Dr. G. Saucy for his continued support throughout this work.

Registry No. 1 (X = O), 514-78-3; **3**, 5056-17-7; **4**, 20013-73-4; **5**, 72008-25-4; **6**, 63184-57-6; **7** (R = Ac), 63184-83-8; **7** (R = H), 64095-63-2; (±)-**8**, 81276-62-2; (*E*)-**9**, 63184-87-2; (*Z*)-**9**, 72008-48-1; **10**, 60068-02-2; (*E*)-**11**, 63184-82-7; **12**, 64095-45-0; **13**, 63184-86-1; **14**, 13395-71-6; **15**, 72008-26-5; **15**-bromide, 79749-53-4; (2*E*,4*E*)-**16**, 63184-93-0; (2*E*,4*Z*)-**16**, 81276-63-3; (±)-(*E*)-**17**, 30685-95-1; **18**, 37677-81-9; (±)-**19**, 71597-08-5; **20**, 72008-46-9; **21**, 67777-15-5; (±)-**22**, 81276-64-4; **23**, 72008-45-8; **24** (X = ClO_4), 72008-44-7; 3-hydroxy-3-methyl-1-penten-4-yne, 3230-69-1; (*E*)-3-methyl-2-penten-4-yn-1-ol, 6153-06-6; methyl isobutyrate, 547-63-7; ethyl vinyl ketone, 1629-58-9; vinyl chloride, 75-01-4.

Synthesis of 2,2′-Dinorcanthaxanthin

Michael Rosenberger* and Patrick J. McDougal

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received November 23, 1981

A short convergent synthesis of the title compound has been developed from 2-methylcyclopentane-1,3-dione, (*E*)-3-methyl-2-penten-4-ynol, and (2*E*,4*E*,6*E*)-2,7-dimethyl-2,4,6-octatriene-1,8-dial.

Among the dinorcarotenoids, 2,2′-dinorcanthaxanthin and its oxidation products, actinioerythrol[1] and violerythrin,[2] show interesting tinctorial properties and could prove to be useful as food-coloring agents.[3] To date, syntheses leading to the 2,2′-dinorcarotenoids, in particular, 2,2′-dinorcanthaxanthin (**1**, $n = 1$), have suffered from low yields because of difficulty accessible synthons containing the functionalized cyclopentane ring system.[4] The successful synthesis of canthaxanthin[5] (**1**, $n = 2$) employing a Wittig coupling of a C_{15} phosphonium salt **2** ($n = 2$) with the symmetrical dialdehyde[6] **3** led us to develop a similar route for the synthesis of **1** ($n = 1$), which is the subject of this paper.

The desired phosphonium salt **2** ($n = 1$) was prepared from the fragments **4** and **5**[5] (Figure 1). The synthesis of the required cyclopentenone **4** was achieved through alkylation[7] of the keto–enol ether **6**, which was readily available from the steroid intermediate 2-methylcyclopentane-1,3-dione (Figure 2). Slow addition of methyl iodide to the enolate of **6**, formed with lithium diisopropyl amide (LDA), at low temperature (−70 °C) resulted in a mixture of equal amounts of starting ketone **6**, monomethylated material **7**, and the desired product **4**. The rapid addition of methyl iodide to the cold enolate solution is accompanied by a fast temperature rise (−70→0 °C) and leads to the formation of *only* the monomethylated derivative **7**. However, by the repeated addition of LDA followed by methyl iodide, and analyzing the progress of the reaction by gas–liquid chromatography, it was possible to convert **6** into **4** in better than 70% yield. Condensation of the lithium salt of **5** with **4** yielded the desired 1,2-addition product,[8] **11**, after treatment with water.[9] Exposure of **11** to dilute aqueous acid then yielded the crystalline alcohol **12**.

When impure samples of **4** were employed in the above sequence, distillation of the reaction product gave a new material identified as **13** as well as **11**. This new product possibly arises from the dehydration of **15** which is formed from **8**, a contaminant of **4**, produced in the alkylation sequence (compound **8** probably arises from the alkylation of the dianion **9** rather than further alkylation of **4** as reexposure of **4** to the alkylation conditions gave only unchanged starting material). Hydrolysis of **13** with dilute aqueous acid yielded the hydroxy ketone **14**, which has similar properties to **12** but contains an extra methyl group.

Hydrogenation of **12** under the conditions employed previously[5] proved disappointing in that mixtures of overreduced products and starting material were formed. The catalytic hydrogenation of dienynes, such as **12**, has been a persistent problem in polyene chemistry.[10] Although some authors[11] have reported quantitative yields of trienes, many more have experienced problems of overreduction.[12] The desired reduction was eventually achieved with a Lindlar catalyst[13] poisoned with quinoline in ethyl acetate. Under these conditions the expected 2*E*,4*Z* isomer **16** was obtained in approximately 90% yield (^1H NMR analysis; Figure 3). The stereochemistry about the new double bond was confirmed by oxidation of **16** to the aldehyde **17**, which was identical with a sample prepared by the hydrogenation of **18**. Isomerization of **17** with iodine and light gave the expected all-trans isomer **19**.

Treatment of **16** with phosphorus tribromide gave a very unstable bromo compound which was immediately converted to the phosphonium salt **2** ($n = 1$) with triphenylphosphine in refluxing benzene. Condensation of the crude salt with the dialdehyde **3** then yielded 2,2′-

(1) Lederer, E.;Fabre, R. *Bull. Soc. Chim. Biol.* **1934**, *16*, 105.
(2) Heilbron, I. M.; Jackson, H.; Jones, R. N. *Biochem. J.* **1935**, *29*, 1384.
(3) The structures of these materials were not determined until recently. Hertzberg, S.; Liaaen-Jensen, S. *Acta Chem. Scand.* **1969**, *23*, 3290.
(4) Kienzle, F.; Minder, R. E. *Helv. Chim. Acta* **1976**, *59*, 439.
(5) (a) A preliminary account of this work was presented at the Fifth International Symposium on Carotenoids, July 1978, Madison, WI. Rosenberger, M.; McDougal, P.; Saucy, G.; Bahr, J. *Pure Appl. Chem.* **1979**, *51*, 871. (b) The full paper has been accepted for publication. Rosenberger, M.; McDougal, P.; Bahr, J. *J. Org. Chem.* **1982**, in press.
(6) "Carotenoids"; Isler, O., Ed.; Birkhauser Verlag: Basel and Stuttgart, **1971**.
(7) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(8) Enol ethers of α-formylcyclopentanones give predominantly products of 1,4 addition. Ferro, M. P. Ph.D. Dissertation, University of Michigan, Ann Arbor, MI, 1980.
(9) In general, these adducts do not need an acid treatment to form the ketones. In some cases these vinylogous hemiacetals are even stable to chromatography on silica gel.
(10) Marvell, E. N. *Synthesis* **1973**, *8*, 457.
(11) Mildner, P.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 3294.
(12) Marvell, E. N.; Tashiro, J. *J. Org. Chem.* **1965**, *30* 3991.
(13) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446.

0022-3263/82/1947-2134$01.25/0

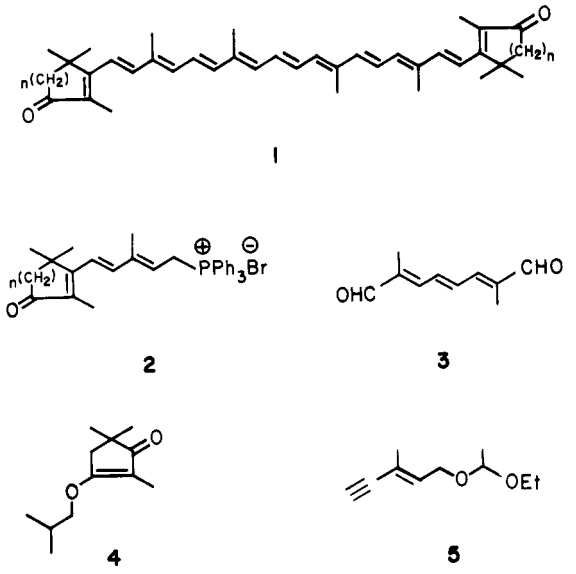

Figure 1.

dinorcanthaxanthin in approximately 60% yield. This Wittig coupling reaction was not as efficient as in the synthesis of canthaxanthin. The lower yields of the dinorcarotenoid can be explained by the instability of the ylide formed from **2** (n = 1). In this condensation the monoadduct **20** is rapidly formed, while the addition of the second C_{14} unit is slow and allows the ylide time to be involved in other reactions.

In summary, the work described permits ready access to 2,2'-dinorcanthaxanthin, a compound with interesting tinctorial properties; the method is also suitable for making the more highly oxygenated derivatives as well.[14]

Experimental Section[15]

3-Isobutoxy-2-methyl-2-cyclopentenone (6). A mixture of 2-methylcyclopentane-1,3-dione (45 g, 0.4 mol), isobutyl alcohol (60 mL), *p*-toluenesulfonic acid (PTSA; 1 g), and benzene (250 mL) was heated at reflux for 6 h in conjunction with a water-cooled Dean–Stark trap. After this time more isobutyl alcohol (40 mL) and PTSA (0.5 g) were added, and the mixture was heated at reflux for 10 h as before. After the reaction mixture had cooled to room temperature, triethylamine (4 mL) was added, the solvents were removed in vacuo, and the residue was distilled to yield **6** (67.3 g, 100%): bp 110 °C (1.5 mm); ^{1}H NMR (CCl_4) δ 4.0 (d, 2, J = 3 Hz, $OCH_2CH(CH_3)_2$), 1.60 (t, 3, J = 1 Hz, C_2-CH_3), 1.0 (d, 6, J = 6 Hz, $OCH_2CH(CH_3)_2$); mass spectrum, m/e 168 (M^+). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.78; H, 9.56.

3-Isobutoxy-2,5,5-trimethyl-2-cyclopentenone (4). A solution of LDA in tetrahydrofuran (THF) was prepared as follows. *n*-Butyllithium (2.3 M in hexane, 326 mL) was added to THF (390 mL) at −70 °C and treated with diisopropylamine (84 g, 0.83 mol). After being stirred for a further 20 min at −70 °C, the clear solution was warmed to 0 °C and used in the following preparation.

The keto–enol ether **4** (55 g, 0.327 mol) was added to a solution of LDA (365 mL) at −70 °C, and the mixture was stirred for 5 min and then carefully treated with methyl iodide (46.2 g, 0.325 mol). After complete addition the mixture was warmed to room temperature, stirred an additional 15 min, and cooled to −70 °C. More base (255 mL) was then added followed by more methyl iodide and the above process was then repeated 3 more times (base, 109, 73, and 36.4 mL; methyl iodide, 13.8, 9.2, and 4.6 g). After each addition an aliquot was removed from the reaciton mixture, quenched with water, and analyzed by GLC. After the final addition of base and alkylating agent, water was added, and the products were isolated with ether and distilled (flash distillation) to yield the mixture of alkylation products (60 g), bp 86 °C (0.5 mm), containing 87.6% **4**. Distillation through an 18-in. Goodloe column at 320 mm gave **4** (47.2 g, 73%, 95% pure by GLC): ^{1}H NMR ($CDCl_3$) δ 3.95 (d, 2, J = 6 Hz, $OCH_2CH(CH_3)_2$), 2.53 (s, 2, H-4), 1.65 (s, 3, C_2-CH_3), 1.16 (s, 6, C_5-CH_3), 1.03 (d, 6, J = 6 Hz, $OCH_2CH(CH_3)_2$). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.11; H, 10.27.

(*E*)-3-Methyl-5-(3-oxo-2,5,5-trimethyl-1-cyclopenten-1-yl)-2-penten-4-ynol (12). A solution of **5** (36.8 g, 0.219 mol) in ether (200 mL) was cooled to −60 °C and treated with *n*-butyllithium (1.6 M in hexane, 137 mL) and subsequently warmed to room temperature. To this mixture was added the keto–enol ether **4** (29 g, 148 mmol) dissolved in ether (100 mL), and after being stirred for a further 45 min, the reaction mixture was washed with brine (saturated), dried ($MgSO_4$), and concentrated to yield the curde adduct **11** as an oil (59.4 g): ^{1}H NMR ($CDCl_3$) δ 6.17 (t, 1, J = 6 Hz, H-2), 4.77 (q, 1, J = 5 Hz, $OCHCH_3$), 6.9 (d, 2, J = 6 Hz, H-1), 3.58 (m, 1, OCH_2CH_3), 2.33 (s, 2, H-4), 1.95 (s, 3, C_3-CH_3), 1.83 (s, 3, C_2-CH_3), 1.28 (s, 6, C_5-CH_3). The crude product was dissolved in acetone (200 mL), treated with aqueous sulfuric acid (5%, 100 mL), and left at room temperature for 90 min. Removal of the acetone in vacuo [25 °C (20 mm)] and extraction of the residual aqueous suspension with ether yielded the crude alcohol **12** (33.2 g). Crystallization from a mixture of benzene and hexane gave pure **12** (25.8 g, 80%): mp 66–68 °C; ^{1}H NMR ($CDCl_3$ δ 6.18 (t, 1, J = 6 Hz, H-2), 4.31 (d, 2, J = 6 Hz, H-1), 2.33 (s, 2, H-4), 1.93 (s, 3, C_3-CH_3), 1.83 (s, 3, C_2-CH_3), 1.28 (s, 6, C_5-CH_3). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.32. Found: C, 77.11; H, 8.27.

Isolation of Compounds 13 and 14. When the above sequence was repeated with impure **4** containing **8**, the primary adduct after distillation [120 °C (0.1 mm)] on chromatography on silica gel yielded **13** on elution with 5% and 10% ether–hexane mixtures: ^{1}H NMR ($CDCl_3$) δ 5.97 (t, 1, J = 6 Hz, H-2), 4.75 (q, 1, J = 5 Hz, $OCH(CH_3)_2$), 4.2 (d, 2, J = 6 Hz, H-1), 3.63 (d, 2, J = 6 Hz, $OCH_2CH(CH_3)_2$), 3.65 (m, 2, OCH_2CH_3), 1.98 (s, 3, C_4-CH_3), 1.92 (s, 3, C_3-CH_3), 1.80 (s, 3, C_2-CH_3), 1.67 (s, 6, C_5-CH_3); mass spectrum, m/e 360 (M^+).

Hydrolysis of this material with aqueous acid in acetone as before yielded pure **14** after chromatographic purification on silica gel: ^{1}H NMR ($CDCl_3$) δ 6.13 (t, 1, J = 6 Hz, H-2), 4.28 (d, 2, J = 6 Hz, H-1), 3.0 (s, 1, OH), 2.2 (q, 1, J = 7 Hz, H-4), 1.93 (s, 3, C_3-CH_3), 1.83 (s, 3, C_2-CH_3), 1.26 (s, 3, C_5-CH_3), 1.1(d, 3, J = 7 Hz, C_4-CH_3), 1.05 (s, 3, C_5-CH_3); mass spectrum, m/e 232 (M^+).

(2*E*,4*Z*)-3-Methyl-5-(3-oxo-2,5,5-trimethyl-1-cyclopenten-1-yl)-2,4-pentadienol (16). A mixture of Lindlar catalyst[12] (4 g), anhydrous potassium carbonate (5.5 g), and quinoline (0.009 mL) in ehtyl acetate was saturated with hydrogen at room temperature and pressure. The alcohol **12** (7.7 g) was then added and the hydrogenation was continued for 130 min (rapid hydrogen uptake with no break in the curve). After this period [910 mL of hydrogen consumed at 21 °C (760 mm)], the solids were filtered off, and the mixture was concentrated to yield ~90% pure **16** (7.71 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.35, 5.92 (dd, 2, J = 13 Hz, H-4, H-5), 5.75 (t, 1, J = 7 Hz, H-2), 4.22 (d, 2, J = 7 Hz, H-1), 3.0 (s, 1, OH), 2.33 (s, 2, H-4), 1.67 (s, 3, C_3-CH_3), 1.58 (s, 3, C_2-CH_3), 1.32 (s, 6, C_5-CH_3). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C 76.03; H, 9.41. In the ^{1}H NMR spectrum a complex multiplet at δ 3.6 was used to estimate the approximate purity of this reduction product.

(*E*)-3-Methyl-5-(3-oxo-2,5,5-trimethyl-1-cyclopenten-1-yl)-2-penten-4-ynal (18). A mixture of dichloromethane (400 mL) containing pyridine (31.6 g) was cooled in an ice bath and

(14) Kienzle, F.; Minder, R. E. *Helv. Chim. Acta* **1978**, *61*, 242.

(15) Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All reactions were carried out under an atmosphere of nitrogen. The organic extracts were concentrated with a Buchi rotavapor at water aspirator pressure at 40–50 °C and finally at 0.5 mm at 45 °C. Column chromatography was performed with Merck (Darmstadt) silica gel (0.2–0.5 mm), and thin-layer chromatograms (TLC) were run on Brinkmann silica gel G plates with a UV indicator. Spots were made visible by UV light, spraying with a 10% methanolic solution of phosphomolybdic acid, and heating at 120 °C. Varian HA-100 and A-60 spectrometers were employed to record proton magnetic resonance spectra (^{1}H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-9 spectrometer, and ultraviolet (UV) spectra were recorded on a Cary Model 14M spectrophotometer. Gas–liquid chromatography (GLC) was carried out on a Hewlett Packard 402 gas chromatograph using 20% Carbowax on Chromosorb W.A.W. DMCS (80–100 mesh) in a 2-m glass column.

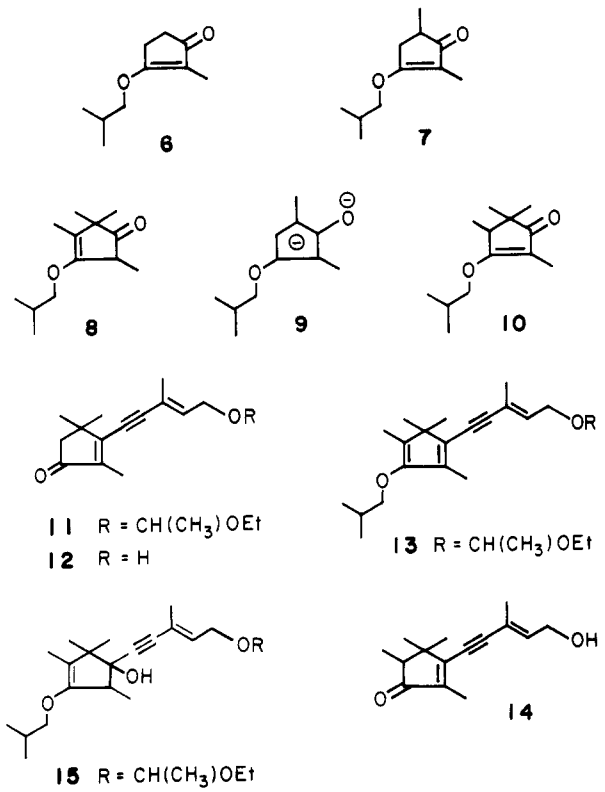

Figure 2.

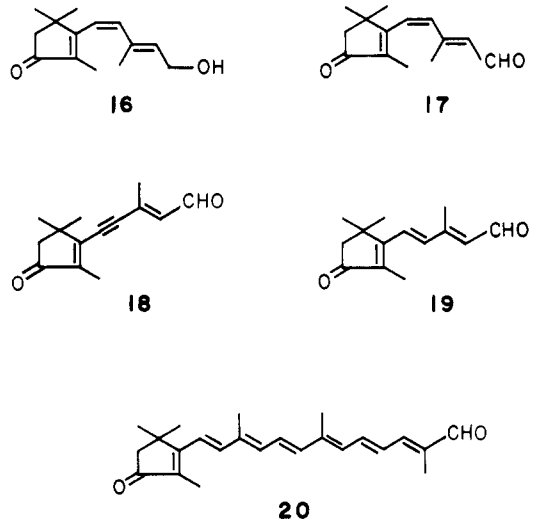

Figure 3.

carefully treated with chromium trioxide (20 g, 0.2 mol). This mixture was then stirred for 15 min, treated with a solution of the alcohol **12** (14 g, 64 mmol) dissolved in dichloromethane, and then stirred for a further 5 h at room temperature. After the addition of chloroform (500 mL) the mixture was washed free of chromium salts with an acidic solution of sodium bisulfite. After the mixture dried ($MgSO_4$), the solvents were removed in vacuo to yield the crude aldehyde (12.75 g, 92%) as a solid. The analytical sample was crystallized from 2-propanol: mp 67–72 °C; ^{1}H NMR ($CDCl_3$) δ 10.1 (d, 1, J = 8 Hz, H-1), 6.30 (dq, 1, J = 8, 1 Hz, H-2), 2.43 (d, 3, J = 1 Hz, C_3-CH_3), 2.37 (s, 2, H-4), 1.87 (s, 3, C_2-CH_3), 1.33 (s, 6, C_5-CH_3); UV max (2-propanol) 238 nm, (ϵ 10 900), 313 (23 000).

Aldehydes 17 and 19. A suspension of a Lindlar catalyst (300 mg) in ethyl acetate (25 mL) was saturated with hydrogen and then treated with the aldehyde **18** (500 mg, 2.3 mmol). Hydrogenation was then continued until 58.1 mL of hydrogen had been consumed [20 °C (760 mm)]. The solids were filtered off and the solvents were removed in vacuo to yield a 2:1 mixture of **17** and **19**. Chromatography on silica gel yielded the pure cis isomer **17** on elution with 10% benzene in hexane: ^{1}H NMR ($CDCl_3$) δ 10.1 (d, 1, J = 8 Hz, H-1), 6.45 (s, 2, H-4, H-5), 5.92 (d, 1, J = 8 Hz, H-2), 2.33 (s, 2, H-4), 2.23 (s, 3, C_3-CH_3), 1.57 (s, 3, C_2-CH_3), 1.33 (s, 6, C_5-CH_3). When the same hydrogenation was carried out in the presence of anhydrous potassium carbonate (550 mg) and quinoline (0.006 mL), primarily the all-trans isomer was obtained.

Exposure of the cis isomer **17** to a trace of iodine in $CDCl_3$ and light (72 h) yielded the trans product **19**: ^{1}H NMR ($CDCl_3$) δ 10.26 (d, 1, J = 7 Hz, H-1), 6.88 (s, 2, H-4, H-5), 6.10 (d, 1, J = 7 Hz, H-2), 1.88 (s, 3, C_3-CH_3), 1.33 (s, 6, C_5-CH_3).

Oxidation of the alcohol **16** with chromium trioxide and pyridine yielded the aldehyde corresponding to **17**, thus confirming the stereochemistry of the reduction product from **12**.

[(2*E*,4*E*)-3-Methyl-5-(3-oxo-2,5,5-trimethyl-1-cyclopenten-1-yl)-2,4-pentadienyl]triphenylphosphonium Bromide (2, *n* = 1). A solution of the crude hydrogenation product **16** (1.64 g, 7.45 mmol, ~20% overreduction) in ether (15 mL) was cooled to −60 °C, treated with phosphorus tribromide (1.08 g) in ether (3 mL), stirred for a further 1 h at −60 °C, and then warmed slowly to room temperature. Water was then carefully added and the ether was then washed with brine, dried ($MgSO_4$), and filtered. Benzene (20 mL) was then added and the ether was removed in vacuo to yield a solution of the bromide in benzene. To this solution was added triphenylphosphine (1.95 g, 7.44 mmol) in benzene (20 mL) and the mixture was then concentrated to half volume in vacuo and then heated at reflux for 90 min. Anhydrous ether (30 mL) was then added and the mixture was decanted and the residual salt was then washed twice (2 × 10 mL) with more ether and dried. This crude salt (3.1 g, 79%) which showed several minor impurities by TLC analysis (*n*-butyl acetate–formic acid–water, 40:9:1) was used in the next step. **2**: ^{1}H NMR ($CDCl_3$) δ 7.8 (m, 15, phenyl H), 6.5 (dd, 2, J = 15 Hz, H-4, H-5), 5.7 (m, 1, H-2), 5.0 (dd, 2, J = 8, 16 Hz, H-1), 2.3 (s, 2, H-4), 2.8 (s, 3, C_2-CH_3), 2.6 (m, 3, C_3-CH_3), 1.2 (2 s, 6, C_5-CH_3).

2,2′-Dinorcanthaxanthin (1, *n* = 1). A mixture of the crude phosphonium salt **2** (*n* = 1, 12 g, 22.9 mmol) and the dialdehyde **3** (1.18 g, 7.2 mmol) dissolved in dichloromethane (150 mL) was cooled to −10 °C and over a period of 45 min was treated with a solution of sodium methoxide in methanol (15.6 mL, 1.41 M). After complete addition of the base, the reaction mixture was warmed to room temperature and stirred for a further 2 h. Water was then added, the organic phase was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (150 g, 20% ether–dichloromethane) to yield two major fractions, 2,2′-dinorcanthaxanthin and the monoadduct **20** (2 g).

The monoadduct **20** (2 g, 5.7 mmol) was dissolved in dichloromethane (30 mL) containing more phosphonium salt (2.8 g, 5.3 mmol) and treated with sodium methoxide (3.66 mL, 1.41 M) as before. Workup and chromatography as before yielded more of the desired product. The combined 2,2′-dinorcanthaxanthin fractions were crystallized from a methanol–dichloromethane mixture to yield pure material (2.34 g, 60%): mp 218–222 °C; UV max (ethanol–2% dichloromethane) 245 nm, 277, 323, 505 (ϵ 10 200, 12 500, 24 300, 120 000); mass spectrum, m/e 536 (M^+). A sample purified as in ref 4 had the following: mp 230–232 °C; UV max (hexane–0.4% dichloromethane) 461 nm, 488, 521 ($E_1^{1\%}$, 1820, 2406, 1960). Anal. Calcd for $C_{38}H_{48}O_2 \cdot CH_3OH$: C, 82.35; H, 9.21. Found: C, 82.65; H, 8.81.

As in the case of canthaxanthin these carotenoids sequester solvents, such as chloroform, dichloromethane, and methanol, which results in variable melting points and microanalytical data.

Acknowledgment. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ, for supplying most of the spectroscopic data and all the microanalytical data. We also than Dr. G. Saucy for his continued encouragement and support throughout this work.

Registry No. **1** (*n* = 1), 58626-46-3; **2** (*n* = 1), 59534-47-3; **3**, 5056-17-7; **4**, 63184-95-2; **5**, 63184-82-7; **6**, 22117-97-1; **7**, 72419-98-8; **8**, 72008-33-4; **11**, 81340-51-4; **12**, 64095-49-4; **13**, 72008-41-4; **14**, 72008-42-5; **16**, 64095-50-7; **16** bromide, 64095-51-8; **17**, 72008-34-5; **18**, 81340-52-5; **19**, 59534-40-6; **20**, 81340-53-6; 2-methylcyclopentane-1,3-dione, 765-69-5.