(d, 6, vinyl H), 7.62 (s, 10, Ar H); ^{13}C NMR 147.78, 134.52, 128.06, 127.78, 125.67, and 117.63 (Ar and Vinyl C), 48.71 and 41.99 ppm (allyl and quaternary aliphatic carbons); mass spectrum, *m/e* (relative intensity) 248 (0.06, M^+), 207 (0.5, M - 41), 129 (100).

Reaction of Benzophenone Dimethyl Ketal with Allyltrimethylsilane and Boron Trifluoride. Dry boron trifluoride gas was introduced to a solution of benzopheone dimethyl ketal (2.28 g, 10 mmol) and allyltrimethyl silane (2.4 g, 21 mmol) in 30 mL of methylenechloride at 0 °C for 15 min. The cold organic solution was quenched with 40 mL of 1 M sodium carbonate solution, and the phases were separated. After drying and evaporation of the solvent, there was obtained 2.02 g of a light amber oil which was chromatographed on silica gel eluted with 1:1 cyclohexane/methylene chloride to yield 1.86 g (75%) of pure **21**.

Registry No. **1**, 91-01-0; **2**, 574-42-5; **3**, 101-81-5; **4**, 617-94-7; **5** (isomer I), 6258-73-7; **5** (isomer II), 6362-80-7; **6**, 3910-35-8; **7**, 4286-85-5; *cis*-**8**, 40595-35-5; *trans*-**8**, 40595-34-4; **9**, 81194-40-3; **10**, 81194-41-4; **11**, 19303-32-3; **12**, 530-48-3; **13**, 6480-80-4; **14**, 1075-74-7; **15a**, 81194-42-5; **15b**, 81194-43-6; **15c**, 81194-44-7; **16a**, 4286-85-5; **16c**, 10340-49-5; **17** (isomer I), 81194-45-8; **17** (isomer II), 81194-46-9; **18**, 81194-47-0; **19**, 7087-22-1; **21**, 81194-48-1; **22a**, 2235-01-0; **22b**, 2186-93-8; **22c**, 81194-49-2; triphenylmethane, 519-73-3; polystyrene, 9003-53-6; 4-(2-methoxyphenyl)-4-(3-methoxyphenyl)-1-butene, 81194-50-5; 4-(3-hydroxyphenyl)-4-methyl-1-pentene, 81194-51-6; 4-phenyl-4-methyl-1-pentene, 66622-39-7; 4-(*p*-isopropylphenyl)-4-methyl-1-pentene, 81194-52-7; benzophenone, 119-61-9; allyltrimethylsilane, 762-72-1; titanium tetrachloride, 7550-45-0; boron trifluoride, 7637-07-2; 1,1-diphenylethanol, 599-67-7; 4-(*p*-hydroxyphenyl)-4-methyl-1-pentene, 35029-26-6; (2-methoxyphenyl)(3-methoxyphenyl)methanol, 81194-53-8; 1,1-bis(4-methoxyphenyl)-ethanol, 728-87-0; 2-(4-isopropylphenyl)-2-propanol, 3445-42-9; 2-(3-hydroxyphenyl)-2-propanol, 7765-97-1; 2-(4-hydroxyphenyl)-2-propanol, 2948-47-2; 1-phenylethanol, 98-85-1; cyclohexanol, 108-93-0; 2-methyl-2-propanol, 75-65-0; 4,4-bis(4-methoxyphenyl)-1-pentene, 81194-54-9.

Canthaxanthin. A New Total Synthesis

Michael Rosenberger,* Patrick McDougal, and Julie Bahr

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

Received November 23, 1981

A new synthesis of canthaxanthin via a Wittig coupling of the C_{15} phosphonium salt **16** and the symmetrical dialdehyde **3** is reported. Several routes to the key phosphonium salt via substituted cyclohexenones **4** and **10** and α-ionone are described.

Recent results on the pharmacological effects of the coal-tar-based azo dyes has led to the withdrawl of the food coloring agent Red No. 2 from the certified list of dyes permitted for the use in foods and drugs. The need for safe red coloring agents for human use has generated renewed interest in canthaxanthin **1** (X = O), a natural carotenoid[1] which exhibits excellent tinctorial properties.[2]

The present commerical process used to manufacture canthaxanthin[1] is based on the oxidation of β-carotene[3] **1** (X = H: Figure 1) and proceeds through the intermediate acetate **1** (X = H, OAc) and alcohol **1** (X = H, OH). To provide a more convergent synthesis, we examined an approach to canthaxanthin based on the "C_{15} + C_{10}" (**2** + **3**) scheme which had been used previously for the synthesis of β-carotene.[4]

The most attractive feature of such a synthetic plan is that the final product is constructed in the last step from *small* fragments which avoids the problems associated with performing chemical transformations at the C_{40} level.[5]

Numerous avenues are available for the synthesis of the symmetrical dialdehyde **3**.[1] Our main task was the construction of the phosphorane **2**, which is described in this publication.[6]

Our first approach to build up the C_{15} carbon skeleton of **2** was to employ 2,6,6-trimethyl-2-cyclohexenone **4**[7] and the six-carbon acetylene derivative **5**.[8] Acetic acid treatment of adduct **6**, formed from **4** and **5**, readily gave acetate **7** (R = Ac) and diol **7** (R = H) after hydrolysis (Figure 2). Oxidation of **7** (R = H) then yielded ketone **8** which on treatment with acid gave the new ketone **9**. While the overall process works, the oxidation and acid rearrangement steps **7** (R = H)-**9** are poor and the final product **9** is a mixture of double bond isomers with the cis isomer predominating. To circumvent these problems, we used compound **10** in place of **4** and employed trans enyne **11** for the six-carbon unit (Figure 3).[8]

Substituted cyclohexenone **10** was prepared by condensing methyl isobutyrate with ethyl vinyl ketone to give keto ester **12** which on base cyclization yielded crystalline β-diketone **13** in 75% overall yield. Exposure of this material to isobutyl alochol and acid yielded only *one* enol ether, **10** (90%), the structure of which was established by reduction to trimethylcyclohexenone **14** with lithium aluminum hydride. Condensation of **11** with **10** followed by acid hydrolysis gave crystalline trans keto alcohol **9** in 90% yield. Hydrogenation of **9** resulted in the formation of alcohol **15** containing a cis double bond. Exposure of this material to phosphorus tribromide followed by triphenylphosphine gave the desired all-trans phosphonium salt **16** containing approximately 10% of the cis isomer.[9] Condensation of the crude salt **16** with dialdehyde **3** yielded canthaxanthin in 80% yield after isomerization of the mother liquor materials.[10]

Having shown that this route to canthaxanthin was viable, the next goal was to establish an economical route to **16**. This was achieved through the use of α-ionone (**17**),

(1) Isler, O. "*Carotenoids*", Birkhauser Verlag, Basel and Stuttgart, 1971.

(2) Isler, O.; Ofner, A.; Siemers, G. F. *Food Technol.* **1958**, *12*, 1. Bunnell, R. H.; Borenstein, B. *Ibid.* **1967**, *21*, 13. Emodi, A.; Scialpi, L.; Antoshkiw, T. *Ibid.* **1976**, 58. Emodi, A. *Ibid.* **1978**, 38.

(3) Petracek, F. J.; Zechmeister, L. *J. Am. Chem. Soc.* **1956**, *78*, 1427. Entschel, R.; Karrer, P. *Helv. Chim. Acta* **1958**, *41*, 402.

(4) Pommer, H. *Angew. Chem.* **1960**, *72*, 911.

(5) These are mainly solubility problems and the intrinsic instability of these polyenes.

(6) A preliminary account of this work was presented at the Fifth International Symposium on Carotenoids, Madison, WI, July 1978. Rosenberger, M.; McDougal, P.; Saucy, G.; Bahr, J. *Pure Appl. Chem.* **1979**, *51*, 871.

(7) Olson, G. L.; Cheung, H. C.; Morgan, K. D.; Borer, R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 567 and references cited therein.

(8) The free alcohol is a key intermediate used in the synthesis of vitamin A. Acid treatment yields (*Z*)-3-methyl-2-penten-4-yn-1-ol, the vitamin intermediate (see ref 1), and (*E*)-3-methyl-2-penten-4-yn-1-ol.

(9) The C_4 and C_5 protons appear as a singlet in the ^1H NMR spectrum; δ 6.35 (cis) and 6.16 (trans).

(10) Care has to be exercised in crystallizing **1** as the thermal isomerization into a mixture of double bond isomers is a facile process.

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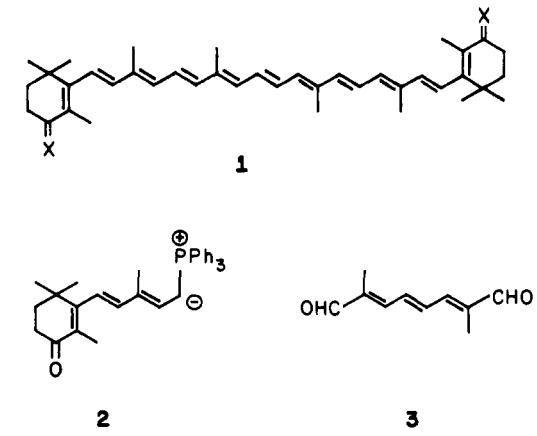

Figure 1.

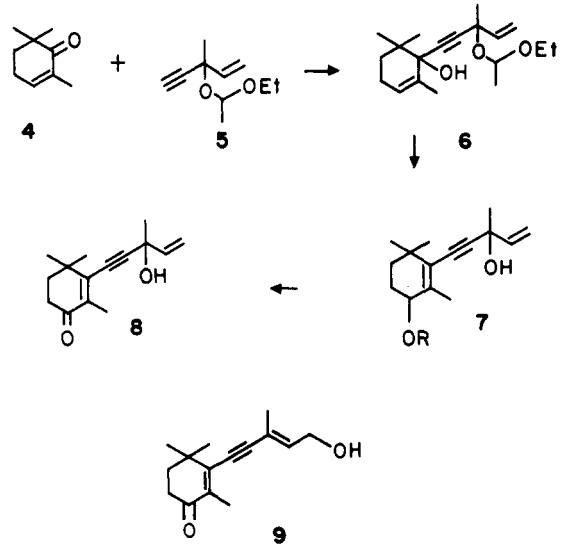

Figure 2.

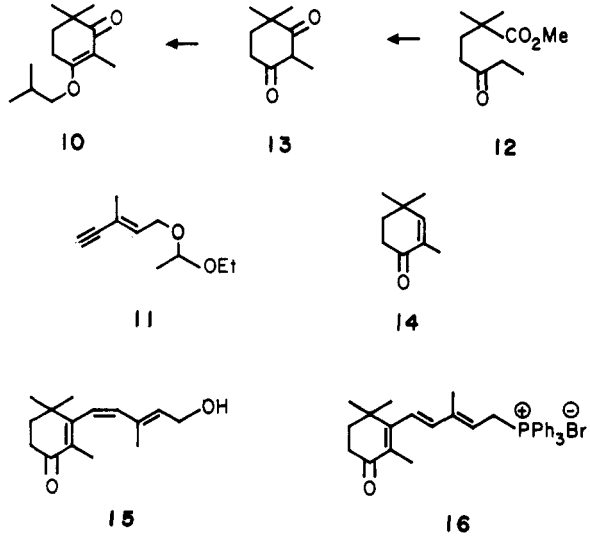

Figure 3.

which is available from ψ-ionone, a key intermediate in the industrial manufacture of vitamin A.[1]

Epoxidation of 17[11] resulted in a mixture of epoxides 18 in which one isomer predominates (~92%; Figure 4).[12]

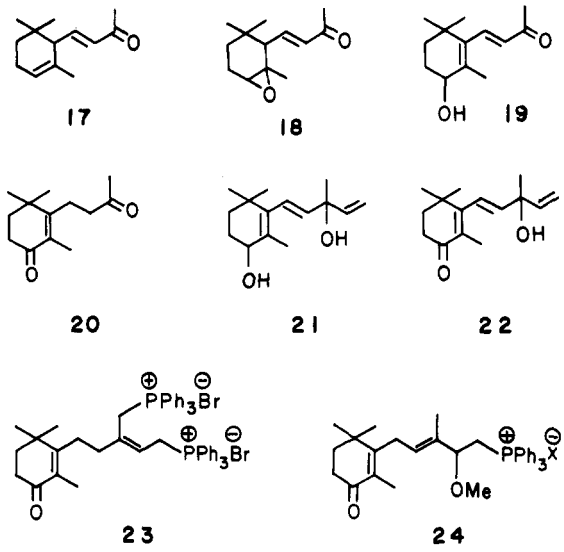

Figure 4.

Exposure of this epoxide mixture to sodium methoxide then resulted in the smooth conversion to 4-hydroxy-β-ionone (**19**) in excellent yield. While this is not an unprecedented reaction,[13] surprisingly no impurity other than diketone **20** was formed in this sequence. Addition of vinylmagnesium chloride[14] to **19** gave diol **21** which on Oppenaur oxidation[15] with aluminum isopropoxide and acetone yielded hydroxy ketone **22** in 60% overall yield from α-ionone.

The transformation of keto alcohol **22** into the phosphonium salt **16** proved troublesome at first. For example, exposure of **22** to phosphorus tribromide and subsequently triphenylphosphine gave a mixture of salts **16** and **23**.[16] Treatment of **22** with triphenylphosphine in methanolic sulfuric acid, a classical route to compounds such as **2** (X = H),[1] gave only **24** isolated as the perchlorate salt (Figure 4, X = ClO_4). The above problems could be avoided by treating the alcohol **22** with triphenylphosphine hydrobromide in dichloromethane, which afforded the desired salt **16** in excellent yield.

In summary, the work described offers an efficient route to the important carotenoid, canthaxanthin, starting from readily available materials and employing straightforward chemical operations.

Experimental Section[17]

3-(1-Ethoxyethoxy)-3-methyl-1-penten-4-yne (5). Ethyl vinyl ether (35 mL) was cooled to 5 °C and treated with *p*-toluenesulfonic acid (100 mg) followed by the slow addition of 3-hydroxy-3-methyl-1-penten-4-yne (freshly distilled, 20 g, 208

(11) Karrer, P.; Sturzinger, H. *Helv. Chim. Acta* **1946**, *29*, 1829.
(12) Eugster, C. H.; Eschemmoser, W.; Haag, A. *Helv. Chim. Acta* **1980**, *63*, 10 and references cited therein.

(13) Heather, J. B.; Mittal, R. S. D.; Sih, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 3663. Kaiser, R.; Lamparski, D. *Helv. Chim. Acta* **1978**, *61*, 2328.
(14) Use of vinylmagnesium bromide in this reaction results in extensive reduction (~30%) of the keto group to yield the diol.
(15) Djerassi, C. *Org. React. (NY)* **1951**, *6*, 207.
(16) This possibly arises by dehydration of **22** followed by the 1,4 addition of HBr to yield the dibromo compound.
(17) Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. All reactions were carried out under an atmosphere of nitrogen, and 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 (H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrometer, and ultraviolet (UV) spectra were recorded on a Cary Model 14M spectrophotometer.

mmol). After the initial exothermic reaction had subsided, the reaction mixture was kept at room temperature for 10 min, quenched with triethylamine (0.5 mL), and then distilled to yield the pure acetal **5** (33 g, 94%): bp 67–71 °C (20 mm).

(*E*)-4,8-Dimethyl-3,5-dioxa-7-decen-9-yne (11). In the same manner as in the previous example, (*E*)-3-methyl-2-penten-4-yn-1-ol (20 g) yielded the acetal **11** (32.1 g, 92%): bp 44–45 °C (0.5 mm); ^{1}H NMR (CCl_4) δ 5.9 (tq, 1, J = 6, 2 Hz, H-7), 4.6 (q, 1, J = 5 Hz, H-4), 4.0 (d, 2, J = 6 Hz, H-6), 3.45 (m, 2, H-2), 2.7 (s, 1, H-10), 1.8 (d, 3, J = 2 Hz, C_8-CH_3), 1.2 (d, 3, J = 5 Hz, C_4-CH_3), 1.17 (t, 3, J = 5 Hz, H-1).

***rac*-5-(2,6,6-Trimethyl-3-acetoxy-1-cyclohexen-1-yl)-3-methyl-3-hydroxy-1-penten-4-yne (7, R = Ac).** A solution of **5** (3.4 g, 20 mmol) in ether (30 mL) was cooled to −60 °C, treated with *n*-butyllithium (10.6 mL, 1.9 M in hexane), warmed to 0 °C, stirred for 5 min, and cooled to −20 °C. To this clear solution was added 2,6,6-trimethyl-2-cyclohexenone (2.28 g, 16.5 mmol) dissolved in ether (5 mL). After complete addition, the reaction mixture was warmed to room temperature, stirred for 1 h, and then quenched with acetic acid (10 mL). After a further 10 min at room temperature, more ether was added and the mixture was washed with brine, dried ($MgSO_4$), and concentrated to dryness to yield the crude adduct **6** (5.5 g). This product showed the expected ^{1}H NMR spectrum for a 1:1 mixture of diastereomers.

A solution of alcohol **6** (9.5 g, 31 mmol) in acetic acid (40 mL) was heated for 90 min at 45 °C and then concentrated (45 °C, 0.5 mm). The residue was dissolved in hexane and chromatographed on silica gel (400 g). Elution with hexane–ether mixtures (4:1 and 3:1) yielded the pure acetate **7** (R = Ac, 4.3 g, 50%): bp 165 °C (0.09 mm); ^{1}H NMR (CCl_4) δ 5.8, 5.2 (m, 3, H-1, H-2), 5.25 (br t, 1, H-3), 2.77 (br s, 1, OH), 2.03 (s, 3, $OCOCH_3$), 1.83 (s, 3, C_2-CH_3), 1.57 (s, 3, C_3-CH_3); UV_{max} (ethanol) 232 nm (ε 14 500); IR ($CHCl_3$) 3700 (C≡CH), 3400 (OH), 1728, 1230 cm^{-1} ($OCOCH_3$).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.94; H, 8.71.

Elution with a 40% ether–hexane mixture yielded the unrearranged alcohol derived from **6** (0.4 g), while a 60% ether–hexane mixture gave diol **7** (R = H, 0.7 g). Both of these materials were identified by ^{1}H NMR, and diol **7** (R = H) was also compared to an authentic sample prepared from acetate **7** (R = Ac) by hydrolysis.

***rac*-5-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)-3-methyl-3-hydroxy-1-penten-4-yne (8).** Mono acetate **7** (R = Ac; 4.1 g, 14.9 mmol) was dissolved in methanol (15 mL) containing potassium hydroxide (1.5 g, 22.9 mmol) and water (5 mL) and the solution left at room temperature for 3 h. Water was then added, and the organic products were extracted into ether. Removal of the solvents in vacuo yielded diol **7** (R = H, 3.45 g), which was identical with the sample isolated in the previous experiment. The crude diol (3.4 g) was dissolved in dichloromethane (20 mL) and added to a mixture of chromium trioxide (3 g) and pyridine (6 g) in more dichloromethane (100 mL) at 10 °C. The reaction mixture was then stirred for a further 2 h at room temperature and then treated with ether (250 mL). The solids were filtered off, the solvents were removed in vacuo and the residue was purified by chromatography on silica gel (150 g). Elution with 30% and 40% ether–hexane mixtures gave pure **8** (2.7 g, 78%): bp 160–165 °C (0.01 mm); ^{1}H NMR (CCl_4) δ 5.6 (m, 3, H-1, H-2), 4.0 (br s, 1, OH), 2.4 (t, 2, J = 6 Hz, H-4), 1.86 (s, 3, C_2-CH_3), 1.6 (s, 3, C_3-CH_3), 1.27 (s, 6, C_6-CH_3); IR (film) 3400 (OH), 2200 (C≡C), 1650, 1560 (cyclohexenone), 922 (CH=CH_2) cm^{-1}; UV_{max} (ethanol) 279 nm (ε 20 300).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.33; H, 8.79.

5-Oxo-2,2-dimethylheptanoic Acid Methyl Ester (12). A solution of *n*-butyllithium in hexane (224 mL, 2.2 M) was added to tetrahydrofuran (300 mL) at −60 °C followed by the addition of diisopropylamine (52 g, 0.515 mol). The mixture was then warmed to room temperature, stirred for a further 5 min, and then cooled to −70 °C. Methyl isobutyrate (50 g, 0.49 mol) was then slowly added, and after the complete addition, the reaction mixture was stirred at −70 °C for a further 90 min. Freshly distilled ethyl vinyl ketone (40 mL) dissolved in tetrahydrofuran (60 mL) was then added over a period of 10 min. The mixture was then stirred for 30 min at −60 °C and 2 h at room temperature and then quenched with aqueous acetic acid and brine (pH ~9). Ether was added and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Distillation of the residue yielded the pure keto ester **12** (81 g, 89%): bp 65–66 °C (0.5 mm); IR (film) 1735, 1712 (ester and ketone) cm^{-1}; ^{1}H NMR (CCl_4) δ 3.6 (s, 3, OCH_3), 2.4 (q, 2, J = 7 Hz, H-6), 2.2 (m, 2, H-4), 1.7–1.8 (m, 2, H-3), 1.1 (s, 6, C_2-CH_3), 1.0 (t, 3, J = 7 Hz, H-7).

2,6,6-Trimethylcyclohexane-1,3-dione (13). Sodium hydride (15.4 g, 57% dispersion in oil, 0.366 mol) was washed with hexane, suspended in ether (350 mL), and treated with keto ester **12** (62 g, 0.333 mol) and methanol (0.5 mL). The mixture was then heated at reflux for 3 h, cooled with ice, and treated with water. The ether layer was extracted twice with water, and the combined aqueous extracts were acidified with sulfuric acid (6 M to pH 1). The extraction with ether and concentration of the ether extract gave the crude diketone as a solid. This material was treated with cold (−10 °C) isopropyl ether (100 mL) and filtered to yield the desired product **13** (43.6 g, 85%), mp 115–116 °C. Crystallization from isopropyl ether gave the analytical sample: mp 115–116 °C.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.15; H, 9.25.

2,6,6-Trimethyl-3-isobutoxy-2-cyclohexenone (10). Diketone **13** (43.6 g, 0.283 mol) was added to a mixture of benzene (250 mL), isobutyl alcohol (50 mL), and *p*-toluenesulfonic acid (0.5 g) and the mixture was heated at reflux for 3 h in conjunction with a Dean and Stark water separator. After this period, the reaction mixture was cooled to room temperature, washed with an aqueous sodium carbonate solution, and brine and then concentrated in vacuo. Distillation of the residue yielded pure **10** (54.6 g, 91%): bp 104–107 °C (0.1 mm); IR (film) 1650, 1625 cm^{-1} (keto enol ether); ^{1}H NMR (CCl_4) δ 3.8 (d, 2, J = 7 Hz, OCH_2), 2.6 (br t, 2, J = 6 Hz, H-4), 2.0 (m, 1, J ~ 7 Hz, $CH(CH_3)_2$), 1.8 (t, 2, J = 6 Hz, H-5), 1.6 (t, 3, J ~ 2 Hz, C_2-CH_3) 1.37 (s, 6, C_6-CH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.08; H, 10.72.

5-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)-1-hydroxy-3-methyl-2-penten-4-yne (9). The protected acetylenic alcohol **11** (18.6 g, 0.111 mol) was dissolved in ether (100 mL), cooled to −60 °C, and treated with *n*-butyllithium (52.2 mL, 2.2 M in hexane) and then stirred at room temperature for 15 min. This clear pale-yellow solution was then cooled to −10 °C and treated with ketone **10** (21 g, 0.1 mol) dissolved in ether (50 mL). The reaction mixture was then warmed to 22 °C and stirred for a further 1 h. More ether was then added and the mixture was then washed with brine and concentrated in vacuo and the residue was then dissolved in acetone (140 mL) and treated with aqueous sulfuric acid (5%, 75 mL). After 8 h at room temperature, most of the acetone was removed in vacuo at room temperature and the residue was extracted with ether. The combined ether extracts were washed (brine), dried ($MgSO_4$), and concentrated to yield the crude adduct **9** as a solid. Crystallization from aqueous acetone yielded pure material (20.5 g, 88%): mp 102–105 °C; ^{1}H NMR ($CDCl_3$) δ 6.17 (tq, 1, J = 7, 2 Hz, H-2), 4.3 (d, 2, J = 7 Hz, H-1), 3.03 (br s, 1, OH), 2.5 (t, 2, J ~ 6 Hz, H-4), 1.97 (br s, 6, C_2-CH_3, C_3-CH_3), 1.45 (s, 6, C_6-CH_3).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.54; H, 8.67. Found: C, 77.61; H, 8.84.

(2*E*,4*Z*)-5-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)-1-hydroxy-2,4-pentadiene (15). The acetylenic substrate **9** (4.6 g, 19.8 mmol) was dissolved in toluene (80 mL) containing anhydrous potassium carbonate (1.2 g) and a Lindlar catalyst[18] (0.7 g) and hydrogenated at room temperature and pressure [20 °C (760 mm)]. After 3 h, the reaction was stopped (616 mL of hydrogen consumed), the solids were filtered off and the solvents were removed in vacuo. Chromatography of the residue on silica gel (400 g) yielded the major component **15** (3.35 g, 72%) on elution with a 70% ether–hexane mixture: UV_{max} (ethanol) 236 nm (ε 13 700); ^{1}H NMR ($CDCl_3$) δ 6.1 (dd, 2, J = 13 Hz, H-4, H-5), 5.73 (t, 1 J = 6 Hz, H-2), 4.22 (d, 2, J = 6 Hz, H-1), 2.74 (br s, 1, OH), 2.5 (t, 2, J = 6 Hz, H-4), 1.9 (m, 2, H-5), 1.67 (br s, 6, C_2-CH_3, C_3-CH_3), 1.21 (s, 6, C_6-CH_3).

(2*E*,4*E*)-[5-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)-3-methyl-2,4-pentadien-1-yl]triphenylphosphonium Bromide

(18) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446.

(16). A solution of alcohol **15** (3.2 g, 13.7 mmol) in ether (25 mL) was cooled to −60 °C and treated with phosphorus tribromide (2.5 mL) in ether (10 mL). The mixture was then warmed to room temperature over a period of 5 min and carefully quenched with water and the ether layer was washed (brine, sodium carbonate solution), dried ($MgSO_4$), and concentrated in vacuo to yield the crude bromo compound (3.2 g, 78%); ^1H NMR (CCl_4) δ 6.1 (dd, 2, J = 13 Hz, H-4, H-5), 5.8 (t, 1, J = 7 Hz, H-2), 4.0 (d, 2, J = 7 Hz, H-1), 1.8, 1.6 (2 s, 6, C_2-CH_3, C_3-CH_3), 1.2 (s, 6, C_6-CH_3). This crude bromo compound (3.2 g) was dissolved in benzene (25 mL) containing triphenylphosphine (3.5 g) and heated to reflux. The mixture was then cooled, treated with ether (50 mL), and decanted, and the residue was dried to yield the salt as a glass (5.3 g, 69%). This material was used as such in the preparation of canthaxanthin.

Canthaxanthin (1, X = O). The crude phosphonium salt **16** (5.3 g, 9.48 mmol) was dissolved in dichloromethane (40 mL) containing dialdehyde **3** (650 mg, 3.96 mmol) and cooled to −10 °C. A solution of sodium methoxide in methanol (from Na, 285 mg, 12.39 mmol, in methanol, 3 mL) was then added over 5 min and the highly colored reaction mixture was stirred for a further 1 h at −10 °C. More dichloromethane was added and the mixture was washed (brine), dried ($MgSO_4$), concentrated, and chromatographed on silica gel (200 g). Elution with 10% and 20% ethyl acetate–benzene mixtures gave the carotenoid fraction (2.1 g). Crystallization from methanol yielded pure *all-trans*-canthaxanthine (1.75 g, 78%): mp 205–207 °C; UV_{max} (ethanol, 1% dichloromethane) 475 nm (ϵ 97 000). This material was identical with an authentic sample by HPLC (7% ethyl acetate–heptane, silica, SRII, Separation Laboratories).

***rac*-(3*E*)-4-(2,6,6-Trimethyl-3-hydroxy-1-cyclohexen-1-yl)-3-buten-2-one (19).** A solution of racemic α-ionone (202.5 g, 0.99 mol, 94% purity GLC analysis, area percent) was dissolved in dichloromethane (1.1 L) containing anhydrous sodium acetate (50 g) and the solution was cooled to 15 °C. Peracetic acid (250 mL, 40% in acetic acid) was then added over 30 min and the mixture was then stirred for a further 2.5 h with intermitant cooling and then for 3 h more at room temperature. After this time, the reaction mixture was washed with water, aqueous potassium metabisulfite solution (10%), sodium hydroxide solution (2 M), and water and then concentrated to yield the crude epoxide mixture (236 g). This material exhibited the same ^1H NMR spectrum as a distilled sample.

The total crude product was dissolved in methanol (800 mL), treated with sodium methoxide in methanol (100 mL, 1.4 M), and heated at reflux for 3 h. The mixture was then cooled to room temperature, treated with acetic acid (9 mL), and water (180 mL) and then extracted with hexane saturated with 80% methanol–water. The hexane extracts were backwashed with 80% methanol–water (saturated with hexane) and the combined methanol–water extracts were concentrated and then extracted with ether. Removal of the ether yielded the crude hydroxy ketone **19** (204.1 g, 99%).

A sample of this material on distillation yielded an analytical sample: bp 130–140 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 7.25 (d, 1, J = 17 Hz, H-4), 6.1 (d, 1, J = 17 Hz, H-3), 4.0 (br t, 1, J = 4 Hz, H-3), 3.0 (s, 1, OH), 2.3 (s, 3, H-4), 1.9 (s, 3, C_2-CH_3), 1.1 (s, 6, C_6-CH_3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.65; H, 9.60.

When the epoxy ketone **18** (1.8 g) was dissolved in methanolic sodium methoxide (15 mL, 1.41 M) and heated at reflux for 1 h and the crude product was chromatographed on silica gel (40 g), elution with a 20% ethyl acetate–benzene mixture yielded the diketone **20** (0.15 g): ^1H NMR ($CDCl_3$) δ 2.6 (br s, 4, H-2, H-6), 2.2 (s, 3, H-4), 1.66 (s, 3, C_2-CH_3), 1.2 (s, 6, C_4-CH_3); IR (film) 1710 (methyl ketone), 1665, 1600 (cyclohexenone) cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 75.25; H, 9.66.

***rac*-(4*E*)-5-(2,6,6-Trimethyl-3-oxo-1-cyclohexen-1-yl)-3-hydroxy-3-methyl-1,4-pentadiene (22).** The crude keto alcohol **19** (204 g) was dissolved in tetrahydrofuran (1 L), cooled to −30 °C, and treated with vinylmagnesium chloride (680 mL, 3.3 M) in tetrahydrofuran. The mixture was then stirred for a further 30 min at 10 °C and then treated with ether (1 L) and a saturated aqueous ammonium chloride solution (250 mL). The solids were filtered off and the solvents were removed in vacuo to yield the crude diol **21** (231.8 g). A sample (1 g) was chromatographed on silica gel (100 g) to yield analytically pure material on elution with a 1:1 mixture of ethyl acetate and benzene: ^1H NMR ($CDCl_3$) δ 6.1, 5.6 (dd, 2, J = 17 Hz, H-4, H-5), 6.0, 5.2 (2 m, 3, H-1, H-2), 4.0 (t, 1, $J \sim$ 5 Hz, H-3), 2.3 (s, 2, OH), 1.8 (s, 3, C_2-CH_3), 1.4 (s, 3, C_3-CH_3), 1.0 (s, 6, C_6-CH_3).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.79; H, 10.06.

The impure diol (9.9 g) was dissolved in a mixture of acetone and dichloromethane (100 mL, 1:1) containing aluminum isopropoxide (20 g) and heated at reflux for 5 h. The mixture was then cooled in ice, acidified with aqueous sulfuric acid (2 N); the organic phase was dried ($MgSO_4$) and concentrated. Chromatography of the residue on silica gel (400 g) yielded pure **22** (6.05 g, 62% yield from α-ionone): ^1H NMR ($CDCl_3$) δ 6.3, 5.7 (dd, 2, J = 17 Hz, H-4, H-5), 6.0 (dd, 1, J = 11, 17 Hz, H-2), 5.25 (d, 1, J = 17 Hz, trans H-1), 5.1 (d, 1, J = 11 Hz, cis H-1), 2.4 (m, 2, H-4), 1.8 (s, 3, C_2-CH_3), 1.45 (s, 3, C_3-CH_3), 1.1 (s, 6, C_4-CH_3).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.89; H, 9.46. Found: C, 76.92; H, 9.39.

Phosphonium Salts 16, 23, and 24. Hydroxy ketone **22** (136.6 g, 0.517 mol, 84% purity) was dissolved in ether (1 L), cooled to −20 °C, exposed to phosphorus tribromide (50 mL) in ether (250 mL) and then stirred at room temperature for 1 h. After cooling to 5 °C, the reaction mixture was washed with water, saturated aqueous sodium bicarbonate solution, and brine and dried ($MgSO_4$). Removal of the solvents gave the crude bromide (147 g) which was dissolved in benzene (1 L) containing triphenylphosphine (144 g, 0.55 mol) and heated at reflux for 90 min. This mixture was then cooled and treated with ether (1 L) and stirred for 1 h. The solids were filtered off and dried to yield the mixture of phosphonium salts **23** and **16** (296.7 g, TLC, silica gel, 40:9:1 *n*-butyl acetate–formic acid–water). This material was dissolved in dichloromethane (2.5 L) and treated with ether (1.25 L) at room temperature and then filtered. The filter cake (45.7 g) was then crystallized from methanol to yield **23** (38.5 g, 8%): mp 261–63 °C; ^1H NMR (Me_2SO-d_6) δ 8.0 (m, 30, phenyl H), 5.27 (m, 1, H-4), 4.97 (d, 2, J = 16 Hz, CH_2-P), 4.0 (br t, 2, H-5), 2.7 (br t, 2, H-4), 2.28 (m, 2, H-1), 2.0 (m, 2, H-2), 1.58 (br t, 2, H-5), 1.26 (s, 3, C_2-CH_3), 0.80 (s, 6, C_6-CH_3); UV_{max} (ethanol) 228 nm (ϵ 51 400).

Anal. Calcd for $C_{51}H_{52}OP_2Br_2$: C, 67.84; H, 5.81; P, 6.87; Br, 17.7. Found: C, 67.88; H, 5.90; P, 7.07; Br, 17.95.

Compound **24** was formed as follows. Triphenylphosphine (5.5 g, 21 mmol) in methanol (20 mL) was treated with sulfuric acid (2 g) and the clear solution was treated with **22** (4.6 g, 20.7 mmol). Ether was then added and the insoluble salt was extracted into water and the clear aqueous phase was treated with an excess of sodium perchlorate in water. The solids were filtered off and crystallized from methanol to give **24** (X = ClO_4, 4.4 g, 38%) as a 1:1 mixture of double bond isomers: mp 166–168 °C; ^1H NMR (Me_2SO-d_6) δ 8.0 (m, 15, phenyl H), 5.14 (m, 1, H-2), 5.08 (2 t, total 1, J = 6 Hz, H-4), 3.8 (m, 2, H-5), 3.1 (s, 3, OCH_3), 2.89 (t, 2, H-1), 2.34 (t, 2, H-4), 1.68 (t, 2, H-5), 1.62 (br s, 3, C_3-CH_3), 1.41 (s, 3, C_2-CH_3), 0.97 (s, 6, C_6-CH_3).

Anal. Calcd for $C_{34}H_{40}O_6PCl$: C, 66.82; H, 6.6; Cl, 5.80; P, 5.07. Found: C, 66.83; H, 6.76; Cl, 6.06; P, 5.05.

Compound **16** is best prepared as follows. Hydroxy ketone (**22**, 10.7 g, 35.9 mmol, chromatographically pure) was dissolved in dichloromethane (25 mL) and added to a mixture of triphenylphosphine hydrobromide (14.4 g, 42 mmol) and dichloromethane (50 mL) and left at room temperature for 1 h. The solvents were then removed in vacuo and the residue was digested with ether and dried to yield the crude salt (23.5 g) as a solid (84% pure by ^1H NMR, 98%): ^1H NMR ($CDCl_3$) δ 7.8 (m, phenyl H), 6.3 (s, H-4, H-5, cis isomer, 5–10%), 6.15 (s, H-4, H-5, trans isomer), 5.5 (br t, 1, J = 6 Hz, H-2), 4.8 (br dd, 2, J = 6, 15 Hz, H-1), 2.4 (t, 2, H-4), 1.1 (s, 6, C_6-CH_3).

Use of this material (14.6 g) and dialdehyde **3** (1.64 g, 10 mmol) as before, yielded canthaxanthin (4.69 g, 83%): mp 201–203 ° dec.

Acknowledgment. We thank the personnel of the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, NJ, for supplying most of the spectroscopic and all the microanalytical data. We offer special thanks to

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′-

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