The Organoalkali Route to Vitamin A and β-Carotene

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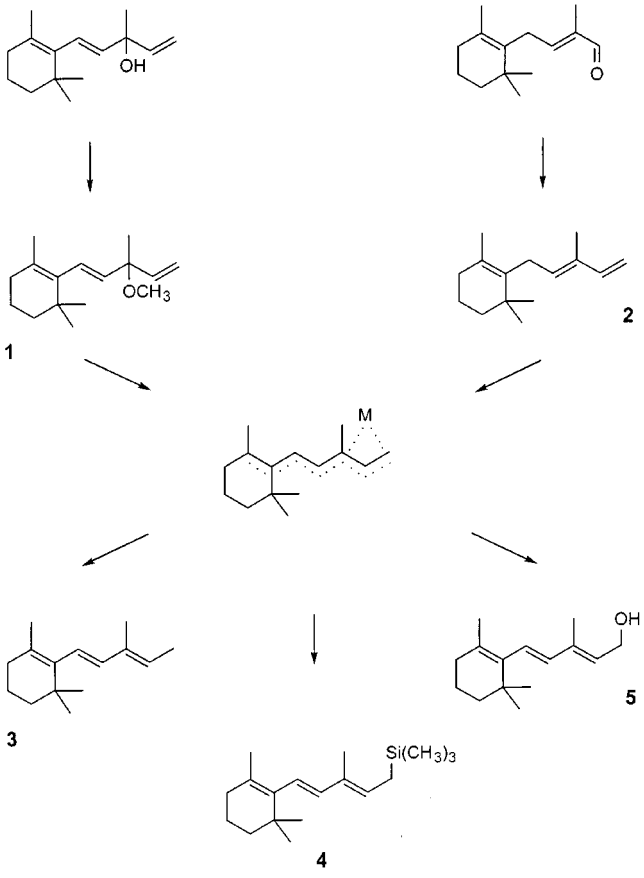
The reductive cleavage of methyl vinyl-β-ionyl ether (**1**) or the deprotonation of 3,2′,6′,6′-tetramethyl-5-(1-cyclohexenyl)-1,3-pentadiene (**2**) gives rise to an organometallic C_{15} species that combines selectively with a variety of electrophiles at the terminal chain position. Its reaction with aldehydes, however, is less clean. In particular, (*E*)-β-formyl-2-butenyl acetate gives the expected adduct **7a** and, after dehydration, vitamin A acetate only in poor yield. The same is true for the analogous reaction with 2,7-dimethyl-2,4,6-octatriendial, which ultimately affords β-carotene. Vitamin A acetate can also be prepared, this time in moderate yield, by functionalization through consecutive deprotonation, borylation, oxidation and acetylation of a C_{20} pentaene hydrocarbon having the required skeleton. Both the C_{15} and the C_{20} organometallic key intermediates adopt spontaneously a zigzag-like outstretched conformation which, upon electrophilic trapping, directly and exclusively leads to the all-(*E*) configuration.

3-Methoxy-3-methyl-1-(2,6,6-trimethyl-1-cyclohexenyl)-1,4-pentadiene (**1**), quantitatively obtained by the treatment of vinyl-β-ionol with sodium hydride and methyl iodide in tetrahydrofuran or with dimethyl sulfate in the presence of sodium hydroxide under phase-transfer conditions, is readily cleaved by lithium metal or sodium/potassium alloy. The resulting heptatrienyl-type organometallic C_{15} entity[1−3] can be trapped by standard electrophiles to afford, for example, the hydrocarbon **3**, the silane **4** or the alcohol **5**. As we have found more recently, the same C_{15} species can be generated conveniently by the deprotonation of 3-methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-1,3-pentadiene (**2**) with *sec*-butyllithium or the superbasic mixture of butyllithium and potassium *tert*-butoxide. The required triene is easily prepared by a Wittig olefination of (*E*)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexenyl)-2-butenal,[4−5] the key building block in the Isler/Hoffmann-LaRoche syntheses of vitamin A[5−7] and β-carotene.[7−8]

(*E*)-3-Formyl-2-butenyl acetate is, along with vinyl-β-ionol, the major component of the Pommer/BASF route[9−10] to vitamin A. When this aldehyde was allowed to react with the organometallic C_{15} species, regardless of



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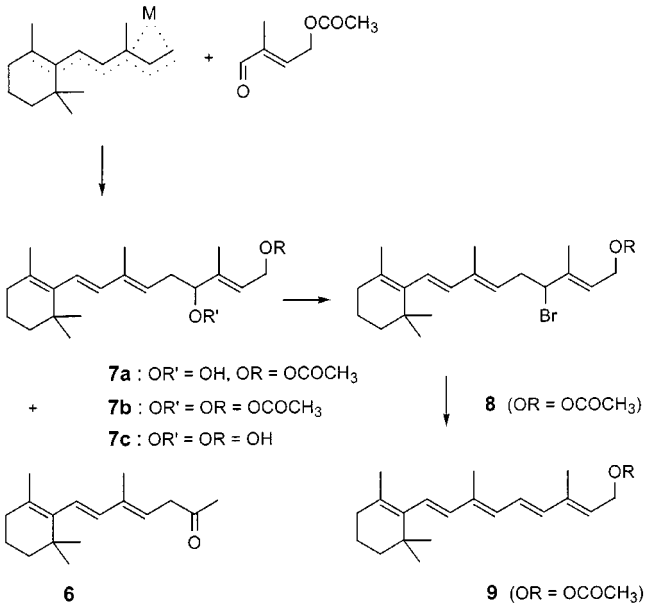
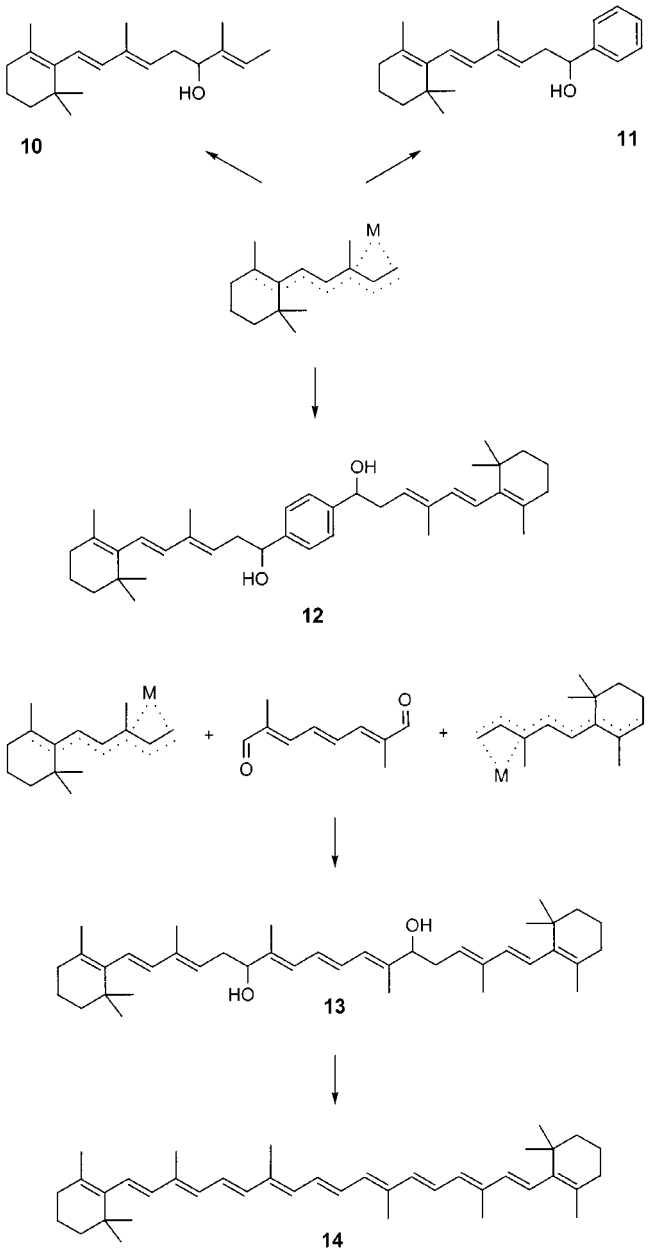
whether it was generated from the ether **1** or the triene **2**, the adduct **7a** was indeed obtained, although only in poor yield (around 30%). Substantial amounts (20−25%) of the ketone **6** and the hydrocarbon **3** invariably formed as by-products. Obviously, the organometallic intermediate does not discriminate sufficiently between the two functional groups of the C_5 electrophile. By attack of the ester function and ensuing acetyl transfer, it forms the β,γ-unsaturated ketone **6**, and by deprotonation of the latter the hydrocarbon **3**. The adduct **7a** can be acetylated to give the diacetate **7b**, hydrolyzed to afford the diol **7c** and, with phosphorus tribromide, it can be converted into the bromoester **8**, which can be dehydrobrominated in situ with 1,5-diazo-5-bicyclo-[4.3.0]nonene to afford vitamin A acetate (**9**, 31%).

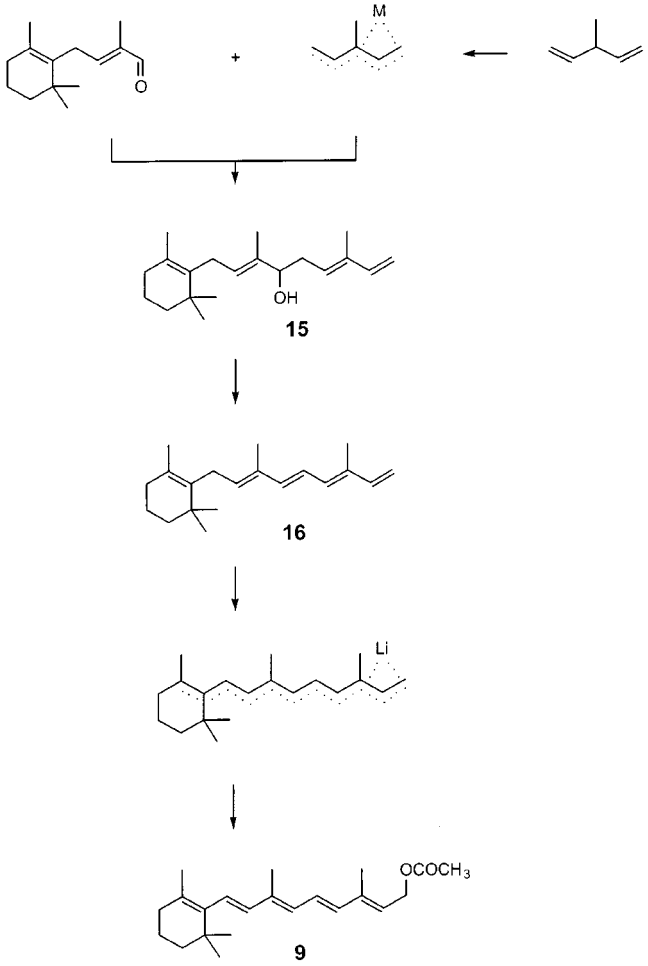


Aldehydes are known to lack regioselectivity when combining with delocalized polar organometallics.[11−12] Presumably for this reason, even simple aldehydes harboring no additional functional groups give only moderate yields. Thus, the adducts **10** and **11** derived from tiglic aldehyde and benzaldehyde are isolated in not more than 57% and 68% yield. The twofold reaction performed with terephthal dehyde affords a still lower yield of the diol **12** (39%). The product is presumably composed of a 1:1 *meso*/*dl* mixture which apparently crystallizes as a molecular compound, as evidenced by a narrow melting range (mp 35−37 °C).

Despite the discouraging yield encountered with terephthaldehyde, our organometallic C_{15} building block was allowed to react with another difunctional electrophile. The addition to (2*E*,4*E*,6*E*)-2,7-dimethyl-2,4,6-octatrienedial afforded the diol **13** (39%). Dehydration of the latter using Burgess' reagent [(methoxycarbonylsulfamoyl)triethylammonium hydroxide][13] afforded β-carotene (**14**) in 32% yield (relative to the dialdehyde).



The C_{20} backbone of vitamin A can be assembled by connecting C_{15} + C_5 modules ("Pommer pattern") or C_{14} + C_6 modules ("Isler pattern"). To elaborate an organoalkali version of the second option too, we have first combined the organometallic C_6 unit[12,14,15] generated from 3-methyl-1,4-pentadiene with butyllithium, in the presence or absence of potassium *tert*-butoxide, with the C_{14} aldehyde mentioned above. Burgess dehydration[13] of the resulting C_{20} alcohol **15** (84%) gave the pentaene **16** (81%). The latter was converted into pure all-*trans* vitamin A acetate (**9**; 41%) by the consecutive treatment with lithium diisopropylamide, fluorodimethoxyborane, hydrogen peroxide and acetic acid anhydride. No trace of stereoisomers was detected by chromatography.



The new routes leading to vitamin A and β-carotene are compromised by moderate or even poor yields. For this reason, they have little chance of competing with optimized industrial processes. Although some critical steps could be improved significantly, the disappointing regioselectivity of the delocalized polar organometallic species towards aldehydes will always remain a serious handicap that is tough to control or to compensate for. Regiochemical unreliability is a problem that only afflicts reactions driven by an electron flow from charge-excess to slightly electrophilic centers. In contrast, only the terminal positions are linked together when olefins become attached to delocalized cations, for example to the carbenium-oxonium ions acting as the key intermediates in enamine condensations of the Müller-Cunradi and Pieroh type,[16−20] or their modern dienether extensions.[21−24]

The singular and most fascinating feature of polar pentadienyl-, heptatrienyl- and nonatetraenylmetal compounds is their stereochemical behavior. Whereas pentadienylpotassium and 2,4-dialkyl-substituted congeners coil up in tetrahydrofuran solution to form a U-shaped (horseshoe-like) open-sandwich structure, pentadienyllithiums and -potassiums carrying branching alkyl groups at the anti-nodal positions exhibit a marked tendency to adopt a W-shaped (zigzag-like) structure, with a maximally outstretched geometry.[2,15] This gives rise to all-(*E*) configurations upon electrophilic trapping.

The heptatrienyl type C_{15} and the undecapentadienyl type C_{20} species clearly follow this trend and favor the zigzag-like outstretched conformation. After electrophilic interception, the all-(*E*) isomers were found exclusively. Thus, these organometallic intermediates offer effortless and spontaneous stereoselectivity.

Experimental Section

General: For standard procedures and abbreviations, see an earlier publication from this laboratory.[25] ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, all samples being dissolved in deuterochloroform. The DEPT[26] sequence was employed to corroborate critical structure assignments.

2-[(1*E*)-3-Methoxy-3-methyl-1,4-pentadienyl]-1,3,3-trimethylcyclohexene (1): (*E*)-3-methyl-1-(2,6,6-trimethyl-1-cyclohexenyl)-1,4-pentadien-3-ol[27−29] (26 mL, 22 g, 0.10 mol) in tetrahydrofuran (25 mL) was added dropwise, in the course of 15 min., to a suspension of sodium hydride (7.2 g, 0.30 mol) in tetrahydrofuran (25 mL) containing methyl iodide (9.4 mL, 21 g, 0.15 mol) with vigorous stirring. As soon as the gas evolution had ceased the mixture was heated under reflux (≈75 °C) for 1 h. Upon distillation a colorless liquid was collected; bp 143−145 °C/8 Torr; n_D^{20} = 1.4901; yield 22.1 g (94%). − ^{1}H NMR: δ = 6.04 (d, *J* = 16.4 Hz, 1 H), 5.91 (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.42 (d, *J* = 16.3, 1 H), 5.23 (d, *J* = 17.6, 1 H), 5.17 (d, *J* = 10.8 Hz, 1 H), 3.24 (s, 3 H), 1.98 (t, *J* = 6.1 Hz, 2 H), 1.68 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.40 (s, 3 H), 1.00 (s, 3 H). − ^{13}C NMR: δ = 142.1 (CH), 137.2 (C), 136.5 (CH), 128.2 (CH), 128.0 (C), 114.2 (CH_2), 78.2 (C), 50.8 (CH_3), 39.4 (CH_3), 33.9 (C), 32.5 (CH_2), 28.8 (CH_3), 23.8 (CH_3), 21.4 (CH_3), 19.2 (CH_2). − MS: *m*/*z* (%) = 234 (56), [M$^+$], 219 (29), 203 (65), 133 (43), 119 (100), 105 (83), 85 (34). − $C_{16}H_{26}O$ (234.38): calcd. C 81.99, H 11.18; found C 82.05, H 11.08.

1,3,3-Trimethyl-2-[(2*E*)-3-methyl-2,4-pentadienyl]cyclohexene (2): The "instant ylide"[30−31] mixture of methyltriphenylphosphonium bromide (89 g, 0.25 mol) and sodium amide (9.8 g, 0.25 mol) was suspended in diethyl ether (0.15 L). After 45 min. of vigorous stirring, (*E*)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexenyl)-2-butenal[4−5] (57 mL, 52 g, 0.25 mol) was added. After a further 45 min. the mixture was poured into ice-cold hexanes (0.50 L). The solution was decanted from the pasty precipitate and filtered through kieselguhr (diatomite). Distillation gave a colorless liquid; bp 90−92 °C/1 Torr (ref.:[32] bp 60−62 °C/0.1 Torr); n_D^{20} = 1.5141; yield 44.0 g (87%). − ^{1}H NMR: δ = 6.37 (dd, *J* = 17.5, 10.9 Hz, 1 H), 5.35 (t, *J* = 6.6 Hz, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 4.91 (d, *J* = 10.9 Hz, 1 H), 2.86 (d, *J* = 6.5 Hz, 2 H), 1.94 (t, *J* = 6.2 Hz, 2 H), 1.79 (s, 3 H), 1.66 (m, 2 H), 1.55 (s, 3 H), 1.4 (m, 2 H), 0.98 (s, 6 H). − ^{13}C NMR: δ = 141.6 (CH), 136.1 (C), 134.4 (CH), 132.5 (C), 128.1 (C), 109.8 (CH_2), 39.7 (CH_2), 34.5 (C), 32.8 (CH_2), 28.2 (CH_3), 27.5 (CH_2), 19.7 (CH_3), 19.5 (CH_2), 11.7 (CH_3). − MS: *m*/*z* (%) = 204 (12) [M$^+$], 133 (41), 119 (100), 105 (75), 93 (79), 81 (63).

1,3,3-Trimethyl-2-[(1*E*,3*E*)-3-methyl-1,3-pentadienyl]cyclohexene (3): Butyllithium (25 mmol) in hexanes (20 mL) and (*E*)-3-methyl-

5-(2,6,6-trimethyl-1-cyclohexenyl)-1,3-pentadiene (**2**; 5.4 mL, 5.1 g, 25 mmol) were added consecutively to a suspension of potassium *tert*-butoxide (2.8 g, 25 mmol) in hexanes (25 mL). After 1 h of vigorous stirring at 25 °C, the solvent was stripped off and replaced by precooled (−75 °C) tetrahydrofuran (50 mL). The red solution was then immediately treated with a precooled (−75 °C) solution of hydrogen chloride (25 mmol) in diethyl ether (10 mL). The mixture was absorbed on silica gel (10 mL) and the powder, when dry, poured on top of a column filled with more silica gel (0.25 L). Elution with a 1:4 (v/v) mixture of diethyl ether and hexane, followed by distillation, afforded a colorless liquid; bp 90−91 °C/0.5 Torr (ref.:[33] bp 70−75 °C/0.1 Torr); n_D^{20} = 1.4611; yield 3.7 g (73%). − ^{1}H NMR: δ = 6.03 (d, *J* = 16.6 Hz, 1 H), 5.98 (d, *J* = 16.6 Hz, 1 H), 5.51 (q, *J* = 7.0 Hz, 1 H), 2.01 (t, *J* = 8.8 Hz, 2 H), 1.80 (s, 3 H), 1.77 (d, *J* = 7.0 Hz, 3 H), 1.70 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.03 (s, 6 H). − ^{13}C NMR: δ = 137.9 (C), 137.9 (CH), 134.9 (C), 128.2 (C), 125.3 (CH), 124.0, CH), 39.7 (CH_2), 34.4 (C), 33.1 (CH_2), 29.1 (CH_3), 21.6 (CH_3), 19.4 (CH_2), 13.8 (CH_3), 11.9 (CH_3). − MS: *m*/*z* (%) = 204 (16) [M^+ + H], 204 (13) [M^+], 189 (9), 133 (44), 119 (100).

[(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-2,4-pentadienyl]trimethylsilane (4): An analogous reaction was quenched with chlorotrimethylsilane (3.2 mL, 2.7 g, 25 mmol) to give a colorless liquid; bp 114−115 °C/0.1 Torr (ref.:[34] bp 110 °C/0.4 Torr); n_D^{20} = 1.5617; yield 4.9 g (71%). − ^{1}H NMR: δ = 6.04 (d, *J* = 16.3 Hz, 1 H), 5.89 (d, *J* = 16.3 Hz, 1 H), 5.49 (t, *J* = 8.9 Hz, 1 H), 2.01 (t, *J* = 6.6 Hz, 2 H), 1.74 (s, 3 H), 1.71 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.03 (s, 6 H), 0.02 (s, 9 H). − ^{13}C NMR: δ = 138.3 (CH), 138.0 (C), 131.9 (C). 127.8 (C), 127.5 (CH), 122.5 (CH), 122.1 (CH), 39.5 (CH_2), 34.2 (C), 32.9 (CH_2), 29.3 (CH_3), 21.5 (CH_3), 19.9 (CH_2), 19.3 (CH_2), 12.0 (CH_3), −1.6 (CH_3).

(2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexenyl)-2,4-pentadien-1-ol (5): An analogous reaction, performed as described above (see preparation of hydrocarbon **3**), was terminated by the consecutive addition of fluorodimethoxyborane diethyl etherate[35−36] (7.5 mL, 6.6 g, 40 mmol), 30% aqueous hydrogen peroxide (4.0 mL, 40 mmol) and a 3.0 M aqueous solution (15 mL) of sodium hydroxide (45 mmol). After stirring for 1 h at 25 °C, the product was isolated by chromatography (support: silica gel; eluent: diethyl ether and hexanes in a 2:3 ratio) and distillation as a colorless liquid; bp 132−134 °C/0.1 Torr (ref.:[37] bp 140−145 °C/0.3 Torr); n_D^{20} = 1.4756; yield 3.0 g (54%). − ^{1}H NMR: δ = 6.15 (d, *J* = 16.1 Hz, 1 H), 6.04 (d, *J* = 16.1 Hz, 1 H), 5.63 (t, *J* = 7.0 Hz, 1 H), 4.31 (d, *J* = 7.0 Hz, 2 H), 2.01 (t, *J* = 6.2 Hz, 2 H), 1.86 (s, 3 H), 1.69 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.01 (s, 3 H). − ^{13}C NMR: δ = 137.8 (C), 137.2 (CH), 136.7 (C), 129.0 (C), 128.7 (CH), 126.9 (CH), 59.3 (CH_2), 39.5 (CH_2), 34.2 (C), 32.9 (CH_2), 28.9 (CH_3), 21.7 (CH_3), 19.4 (CH_2), 12.4 (CH_3). − MS: *m*/*z* (%) = 220 (8) [M^+], 203 (7), 159 (5), 133 (16), 119 (100), 105 (38), 91 (21), 77 (11).

NOESY[38] cross peaks between δ = 4.31 and 1.86 and δ = 6.04 and 5.63 corroborated the assigned (*E*,*E*) configuration.

(4*E*,6*E*)-5-Methyl-7-(2,6,6-trimethyl-1-cyclohexenyl)-4,6-heptatrien-2-one (6): An analogous reaction was carried out with acetyl chloride (25 mL, 28 g, 35 mmol; inverse addition). The product was isolated by distillation as a colorless liquid; bp 131−133 °C/1 Torr; yield 4.2 g (68%). − ^{1}H NMR: δ = 6.08 (s, 2 H), 5.63 (t, *J* = 7.0 Hz, 1 H), 3.33 (d, *J* = 7.0 Hz, 2 H), 2.10 (s, 3 H), 1.7 (m, 12 H), 1.00 (s, 6 H). − MS: *m*/*z* (%) = 146 [M^+], 43 (100). − $C_{17}H_{26}O$ (246.39): calcd. C 82.87, H 10.64; found C 82.94, H 10.99.

(2*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatriene-1,4-diyl Diacetate (7b): At −75 °C, a 0.5 M solution of biphenyl/lithium (1:1) adduct (hydrobiphenylyllithium, 50 mmol) in tetrahydrofuran (0.10 L) was added dropwise to ether **1** (5.8 g, 25 mmol) in tetrahydrofuran (25 mL). At the end of the addition the bluish-green color persisted, but disappeared as soon as the solution was treated, still at −75 °C, with (*E*)-4-acetoxy-2-methyl-2-butenal[39−43] (3.3 mL, 3.6 g, 15 mmol) and, 15 min. later, with acetic acid anhydride (4.7 mL, 5.1 g, 50 mmol). Chromatography on thoroughly degassed (ultrasound!) and nitrogen-saturated silica gel (0.30 L) in the dark, using degassed eluents with progressively increasing polarity (diethyl ether/hexanes mixture varying from 0:1 over 1:4 to 1:2) enabled the isolation, along with other products (e.g., 31% of hydrocarbon **3**), of the diacetate **7b** as a yellowish liquid; m.p. −34 to −32 °C; n_D^{20} = 1.5651; yield 3.1 g (32%). − ^{1}H NMR: δ = 6.03 (d, *J* = 16.4 Hz, 1 H), 5.98 (d, *J* = 16.4 Hz, 1 H), 5.59 (t, *J* = 6.9 Hz, 1 H), 5.28 (t, *J* = 7.2 Hz, 1 H), 5.19 (t, *J* = 6.6 Hz, 1 H), 4.62 (d, *J* = 6.9 Hz, 2 H), 2.55 (dt, *J* = 15.1, 7.2 Hz, 1 H), 2.46 (dt, *J* = 15.1, 6.6 Hz, 1 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.99 (t, *J* = 6.2 Hz, 2 H), 1.78 (s, 3 H), 1.71 (s, 3 H), 1.67 (s, 3 H), 1.6 (m, 2 H), 1.4 (m, 2 H), 1.01 (s, 6 H). − ^{13}C NMR: δ = 170.8 (C), 170.0 (C), 138.4 (C), 137.7 (C), 137.4 (CH), 136.4 (C), 128.5 (C), 125.1 (CH), 124.5 (CH), 121.4 (CH), 77.5 (CH), 60.6 (CH_2), 39.4 (CH_2), 34.0 (C), 32.7 (CH_2), 31.7 (CH_2), 28.7 (CH_3), 21.6 (CH_3), 21.1 (CH_3), 20.9 (CH_3), 19.2 (CH_2), 12.6 (CH_3), 12.3 (CH_3). − MS: *m*/*z* (%) = 388 (2) [M^+], 328 (23), 253 (27), 203 (52), 119 (100), 105 (87), 83 (53). − $C_{24}H_{36}O_4$ (388.54): calcd. C 74.19, H 9.34; found C 74.12, H 9.50.

Virtually the same result was found when the organometallic C_{15} intermediate was generated from the triene **2** (25 mmol) by reaction with butyllithium activated with potassium *tert*-butoxide (as described for the preparation of the hydrocarbon **3**) rather than by the biphenyl/lithium-promoted reductive cleavage of ether **1** (see above).

(2*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatriene-1,4-diol (7c): A reaction mixture was prepared in the same way as above but, after the addition of acetic acid anhydride, it was treated with ammonium dihydrogen phosphate (25 g, 0.21 mol) in water (50 mL) for 1 h at 25 °C and then with sodium hydrogen sulfite (5.0 g, 48 mmol) for 15 min. The organic layer obtained after extraction under nitrogen with diethyl ether (3 × 25 mL) and washing with brine (3 × 25 mL), was concentrated and submitted to chromatography on degassed silica gel (0.25 L) applying a hexanes → diethyl ether gradient for the elution. The products were collected in this order: hydrocarbon **3** (1.0 g, 20%), biphenyl (7.7 g, 98%), (4*E*,6*E*)-5-methyl-7-(2,6,6-trimethyl-1-cyclohexenyl)-4,6-heptadien-2-one (**6**, see above; 1.4 g, 22%) and diol (**6c**; 2.1 g, 28%). The latter product, a yellow oil, was purified by crystallization from pentane; m.p. 69.0−71.5 °C; yield 2.0 g (26%). − ^{1}H NMR: δ = 6.05 (s, 2 H), 5.68 (t, *J* = 7.0 Hz, 1 H), 5.35 (t, *J* = 7.5 Hz, 1 H), 4.17 (d, *J* = 7.0 Hz, 2 H), 4.06 (t, *J* = 7.0 Hz, 1 H), 3.05 (s, 1 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 1.8 (m, 15 H), 1.0 (s, 6 H). − MS: *m*/*z* (%) = 304 (2) [M^+], 66 (100). − $C_{20}H_{32}O_2$ (304.47): calcd. C 79.90, H 10.59; found C 79.11, H 10.66.

(2*E*,6*E*,8*E*)-4-Hydroxy-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatriene Acetate (7a): The reaction was repeated as described above (see the preparation of diacetate **7b**) but, after the addition of the aldehyde, the mixture was treated with acetic acid (2.9 mL, 3.1 g, 50 mmol) rather than with its anhydride. Elution from silica gel with a 1:4 (v/v) mixture of diethyl ether and hexanes afforded an almost colorless oil; m.p. −27 to −25 °C; yield 2.4 g (28%). − ^{1}H NMR: δ = 6.04 (s, 2 H), 5.63 (t, *J* = 6.9 Hz, 1 H), 5.39 (t, *J* = 7.2 Hz, 1 H), 4.65 (d, *J* = 6.9 Hz, 2 H), 4.12 (t, *J* = 6.3 Hz, 1 H), 2.44 (t, *J* = 6.9 Hz, 2 H), 2.06 (s, 3 H), 2.00 (t,

J = 6.3 Hz, 2 H), 1.82 (s, 3 H), 1.79 (s, 3 H), 1.69 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.01 (s, 6 H). − ^{13}C NMR: δ = 170.9 (C), 142.6 (C), 137.6 (C), 137.4 (CH), 136.4 (C), 128.3 (C), 125.9 (CH), 124.9 (CH), 119.3 (CH), 75.9 (CH), 60.7 (CH_2), 39.3 (CH_2), 34.0 (CH_2), 33.9 (C), 32.7 (CH_2), 28.6 (CH_3), 21.4 (CH_3), 20.7 (CH_3), 19.0 (CH_2), 12.2 (CH_3), 12.1 (CH_3). − MS: m/z (%) = 304 (5) [M^+], 203 (58), 119 (100), 105 (78), 83 (68). − $C_{22}H_{34}O_3$ (346.51): calcd. C 76.26, H 9.89; found C 75.62, H 9.92.

(2*E*,6*E*,8*E*)-4-Bromo-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrienyl acetate (8): At −75 °C, phosphorus tribromide (0.95 mL, 2.7 g, 10 mmol) was added to a solution of the hydroxyacetate **7a** (3.5 g, 10 mmol) in dichloromethane (20 mL). The mixture was allowed to warm to 25 °C before it was poured onto ice (25 g). The organic layer was decanted, washed with brine (25 mL), dried and the solvents were evaporated. The dark-green residue (3.2 g, crude) proved to be too unstable to be purified.

(2*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,4,6,8-nonatetraenyl Acetate (vitamin A acetate, 9): At −75 °C, 1,5-diaza-5-bicyclo[4.3.0]nonene ("DBN", 2.4 mL, 2.5 g, 20 mmol) was added to a solution of the crude bromo compound **8** (see above) dissolved in hexanes (50 mL). After 6 h at 25 °C, the mixture was absorbed on degassed alumina (0.35 L, Brockmann activity I) and eluted in the dark with diethyl ether and hexanes in a volume ratio of 1:9. The yellowish oil obtained was crystallized from pentanes; colorless needles; m.p. 54−56 °C (ref.:[6,44] m.p. 57−58 °C); yield 1.0 g (31%). − ^{1}H NMR: δ = 6.65 (dd, J = 15.1, 11.4 Hz, 1 H), 6.29 (d, J = 15.1 Hz, 1 H), 6.19 (d, J = 15.8 Hz, 1 H), 6.13 (d, J = 15.8 Hz, 1 H), 6.09 (d, J = 11.4 Hz, 1 H), 5.62 (t, J = 7.3 Hz, 1 H), 4.74 (d, J = 7.3 Hz, 2 H), 2.08 (s, 3 H), 2.02 (t, J = 6.2 Hz, 2 H), 1.97 (s, 3 H), 1.90 (s, 3 H), 1.72 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.03 (s, 6 H). − ^{13}C NMR: δ = 171.3 (C), 139.2 (CH), 137.7 (C), 137.5 (CH, 136.5 (CH), 135.7 (C), 129.3 (C), 127.0 (CH), 125.8 (C), 124.4 (CH), 61.3 (CH_2), 39.6 (CH_2), 34.2 (C), 33.1 (CH_2), 29.0 (CH_3), 21.6 (CH_2), 21.0 (CH_3), 19.2 (CH_2), 12.6 (CH_3). − MS: m/z (%) = 328 (65) [M^+], 269 (100), 253 (53), 119 (36), 105 (51), 91 (45).

(2*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrien-4-ol (10): The triene **2** (5.4 mL, 5.1 g, 25 mmol) was treated with butyllithium in the presence of potassium *tert*-butoxide as described previously (see the preparation of the hydrocarbon **3**). (*E*)-2-Methyl-2-butenal (tiglic aldehyde; 2.4 mL, 2.1 g, 25 mmol) was added to the solution of the organometallic intermediate in neat tetrahydrofuran (50 mL) cooled to −75 °C. After warming to 25 °C, the reaction mixture was neutralized with a saturated aqueous solution of ammonium chloride (50 mL) and exhaustively extracted with diethyl ether (5 × 20 mL). The combined organic layers were dried, concentrated and absorbed on silica gel (50 mL). When dry, the powder was poured on top of a column filled with more silica gel (0.30 L) and eluted with a 2:3 (v/v) mixture of diethyl ether and hexanes to collect a yellowish oil; m.p. −38 to −36 °C; n_D^{20} = 1.5153; yield 4.1 g (57%). − ^{1}H NMR: δ = 6.03 (s, 1 H), 5.53 (q, J = 6.9 Hz, 1 H), 5.39 (dd, J = 7.4, 6.3 Hz, 1 H), 4.08 (dd, J = 7.4, 6.3 Hz, 1 H), 2.47 (dt, J = 15.1, 7.4 Hz, 1 H), 2.38 (dt, J = 15.1, 6.3 Hz, 1 H), 2.01 (t, J = 6.3 Hz, 2 H), 1.83 (s, 3 H), 1.69 (s, 3 H), 1.69 (s, 3 H), 1.66 (d, J = 6.9 Hz, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.02 (s, 6 H). − ^{13}C NMR: δ = 137.6 (C), 137.5 (CH), 137.4 (C), 136.3 (C), 128.3 (C), 127.0 (CH), 125.7 (CH), 120.7 (CH), 77.1 (CH), 39.7 (CH_2), 34.5 (CH_2), 34.3 (C), 32.9 (CH_2), 28.9 (CH_3), 21.6 (CH_3), 19.4 (CH_2), 13.2 (CH_3), 12.7 (CH_3), 11.4 (CH_3). − MS: m/z (%) = 271 (6), 204 (62), 189 (15), 147 (14), 133 (37), 119 (100), 105 (60), 91 (33), 85 (57). − $C_{20}H_{32}O$ (288.47): calcd. C 83.27, H 11.18; found C 83.70, H 11.17.

(3*E*,5*E*)-4-Methyl-1-phenyl-6-(2,6,6-trimethyl-1-cyclohexenyl)-3,5-hexadien-1-ol (11): This reaction was performed as above but with benzaldehyde (2.5 mL, 2.6 g, 25 mmol) instead of tiglic aldehyde; m.p. −49 to −47 °C; n_D^{20} = 1.4619; yield 5.3 g (68%). − ^{1}H NMR: δ = 7.4 (m, 4 H), 7.3 (m, 1 H), 6.03 (s, 2 H), 5.46 (dd, J = 7.9, 6.6 Hz, 1 H), 4.77 (ddd, J = 7.9, 6.6, 3.3 Hz, 1 H), 2.68 (dt, J = 14.6, 7.9 Hz, 1 H), 2.59 (dt, J = 14.6, 6.6 Hz, 1 H), 2.02 (d, J = 3.3 Hz, 1 H), 2.01 (t, J = 6.2 Hz, 2 H), 1.79 (s, 3 H), 1.70 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.02 (s, 3 H). − ^{13}C NMR: δ = 144.0 (C), 137.6 (C), 137.4 (CH), 136.8 (C), 128.8 (C), 127.3 (CH), 125.9 (CH), 125.6 (CH), 125.1 (CH), 73.9 (CH), 39.4 (CH_2), 38.3 (CH_2), 34.0 (C), 32.6 (CH_2), 28.8 (CH_3), 21.6 (CH_3), 19.3 (CH_2), 12.5 (CH_3). − MS: m/z (%) = 310 (12), 293 (7), 204 (55), 189 (14), 173 (5), 147 (11), 133 (36), 119 (99), 105 (100), 91 (39), 77 (62). − $C_{22}H_{30}O$ (314.48): calcd. C 85.11, H 9.74; found C 85.04, H 9.81.

1,4-Phenylenebis-1,1′-[(3*E*,5*E*)-4-methyl-6-(2,6,6-trimethyl-1-cyclohexenyl)-3,5-hexadien-1-ol] (12): This reaction was performed as above but with terephthaldehyde (1.6 g, 12 mmol) instead of tiglic aldehyde; colorless pillars; m.p. 35−36 °C; yield 3.2 g (49%). − ^{1}H NMR: δ = 7.38 (s, 2 H), 6.04 (s, 2 H), 5.46 (t, J = 7.2 Hz, 1 H), 4.8 (m, 1 H), 2.68 (dt, J = 14.9, 7.2 Hz, 1 H), 2.59 (dt, J = 14.9, 5.9 Hz, 1 H), 2.01 (t, J = 6.0 Hz, 2 H), 1.99 (d, J = 3.4 Hz, 1 H), 1.80 (s, 3 H), 1.69 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.02 (s, 6 H). − ^{13}C NMR: δ = 143.5 (C), 137.5 (C), 137.2 (CH), 137.1 (C), 128.5 (C), 125.9 (CH), 125.8 (CH), 125.4 (CH), 73.9 (CH), 39.6 (CH_2), 38.4 (CH_2), 34.2 (C), 32.6 (CH_3), 28.9 (CH_3), 21.7 (CH_3), 19.3 (CH_2), 12.6 (CH_3). − $C_{38}H_{54}O_2$ (542.84): calcd. C 84.04, H 10.03; found C 83.91, H 9.87.

(1*E*,3*E*,7*E*,9*E*,11*E*,15*E*,17*E*)-3,7,12,16-Tetraamethyl-1,18-bis(2,6,6-trimethyl-1-cyclohexenyl)-1,3,7,9,11,15,17-octadecaheptaene-6,13-diyl diacetate (13): This reaction was performed as above but with (2*E*,4*E*,6*E*)-2,7-dimethyl-2,4,6-octatrienedial[45−47] (2.0 g, 12 mmol) instead of tiglic aldehyde. However, instead of being hydrolyzed, the adduct was treated at −75 °C with acetic acid anhydride (4.7 mL, 5.1 g, 50 mmol). Elution from alumina (0.30 L, Brockmann activity I) with a 2:3 (v/v) mixture of diethyl ether and hexanes afforded a faintly yellowish oil; m.p. −18 to −15 °C; n_D^{20} = 1.5721; yield 3.2 g (41%). − ^{1}H NMR: δ = 6.4 (m, 1 H), 6.1 (m, 1 H), 6.03 (d, J = 16.8 Hz, 1 H), 5.98 (d, J = 16.8 Hz, 1 H), 5.28 (t, J = 6.8 Hz, 1 H), 5.22 (d, J = 6.8 Hz, 1 H), 2.58 (dt, J = 15.2, 7.5 Hz, 1 H), 2.47 (dt, J = 15.2, 6.8 Hz, 1 H), 2.06 (s, 3 H), 1.99 (t, J = 6.0 Hz, 2 H), 1.80 (s, 6 H), 1.68 (s, 3 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.00 (s, 6 H). − $C_{44}H_{64}O_4$ (656.99): calcd. C 80.44, H 9.82; found C 80.51, H 9.91.

all-(*E*)-1,1′-(3,7,12,16-Tetramethyl-1,3,5,7,9,11,13,15,17-octadecanonaene-1,18-diyl)bis(2,6,6-trimethylcyclohexene) [β,β-carotene; 14]: The reaction was performed as described in the preceding paragraph, the only difference being that acetic acid anhydride was replaced by triethyl(methoxycarbonylsulfamoyl)ammonium hydroxide[13] (7.1 g, 30 mmol). After 1 h at 25 °C, the mixture was poured into water (0.25 L) and extracted with hexanes (5 × 25 mL). The combined organic layers were dried and the solvents evaporated. Chromatography (same conditions as above) of the residue in the dark and with strict exclusion of air gave a viscous, dark colored oil that crystallized from a mixture of methanol and hexane as violet platelets; m.p. 184−186 °C (dec.; ref.:[48] m.p. 182.0−182.5 °C); yield 2.3 g (36%). − ^{1}H NMR: δ = 6.6 (m, 2 H), 6.34 (d, J = 14.6 Hz, 1 H), 6.3 (m, 1 H), 6.2 (m, 3 H), 2.04 (t, J = 6.3 Hz, 2 H), 1.73 (s, 3 H), 1.99 (s, 6 H), 1.6 (m, 2 H), 1.5 (m, 2 H), 1.05 (s, 6 H). − ^{13}C NMR: δ = 138.8 (CH), 138.0 (C), 137.3 (CH), 136.4 (C), 136.0 (C), 132.4 (CH), 130.8 (CH), 130.0 (CH), 129.3 (C),

126.7 (CH), 125.1 (CH), 39.8 (CH_2), 34.4 (C), 33.2 (CH_2), 29.0 (CH_3), 21.7 (CH_3), 19.4 (CH_2), 12.8 (CH_3).

(2*E*,6*E*)-3,7-Dimethyl-1-(2,6,6-trimethyl-1-cyclohexenyl)-2,6,8-nonatrien-4-ol (15): Potassium *tert*-butoxide (11 g, 0.10 mol) was added to a solution of butyllithium (0.10 mol) and 3-methyl-1,4-pentadiene (12 mL, 8.2 g, 0.10 mol) in hexanes (0.20 L) at 0 °C. The suspension was stirred vigorously for 45 min. The solvent was stripped off under reduced pressure and replaced by precooled (−75 °C) tetrahydrofuran (0.25 L). (*E*)-2-Methyl-4-(2,6,6-trimethyl-1-cyclohexenyl)-2-butenal (22 mL, 21 g, 0.10 mol) was added dropwise in the course of 5 min. After 15 min. at −75 °C, the mixture was allowed to reach 25 °C before being poured into a saturated aqueous solution (0.25 L) of ammonium chloride. The product was extracted with diethyl ether (3 × 0.10 L) and absorbed on silica gel (50 mL). When dry, the powder was added to a column filled with more silica (0.50 L) and eluted with a 1:4 (v/v) mixture of diethyl ether and hexane to afford a colorless, viscous oil; m.p. −41 to −38 °C; bp 168−170 °C/0.1 Torr; yield 24 g (84%). − ^{1}H NMR: δ = 6.34 (d, *J* = 17.5, 10.7 Hz, 1 H), 5.42 (t, *J* = 7.4 Hz, 1 H), 5.26 (t, *J* = 7.3 Hz, 1 H), 5.11 (d, *J* = 17.5 Hz, 1 H), 4.95 (d, *J* = 10.7 Hz, 1 H), 4.07 (t, *J* = 6.8 Hz, 1 H), 2.73 (d, *J* = 6.2 Hz, 2 H), 2.5 (m, 1 H), 2.4 (m, 1 H), 1.93 (t, *J* = 6.2 Hz, 2 H), 1.77 (s, 3 H), 1.68 (s, 3 H), 1.6 (m, 2 H), 1.53 (s, 3 H), 1.4 (m, 2 H), 0.98 (s, 3 H), 0.96 (s, 3 H). − ^{13}C NMR: δ = 141.1 (CH), 136.3 (C), 135.8 (C), 134.8 (C), 128.6 (CH), 128.3 (CH), 127.8 (C), 110.9 (CH_2), 77.3 (CH), 39.1 (CH_2), 34.2 (C), 33.5 (CH_2), 32.3 (CH_2), 27.8 (CH_3), 27.7 (CH_3), 26.4 (CH_2), 19.4 (CH_3), 19.2 (CH_2), 11.8 (CH_3), 11.3 (CH_3). − MS: *m*/*z* (%) = 288 (1) [M^+], 271 (7), 207 (37), 189 (22), 163 (10), 119 (89), 95 (83), 81 (100). − $C_{20}H_{32}O$ (288.47): calcd. C 83.27, H 11.18; found C 82.93, H 10.82.

1,3,3-Trimethyl-2-[(2*E*,4*E*,6*E*)-3,7-dimethyl-2,4,6,8-nonatetraenyl]cyclohexene (16): A solution of the alcohol **15** (15 mL, 14 g, 50 mmol) in tetrahydrofuran (50 mL) was added dropwise, in the course of 15 min., to a solution of triethyl(methoxycarbonylsulfamoyl)ammonium hydroxide[13] (13 g, 55 mmol) in tetrahydrofuran (0.10 L). After 15 min. at 25 °C, the mixture was poured into water (0.25 L). The product was extracted with diethyl ether (3 × 50 mL) before being purified by chromatography on alumina (0.50 L, Brockmann grade I), with pentane as the eluent, and distillation to afford a viscous colorless oil; m.p. −8 to −6 °C; bp 138−139 °C/0.1 Torr; yield 10.4 g (81%). − ^{1}H NMR: δ = 6.44 (dd, *J* = 15.1, 11.1 Hz, 1 H), 6.43 (dd, *J* = 17.2, 10.6 Hz, 1 H), 6.30 (d, *J* = 15.1 Hz, 1 H), 6.11 (d, *J* = 11.1 Hz, 1 H), 5.39 (t, *J* = 6.8 Hz, 1 H), 5.18 (d, *J* = 17.2 Hz, 1 H), 5.03 (d, *J* = 10.6 Hz, 1 H), 2.86 (d, *J* = 6.8 Hz, 2 H), 1.95 (t, *J* = 6.4 Hz, 2 H), 1.89 (s, 3 H), 1.85 (s, 3 H), 1.6 (m, 2 H), 1.53 (s, 3 H), 1.4 (m, 2 H), 0.97 (s, 6 H). − ^{13}C NMR: δ = 141.3 (CH), 138.7 (CH), 136.0 (C), 135.2 (CH), 134.0 (C), 132.6 (C), 132.0 (CH), 128.0 (C), 121.9 (CH), 111.5 (CH_2), 39.7 (CH_2), 34.9 C), 32.8 (CH_2), 28.2 (CH_3), 27.8 (CH_2), 19.7 (CH_2), 19.5 (CH_2), 12.5 (CH_3), 12.0 (CH_3). − MS: *m*/*z* (%) = 271 (100) [M^+ + H], 255 (27), 133 (44), 119 (72), 105 (51), 91 (50), 81 (28). − $C_{20}H_{30}$ (270.46): calcd. C 88.82, H 11.18; found C 88.62, H 11.27.

Vitamin A Acetate (9): At −75 °C, diisopropylamine (3.5 mL, 2.5 g, 25 mmol), hexamethylphosphoric triamide (10 mL) and triene **16** (6.1 g, 25 mmol) were added consecutively to butyllithium (25 mmol) in tetrahydrofuran (0.10 L) and hexanes (20 mL). After 15 h at −75 °C, the mixture was treated with fluorodimethoxyborane diethyl etherate[35−36] (7.5 mL, 6.6 g, 40 mmol) and, 5 min. later, with a 30% aqueous solution (8.0 mL) of hydrogen peroxide (80 mmol) followed by a 3.0 M aqueous solution (30 mL) of sodium hydroxide (90 mmol). The mixture was stirred vigorously for 2 h at 25 °C before being saturated with sodium chloride. The organic layer was then decanted and the solvents evaporated. The residue was dissolved in dichloromethane (50 mL) and pyridine (50 mL), treated with acetyl chloride (3.6 mL, 3.9 g, 50 mmol) and kept 3 h at 25 °C. The mixture was poured into ice-water (0.10 kg), the organic phase was decanted and the aqueous phase extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (2 × 25 mL), concentrated and eluted in the dark from degassed alumina (0.30 L, Brockmann grade I) with diethyl ether/hexanes in the volume ratio of 1:9. The product, a slightly yellowish oil, became colorless upon crystallization from pentanes at −20 °C and exhibited the same physical and spectral properties as specified above; yield 3.4 g (41%).

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