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BIOMIMETIC SYNTHESIS OF BACTERIAL C_{50} CAROTENOIDS DECAPRENOXANTHIN AND C.p. 450.

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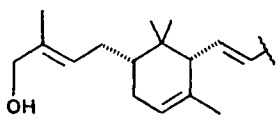
Abstract : *Alkylation of the distal double bond of pseudoionone 4 has been carried out with isoprene epoxide ($ZnCl_2/MeNO_2$) leading directly to α-cis 10a, α-trans 10b and γ 10c hydroxyprenylionones. The α-cis and γ-isomers have been converted in few steps into the C_{50} carotenoids decaprenoxanthin 1 and C.p. 450 3 respectively.*

Our interest in biomimetic prenylation reactions led us to develop a novel approach to C_{45} or C_{50} carotenoids involving electrophilic prenylation-cyclisation of pseudoionone [1]. This approach parallels the biosynthesis of these carotenoids where it is suggested that electrophilic attack at C-2 (and C-2') by extra C_5 unit(s) triggers the cyclisation [2]. Three bicyclic C_{50} carotenoid diols are known :decaprenoxanthin 1 from Flavobacterium dehydrogenans with substituted ε-end groups A [3], sarcinaxanthin 2 from Sarcina lutea with substituted γ-end groups B [4], and C.p.450 3 from Corynebacterium poinsettiae with two substituted β-end groups C [5]. We report here stereoselective syntheses of decaprenoxanthin 1 and C.p. 450 3 using as a key step a hydroxyalkylation-cyclisation of pseudoionone with isoprene epoxide.



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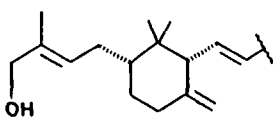

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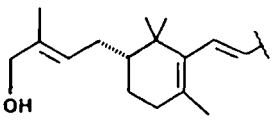

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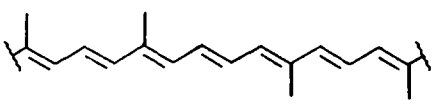
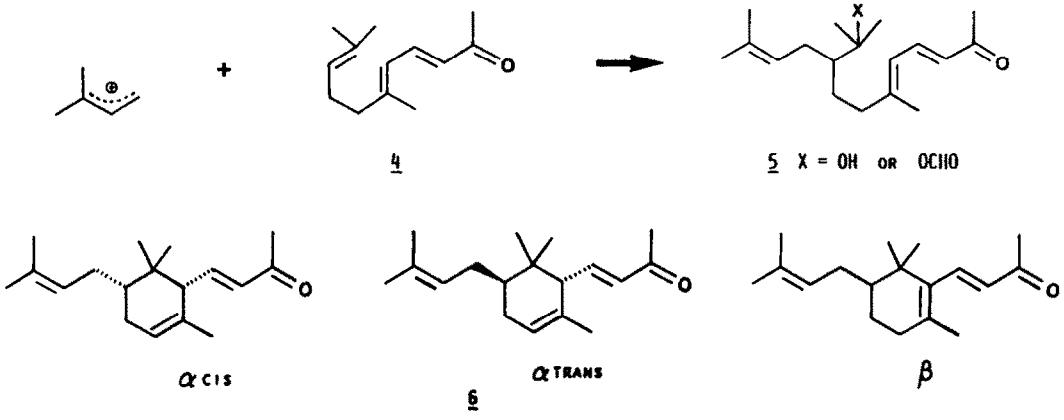


P

1 A - P - A
2 B - P - B
3 C - P - C

It has been already shown that pseudoionone 4 is prenylated at the C-2 * position and the product 5 can be cyclised to the expected 2-prenylionones α-cis or α-trans or β 6 [1]. Such ionone derivatives are convenient building blocks for subsequent syntheses of C_{50}carotenoids according to the classical $C_{15} + C_{10} + C_{15}$ route used for C_{40}carotenoids [6]. Allylic oxidation (SeO_2, t-BuOOH [7]) of the terminal double bond(s) would then give the terminal E-allylic alcohol function, thus providing a shorter and more stereoselective synthesis of C_{50}carotenoids than the multistep approach already reported for decaprenoxanthin from methylheptenone [8].

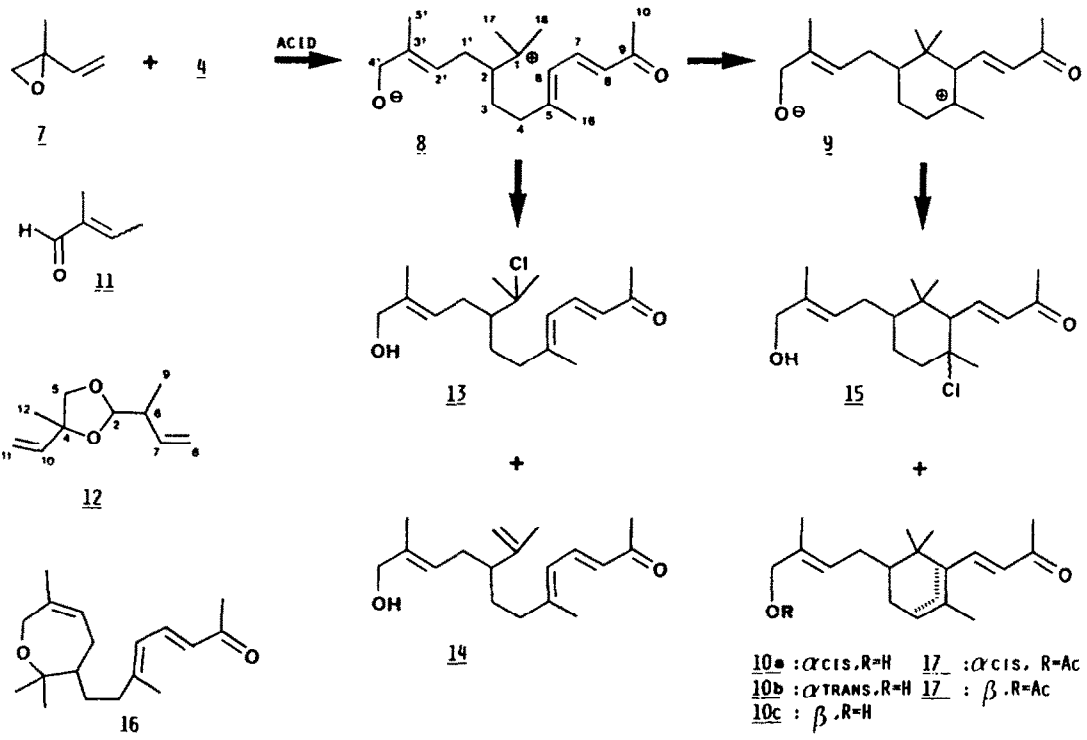


A more convergent route was explored using the readily available isoprene epoxide [9]. Many examples of polyolefinic epoxide cyclisations in an acidic medium have been reported in connection with the well known enzymic polycyclization of 2,3-oxidosqualene into lanosterol by the 2,3-oxidosqualene-lanosterol cyclase [10]. However no intermolecular example of this direct olefine-epoxide alkylation has been yet described, although some cases of hydroxyalkylation of aromatic rings with epoxides are known [11]. It seemed reasonable to expect an acid promoted alkylation of the most nucleophilic distal double bond of pseudoionone 4 with isoprene epoxide 7, with the formation of the new C-C bond at the terminal carbon of 7. With respect to the stereochemistry of the new double bond formed, little information was available from literature : solvolysis of 7 in phenol/sodium phenoxide produced a mixture of E and Z-(4-hydroxyprenyl)-phenol [12] whereas acid promoted opening of the homologous α-cyclopropylepoxide led to the E-double bond with high stereoselectivity [13].

I - Synthesis of the C_{18} hydroxyprenylionones 10.

Pseudoionone 4 and isoprene epoxide 7 were treated under various conditions with Lewis acid promoters. After work-up, the crude reaction mixture was freed from excess 4 by flash chromatography and the polar residue analysed by TLC, GLC/MS and PMR. PMR signals at δ 3.95-4.05, singulet for the primary allylic hydroxyl, and at δ 0.7-1.0, two singulets, for the 17,18-gem-dimethyl groups were of particular diagnostic value for the expected reaction. Extensive chromatography at the outcome of the first alkylation experiments enable isolation of the prenylated products which were later identified as the desired α-cis, α-trans and β-hydroxyprenyl-ionones 10 together with other minor derivatives 13, 14 or 15. Samples of which were used to monitor the search for acceptable reaction conditions. The results of various hydroxyprenylation experiments are summarized in Table I.

* The numbering system of carotenoids is used throughout. For Chemical Abstracts Nomenclature see experimental part.



Entry	7 mmoles	4 [a] mmoles	Acid mmoles	Solvent ml	Temp. °C	Time min	Conversion of 4 %	HYDROXYPRENYLATED PRODUCTS: total yield calc. on converted 4	Proportion % 10	13	15 [f]
1	50	100	$ZnCl_2$ 200	$MeNO_2$ 250	-15	45	20 [d]	65 [d]	75	--	25
2	50	100	$ZnCl_2$ 200	$MeNO_2$ 250	-15 [b]	120	23 [d]	55 [d]	85	--	15
3	2	2	$ZnCl_2$ 4	$MeNO_2$ 5	-15	45	25 [e]	70 [e]	75	--	25 [g]
4	30	30	$ZnCl_2$ 60	$EtNO_2$ 75	-60	45	22 [d]	45 [d]	20	65	15
5	40	40	$ZnCl_2$-Et_2O [c] 80	$MeNO_2$ 100	-20	60	20 [d]	35 [d]	13	65	22
6	30	30	$ZnCl_2$ 60	CH_2Cl_2 75	-30	120	20 [d]	30 [d]	50	40	10
7	2	2	$SnCl_4$ 2.2	$MeNO_2$ 5	-20	15	20 [e]	42 [e]	55	--	45
8	2	2	BF_3-Et_2O 2.2	$MeNO_2$ 5	-20	15	30 [e]	< 2 [e]	not analysed		
9	1	2	$LiClO_4$ 4	$MeNO_2$ 5	-15	180	< 5 [e]	< 2 [e]	not analysed		
10	1	2	$Mg(NO_3)_2$ 4	$MeNO_2$ 5	+70	600	< 5 [e]	< 2 [e]	not analysed		

Table I : Hydroxyprenylation of pseudoionone 4 with isoprene epoxide 7.

a) In all runs decanol acetate was added as internal standard and isoprene epoxide was added dropwise over 20 to 30 min, except for entries 7 and 8 over 5 min. 90-95 % E-4 was used for all runs. b) 60 min at -15°C and then reaction mixture was allowed to warm up to room temperature. c) Dry $ZnCl_2$ was preliminarly dissolved in 3 molar eq. dry diethyl ether. d) Isolated yields. e) Evaluated by GLC comparison with entries 1 and 2. Each analysis was performed on the free and TMS derivatived crude reaction extract. f) Containing small amounts of 14 (up to 20%) and several uncharacterised minor components. g) Similar results were obtained when this reaction was conducted in $EtNO_2$ instead of $MeNO_2$.

The main features of this reaction were the following :

i) The $MeNO_2/ZnCl_2$ system appeared to be critical for the expected alkylation reaction. Dichloromethane could also be used but the reaction was ineffective with THF, MeCN or DMF. Although under all conditions investigated the reaction was clean with moderate conversion of pseudoionone to the expected products (20-25 %) the addition of more epoxide did not improve the yield (entries 1 and 3). The reason for this low conversion is not clear ; deactivation of the Lewis acid by the products can be suggested. In all runs isoprene epoxide was added to the dilute Lewis acid-pseudoionone solution since undesired by-products were formed when 7 was allowed to react with $ZnCl_2$ under the reaction conditions : thus tiglic aldehyde (E,Z) 11 [14] and the original fragrant 1,3-dioxolane 12 [15] (the four diastereoisomers being found) were isolated from the reaction mixture. With Lewis acids milder than $ZnCl_2$, such as $LiClO_4$ or $Mg(NO_3)_2$ [16] (entries 9 and 10) no or little alkylation occurred, whereas the use stronger acids such as BF_3-Et_2O or $SnCl_4$ (entries 8 and 7), resulted in more complex reaction mixtures (α-ionone was formed with $SnCl_4$). An attempt to use zinc triflate [17] was also unsuccessfull.

ii) The reaction temperature proved to be an important factor. When the reaction was conducted at -60°C (entry 4) in the $EtNO_2/ZnCl_2$ system, a considerable proportion of the hydroxyprenylated mixture consisted of acyclic chloro ketone 13. Its structure was established on the basis of MS, PMR and CMR (Table II) data. This acyclic chloro-compound 13 was also predominantly formed in CH_2Cl_2 (entry 6) or when the couple $ZnCl_2/Et_2O$ was used (entry 5). Another acyclic prenylated-derivative was also formed but in low yield in all the reaction mixtures ; its structure 14 was assigned on the basis of spectroscopic data : olefinic PMR signals at 4.73 and 4.82(broad singulets) were consistent with the existence of the isopropenyl moiety.

At higher temperatures (entries 1,2,3) compound 13 was no longer observed in the reaction mixture which now consisted mainly of the expected isomeric hydroxyprenylionones 10 (see below) together with an appreciable amount of the cyclised chloroketone 15. Its MS(CI) spectrum (M^++1 at 313 and M^++3 at m/z 315) as well as its PMR (δ 0.91 and 1.02, 2s for a 17,18-gemdimethyl group and 1.43, s, 16-Me) and CMR (δ 71.8 for C-5, see Table II) were fully consistent with the proposed structure 15. Interestingly, only one cyclic chloro-compound was found ; a 2,6-cis stereochemistry of the chains can be tentatively assigned to 15 from PMR and CMR data but the stereochemistry of the chlorine atom remains ambiguous.

The possibility that the cyclic chloride 15 was formed through cyclisation of 13, which has been shown in another case [18], was checked by treating 13 under standard $MeNO_2/ZnCl_2$ conditions at -15°C. Surprisingly no 15 could be detected. On the other hand, when the reaction mixture (entry 2) was allowed to warm up to room temperature the proportion of 15 decreased, but the question whether it is converted to the hydroxyprenylketones 10 still remains to be clarified. These latter conditions were used for the synthesis of the expected C_{18} synthons 10 on a preparative scale.

iii) All the compounds isolated were formed with complete 1,4-regioselectivity in the alkylation of isoprene epoxide, which was associated with almost exclusive E-stereochemistry [19] (>95% from PMR) of the resulting double bond in the isoprene epoxide derived moiety. The question as to whether the possible 2'Z-intermediate cation 8 has been consumed by cyclization into cyclic ethers like 16 has been investigated, but they could not be detected either by TLC or by GLC analysis of the crude reaction mixtures performed before and after silylation.

iv) The hydroxyprenylionone isomers were easily separated by two successive silica gel column chromatography steps. The initial purification, performed on the free hydroxyketones mixture, allowed separation of the pure α-trans 10b isomer. The α-cis 10a and β 10c isomers were finally separated, as their acetates 17a and 17b respectively, after further column chromatography. No γ isomer was detected in the reaction mixture. The three isolated α-cis, α-trans and β-iso-

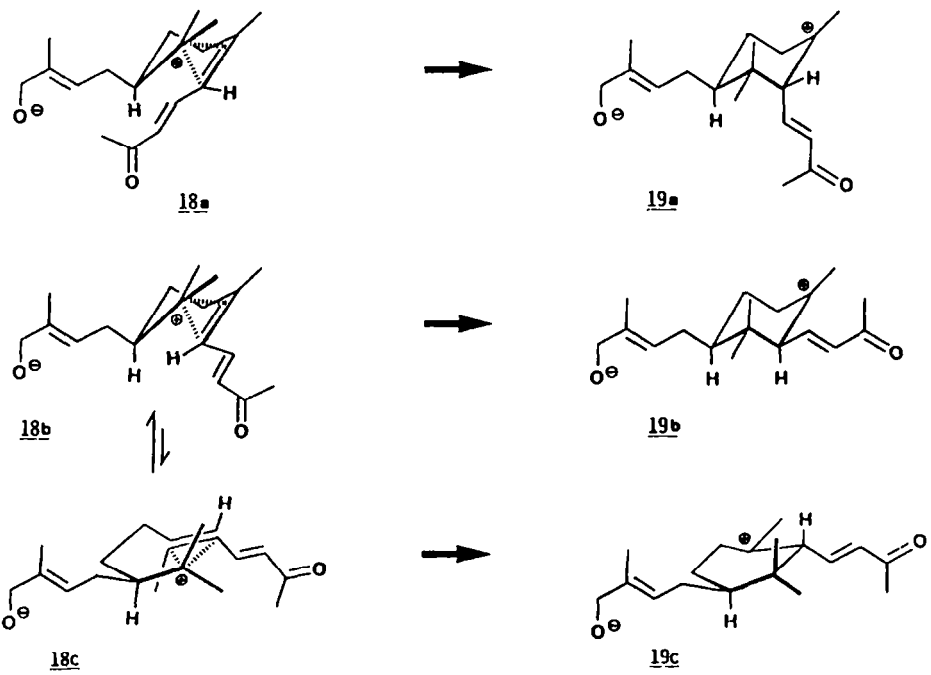
mers were identified by comparison of their PMR and CMR spectra with those of the corresponding irones [20], synthetic irone precursors [21] or natural C_{50}carotenoids [3,5].

carbon	13	15	10a	10b	10c	carbon	13	15	10a	10b	10c
1	75.4	37.8	35.8	35.4	37.4	10	27.7	26.6	26.7	26.8**	27.4**
2	50.7	47.9	44.0	37.8	45.3	16	17.6	34.5	22.7	22.4	21.9
3	29.7	23.5	27.6*	27.5*	23.0	17	30.6	16.9	16.4	21.6	22.5
4	39.8	42.9	122.3	122.5	32.5	18	31.3	29.3	26.7	26.5**	27.2**
5	150.6	71.8	131.1	131.2	135.9*	1'	29.7	28.2	28.4*	29.3*	28.1
6	123.8	61.0	55.7	56.5	134.0*	2'	124.6	124.6	124.3	124.2	125.2
7	139.2	145.7	148.8	148.1	143.7	3'	135.0	135.6	135.0	135.0	135.3
8	128.4	135.4	133.7	131.9	132.2	4'	68.7	68.4	68.1	68.2	68.7
9	198.4	197.8	197.4	198.0	198.2	5'	14.2	13.9	13.7	13.7	13.9

Any values with * and ** for one given compound may be reversed.

Table II : CMR spectra of 13, 15, 10a, 10b, 10c.

As expected, the stereochemical course of cyclisation of the intermediate cation 8 was shown to be highly dependent on the stereochemistry of the 5,6-double bond of pseudoionone (Table III). Z-pseudoionone gave, through the cyclic cation 9, almost exclusively the α-trans 10b isomer. This result is in agreement with a similar observation during a synthesis of irones [21]. Without presuming whether the alkylation-cyclisation reaction follows a concerted or a two step process, the cyclisation of the potential corresponding cation 18a, where the hydroxyprenyl chain at C-2 is assumed to be equatorial, will preferentially lead to the 2,6-trans cation 19a. Subsequent deprotonation at C-4 then gives the thermodynamically more stable α-trans 10b isomer.



Hydroxyprenylation-cyclisation of E-pseudoionone gave a mixture of α-trans 10b (40 %), α-cis 10a (45 %) and β 10c (15 %). Obviously the cyclisation step is, in this case, much less selective. Since the α-cis 10a isomer was shown not to equilibrate under the reaction conditions used ($ZnCl_2$/ $MeNO_2$, 1h, 25°C) the α-cis/α-trans isomeric composition must reflect two different kinetically controlled courses of the cyclisation step. The experimental results suggest that, in this case, the cyclisation can occur through either the chair-type 18b or the boat like 18c transition states, giving the cis 19b or the trans 19c intermediates respectively. It is well known (see below) that in the irone family the α-cis is less stable than the α-trans isomer and the difference in energy might be partially reflected in the transition states 18b or 18c leading respectively to α-cis 10a or α-trans 10b.

Equilibration of the α-cis, α-trans, β mixture was carried out under the alkaline conditions (KOH/MeOH) used for irones [20a] (Table III). Here again the β-isomer 10c proved the more stable, whereas the α-cis 10a almost completely disappeared.

conditions	proportions		
	α-cis	α-trans	β
from Z-4		>95	
from E-4	45	40	15
KOH equilibration	3	35	60
KOH equil. of irones [20a]	10	32	58

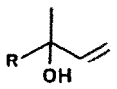
Table III : Isomeric proportions of 10 according to conditions.

Having developed the best conditions to obtain the expected C_{18} building blocks, either α-cis 10a (starting from E-pseudoionone) or β 10c (from base equilibration), we turned our attention towards the second part of the C_{50}carotenoid syntheses.

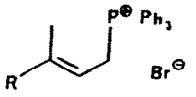
II - Synthesis of decaprenoxanthin 1

The plan for the synthesis of both decaprenoxanthin 1 and C.p. 450 3 from our C_{18} synthons involved three classical steps of carotenoid strategy, vinylation to the corresponding vinyl β-ionol derivatives, conversion into the primary phosphonium salt and final Wittig condensation with the central C_{10} dialdehyde 20 [22].

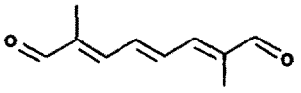
17a : R = A, ACETYLATED
10c : R = C



21a : R = A
21b : R = C



22a : R = A
22b : R = C



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The acetate of 2,6-cis 2-hydroxyprenyl α-ionone 17a was treated with an excess of vinylmagnesium bromide to give the hydroxyprenyl vinyl cis-α-ionol 21a as a mixture of diastereoisomers. Quantitative elimination of the acetyl group took place during the reaction. Subsequent transformation of 21a into the corresponding phosphonium salt 22a was carried out with triphenylphosphonium bromide in methanol. The yield was 58 % for these two steps. Finally, condensation of 22a with the C_{10} dial 20 in a two phase system [23] (CH_2Cl_2-aqueous KOH) afforded pure E,Z-decaprenoxanthin after silica gel column purification (71 % yield from the C_{10} dial). Two successive crystallizations gave all E-decaprenoxanthin (m.p. 162-164°C) as a single isomer. All spectroscopic data were fully consistent with those reported for natural decaprenoxanthin [3, 24]. Particularly the PMR signals at δ 4.05 (s, 4H) indicated the E-stereochemistry of the hydroxyprenyl end of chains and at δ 0.76 and 0.96 (2s, 6H each, gemdimethyl groups) were consistent with the 2,6-cis, 2',6'-cis configuration of the ε-rings A [3].

III - Synthesis of C.p. 450.

It is worth noting at this stage that when we started our syntheses, the C_{50} carotenoid C.p. 450 had been formulated as unsymmetrical with two differently substituted β-end groups containing both primary allylic hydroxygroups at one end and a dimethylallyl group at the other end [25]. However some ambiguity seemed to exist since Milborrow [26] has claimed the alkaline isomerisation of sarcinaxanthin 2 to decaprenoxanthin 1 and a "symmetrical C.p. 450" exhibiting the same chromatographic behaviour as natural C.p. 450. About the time we achieved our synthesis of "symmetrical C.p. 450", the structure of natural C.p. 450 from Corynebactorium Poinsettiae has been revised as being symmetrical with two hydroxyprenyl β-end groups C [5,27].

The synthesis of C.p. 450 followed the preceeding route from 2-hydroxyprenyl β-ionone 10c. The phosphonium salt 22b was prepared from 10c through the hydroxyprenyl vinyl β-ionol 21b in 51 % yield. Wittig condensation of the phosphorane derived from 22b with the dial 20 under the heterogenous conditions used above afforded C.p. 450 3 (yield 30 % from the dial) from which the major all E-isomer has been purified by chromatography and subsequent crystallization (m.p. 158-160°C). All spectroscopic data were in full agreement with those reported for natural C.p. 450 [5,24]. PMR signals at δ 0.92 and 1.08 (6H each) particularly correlate with those reported for the gemdimethyl groups of β-rings C of natural C.p. 450.

EXPERIMENTAL

Melting points are determined in a Reichert apparatus and are not corrected. IR spectra were measured on a Perkin-Elmer 599 ($CHCl_3$) and UV spectra on a Varian Superscan 3 spectrophotometers. PMR and CMR spectra were recorded on a Cameca 250 (250 MHz) or Bruker WH80 (80 MHz) and Bruker WP90 (22.63 MHz) spectrometers respectively ($CDCl_3$; δ, ppm from TMS). Mass spectra were obtained either by GC-MS coupling or direct introduction on a Nermag R10-10 apparatus using either electron impact (EI) or chemical ionisation (CI, NH_3) modes. Microanalysis were determined by the Service Central d'Analyse du CNRS 69390 VERNAISON (FRANCE).

GLC analysis were performed on a Girdel serie 30 chromatograph using 10 % OV 101 on Chromosorb WHP 100-120 with temperature programmation from 120 to 290°C at 10°C/min. Silylethers were prepared by addition of HMDS-TMCS (2:1) in pyridine to the sample and heating 60°C for 20 min [28]. Preparative GLC was performed on a Carlo Erba 4200 instrument using a 2.5 m x 6 mm column of 15 % OV 101 on Chromosorb AW-DMCS 60-80.

TLC was carried out using Merck silica gel 60 F_{254} plastic sheets (Art. 5735). Silica gel 60H (Art. 7736) or 60 (Art. 7734) Merck was used for flash or short column chromatographies. MPLC was performed with a prepacked silica Lobar 440-37 Merck column (Art. 10402) and HPLC was carried out on a TM Analprep EC93 equipped with a Zorbax Sil column and a Pye Unicam UV detector.

All solvents were dried and purified in the usual manner and petroleum ether refers to a fraction boiling under 60°C.

Anhydrous $ZnCl_2$ was prepared by melting twice under vacuum (20 mmHg) and was subsequently crushed to powder under a dry atmosphere.

Isoprene epoxide was synthesised from isoprene via the bromohydrine using described method [9].

Commercial pseudoionone [29] (Z,E-mixture 43:57) was fractionated by repeated distillations until the desired isomeric purity was obtained.

Alkylation of pseudoionone by isoprene epoxide. General procedure according to Table I, entry 2.

Anhydrous $ZnCl_2$ (27.3g, 200 mmol.) was added in one portion to 90 % E-pseudoionone (19.2g, 100 mmol.) in $MeNO_2$ (200 ml) at -15°C under nitrogen with mechanical stirring. Isoprene epoxide (94 % purity, 4.2g, 50 mmol) diluted with 50 ml $MeNO_2$ was added dropwise to this suspension over 30 min. After a further 30 min at -15°C the stirred reaction mixture was allowed to warm up to room temperature for 60 min. The reaction mixture was then poured into saturated $NaHCO_3$ and diluted with diethyl ether (250 ml). Insoluble material was removed by filtration ; after the organic phase of the filtrate was separated the aqueous layer was reextracted with ether (250 ml) and the combined extracts washed with brine and dried over $MgSO_4$. Finally the solvent was removed after taking an aliquot for GLC analysis, to give a pale yellow oil which was submitted to a flash chromatography (gradient ether-pentane). Pseudoionone (14.8g, 77 %) and a fraction containing all hydroxyprenylated compounds (3.7 g) were successively collected. Chromatography of the latter fraction by MPLC (ethylacetate-petroleum ether ; 1:3) gave in order of elution pure 10a, a mixture of 10a and 10c, pure 10b and finally a mixture of 14 and 15.

Separation of 10a and 10c was better achieved after acetylation (Ac_2O-pyridine, overnight, room temperature) and subsequent MPLC separation of the respective acetates 17a and 17b (ethylacetate-toluene-petroleum ether ; 15:4:1).

These purification steps gave 4.7 mmol α-cis (as 10a and 17a), 1.6 mmol β (as 10c and 17b) and 5.1 mmol α-trans 10b isomers (α-cis - α-trans - β : 41,45,14 %) contributing to c.a. 85 % of the hydroprenylated products isolated after flash chromatography (their isomeric purity, checked by GLC was better than 95 % ; in order of increasing retention times :α-trans, α-cis, β-isomers on OV 101 10 %, 250°C).

4β-[2,6,6-Trimethyl 5β- 4-hydroxy 3-methyl 2E-butenyl) 2-cyclohexenyl] 3E-buten 2-one. (2-Hydroxyprenyl α-cis-ionone 10a).

UV (EtOH) : λ max 227 nm (ε 1.4 10^4) ; IR : 3600, 3450, 2960, 2920, 2860, 1680, 1660, 1615 and 1020 cm^{-1} ; PMR : δ 0.78 and 0.93 (6H,2s,17 and 18-Me), 1.53(3H,s,16-Me), 1.66(3H,s,5'-Me), 2.28(3H,s,10-Me), 2.55(1H,d,J=11Hz,6-H), 3.95(2H,s,CH_2OH), 5.45(1H,m,2'H), 5.55 (1H,m,4-H), 6.12 (1H,d,J=16Hz,8-H), 6.55(1H,dd,J=11 and 16Hz,7-H) ; CMR : see table II ; MS(CI) : M^++1 at m/z 277.

4α-[2,6,6-Trimethyl 5β-(4-hydroxy 3-methyl-2E-butenyl) 2-cyclohexenyl] 3E-buten 2-one. (2-Hydroxyprenyl α-trans ionone 10b).

UV(EtOH) : λ max 226 nm (ε 1.6 10^4) ; IR : 3600, 3450, 2960, 2920, 2860, 1680, 1660, 1615, 1255, 990 cm^{-1} ; PMR : δ 0.88 and 0.91 (6H,2s,17 and 18-Me), 1.56(3H,s,16-Me), 1.68(3H,s, 5'-Me), 2.27(3H,s,10-Me). 4.00 (2H,s,CH_2OH), 5.45(1H,m,2'-H), 5.50(1H,m,4-H), 6.10(1H,d,J=16Hz, 8-H) and 6.72(1H,dd,J=16 and 10Hz,7-H) ; CMR : see Table II ; MS(CI) : M^+1 at m/z 277.

4-[2,6,6-Trimethyl 5-(4-hydroxy 3-methyl 2E-butenyl) 1-cyclohexenyl]3E-buten 2-one. (2-Hydroxyprenyl β-ionone 10c)

UV (EtOH) : λ max 292 (ε 7.8 10^3) and 222 nm (ε 8.5 10^3). IR : 3580, 3450, 2960, 2930, 1680, 1660, 1600, 1040 and 980 cm^{-1} ; PMR : δ 0.97 and 1.12 (6H,2s,17 and 18-Me), 1.68(3H,s,5'-Me), 1.76(3H,s,16-Me), 2.33(3H,s,10-Me), 4.02(2H,s,CH_2OH), 5.50(1H,m,2'-H), 6.17(1H, d,J=16.5 Hz,8-H) and 7.31(1H,d,J=16.5Hz,7-H) ; CMR : see Table II ; MS(CI), M^++1 at m/z 277.

4β-[2,6,6-Trimethyl 5β-(4-acetoxy 3-methyl 2E-butenyl) 2-cyclohexenyl] 3E-buten 2-one. (2-Acetoxyprenyl α-cis-ionone 17a)

IR : 2960, 2920, 1725, 1685, 1660, 1615 and 1250 cm^{-1} ; PMR : δ 0.80 and 0.93 (6H,2s,17 and 18-Me), 1.54(3H,s,16-Me), 1.68(3H,s,5'-Me), 2.10(3H,s,CH_3-COO), 2.31(3H,s,10-Me), 2.58(1H,d,J=11Hz,6-H), 4.50(2H,s,CH_2OAc), 5.50(1H,m,2'-H), 5.58(1H,m,4-H), 6.18(1H,d,J=16Hz,8-H) and 6.70(1H,dd,J=16 and 11Hz,7-H) ; GC-MS(EI), m/z (relative intensity) : 318(1) M^+, 303(9), 245(4), 243(3), 215(3), 207(4), 122(43), 121(70), 107(100), 93(67), 91(78) ; Anal.: calc. for $C_{20}H_{30}O_3$, M=318.46 : C 75.43 H 9.50 O 15.07, found : C 74.91 H 9.76 O 15.42.

4-[2,6,6-Trimethyl 5-(4-acetoxy 3-methyl 2E-butenyl) 1-cyclohexenyl]3E-buten 2-one. (2-Acetoxyprenyl β-ionone 17b).

IR : 2960, 2930, 1725, 1680, 1660, 1255, 1205, 1040, 980 cm^{-1} ; PMR : δ 0.98 and 1.13 (6H,2s,17 and 18-Me), 1.69(3H,s,5'-Me), 1.76(3H,s,16-Me), 2.11(3H,s,CH_3-COO), 2.34(3H,s,10--Me), 4.52(2H,s,CH_2OAc), 5.54(1H,m,2'-H), 6.17(1H,d,J=16.5Hz,8-H) and 7.31(1H,d,J=16.5Hz,7H) ; GC-MS(EI), m/z (relative intensity) : 318(2) M^+, 303(63), 243(42), 215(18), 207(17), 121(78), 107(55), 105(83), 93(57), 91(100) ; Anal.: calc. for $C_{20}H_{30}O_3$, M=318.46 : C 75.43, H 9.50, O 15.07, found : C 75.04, H 9.84, O 14.50.

All E 6,12-dimethyl 13-hydroxy 9-isopropenyl 3,5,11-tridecatrien 2-one. (Hydroxyprenyl pseudoionone 14).

The mixture of 14 and 15 was isolated in the most polar fractions of the previous first MPLC purification step on the whole hydroxyprenylated compounds (see general procedure). Subsequent preparative HPLC (ethylacetate- hexane ; 2:3) allowed separation of 14 and 15. 14 : PMR ; δ 1.63 and 1.68 (6H,2s,5' and 17-Me), 1.91(3H,s,16-Me), 2.29(3H,s,10-Me), 4.03(2H,s, CH_2OH), 4.73 and 4.82(2H, 2 broad s,CH_2=), 5.40(1H,m,2'-H), 6.05(1H,d,J=11.5Hz,6-H), 6.12(1H,d, J=15Hz,8-H) and 7.49(1H,dd,J=11.5 and 15Hz,7-H) ; MS(CI) : M^++1 at m/z 277.

4-[2-Chloro 2,6,6-trimethyl 5-(4-hydroxy 3-methyl 2E-butenyl) cyclohexyl]3E-buten 2-one. (2-Hydroxyprenyl hydrochloroionone 15)

The yield of 15 was improved during the alkylation reaction (see general procedure) when the reaction was carried out at -15°C for 45 min (Table I, entry 1). The preceeding work-up

afforded after MPLC (ethylacetate-petroleum ether 1:3) a polar oily fraction highly enriched in 15 (30 % of all hydroxyprenylated products). The cyclic chloro-derivative 15 has been purified by HPLC according to the above conditions but it was advantageously obtained by slow crystallization from the enriched fraction from MPLC ; m.p. 99-101°C (white crystals) : PMR : δ 0.91 and 1.02 (6H,2s,17 and 18-Me), 1.43(3H,s,16-Me), 1.68(3H,s,5'-Me), 2.35(3H,s,10-Me), 4.06(2H,s, CH_2OH), 5.45(1H,m,2'H), 6.10(1H,d,J=16Hz,8-H) and 7.00(1H,dd,J=10 and 16Hz,7-H) ; CMR : see Table II ; MS(CI) : M^++1 at m/z 313 (^{35}Cl) and M^++3 at 315 (^{37}Cl).

All E 9-(1-chloro 1-methylethyl) 6,12-dimethyl 13-hydroxy 3,5,11-tridecatrien 2-one. (Hydroxyprenyl chloro pseudoionone 13).

When the alkylation reaction was carried out in $EtNO_2$ at -60°C with 90 % E-pseudoionone (5.8 g, 30 mmol) and isoprene epoxide (2.5 g, 30 mmol) for 45 min (Table I, entry 4) the usual work-up gave, after column chromatography (gradient of ethylacetate in petroleum ether), pure acyclic chloroderivative 13 as an oil (600 mg, 65 % of the hydroxyprenylated products) ; IR : 3600, 3450, 2960, 2930, 1670, 1620, 995, 600 cm^{-1} ; PMR : δ 0.91 and 1.02(6H,2s,17 and 18-Me), 1.43(3H,s,16-Me), 1.68(3H,s,5'-Me), 2.35(3H,s,10-Me), 4.06(2H,s,CH_2OH), 5.45(1H,m,2'-H), 6.10(1H,d,J=16Hz,8-H), 7.00(1H,dd,J=10 and 16Hz,7-H) ; CMR, see Table II ; MS(CI), M^++1 at m/z 313 (^{35}Cl) and 315 (^{37}Cl).

2-Methyl 2-butenal 11 and 2-(1-methyl 2-propenyl) 4-ethenyl 4-methyl dioxolane 12

Isoprene epoxide (1.68 g, 20 mmol) was treated with dry $ZnCl_2$ (5.4 g., 40 mmol) in CH_2Cl_2 (20 ml) at -15°C for 90 min. Saturated aqueous $NaHCO_3$ was added and the mixture extracted twice with CH_2Cl_2 ; after filtration, the organic phase was washed with brine and dried over $MgSO_4$. Analytical GLC showed c.a. 25 % 11 and 40 % 12 to be formed beside unreacted isoprene epoxide.Fractional distillation and subsequent preparative GLC allowed final purification of 11 (as a E,Z-mixture 75:25 %) and 12 (as two fractions 12a, 58 % and 12b, 42 % from GLC).

PMR and MS spectra for 11 were in agreement with those expected for tiglic aldehyde [14].

From PMR the most volatile 12a fraction (R_t : 9.2 min on OV 101 10 % at 120°C) was assumed to be the 2,4-trans pair of diastereoisomers at C-6 and 12b (R_t : 9.8 min) the 2,4-cis pair of isomers [15c].

IR for 12a and 12b : 3085, 2970, 2930, 2870, 1640, 1130, 1090, 1020, 990, 950 and 920 cm^{-1}. PMR signals were assigned from multiple double irradiation experiments (when signals for diastereoisomers at C-6 were split, the underlined values refer to the main isomer).

12a : PMR : δ 1.10, 1.09(3H,s,J=10.5Hz,9-Me), 1.39(3H,s,12-Me), 2.49 (1H,qdd,J=7,7Hz and 5Hz, 6-H), 3.72 and 3.82(2H,AB system,J=8Hz,5-H_2), 4.90, 4.92(1H,d,J=5Hz,2-H), 5.15(1H,broad d, J=17.5Hz,8Z-H), 5.17(2H,two broad d,J=10.5Hz,8E-H and 11E-H), 5.32(1H,dd,J=1 and 17.5Hz,11Z-H), 5.91(1H,m,7-H) and 5.95(1H,dd,J=10.5 and 17.5Hz,10-H) ; MS(EI), m/z (relative intensity) : 168(7) M^+, 150(10), 137(9), 113(71) and 69(100).

12b : PMR : δ 1.11, 1.09(9-Me), 1.39(12-Me), 2.49(6-H), 3.67 and 3.84(5-H_2), 4.95, 4.98(2-H), 5.14(8E-H and 11E-H), 5.16(8Z-H), 5.34(11Z-H), 5.91(7-H) and 5.98(10-H). All other values are the same as for 12a ; MS(EI), m/z (relative intensity) : 168(1) M^+, 150(5), 137(4), 127(7), 113(60), 69(100).

Base equilibration of mixtures of 10

A mixture of 10 isomers enriched (80 %) in trans α 10b (3.8 g, 13.7 mmol) was allowed to stand for 48 h in MeOH-H_2O (35 ml, 85:15) containing 10 % KOH at room temperature. After extraction with diethyl ether, the organic phase was washed with water, dried over $MgSO_4$ and the solvent evaporated. Usual flash chromatography of the residue (diethyl ether-pentane ; 1:1) gave 2.0 g (53 %) of an oily fraction which was shown from GLC to contain 60 % β 10c, 35 % α-trans 10b and 3 % α-cis 10c isomers. Subsequent MPLC (8% ethylacetate in CH_2Cl_2) afforded 95 % isomerically pure β 10c (1.15 g, 4.2 mmol). Spectroscopic data were identical with those reported for 10c isolated from the initial alkylation reaction.

3-Methyl 5β-[2,6,6-trimethyl 5β-(4-hydroxy-3-methyl 2E-butenyl) 2-cyclohexenyl] 1,4-pentadien 3-ol. (2-Hydroxyprenyl vinyl α-cis-ionol 21a)

To a stirred solution of vinylmagnesium bromide in dry THF (0.25N, 80 ml, 20 mmol) at -30°C was added over 20 min of hydroxyprenyl α-cis-ionone acetate 17a (1.27 g, 4 mmol). The reaction mixture was allowed to warm to room temperature and 25 % ice-cold saturated NH_4Cl solution was added after 1.5 h. The mixture was extracted with diethyl ether and usual work-up including flash chromatography (ethylacetate-CH_2Cl_2 mixtures) gave hydroxyprenylvinyl α-cis-ionol 21a (1.16 g, 95 %) shown to be a mixture of diastereoisomers from GLC analysis and PMR : δ 0.70 and 0.90 (6H,2s,17 and 18-Me), 1.38(3H,s,CH_3-C-OH), 1.52(3H,s,16-Me), 1.64(3H,s,5'-Me), 4.02(2H,s,CH_2OH), 4.98 to 5.55(6H,complex,5'-H,4-H,8-H and -CH=CH_2), 5.98(1H,dd,J=16 and 11Hz, 7-H) ; MS(CI) : M^++1 at m/z 305.

3-Methyl 5-[2,6,6-trimethyl 5-(4-hydroxy 3-methyl 2E-butenyl) 1-cyclohexenyl] 1,4-pentadien 3-ol. (2-Hydroxyprenyl vinyl β-ionol 21b)

21b was similarly prepared from hydroxyprenyl β-ionone 10c (950 mg, 3.4 mmol) and vinylmagnesium bromide in THF (0.25N, 68 ml) except that the reaction mixture was kept at -20°C for 1 h. After work-up the crude product (1.0 g) was directly used for the Wittig reaction as some decomposition occurred on attempted chromatography. MS(CI) : M^++1 at m/z 305.

3-Methyl 5β-[2,6,6-trimethyl 5β-(4-hydroxy 3-methyl 2E-butenyl) 2-cyclohexenyl] 1,4-pentadienyl triphenylphosphonium bromide. (2-Hydroxyprenyl α-cis-ionylidene ethyltriphenylphosphonium bromide 22a)

A solution of 21a (610 mg, 2 mmol) and triphenylphosphonium bromide (720 mg, 2.1

mmol) in dry MeOH (10 ml) was stirred for 30 h at room temperature under N_2. After removing the solvent, the crude oil was chromatographed (SiO_2, MeOH from 0 to 15 % in CH_2Cl_2) to give pure phosphonium bromide 22a (761 mg, 60 %) as an amorphous solid ; PMR : δ 0.69 and 0.88(6H,2s,17 and 18-Me), 1.34(3H,d,J=4Hz,19-Me), 1.48(3H,s,16-Me), 1.66(3H,s,5'-CH_3), 2.36(1H,broad d,J=10Hz, 6-H), 4.04(2H,s,CH_2OH), 4.76(2H,m,11-H_2), 5.46(4H,broad m,4-H,7-H,10-H and 2'-H), 6.06(1H,d,J= 16Hz,8-H) and 7.5 to 8.2(15H,m,aromatic).

3-Methyl 5-[2,6,6-trimethyl 5-(4-hydroxy 3-methyl 2E-butenyl) 1-cyclohexenyl] 2,4-pentadienyl triphenylphosphonium bromide. (2-Hydroxyprenyl β-ionylidene ethyltriphenylphosphonium bromide 22b)

22b was similarly prepared from 21b (610 mg, 2 mmol) and triphenylphosphonium bromide (686 mg, 2 mmol) in dry MeOH (10 ml, 0°C for 1 h, then to room temperature over 1 h). After evaporation of the solvent and flash chromatography as for the α-cis isomer, 22b was obtained as a white powder (660 mg, 53 %). PMR : δ 0.84 and 0.98(6H,2s,17 and 18-Me), 1.41(3H,d,J=4Hz, 19-Me), 1.58(3H,s,16-Me), 1.63(3H,s,5'-Me), 3.95(2H,s,CH_2OH), 4.70(2H,m,11-H_2), 5.30(2H,broad m, 10-H and 5'-H), 5.90(2H,broad s,7-H and 8-H) and 7.5 to 8.0(15H,m,aromatic).

All E,cis-Decaprenoxanthin 1

To a mixture containing 40 % aqueous KOH solution (20 ml) and 314 mg α-cis-phosphonium salt 22a (314 mg, 0.5 mmol) in CH_2Cl_2 (15 ml), the C_{10} dial 20 (41 mg, 0.25 mmol) in CH_2Cl_2 (5 mml) was slowly added under N_2 at room temperature. The course of the reaction was monitored by TLC (diethyl ether-petroleum ether ; 3:2) and further phosphonium salt 22a was added to the reaction mixture until the dial completely disappeared. After decanting the organic phase, the aqueous layer was reextracted twice with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated. Silica gel column chromatography carried out under N_2 (diethyl ether-petroleum ether from 2:3 to 7:3) gave pure decaprenoxanthin (125 mg, 71 % from dial 20). E,cis-decaprenoxanthin (60 mg) was obtained by crystallization from acetone-petroleum ether : mp 162-164°C (litt. 153-155°C) ; UV (petroleum ether) : λ max 267, 439, 470 nm (ε respectively 4.7 10^4, 1.63 10^5 and 1.58 10^5 III/II: 96). PMR, MS and IR data are in full agreement with those reported for natural decaprenoxanthin [3a].

All E, C.p. 450 3

C.p. 450 was prepared from the β-phosphonium salt 22b (310 mg, 0.5 mmol) and the dial 20 (41 mg, 0.25 mmol) according to the above procedure. After work-up, column chromatography gave pure C.p. 450 as a mixture of E,Z-isomers (55 mg, 31 % from the dial 20). All E-3 (37 mg) was obtained by recrystallization from acetone-petroleum ether : mp 158-160°C (Lit. 168-171°C) [25a]. UV (petroleum ether + trace of acetone) : λ max 430, 447, 475 (ε respectively 5.5 10^4, 1.1 10^5 and 9.5 10^4) ; IR : 3600, 3450, 3000, 2960, 2920, 2860, 1600, 1560, 1450, 1380, 1360, 1005 and 970 cm^{-1}. PMR and MS data were consistent with reported values for natural C.p. 450 [5].

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