13,16-Dichloro-5,6,11,18-tetrahydro-5,18:6,11-di-*o*-benzenotrinaphthylene (22). Diene **13** (2.5 mmol) and endoxide **21** (2.5 mmol) were allowed to react in the same manner as in the preparation of **18** to give 1.42 g (91%) of cycloadduct **23** as a white solid: mp 360-361 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, 2 H), 2.31 (br d, 2 H), 4.40 (d, 2 H), 5.29 (s, 2 H), 5.49 (s, 2 H), 6.90 (s, 2 H), 6.98 (m, 4 H) 7.09 (m, 4 H), 7.21 (m, 4 H), 7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 45.61; 48.55, 49.29, 83.06, 123.15, 124.11, 124.46, 126.14, 126.19, 126.57, 126.95, 129.00, 131.13, 141.04, 142.39, 143.95, 145.49; mass spectrum, *m/e* (relative intensity) 620 (0.3), 618 (0.9), 431 (3), 186 (10), 178 (100), 86 (16), 84 (26). Anal. Calcd for $C_{42}H_{28}Cl_2O$: C, 81.42; H, 4.55. Found: C, 81.44; H, 4.53.

Adduct **23** (0.62 g, 1 mmol) was dehydrated in the same manner as **18** to give 0.46 g (76%) of **24** as a pale yellow solid: mp 340-342 °C; ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 2 H), 5.20 (s, 2 H), 5.47 (s, 2 H), 6.89 (m, 4 H), 7.15 (m, 8 H), 7.36 (s, 2 H), 7.45 (m, 4 H), 8.27 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 46.6 (2 peaks overlapped), 49.0, 120.5, 123.3, 124.1, 124.7, 126.0, 126.1, 126.4, 126.9, 127.0, 130.4, 131.3, 140.9, 141.4, 142.6, 142.8, 144.3, 146.0; mass spectrum, *m/e* (relative intensity) 603 (2), 602 (6), 601 (6), 600 (18), 598 (15), 422 (20), 179 (27), 178 (100); high-resolution mass spectrum calcd for $C_{42}H_{26}Cl_2$ 601.5817, found 601.5695.

Dehydrogenation of **24** (0.60 g, 1 mmol) with DDQ in 75 mL of benzene was accomplished as for **19** to give 0.57 g (95%) of **22** as a bluish-yellow solid: mp 380-382 °C; ^{1}H NMR ($CDCl_3$) δ 6.29 (s, 2 H), 6.40 (s 2 H), 6.97 (m, 8 H), 7.39 (s, 2 H), 7.51 (m, 4 H), 7.53 (m, 4 H), 9.26 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 50.72, 51.64, 120.00, 124.06, 124.32, 125.03, 125.72, 127.05, 129.20, 131.66, 140.63, 141.49, 145.95, 146.33; mass spectrum, *m/e* (relative intensity) 602 (3), 601 (10), 600 (40), 598 (48), 422 (16), 420 (26), 264 (18), 262 (14), 178 (46), 44 (100). Anal. Calcd for $C_{42}H_{24}Cl_2$: C, 84.14; H, 4.03. Found: C, 84.22; H, 4.11.

(12) The two isomers were readily distinguished by the fact that the two bridgehead protons in **21** were identical (δ 5.86-5.87) whereas in the 5,6-isomer they were different (δ 5.72, 5.85). Also, the aryl protons in **21** appeared as a sharp singlet (δ 6.82). Finally, the ^{13}C NMR spectrum of **21** showed only five peaks, as required for the C_s symmetry.

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Synthesis of New Aromatic Retinoid Analogues by Low-Valent Titanium Induced Reductive Elimination

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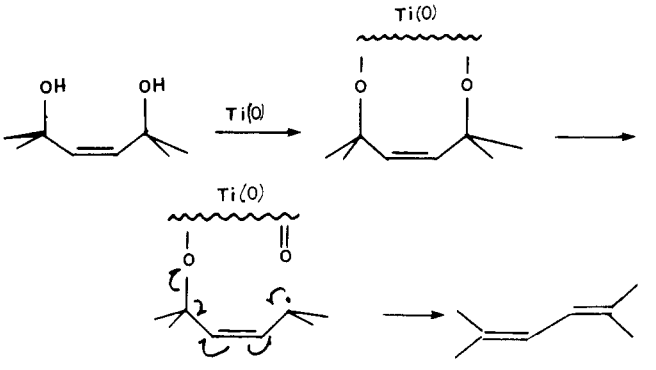
The low-valent titanium reductive elimination reaction, already applied to the stereospecific synthesis of vitamin A and 13-*cis*-retinol, was used to prepare several retinoic acid analogues in the all-trans configuration or in the 13-cis configuration. This highly stereospecific trans-diene formation allowed an improved synthesis of the title compounds without any purification of the intermediates before the final stage.

all-trans-Retinoic acid and its 13-cis isomer are used for the treatment of dermatological diseases such as acne and have been evaluated[1-6] for their possible beneficial effects in several cancerous conditions.[7-9] Unfortunately, their severe biological side effects (hypervitaminosis A syndrome, etc.) render their extensive clinical use difficult.

In an effort to obviate these drawbacks, many new analogues have been prepared.[10-12] Among these new molecules, aromatic analogues were shown to be interesting targets. However, a very small number contains a chroman unit.[11,12] With the hope of finding a less toxic retinoid we have synthesized some new chroman analogues with the low-valent titanium reductive elimination.

Low-valent titanium reductive elimination first used by Walborsky[13] to prepare 1,3-dienes from 2-ene-1,4-diols was



(1) Mayer, H.; Bollag, W.; Hanni, R.; Ruegg, R. *Experientia* **1978**, *34*, 1105.
(2) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W. R.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583.
(3) Dawson, M. I.; Hobbs, P. D.; Chan, R. L. S.; Chao, W. R. *J. Med. Chem.* **1981**, *24*, 1214.
(4) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *25*, 1269.
(5) Lowe, N. J. *J. Am. Acad. Dermatology* **1986**, *15*, 766.
(6) Cunliffe, W. J. *Biochem. Soc. Trans.* **1986**, *14*, 943.
(7) Lotan, R.; Neumann, G.; Lotan, D. *Cancer Res.* **1980**, *40*, 1097.
(8) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413.
(9) Dawson, M. I.; Hobbs, P. D.; Kuhlman, K.; Fung, V. A.; Helmes, C. T.; Chao, W. R. *J. Med. Chem.* **1980**, *23*, 1013.
(10) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9.
(11) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L. S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. *J. Med. Chem.* **1984**, *27*, 1516.
(12) Wangh, K. M.; Berlin, K. D.; Fod, W. T.; Holt, E. M.; Carrol, J. P.; Schomber, P. R.; Thompson, M. D.; Schiff, L. J. *J. Med. Chem.* **1985**, *28*, 116.

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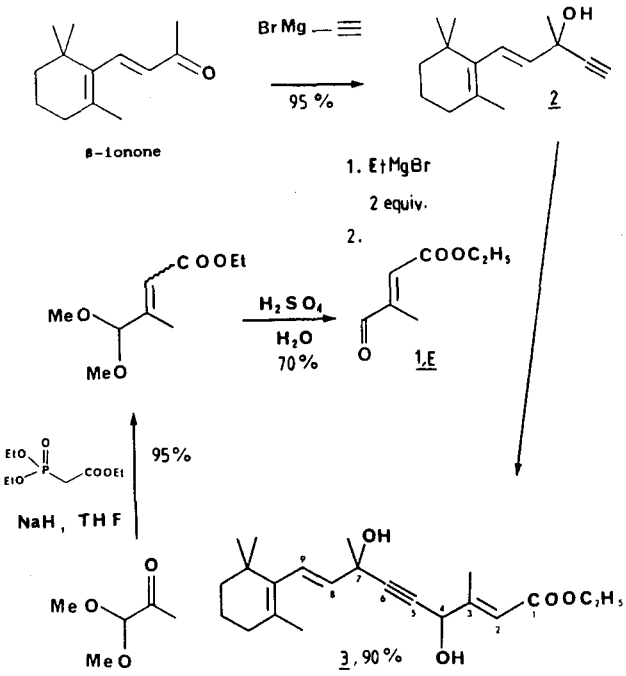
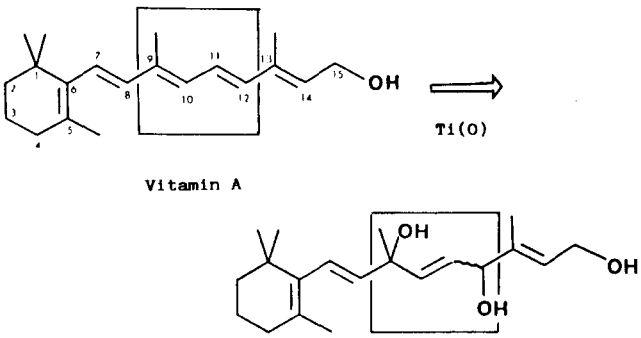
Scheme I



recently utilized to synthetize the central diene unit of dihydrotachysterol[14] and the (*E*,*E*)-1,3-diene central unit of Vitamin A.[15]

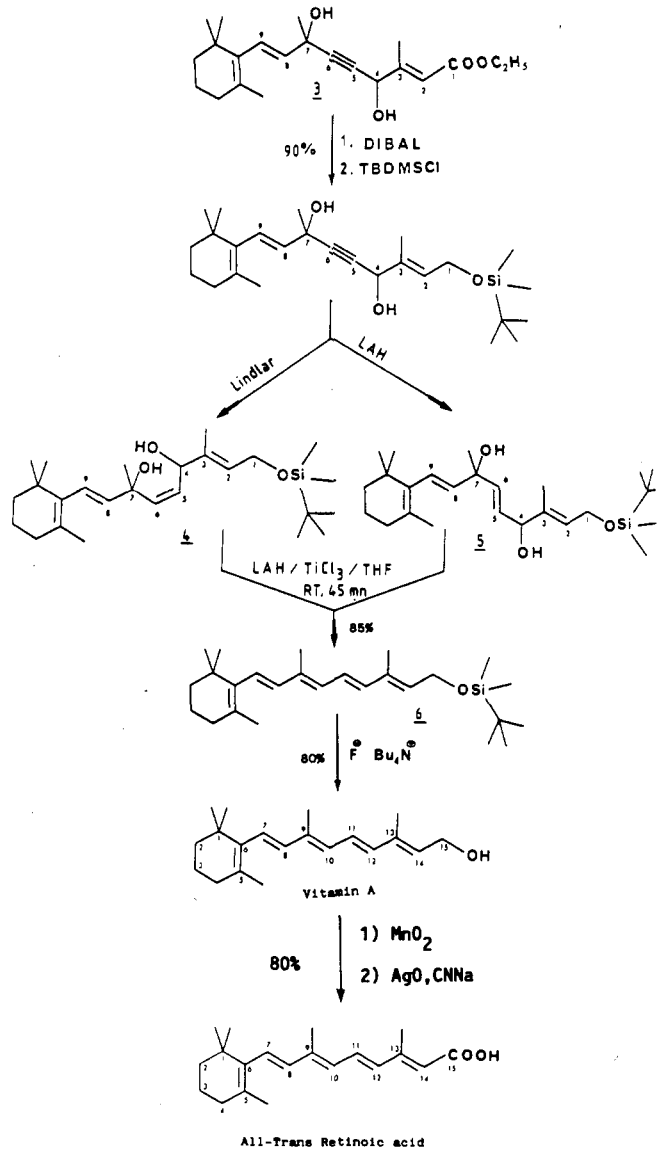


Ethyl γ-oxysenecionate (*E*)-**1** was readily prepared from the dimethyl acetal of pyruvaldehyde by a Wittig reaction, giving a mixture of *E* and *Z* acetals, which were hydrolyzed in the acidic medium with complete isomerization to the pure *E* isomer **1**. Addition of the Grignard reagent derived from ethynyl β-ionol[23] **2** gave in high yield diol **3** as a mixture of diastereoisomers (Scheme I).

After reduction of the ester function with DIBAH and protection of the resulting primary alcohol with a TBDMS group, the triple bond was reduced to the cis isomer **4** with Lindlar catalyst and to the trans isomer **5** with $LiAlH_4$ (Scheme II).

Reductive elimination of both *Z* and *E* isomers **4** and **5** with titanium(0) gave only one product, **6**, in 85% yield.

Scheme II



Removal of the protecting group and purification by flash chromatography afforded pure vitamin A,[16] which can be converted to *all-trans*-retinoic acid by standard methods.[17]

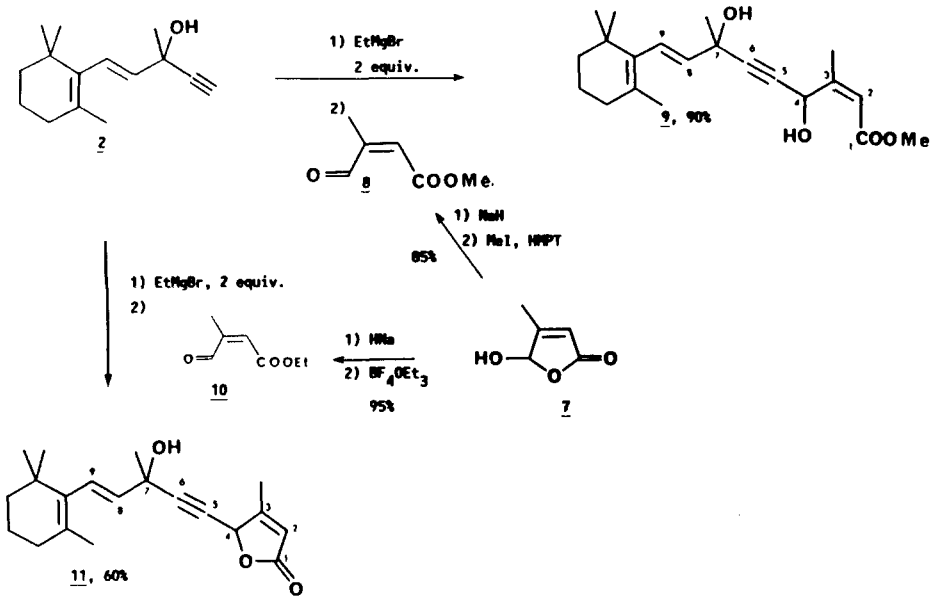
Therefore, the reductive elimination with Ti(0) affords a highly stereoselective route to Vitamin A from the cis or trans allylic diols **4** and **5**. However, the protecting group of the primary alcohol has to be a silyl group. In the case of an acetate protecting group, reductive elimination with Ti(0) gave a mixture of *E* and *Z* isomers.

In a short comunication,[19] we also reported the synthesis of 13-*cis*-retinol by the same methodology: formation of the (*E*,*E*)-1,3-diene central unit from the parent allylic diol **12** by Ti(0)-induced reductive elimination. The main question concerning this synthetic approach was to determine if the *Z* stereochemistry of the terminal double bond in **12** could be maintained during the Ti(0) reductive elimination.

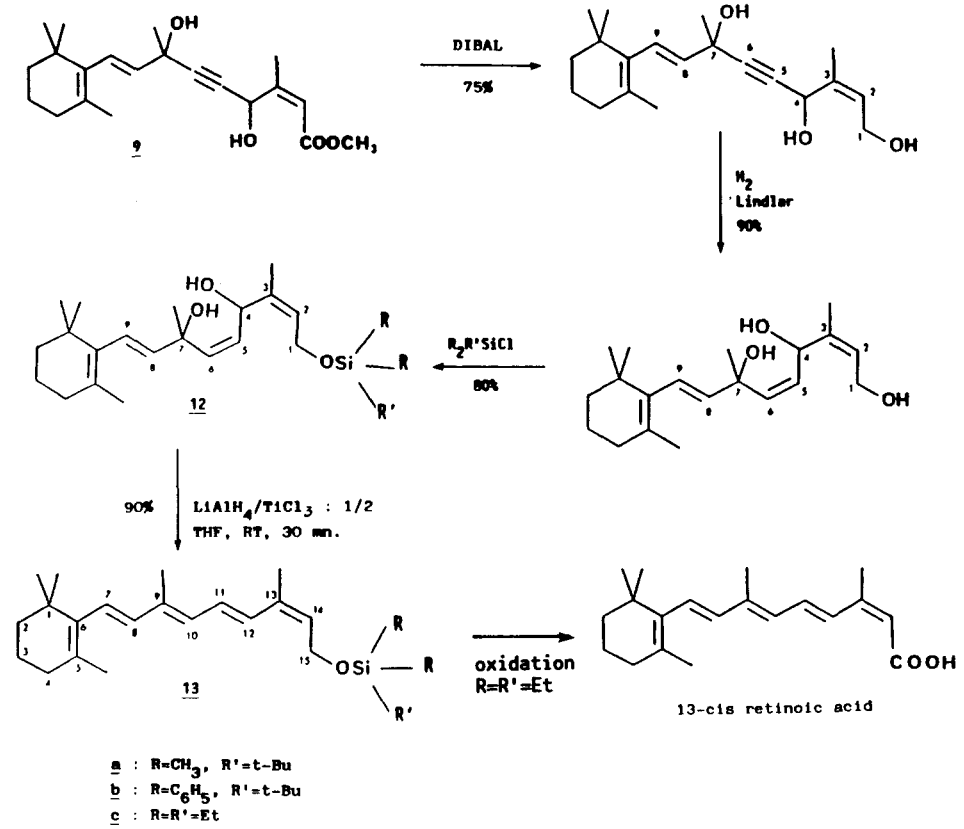
Esters **8** and **10** were obtained in high yield from the readily available hydroxybutenolide[20] **7**. Reaction of the Grignard reagent derived from ethynyl β-ionol **2** with ester **8** gave diol **9** in 90% yield while addition to ester **10** gave lactone **11** in 60% yield. It is interesting to point out that after reduction of the triple bond with Lindlar catalyst, compound **11** was quite stable in presence of Ti(0). In sharp contrast reduction of the corresponding hydroxy

(13) Walborsky, H. M.; Wust, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807.
(14) Solladié, G.; Hutt, J. *J. Org. Chem.* **1987**, *52*, 3560.
(15) Solladié, G.; Girardin, A. *Tetrahedron Lett.* **1988**, *29*, 213.
(16) Liu, R. S.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931.
(17) Barua, A. B.; Verma, K. *Indian J. Chem.* **1977**, *15B*, 665.
(18) Pattenden, G.; Weedon, B. C. L.; *J. Chem. Soc. C* **1968**, 1984.
(19) Solladié, G.; Girardin, A.; Metra, P. *Tetrahedron Lett.* **1988**, *29*, 209.
(20) Bourguignon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889.
(21) Curley, R. W.; Ticoras, C. J. *Synth. Commun.* **1986**, *16*, 627.
(22) Curley, R. W.; Ticoras, C. J. *J. Org. Chem.* **1986**, *51*, 256.
(23) Lugtenburg, J.; Brock, A. D. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 363.

Scheme III



Scheme IV



a : R=CH_3, R'=t-Bu
b : R=C_6H_5, R'=t-Bu
c : R=R'=Et

ester **9** with Ti(0) gave a complex mixture of products that were not identified.

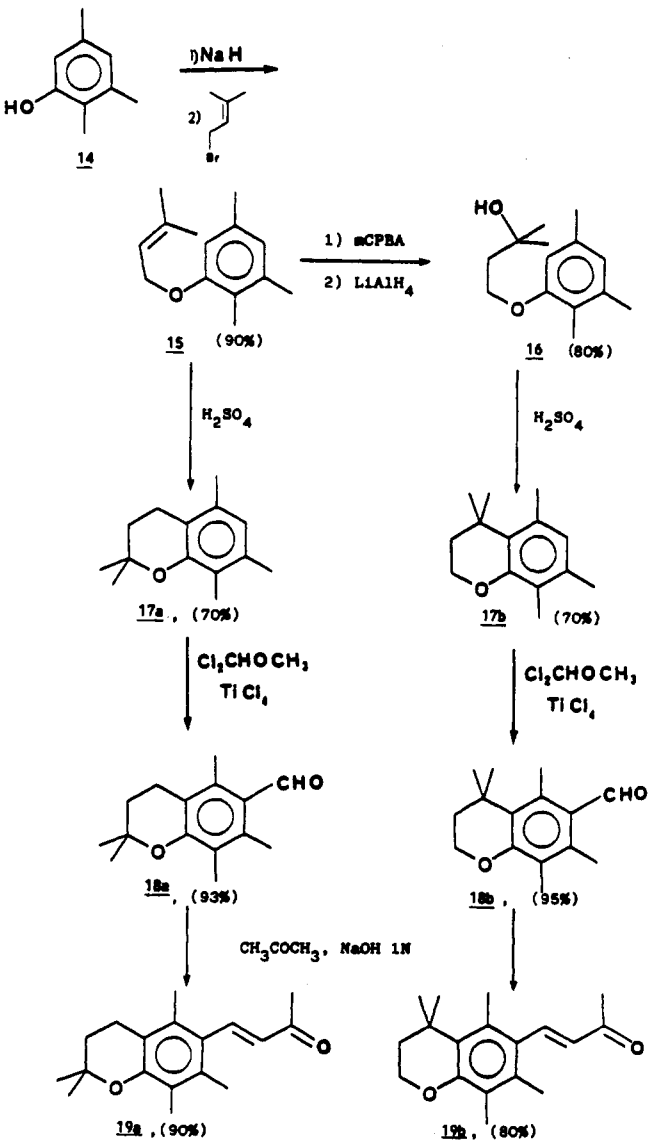
Ester **9** was reduced with DIBAH, the resulting primary alcohol was protected by a silyl group, and the triple bond was hydrogenated with the Lindlar catalyst (Scheme IV). The resulting allylic diols **12a–c** gave a single product (**13a–c**) in high yield upon reductive elimination with Ti(0) as shown by the NMR spectrum (one set of signals for the vinylic hydrogens, consistent with the presence of only one stereoisomer).

Unfortunately, it was not possible to remove the protecting group in compounds **13a** and **13b** without decomposition of the molecule. However, deprotection was achieved in the case of a triethylsilyl group with a mixture of sodium fluoride and pyridinium fluoride at room temperature, giving 13-*cis*-retinol[16] in quantitative yield.

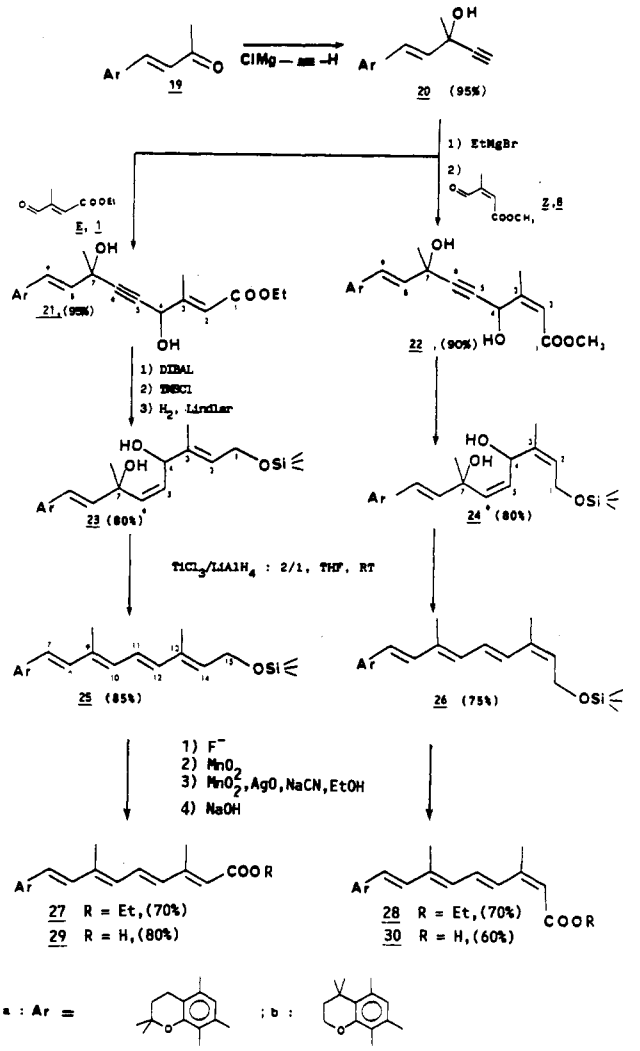
13-*cis*-Retinol was then oxidized to 13-*cis*-retinal with MnO_2, and further conversion to 13-*cis*-ethyl retinoate was accomplished with a mixture of silver and manganous oxide in ethanol with a 60% overall yield. This ester was purified by chromatography and saponified to 13-*cis*-retinoic acid, which was shown to be identical with an authentic sample and pure by HPLC.[16,18] In the 200-MHz NMR spectrum the main characteristic of the 13-cis stereoisomer is the deshielding of H_{12} at 7.75 ppm (6.31 ppm for the same proton in the all-trans isomer).

all-trans- and 13-*cis*-retinoid analogues containing a chroman moiety were obtained from chromans **19a** and

Scheme V



Scheme VI



19b, readily prepared in high yields from 2,3,5-trimethylphenol (**14**). Acid-catalyzed rearrangement of allylic ether **15** gave chroman **17a** (easily identified by comparison with the other chromans described in this paper). The regioisomer (**17b**) was obtained by cationic cyclization of tertiaryl alcohol **16**. Formylation afforded compounds **18a** and **18b** which underwent clean aldol condensation to the α,β-unsaturated ketones **19a** and **19b** with the *E* configuration (Scheme V).

Condensation of ketone **19a** with the acetylenic Grignard reagent gave the corresponding propargylic alcohol **20a**, which after metalation was condensed with ethyl γ-oxysenecionate (*E*)-**1**. The resulting ester (**21a**) was reduced with DIBAH, the primary alcohol was protected with a TMS group, and the triple bond was reduced with Lindlar catalyst. All these reactions gave high yields, and each time the crude product was used without further purification in the next step. Reductive elimination at room temperature gave compound **25a** in 65% overall yield from ester **21a** (Scheme VI). Finally crude tetraene **25a** was deprotected and oxidized in two stages to the corresponding ester **27a** with an overall yield of 70%.

It is interesting to remark that this set of reactions was performed without purification of the intermediates from the propargylic alcohol **20a**. Only the final product, the ester **27a**, was purified by crystallization. The overall yield of isolated product **29a** from the alcohol **20** was 40%.

The same reaction sequence was applied to ester **22a** obtained from methyl γ-oxysenecionate (*Z*)-**8**. The overall yield of acid **30a** from the propargylic alcohol **20a** was 30%. The only intermediate purification was flash-chromatography of ester **28a**. Compounds **29b** and **30b** were obtained by the same method.

The stereochemical purity of the product was confirmed by ^1H NMR spectroscopy and HPLC analysis. The main spectral features that allow easy identification of the stereochemistry of the polyenic chain in the esters are the chemical shifts of H_4 (7.8 ppm in the cis isomer **28a** and 6.3 ppm in the all trans isomer **27a**) and the methyl group on C_3 (2.37 ppm in **27a**, between 2.10 and 2.20 in **28a**).

These examples demonstrate that the low-valent titanium reductive elimination is a very useful method for stereospecific diene synthesis and allows the introduction of a trans diene fragment into a complex polyolefinic chain. The reactions could be performed without purification of the intermediates from the starting propargylic alcohol **20**. In the all-trans series the final ester **27** was purified by crystallization while in the cis series it was necessary to purify ester **28** by flash chromatography. The overall yield of 40% (eight steps) in the case of the all-trans acid **29** and 30% for the cis isomer **30**, show that this method for building polyenic chains is quite efficient.

Experimental Section

Ethyl (*E*)-3-Methyl-4-oxo-2-butenoate (1). (1) Wittig

Condensation of Dimethyl Acetal of Pyruvic Aldehyde and Triethyl Phosphonoacetate. Triethyl phosphonoacetate (142 g, 0.64 mol) in HMPA (10 mL) was dropwise added at 0 °C to sodium hydride (15.3 g, 0.64 mol) in THF (100 mL). After the mixture was stirred for 1 h, commercially available dimethyl acetal of pyruvic aldehyde (72.2 g, 0.64 mol) was added dropwise, and the reaction mixture was stirred for 24 h and then diluted with water (15 mL) and extracted with ether (2 × 100 mL). The organic layers were washed with saturated sodium chloride, dried (Na_2SO_4), and evaporated, giving 103 g (95%) of a liquid, which was shown by NMR to be a E/Z mixture in the ratio 2/1 and used in the next step without further purification. ^1H NMR (60 MHz, $CDCl_3$): δ 1.1 (t, 3 H, CH_3, J = 7 Hz), 1.7 (s, 3 H, vinylic CH_3, Z isomer), 1.9 (s, 3 H, vinylic CH_3, E isomer), 3.1 (s, 6 H, OCH_3, E isomer), 3.2 (s, 6 H, OCH_3, Z isomer), 3.9 (q, 2 H, CH_2, J = 7 Hz), 4.4 (s, 1 H, CH), 5.6 (s, 1 H, vinylic H, Z isomer), 5.8 (s, 1 H, vinylic H, E isomer).

(2) Acetal Hydrolysis. The acetal obtained in the preceding step (10 g, 0.053 mol) was added dropwise to an ice-cold mixture of 4.5 M sulfuric acid (100 mL) and ether (100 mL) and stirred at room temperature for 24 h. The reaction mixture was extracted with ether (2 × 100 mL). The organic layers were washed with a saturated bicarbonate solution (150 mL), water (100 mL), and a saturated sodium chloride solution (150 mL), and the solvent was evaporated. The crude product (5.5 g, 70% yield) was shown to be the pure E isomer by ^1H NMR[21,22] analysis. ^1H NMR (60 MHz, $CDCl_3$): δ 1.2 (t, 3 H, CH_3, J = 8 Hz), 2.0 (s, 3 H, vinylic CH_3), 4.1 (q, 2 H, CH_2, J = 8 Hz), 6.4 (s, 1 H, vinylic H), 9.4 (1 H, C*H*O). IR (CCl_4): 2970 (HC=C), 2820 (OCH_3), 2730 (CHO), 1720, 1700, (C=O) cm^{-1}.

Synthesis of Vitamin A. (1) Ethyl 9-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-3,7-dimethyl-4,7-dihydroxy-(2*E*,8*E*)-nona-2,8-dien-5-ynoate (3). The propargylic alcohol **2**[23] (5 g, 0.023 mol) in THF (10 mL) was added to a solution of ethylmagnesium bromide (0.023 mol) in THF (200 mL). After the mixture was stirred at room temperature for 1 h, aldehyde **1** (2.93 g, 0.023 mol) in THF (5 mL) was rapidly added. The reaction mixture was stirred for 15 min, hydrolyzed with a saturated sodium chloride solution (100 mL), and dried (Na_2SO_4), and the solvent evaporated, giving the crude product **3** in 95% yield (7.9 g), which was used in the next step without further purification. An analytical sample was obtained by chromatography (hexane/ethyl acetate, 70/30, R_f = 0.30). This rather unstable product must be kept at low temperature and used as quickly as possible. ^1H NMR ($CDCl_3$): δ 0.97 (s + t, 9 H, 2 CH_3 on $C_{6'}$ and CH_2CH_3, J = 7 Hz), 1.42–1.64 (m, 4 H, CH_2 on $C_{4'}$ and $C_{5'}$), 1.60 (s, 3 H, CH_3 on C_7), 1.66 (s, 3 H, CH_3 on $C_{2'}$), 1.98 (t, 2 H, CH_2 on $C_{3'}$, J = 6 Hz), 2.24 (s, 3 H, CH_3 on C_3), 4.17 (q, 2 H, OCH_2, J = 7 Hz), 4.89 (broad s, 1 H, H_4), 5.95 (AB, 2 H, H_8 and H_9, J = 16 Hz, $\Delta\nu$ = 159 Hz), 6.12 (broad s, 1 H, H_2).

(2) Ester Reduction in Compound 3. A solution of ester **3** (10 g, 0.028 mol) in THF (150 mL) cooled at −78 °C was treated with a 1.5 M DIBAH solution in toluene (4.1 equiv); 30 min after the end of the DIBAH addition, as determined by TLC monitoring, the reaction mixture was hydrolyzed at −40 °C with a saturated ammonium chloride solution (200 mL) and diluted with ether (150 mL). At 0 °C, 10% HCl was added until the phases separated. The aqueous layer was washed twice with ether (100 mL). The organic phases were washed twice with brine (200 mL), dried (Na_2SO_4), and evaporated, giving the triol in 90% yield (9 g). This crude product was used without further purification in the next step. ^1H NMR (200 MHz, $CDCl_3$): δ 1.00 (s, 6 H, 2 CH_3 on $C_{6'}$), 1.42–1.70 (m, 4 H, CH_2 on $C_{4'}$ and $C_{5'}$), 1.57, 1.67, and 2.00 (3 s, 3 CH_3 on C_3, C_7, and $C_{2'}$), 2.04–2.16 (m, 2 H, CH_2 on $C_{3'}$), 4.24 (d, 2 H, CH_2 on C_1, J = 6 Hz), 4.85 (s, 1 H, H_4), 5.56 (d, 1 H, H_8, J = 16 Hz), 5.75 (t, J = 6 Hz, H_2), 6.37 (d, 1 H, H_9, J = 16 Hz).

(3) Protection of the Primary Hydroxyl Group. To the preceding triol (4 g, 0.012 mol) in DMF solution (40 mL) were added TBDMSCl (1.9 g, 0.012 mol) and imidazole (2.1 g, 0.03 mol), and the reaction mixture was stirred for 18 h at room temperature. After dilution with water (50 mL) and extraction with ether (3 × 80 mL), the organic phases were washed (2 × 100 mL), dried, and evaporated, giving 5.4 g (95% yield) of product. ^1H NMR (200 MHz, $CDCl_3$): same spectrum as the starting triol with one singlet at 0.08 ppm (6 H) and one singlet at 0.91 ppm (9 H).

(4a) 9-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-3,7-dimethyl-1-[(*tert*-butyldimethylsilyl)oxy]-(2*E*,5*Z*,8*E*)-nona-2,5,8-triene-4,7-diol (4). The preceding compound (5.4 g, 0.012 mol) in methanol (100 mL) was reduced with the Lindlar catalyst during 24 h. The product is a mixture of two diastereoisomers (due to the presence of two asymmetric carbons), which can be now separated by chromatography on silica gel (eluant: AcOEt/hexane, 30/70, R_f 0.33 and 0.28). ^1H NMR (200 MHz, $CDCl_3$) isomer R_f 0.33 (2.5 g, 45%): δ 0.1 (s, 6 H, 2 CH_3), 0.92 (s, 9 H, tBu), 0.96 (s, 6 H, 2 CH_3 on $C_{6'}$), 1.41–1.68 (m, 4 H, CH_2 on $C_{4'}$ and $C_{5'}$), 1.49, 1.51, and 1.66 (3 s, 3 CH_3 on C_3, C_7, and $C_{2'}$), 1.90–2.04 (m, 2 H, CH_2 on $C_{3'}$), 2.52–3.06 (m, 2 H, 2O*H*), 4.28 (d, 2 H, CH_2 on C_1, J = 6 Hz), 5.11 (d, 1 H, H_4, J = 7 Hz), 5.41 (dd, 1 H, H_5, J = 12 Hz, J = 7 Hz), 5.61 (d, 1 H, H_8, J = 16 Hz), 5.66 (d, 1 H, H_6, J = 12 Hz), 5.71 (t, 1 H, H_2, J = 6 Hz), 6.10 (d, 1 H, H_9, J = 16 Hz); isomer R_f 0.28, (2.5 g, 45%) δ 0.09 (s, 6 H, 2 CH_3), 0.91 (s, 9 H, tBu), 1.00 (s, 6 H, 2 CH_3 on $C_{6'}$), 1.40–1.70 (m, 4 H, CH_2 on $C_{4'}$ and $C_{5'}$), 1.49 (s, 6 H, CH_3 on C_7 and $C_{2'}$), 1.66 (s, 3 H, CH_3 on C_3), 1.92–2.03 (m, 2 H, CH_2 on $C_{3'}$), 2.75–3.08 (m, 2 H, 2 O*H*), 4.28 (d, 2 H, CH_2 on C_1, J = 6 Hz), 5.07 (d, 1 H, H_4, J = 7 Hz), 5.46 (dd, 1 H, H_5, J = 12 Hz, J = 7 Hz), 5.61 (d, 1 H, H_8, J = 16 Hz), 5.70 (d, 1 H, H_6, J = 12 Hz), 5.70 (t, 1 H, H_2, J = 6 Hz), 6.09 (d, 1 H, H_9, J = 16 Hz).

(4b) 9-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-3,7-dimethyl-1-[(*tert*-butyldimethylsilyl)oxy]-(2*E*,5*E*,8*E*)-nona-2,5,8-triene-4,7-diol (5). The preceding silylated acetylenic compound (2 g, 0.046 mol) in ether (100 mL) was reduced with $LiAlH_4$ (3.5 g, 0.055 mol) at 0 °C in 1 h. Then the reaction mixture was poured on a saturated NaCl solution (80 mL), diluted with water (20 mL), and extracted twice with ether (50 mL). The organic layers were washed with a saturated sodium chloride solution (100 mL), dried (Na_2SO_4), and evaporated. Finally the product was purified by chromatography on silica gel (eluant: hexane/AcOEt, 70/30, R_f = 0.31), yield 1.3 g (65%). ^1H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 6 H, 2 CH_3), 0.90 (s, 9 H, tBu), 0.97 (s, 2 CH_3 on $C_{6'}$), 1.43 (s, 3 H, CH_3 on C_7), 1.46–1.63 (m, 4 H, CH_2 in $C_{4'}$ and $C_{5'}$), 1.65 (s, 6 H, CH_3 on $C_{2'}$ and C_3), 1.89–2.00 (m, 2 H, CH_2 in $C_{3'}$), 4.20 (d, 2 H, H on C_1, J = 7 Hz), 4.56 (d, 1 H, H_4, J = 6 Hz), 5.79 (AB, 2 H, H_8 and H_9, J = 16 Hz, $\Delta\nu$ = 107 Hz), 5.65–5.94 (m, $H_{6'}$, H_5, and H_2).

(5) Reductive Elimination of Diols 4 and 5 to the Silyl Ether of Vitamin A, 6. A lithium aluminium hydride solution in ether (0.176 g, 0.046 mol) was added to 2 equiv of titanium trichloride (1.43 g, 0.093 mol) in THF (100 mL). After the mixture was stirred for 10 min at room temperature, the diols **4** or **5** (1.61 g, 0.036 mol) in THF (20 mL) were added (in the dark). After being stirred for 1 h at room temperature (no more starting material in TLC), the reaction mixture was hydrolyzed with water (10 mL) and 0.1 N HCl (60 mL). The aqueous layer was extracted with ether (2 × 200 mL); the organic layers were washed with a saturated solution of sodium chloride (100 mL), dried, and evaporated, giving a crude yellow oil (1.30 g, 85% yield), which was used in the next step without further purification.

(6) Vitamin A. Tetrabutylammonium fluoride (1.1 g, 0.046 mol) was added to the silyl ether **6** (1.25 g, 0.031 mol) in THF (20 mL) and stirred at room temperature for 2 h in the dark. Then the reaction mixture was filtered over silica gel and purified by chromatography (eluant: AcOEt/hexane, 20/80, R_f = 0.20), yield 0.74 g (80%). ^1H NMR (200 MHz, $CDCl_3$): δ 1.02 (s, 6 H, 2 CH_3 on C_1), 1.36–1.68 (m, 4 H, H on C_2 and C_3), 1.71 (s, 3 H, CH_3 on C_5), 1.87 (s, 3 H, CH_3 on C_{13}), 1.96 (s, 3 H, CH_3 on C_9), 2.02 (t, 2 H, H on C_4, J = 6 Hz), 4.31 (d, 2 H, H on C_{15}, J = 7 Hz), 5.69 (t, 1 H, J = 7 Hz), 6.10 (d, 1 H, H_{10}, J = 11 Hz), 6.13 and 6.14 (2 s, 2 H, H_7 and H_8), 6.28 (d, 1 H, H_{12}, J = 16 Hz), 6.62 (dd, 1 H, H_{11}, J = 16 Hz). This spectrum is identical with that of commercial vitamin A whereas H_7 and H_8 appeared at 6.14 and 6.09 ppm in literature.[16]

***all-trans*-Retinal.** Manganous oxide[24] (1.5 g, 0.017 mol) was added in the dark to a solution of vitamin A (1 g, 0.0035 mol) in dichloromethane (15 mL), and the resulting reaction mixture was stirred at room temperature for 2 h. After filtration on silica gel and evaporation of the solvent, one obtained 1 g (quantitative

(24) Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1104.

yield) of retinal,[16] which was used in the next step without purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 6 H, 2 CH_3), 1.45–1.70 (m, 4 H, H on C_2 and C_3), 1.73 (s, 3 H, CH_3 on C_5), 2.00–2.03 (broad s, 5 H, H on C_4 and CH_3 on C_9), 2.33 (s, 3 H, CH_3 on C_{13}), 5.98 (d, 1 H, H_{14}, J = 8 Hz), 6.20 (d, 1 H, J = 12 Hz), 6.27 (AB, 2 H, H_7, H_8, J = 16.5 Hz, $\Delta\nu$ = 36 Hz), 6.37 (d, 1 H, H_{12}, J = 15 Hz), 7.15 (dd, 1 H, H_{11}, J = 15.5 Hz, J = 12 Hz), 10.12 (d, 1 H, H_{15}, J = 8 Hz).

***all-trans*-Retinoic Acid.** Argentic oxide[25] (0.9 g, 0.007 mol) was added to a solution of retinal (0.2 g, 0.0007 mol) in absolute methanol (15 mL), and then sodium cyanide (170 g, 0.0035 mol) was also added to the reaction mixture.[26] After being stirred at room temperature for 18 h, the reaction mixture was filtered, and the solvent was evaporated. The crude product was either chromatographied (eluant: AcOEt/hexane, 30/70, R_f = 0.70 for retinal and 0.25 for retinoic acid) or crystallized from methanol, yield 160 mg (80%) (30 mg of starting retinal was recovered), mp 179–180 °C dec. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 6 H, 2 CH_3), 1.44–1.62 (m, 4 H, H on C_2 and C_3), 1.72 (s, 3 H, CH_3 on C_5), 2.01–2.06 (broad s, 5 H, H on C_4 and CH_3 on C_9), 2.37 (s, 3 H, CH_3 on C_{13}), 5.80 (s, 1 H, H_{14}), 6.14 (d, 1 H, H_8, J = 16 Hz), 6.15 (d, 1 H, H_{10}, J = 11 Hz), 6.23 (d, 1 H, H_7, J = 16 Hz), 6.31 (d, 1 H, H_{12}, J = 15 Hz), 7.05 (dd, 1 H, H_{12}, J = 15 Hz, J = 11 Hz). This spectrum was identical with that of commercial *all-trans*-retinoic acid and to that in the literature.[16,18]

Methyl (*Z*)-3-Methyl-4-oxo-2-butenoate (8). Sodium hydride (0.13 mol) was added to 4-hydroxy-3-methyl-2-buten-4-olide[20] (7) (15 g, 0.13 mol) in HMPA (100 mL) at 0 °C. After the mixture was stirred for 1 h, methyl iodide (1.5 equiv) was added, and after 20 min of stirring, the reaction mixture was diluted with water (100 mL) and extracted with ether (5 × 50 mL). The organic phases were washed with water (250 mL), with a saturated sodium chloride solution (250 mL), dried ($MgSO_4$), and evaporated. The product was finally distilled, bp 41.3 °C (1 mm), yield 11.7 g (70%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.16 (s, 3 H, vinylic CH_3), 3.82 (s, 3 H, OCH_3), 6.51 (s, 1 H, vinylic H), 9.56 (s, 1 H, C*H*O). IR (CCl_4): 2990 (HC=C), 2895 (CH), 2830 (OCH_3), 2730 (CHO), 1680 (C=O), 1635, 1610 (C=C). Anal. Calcd for $C_6H_8O_3$: C, 56.24; H, 6.24. Found: C, 56.29; H, 6.13.

Synthesis of 13-*cis*-Retinoic Acid. (1) Methyl 9-(2′,6′,6′-Trimethyl-1′-cyclohexen-1′-yl)-4,7-dihydroxy-3,7-dimethyl-(2*Z*,8*E*)-nona-2,8-dien-5-ynoate (9). Compound **9** was prepared as for **3** from **2** (5 g, 0.023 mol) and aldehyde **8** (2.9 g, 0.023 mol), yield 7.2 g (90%). The product was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) of a sample purified by chromatography (eluant: hexane/ethyl acetate, 70/30, R_f = 0.25): δ 0.98 (s, 6 H, 2 CH_3), 1.42–1.70 (m, 4 H, H on $C_{4'}$ and $C_{5'}$), 1.61 (s, 3 H, CH_3 on C_7), 1.66 (s, 3 H, CH_3 on $C_{2'}$), 1.95–2.01 (m, 2 H, H on $C_{3'}$), 2.25 (s, 3 H, CH_3 on C_3), 3.72 (s, 3 H, OCH_3), 4.16 (d, 1 H, OH on C_4, J = 6 Hz), 4.90 (d, 1 H, H_4, J = 6 Hz), 5.56 (d, 1 H, H_8, J = 16 Hz), 6.00 (s, 1 H, H_2), 6.35 (d, 1 H, H_9, J = 16 Hz).

(2) Ester Reduction of Compound 9. The ester reduction of compound **9**, under the conditions used for ester **3**, gave the corresponding triol in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (s, 6 H, 2 CH_3), 1.42–1.75 (m, 13 H, CH_3 on C_3, C_7, $C_{2'}$ and H on $C_{4'}$ and $C_{5'}$), 1.98 (t, 2 H, H on $C_{3'}$, J = 6 Hz), 4.26 (d, 1 H, $H_{4'}$, J = 5 Hz), 4.33 (d, 2 H, H on C_1, J = 6 Hz), 5.56 (d, 1 H, H_8, J = 16 Hz), 5.75 (t, 1 H, H_2, J = 6 Hz), 6.38 (d, H_9, J = 16 Hz).

(3) The reduction of the triple bond with the Lindlar catalyst under the conditions used before gave in 90% yield the corresponding triol. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (s, 6 H, 2 CH_3), 1.40–1.72 (m, 4 H, H on $C_{4'}$ and $C_{5'}$), 1.47 and 1.65 (2 s, 9 H, 3 CH_3 on C_3, C_7, and $C_{2'}$), 1.92–2.02 (m, 2 H, H on $C_{3'}$), 3.65–3.80 (m, 3 H, H on C_1 and O*H*), 4.67 (d, 1 H, H_4, J = 6 Hz), 5.42–5.70 (m, 4 H, H_2, H_5, H_6, H_8), 6.09 (d, 1 H, H_9, J = 16 Hz).

(4) The silyl derivatives **12a–c** were prepared in quantitative yield in the usual experimental conditions already described for compound **4**.

(5) Reductive Elimination of Diol 12c to the Triethylsilyl Ether of 13-*cis*-Retinol (13c). The triethylsilyl ether of 13-*cis*-retinol, **13c**, was prepared by Ti(0) reaction from compound **12c** according the procedure described for vitamin A in 90% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.5 (t, 9 H, CH_2CH_3, J = 7 Hz), 0.9 (q, 6 H, CH_2CH_3, J = 7 Hz), 1.0 (s, 6 H, 2 CH_3 on C_1), 1.5–1.7 (m, 4 H, H on C_2 and C_3), 1.7 (s, 3 H, CH_3 on C_5), 1.9 (s, 3 H, CH_3 on C_{13}), 1.95 (s, 3 H, CH_3 on C_9), 1.95–2.1 (m, 2 H, H on C_4), 4.3 (d, 2 H, H_{15}, J = 8 Hz), 5.5 (t, 1 H, H_{14}, J = 8 Hz), 6.1 (d, 1 H, H_{10}, J = 4 Hz), 6.1 (d, 1 H, H_8, J = 16 Hz), 6.15 (d, 1 H, H_7, J = 16 Hz), 6.6 (d, 1 H, H_{12}, J = 16 Hz), 6.65 (dd, 1 H, H_{11}, J = 16 Hz, J = 11 Hz).

(6) Ethyl 13-*cis*-Retinoate. (a) Desilylation of Compound 13c. The crude product **13c** (1 g, 0.0025 mol) in a mixture THF/CH_3CN, 30/70 (15 mL), was treated by sodium fluoride (0.53 g, 0.0125 mol) and pyridinium fluoride (0.025 g, 0.003 mol) for 5 h in the dark and under anhydrous conditions. The reaction mixture was then hydrolyzed with 10 mL of a saturated NaCl solution and 10 mL of water and extracted with ether (2 × 10 mL). The organic layers were dried over sodium sulfate and evaporated.

(b) Oxidation to Aldehyde. The preceding crude product in CCl_4 (15 mL) was treated with MnO_2 (1.5 g, 0.0125 mol) for 30 min in the dark and with vigorous stirring. After filtration on silica gel, the solvent was evaporated.

(c) Oxidation to Ethyl Carboxylate. The preceding aldehyde in absolute ethanol (15 mL) was treated in the dark with sodium cyanide (0.860 g, 0.0017 mol), 2.6 g of a mixture of argentic oxide (1.5 g), and MnO_2 (8.5 g) at 40 °C for 14 h. After filtration and evaporation of the solvant, the product was chromatographed on silica gel (eluant: AcOEt/hexane, 298, R_f = 0.16), yield 0.650 g (60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (s, 6 H, 2 CH_3), 1.29 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.44–1.68 (m, 4 H, H on C_2 and C_3), 1.71 (s, 3 H, CH_3 on C_5), 1.99 (s, 3 H, CH_3 on C_9), 1.99–2.07 (m, 2 H, H on C_4), 2.07 (s, 3 H, CH_3 on C_{13}), 4.17 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.64 (s, 1 H, H_{14}), 6.14 (d, 1 H, H_8, J = 6 Hz), 6.25 (d, 1 H, H_{10}, J = 12 Hz), 6.27 (d, 1 H, H_7, J = 16 Hz), 6.98 (dd, 1 H, H_{11}, J = 15 Hz, J = 12 Hz), 7.77 (d, 1 H, H_{12}, J = 15 Hz).

(7) 13-*cis*-Retinoic Acid. Ethyl 13-*cis*-retinoate (0.1 g, 0.003 mol) in ethanol (5 mL) was treated in the dark by a 6 M sodium hydroxide solution (5 mL) at 50 °C until complete dissolution of the solid. Then the reaction mixture was diluted with water (10 mL), and the alcohol was evaporated. The aqueous layer was acidified with a 10% HCl solution until pH = 3. The acid was extracted with ether; the organic extract was dried over sodium sulfate and evaporated. The crude acid was recrystallized in methanol, yield 0.07 g (70%), mp 167–170 °C dec (lit.[18] mp 172–173 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 6 H, 2 CH_3), 1.46–1.49 (m, 2 H, H on C_2), 1.6–1.66 (m, 2 H, H on C_3), 1.72 (s, 3 H, CH_3 on C_5), 2.01 (s, 3 H, CH_3 on C_9), 2.02–2.05 (m, 2 H, H on C_4), 2.11 (s, 3 H, CH_3 on C_{13}), 5.67 (s, 1 H, H_{14}), 6.18 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_{10}, J = 11.4 Hz), 6.30 (d, 1 H, H_7, J = 16 Hz), 7.04 (dd, 1 H, H_{11}, J = 15.3 Hz, J = 11.4 Hz), 7.75 (d, 1 H, H_{12}, J = 15 Hz). The NMR spectrum is identical with that described in the literature,[16] and the purity of the product was checked by HPLC.

Synthesis of 4-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-*trans*-3-buten-2-one (19a). (1) 2,2,5,7,8-Pentamethylchroman (17a). Concentrated sulfuric acid (10 mL) was slowly added to a solution of 10 g (0.049 mol) of 2-methyl-4-[(2′,3′,5′-trimethylphenyl)oxy]-2-butene, **15**, in 200 mL of pentane. After 10 min the mixture was diluted with 200 mL of ether and 200 mL of water. The organic layer was washed with a saturated sodium bicarbonate solution (100 mL), water (100 mL), and sodium chloride (100 mL). After drying (Na_2SO_4) and evaporation of the solvent, 7 g (70%) of crude chroman **17a** was obtained and used in the next step without any further purification, bp 108–9 °C (0.9 mm). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 6 H, 2 CH_3 on C_2), 1.79 (t, 2 H, CH_2, J = 7 Hz), 2.07, 2.16, 2.20 (3 s, 3 × 3 H, CH_3 on C_5, C_7, and C_8), 2.60 (t, 2 H, H_2 on C_4), 6.55 (s, 1 H, arom). Anal. Calcd for $C_{14}H_{20}O$: C, 82.34; H, 9.87. Found: C, 82.48; H, 9.89.

(2) 2,2,5,7,8-Pentamethyl-6-formylchroman (18a) was prepared by the same method as chroman **18b**, yield 95%. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.3 s, 6 H, 2 CH_3), 1.8 (t, 2 H, CH_2, J = 7 Hz), 2.1, 2.2, and 2.25 (3 s, 3 × 3 H, 3 CH_3), 2.6 (t, 2 H, CH_2, J = 7 Hz), 10.0 (s, 1 H, CHO).

(3) 4-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-*trans*-3-buten-2-one (19a). The aldehyde **18a** (10 g, 0.043 mmol) in acetone (30 mL) was treated with a 1 M sodium hydroxide solution (10 mL) for 8 h at room temperature. The mixture was then diluted

(25) Jirsa, F. *Zeitschrift fur Allgemeine Chemie* **1935**, *225*, 302.
(26) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

with 100 mL of water and 100 mL of ether. The aqueous layer was extracted with ether (2 × 100 mL). The organic layers were washed with a saturated sodium chloride solution (100 mL) and evaporated. The product was recrystallized from hexane, yield 11.6 g (95%), mp 74–75 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6 H, 2 CH_3), 1.82 (t, 2 H, CH_2, J = 7 Hz), 2.13, 2.19, and 2.22 (3 s, 3 × 3 H, 3 CH_3), 2.39 (s, 3 H, $COCH_3$), 2.64 (t, 2 H, CH_2, J = 7 Hz), 6.18 (d, 1 H, HC=, J = 16.5 Hz), 7.73 (d, 1 H, =$CHCOCH_3$, J = 16.5 Hz). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.41; H, 8.83.

Synthesis of 4-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-*trans*-3-buten-2-one (19b). (1) 4,4,5,7,8-Pentamethylchroman (17b). (a) Epoxidation. The dimethylallyl ether **15** (35 g, 0.17 mol) was dissolved in a 1/1 mixture of acetone and chloroform (400 mL). One equivalent of sodium bicarbonate was added, and a solution of *m*-chloroperbenzoic acid (21 g, 0.19 mol) in a 1/1 mixture of acetone and chloroform (200 mL) was dropwise added, and the mixture was stirred for 18 h. After concentration of the solution to 300 mL and filtration, the organic layer was washed with a saturated sodium bicarbonate solution (200 mL) and a saturated sodium chloride solution (200 mL), dried over sodium sulfate, and evaporated. The crude product was used in the next step without further purification, yield 30.2 g (80%). ^{1}H NMR (60 MHz, CCl_4): δ 1.15 and 1.2 (2 s, 6 H, *gem*-dimethyl), 1.09, 2.05, and 2.1 (3 s, 9 H, 3 CH_3), 2.8 (t, 1 H, HCO, J = 5 Hz), 3.8 (d, 2 H, OCH_2, J = 5 Hz), 6.3 and 6.4 (2 s, 2 H, arom).

(b) Reductive Opening of the Epoxide. The preceding epoxide (16 g, 0.073 mmol) in ether solution (150 mL) was dropwise added to $LiAlH_4$ (2.7 g) in ether (100 mL). After 30 min the excess of $LiAlH_4$ was decomposed carefully by ethyl acetate, 50 mL of water, and a 10% HCl solution. The aqueous layer was extracted with ether (2 × 100 mL). The organic layers were washed with water (100 mL), dried over magnesium sulfate, and evaporated, giving a colorless liquid, yield 16 g (95%). ^{1}H NMR (60 MHz, CCl_4): δ 1.5 (s, 6 H, 2 CH_3), 2.1 (t, 2 H, CH_2, J = 6 Hz), 2.2, 2.35, and 2.4 (3 s, 9 H, 3 CH_3), 3.1 (m, 1 H, OH), 4.2 (t, 2 H, OCH_2, J = 6 Hz), 6.5 (broad s, 2 H, arom).

(c) Cyclization. The preceding alcohol **16** (16 g, 73 mmol) in ether (30 mL) was dropwise added to 90% sulfuric acid cooled at 0 °C. After being stirred for 30 min, the mixture was diluted with 50 mL of ether and 50 mL of water. The organic layer was washed with 1 N sodium hydroxide (100 mL), saturated sodium bicarbonate (100 mL), and water (100 mL). After drying (Na_2SO_4), the solvent was evaporated giving a yellow liquid, which was used in the next step without any purification, yield 11.5 g (70%), bp 106 °C (0.9 mm). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 6 H, 2 CH_3), 1.80 (t, 2 H, CH_2, J = 5 Hz), 2.05, 2.17, and 2.42 (3 s, 9 H, 3 CH_3), 4.11 (t, 2 H, OCH_2, J = 5 Hz), 6.49 (s, 1 H, arom).

(2) 4,4,5,7,8-Pentamethyl-6-formylchroman (18b). To a solution of chroman **17b** (10 g, 0.050 mmol) in benzene (150 mL) was added α,α-dichloromethyl ether (2 equiv, 11.5 g) at room temperature. Then titanium tetrachloride (24 g, 0.12 mol) was dropwise added. After being stirred for 30 min, the reaction mixture was decomposed as usual, giving 11 g of crude **18b**, which was used without further purification, yield 11 g (95%). ^{1}H NMR (60 MHz, CCl_4): δ 1.3 (s, 6 H, 2 CH_3), 1.7 (t, 2 H, CH_2, J = 5 Hz), 1.9, 2.2, and 2.5 (3 s, 9 H, 3 CH_3), 4.0 (t, 2 H, OCH_2, J = 5 Hz), 10.4 (s, 1 H, CHO).

(3) 4-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-*trans*-3-buten-2-one (19b) was prepared by the same procedure as in the preceding case. The product was purified by chromatography on silica gel (AcOEt/*n*-hexane, 10/90, R_f = 0.3), yield 80%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.45 (s, 6 H, 2 CH_3), 1.84 (t, 2 H, CH_2, J = 5 Hz), 2.11, 2.17, and 2.37 (3 s, 3 CH_3), 2.36 (s, 3 H, CH_3), 4.14 (t, 2 H, OCH_2, J = 5 Hz), 6.12 (d, 2 H, HC=, J = 17 Hz), 7.67 (d, 1 H, =$CHCOCH_3$, J = 17 Hz). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.52; H, 8.61.

Synthesis of 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic Acid (29a). (1) 5-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3-methyl-3-hydroxypent-4(*E*)-en-1-yne (20a). The α,β-unsaturated ketone **19a** (10 g, 0.037 mol) in THF (20 mL) was dropwise added to a solution of acetylenemagnesium bromide[19] (prepared from 1.7 g of magnesium) at room temperature. After being stirred for 1 h, the reaction mixture was poured into saturated ammonium chloride (100 mL) and extracted with ether (3 × 50 mL). The organic layers were washed with water (50 mL) and saturated sodium chloride (50 mL). After drying (Na_2SO_4), the solvent was evaporated to give a crude product (liquid), which was used in the next step without further purification, yield 10.9 g (90%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6 H, 2 CH_3), 1.69 (s, 3 H, CH_3 on C_3), 1.82 (t, 2 H, CH_2 on $C_{3'}$, J = 7 Hz), 2.12, 2.16, and 2.19 (3 s, 3 × 3 H, 3 CH_3 on $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (s + t, 3 H, CH_2 on $C_{4'}$ and H_1, J = 7 Hz), 5.66 (d, 1 H, H_4, J = 16 Hz), 6.90 (d, 1 H, H_5, J = 16 Hz). IR (CCl_4): 3600 (OH), 3370 (OH), 3310 (H–C), 2920, 2870, and 2860 cm^{-1}.

(2) Ethyl 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-4,7-dihydroxy-(2*E*,8*E*)-nona-2,8-dien-5-ynoate (21a). The propargylic alcohol **20a** (8 g, 0.027 mol) in THF (20 mL) was added to a solution of ethylmagnesium bromide (2 equiv) in THF (20 mL). After being stirred at room temperature for 1 h, ethyl (*E*)-γ-oxysenecionate, **1** (0.027 mol), in THF (5 mL) was rapidly added. The reaction mixture was stirred for 15 min, hydrolyzed with saturated ammonium chloride (30 mL), and extracted with ether (2 × 30 mL). The organic layers were washed with saturated sodium chloride (100 mL) and dried over sodium sulfate, and the solvent was evaporated, giving the crude product **21a** in 95% yield (11.6 g). ^{1}H NMR ($CDCl_3$): δ 1.29 (s + t, 6 H + 3 H, 2 CH_3 on $C_{2'}$ and CH_2CH_3, J = 7 Hz), 1.68 (s, 3 H, CH_3 on C_7), 1.82 (t, 2 H, CH_2 on $C_{3'}$, J = 7 Hz), 2.11, 2.15, 2.16, and 2.19 (4 s, 4 × 3 H, CH_3 on C_3, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.63 (t, 2 H, CH_2 on $C_{4'}$, J = 7 Hz), 4.17 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.65 (d, 1 H, H_8, J = 16 Hz), 5.59 (s, 1 H, H_4), 6.51 (s, 1 H, H_2), 6.89 (d, 1 H, H_9, J = 16 Hz).

(3) 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-4,7-dihydroxy-1-[(trimethylsilyl)oxy]-(2*E*,5*Z*,8*E*)-nona-2,5,8-triene (23a). (a) Ester Reduction in Compound 21a. A solution of ester **21a** (10 g, 0.037 mol) in THF (100 mL) cooled at −20 °C was treated with a 1.5 M DIBAH solution in hexane (4.1 equiv). By TLC monitoring, 10 min after the end of the DIBAH addition, the reaction mixture was hydrolyzed at −20 °C with saturated ammonium chloride (80 mL) and diluted with ether (100 mL). At 0 °C, 10% hydrochloric acid was added until the phases separated. The aqueous layer was extracted twice with ether (60 mL). The organic phases were washed twice with brine (150 mL), dried with sodium sulfate, and evaporated, yield 80% (6.8 g). This crude product was used without further purification in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6 H, 2 CH_3 on $C_{2'}$), 1.82 (t, 2 H on $C_{3'}$, J = 7 Hz), 1.70, 1.71, 2.11, 2.16, and 2.19 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (t, 2 H on $C_{4'}$, J = 7 Hz), 4.26 (d, 2 H on C_1, J = 6 Hz), 4.86 (s broad, 1 H, H_4), 5.65 (d, 1 H, H_8, J = 16 Hz), 5.73 (t, 1 H, H_2, J = 6 Hz), 6.89 (d, 1 H, H_9, J = 16 Hz).

(b) Protection of the Primary Hydroxyl Group. To the preceding triol (11 g, 0.030 mol) in DMF solution (100 mL) were added TMSCl (0.03 mol) and imidazole (0.075 mol), and the reaction mixture was stirred for 18 h at room temperature. After dilution with water (100 mL) and extraction with ether (3 × 100 mL), the organic phases were washed with water (2 × 100 mL), dried, and evaporated, quantitative yield, 14 g. ^{1}H NMR (200 MHz, $CDCl_3$): same spectrum as the starting triol with one singlet at 0.1 ppm (9 H).

(c) Catalytic Reduction of the Triple Bond. The preceding compound (14 g, 0.030 mol) in methanol (150 mL) was reduced with the Lindlar catalyst during 24 h. Quantitative yield, 14 g.

The product is a mixture of two diastereoisomers (due to the presence of two asymmetric carbons), which can be now seen in TLC. ^{1}H NMR (200 MHz, $CDCl_3$): the resulting double bond was identified by a multiplet (H_5 and H_6) between 5.40 and 5.67 ppm.

(4) 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-1-[(trimethylsilyl)oxy]-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraene (25a). A lithium aluminium hydride solution in ether (250 mL, 0.038 mol) was added to titanium trichloride (12 g, 0.077 mol) in THF (100 mL). After the mixture was stirred for 10 min at room temperature, the crude product **23a** (0.030 mol, 0.8 equiv) in THF (150 mL) was added (in the dark). After being stirred for 1 h at room temperature (no more starting material in TLC), the reaction mixture was hydrolyzed with water (100 mL) and 0.1 N HCl (500 mL). The aqueous phase was extracted with ether (2 × 200 mL); the organic layers were washed with saturated sodium chloride (150 mL), dried, and evaporated, giving a crude oil, yield 11.2 g (85%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (s,

9 H, $SiMe_3$), 1.31 (s, 6 H, 2 CH_3 on $C_{2'}$), 1.80 (t, 2 H on $C_{3'}$, J = 6.5 Hz), 1.86, 1.96, 2.10, 2.13, and 2.18 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (t, 2 H on $C_{4'}$, J = 6.5 Hz), 4.30 (d, 2 H on C_1, J = 7 Hz), 5.60 (t, 1 H on C_2, J = 7 Hz), 6.09 (d, 1 H, H_6, J = 11 Hz), 6.10 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_4, J = 16 Hz), 6.61 (dd, 1 H, H_5, J = 16 Hz, J = 11 Hz), 6.72 (d, 1 H, H_9, J = 16 Hz).

(5) Ethyl 9-(2′,2′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoate (27a). (a) Desilylation. To a solution of ether **25a** (11 g, 0.025 mol) in a carefully dried mixture THF/CH_3CN, 30/70 (150 mL), were added anhydrous sodium fluoride (5 equiv) and pyridinium fluoride (0.1 equiv). After 5 h in the dark, there is no more starting compound. The reaction mixture was hydrolyzed with water (100 mL) and extracted with ether (2 × 150 mL). The organic phases were washed with a saturated sodium chloride solution (200 mL), dried, and evaporated.

(b) The preceding crude alcohol in anhydrous carbon tetrachloride (150 mL) was oxidized in 30 min with MnO_2 (5 equiv) at room temperature and in the dark. The reaction mixture was then sittered on silica gel and evaporated. Quantitative yield (TLC). The crude aldehyde was used in the next step without any purification.

(c) The crude aldehyde in 99.95% grade ethanol (150 mL) was treated in the dark with sodium cyanide (8.6 g, 0.017 mol) and a mixture of AgO/MnO_2 (3.9 g/22 g). The reaction mixture was stirred at 40 °C for 14 h. After filtration, the solvent was evaporated and the product **27a** was crystallized in hexane, overall yield 7.1 g (70%) (from **25a**), mp 126 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.32 (s, 6 H, 2 CH_3 on C_2), 1.81 (t, 2 H on $C_{3'}$, J = 6.5 Hz), 2.11, 2.13, 2.17, and 2.20 (4 s, 4 × 3 H, CH_3 on C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.37 (s, 3 H, CH_3 on C_3), 2.64 (t, 2 H, CH_2 on $C_{4'}$, J = 6.5 Hz), 4.18 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.78 (s, 1 H, H_2), 6.18 (d, 1 H, H_6, J = 12 Hz), 6.19 (d, 1 H, H_8, J = 16 Hz), 6.31 (d, 1 H, H_4, J = 15 Hz), 6.72 (d, 1 H, H_9, J = 16 Hz), 7.02 (dd, 1 H, H_5, J = 15 Hz, J = 12 Hz). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.29; H, 8.87.

(6) 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic Acid (29a). Saponification of ester **27a** (5 g, 0.012 mol) was conducted in ethanol (30 mL) and acetone (30 mL) by heating at 50 °C for 30 min in presence of 7 g (0.18 mol) of sodium hydroxide. The reaction mixture was then diluted with water (100 mL) and ether (100 mL) and acidified with 20% HCl until pH = 2. The aqueous layer was extracted three times with ether (3 × 50 mL). The organic phases were washed with saturated sodium chloride (3 × 100 mL), dried, and evaporated. The crude product was crystallized from acetone, yield 80% (3.7 g), mp 195–197 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6 H, CH_3 on $C_{2'}$), 1.82 (t, 2 H on $C_{3'}$, J = 6.5 Hz), 2.13, 2.17, 2.18, 2.20 (4 s, 4 × 3 H, CH_3 on C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.38 (s, 3 H, CH_3 on C_3), 2.64 (t, 2 H on $C_{4'}$, J = 6 Hz), 5.82 (s, 1 H, H_2), 6.19 (d, 1 H, H_6, J = 13.5 Hz), 6.20 (d, 1 H, H_8, J = 16 Hz), 6.34 (d, 1 H, H_4, J = 15 Hz), 6.75 (d, 1 H, H_9, J = 16 Hz), 7.08 (dd, 1 H, H_5, J = 15 Hz, J = 13.5 Hz). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.15; H, 8.41.

Synthesis of 9-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic Acid (29b). (1) 5-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3-methyl-3-hydroxypent-4-en-1-yne (20b) was prepared as compound **20a** from the ketone **19b**, yield 90%. ^1H NMR (200 MHz, $CDCl_3$): δ 1.43 (s, 6 H, 2 CH_3 en 4′), 1.67 (s, 3 H, CH_3 on 3), 1.83 (t, 2 H, CH_2 on 3′, J = 5 Hz), 2.11, 2.17, 2.34 (3 s, 3 × 3 H, CH_3 on 5′, 7′, and 8′), 2.64 (s, 1 H, H_1), 4.15 (t, 2 H, CH_2 on 2′, J = 5 Hz), 5.63 (d, 1 H, H_4, J = 16 Hz), 6.83 (d, 1 H, H_5, J = 16 Hz). IR (CCl_4) 3600 (OH), 3380 (OH), 3300 (H–C), 3960, 3920 cm^{-1}.

(2) Ethyl 9-(4′,4′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-4,7-dihydroxy-(2*E*,8*E*)-nona-2,8-dien-5-ynoate (21b) was prepared from the propargylic alcohol **20b** by the method described for the synthesis of **21a**, yield 95%. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.46 (s, 6 H, 2 CH_3), 1.85 (t, 2 H on $C_{3'}$, J = 7 Hz), 1.70 (s, 3 H, CH_3 on C_7), 2.12, 2.15, 2.16, and 2.19 (4 s, 4 × 3 H, CH_3 on C_3, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.14 (t, 2 H on $C_{2'}$, J = 7 Hz), 4.17 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.65 (s, 1 H, H_8, J = 16 Hz), 5.59 (s, 1 H, H_4), 6.51 (s, 1 H, H_2); 6.89 (d, 1 H, H_9, J = 16 Hz).

(3) Ethyl 9-(4′,4′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoate (27b) was prepared by the same reaction sequence as the ester **27a**, overall yield 55%, mp 122 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.45 (s, 6 H, 2 CH_3 on $C_{4'}$), 1.81 (t, 2 H on $C_{3'}$, J = 5 Hz), 2.11, 2.17, 2.20, 2.36, and 2.37 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.15 (t, 2 H, CH_2 on $C_{3'}$, J = 5 Hz), 4.18 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.78 (s, 1 H, H_2), 6.18 (d, 1 H, H_6, J = 12 Hz), 6.19 (d, 1 H, H_7, J = 16 Hz), 6.31 (d, 1 H, H_4, J = 15 Hz), 6.72 (d, 1 H, H_8, J = 16 Hz), 7.02 (dd, 1 H, H_5, J = 15 Hz, J = 12 Hz). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.20; H, 8.72.

(4) 9-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*E*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic acid (29b) was obtained by saponification of **27a**, yield 80%, mp 188–190 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.46 (s, 6 H, CH_3 on $C_{4'}$), 1.82–1.87 (m, 2 H, CH_2 on $C_{3'}$), 2.13 and 2.18 (2 s, 9 H and 3 H, CH_3 on C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.38 (s, 3 H, CH_3 on C_3), 4.13–4.18 (m, 2 H, CH_2 on $C_{2'}$), 5.82 (s, 1 H, H_2), 6.17 (d, 1 H, H_8, J = 16 Hz), 6.18 (d, 1 H, H_6, J = 10 Hz), 6.34 (d, 1 H, H_6, J = 15 Hz), 6.68 (d, 1 H, H_4, J = 16 Hz), 7.8 (dd, 1 H, H_5, J = 15 Hz, J = 10 Hz). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.70; H, 8.50.

Synthesis of 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic Acid (30a). (1) Methyl 9-(2′,2′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-4,7-dihydroxy-(2*Z*,8*E*)-nona-2,8-dien-5-ynoate (22a) was prepared from the ester (*Z*)-**8** and the propargylic alcohol **20a** by the method used to obtain the ester **21a**, yield 90%. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.30 (s, 6 H, 2 CH_3 on $C_{2'}$), 1.68 (s, 3 H, CH_3 on C_7), 1.82 (t, 2 H, CH_2 on $C_{3'}$, J = 7 Hz), 2.11, 2.15, 2.16, 2.17 (4 s, 4 × 3 H, CH_3 on C_3, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (t, 2 H on $C_{4'}$, J = 7 Hz), 3.80 (s, 3 H, OCH_3), 5.65 (d, 1 H, H_8, J = 16 Hz), 5.58 (s, broad pic, 1 H, H_4), 6.51 (s, 1 H, H_2), 6.89 (d, 1 H, H_9, J = 16 Hz).

(2) 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-1-[(trimethylsilyl)oxy]-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraene (26a) obtained by reductive elimination with Ti(0) in the conditions described for compound **25a**, overall yield 60%. ^1H NMR (200 MHz, $CDCl_3$): δ 0.11 (s, 9 H, CH_3 on Si), 1.32 (s, 6 H, CH_3 on $C_{2'}$), 1.81 (t, 2 H, H_2 on $C_{3'}$, J = 6.5 Hz), 1.75, 1.90, 2.11, 2.13, 2.16 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (t, 2 H on $C_{4'}$, J = 6.5 Hz), 4.32 (d, 2 H, H_2 on C_1, J = 8 Hz), 5.50 (t, 1 H, H_1, J = 8 Hz), 6.17 (d, 1 H, H_6, J = 11.5 Hz), 6.22 (d, 1 H, H_8, J = 16 Hz), 6.57 (d, 1 H, H_4, J = 16 Hz), 6.63 (dd, 1 H, H_5, J = 16 Hz, J = 11.5 Hz), 6.70 (d, 1 H, H_9, J = 16 Hz).

(3) Ethyl 9-(2′,2′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoate (28a) was obtained by the procedure described for the preparation of **27a**. The product was purified by chromatography (AcOEt/*n*-hexane, 10/90, R_f = 0.6), overall yield 70%, mp 112.5–113.5 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 1.27 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.32 (s, 6 H, CH_3 on $C_{2'}$), 1.82 (t, 2 H on $C_{3'}$, J = 7 Hz), 2.08, 2.10, 2.13, 2.17, 2.20 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.65 (t, 2 H on $C_{4'}$, J = 7 Hz), 4.16 (q, 2 H, CH_2CH_3, J = 7 Hz), 5.65 (s, 1 H, H_2), 6.20 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_6, J = 11.5 Hz), 6.71 (d, 1 H, H_9, J = 16 Hz), 7.01 (dd, 1 H, H_5, J = 15 Hz, J = 11.5 Hz), 7.80 (d, 1 H, H_4, J = 15 Hz). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.16; H, 8.77.

(4) 9-(2′,2′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic acid (30a) was obtained by saponification according the procedure described for **29a**. The product was chromatographied (AcOEt/*n*-hexane, 10/90, R_f = 0.6), yield 80%, mp 190–193 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6 H, CH_3 on $C_{2'}$), 1.85 (t, 2 H, H_2 on $C_{3'}$, J = 7.5 Hz), 2.08, 2.10, 2.13, 2.17, 2.20 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 2.64 (t, 2 H, H_2 on $C_{4'}$, J = 7.5 Hz), 5.68 (s, 1 H, H_2), 6.22 (d, 1 H, H_8, J = 16 Hz), 6.30 (d, 1 H, H_6, J = 11.5 Hz), 6.74 (d, 1 H, H_9, J = 16 Hz), 7.07 (dd, 1 H, H_5, J = 15.5 Hz, J = 11.5 Hz), 7.76 (d, 1 H, H_4, J = 15.5 Hz). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.62; H, 8.38.

Synthesis of 9-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic Acid (30b). (1) Methyl 9-(4′,4′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-4,7-dihydroxy-(2*Z*,8*E*)-nona-2,8-dien-5-ynoate (22b) was prepared from the propargylic alcohol **20b** by the method described for the synthesis of **22a**, yield 90%. ^1H

NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 6 H, 2 CH_3 on $C_{4'}$), 1.70 (s, 3 H, CH_3 on C_7), 1.85 (t, 2 H, H_2 on $C_{3'}$, J = 5 Hz), 2.12, 2.16, 2.17, 2.32 (4 s, 4 × 3 H, CH_3 on C_3, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 3.80 (s, 3 H, OCH_3), 4.15 (t, 2 H, H_2 on $C_{2'}$, J = 5 Hz), 5.61 (s, broad pic, 1 H, H_4), 5.65 (d, 1 H, H_8, J = 16 Hz), 6.51 (s, 1 H, H_2), 6.90 (d, 1 H, H_9, J = 16 Hz).

Ethyl 9-(4′,4′,5′,7′,8′-pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoate (28b) was obtained by the same procedure as the ester **28a** from the ester **22b**, overall yield 60%, mp 110–112 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, 3 H, CH_2CH_3, J = 7 Hz), 1.32 (s, 6 H, CH_3 on $C_{4'}$), 1.81 (t, 2 H on $C_{3'}$, J = 5 Hz), 2.08, 2.10, 2.13, 2.17, 2.20 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.12–4.23 (m, 4 H, CH_2CH_3 and H_2 on $C_{2'}$), 5.65 (s, 1 H, H_2), 6.20 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_6, J = 11.5 Hz), 6.71 (d, 1 H, H_9, J = 16 Hz), 7.01 (dd, 1 H, H_5, J = 15 Hz, J = 11.5 Hz), 7.80 (d, 1 H, H_4, J = 15 Hz). Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.59; H, 8.79.

9-(4′,4′,5′,7′,8′-Pentamethyl-6′-chromanyl)-3,7-dimethyl-(2*Z*,4*E*,6*E*,8*E*)-nona-2,4,6,8-tetraenoic acid (30b) was obtained by saponification of the ester **28b**, yield 60%, mp 195 °C dec. ^1H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 6 H, CH_3 on $C_{4'}$), 1.82–1.87 (m, 2 H, CH_2 on $C_{3'}$), 2.08, 2.13, 2.18, 2.22, 2.28 (5 s, 5 × 3 H, CH_3 on C_3, C_7, $C_{5'}$, $C_{7'}$, and $C_{8'}$), 4.13–4.18 (m, 2 H, CH_2 on $C_{2'}$), 5.65 (s, 1 H, H_2), 6.15 (d, 1 H, H_8, J = 16 Hz), 6.28 (d, 1 H, H_6, J = 10 Hz), 6.71 (d, 1 H, H_9, J = 16 Hz), 7.06 (dd, 1 H, H_5, J = 15 Hz, J = 10 Hz), 7.73 (d, 1 H, H_4, J = 15 Hz). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.77; H, 8.61.

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Registry No. 1*E*, 62054-49-3; 1*E* (dimethyl acetal), 65527-84-6; 1*Z* (dimethyl acetal), 70423-44-8; (±)-**2**, 94369-94-5; (±)-**3** (isomer 1), 118304-67-9; (±)-**3** (isomer 2), 118333-95-2; (±)-**3** (triol, isomer 1), 118304-71-5; (±)-**3** (triol, isomer 2), 118333-96-3; (±)-**4** (isomer 1), 118304-68-0; (±)-**4** (isomer 2), 118304-64-6; (±)-**4** (alkyne, isomer 1), 118304-70-4; (±)-**4** (alkyne, isomer 2), 118304-66-8; (±)-**5** (isomer 1), 118304-65-7; (±)-**5** (isomer 2), 118304-69-1; **6**, 118353-70-1; **6** (alcohol), 68-26-8; **6** (aldehyde), 116-31-4; **6** (acid), 302-79-4; (±)-**7**, 78646-59-0; **8**, 96928-85-7; **9**, 119947-50-2; **9** (triol), 119947-83-0; **10**, 62054-50-6; **11**, 119947-51-2; **12a**, 120306-88-9; **12b**, 119947-81-8; **12c**, 119947-82-9; **12** (triol), 119996-77-9; **13a**, 118304-54-4; **13b**, 118304-57-7; **13c**, 118304-60-2; **13** (alcohol), 2052-63-3; **13** (aldehyde), 472-86-6; **13** (acid), 59699-82-0; **13** (acid, ethyl ester), 4759-48-2; **14**, 697-82-5; **15**, 119947-52-3; (±)-**15** (epoxide), 119947-80-7; **16**, 119947-53-4; **17a**, 55646-01-0; **17b**, 40614-29-7; **18a**, 119947-54-5; **18b**, 119947-77-2; **19a**, 119947-55-6; **19b**, 119947-78-3; (±)-**20a**, 119947-56-7; (±)-**20b**, 119947-79-4; (±)-**21a** (isomer 1), 119947-57-8; (±)-**21a** (isomer 2), 119947-86-3; (±)-**21a** (triol, isomer 1), 119947-71-6; (±)-**21a** (triol, isomer 2), 119947-90-9; (±)-**21b** (isomer 1), 119947-63-6; (±)-**21b** (isomer 2), 119947-87-4; (±)-**21b** (triol, isomer 1), 119947-72-7; (±)-**21b** (triol, isomer 2), 119947-91-0; **22a**, 119947-58-9; **22a** (triol), 120306-91-4; **22b** (triol), 120306-92-5; **22b**, 119947-64-7; (±)-**23a** (isomer 1), 119947-59-0; (±)-**23a** (isomer 2), 119947-84-1; (±)-**23a** (alkyne isomer 1), 119947-69-2; (±)-**23a** (alkyne isomer 2), 119947-88-5; (±)-**23b** (isomer 1), 119947-65-8; (±)-**23b** (isomer 2), 119947-85-2; (±)-**23b** (alkyne isomer 1), 119947-70-5; (±)-**23b** (alkyne, isomer 2), 119947-89-6; **24a**, 120306-89-0; **24a** (5,6-didehydro), 120306-93-6; **24b**, 120306-90-3; **24b** (5,6-didehydro), 120306-94-7; **25a**, 119947-60-3; **25a** (alcohol), 119947-73-8; **25b**, 119947-66-9; **25b** (alcohol), 119947-74-9; **26a**, 120020-73-7; **26a** (alcohol), 120020-79-3; **26b**, 120020-76-0; **26b** (alcohol), 120020-80-6; **27a**, 119947-61-4; **27b**, 119947-67-0; **28a**, 120020-74-8; **28b**, 120020-77-1; **29a**, 119947-62-5; **29a** (aldehyde), 119947-75-0; **29b**, 119947-68-1; **29b** (aldehyde), 119947-76-1; **30a**, 120020-75-9; **30a** (aldehyde), 120020-81-7; **30b**, 120020-78-2; **30b** (aldehyde), 120020-82-8; $(MeO)_2CHCOCH_3$, 6342-56-9; β-ionone, 79-77-6.

6-Substituted Bicyclo[2.2.1]hept-5-en-2-one Ketals

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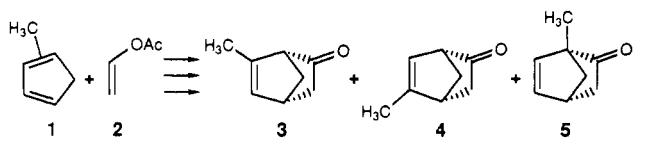
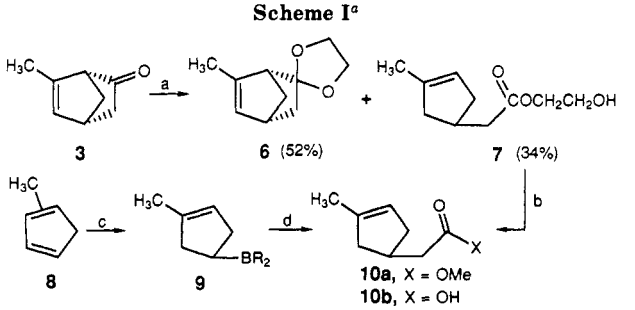
Structurally specific syntheses of isomerically pure 6-substituted bicyclo[2.2.1]hept-5-en-2-one ketals were explored. A conversion of the Diels–Alder adduct of itaconic anhydride with cyclopenta-1,3-diene into a ketal of 6-methylbicyclo[2.2.1]hept-5-en-2-one was accomplished, but the last step, an oxidative vicinal bisdecarboxylation, gave only a 35% yield. The ethylene ketal of 6-methylbicyclo[2.2.1]hept-5-en-2-one was prepared in 80% overall yield from bicyclo[2.2.1]hept-5-en-2-one by a regioselective replacement of hydrogen with a methyl group. Practical syntheses of the 6-bromo, 6-carbomethoxy, 6-phenylthio, and 6-trimethylsilyl analogues were accomplished similarly.

We recently demonstrated that carbonyl-masked derivatives of 6-methylbicyclo[2.2.1]hept-5-en-2-one (**3**) are valuable intermediates for the total synthesis of spatane diterpenes.[1] A Diels–Alder strategy provides a practical route to multimolar quantities of 6-methylbicyclo[2.2.1]-hept-5-en-2-one (**3**) from methyl-1,3-cyclopentadiene (**1**) and vinyl acetate (**2**)[2] since the isomeric coproducts **4** and **5** are separable by spinning-band distillation.[2d] However,



Scheme I[a]



[a] (a) Ethylene glycol/*p*-TsOH/benzene/Dean–Stark trap/boil 2.5 h; (b) *p*-TsOH/THF/H_2O/boil/48 h, then CH_2N_2/ether; (c) borane/THF; (d) t-BuOH/t-BuOK/$BrCH_2COOMe$, then 1 N $NaOH/H_2O_2$.

ethylene ketalization of **3** gave the ketal in disappointingly low yield (vide infra) under conditions that give an excellent yield of ketal from the 6-unsubstituted analogue bicyclo[2.2.1]hept-5-en-2-one.[3] To improve the availability

(1) Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211.

(2) (a) Krieger, H.; Mason, S.-E. *Suomen Kemistilehti B* **1970**, *43*, 318. (b) Mason, S.-E.; Krieger, H. *Ibid.* **1969**, *42*, 1. (c) Brown, H. C.; Peters, E. N.; Ravindranathan, M. *J. Am. Chem. Soc.* **1975**, *97*, 7449: the procedure is easily performed on a multikilogram scale, and the reported yield of **3** can be more than doubled by employing Swern rather than Jones oxidation of intermediate methylbicyclo[2.2.1]hept-5-enols. (d) Goering, H. L.; Chang, C.-S. *J. Org. Chem.* **1975**, *40*, 2565.

(3) Monti, S. A.; Yuan, S.-S. *J. Org. Chem.* **1971**, *36*, 3350.

0022-3263/89/1954-2628$01.50/0