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METHODS OF SYNTHESIS AND TECHNOLOGY OF DRUG MANUFACTURE

SYNTHETIC INVESTIGATIONS ON THE CHEMISTRY OF POLYENE COMPOUNDS. LVI.* SYNTHESIS OF (ALL-E)-9-(4-METHOXY-2,3,6-TRIMETHYLPHENYL)-3,7-DIMETHYLNONA-2,4,6,8-TETRAENOIC ACID

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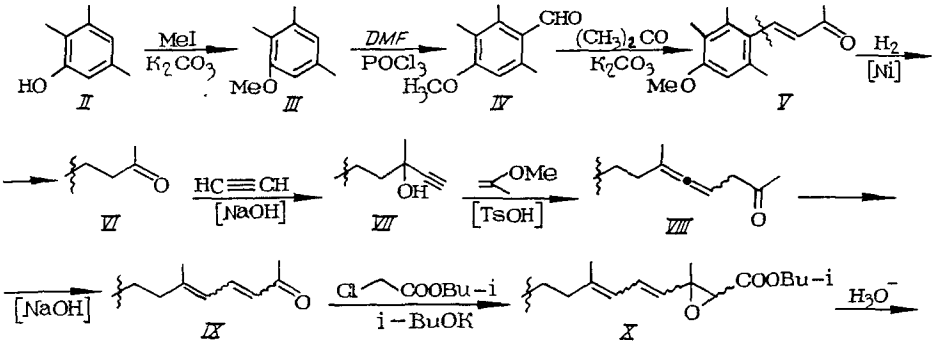
Aromatic analogs of retinoic acid have been used in recent years for the treatment of several serious dermatological illnesses accompanied by disturbance of keratinization processes. For example (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid acitretin (I) and its derivatives are used in the therapy of psoriasis, ichthyosis, Darier's disease, and serious forms of erythrodermia [2].

The synthesis of acitretin (I) was carried out for the first time by Bollag and coworkers by a scheme comprising the condensation of various intermediates by the Wittig reaction or by the Horner phosphonate modification. Only the method using the reaction of 5-(4-methoxy-2,3,6-trimethylphenyl)penta-2,4-dienylidenetriphenyphosphorane with 2-methyl-3-formylcrotonic acid has acquired industrial value [3-6]. Other variants for obtaining this compound are known, such as using the alkylation of sulfones according to Julia [7], the Grignard reaction with ethoxyethylmagnesium bromide [8], or the aldol condensation with esters of β-methylglutaconic acid [9].

The present communication is devoted to the synthesis of acitretin (I) by the scheme used by us previously to obtain esters of 3,7,11,15-tetramethylhexadeca-2,4,6,8-tetraenoic acid and vitamin A_2 acid [1, 10].



*For communication LV see [1].

†Deceased.

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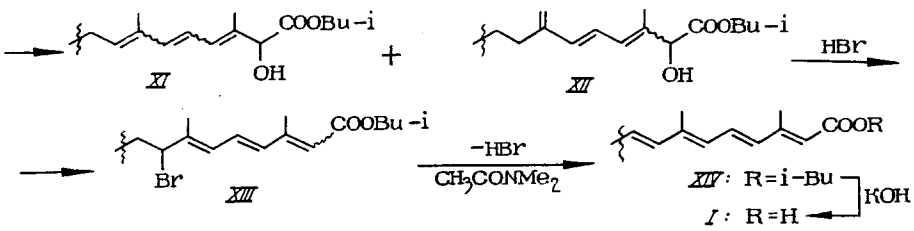

The key stage of the synthesis is the preparation of the glycide ether (X) by the Darzens reaction from the conjugated dienone (IX) with subsequent fission of the oxirane ring under acid conditions and dehydration of the α-hydroxy ester (XI) formed.

The initial 4-(4-methoxy-2,3,6-trimethylphenyl)-but-3-en-2-one (V) was obtained from 2,3,5-trimethylphenol (II) by the known method of [6]. Hydrogenation of the ketone (V) was carried out in the presence of Raney nickel [11]. Ethynylation of the dihydroketone (VI) in liquid ammonia in the presence of catalytic quantities of alkali [12] gave the acetylenic carbinol (VII) in 83% yield.

The condensation of acetylenic alcohols with 2-methoxypropene with a Claisen rearrangement is widely used for the synthesis of dienones [12, 13]. The allenic ketone (VIII) was obtained by the reaction of the acetylenic carbinol (VII) in the presence of p-toluenesulfonic acid at 130-135°C. Compound (VIII) contained two isomers in a 95:5 ratio according to the data of PMR analysis. The key dienone (IX) was obtained by a prototrophic rearrangement of compound (VIII) in methanol in the presence of alkali. Compound (IX) was obtained as 4 isomers at C^3 and C^5 double bonds, the ratio being 61% (3E, 5Z), 17% (3E, 5E), 13% (3Z, 5E), and 9% (3Z, 5Z) (according to PMR analysis). The mixture of isomers of (IX) was taken further in the synthesis without separation.

The condensation of dienone (IX) with isobutyl monochloroacetate in the presence of potassium isobutylate [10] led to the glycide ester (X) as a mixture of diene isomeric oxiranes (60:40 according to PMR analysis). Fission of the oxirane ring occurred on treating crude compound (X) with hydrochloric acid in aqueous methanel, and the vicinal diol formed initially then underwent prototrophic rearrangement. As a result a mixture was obtained of 4 geometric isomers of the triene α-hydroxyester (XI) [containing 41% (3E, 7E) and (3E, 7Z) isomers and 10% (3Z, 7E) and (3Z, 7Z) isomers] and 2 geometric isomers of compound (XII) [containing 38 and 11% of the (3E) and (3Z) isomers respectively by PMR analysis]. This mixture was used in the next stage without separation.

In the concluding stages the mixture of α-hydroxyester (XI) and its structural isomer (XII) was treated with phosphorus tribromide in a medium of hexane and ether. A nucleophilic replacement of the hydroxyl group by bromine occurred with simultaneous allytic rearrangement. This led to the regioselective formation of the unstable bromide (XIII) as a mixture of (2E) and (2Z) isomers in a ratio of 9:1 (by PMR analysis). Solvolysis of the mixture of bromides (XIII) in dimethylacetamide led to elimination of hydrogen bromide and the formation of a mixture of isomers of acitretin isobutyl ester (XIV) in which more than 90% was the (all-E) and (2Z) isomers and less than 10% was (6Z) and (2Z, 6Z) isomers. The content of (2E) and (2Z) isomers in the mixture obtained was practically the same as in the initial mixture of bromides which indicates the stereodirected course of the dehydrobromination reaction. After chromatographic purification and crystallization the isobutyl ester of (all-E)-acitretin (XIV) was obtained in 52% yield based on the dienone (IX). Saponification of compound (XIV) with potassium hydroxide in aqueous alcohol gave acitretin (I) identical in physicochemical properties with samples described in the literature [13].

EXPERIMENTAL

The UV spectra were measured on Specord UV-VIS and Specord M 40 instruments, and IR spectra on a Perkin–Elmer 180 instrument in CCl_4 solutions of concentration 50 mg/ml. The PMR spectra were measured on Bruker WP 200 SY and AM 400 instruments with operating frequencies for protons of 200.13 and 400.13 MHz respectively. Chemical shifts are given in the δ scale relative to tetramethylsilane (δ = 0). Chemical shifts are given with a precision of ±0.01 ppm and coupling constants to ±0.1 Hz.

2,3,5-Trimethylanisole (III). 2,3,5-Trimethylphenol (14.9 g) was stirred in ethanol (55 ml) and water (5.5 ml). Potassium hydroxide (7.1 g) was added to the suspension obtained. Methyl iodide (8.2 ml) was added dropwise with stirring to the clear solution at 0-5°C. Stirring was continued for 2 h at 20-25°C and for 12 h at 60°C. Water (150 ml) was added to

the reaction mixture, which was then extracted with ether. The extract was washed sequentially with 3% NaOH and twice with water, then dried over Na_2SO_4. The solvent was evaporated and the residue distilled in vacuum. Yield was 13.72 g (83.5%) of colorless liquid, bp 106-108°C (10 mm Hg), n_D^{20} 1.5218 [6].

2,3,6-Trimethyl-n-anisaldehyde (IV). Phosphorus oxychloride (7.3 ml) was added dropwise with stirring to DMF (6.1 ml) at 10-20°C during 15 min. At the end of the addition the temperature of the reaction mixture had increased to 25°C. The reaction mixture was then cooled to 10°C and 2,3,5-trimethylanisole (10 g) (III) was added at 10-20°C. The mixture obtained was heated to 110°C and maintained at this temperature for 6 h. At the end of the reaction the mixture was cooled to 20-25°C and poured onto ice/water (130 g). Benzene (100 ml) and sodium acetate (33 g) were added to the mixture, which was stirred for 1 h, and the organic layer separated. The aqueous layer was extracted with benzene. The combined organic extract was washed with 1.5% HCl and water, dried over Na_2SO_4, and filtered through activated carbon. The solvent was removed in vacuum, and the residue crystallized from hexane. Yield was 7.71 g (65.0%) of light yellow crystals of mp 63-65°C [6].

4-(4-Methoxy-2,3,6-trimethylphenyl)but-3-en-2-one (V). Acetone (93 ml) and water (37 ml) were added to 2,3,6-trimethyl-4-anisaldehyde (6.91 g) and then 10% NaOH (19.4 ml) was added with stirring at 0-5°C during 30 min. The reaction mixture was stirred at 20-25°C for 7 h, then acidified to pH 4-5 with AcOH, and the solvent removed in vacuum. The residue was extracted with ether, the ether solution washed with 5% sodium bicarbonate solution and with water, and dried over Na_2SO_4. The solvent was removed in vacuum and the product distilled. Yield was 6.3 g (74.6%) of bp 125-130°C (0.1 mm Hg) [6], yellow crystals, mp 55-56°C (from hexane).

4-(4-Methoxy-2,3,6-trimethylphenyl)butan-2-one (VI). The ketone (V) (4.0 g) was dissolved in alcohol (70 ml) and hydrogenated at atmospheric pressure in the presence of Raney nickel suspension (1 ml). The hydrogenation was stopped after absorption of 1 mole hydrogen, the catalyst was separated from the solution, and the solvent removed. A crude product was obtained which was recrystallized from hexane. Yield was 3.43 g (85%) of light yellow crystals having mp 86.5-87°C [11]. PMR spectrum (200 MHz, C_6D_6, δ, ppm): 1.68 s (3H, C^1H_3), 2.02 s, 2.17 s, 2.25 s (9H, $3CH_3$ arom.), 2.11-2.26 m (2H, C^3H_2), 2.76-2.95 m (2H, C^4H_2), 3.42 (3H, CH_3O), 6.43 s (1H, H arom.).

5-(4-Methoxy-2,3,6-trimethylphenyl)-3-methylpent-1-yn-3-ol (VII). Compound (VI) (4 g), benzene (40 ml), and 5% alcoholic KOH solution (7.5 ml) were loaded into an autoclave. The autoclave was sealed hermetically, ammonia (90 g, 150 ml) added, and acetylene passed in until the mixture was saturated (initial pressure in the autoclave was 1.2 MPa). Reaction was continued for 48 h. The ammonia was then removed from the reaction mixture, the residue was washed with 5% H_2SO_4, and then with water to neutral reaction. The aqueous solutions were extracted with benzene. The benzene extracts were combined, the solvent removed in vacuum, and the residue recrystallized from hexane. Yield was 3.71 g (83%) of white crystals having mp 55.5-57°C. PMR spectrum (200 MHz, C_6D_6, δ, ppm): 1.38 s (3H, CH_3 at C^3), 1.58-1.82 m (2H, C^4H_2), 1.64 br s (1H, OH at C^3), 2.10 s (1H, C^1H), 2.19 s, 2.27 s, 2.32 s (9H, CH_3 arom.), 2.82-3.01 m (2H, C^5H_2), 3.46 s (3H, CH_3O), 6.47 s (1H, H arom.).

8-(4-Methoxy-2,3,6-trimethylphenyl)-6-methylocta-3,5-dien-2-one (IX). A solution of p-toluenesulfonic acid (0.0024 g) in acetone (0.07 ml) was added dropwise with stirring to a solution of the carbinol (VII) (1.6 g) in 2-methoxypropene (3.0 ml) cooled to 10-15°C. The mixture was transferred to a glass ampul, which was sealed, and heated in an oil bath at 135°C for 4 h (solution A).

In order to measure the PMR spectrum of the allenic ketone (VIII) a small sample of solution A was neutralized with sodium acetate and evaporated to dryness in vacuum. PMR spectrum of compound (VIII) (200 MHz, C_6D_6, δ, ppm): 1.68 d and 1.70 d [3H, $^4J(CH_3$ at C^6, $C^4H)$ 2.9 Hz, CH_3 at C^6, isomers], 1.73 s (3H, C^1H_3), 2.14 s, 2.26 s, and 2.27 s (9H, $3CH_3$ arom.), 2.00-2.20 m (2H, C^7H_2), 2.76 d and 2.99 d [2H, $^3J(C^3H_2$, $C^4H)$ 7.1 Hz, C^3H_2, isomers], 2.70-2.86 m (2H, C^8H_2), 3.46 s (3H, CH_3O), 5.27 and 5.43 m [1H, $^3J(C^4H$, $C^3H_2)$ 7.1 Hz, $^4J(CH_3$ at $C^6)$, 2.9 Hz, C^4H, isomers], 6.48 br s (1H, H arom.). The ratio of isomers of compound (VIII) was 95:5, as measured by the ratio of the integrated intensities of the signals of the C^4H proton of the isomers with δ 5.27 and 5.47 ppm.

At the end of the reaction, the solution A was transferred to a flask, cooled to 2-5°C, and a solution of NaOH [prepared by mixing 30% NaOH (0.013 ml) with methanol (1 ml)] added dropwise with vigorous stirring. After the end of adding the alkaline solution the temperature of the reaction mixture had risen to 8-10°C, and stirring was continued at this temperature for 40 min. The reaction mixture was then neutralized with AcOH, and the solvent removed in vacuum. Water (5 ml) was added to the residue, the solution extracted with ether, the ether solution was washed with water, dried over Na_2SO_4, and the solvent removed in vacuum. The residue was crystallized from hexane. Yield was 1.5 g (81%), of light yellow

crystals having mp 82-84°C. UV spectrum (hexane, λ_{max}, nm): 283. PMR spectrum (400 MHz, C_6D_6, δ, ppm): 1.72 d [1.83H, $^4J(CH_3$ at C^6, $C^5H)$ 1.1 Hz, CH_3 at C^6, (3E, 5Z) isomer], 1.78 d [0.51H, $^4J(CH_3$ at C^6, $C^5H)$ 1.1 Hz, CH_3 at C^6, (3E, 5E) isomer], 1.76 d [0.39H, $^4J(CH_3$ at C^6, $C^5H)$ 1.5 Hz, CH_3 at C^6, (3Z, 5E) isomer], 1.85 d [0.27H, $^4J(CH_3$ at C^6, $C^5H)$ 0.6 Hz, CH_3 at C^6, (3Z, 5Z) isomer], 1.98 s [0.27H, C^1H_3, (3Z, 5Z) isomer], 1.99 s [0.39H, C^1H_3, (3Z, 5E) isomer], 2.05 s [1.83H, C^1H_3, (3E, 5Z) isomer], 2.06 s [0.51H, C^1H_3, (3E, 5E) isomer], 2.17-2.40 s {9H, $3CH_3$ arom., [3(E, Z), 5(E, Z)] isomers}, 2.30-2.40 m {2H, C^7H_2, [3(E, Z), 5(E, Z)] isomers}, 2.69-2.88 m {2H, C^8H_2, [3(E, Z), 5(E, Z)] isomers}, 3.54 s [2.22H, CH_3O, (3E, 5Z) and (3Z, 5E) isomers], 3.56 s [0.78H, CH_3O, (3E, 5E) and (3Z, 5Z) isomers], 5.71 br d [0.09H, $^3J(C^3H, C^4H)$ 11.6 Hz, C^3H, (3Z, 5Z) isomer], 5.80 br d [0.13H, $^3J(C^3H, C^4H)$ 11.6 Hz, C^3H, (3Z, 5E) isomer], 5.89 br d [0.61H, $^3J(C^5H, C^4H)$ 11.5 Hz, C^5H, (3E, 5Z) isomer], 6.04 br d [0.17H, $^3J(C^5H, C^4H)$ 11.5 Hz, C^5H, (3E, 5E) isomer], 6.09 d [0.61H, $^3J(C^3H, C^4H)$ 15.3 Hz, C^3H, (3E, 5Z) isomer], 6.12 d [0.17H, $^3J(C^3H, C^4H)$ 15.3 Hz, C^3H, (3H, 5E) isomer], 6.55 s [0.74H, H arom., (3E, 5Z) and (3Z, 5E) isomers], 6.58 s [0.09H, H arom., (3Z, 5Z) isomer], 6.60 s [0.09H, H arom., (3E, 5E) isomer], 6.66 t [0.13H, $^3J(C^4H, C^5H)$ and $^3J(C^4H, C^3H)$ 11.6 Hz, C^4H, (3Z, 5E) isomer], 6.69 t [0.09H, $^3J(C^4H, C^5H)$ and $^3J(C^4H, C^3H)$ 11.6 Hz, C^4H, (3Z, 5Z) isomer], 7.37 d d [0.61H, $^3J(C^4H, C^3H)$ 15.3 Hz, $^3J(C^4H, C^5H)$ 11.5 Hz, C^4H, (3E, 5Z) isomer], 7.56 d d [0.17H, $^3J(C^4H, C^3H)$ 15.3 Hz, $^3J(C^4H, C^5H)$ 11.5 Hz, C^4H, (3E, 5E) isomer], 7.87 br d [0.09H, $^3J(C^5H, C^4H)$ 11.6 Hz, $^4J(C^5H, CH_3$ at C6) 0.6 Hz, C^5H, (3Z, 5Z) isomer], 7.98 br d [0.13H, $^3J(C^5H, C^4H)$ 11.6 Hz, $^4J(C^5H, CH_3$ at $C^6H)$ 1.5 Hz, C^5H, (3Z, 5E) isomer]. The ratio of isomers of the dienone (IX) was determined from the integrated intensities of the signals with δ 5.89 ppm [C^5H, (3E, 5Z) isomer], δ 7.56 ppm (C^4H, (3E, 5E) isomer], δ 7.87 [C^5H, (3Z, 5Z) isomer], and δ 7.98 ppm [C^5H, (3Z, 5E) isomer]. The ratio of the (3E, 5Z):(3E, 5E):(3Z, 5E):(3Z, 5Z) isomers was 61:17:13:9.

Isobutyl Ester of (all-E)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic Acid (XIV). Butoxyanisole (5 mg) was added to a solution of the dienone (IX) (0.55 g) and isobutyl monochloroacetate (0.39 ml) in ether (5 ml) in an atmosphere of nitrogen. The solution was cooled to −10 to −15°C, a mixture of a 25% toluene solution (1.5 g, 2.1 ml) of potassium isobutylate and ether (5 ml), also cooled to −10 to −15°C was added dropwise with stirring. The reaction mixture was kept for 15 min at −10 to −15°C [solution D, UV spectrum (hexane, λ_{max}, nm): 256].

In order to confirm the structure of the glycide ester (X) a test sample of solution D was neutralized with solid carbon dioxide, the ether solution obtained was washed with water, dried over Na_2SO_4, and the solvent removed in vacuum. PMR spectrum of compound (X) (400 MHz, C_6D_6, δ, ppm): 0.95 d and 0.96 d [6H, $^3J(CH_3, CH)$ 6.7 Hz, $2CH_3$ in i-Bu, isomers at the epoxide ring], 1.46 s and 1.48 s (3H, CH_3 at C^3, isomers at the epoxide ring), 1.87 br s and 1.89 br s (3H, CH_3 at C^7, isomers), 1.85-2.00 m (1H, CH in i-Bu), 2.14 s (3H, CH_3 arom.), 2.26 s and 2.27 s (3H, CH_3 arom., isomers), 2.32 s and 2.33 s (3H, CH_3 arom., isomers), 2.38-2.43 m (2H, C^9H_2), 3.32 s and 3.47 s (1H, C^2H, isomers at the epoxide ring), 3.74 s and 3.75 s (3H, CH_3O, isomers), 3.93 d and 3.97 d [2H, $^3J(CH_2, CH)$ 6.7 Hz, CH_2 in i-Bu, isomers at the epoxide ring], 5.32 d and 5.57 d [1H, $^3J(C^4H, C^5H)$ 15.3 Hz and $^3J(C^4H, C^5H)$ 15.6 respectively, C^4H, isomers], 5.83 br d and 5.85 br d [1H, $^3J(C^6H, C^5H)$ 10.8 Hz and $^3J(C^6H, C^5H)$ 11.0 Hz respectively, C^6H, isomers], 6.49 d d and 6.58 d d [1H, $^3J(C^5H, C^4H)$ 15.3 Hz, $^3J(C^5H, C^6H)$ 10.8 Hz and $^3J(C^5H, C^4H)$ 15.6 Hz, $^3J(C^5H, C^6H)$ 11.0 Hz, C^5H, isomers], 6.52 s (1H, H arom.). The ratio of isomers at the epoxide ring was 60:40, and was determined from the ratio of the integrated intensities of the signals of the C^2H proton of the isomers at δ 3.32 and 3.47 ppm.

A mixture of 17% HCl (5 ml) and acetone (22 ml) cooled to 0°C was added with stirring to solution D at −5 to −10°C. After storing for 2 h the reaction mixture was neutralized with sodium bicarbonate solution, diluted with cold water, and the reaction product extracted with ether. The ether extract was dried over Na_2SO_4 and the solvent removed in vacuum. A mixture (0.69 g) of the α-hydroxy-ester (XI) and its structural isomer (XII) was obtained as a light brown oil, unstable on storage. UV spectrum (hexane, λ_{max}, nm) 215, 282. IR spectrum (CCl_4, cm^{-1}): 3530 (OH), 1730 (C=O ester). PMR spectrum of the mixture of compounds (XI) and (XII) (400 MHz, deuterocyclohexane-D_6, δ, ppm): 0.92 d [6H, $^3J(CH_3, CH)$ 6.7 Hz, $2CH_3$ in i-Bu], 1.62-1.78 m (1H, CH in i-Bu), 1.70-2.30 br s [4.53H, CH_3 at C^3 (XI, XII), CH_3 at C^7 (XI)], 2.05-2.30 s (9H, $3CH_3$ arom.), 2.30-2.40 m [0.98H, C^8H_2, (XII)], 2.65-2.80 [0.98H, C^9H_2, (XII)], 3.41 d and 3.46 br d {1.02H, $^3J(C^9C_2, C^8H)$ 6.6 Hz, C^9H, (XI) [3(E, Z), 7E] and 3(E, Z), 7Z] isomers}, 3.66 s [1.53H, CH_3O, (XI)], 3.67 s [1.47H, CH_3O, (XII)], 3.80-3.90 d (2H, CH_2 in i-Bu), 4.41 s and 4.47 s {0.51H, O^2H (XI), [3E, 7(E, Z)] isomers}, 4.44 s [0.38H, C^2H (XII), (3E) isomer], 5.00 br s and 5.02 br s {0.98H, CH_2 (XII), [3(E, Z) isomers}, 5.09 s and 5.17 {0.51H, C^2H, (XI), [3Z, 7(E, Z)] isomers}, 5.15 s [0.11H, C^2H, (XII), (3Z) isomer], 5.15 br t and 5.28 br t {0.51H, $^3J(C^8C, C^9H_2)$ 6.6 Hz, C^8H, (XI), [3(E, Z), 7E] and [3(E, Z), 7Z] isomers}, 5.80-7.20 m (4H, H arom., C^4H, C^5H, C^6H). The ratio of isomers in the mixture was determined from the integrated intensities of the signals of the C^9H_2 methylene group protons of the (7E) and (7Z) isomers of compound (XI) with δ 3.41 and 3.46 ppm, the signals of the methine proton of the CHOH group with δ 5.00 and

5.02 ppm, and the signals with δ 5.09, 5.15, and 5.17 ppm formed by the methine proton of the CHOH group of the (3E) isomers of compounds (XI) and (XII).

Hexane (4 ml) and anhydrous ether (3 ml) were added to the mixture (0.69 g) of compounds (XI) and (XII). The solution obtained was cooled to 10-15°C and a solution of phosphorus tribromide (0.23 ml) in hexane (3 ml) was added dropwise with stirring. The reaction mixture was stored for 50 min at 18-20°C [solution B, UV spectrum (hexane, λ_{max}, nm): 301, 314, 330].

To confirm the structure of the bromide (XIII) a sample of solution B was washed with cold water, dried over Na_2SO_4, and the solvent removed in vacuum. PMR spectrum of the mixture of the (all-E) and (2Z, 4E, 6E) isomers of compound (XIII) (200 MHz, deuterocyclohexane-D_6, δ, ppm): 0.92 d {6H, $^3J(CH_3, CH)$ 7.0 Hz, $2CH_3$ in i-Bu, [2(E, Z), 4E, 6E] isomers}, 1.75-1.99 m {1H, $^3J(CH, CH_3)$ and $^3J(CH, CH_2)$ 7.0 Hz, CH in i-Bu, [2(E, Z), 4E, 6E] isomers], 1.89 s [2.7H, CH_3 at C^7, (all-E) isomer], 2.04 s, 2.09 s, 2.18 s [8.1H, $3CH_3$ arom., (all-E) isomer], 2.30 d [3H, $^4J(CH_3$ at C^3, $C^2H)$ 1.0 Hz, CH_3 at C^3, (all-E) isomer], 1.75-2.40 s [1.5H, $3CH_3$ arom., CH_3 at C^3, CH_3 at C^7, (2Z, 4E, 6E) isomer], 3.13 d d {1H, $^3J(C^9H', C^9H'')$ 15.0 Hz, $^3J(C^9H', C^8H)$ 5.8 Hz, C^9H', [2(E, Z), 4E, 6E] isomers}, 3.38 d d {1H, $^2J(C^9H'', C^9H')$ 15.0 Hz, $^3J(C^9H', C^8H)$ 7.4 Hz, C^9H'', [2(E, Z), 4E, 6E] isomers}, 3.67 s {3H, CH_3O, [2(E, Z), 4E, 6E] isomers}, 3.83 d {2H, $^2J(CH_2, CH)$ 7.0 Hz, CH_2 in i-Bu, [2(E, Z), 4E, 6E)] isomers}, 4.62 d d [0.9H, $^3J(C^8H, C^9H'')$ 7.4 Hz, $^3J(C^8H, C^9H')$, 5.8 Hz, C^8H, (all-E) isomer], 4.49-4.70 d d [0.1H, $^3J(C^8H, C^9H'')$ 7.4 Hz, $^3J(C^8H, C^9H')$ 5.8 Hz, C^8H, (2Z, 4E, 6E) isomer], 5.62 br s [0.1H, C^2H, (2Z, 4E, 6E) isomer], 5.71 br s [0.9H, C^2H, (all-E) isomer], 6.03 br d [0.9H, $^3J(C^6H, C^5H)$ 10.9 Hz, C^6H, (all-E) isomer], 6.15 d [0.9H, $^3J(C^4H, C^5H)$ 15.4 Hz, C^4H, (all-E) isomer], 5.98-6.25 br d [0.9H, $^3J(C^6H, C^5H)$ 10.9 Hz, C^6H, (2Z, 4E, 6E) isomer], 6.43 s {1H, H arom., [2(E, Z), 4E, 6E] isomer}, 6.67 d d [0.1H, $^3J(C^5H, C^4H)$ 15.4 Hz, $^3J(C^5H, C^6H)$ 10.9 Hz, C^5H, (2Z, 4E, 6E) isomer], 6.71 d d [0.9H, $^3J(C^5H, C^4H)$ 15.4 Hz, $^3J(C^5H, C^6H)$ 10.9 Hz, C^5H, (all-E) isomer], 7.92 d [0.1H, $^3J(C^4H, C^5H)$ 15.4 Hz, C^4H, (2Z, 4E, 6E) isomer]. The ratio of (2E) and (2Z) isomers of compound (XIII) was determined from the ratio of the integrated intensities of the signals of the protons at C^2 with δ 5.72 and 5.62 ppm respectively.

The solution B was cooled to 0-5°C, a solution of dimethylacetamide (13 ml) in CH_2Cl_2 (5.5 ml) cooled to 5-10°C was added, and the mixture stirred for 2 h at 34°C. The reaction mixture was then poured into cold water and the product extracted with ether. The ether extract was washed sequentially with a saturated solution of sodium bicarbonate and with water, dried over Na_2SO_4, and the solvent removed in vacuum. The residue, containing (all-E) compound (XIV) and its (2Z) isomer in a ratio of 88:12 (by PMR analysis), was chromatographed on a column of silica gel in the system hexane–ether, gradually increasing the ether concentration from 0 to 10%. The fractions collected were analyzed by TLC on Silufol UV 254 plates in the system hexane–ether–benzene, 10:1:1. The fractions containing the compound with R_f 0.65 were combined, the solvent removed in vacuum, and the (2Z, 4E, 6E) isomer of ester (XIV) (0.012 g) was obtained as a thick yellow oil. The fractions containing the (all-E) ester (R_f 0.65) were combined, and the solvent removed in vacuum. The oily product crystallized on standing. The yield was 0.32 g [52% calculated on ketone (IX)] of yellow crystals with mp 83-86°C. UV spectrum [hexane, λ_{max}, nm, (ε)]: 362 (43,930).

PMR spectrum of (all-E) compound (XIV) (400 MHz, $CDCl_3$, δ, ppm): 0.96 d [6H, $^3J(CH_3, CH)$ 6.7 Hz, $2CH_3$ in i-Bu], 1.91-2.03 m (1H, CH in i-Bu), 2.11 br s (3H, CH_3 at C^7), 2.15 s, 2.24 s, 2.30 s (9H, $3CH_3$ arom.), 2.37 d [3H, $^4J(CH_3$ at C^3, $C^2H)$ 1.0 Hz, CH_3 at C^3], 3.81 s (3H, CH_3O arom.), 3.91 d [2H, $^3J(CH_2, CH)$ 6.7 Hz, CH_2 in i-Bu], 5.81 br s (1H, C^2H), 6.19 br d [1H, $^3J(C^6H, C^5H)$ 11.6 Hz, C^6H), 6.25 d [1H, $^3J(C^8H, C^9H)$ 16.3 Hz, C^8H], 6.32 d [1H, $^3J(C^4H, C^5H)$ 15.1 Hz, C^4H], 6.60 br s (1H, H arom.), 6.68 d [1H, $^3J(C^9H, C^8H)$ 16.3 Hz, C^9H], 7.02 d d [1H, $^3J(C^5H, C^4H)$ 15.1 Hz, $^3J(C^5, C^6H)$ 11.4 Hz, C^5H].

PMR spectrum of the (2Z, 4E, 6E, 8E) isomer of compound (XIV) (400 MHz, $CDCl_3$, δ, ppm): 0.95 d [6H, $^3J(CH_3, CH)$ 6.7 Hz, $2CH_3$ in i-Bu], 1.91-2.03 m (1H, CH in i-Bu), 2.09 d [3H, $^4J(CH_3$ at C^3, C^2H, CH_3 at $C^3)$], 2.10 br s (3H, CH_3 at C^7), 2.15 s, 2.24 s, 2.30 s (9H, $3CH_3$ arom.), 3.82 s (3H, CH_3O arom.), 3.90 d [2H, $^3J(CH_2, CH)$ 6.7 Hz, CH_2 in i-Bu], 5.68 br s (1H, C^2H), 6.25 d [1H, $^3J(C^8H, C^9H)$ 16.3 Hz, C^8H], 6.29 br d [1H, $^3J(C^6H, C^5H)$ 11.4 Hz, C^6H], 6.60 br s (1H, arom.), 6.67 d [1H, $^3J(C^9H, C^8H)$ 16.3 Hz, C^9H], 7.00 d d [1H, $^3J(C^5H, C^4H)$ 15.3 Hz, $^3J(C^5H, C^6H)$ 11.4 Hz, C^5H], 7.81 d [1H, $^3J(C^4H, C^5H)$ 15.3 Hz, C^4H].

The ratio of the (2E) and (2Z) isomers of compound (XIV) was determined from the ratio of the integrated intensities of the signal of the C^2 proton at δ 5.81 ppm for the (2E) isomer and of the C^4 proton at 7.81 ppm for the (2Z) isomer.

(all-E)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic Acid (I). A solution of KOH (0.31 g) in water (0.62 ml) was added to a solution of the isobutyl ether (XIV) (0.31 g) in ethanol (3.1 ml) in an atmosphere of nitrogen. The mixture obtained was heated at the boiling point for 45 min, cooled, the alcohol removed in vacuum, and the residue poured onto ice. The aqueous solution was washed with ether, acidified with 15% HCl to pH 3-4, and the acid (I) ex-

tracted with CH_2Cl_2. The extract was dried over $CaCl_2$, filtered, and the CH_2Cl_2 removed in vacuum. The residue was crystallized from a mixture of ethanol and ethyl acetate. Yield was 0.23 g (88.5%) of yellow crystals of mp 219-221°C. UV spectrum [acidified ethanol, λ_{max}, nm, (ε)]: 358 (42,000). PMR spectrum (200 MHz, $CDCl_3$, δ, ppm): 2.12 br s (3H, CH_3 at C^7), 2.15 s, 2.24 s, 2.30 s (9H, $3CH_3$ arom.), 2.38 d [3H, $^4J(CH_3$ at C^3, $C^2H)$ 1.2 Hz, CH_3 at C^3], 3.82 s (3H, CH_3O), 5.82 br s (1H, C^2H), 6.20 br d [1H, $^3J(C^6H$, $C^5H)$ 11.6 Hz, C^6H], 6.25 d [1H, $^3J(C^8H$, $C^9H)$ 16.3 Hz, C^8H], 6.35 d [1H, $^3J(C^4H$, $C^5H)$ 15.2 Hz, C^4H], 6.60 br s (1H, H arom.), 6.71 d [1H, $^3J(C^9H$, $C^8H)$ 16.3 Hz, C^9H], 7.07 d d [1H, $^3J(C^5H$, $C^4H)$ 15.2 Hz, $^3J(C^5H$, $C^6H)$ 11.6 Hz, C^5H] [15]. Found, %: C 77.22, H 7.58. $C_{21}H_{26}O_3$. Calculated, %: C 77.27, H 8.03.

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