ was treated with 100 $cm^3$ of 5% aqu. NaOH. This caused hydrolysis of **7c**–**7e** and **7i** to **8c**–**8e** and **8i**. After filtration from unreacted phtalide **4**, the aqueous solutions of the dicarboxylic acid sodium salts were acidified with 10% HCl. The precipitated acids **8c**–**8e** and **8i** were filtered off and purified by crystallization. Therefore, the yield resulting from the use of phtalides **4c**–**4e** and **4i** is represented in part by the amount of isolated dicarboxylic acids **8c**–**8e** and **8i**.

*2-[2-Methoxycarbonyl-1-(4-methoxyphenyl)-but-3-enyl]benzoic acid* (**6a**, $C_{20}H_{20}O_5$)

Mp 135–137°C (benzene); $R_f = 0.10$ (benzene:diethyl ether:acetic acid = 95:4:1); IR (KBr): $\bar{\nu} = 1738$, $1692\,cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 7.99–7.90$ (m, 1Ar-H), 7.58–7.42 (m, 2Ar-H), 7.35–7.22 (m, 3Ar-H), 6.82–6.79 (m, 2Ar-H), 5.81–5.51 (m, 2H, =CH– and $CH_2$=), 5.20–4.99 (m, 2H, $CH_2$= and $Ar_2CH$–), 4.03–3.89 (m, –C*H*–COOMe), 3.74 (s, OMe), 3.54 (s, COOMe) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 174.6$, 159.7, 145.6, 136.1, 135.7, 134.3, 132.9, 130.8, 130.7, 129.4, 128.0, 127.8, 120.8, 115.4, 58.0, 56.7, 53.4, 47.6 ppm.

*2-Methoxy-6-[2-methoxycarbonyl-1-(4-methoxyphenyl)-but-3-enyl]benzoic acid* (**6b**, $C_{21}H_{22}O_6$)

Mp 94–96°C (benzene); $R_f = 0.11$ (benzene:diethyl ether:acetic acid = 95:4:1); IR (KBr): $\bar{\nu} = 1731$, $1704\,cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 8.96$ (br s, COOH), 7.42–7.22 (m, 4Ar-H), 6.97–6.74 (m, 1Ar-H), 6.82–6.74 (m, 2Ar-H), 5.88–5.70 (m, =CH–), 5.16–5.03 (m, $CH_2$=), 4.70–4.64 (m, $Ar_2CH$–), 3.97–3.91-(m, –C*H*–COOMe), 3.85 (s, OMe), 3.72 (s, OMe), 3.51 (s, COOMe) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 172.8$, 171.8, 158.3, 156.2, 140.9, 134.3, 133.5, 130.9, 128.8, 128.3, 123.2, 113.9, 108.9, 55.9, 55.7, 55.1, 52.0, 48.5 ppm.

*2-[(E)-4-Methoxycarbonyl-1-(4-metoxyphenyl)-but-3-enyl]benzoic acid* (**7a**, $C_{20}H_{20}O_5$)

Oil; $R_f = 0.03$ (benzene:diethyl ether = 95:5); IR (KBr): $\bar{\nu} = 1720$, 1657 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 9.19$ (br s, COOH), 7.93–7.89 (m, 1Ar-H), 7.44–7.36 (m, 1Ar-H), 7.25–7.14 (m, 4Ar-H), 7.03–6.88 (m, –CH=), 6.78–6.74 (m, 2Ar-H), 5.83 (d, $J = 15.7$ Hz, =C*H*–COOMe), 5.36 (t, $J = 7.4$ Hz, $Ar_2CH$–), 3.72 (s, OMe), 3.59 (s, COOMe), 2.92–2.85 (m, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 173.6$, 167.1, 158.0, 147.7, 145.9, 135.3, 132.2, 131.0, 129.2, 128.5, 126.1, 122.2, 113.8, 55.1, 51.4, 43.5, 38.7 ppm.

*2-Methoxy-6-[(E)-4-methoxycarbonyl-1-(4-methoxyphenyl)-but-3-enyl]benzoic acid* (**7b**, $C_{21}H_{22}O_6$)

Oil; $R_f = 0.07$ (benzene:diethyl ether:acetic acid = 95:4:1); IR (KBr): $\bar{\nu} = 1728$, 1657 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 7.70$ (br s, COOH), 7.38–7.16 (m, 4Ar-H), 6.95–6.73 (m, 4H, –CH= and Ar-H), 5.83 (d, $J = 15.7$ Hz, =C*H*–COOMe), 4.39 (t, $J = 7.9$ Hz, $Ar_2CH$–), 3.84 (s, OMe), 3.74 (s, OMe), 3.65 (s, COOMe), 2.97–2.87 (m, $CH_2$) ppm.

*3-Metoxy-2-[(E)-4-methoxycarbonyl-1-(4-methoxyphenyl)-but-3-enyl]benzoic acid* (**7e**, $C_{21}H_{22}O_6$)

Mp 168–170°C (benzene); IR (KBr): $\bar{\nu} = 1718$, 1677 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 9.10$ (br s, COOH), 7.44–7.19 (m, 5Ar-H), 7.06–6.75 (m, 3H, Ar-H and –CH=), 5.81 (d, $J = 15.7$ Hz, =C*H*–COOMe), 5.15 (t, $J = 7.8$ Hz, $Ar_2CH$–), 3.74 (s, OMe), 3.65 (s, 6H, OMe and COOMe), 3.27–3.12 (m, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 173.7$, 167.1, 158.4, 157.5, 148.6, 134.7, 133.2, 131.8, 129.1, 127.6, 122.4, 121.8, 115.5, 113.1, 55.6, 55.2, 51.4, 41.3, 34.6 ppm.

*2-[(E)-4-Methoxycarbonyl-1-(2-methoxyphenyl)-but-3-enyl]benzoic acid* (**7f**, $C_{20}H_{20}O_5$)

Mp 137–138°C (benzene); IR (KBr): $\bar{\nu} = 1723$, 1683 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 9.85$ (br s, COOH), 7.95–7.90 (m, 1Ar-H), 7.48–7.36 (m, 1Ar-H), 7.32–7.14 (m, 4Ar-H), 7.10–6.89 (m, 2H, Ar-H and –CH=), 6.80–6.76 (m, 1Ar-H), 5.85 (d, $J = 15.7$ Hz, =C*H*–COOMe), 5.59 (t, $J = 6.7$ Hz, $Ar_2CH$–), 3.67 (s, 6H, OMe, COOMe), 3.00–2.93 (m, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 175.0$, 158.7, 149.2, 147.1, 133.9, 133.2, 132.3, 131.1, 130.1, 129.2, 128.7, 127.5, 123.8, 121.9, 112.1, 56.7, 52.9, 39.7, 38.8 ppm.

*2-[(E)-1-(2,5-Dimethoxyphenyl)-4-methoxycarbonylbut-3-enyl]-6-methoxybenzoic acid* (**7g**, $C_{22}H_{24}O_7$)

Mp 83–85°C (benzene:*n*-hexane = 8:2); IR (KBr): $\bar{\nu} = 1736$, 1683 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 7.72$–7.61 (m, 2Ar-H), 7.38–7.06 (m, 5H, Ar-H and CH=), 6.18 (d, $J = 15.7$ Hz, =C*H*–COOMe), 5.22 (t, $J = 7.8$ Hz, $Ar_2CH$–), 4.22 (s, OMe), 4.10 (s, OMe), 4.03 (s, OMe), 4.01 (s, COOMe), 3.27–3.12 (m, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 169.0$, 164.6, 153.3, 147.1, 143.0, 136.6, 130.8, 122.3, 120.1, 114.8, 114.2, 111.3, 110.9, 109.0, 56.0, 55.7, 55.6, 51.3, 39.2, 37.5 ppm.

*2-[(E)-1-(2,5-Dimethoxyphenyl)-4-methoxycarbonylbut-3-enyl]benzoic acid* (**7h**, $C_{21}H_{22}O_6$)

Mp 86–88°C (benzene:*n*-hexane = 8:2); IR (KBr): $\bar{\nu} = 1723$, 1684 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$): $\delta = 10.85$ (br s, COOH), 7.30–7.04 (m, 3Ar-H), 6.88–6.66 (m, 3H, Ar-H and –CH=), 6.44–6.33 (m, 2Ar-H), 5.80 (d, $J = 15.7$ Hz, =C*H*–COOMe), 4.74 (t, $J = 8.0$ Hz, $Ar_2CH$–), 3.79 (s, OMe), 3.73 (s, OMe), 3.63 (s, COOMe), 2.95–2.88 (m, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$): $\delta = 173.8$, 172.1, 159.6,

158.0, 156.4, 150.5, 143.4, 130.7, 128.4, 127.8, 123.2, 121.8, 119.6, 108.9, 104.0, 98.5, 55.9, 55.2, 55.0, 38.5, 37.9 ppm.

*(E)-5-(2-Carboxy-6-methoxyphenyl)-5-(2-methoxyphenyl)pent-2-enoic acid*
(**8c**, $C_{20}H_{20}O_6$)

Mp 194–196°C (*Me*OH); IR (KBr): $\bar{\nu} = 1703$, 1693 $cm^{-1}$ (CO); $^1$H NMR (*DMSO*-$d_6$): $\delta = 12.19$ (s, 2COOH), 7.46–7.42 (m, 1Ar-H), 7.17–7.05 (m, 3Ar-H), 6.94–6.72 (m, 3Ar-H), 5.82–5.68 (m, CH=CH), 5.31–5.23 (m, $Ar_2CH$–), 3.62 (s, OMe), 3.60 (s, OMe), 3.22–3.02 (m, $CH_2$) ppm; $^{13}$C NMR (*DMSO*-$d_6$): $\delta = 170.7$, 167.8, 157.3, 148.6, 146.8, 135.1, 129.9, 128.8, 126.8, 122.8, 122.3, 121.2, 119.3, 114.0, 110.0, 55.3, 54.8, 39.5, 33.2 ppm.

*(E)-5-(2-Carboxy-5-methoxyphenyl)-5-(2-methoxyphenyl)pent-2-enoic acid*
(**8d**, $C_{20}H_{20}O_6$)

Mp 235–237°C (*Me*OH); IR (KBr): $\bar{\nu} = 1681$, 1662 $cm^{-1}$ (CO); $^1$H NMR ($CDCl_3$): $\delta = 7.89$–7.85 (m, 1Ar-H), 7.26–7.14 (m, 2Ar-H), 6.98–6.64 (m, 5H, Ar-H and –CH=), 5.80 (d, $J = 15.7$ Hz, =C*H*–COOH), 6.11–6.03 (m, $Ar_2CH$–), 3.73 (s, OMe), 3.66 (s, OMe), 3.00–2.87 (m, $CH_2$) ppm; $^{13}$C NMR ($CDCl_3$): $\delta = 169.0$, 167.8, 161.7, 157.3, 147.9, 147.4, 132.7, 131.6, 127.6, 123.2, 123.1, 120.3, 114.7, 110.8, 110.1, 55.3, 55.1, 38.3, 37.0 ppm.

*(E)-5-(2-Carboxy-6-methoxyphenyl)-5-(4-methoxyphenyl)pent-2-enoic acid*
(**8e**, $C_{20}H_{20}O_6$)

Mp 189–191°C (*Me*OH); IR (KBr): $\bar{\nu} = 1720$, 1693 $cm^{-1}$ (CO); $^1$H NMR ($CDCl_3$): $\delta = 7.26$–7.17 (m, 3Ar-H), 6.95–6.72 (m, 5H, Ar-H and –CH=), 5.73 (d, $J = 15.6$ Hz, =C*H*–COOH), 5.02 (t, $J = 7.8$ Hz, $Ar_2CH$–), 3.74 (s, OMe), 3.65 (s, OMe), 3.30–2.99 (m, $CH_2$) ppm; $^{13}$C NMR ($CDCl_3$): $\delta = 170.6$, 167.9, 158.2, 157.2, 148.1, 134.8, 134.1, 131.8, 129.0, 127.3, 122.6, 121.3, 114.2, 112.8, 55.3, 55.0, 41.7, 34.2 ppm.

*(E)-5-(2-Carboxy-3-methoxyphenyl)-5-(2,4-dimethoxyphenyl)pent-2-enoic acid*
(**8i**, $C_{21}H_{22}O_7$)

Mp 111–113°C (benzene:*n*-hexane = 8:2); IR (KBr): $\bar{\nu} = 1710$, 1698 $cm^{-1}$ (CO); $^1$H NMR ($CDCl_3$): $\delta = 9.50$ (br s, 2COOH), 7.51–7.41 (m, 2Ar-H), 7.30–7.12 (m, 3H, Ar-H and –CH=), 6.84–6.72 (m, 2Ar-H), 6.18 (d, $J = 15.7$ Hz, =C*H*–COOH), 5.12 (t, $J = 7.5$ Hz, $Ar_2CH$–), 4.19 (s, OMe), 4.13 (s, OMe), 4.02 (s, OMe), 3.33–3.26 (m, $CH_2$) ppm; $^{13}$C NMR ($CDCl_3$): $\delta = 173.9$, 172.2, 159.7, 158.1, 156.5, 150.6, 143.4, 130.8, 128.4, 127.9, 123.3, 122.9, 122.0, 119.7, 109.0, 104.1, 98.6, 55.3, 55.2, 38.6, 38.0 ppm.

## Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research from the State Committee for Scientific Research (KBN), that is gratefully acknowledged.

## References

[1] Part 28: Bieniek A, Epsztajn J, Plotka MW (2003) Monatsh Chem **134**: 533
[2] Hall SE (1991) Med Res Rev **11**: 503
[3] Rolin S, Dogue JM, Michoux C, Delarge J, Masereel B (2001) Prostagl Leukot and Ess Fat Acids **65**: 67

[4] Gore VG, Narasimhan NS (1988) J Chem Soc Perkin Trans 1 481
[5] Clark RD, Jahangir A (1995) Org React **47**: 1
[6] Mao C-L, Barnish JT, Hauser CR (1969) J Heterocycl Chem **6**: 83
[7] Narasimhan NS, Patil PA (1987) J Chem Soc Chem Communn 191
[8] Epsztajn J, Bieniek A, Kowalska JA (1996) Monatsh Chem **127**: 701
[9] Reetz MT, Walz P, Hübner F, Hüttenhaim SH, Haimbach H, Schwelluns K (1984) Chem Ber **117**: 322
[10] Hunt JT, Molley MF, Gougantes JZ (1990) Heterocycles **31**: 1359
[11] Epsztajn J, Bieniek A, Kowalska JA, Kulikiewicz KK (2000) Synthesis **11**: 1603
[12] Bieniek A, Epsztajn J, Kulikiewicz KK (2003) Synthetic Commun **33**: 667
[13] Casiraghi G, Zauardi F, Appendino G, Roussou G, (2000) Chem Rev **100**: 1929
[14] Epsztajn J, Bieniek A, Kowalska JA (1991) Tetrahedron **47**: 1697
[15] Epsztajn J, Bieniek A, Kowalska JA, Scianowski J (1992) Monatsh Chem **123**: 1125
[16] Mukaiyama T, (1977) Angew Chem Int Ed Engl **16**: 817
[17] Mukaiyama T, Murakami M (1987) Synthesis 1043
[18] Reetz MT (1982) Top Curr Chem **106**: 1
[19] Boch T (1994) Angew Chem Int Ed Engl **33**: 417
[20] Mahrwald RJ (1999) Chem-Ztg **341**: 191
[21] Seebach D (1979) Angew Chem Int Ed Engl **18**: 239
[22] Mukaiyama T, Ischida A (1975) Chem Lett 319
[23] Mukaiyama T, Ischida A (1975) Chem Lett 1201
[24] Mukaiyama T, Ischida A (1977) Chem Lett 467
[25] Fleming I, Lee TV (1981) Tetrahedron Lett **22**: 705
[26] Chow H-F, Fleming I (1998) J Chem Soc Perkin Trans 1 2651
[27] Node M, Nishide K, Ochiai M, Fuji K, Fujita E (1981) J Org Chem **46**: 5163
[28] Angle SR, Louie MS (1989) Tetrahedron Lett **30**: 5741
[29] Angle SR, Louie MS (1991) J Org Chem **56**: 2853 and ref therein
[30] Krohn K, Schaefer G (1996) Liebigs Ann Org Bioorg Chem **2**: 265