Synthesis of Bixin and Three Minor Carotenoids from Annatto (*Bixa orellana*)

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The three apocarotenoids methyl (9*Z*)-8′-oxo-6,8′-diapocaroten-6-oate (**2**), methyl (9*Z*)-10′-oxo-6,10′-diapocaroten-6-oate (**4**), and methyl (9*Z*)-14′-oxo-6,14′-diapocaroten-6-oate (**5**), recently isolated from annatto, were synthesized. The key step of all three syntheses was the *Wittig* reaction of the (*Z*)-terminus **6** with the phosphonium salts **15**, **18**, and **24**, carrying the polyene chain. Bixin (**1**) was synthesized from **2** in a *Horner-Emmons* reaction.

1. Introduction. – Annatto, widely used as a colorant for dairy and other food products, is the highly colored extract of the seed coat of *Bixa orellana*, a rapidly growing tree, native to tropical America. More than 80% of the carotenoids in annatto consists of bixin (6′-methyl hydrogen (9′*Z*)-6,6′-diapocarotene-6,6′-dioate; **1**) [1][2]. Bixin was first isolated in 1825 [3], and it was known as the first naturally occurring (*Z*)-carotenoid, but the structure was not established until 1961 [4]. Other carotenoids from annatto have been detected in trace amounts. *Jondiko* and *Pattenden* isolated the apocarotenoid methyl (9*Z*)-8′-oxo-6,8′-diapocaroten-6-oate (**2**) [5], and *Mercadante et al.* isolated and identified 13 new apocarotenoids by means of UV/VIS, MS, and ^{1}H-NMR spectra [6–8]. Methyl bixin (dimethyl (9*Z*)-6,6′-diapocarotene-6,6′-dioate; **3**), another minor carotenoid of annatto, was synthesized by *Pattenden et al.* [9]. The present study reports the first total synthesis of bixin (**1**) and of three minor carotenoids isolated from annatto, namely methyl (9*Z*)-8′-oxo-6,8′-diapocaroten-6-oate (**2**), methyl (9*Z*)-10′-oxo-6,10′-diapocaroten-6-oate (**4**), and methyl (9*Z*)-14′-oxo-6,14′-diapocaroten-6-oate[2]) (**5**).

2. Results and Discussion. – 2.1. *Preamble.* The strategy of the synthesis of the apocarotenoids **2**, **4**, and **5** was based on the synthesis of methyl bixin [9]. The key step is the *Wittig* reaction of the (*Z*)-terminus **6** with the different phosphonium salts carrying the polyene chain. Bixin (**1**) was synthesized by elongating **2** by a *Horner-Emmons* reaction (*Scheme 1*).

Starting from the lactol **7**, the (*Z*)-terminus **6** was synthesized *via* the corresponding acid **8** and the acid chloride **9** according to [9][11] in three steps, in an overall yield of 25% (*Scheme 2*).

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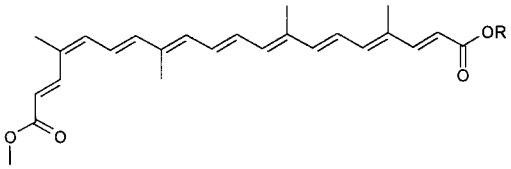
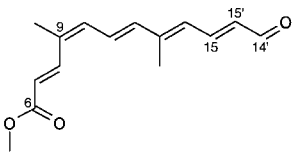
[1]) Diploma work and part of the planned Ph.D. thesis of *A. H.*

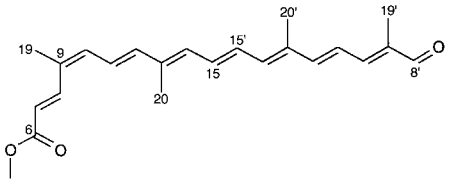
[2]) According to the nomenclature rules [10], compound **5** is not a carotenoid since the two central methyl groups of the C_{40}-skeleton are not retained. Because **5** may be a degradation product of an annatto carotenoid, the *IUPAC* nomenclature for carotenoids was applied.



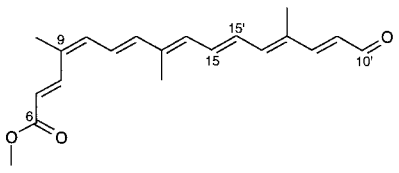
1 R = H; bixin
3 R = Me; methyl bixin



5 methyl (9Z)-14'-oxo-6,14'-diapocaroten-6-oate[2])



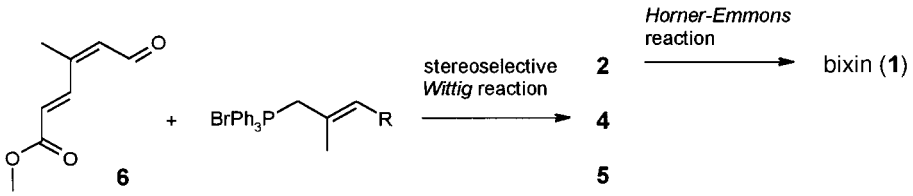
2 methyl (9Z)-8'-oxo-6,8'-diapocaroten-6-oate



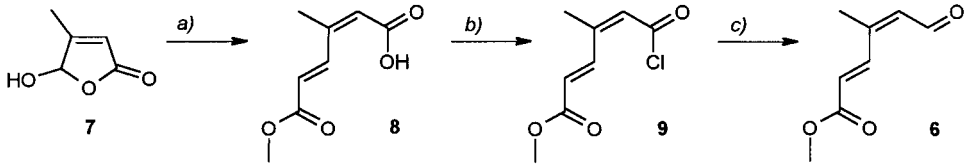
4 methyl (9Z)-10'-oxo-6,10'-diapocaroten-6-oate

2.2. *Methyl (9Z)-8'-Oxo-6,8'-diapocaroten-6-oate* (**2**; *Scheme 3*). The C_{10}-dial **10** was reduced with $NaBH_4$ to the hydroxy aldehyde **11** according to the method of *Pattenden et al.* [9]. The aldehyde function of the phosphonium salt **12** was protected as dimethyl acetal **13** [12]. The *Wittig* reaction of **11** and **13** afforded, after removal of the protecting group, the C_{15} compound **14** in 70% yield, as a (*E*/*Z*)-isomer mixture. The (all-*E*)-isomer was obtained by repeated crystallization (27% yield) and transformed with $PPh_3 \cdot HBr$ into the phosphonium salt **15**, which was precipitated in cold Et_2O/hexane and used for the next step without further purification. At $-20°$, the *Wittig* reaction of crude **15** with the (*Z*)-terminus **6** using NaH as base gave, after flash chromatography (FC, silica gel) and crystallization, carotenoid **2** in 29% yield (4.6% total yield rel. to **10**) as main product. Under these reaction conditions, no (*E*/*Z*)-isomerization at the C(9)=C(10) bond took place, whereas under various other

Scheme 1

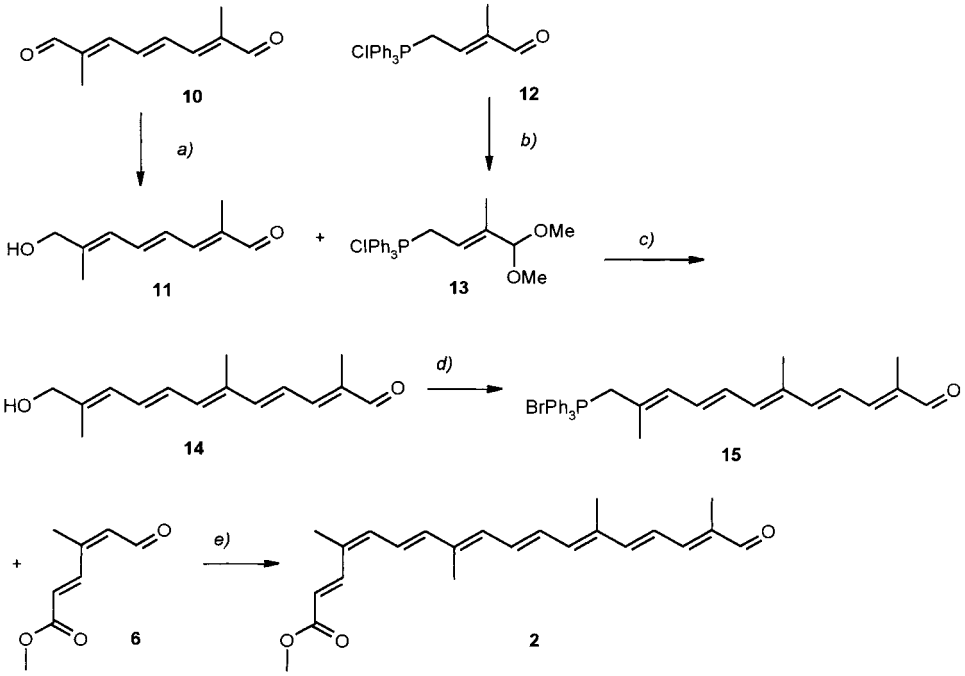


Scheme 2



a) $(MeO)_2P(O)CH_2CO_2Me$, NaOMe, Et_2O/MeOH; 93%. *b)* $SOCl_2$; 59%. *c)* $LiAlH(OCMe_3)_3$, diglyme; 45%.

Scheme 3



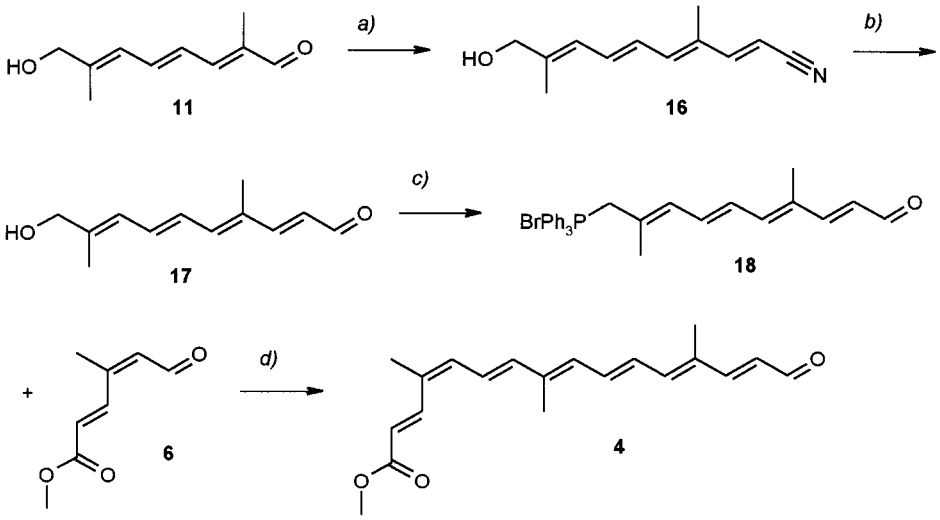
a) $NaBH_4$, EtOH; 76%. *b)* $HC(OMe)_3$, H^+, MeOH; 99%. *c)* 1. NaOMe, MeOH; 2. AcOH, H_2O, MeOH; 70%; repeated crystallization: 27%. *d)* $Ph_3P \cdot HBr$, MeOH; 78%. *e)* NaH, CH_2Cl_2; 29%.

conditions (*e.g.*, CH_2Cl_2, NaOMe, room temperature), mainly the (all-*E*)-isomer of **2** was formed.

2.3. *Methyl (9Z)-10′-Oxo-6,10′-diapocaroten-6-oate* (**4**; *Scheme 4*). In a stereoselective *Horner-Emmons* reaction, the C_{10}-hydroxy aldehyde **11** was elongated to the C_{12}-hydroxy nitrile **16** in 88% yield. Reduction with an excess of DIBAH (diisobutylaluminium hydride) at $-70°$ gave the hydroxyaldehyde **17**. The bromination of the latter was carried out with PBr_3 at $-10°$, and the very labile bromide was immediately dissolved in *t*-BuOMe and converted with PPh_3 to the C_{12}-phosphonium salt **18**. After precipitation of the crude product in cold Et_2O/hexane, an orange powder was obtained. To prevent formation of the (all-*E*)-**4** during the coupling reaction with the (*Z*)-terminus **6**, the same reaction conditions (NaH, CH_2Cl_2, $-20°$) were chosen as in the last step of the synthesis of **2**. FC (silica gel), and crystallization gave carotenoid **4** in 22% yield (6.0% total yield rel. to **11**).

2.4. *Methyl (9Z)-14′-Oxo-6,14′-diapocaroten-6-oate* (**5**; *Scheme 5*). The stereoselective *Horner-Emmons* reaction of 2,2-dimethoxyethanal (**19**) with ethyl 2-(diethoxyphosphinyl)propanoate gave, after cleavage of the acetal group with aq. trifluoroacetic acid, the C_5 compound **20** in 78% yield. Then, formyl ester **20** was elongated with diethyl (cyanomethyl)phosphonate to give the cyano ester **21** as a 4:1 mixture of (*E*/*Z*)-isomers, and (all-*E*)-**21** was obtained by FC in 43% yield. With

Scheme 4



a) $(EtO)_2P(O)CH_2CN$, NaH, THF; 88%. *b)* DIBAH, THF/hexane; 69%. *c)* 1. PBr_3, pyridine, CH_2Cl_2; 2. PPh_3, *t*-BuOMe; 45%. *d)* NaH, CH_2Cl_2; 22%.

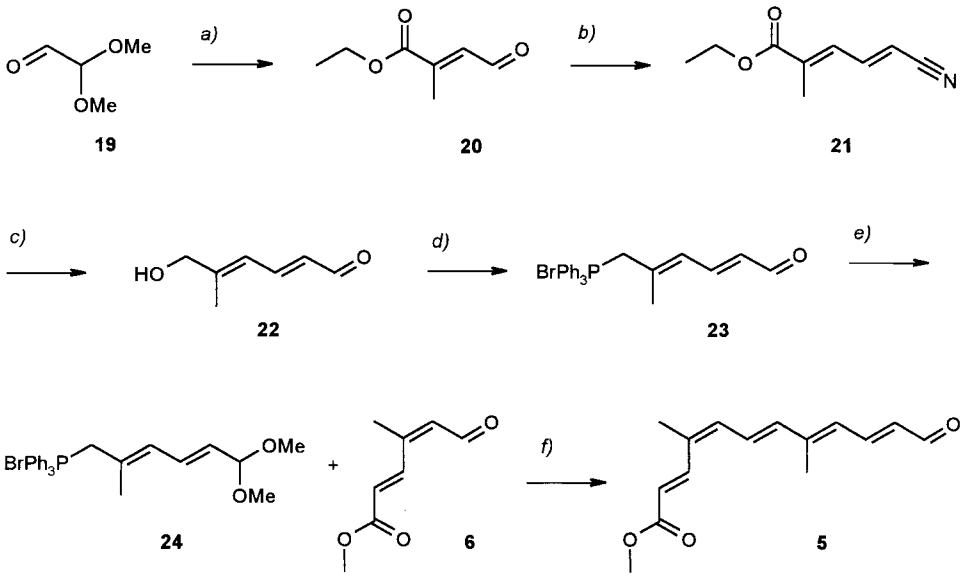
DIBAH at $-70°$, the ester and the nitrile function of **21** were reduced and the obtained hydroxy aldehyde **22** transformed to the phosphonium salt **23** by bromination with *N*-bromosuccinimide (NBS) according to the method of *Haugan* [12], followed by the reaction of the very labile bromide with PPh_3 in AcOEt at room temperature. The *Wittig* reaction of phosphonium salt **23** with the (*Z*)-terminus **6** gave carotenoid **5** in a very poor yield and, therefore, the aldehyde function of **23** was protected as a dimethyl acetal (almost quant. yield) prior to the *Wittig* reaction [12]. The stereoselective coupling reaction of the protected phosphonium salt **24** with the (*Z*)-terminus **6** was carried out in CH_2Cl_2 at room temperature using NaOMe as base. Cleavage of the acetal moiety with aqueous formic acid for 10 min at room temperature led to carotenoid **5**, which was separated from different minor (*E*/*Z*)-isomers by FC (silica gel) and crystallized (34% yield; 3.0% total yield rel. to **19**).

2.5. *6′-Methyl Hydrogen (9′Z)-6,6′-Diapocarotene-6,6′-dioate (= Bixin*; **1**; *Scheme 6*). Treatment of carotenoid **2** and (diethoxyphosphinyl)acetate **25** in benzene with BuLi at room temperature, followed by deprotection of the carboxylic acid with aqueous formic acid afforded bixin (**1**) which was purified by FC (silica gel) and crystallization (26% yield).

Natural bixin, isolated from annatto, was purified by repeated crystallization and used as a reference for UV/VIS, IR, ^{1}H- and ^{13}C-NMR, and mass spectroscopy.

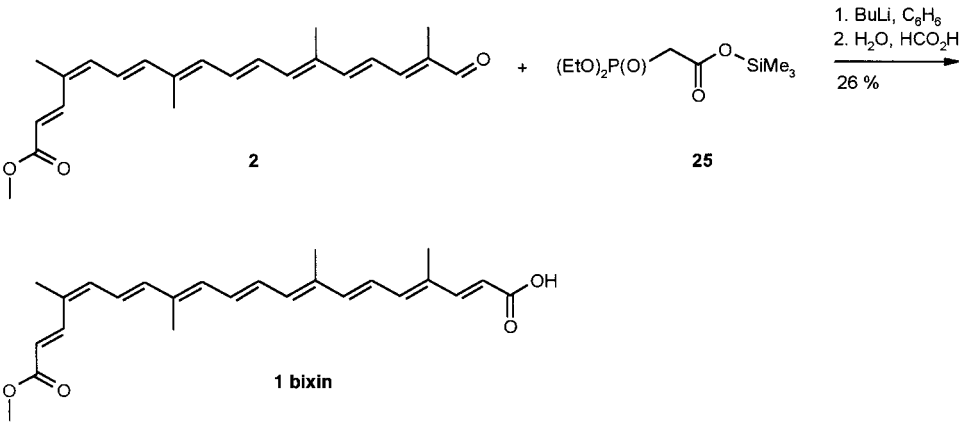
3. Spectroscopical Studies. – The ^{1}H- and ^{13}C-NMR, UV/VIS, and MS data of the three apocarotenoids **2**, **4**, and **5** are in full agreement with the data of the natural compounds, previously reported [6–8]. Using ^{1}H- and ^{13}C-NMR, DEPT, and COSY experiments, all protons and C-atoms of the three apocarotenoids were unambiguously

Scheme 5



a) 1. $(EtO)_2P(O)CH(Me)CO_2Et$, NaH, THF; 2. CF_3CO_2H, H_2O, THF; 78%. *b)* $(EtO)_2P(O)CH_2CN$, NaH, THF; 43%. *c)* DIBAH, THF/hexane; 55%. *d)* 1. NBS, Me_2S, CH_2Cl_2; 2. PPh_3, AcOEt; 49%. *e)* $HC(OMe)_3$, H^+, MeOH; 99%. *f)* 1. NaOMe, CH_2Cl_2; 2. HCO_2H, H_2O, CH_2Cl_2; 34%.

Scheme 6



assigned (*Tables 1* and *2*). The UV/VIS spectra of **2**, **4**, and **5** in *t*-BuOMe show the expected λ_{max} and a fine structure typical for acyclic carotenoids.

^{1}H- and ^{13}C-NMR, UV/VIS, IR, and mass spectra, and m.p. of synthetic bixin (**1**) are identical with our data of natural bixin isolated from annatto. They are also in full agreement with the data of the natural compound reported in the literature (^{1}H- and ^{13}C-NMR, MS: [13]; UV/VIS: [8]; IR: [14]; M.p.: [15]), except for the ^{13}C-NMR values

Table 1. *^{1}H-NMR Data of* **2** (500 MHz, $CDCl_3$), *and of* **4** *and* **5** (300 MHz, $CDCl_3$). Chemical shifts δ in ppm and coupling constants J in Hz.

	2		**4**		**5**	
MeO	3.80	(*s*)	3.80	(*s*)	3.81	(*s*)
H–C(7)	5.93	(*d*, $J=15.5$)	5.94	(*d*, $J=15.4$)	5.99	(*d*, $J=15.4$)
H–C(8)	7.97	(*d*, $J=15.5$)	7.97	(*d*, $J=15.4$)	7.95	(*d*, $J=15.4$)
H–C(10)	6.37	(*d*, $J=11.6$)	6.38	(*d*, $J=11.4$)	6.39	(*d*, $J=11.5$)
H–C(11)	6.90	(*dd*, $J=11.6$, 14.8)	6.93	(*dd*, $J=11.4$, 14.7)	7.08	(*dd*, $J=11.5$, 15.0)
H–C(12)	6.42	(*d*, $J=14.8$)	6.42	(*d*, $J=14.7$)	6.44	(*d*, $J=15.0$)
H–C(14)	6.34	(*d*, $J=11.5$)	6.35	(*m*, *ABMX*)	6.41	(*d*, $J=11.6$)
H–C(15)	6.78	(*dd*, $J=11.5$, 14.2)	6.86	(*m*, *ABMX*)	7.52	(*dd*, $J=11.6$, 15.0)
Me(19)	1.97	(*s*)	1.98	(*s*)	2.00	(*s*)
Me(20)	2.03	(*s*)	1.98	(*s*)	2.14	(*d*, $J=1.1$)
H–C(8′)	9.47	(*s*)				
H–C(10′)	6.95	(*m*, *ABM*)	9.60	(*d*, $J=7.7$)		
H–C(11′)	6.71	(*m*, *ABM*)	6.21	(*dd*, $J=7.7$, 15.4)		
H–C(12′)	6.73	(*m*, *ABM*)	7.17	(*d*, $J=15.4$)		
H–C(14′)	6.46	(*d*, $J=11.7$)	6.62	(*m*, *ABMX*)	9.65	(*d*, $J=7.9$)
H–C(15′)	6.69	(*dd*, $J=11.7$, 14.2)	6.68	(*m*, *ABMX*)	6.22	(*dd*, $J=7.9$, 15.0)
Me(19′)	1.91	(*s*)				
Me(20′)	2.02	(*s*)	2.04	(*s*)		

Table 2. *^{13}C-NMR Data of* **2** (125.8 MHz, $CDCl_3$), *and of* **4** *and* **5** (75.5 MHz, $CDCl_3$). Chemical shifts δ in ppm.

	2	**4**	**5**		**2**	**4**	**5**
MeO	51.57	51.61	51.71				
C(6)	167.90	167.89	167.72				
C(7)	117.64	117.97	118.95				
C(8)	140.33	140.28	139.91	C(8′)	194.51		
C(9)	131.88	132.44	134.43	C(9′)	136.94		
C(10)	137.72	137.54	136.70	C(10′)	149.07	193.62	
C(11)	123.73	124.45	127.18	C(11′)	123.02	127.53	
C(12)	140.13	139.89	138.68	C(12′)	145.68	156.27	
C(13)	137.88	134.40	145.74	C(13′)	135.89	139.28	
C(14)	133.85	133.40	130.32	C(14′)	137.16	140.73	193.49
C(15)	132.52	134.84	146.96	C(15′)	130.26	129.53	131.84
C(19)	20.25	20.30	20.40	C(19′)	9.61		
C(20)	13.01	12.74	13.42	C(20′)	12.69	13.12	

of C(8′) and C(10) which are different from those given in [13]. The ^{1}H- and ^{13}C-NMR spectra of **1** (see *Table 3*) exhibit the characteristic signals for a (9′*Z*)-isomer that are in accordance with the data reported by *Englert* [16], especially for *H*–C(8′) and C(8′) and *C*H_3(19′). The UV/VIS spectrum (*t*-BuOMe) of **1** shows maxima at 428, 453, and 484 nm and a prominent fine structure. The '*cis*-peak' at 354 nm is weak due to the position of the (*Z*)-double bond at the end of the polyene chain. In the MS of **1**, the molecular ion is observed at *m*/*z* 394, and major fragments appear at *m*/*z* 288 ([*M* – xylene]$^+$), 106 (xylene$^+$) and 91 (toluene$^+$).

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Table 3. *^{1}H-NMR* (500 MHz, $CDCl_3$) *and ^{13}C-NMR* (125.8 MHz, (D_6)DMSO[a]) *Data of* **1**. Chemical shifts δ in ppm and coupling constants J in Hz.

	δ(H)			δ(C)
MeO	3.80	(*s*)	MeO	51.47
			C(6′)	166.95
H–C(7′)	5.92	(*d*, J(7′,8′) = 15.6)	C(7′)	117.75
H–C(8′)	7.97	(*d*, J(8′,7′) = 15.6)	C(8′)	140.01
			C(9′)	131.27
H–C(10′)	6.38	(*d*, J(10′,11′) = 11.3)	C(10′)	138.13
H–C(11′)	6.87	(*dd*, J(11′,10′) = 11.3, J(11′,12′) = 14.9)	C(11′)	123.25
H–C(12′)	6.42	(*d*, J(12′,11′) = 14.9)	C(12′)	140.69
			C(13′)	136.80
H–C(14′)	6.33	(*d*, *ABXY*, J(14′,15′) ≈ 10.0)	C(14′)	134.62
H–C(15′)	6.71	(*m*, *ABXY*)	C(15′)	131.40
Me(19′)	1.97	(*s*)	C(19′)	20.01
Me(20′)	2.02	(*s*)	C(20′)	12.76
			C(6)	167.88
H–C(7)	5.89	(*d*, J(7,8) = 15.6)	C(7)	117.30
H–C(8)	7.47	(*d*, J(8,7) = 15.6)	C(8)	148.27
			C(9)	133.51
H–C(10)	6.55	(*d*, J(10,11) = 10.0)	C(10)	139.15
H–C(11)	6.64	(*dd*, J(11,10) = 10.0, J(11,12) = 15.7)	C(11)	124.89
H–C(12)	6.55	(*d*, J(12,11) = 15.7)	C(12)	141.54
			C(13)	136.76
H–C(14)	6.38	(*d*, *ABXY*, J(14,15) ≈ 11.1)	C(14)	134.79
H–C(15)	6.68	(*m*, *ABXY*)	C(15)	131.53
Me(19)	1.97	(*s*)	C(19)	12.56
Me(20)	2.00	(*s*)	C(20)	12.65

[a]) DMSO was chosen because of the poor solubility of bixin in $CDCl_3$.

chemicals, and to Dr. *F. Khachik*, Department of Chemistry and Biochemistry, University of Maryland, for the sample of natural bixin.

Experimental Part

1. *General*. The reagents were purchased from *Fluka Chemie AG* or obtained from *F. Hoffmann-La Roche Ltd.*, Basel (**7**, **10**, **12**). All experiments were carried out under N_2 or Ar. Solvents were distilled prior to use or purchased in HPLC quality. TLC: silica gel *KG 60 F_{254}* (*Merck*). Flash chromatography (FC): silica gel *60* (*J. T. Baker*, 40–63 μm). M.p.: *Büchi 510*; not corrected. UV/VIS Spectra: *Perkin-Elmer-Lambda-6* spectrophotometer; λ_{max} in nm. IR Spectra: *Perkin-Elmer-1600-FTIR* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Bruker AC-300* (300 and 75.5 MHz, resp.), *Bruker AM-500* (500 and 125.8 MHz, resp.); in $CDCl_3$ and (D_6)-DMSO, resp.; chemical shifts δ in ppm rel. to $CDCl_3$ (= 7.27 and 77.0 ppm, resp.) or (D_6)DMSO (= 2.52 and 39.7 ppm, resp.); J in Hz. Mass spectra: *Varian MAT CH-7A*; *m*/*z* (rel. intensity in %); ionization energy 70 eV.

2. *(2Z,4E)-6-Methoxy-3-methyl-6-oxohexa-2,4-dienoic Acid* (**8**). Compound **8** was synthesized according to [11]. Yield 93%. White powder. M.p. 132–135°. UV/VIS (THF): 275. IR ($CHCl_3$): 3518*w*, 2956*w*, 1719*s*, 1703*s*, 1635*m*, 1601*m*, 1438*m*, 1288*m*, 1258*m*, 1172*m*, 1121*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.09 (*s*, Me–C(3)); 3.81 (*s*, MeO); 5.99 (*s*, H–C(2)); 6.23 (*d*, J = 16.0, H–C(5)); 8.60 (*d*, J = 16.0, H–C(4)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 20.83 (*Me*–C(3)); 51.96 (MeO); 122.72 (C(2)); 124.74 (C(5)); 139.93 (C(4)); 149.74 (C(3)); 166.87 (C(6)); 170.38 (C(1)). EI-MS: 170 (51, M^+), 155(15), 139(44), 125(100), 121(71), 111(96), 97(33), 93(56), 83(37), 69(34), 65(44), 55(46), 39(53).

3. *(2Z,4E)-6-Methoxy-3-methyl-6-oxohexa-2,4-dienoyl Chloride* (**9**). Acid chloride **9** was synthesized according to [9]. Yield 59%. White needles. M.p. 46–47°. UV/VIS (THF): 278. IR ($CHCl_3$): 3034*m*, 2956*w*, 2360*w*, 1790*m*, 1753*m*, 1720*s*, 1625*w*, 1580*m*, 1439*m*, 1317*m*, 1290*s*, 1070*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.10

(*s*, Me–C(3)); 3.80 (*s*, MeO); 6.25 (*s*, H–C(2)); 6.32 (*d*, *J* = 15.8, H–C(5)); 8.19 (*d*, *J* = 15.8, H–C(4)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 20.47 (*Me*–C(3)); 52.12 (MeO); 127.69 (C(2)); 127.81 (C(5)); 138.88 (C(4)); 151.54 (C(3)); 163.21 (C(1)); 166.16 (C(6)). EI-MS: 190 (12, M^+(^{37}Cl)), 188 (31, M^+(^{35}Cl)), 157(25), 153(85), 131(30), 129(76), 125(100), 121(95), 93(53), 65(37), 39(21).

4. *Methyl (2*E*,4Z)-4-Methyl-6-oxohexa-2,4-dienoate* (**6**). Ester **6** was synthesized according to [9]. Yield 45%. White needles. M.p. 48°. UV/VIS (THF): 276. IR ($CHCl_3$): 3541*w*, 3038*w*, 2960*w*, 2874*w*, 2854*w*, 2771*w*, 1724*s*, 1678*s*, 1634*m*, 1595*m*, 1439*m*, 1288*s*, 1179*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.11 (*s*, Me–C(4)); 3.80 (*s*, MeO); 6.07 (*d*, *J* = 7.8, H–C(5)); 6.23 (*d*, *J* = 15.6, H–C(2)); 8.21 (*d*, *J* = 15.6, H–C(3)); 10.26 (*d*, *J* = 7.8, H–C(6)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 20.70 (*Me*–C(4)); 52.07 (MeO); 125.03 (C(2)); 133.23 (C(5)); 138.08 (C(3)); 150.51 (C(4)); 166.34 (C(1)); 189.56 (C(6)). EI-MS: 154 (97, M^+), 139(34), 125(43), 122(32), 111(11), 95(100), 67(33), 41(20).

5. *(all-*E*)-8-Hydroxy-2,7-dimethylocta-2,4,6-trienal* (**11**). Hydroxyaldehyde **11** was synthesized according to [9]. Yield 76%. Yellow semicrystalline powder. M.p. 58–59°. UV/VIS (THF): 326. IR ($CHCl_3$): 3605*w*, 3020*m*, 2921*w*, 2854*w*, 1671*s*, 1610*s*, 1221*s*, 1210*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.87 (*s*, Me–C(7)); 1.88 (*s*, Me–C(2)); 4.16 (*s*, 2 H–C(8)); 6.32 (*d*, *J* = 11.8, H–C(6)); 6.65 (*dd*, *J* = 11.7, 14.4, H–C(4)); 6.93 (*dd*, *J* = 11.8, 14.4, H–C(5)); 6.94 (*d*, *J* = 11.7, H–C(3)); 9.45 (*s*, H–C(1)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 9.51 (*Me*–C(2)); 14.54 (*Me*–C(7)); 67.74 (C(8)); 123.85 (C(6)); 126.97 (C(4)); 136.94 (C(5)); 137.14 (C(2)); 143.99 (C(7)); 148.93 (C(3)); 194.69 (C(1)). EI-MS: 166 (85, M^+), 148(57), 109(64), 108(62), 105(51), 95(91), 91(61), 79(52), 77(50), 67(49), 55(46), 43(100), 29(39), 18(43).

6. *[(*E*)-4,4-Dimethoxy-3-methylbut-2-enyl]triphenylphosphonium Chloride* (**13**). A soln. of [(*E*)-3-methyl-4-oxobut-2-enyl]triphenylphosphonium chloride (5.0 g, 13.1 mmol; **12**), trimethyl orthoformate (1.65 ml, 15.1 mmol), and 1% TsOH/MeOH (0.10 ml) in MeOH (70 ml), was stirred for 18 h at 35°. The soln. was cooled to 0° and treated with 1% Et_3N in MeOH (0.15 ml) under vigorous stirring for 30 min at 0°. Then, the solvent and the excess of trimethyl orthoformate were evaporated: 5.60 g (99%) of **13**. Yellow viscous oil. UV/VIS (MeOH): 275. IR ($CHCl_3$): 3639*w*, 3327*m*, 2938*s*, 2835*m*, 2466*w*, 2367*w*, 1442*m*, 1343*m*, 1242*m*, 1115*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20 (*d*, *J* = 3.7, Me–C(3)); 2.97 (*s*, 2 MeO); 4.22 (*d*, *J* = 1.8, H–C(4)); 4.48 (*dd*, *J* = 7.7, 15.5, 2 H–C(1)); 5.43 (*dt*, *J* = 6.7, 7.7, H–C(2)); 7.49–7.71 (*m*, arom. H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 12.5 (*d*, *J* = 12, *Me*–C(3)); 23.7 (*d*, *J* = 201, C(1)); 53.6 (*s*, MeO); 105.5 (*d*, *J* = 10, C(4)); 112.7 (*d*, *J* = 36, C(2)); 117.8 (*d*, *J* = 340, C_{ipso}); 130.3 (*d*, *J* = 49, C_o); 133.6 (*d*, *J* = 39, C_m); 135.0 (*d*, *J* = 12, C_p); 142.8 (*d*, *J* = 12, C(3)).

7. *(all-*E*)-12-Hydroxy-2,6,11-trimethyldodeca-2,4,6,8,10-pentaenal* (**14**). To a soln. of **13** (5.55 g, 13.0 mmol) and **11** (1.84 g, 11.1 mmol) in MeOH (70 ml), 1N NaOMe in MeOH (21 ml) was added dropwise. The mixture was stirred for 23 h and then cooled to 0°, and AcOH (30 ml) and H_2O (50 ml) were added. After stirring for 30 min at 0°, the soln. was partitioned between CH_2Cl_2 and H_2O. The org. phase was washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and evaporated. Purification by FC (silica gel, hexane/AcOEt 3:1) gave 1.80 g (70%) of **14** ((*E*/*Z*)-isomers). Repeated crystallization from hot hexane/acetone afforded 0.69 g (27%) of (all-*E*)-**14**. Orange crystals. M.p. 127–128°. UV/VIS (THF): 382, 398. IR ($CHCl_3$): 3616*w*, 3028*w*, 2927*w*, 2862*w*, 1665*s*, 1613*s*, 1563*s*, 1411*w*, 1383*w*, 1292*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.84 (*s*, Me–C(11)); 1.89 (*s*, Me–C(2)); 1.97 (*s*, Me–C(6)); 4.13 (*s*, 2 H–C(12)); 6.24 (*d*, *J* = 10.3, H–C(10)); 6.40 (*d*, *J* = 10.7, H–C(7)); 6.53–6.75 (*m*, H–C(4), H–C(5), H–C(8), H–C(9)); 6.93 (*d*, *J* = 9.2, H–C(3)); 9.43 (*s*, H–C(1)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 9.57 (*Me*–C(2)); 12.58 (*Me*–C(6)); 14.41 (*Me*–C(11)); 68.08 (C(12)); 122.55 (C(4)); 124.88 (C(10)); 128.54 (C(8)); 131.96 (C(9)); 134.86 (C(6)); 139.70 (C(2)); 137.11 (C(7)); 140.25 (C(11)); 146.00 (C(5)); 149.36 (C(3)); 194.62 (C(1)). EI-MS: 232 (100, M^+), 199(20), 157(23), 145(24), 131(21), 119(27), 105(30), 91(34), 43(27).

8. *[(all-*E*)-2,7,11-Trimethyl-12-oxododeca-2,4,6,8,10-pentaenyl]triphenylphosphonium Bromide* (**15**). A soln. of **14** (0.1 g, 0.43 mmol) and $PPh_3 \cdot HBr$ (0.15 g, 0.44 mmol) in MeOH (20 ml) was stirred for 7 d at r.t. in total darkness. The soln. was evaporated and the residue dissolved in a small amount of CH_2Cl_2 and precipitated in a vigorously stirred ice-cold mixture of Et_2O (150 ml) and hexane (20 ml). The precipitate was filtered and washed 2 × with cold Et_2O. Drying under h.v. gave 0.19 g (78%) of **15** as orange powder.

9. *Methyl (9Z)-8′-Oxo-6,8′-diapocaroten-6-oate* (**2**). To a suspension of NaH (9 mg, 0.38 mmol) in CH_2Cl_2 (10 ml) at −20°, **6** (30 mg, 0.20 mmol) in CH_2Cl_2 (2 ml) and **15** (0.12 g, 0.21 mmol) in CH_2Cl_2 (2 ml) were added separately and simultaneously within 30 min. The mixture was warmed to r.t. overnight and partitioned between Et_2O and H_2O. The org. phase was washed with H_2O, dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/AcOEt 8:1 + 0.5% Et_3N), and recrystallization from warm hexane/benzene resulted in 20 mg (29%) of **2**. Red needles. M.p. 149–150°. UV/VIS (*t*-BuOMe): 341, 419, 443, 472. IR ($CHCl_3$): 3532*w*, 3306*w*, 3036*m*, 3006*m*, 2952*m*, 2925*m*, 2858*m*, 1698*s*, 1666*s*, 1612*s*, 1574*s*, 1532*m*, 1436*m*, 1274*m*, 1178*s*. ^{1}H-NMR (500 MHz, $CDCl_3$):

Table 1. ^{13}C-NMR (125.8 MHz, $CDCl_3$): *Table 2*. EI-MS: 352 (100, M^+), 246 (58), 197 (12), 157 (16), 106 (35), 105 (29), 91 (30), 77 (13).

10. *(all-*E*)-10-Hydroxy-4,9-dimethyldeca-2,4,6,8-tetraenenitrile* (**16**). A soln. of diethyl (cyanomethyl)-phosphonate (5.31 g, 30 mmol) in THF (10 ml) was added dropwise to a suspension of NaH (0.72 g, 30 mmol) in THF (100 ml) at 0° and stirred for 1 h. A soln. of **11** (2.5 g, 15 mmol) in THF (20 ml) was added dropwise. After stirring for 30 min at r.t., ice was added and the mixture partitioned between Et_2O and H_2O. The org. phase was dried ($MgSO_4$) and evaporated. Purification by FC (silica gel, hexane/AcOEt 7:3) gave 2.5 g (88%) of **16**. Yellow crystals. M.p. 135–136°. UV/VIS (THF): 338, 356. IR ($CHCl_3$): 3604*w*, 3011*w*, 2927*w*, 2862*w*, 2215*s*, 1583*s*, 1449*w*, 1400*w*, 1379*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.85 (*s*, Me–C(9)); 1.87 (*s*, Me–C(4)); 4.14 (*s*, 2 H–C(10)); 5.27 (*d*, J = 16.2, H–C(2)); 6.26 (*d*, J = 11.4, H–C(8)); 6.42 (*d*, J = 11.4, H–C(5)); 6.52 (*dd*, J = 11.4, 14.0, H–C(6)); 6.72 (*dd*, J = 11.4, 14.0, H–C(7)); 7.05 (*d*, J = 16.2, H–C(3)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 11.82 (*Me*–C(4)); 14.49 (*Me*–C(9)); 67.89 (C(10)); 93.55 (C(2)); 119.14 (C(1)); 124.34 (C(8)); 127.50 (C(6)); 132.34 (C(4)); 134.35 (C(7)); 139.66 (C(5)); 141.84 (C(9)); 154.23 (C(3)). EI-MS: 189 (70, M^+), 160 (22), 146 (35), 132 (55), 104 (39), 91 (36), 79 (38), 43 (39), 28 (100), 18 (68).

11. *(all-*E*)-10-Hydroxy-4,9-dimethyldeca-2,4,6,8-tetraenal* (**17**). During 30 min, 1N DIBAH in hexane (20 ml) was added to a soln. of **16** (1 g, 5.3 mmol) in THF (70 ml) at –70°. The mixture was warmed to r.t. within 5 h and stirred at r.t. for another 2 h. The mixture was cooled to 0°, hydrolyzed with sat. aq. NH_4Cl soln. (130 ml) for 1 h, and diluted with Et_2O. The org. phase was washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/AcOEt 3:2) afforded 0.70 g (69%) of **17**. Yellow crystals. M.p. 82–83°. UV/VIS (THF): 352, 366. IR ($CHCl_3$): 3610*w*, 3034*w*, 2925*w*, 2859*w*, 2821*w*, 2739*w*, 1667*s*, 1580*s*, 1390*w*, 1128*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.86 (*s*, Me–C(9)); 1.94 (*s*, Me–C(4)); 4.14 (*s*, 2 H–C(10)); 6.18 (*dd*, J = 7.7, 15.5, H–C(2)); 6.28 (*d*, J = 11.0, H–C(8)); 6.57 (*m*, H–C(5), H–C(6)); 6.74 (*m*, H–C(7)); 7.16 (*d*, J = 15.5, H–C(3)); 9.57 (*d*, J = 7.7, H–C(1)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 12.63 (*Me*–C(4)); 14.50 (*Me*–C(9)); 67.92 (C(10)); 124.45 (C(8)); 127.29 (C(2)); 127.94 (C(6)); 133.52 (C(4)); 134.42 (C(7)); 140.91 (C(5)); 141.94 (C(9)); 156.80 (C(3)); 193.83 (C(1)). EI-MS: 192 (100, M^+), 161 (22), 145 (29), 131 (34), 105 (61), 95 (41), 91 (52), 79 (31), 77 (28), 55 (25), 43 (33).

12. *[(all-*E*)-2,7-Dimethyl-10-oxodeca-2,4,6,8-tetraenyl]triphenylphosphonium Bromide* (**18**). To a soln. of **17** (0.82 g, 4.3 mmol) and pyridine (0.19 ml, 2.4 mmol) in CH_2Cl_2 (20 ml) at –10°, a soln. of PBr_3 (0.40 ml, 4.3 mmol) in CH_2Cl_2 (8 ml) was added during 20 min and stirred for 30 min at –10°. The mixture was hydrolyzed with sat. aq. $NaHCO_3$ soln. (30 ml) and extracted with Et_2O. The org. phase was filtered, washed with brine and H_2O, dried ($MgSO_4$), and evaporated. The very labile bromide was immediately dissolved in *t*-BuOMe (20 ml), and PPh_3 (1.1 g, 4.3 mmol) was added. The mixture was stirred for 72 h at r.t. in total darkness. The precipitate was filtered, redissolved in a small amount of CH_2Cl_2, and precipitated again in a vigorously stirred ice-cold mixture of Et_2O (500 ml) and hexane (300 ml). The solid material was filtered and washed 2 × with cold Et_2O. Drying under h.v. gave 1.0 g (45%) of **18** as orange powder.

13. *Methyl (9*Z*)-10′-Oxo-6,10′-diapocaroten-6-oate* (**4**). To a suspension of NaH (9 mg, 0.38 mmol) in CH_2Cl_2 (10 ml) at –20°, **6** (30 mg, 0.20 mmol) in CH_2Cl_2 (2 ml) and **18** (0.11 g, 0.21 mmol) in CH_2Cl_2 (2 ml) were added separately and simultaneously within 30 min. The mixture was warmed to r.t. overnight and partitioned between Et_2O and H_2O. The org. phase was washed with H_2O, dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/AcOEt 6:1 + 0.5% Et_3N) and recrystallization from warm hexane/benzene resulted in 13 mg (22%) of **4**. Red needles. M.p. 130–131°. UV/VIS (*t*-BuOMe): 324, 401, 423, 449. IR ($CHCl_3$): 3530*w*, 3038*w*, 3004*w*, 2952*w*, 1702*m*, 1666*s*, 1612*m*, 1584*s*, 1542*m*, 1436*m*, 1280*m*, 1166*m*, 1128*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75.5 MHz, $CDCl_3$): *Table 2*. EI-MS: 312 (100, M^+), 206 (12), 171 (12), 157 (17), 145 (32), 143 (19), 119 (16), 106 (16), 105 (22), 95 (11), 91 (35).

14. *Ethyl (2*E*)-2-Methyl-4-oxobut-2-enoate* (**20**). To a suspension of NaH (0.84 g, 35.0 mmol) in THF (150 ml) at 0°, ethyl 2-(diethoxyphosphinyl)propanoate (7.5 ml, 35.0 mmol) in THF (30 ml) was added dropwise and stirred for 1 h at 0°. A soln. of 2,2-dimethoxyethanal (4.2 g, 40.2 mmol; **19**) in *t*-BuOMe (5 ml) was added dropwise. After stirring for 15 min at 0° and for 15 min at r.t., the soln. was reduced to *ca*. 60 ml. CF_3COOH (30 ml) and H_2O (30 ml) were added, and the mixture was stirred for 1 h at r.t. and diluted with Et_2O. The org. layer was washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/*t*-BuOMe 6:1 + 0.5% Et_3N) afforded 3.9 g (78%) of **20**. Yellow oil. UV/VIS (*t*-BuOMe): 221. IR ($CHCl_3$): 3553*w*, 3033*m*, 2986*m*, 2964*m*, 2934*m*, 2862*m*, 2768*w*, 1718*s*, 1684*s*, 1369*m*, 1333*m*, 1256*s*, 1145*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.34 (*t*, J = 7.2, *Me*CH_2O); 2.33 (*d*, J = 1.5, Me–C(2)); 4.29 (*q*, J = 7.2, MeCH_2O); 6.81 (*dq*, J = 1.5, 7.7, H–C(3)); 10.20 (*d*, J = 7.7, H–C(4)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.18 (*Me*CH_2); 14.05 (*Me*–C(2)); 61.86 (MeCH_2O); 133.42 (C(3)); 145.82 (C(2)); 167.18 (C(1)); 191.75 (C(4)). EI-MS: 142 (36, M^+), 113 (89), 97 (100), 96 (81), 85 (53), 69 (82), 68 (84), 67 (52), 41 (66), 40 (47), 39 (59), 29 (62), 18 (33).

15. *Ethyl (2*E*,4*E*)-2-Methyl-5-cyanopenta-2,4-dienoate* (**21**). A soln. of diethyl (cyanomethyl)phosphonate (3.41 ml, 21.7 mmol) in THF (10 ml) was added within 30 min to a vigorously stirred suspension of NaH (0.52 g, 21.7 mmol) in THF (70 ml) at 0°. After stirring for 45 min at 0°, **20** (2.8 g, 19.7 mmol) in THF (10 ml) was added during 30 min. After 1 h, the mixture was diluted with Et_2O, washed with sat. aq. NH_4Cl soln. and H_2O, dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/AcOEt 15:1 to 10:1) gave 1.40 g (43%) of **21**. White crystalline substance. M.p. 66–67°. UV/VIS (*t*-BuOMe): 271. IR ($CHCl_3$): 3548*w*, 3034*w*, 2986*w*, 2940*w*, 2220*m*, 1708*s*, 1370*m*, 1286*s*, 1232*s*, 1108*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.33 (*t*, *J* = 7.2, *Me*CH_2); 2.06 (*d*, *J* = 1.5, Me–C(2)); 4.25 (*q*, *J* = 7.2, MeCH_2O); 5.65 (*d*, *J* = 15.6, H–C(5)); 7.16 (*dq*, *J* = 1.5, 11.8, H–C(3)); 7.33 (*dd*, *J* = 11.8, 15.6, H–C(4)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 13.43 (*Me*CH_2); 14.16 (*Me*–C(2)); 61.39 (Me*C*H_2O); 104.29 (C(5)); 117.42 (CN); 133.31 (C(3)); 136.53 (C(2)); 144.64 (C(4)); 166.87 (C(1)). EI-MS: 165 (100, M^+), 137 (80), 120 (80), 119 (55), 92 (47), 91 (58), 65 (39), 28 (17), 18 (31).

16. *(2*E*,4*E*)-6-Hydroxy-5-methylhexa-2,4-dienal* (**22**). To a soln. of **21** (1.35 g, 8.2 mmol) in THF (100 ml) at −70°, 1N DIBAH in hexane (40 ml) was added within 30 min. The mixture was warmed to r.t. within 4 h, stirred at r.t. for 1 h, and hydrolyzed with sat. aq. NH_4Cl soln. (200 ml) at 0°. Stirring was continued at 0° for 10 min and at r.t. for 30 min. Most of the THF was evaporated and the product extracted with Et_2O. The combined Et_2O phases were washed with H_2O, dried ($MgSO_4$), evaporated, and purified by FC (silica gel, *t*-BuOMe): 0.57 g (55%) of **22**. Yellow oil. UV/VIS (*t*-BuOMe): 280. IR ($CHCl_3$): 3608*w*, 3426*w*, 3006*m*, 2964*m*, 2928*m*, 2856*m*, 1678*s*, 1640*s*, 1126*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.94 (*s*, Me–C(5)); 4.21 (*d*, *J* = 5.5, 2 H–C(6)); 6.18 (*dd*, *J* = 7.9, 15.1, H–C(2)); 6.45 (*d*, *J* = 11.6, H–C(4)); 7.44 (*dd*, *J* = 11.6, 15.1, H–C(3)); 9.62 (*d*, *J* = 7.9, H–C(1)). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 14.67 (*Me*–C(5)); 66.98 (C(6)); 121.41 (C(2)); 131.08 (C(4)); 147.86 (C(3)); 150.72 (C(5)); 194.28 (C(1)). EI-MS: 126 (73, M^+), 97 (100), 95 (83), 79 (18), 55 (19), 43 (21), 41 (24), 39 (22).

17. *[(2*E*,4*E*)-2-Methyl-6-oxohexa-2,4-dienyl]triphenylphosphonium Bromide* (**23**). To a soln. of NBS (0.34 g, 1.9 mmol) in CH_2Cl_2 (8 ml) at 0°, Me_2S (0.15 ml, 2.0 mmol) was added under vigorous stirring. The mixture was further cooled to −20°, and **22** (0.17 g, 1.3 mmol) in CH_2Cl_2 (5 ml) was added under vigorous stirring. The mixture was warmed to r.t., maintained at r.t. for 3 h, and partitioned between Et_2O and H_2O. The org. layer was washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and evaporated. The very labile bromide was immediately dissolved in AcOEt (8 ml), and PPh_3 (0.4 g, 1.5 mmol) was added. The soln. was stirred for 40 h at r.t. in total darkness. The precipitate was filtered and washed 2 × with cold Et_2O. Drying under h.v. afforded 0.30 g (49%) of **23** as orange powder, which was directly used for the next reaction.

18. *[(2*E*,4*E*)-6,6-Dimethoxy-2-methylhexa-2,4-dienyl]triphenylphosphonium Bromide* (**24**). A soln. of **23** (0.30 g, 0.66 mmol), trimethyl orthoformate (84 µl, 0.77 mmol), and 1% TsOH/MeOH (0.20 ml) in MeOH (8 ml) was stirred for 10 h at 35°. The soln. was cooled to 0° and treated with 1% Et_3N/MeOH (0.30 ml) under vigorous stirring. After stirring for 30 min at 0°, the mixture was evaporated and the residue dried under h.v.: 0.33 (99%) of **24**. Yellow viscous substance.

19. *Methyl (9*Z*)-14′-Oxo-6,14′-diapocaroten-6-oate*[2]) (**5**). To a soln. of **24** (0.29 g, 0.58 mmol) in CH_2Cl_2 (15 ml) at r.t., **6** (81 mg, 0.53 mmol) in CH_2Cl_2 (4 ml) and 1N NaOMe in MeOH (1 ml) were added separately and simultaneously during 30 min. After stirring for 20 min, the soln. was reduced to *ca.* 8 ml, and formic acid (2 ml) and H_2O (2 ml) were added. The mixture was stirred for 10 min at r.t. and partitioned between Et_2O and H_2O. The org. layer was washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried ($MgSO_4$), and evaporated. FC (silica gel, hexane/*t*-BuOMe 3:1 + 0.5% Et_3N) and recrystallization from hexane/benzene yielded 45 mg (34%) of **5**. Orange needles. M.p. 128°. UV/VIS (*t*-BuOMe): 281, 356, 372, 392. IR ($CHCl_3$): 3528*w*, 3034*w*, 3004*w*, 2952*w*, 2820*w*, 1702*m*, 1670*s*, 1608*s*, 1572*m*, 1436*m*, 1278*s*, 1176*s*, 1134*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): *Table 1*. ^{13}C-NMR (75.5 MHz, $CDCl_3$): *Table 2*. EI-MS: 246 (100, M^+), 217 (25), 187 (24), 185 (23), 159 (23), 157 (35), 143 (26), 128 (20), 105 (18), 95 (18), 91 (20).

20. *6′-Methyl Hydrogen (9′*Z*)-6,6′-Diapocarotene-6,6′-dioate (= Bixin*; **1**). To a soln. of trimethylsilyl (diethoxyphosphinyl)acetate (52 µl, 0.20 mmol; **25**) in benzene (1.5 ml) at 10°, 1.6N BuLi in hexane (0.13 ml) was added dropwise. The mixture was stirred for 1 h at r.t. Then, **2** (60 mg, 0.17 mmol) in benzene (0.5 ml) was added dropwise. After stirring for 3 h at r.t., the dark red soln. was partitioned between CH_2Cl_2 and 2% aq. formic acid. The org. phase was washed 3 × with H_2O, dried ($MgSO_4$), and evaporated. The product was purified by FC (silica gel, AcOEt/MeOH 20:1) and recrystallized from warm AcOEt/hexane: 18 mg (26%) of **1**. Red needles. M.p. 197–199°. UV/VIS (*t*-BuOMe): 354, 428, 453, 484. IR ($CHCl_3$): 3520*w*, 3034*m*, 3000*m*, 2954*m*, 2921*m*, 2860*w*, 1708*s*, 1612*s*, 1566*m*, 1436*m*, 1278*s*, 1194*s*, 1174*s*, 1132*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): *Table 3*. ^{13}C-NMR (125.8 MHz, (D_6)DMSO): *Table 3*. EI-MS: 394 (23, M^+), 288 (22), 145 (11), 106 (52), 105 (27), 91 (100), 77 (12), 28 (20), 18 (14).

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