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Synthesis of Methyl 3-Bromomethylbut-3-enoate and Its Reactions with Aldehydes and Tributylchlorostannane in the Presence of Zinc

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Abstract—Methyl 3-bromomethylbut-3-enoate smoothly reacted with prenal, β-ionylideneacetaldehyde, benzyloxyacetaldehyde, and tributylchlorostannane in the presence of zinc and aqueous ammonium chloride in tetrahydrofuran to give the corresponding δ-hydroxy-β-methylidenecarboxylic acid esters. In the absence of ammonium chloride, satisfactory yields of the products were obtained only in the reactions with prenal and benzyloxyacetaldehyde; these reactions involved lactonization of intermediate δ-hydroxy-β-methylidenecarboxylic acid esters, and the double carbon–carbon bond migrated to the conjugated position with the lactone carbonyl group. The condensation of β-ionylideneacetaldehyde with methyl 3-bromomethylbut-3-enoate was successfully used to obtain isotretinoin. Initial methyl 3-bromomethylbut-3-enoate was synthesized in a good yield from readily accessible ethyl 3,3-diethoxypropionate via cyclopropanation with ethylmagnesium bromide in the presence of titanium tetra(isopropoxide), oxidation of the acetal moiety to ester, and cleavage of the cyclopropane ring in intermediate methyl (1-methylsulfonyloxycyclopropyl)acetate.

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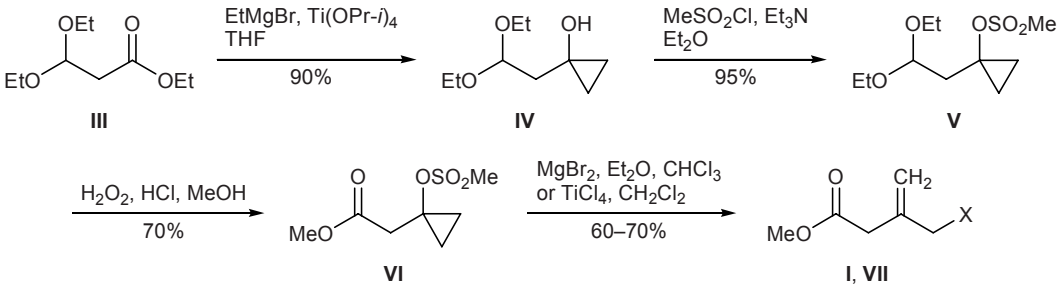
The use of nucleophilic C_5 building blocks with isopentane carbon skeleton in the synthesis of isoprenoids is advantageous due to attributive correspondence of the results of their reactions with carbon electrophiles to those of the transformations of isopentenyl pyrophosphate in fundamental biosynthesis processes [1]. Derivatives of 3-methylbut-2-enoic acid belong to the most frequently used compounds of this type; carbanionic center therein is generally generated via deprotonation or replacement of halogen by metal [2–17]. Derivatives of isomeric 3-methylbut-3-enoic acid have been studied to a considerably lesser extent; as far as we know, their use in synthesis has been reported only in recent publications on asymmetric allylation of aldehydes with ethyl 3-(tributylstannylmethyl)but-3-enoate [18, 19]. The latter was obtained by low-temperature stannylation of 3-chloro-2-(chloromethyl)prop-1-ene, followed by ethoxycarbonylation of 3-tributylstannyl-2-(tributylstannylmethyl)prop-1-ene [20]. It was shown that this transformation ensures chain extension by five carbon atoms with formation of δ-hydroxy-β-methylidenealkanoic acids or (after migration of the double carbon–carbon bond to the conjugated position) (*E*)-δ-hydroxy-β-methyl-α,β-unsaturated acids.

In the present article we report on the synthesis of methyl 3-bromomethylbut-3-enoate (**I**) and its condensation with electrophiles in the presence of metallic zinc, as well as on the use of compound **I** as isoprenoid building block in the synthesis of isotretinoin (**II**) [3, 7, 21–28]. The reaction of readily accessible ethyl 3,3-diethoxypropionate (**III**) with ethylmagnesium bromide in the presence of titanium(IV) isopropoxide [29, 30] gave 1-substituted cyclopropanol **IV** which was treated with methanesulfonyl chloride. Oxidation of the acetal moiety in the resulting methanesulfonate **V** with a mixture of hydrogen peroxide and concentrated hydrochloric acid in methanol [31] led to ester **VI**, and replacement of the methylsulfonyloxy group by bromine by the action of magnesium bromide via cationic cyclopropyl–allyl isomerization [32, 33] afforded compound **I** in an overall yield of 42% (Scheme 1). Likewise, the corresponding chlorine-containing compound **VII** was obtained by treatment of **VI** with titanium tetrachloride in methylene chloride.

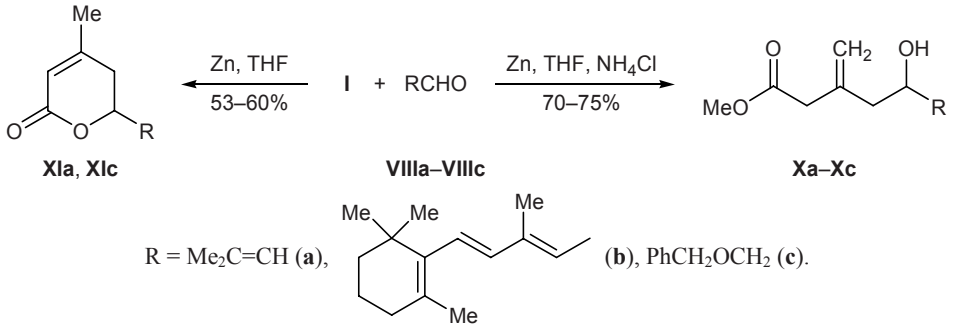
Allyl halides **I** and **VII** were then used as nucleophilic C_5 building blocks in reactions with aldehydes **VIIIa**–**VIIIc** and tributylchlorostannane (**IX**). The latter were selected as electrophiles, taking into account

Scheme 1.



I, X = Br; **VII**, X = Cl.

Scheme 2.

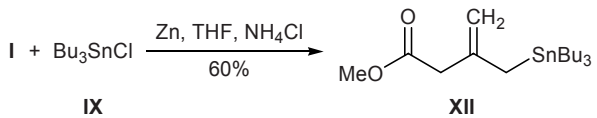


R = Me_2C=CH (**a**), (**b**), $PhCH_2OCH_2$ (**c**).

that the expected condensation products could be promising as intermediate products in the synthesis of bioactive compounds [6, 7, 19, 34]. Aldehydes **VIIIa**–**VIIIc** reacted with allyl bromide **I** taken in a slight excess and zinc powder in a mixture of tetrahydrofuran with a saturated aqueous solution of ammonium chloride [35–39] to produce the corresponding δ-hydroxy-β-methylidenealkanoic acid esters **Xa**–**Xc** in good yields. When the reaction was carried out in the absence of ammonium chloride, the allylation of aldehydes **VIIIa** and **VIIIc** was accompanied by lactonization and migration of the double C=C bond to the conjugated position, As a result, unsaturated δ-lactones **XIa** and **XIc** were obtained (Scheme 2). Under analogous conditions, β-ionylideneacetaldehyde (**VIIIb**) gave rise to a complex mixture of products.

The allylation of tributylchlorostannane (**IX**) with compound **I** in the presence of zinc and aqueous ammonium chloride [40, 41] involved no considerable problems, and functionally substituted allylstannane **XII** was isolated in a moderate yield by column chromatography (Scheme 3). As with aldehyde **VIIIc**, no satisfactory results were obtained when the reaction was performed in the absence of ammonium chloride. Our attempts to react allyl chloride **VII** with aldehydes **VIII** and tributilchlorostannane (**IX**) in the presence of zinc were unsuccessful, regardless of whether NH_4Cl was added to the reaction mixture or not.

Scheme 3.



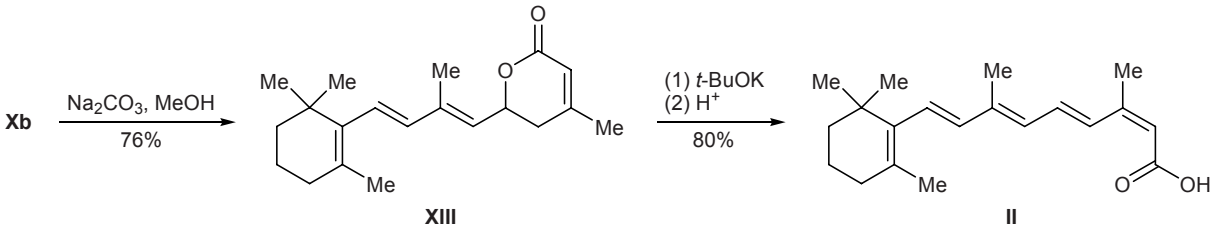
The cyclization of δ-hydroxy-β-methylidene derivative **Xb** and subsequent double bond migration in the lactone thus formed were used to obtain isotretinoin (**II**). By treatment of compound **Xb** with sodium carbonate in methanol at room temperature we obtained lactone **XIII** in a high yield, and intramolecular 1,2-elimination in **XIII** by the action of potassium *tert*-butoxide in tetrahydrofuran [21], followed by acidification, afforded isotretinoin **II** (Scheme 4). The yield of **II** calculated on the initial aldehyde **VIIIb** was 46%.

We can conclude that successful allylation of electrophilic substrates **VIII** and **IX** with substituted allyl bromide **I** by the action of zinc in aqueous–organic medium makes compound **I** promising as nucleophilic C_5 building block.

EXPERIMENTAL

The ^1H and ^{13}C NMR were recorded from solutions in chloroform on a Bruker AC 400 spectrometer at 400 and 100 MHz, respectively. The IR spectra were meas-

Scheme 4.



ured from solutions in carbon tetrachloride on Specord 75 IR and Vertex 70 instruments. The products were isolated by chromatography on silica gel (70–230 mesh, Merck). All solvents were purified by standard procedures prior to use. The elemental compositions were determined by a semimicro method. The melting points were determined on an Apotec melting point apparatus.

1-(2,2-Diethoxyethyl)cyclopropan-1-ol (IV). A solution of 150 mmol of ethylmagnesium bromide in 100 ml of THF was added over a period of 6 h under stirring to a solution of 9.5 g (50 mmol) of ethyl 3,3-diethoxypropionate (**III**) [42] and 2.8 ml (10 mmol, 20 mol %) of titanium(IV) isopropoxide in 50 ml of THF. The mixture was stirred for 12 h, the solvent was removed under reduced pressure, and 100 ml of methylene chloride and 15 ml of a saturated aqueous solution of ammonium chloride were added to the residue. The mixture was filtered, the precipitate was washed with methylene chloride (3×50 ml), and the organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3×50 ml) and a solution of NaCl (50 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure to isolate 7.83 g (90%) of alcohol **IV** as an oily liquid whose spectral parameters were in agreement with those given in [43].

1-(2,2-Diethoxyethyl)cyclopropyl methanesulfonate (V). A solution of 8.6 ml (62 mmol) of triethylamine and 3.6 ml (37 mmol) of methanesulfonyl chloride in 20 ml of anhydrous diethyl ether was added under stirring to a solution of 5.38 g (31 mmol) of compound **IV** in 35 ml of anhydrous diethyl ether, cooled to 0°C. The mixture was stirred for 2 h, treated with a saturated aqueous solution of $NaHCO_3$ (40 ml), and stirred for 1 h more. The organic layer was separated, the aqueous phase was extracted with diethyl ether (3×25 ml), and the extracts were combined with the organic phase, washed with a solution of sodium chloride (50 ml), and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was distilled off to obtain 7.49 g (95%) of compound **V** as an oily liquid. IR spectrum, ν, cm^{-1}: 1331, 1171, 1145 (CO_2). ^1H NMR spectrum, δ, ppm: 0.78–0.82 m (2H, CH_2), 1.19 t (6H, C**H**$_3$CH$_2$, J = 7 Hz), 1.21–1.25 m (2H, CH_2), 2.13 d (2H, CHC**H**$_2$C, J = 5.4 Hz), 3.00 s (3H, CH_3S), 3.49–3.57 m (2H, CH_2O), 3.62–3.70 m (2H, CH_2O), 4.78 t (1H, OCHO, J = 5.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 11.55 (CH_2, cyclopropane), 15.24 (CH_3), 39.83 (CH_3), 40.33 (CH_2), 62.05 (COS), 63.78 (CH_2), 100.89 (CH). Found, %: C 47.74; H 7.93. $C_{10}H_{20}O_5S$. Calculated, %: C 47.60; H 7.99.

Methyl (1-methylsulfonyloxycyclopropyl)acetate (VI). A solution of 42.25 g (166 mmol) of compound **V** in 260 ml of methanol was cooled to 0°C, 21.1 ml of concentrated hydrochloric acid was added, 28.9 ml of 33% hydrogen peroxide was then added, and the mixture was stirred for 1 h and heated for 5 h at 50–55°C. The mixture was then cooled to 0°C, 14.2 ml of concentrated hydrochloric acid and 19.4 ml of 33% hydrogen peroxide were added, and the mixture was heated again for 5 h at 50–55°C. The most part of methanol was removed under reduced pressure, the residue was diluted with ethyl acetate and neutralized with a saturated aqueous solution of $NaHCO_3$, and the organic layer was separated and dried over Na_2SO_4. Removal of the solvent gave 24.18 g (70%) of compound **VI** as an oily liquid whose spectral parameters were in agreement with those given in [43].

Methyl 3-bromomethylbut-3-enoate (I). A solution of 23.28 g (112 mmol) of methanesulfonate **VI** in 150 ml of chloroform was added dropwise under stirring to a solution of $MgBr_2$ prepared from 8.06 g (336 mmol) of magnesium turnings and 29.7 ml of 1,2-dibromoethane in 200 ml of anhydrous diethyl ether. The mixture was heated for 8 h under reflux with stirring and treated with 100 ml of water. The organic layer was separated, and the aqueous phase was extracted with chloroform (3×100 ml). The extracts were combined with the organic phase, washed in succession with a saturated aqueous solution of $NaHCO_3$ (3×75 ml) and a solution of NaCl (150 ml) and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was subjected to chromatography using petroleum ether–ethyl acetate

(40:1) as eluent to isolate 15.26 g (70%) of compound **I** as a yellowish oily liquid. IR spectrum: ν 1743 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 3.24 s (2H, CH_2CO), 3.70 s (3H, CH_3O), 4.18 s (2H, CH_2Br), 5.13 br.s (1H, CH_2=), 5.31 br.s (1H, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 38.23 (CH_2Br), 47.64 (CH_2), 51.98 (CH_3O), 118.94 (CH_2), 138.24 (C), 171.13 (C=O). Found, %: C 37.45; H 4.65. $C_6H_9BrO_2$. Calculated, %: C 37.33; H 4.70.

Methyl 3-chloromethylbut-3-enoate (VII). A solution of 4.3 ml (39 mmol) of titanium tetrachloride in 60 ml of anhydrous methylene chloride was cooled to 0°C, a solution of 4.00 g (19 mmol) of methanesulfonate **VI** in 10 ml of methylene chloride was added, and the mixture was stirred for 6 h and treated with a saturated aqueous solution of $NaHCO_3$ (20 ml). The organic phase was separated, the aqueous phase was extracted with methylene chloride (3×15 ml), and the extracts were combined with the organic phase, washed with a saturated aqueous solution of NaCl (40 ml), and dried $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography using petroleum ether–ethyl acetate (40:1) as eluent to isolate 1.71 g (60%) of allyl chloride **VII** as an oily liquid. IR spectrum: ν 1744 cm^{-1} (C=O). ^{1}H NMR spectrum, δ, ppm: 3.23 s (2H, CH_2CO), 3.69 s (3H, CH_3O), 4.17 s (2H, CH_2Cl), 5.11 br.s (1H, CH_2=), 5.29 br.s (1H, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 38.17 (CH_2), 47.61 (CH_2Cl), 51.93 (CH_3O), 118.90 (CH_2), 138.21 (C), 171.10 (CO). Found, %: C 48.64; H 6.07. $C_6H_9ClO_2$. Calculated, %: C 48.50; H 6.11.

Methyl δ-hydroxy-β-methylidene carboxylates Xa–Xc (*general procedure***).** A saturated solution of ammonium chloride, 25 ml, was added to a solution of 4 mmol of aldehyde **VIIIa**, **VIIIb** [44], or **VIIIc** in 2.5 ml of THF, 0.32 g (5 mmol) of zinc powder was added under vigorous stirring, and a solution of 1.00 g (5 mmol) of allyl bromide **I** in 2.5 ml of tetrahydrofuran was added over a period of 20 min. The mixture was vigorously stirred for 1 h and extracted with diethyl ether (3×15 ml), and the extracts were combined, washed with a saturated solution of $NaHCO_3$ (20 ml), and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the product was isolated by column chromatography using petroleum ether–ethyl acetate (25:1) as eluent.

Methyl 5-hydroxy-7-methyl-3-methylideneoct-6-enoate (Xa). Yield 0.57 g (70%). IR spectrum, ν, cm^{-1}: 3615 (OH), 1741 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.67 s (3H, CH_3), 1.70 s (3H, CH_3), 2.01 br.s (1H, OH), 2.24–2.32 m (2H, C**H**$_2$CHOH), 3.07 d (1H, CH_2CO, J = 15.3 Hz), 3.14 d (1H, CH_2CO, J = 15.3 Hz), 3.68 s (3H, CH_3O), 4.46 d.t (1H, C**H**OH, J_1 = 9, J_2 = 5.6 Hz), 5.02 br.s (1H, CH_2=), 5.05 br.s (1H, CH_2=), 5.16 d (1H, CH=, J = 9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.13 (CH_3), 25.65 (CH_3), 41.64 (CH_2), 44.36 (CH_2), 51.90 (CH_3O), 66.40 (CH), 117.34 (CH_2=), 127.17 (CH), 135.17 (C), 138.92 (C), 172.07 (CO). Found, %: C 66.77; H 9.10. $C_{12}H_{18}O_3$. Calculated, %: C 66.64; H 9.15.

Methyl (6*E*,8*E*)-5-hydroxy-7-methyl-3-methylidene-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-6,8-dienoate (Xb). Yield 1.04 g (75%). IR spectrum, ν, cm^{-1}: 3615 (OH), 1741 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.99 s (6H, CH_3), 1.41–1.46 m [2H, C**H**$_2$C$(CH_3)_2$], 1.54–1.62 m (2H, CH_2C**H**$_2CH_2$), 1.67 s (3H, CH_3C=C), 1.85 s (3H, CH_3C=CH), 1.97–2.00 m (2H, C**H**$_2CCH_3$), 2.32–2.35 m (2H, C**H**$_2$CHOH), 3.11 d (1H, CH_2CO, J = 15.3 Hz), 3.17 d (1H, CH_2CO, J = 15.3 Hz), 3.70 s (3H, CH_3O), 4.65 d.t (1H, C**H**OH, J_1 = 8.2, J_2 = 6.4 Hz), 5.07 br.s (1H, CH_2=), 5.09 br.s (1H, CH_2=), 5.40 d (1H, C**H**CHOH, J = 8 Hz), 5.99 d (1H, CC**H**CH, J = 16.1 Hz), 6.10 d (1H, CC**H**CH, J = 16.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.75 (9-CH_3),19.19 (C^3), 21.56 (5-CH_3), 28.82 (CH_3), 32.82 (C^4), 34.12 (C^1), 39.43 (C^2), 41.65 (C^{14}), 44.35 (C^{12}), 51.95 (CH_3O), 66.42 (C^{11}), 117.68 (CH_2=), 126.94 (C^7), 128.92 (C^5), 131.78 (C^{10}), 135.95 (C^9), 136.96 (C^8), 137.46 (C^{13}), 138.72 (C^6), 172.08 (C^{15}). Found, %: C 76.98; H 9.63. $C_{21}H_{32}O_3$. Calculated, %: C 75.86; H 9.70.

Methyl 3-[3-(benzyloxy)-2-hydroxypropyl]but-3-enoate (Xc). Yield 0.80 g (73%). IR spectrum, ν, cm^{-1}: 3589 (OH), 1742 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.25 d.d (1H, C**H**$_2$CHOH, J_1 = 14.3, J_2 = 8.7 Hz), 2.32 d.d (1H, C**H**$_2$CHOH, J_1 = 14.3, J_2 = 4 Hz), 2.73 br.s (1H, OH), 3.07–3.16 m (2H, CH_2CO), 3.39 d.d (1H, C**H**$_2$OBzl, J_1 = 9.5, J_2 = 7.2 Hz), 3.49 d.d (1H, C**H**$_2$OBzl, J_1 = 9.5, J_2 = 3.8 Hz), 3.67 s (3H, CH_3O), 3.93–3.99 m (1H, C**H**OH), 4.55 s (2H, C**H**$_2$Ph), 5.01 br.s (1H, CH_2=), 5.05 br.s (1H, CH_2=), 7.27–7.36 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 40.09 (CH_2), 41.46 (CH_2), 51.80 (CH_3O), 68.41 (CHOH), 73.29 (**C**H$_2$Ph), 73.97 (**C**H$_2$OBzl), 117.06 (CH_2=), 127.64 (C^o, C^p), 128.33 (C^m), 137.86 (C^i), 138.70 (C), 171.99 (CO). Found, %: C 68.36; H 7.54. $C_{15}H_{20}O_4$. Calculated, %: C 68.16; H 7.63.

Lactones XIa and XIc (*general procedure***).** Aldehyde **VIIIa** or **VIIIc**, 5.0 mmol, was dissolved in 3 ml of anhydrous THF, 1.00 g (5 mmol) of allyl bromide **I** and 0.55 g (9 mmol) of zinc powder were added to the

solution, and the mixture was heated for 20 min under reflux with stirring. The solvent was distilled off under reduced pressure, 25 ml of diethyl ether and 3 ml of a saturated aqueous solution of NH_4Cl were added to the residue, the mixture was filtered, and the organic phase was separated, washed with a saturated aqueous solution of NH_4Cl (3×15 ml), and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the product was isolated by column chromatography using petroleum ether–ethyl acetate (20:1) as eluent.

4-Methyl-6-(2-methylprop-1-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (XIa). Yield 0.49 g (60%). IR spectrum: ν 1729 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.66 s (3H, CH_3), 1.71 s (3H, CH_3), 1.94 s (3H, CH_3), 2.17 d.d (1H, C**H**$_2$CHO, J_1 = 17.9, J_2 = 4.1 Hz), 2.33 d.d (1H, C**H**$_2$CHO, J_1 = 17.9, J_2 = 11.1 Hz), 5.04 d.d.d (1H, CH_2C**H**O, J_1 = 11.1, J_2 = 8.7, J_3 = 4.1 Hz), 5.26 d [1H, C**H**=C(CH_3)$_2$, J = 8.7 Hz], 5.75 br.s (1H, CHCO). ^{13}C NMR spectrum, δ_C, ppm: 18.18 (CH_3), 22.82 (CH_3), 25.53 (CH_3), 34.88 (CH_2), 74.05 (CH), 116.35 (CH), 121.95 (CH), 139.11 (C), 157.03 (C), 165.12 (CO). Found, %: C 72.39; H 8.32. $C_{10}H_{14}O_2$. Calculated, %: C 72.26; H 8.49.

6-(Benzyloxymethyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (XIc). Yield 0.61 g (53%). IR spectrum: ν 1731 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.26 d.d (1H, C**H**$_2$CHO, J_1 = 17.9, J_2 = 4 Hz), 2.55 d.d (1H, C**H**$_2$CHO, J_1 = 17.9, J_2 = 11.7 Hz), 3.63–3.71 m (2H, C**H**$_2$OBzl), 4.53–4.57 m (1H, CH_2C**H**O), 4.59 br.s (2H, C**H**$_2$Ph), 5.80 br.s (1H, CHCO), 7.28–7.40 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 22.95 (CH_3), 31.33 (CH_2), 70.74 (**C**H_2OBzl), 73.59 (**C**H_2Ph), 75.86 (CH), 116.20 (CH), 127.96 (C^o), 128.31 (C^m), 128.41 (C^p), 131.61 (C^i), 157.07 (C), 164.51 (CO). Found, %: C 72.47; H 6.86. $C_{14}H_{16}O_3$. Calculated, %: C 72.39; H 6.94.

Methyl 3-(tributylstannylmethyl)but-3-enoate (XII). Tributylchlorostannane, 7 g (22 mmol), was dissolved in 10 ml of THF, 130 ml of a saturated aqueous solution of NH_4Cl and 1.68 g (26 mmol) of zinc powder were added under vigorous stirring, and a solution of 5 g (26 mmol) of allyl bromide **I** in 26 ml of THF was added over a period of 20 min. An additional portion of zinc, 1.68 g (26 mmol), was then added, and the mixture was stirred for 1 h and extracted with diethyl ether (3×75 ml). The extracts were combined, washed with a saturated aqueous solution of $NaHCO_3$ (40 ml), and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography using petroleum ether–ethyl acetate (80:1) as eluent to isolate 5.16 g (60%) of compound **XII** as a colorless oily liquid. IR spectrum: ν 1742 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 0.78–0.95 m (15H, CH_3), 1.24–1.33 m (6H, C**H**$_2$$CH_2$Sn), 1.39–1.53 m (6H, CH_3C**H**$_2$), 1.84 s (2H, CH_2Sn), 2.95 s (2H, CH_2CO), 3.68 s (3H, CH_3O), 4.59 br.s (1H, CH_2=), 4.68 br.s (1H, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 9.44 (CH_2), 13.63 (CH_3), 18.85 (CH_2), 27.30 (CH_2), 29.00 (CH_2), 43.78 (CH_2), 51.74 (CH_3O), 109.13 (CH_2=), 142.75 (C), 171.89 (CO). Found, %: C 54.83; H 9.08. $C_{19}H_{38}O_2Sn$. Calculated, %: C 54.70; H 9.18.

4-Methyl-6-[(1*E*,3*E*)-2-methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)buta-1,3-dien-1-yl]-5,6-dihydro-2*H*-pyran-2-one (XIII). Sodium carbonate, 0.8 g, was added to a mixture of 1 g (3 mmol) of alcohol **Xb** in 20 ml of methanol, and the mixture was stirred for 2 h at room temperature, treated with 20 ml of water, and extracted with diethyl ether (3×20 ml). The extracts were combined and dried over $MgSO_4$, the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography using petroleum ether–ethyl acetate (25:1) as eluent to isolate 0.7 g (76%) of compound **XIII** as a bright yellow oily liquid whose spectral parameters were consistent with those reported in [17].

(2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-en-1-yl)nona-2,4,6,8-tetraenoic acid (II, isotretinoin). A solution of 0.4 g (1 mmol) of compound **XIII** in 2 ml of tetrahydrofuran was cooled to 0°C, 0.13 g (1 mmol) of potassium *tert*-butoxide was added under argon, and the mixture was stirred for 1 h. The mixture was then treated with 10 ml of diethyl ether and 2 ml of 1 N hydrochloric acid, the organic phase was separated, the aqueous phase was extracted with diethyl ether (3×10 ml), and the extracts were combined with the organic phase and dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized twice from methanol to obtain 0.32 g (80%) of isotretinoin (**II**) as yellow–orange crystals with mp 171–173°C; published data [21]: mp 171–172°C (from MeOH). The spectral parameters of the product coincided with those reported in [23].

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