Ethyl *p*-(2-methyl-3-oxopropyl)- and *p*-(2-methyl-3-oxo-1-propenyl)benzoates: preparation and use in the synthesis of biologically active derivatives of *p*-(nor-polyprenyl)benzoic acids

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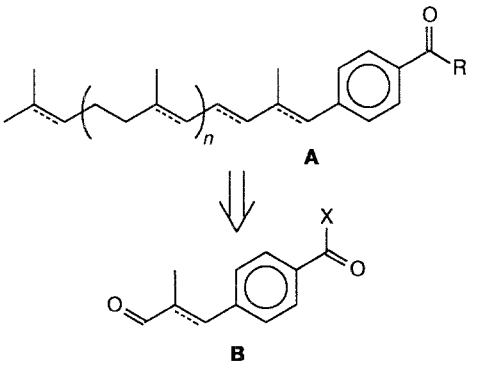
Novel ways for preparing the title compounds have been developed. Saturated (**1**) and unsaturated (**2**) aldehydoesters, which are easily accessible by a Pd-catalyzed reaction of ethyl 4-bromobenzoate with methallyl alcohol and aldol condensation of ethyl 4-formylbenzoate with propanal, respectively, are strategically advantageous intermediates for the synthesis. The results of the *in vitro* assays of some of the synthesized compounds are compared with the known data on their pharmacological effects *in vivo*.

Key words: ethyl *p*-(2-methyl-3-oxopropyl)- and *p*-(2-methyl-3-oxo-1-propenyl)benzoates, synthesis; derivatives of *p*-(nor-polyprenyl)benzoic acids, antitumor and antiatherogenic activity.

In 1980-s the Eisai company (Japan) patented a large group of *p*-substituted benzoic acids and their derivatives of the general formula **A** (n = 0 or 1, R = OH, OAlk, NHR′, NR′R″) with a saturated or unsaturated aliphatic chain. Some members of this group possess antitumor,[1] hypolipidemic,[2] and anticoagulant activity.[3] By virtue of the low toxicity and the absence of apparent side effects, they are promising for prolonged courses of the medical treatment of malignant skin tumors, hypercholesterolemia, and the multiple vascular thrombosis syndrome.



The following pathways have been used for assembling the carbon skeleton of type **A** compounds:[1,2] a) the Horner reaction between diethyl 4-methoxycarbonylbenzylphosphonate and isoprenoid ketones (pseudoionone, geranylacetone, 6-methyl-5-hepten-2-one, and the like); b) the Horner reaction between diethyl 3-(4-methoxycarbonyl)phenyl-2-methyl-2-propenylphosphonate and citral or its analogs; c) the Wittig reaction of the above-mentioned ketones with benzyltriphenylphosphonium bromide followed by formylation at the *para*-position of the benzene ring by the CO—$HAlCl_4$—CuCl system or according to Vilsmeier. The laborious preparation of these phosphonates, the absence of stereospecificity in the formation of the double bonds with ketones or citral, and the use of methyl lithium or alkali metal hydrides and alkoxides in anhydrous media as the bases are considered to be the drawbacks of these methods.

Recently[4,5] we suggested an alternative route for the preparation of type **A** compounds based on the use of functionalized type **B** aldehydes containing a double or a single bond (X = H, OAlk) as the key building blocks, and their reaction with isoprenoid triphenylphosphonium halides of the complementary structure. The "olefinic" building block **B** was prepared in several steps; the optimal path is alkoxyalkene-acetal condensation.[5] In the present communication, we consider two single-step methods for the synthesis of saturated (**1**) and unsaturated (**2**) synthetic equivalents of block **B**. One of them is convenient for preparing type **A** compounds with a saturated side chain (hypolipidemics and anticoagulants), while the other is suitable for the synthesis of those with a styrene double bond (antitumor compounds).

Bifunctional block **1** was prepared in 76 % yield by the Pd-catalyzed reaction of ethyl *p*-bromobenzoate with methallyl alcohol.[6]

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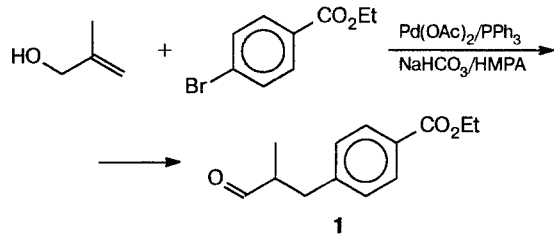
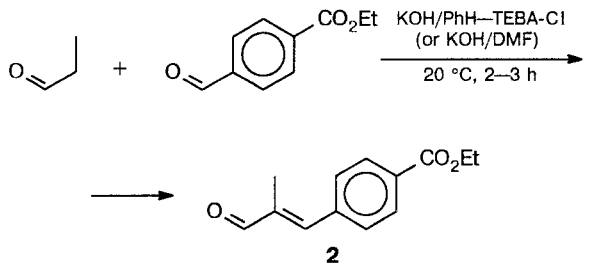


1

An apparent method for the synthesis of enal **2** is the aldol condensation of ethyl 4-formylbenzoate with propanal. However, the most widely used versions of the condensation of benzaldehydes with *n*-alkanals, *i.e.*, those involving alcoholic or water-alcoholic solutions of alkalis (see, for example, Refs. 7, 8) turned out to be unsuitable for preparing enal **2**; under these conditions the yield of the target product did not exceed 15 %. In order to minimize the possible side reactions, we tested several versions of the aldol condensation under the conditions of phase transfer catalysis. The best results were obtained with two heterogeneous systems: KOH(solid)/DMF and KOH(solid)/PhH/$[PhCH_2NEt_3]Cl$ in which the presence of a catalytic amount of the solid base is sufficient for the successful synthesis. Both versions afford the geometrically homogeneous (*E*)-isomer of ethyl *p*-(2-methyl-3-oxo-1-propenyl)benzoate (**2**).

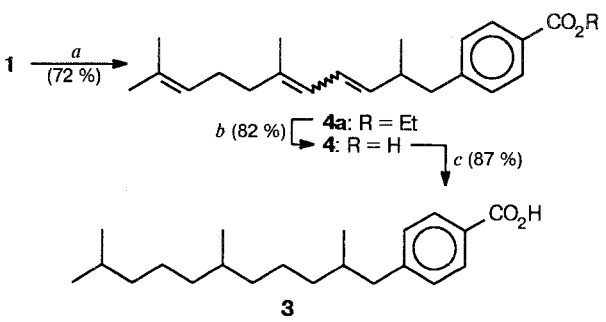


2

Aldehyde **1** was used for the preparation of *p*-(2,6,10-trimethylundecyl)benzoic acid (**3**), a hypolipidemic substance, which decreases the level of cholesterol in rat blood 1.5 times more efficiently than the known hypolipidemic, chlofibrate.[2] The Wittig reaction between compound **1** and geranyltriphenylphosphonium bromide yielded ethyl *p*-(2,6,10-trimethyl-3,5,9-undecatrienyl)benzoate (**4a**). The saponification of **4a** to the corresponding acid (**4**) followed by the exhaustive hydrogenation of the double bonds in the latter afforded the target acid **3** in 39.0 % overall yield over four synthetic steps (Scheme 1).

The reproduction of previously[5] described conditions of the Wittig reaction with enal **2** obtained by aldol condensation and the saponification of the intermediate ester (**5a**) yielded *p*-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)benzoic acid **5**, which efficiently suppresses malignant skin carcinoma in rats (see Ref. 1). Hydrogenation of **5** gave acid **3**, which was then converted to diethanolamide (**6**); according to the data of Ref. 3, this

Scheme 1



3

Reagents and conditions:
a. $[GerPPh_3]Br—K_2CO_3—(CH_2CH_2O)_2$, Δ;
b. KOH—H_2O—EtOH;
c. H_2—Pd/C—EtOH.

compound may be of interest as an inhibitor of blood erythrocyte agglutination. The overall yields of acids **5** and **3** prepared by this route, based on the starting formylbenzoate, were 48.0 and 40.3 % over three and four synthetic steps, respectively (Scheme 2).

The reaction of enal **2** with 3-methylbutyltriphenylphosphonium bromide and the subsequent transformations of the resulting diene ester **7a** and the corresponding acid **7** resulted in *p*-(2,6-dimethylheptyl)benzoic acid (**8**), which also possesses strong hypolipidemic activity (see Ref. 2). The yield of compound **8** was 53.4 % over four synthetic steps.

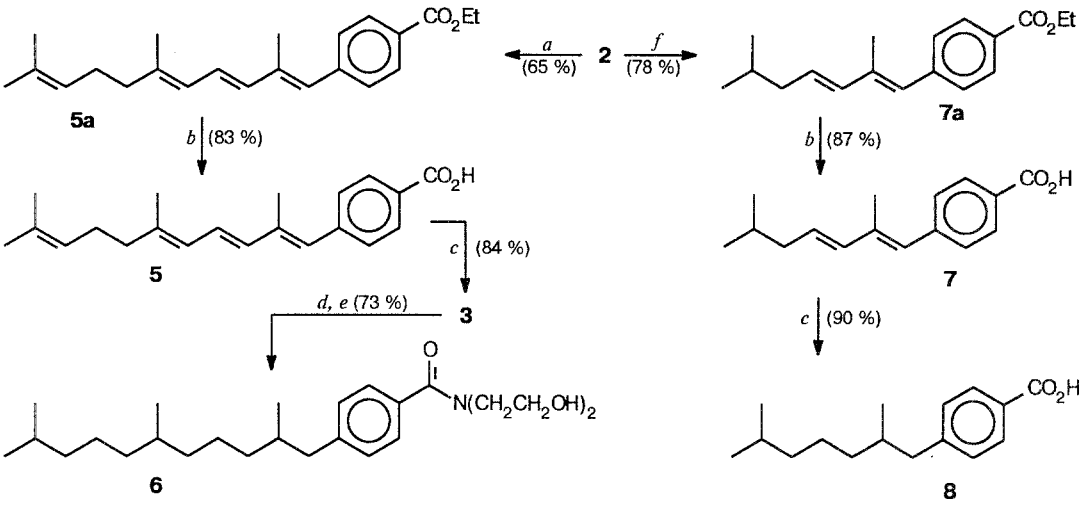
It should be noted that the overall yields of compounds **3**, **5**, **8**, and **6** synthesized according to the known schemes[1—3] do not exceed 15—20 % based on the limiting starting compounds.

The biological activities of compounds **3**, **5**, **5a**, and **8** have only been determined previously in experimental animals.[1,2] It is of interest to juxtapose the data on the pharmacological action of these compounds on intact animals with the results of their assay in cell cultures.

Antitumor compounds **5** and **5a** in a CaOv(h) ovary carcinoma cell culture exhibited only boundary cytotoxicity ($CE_{50} = 4 \cdot 10^{-4}$ and $2 \cdot 10^{-4}$ mol L^{-1}, respectively); the retardation of the incorporation of ^3H-thymidine into the tumor cells was irreversible only for ester **5a**. Similar boundary cytotoxicity is exhibited by ester **5a** with respect to pigmentless (BRO) and pigmentary (MS) human melanoma cell cultures ($CE_{50} = 2.5 \cdot 10^{-4}$ and $6 \cdot 10^{-4}$ mol L^{-1}, respectively). At the same time, in the case of ascites stomach tumor (Erlich ascites tumor) ester **5a** does not extend the life-span of mice, whereas acid **5** when introduced intraperitoneally in the course of five days (beginning on the 3-rd day after the inoculation of the tumor) in a dose of 100 mg $(kg\ day)^{-1}$ caused an extension of the life-span of mice by 25 %.

Acid **3**, which was more active than **8** in the experiments on lowering *in vivo* the level of cholesterol in rat blood,[2] virtually did not decrease the content of cholesterol in cell lipoproteides when tested in a smooth-

Scheme 2



Reagents and conditions: *a*. [GerPPh$_3$]Br—K_2CO_3(sol.)—$(CH_2CH_2O)_2$, Δ; *b*. KOH—H_2O—EtOH; *c*. H_2—Pd/C—EtOH; *d*. $SOCl_2$/PhH, Δ; *e*. $HN(CH_2CH_2OH)_2/Et_2O$, 0 °C; *f*. [$Me_2CH(CH_2)_2PPh_3$]Br—K_2CO_3—$(CH_2CH_2O)_2$, Δ.

muscle cell culture from human aorta (see Ref. 9) in doses ranging from 10^{-6} to 10^{-4} mol L^{-1}. Acid **8**, which was less active *in vivo*, in the aorta cell culture decreased the level of cholesterol in protein substantially: from 106±5 μg/mg in the control to 80±4 μg/mg at a concentration of acid **8** equal to $1 \cdot 10^{-4}$ mol L^{-1} ($P < 0.05$).

The results obtained make it possible to suggest that the pharmacological activity in the group of type **A** compounds (with various extents of saturation of the side chain and chain lengths, and different ligands at the carbonyl group) observed at the level of an intact organism can have a different mechanism at the cell level and different tissue specificity.

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Experimental

The course of the reactions and the purity of the products were monitored by TLC (Silufol plates) and GLC. GLC analyses were carried out on a LKhM-80 chromatograph equipped with a flame ionization detector, using nitrogen as the carrier gas, a glass column (1.5 m × 3 mm) packed with 5 % SE-30 or OV-17 on Chromaton N-AW-DMCS. ^{1}H NMR spectra were recorded on JEOL FX-90Q (90 MHz) and Bruker WM-250 (250 MHz) spectrometers for solutions in $CDCl_3$.

Ethyl *p*-(2-methyl-3-oxopropyl)benzoate (1) was prepared in 76 % yield as described in Ref. 6. B.p. 120—124 °C (0.5 Torr); n_D^{20} 1.5188. ^{1}H NMR, δ: 1.03 (d, J = 7 Hz, 3 H, CH_3); 1.35 (t, J = 7 Hz, 3 H, CH_3); 2.65 (m, 2 H, CH_2); 3.1 (t, J = 7 Hz, 1 H, CH); 4.3 (q, J = 7 Hz, 2 H, OCH_2); 7.9 and 7.15 (A_2B_2-system, 4 H, Ar); 9.65 (d, J = 1.5 Hz, 1 H, CHO).

Ethyl *p*-(2-methyl-3-oxo-1-propenyl)benzoate (2). ***A.*** Ethyl 4-formylbenzoate (1.78 g, 10 mmol) was added in one portion at ~20 °C to a stirred mixture of 0.1 g of KOH and 0.05 g of TEBA-Cl, and then a solution of propanal (0.70 g, 12 mmol) in 5 mL of benzene was slowly added dropwise. The mixture was stirred until the reaction was over (~ 3 h, GLC monitoring) and diluted with ~100 mL of water. The organic phase was separated and dried with $MgSO_4$. Removal of the solvent gave enal **2** (1.96 g, 90 %) as a light-yellow crystalline solid, which was pure according to GLC, TLC, and the ^{1}H NMR spectrum, and identical with that described previously.[4] ^{1}H NMR, δ: 1.35 (t, J = 7 Hz, 3 H, CH_3); 2.0 (d, J = 1.5 Hz, 3 H, CH_3C=); 4.35 (q, J = 7 Hz, CH_2); 7.2 (s, 1 H, CH=); 7.7 and 8.0 (A_2B_2-system, 4 H, Ar); 9.55 (s, 1 H, CHO).

B. Ethyl 4-formylbenzoate (1.78 g, 10 mmol) was added in one portion at ~20 °C with stirring to 0.1 g of KOH in 30 mL of DMF and then a solution of propanal (0.7 g, 12 mmol) was slowly added dropwise. The mixture was stirred until the reaction was over (~2 h, the GLC monitoring), diluted with water (~150 mL), and extracted with benzene. The organic extract was washed twice with water and dried with $MgSO_4$. Enal **2** (1.9 g, 88 %) was isolated as described above.

Reactions of aldehydes 1 and 2 with triphenylphosphonium salts were carried out as described in the previous papers.[4,5] This procedure was used for preparing compounds **4a**, **5a**, and **8**, which were purified by column chromatography on SiO_2 (a 1 : 1 hexane—benzene mixture as the eluent). Aldehyde **1** (1.1 g, 5 mmol) and geranyltriphenylphosphonium bromide

(2.4 g, 5 mmol) afforded ester **4a** (1.25 g, 72 %) as a light-yellow viscous oil. ^{1}H NMR, δ: 1.0 (t, J = 7 Hz, 3 H, CH_3); 1.4 (t, J = 7 Hz, 3 H, CH_3); 1.5—1.8, 2.05, and 2.65 (all m, 16 H, 3 CH_3, 3 CH_2, 1 CH); 4.35 (q, J = 7 Hz, 2 H, OCH_2); 5.1 (m, 2 H, 2 CH=); 5.8—6.1 (m, 1 H, CH=); 7.1—7.5 and 7.95 (m, 5 H, Ar and CH=).

Aldehyde **2** (1.09 g, 5 mmol) and 2.4 g of geranyltriphenylphosphonium bromide prepared from linalool according to the known procedure[10] gave ester **5a** (1.1 g, 65 %) as a light-yellow viscous oil identical with that described previously.[4] ^{1}H NMR, δ: 1.4 (t, J = 7 Hz, 3 H, CH_3); 1.5—2.4 (m, 16 H, 4 CH_3, 2 CH_2); 4.35 (q, J = 7 Hz, 2 H, OCH); 5.1 (br.s, 1 H, CH=); 5.9 and 6.7 (both m, 4 H, 4 CH=); 7.3 and 8.0 (A_2B_2-system, 4 H, Ar).

Ester **7a** (2.1 g, 78 %) was synthesized in a similar way from aldehyde **2** (1.01 g, 5 mmol) and isopentyltriphenylphosphonium bromide (2.07 g, 5 mmol) as a light-yellow oil. ^{1}H NMR, δ: 0.95 (d, 6 H, 2 CH_3); 1.40 (t, J = 7 Hz, CH_3); 2.05 (dd, J = 1.5 Hz, 3 H, CH_3C=); 5.9—6.4 (m, 2 H, 2 CH=); 7.3—8.0 (m, 5 H, Ar and CH=).

Acids 4, 5, and 7 were prepared by the alkaline hydrolysis of esters **4a**, **5a**, and **7a** according to the known procedure.[2] After purification by column chromatography on SiO_2 (a 1 : 1 hexane—benzene mixture as the eluent) the acids were isolated as slightly colored oils.

The yield of **4** was 82 %. ^{1}H NMR, δ: 1.0 (t, J = 7 Hz, CH_3); 1.7—2.4 (m, 16 H, 3 CH_3, 3 CH_2, CH); 5.1 (br.s, 2 H, 2 CH=); 5.1—6.3 (m, 1 H, CH=); 7.3—7.6 and 8.0 (both m, 5 H, Ar, CH=); 10.4 (br.s, 1 H, COOH).

The yield of **5** was 83 %. ^{1}H, NMR, δ: 1.5—2.1 (m, 16 H, 4 CH_3, 2 CH_2); 5.1 (br.s, 1 H, CH=); 5.9 and 6.3—6.7 (both m, 4 H, 4 CH=); 7.3 and 8.0 (4 H, Ar); 10.35 (br.s, 1 H, COOH).

The yield of **7** was 87 %. ^{1}H NMR, δ: 0.95 and 1.0 (both s, 6 H, 2 CH_3); 1.3 (m, 1 H, CH); 2.00—2.3 (m, 5 H, CH_3C=, CH_2C=); 5.5—5.8 and 5.9—6.5 (both m, 3 H, 3 CH=); 7.4 and 8.1 (A_2B_2-system, 4 H, Ar); 9.4 (br.s, 1 H, COOH).

Acids 3 and 8 were prepared by hydrogenation of **5** (or **4**) and **7** over 5 % Pd/C in ethanol as described in Ref. 2. Acids **3** and **8** were colorless viscous oils, which were purified by column chromatography on SiO_2 ($CHCl_3$ as the eluent).

The yield of **3** was 84 % (from **5**) or 87 % (from **4**). ^{1}H NMR, δ: 0.89 and 0.92—0.96 (d, 3 H + m, 9 H, 4 CH_3); ~1.3—~1.9 (m, 14 H, 6 CH_2 + 2 CH); 2.3—2.6 (m, 3 H, $ArCH_2$ and CH); 7.25 and 8.0 (A_2B_2-system, J = 8 Hz, 4 H, Ar); 12.2 (br.s, 1 H, COOH).

The yield of **8** was 90 %. ^{1}H NMR, δ: 0.8—0.95 (m, 9 H, 3 CH_3); ~1.25 (m, 6 H, 3 CH_3); 2.4—2.7 (m, 4 H, $ArCH_2$ + + 2 CH); 7.25 and 8.0 (A_2B_2-system, J = 8 Hz, 4 H, Ar); 11.85 (br.s, 1 H, COOH).

***N,N*-Di(β-hydroxyethyl)-4-(2,6,10-trimethylundecyl)benzamide (6).** Acid **3** was dissolved in dry benzene and treated with freshly distilled $SOCl_2$ (boiling, 30 min). The volatile products were evaporated in the vacuum of a rotary evaporator. The residue (acid chloride) was dissolved in abs. Et_2O and treated with dry diethanolamine. Column chromatography on SiO_2 ($CHCl_3$ as the eluent) afforded amide **6** as a colorless oil, homogeneous according to TLC. Yield 73 %. ^{1}H NMR, δ: 0.75—0.92 (m, 12 H, 4 CH_3); 1.1—1.5 (m, 14 H, 6 CH_2 + + 2 CH); 2.0—2.2 (m, 3 H, $ArCH_2$ + CH); 3.65 (m, 8 H, $N(CH_2CH_2OH)_2$); 4.4 (br.s, 2 H, OH); 7.25 and 7.45 (A_2B_2-system, J = 8 Hz, 4 H, Ar).

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