The synthesis of 4-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)benzoic acid based on alkoxy alkene-acetal condensation

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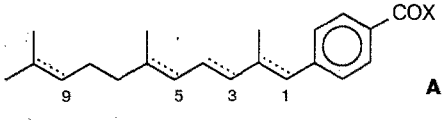
4-(2,6,10-Trimethyl-1,3,5,9-undecatetraenyl)benzoic acid (**1**) was synthesized starting from ethyl 4-formylbenzoate (**2**) and linalool. The key intermediate, ethyl 4-(2-methyl-3-oxo-1-propenyl)benzoate (**5**), was obtained by the addition of diethyl acetal (**3**), prepared from **2**, to ethyl 1-propenyl ether (EPE) followed by the hydrolysis of the resulting adduct.

Key words: 4-ethoxycarbonylbenzaldehyde, diethyl acetal; ethyl 1-propenyl ether; acetal condensation; ethyl 4-(2-methyl-3-oxo-1-propenyl)benzoate; Wittig reaction.

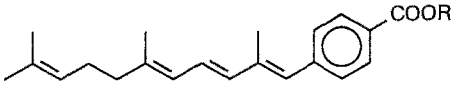
4-(Nor-polyprenyl)benzoic acids and their derivatives of the general type **A** (where ⋯ is a π or σ-bond) are promising medicinals displaying various types of pharmacological activity.[1—4] In the patented procedures for the synthesis of these compounds[2—4] the skeleton assemblage stage involves the Horner—Emmons reaction either between citral (or its analogs) and the esters of 3-(4-ethoxycarbonylphenyl)-2-methyl-2-propenylphosphonic acid or between pseudoionone (or its analogs) and the esters of 4-ethoxycarbonylbenzylphosphonic acid. The resulting ethyl 4-(2,6,10-trimethyl-1,3,5,9-undecatetraenyl)benzoate (**1a**) and the corresponding acid (**1**) obtained by its hydrolysis, as well as their analogs possess antitumor activity and, in addition, can serve as intermediates in the preparation of other compounds having formula **A** which display hypolipidemic and antithrombotic activity.

The drawbacks of the above procedures are the difficulty of preparing the required phosphonates, the use of alkali metal hydrides or alkoxides in anhydrous media as the bases, and low overall yields of the target products.



A

X = OH, OAlk, NR^1R^2



1: R = H
1a: R = Et

In this paper we propose a novel approach to the synthesis of acid **1**. Commercially available ethyl 4-formylbenzoate (**2**) was used as the starting compound. According to the procedure given in ref. 5, it was converted to diethyl acetal **3** (Scheme 1). Contrary to the earlier observations[6] that strong electron-withdrawing substituents in the benzene ring drastically decelerate the addition of acetals of the corresponding benzaldehydes to vinyl ethers, we succeeded in accomplishing the addition of **3** to ethyl 1-propenyl ether (EPE) in the presence of $BF_3 \cdot OEt_2$ at 20—40 °C. Without isolation, the resulting adduct (**4**) was subjected to hydrolysis, which was accompanied by β-elimination of EtOH and afforded ethyl 4-(2-methyl-3-oxo-1-propenyl)benzoate (**5**), which is the key intermediate corresponding to the «eastern» C_{11} moiety of acid **1**. Acetal **3** was not completely consumed in this reaction (extent of conversion ~85 %) and was recovered after the hydrolysis in the form of the starting aldehyde **2**. The yield of the target aldehydo ester **5** from **3** was 66.0 % (or 78.5 % based on reacted **3**).

The «western» C_{10} fragment of acid **1** was obtained from linalool, which was converted to geranyltriphenylphosphonium bromide (GTPB) (see ref. 7). The Wittig reaction between GTPB and **5** in the heterogeneous system K_2CO_3(solid)/dioxane gave ester **1b** in 65 % yield. The alkaline hydrolysis of the latter afforded the target acid **1** (see Scheme 1). The overall yield of acid **1** from compound **2** was 31.3 % over the five steps of the synthesis (or 37.1 % based on the converted **3**), whereas in the known synthetic sequences[2—4] overall yields of **1** and its close analogs based on the limiting starting compound do not exceed 15 %.

It should be noted that aldehydo ester **5** described by us is a convenient building block for preparing not only acid **1** but also other 4-(nor-polyprenyl)benzoic acids and, accordingly, a wide range of known or potential pharmacologically active substances.

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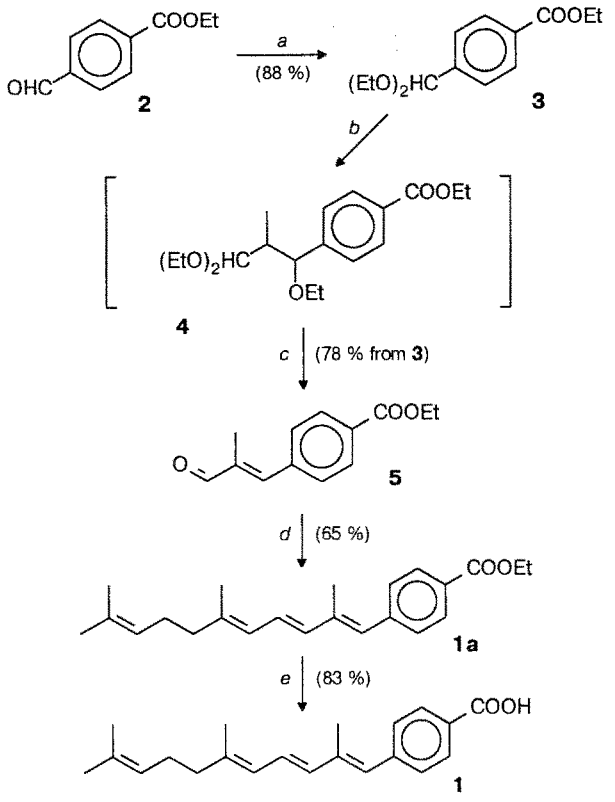
1066-5285/93/4205-0870 $12.50

Scheme 1



a. $HC(OEt)_3$, $HClO_4$ (Cat.), 20—45 °C, 0.5 h;
b. $CH_3CH{=}CHOEt$, $BF_3 \cdot Et_2O$ (Cat.), 20—42 °C, 2 h;
c. AcOH—AcONa—H_2O, ~100 °C, 3.5 h; *d*. $[GerPPh_3]^+Br^-$, $K_2CO_3/(CH_2CH_2O)_2$, 105 °C, 4 h; *e*. KOH—EtOH (aq.), ~80 °C, 2 h.

Experimental

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

4-Ethoxycarbonylbenzaldehyde diethyl acetal (3). A trace amount of $HClO_4$ (in the tip of a capillary) was added to a mixture of aldehyde **2** (3.56 g, *i.e.*, 20 mmol), $HC(OEt)_3$ (3.0 g, *i.e.*, 3.4 mL, 22 mmol), and EtOH (2 mL). The mixture was stirred for ~0.5 h, the temperature being maintained below 50 °C. When the reaction was completed the mixture was cooled and neutralized with an alcohol solution of KOH. Distillation of the mixture yielded 4.45 g (88 %) of acetal **3**; b.p. 122—124 °C (0.4 Torr), n_D^{20} 1.4912. ^1H NMR, δ: 1.2 (t, 6 H, 2 CH_3, J = 7 Hz); 1.35 (t, 3 H, CH_3, J = 7 Hz); 3.55 (q, 2 H, 2 CH_2O, J = 7 Hz); 4.35 (q, 2 H, OCH_2, J = 7 Hz); 5.5 (s, 1 H, $CH(OEt)_2$); 7.5 and 8.0 (both m, 4 H, Ar).

α,β-Enal (5). To 3.4 g (13 mmol) of acetal **3** several drops of $BF_3 \cdot Et_2O$ were added, and then 1.18 g (13 mmol) of EPE was added dropwise with stirring, so that the temperature did not exceed 40 °C. After ~12 h the reaction mixture was diluted with 15 mL of a mixture prepared from AcOH (100 mL), AcONa (10 g), and H_2O (6.5 mL), and refluxed with stirring for 3.5 h. Then the reaction mixture was cooled, poured onto ice, and extracted with ether. The combined ethereal extracts were washed with water, $NaHCO_3$ solution, and once again with water, dried with $MgSO_4$ and the solvent was evaporated. Distillation of the residue after its preliminary purification on a column packed with SiO_2 (1:1 hexane—benzene as the eluent) afforded 0.5 g of the starting aldehydo ester **2** and 1.9 g (78.5 % based on converted **3**) of enal **5** as a light-yellow oil; b.p. 145—150 °C (0.5 Torr); the distilled compound crystallized on storing. ^1H NMR, δ: 1.35 (t, 3 H, CH_3, J = 7 Hz); 2.0 (d, 1 H, $CH_3C{=}$, J = 1.5 Hz); 4.35 (q, 2 H, OCH_2, J = 7 Hz); 7.2 (s, 1 H, CH=); 7.7 and 8.0 (both m, 4 H, Ar); 9.55 (s, 1 H, CHO).

Ester 1a. A mixture of enal **5** (1.09 g, 5 mmol), GTPB (2.48 g, 5 mmol) obtained from linalool by the known procedure,[7] 1.0 g of K_2CO_3, and 50 mmol of H_2O in 5 mL of dioxane was boiled with stirring for 4 h. After the reaction mixture was cooled, the precipitate was filtered off, washed with ether, and the filtrate was concentrated and the residue was purified on a column packed with SiO_2 (1:1 hexane—benzene as the eluent) to give 1.1 g (65 %) of **1a** as a light-yellow oil identical to that described in ref. 4. ^1H NMR, δ: 1.4 (t, 3 H, CH_3, J = 7 Hz); 1.5—2.4 (m, 16 H, 4 CH_3, 2 CH_2); 4.35 (q, 2 H, OCH_2, J = 7 Hz); 5.1 (br.s, 1 H, CH=); 5.9 and 6.4—6.7 (both m, 4 H, 4 CH=); 7.3 and 8.0 (both m, 4 H, Ar).

Acid 1. This acid was prepared in 83 % yield by the alkaline hydrolysis of ester **1a**, as described in ref. 4. ^1H 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 (both m, 4 H, Ar); 10.35 (br.s, 1 H, COOH).

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