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2,6-Cyclolycopene-1,5-diol: Total Synthesis of a Naturally Occurring Oxidation Product of Lycopene

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Abstract

2,6-Cyclolycopene-1,5-diol (**3**) was synthesized in 9 steps starting from α-terpinyl acetate (**11**). This represents the first total synthesis of an oxidative metabolite of lycopene (**2**). The synthesis was performed according to a $C_{15} + C_{10} + C_{15} = C_{40}$ strategy using the Wittig olefination to couple the end groups to the central building block. An intramolecular aldol addition was used to introduce two new stereocenters with a defined relative stereochemistry.

Keywords: Carotenoids; Metabolite; Stereocontrol; Aldol addition; Lycopene

Introduction

Carotenoids play an important role in the chemoprevention of cancer [1] and their application in clinical research [2] has been well established. Most of the studies were performed with β,β-carotene (**1**) and only few investigations included lycopene (**2**), although the latter represents the most abundant carotenoid in human serum [3]. Compared to β,β-carotene (**1**), lycopene (**2**) exhibits higher *in vitro* singlet oxygen quenching ability and radical scavenging properties, both being functions which make lycopene (**2**) an interesting candidate for antioxidant activity studies in humans [4]. Levy *et al.* [5] showed the inhibitory effect of lycopene (**2**) on the growth of human endometrial, mammary and lung cancer cells, and it was demonstrated that a lycopene-rich diet decreases the risk of prostate cancer [6]. Cooked

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tomatoes proved to be significantly more effective than raw fruits. This may be due to improved bioavailability or to the fact that the biologically active compound is not lycopene (**2**) itself. Carotenoids are sensitive against heat, acids and oxygen and therefore oxidation products are easily formed by the processing of tomatoes. In studies on the carotenoid content in human blood serum by Khachik *et al.* [7], a new lycopene metabolite, 2,6-cyclolycopene-1,5-diol (**3**), was identified, and **3** was later also isolated from breast milk [3] and retina [8]. Recently Yokota *et al.* [9] isolated 2,6-cyclolycopene-1,5-diol (**3**) from tomato paste in a concentration of 3 ppm and the compound was named 1,5-dihydroxyiridanyllycopene (Fig. 1).

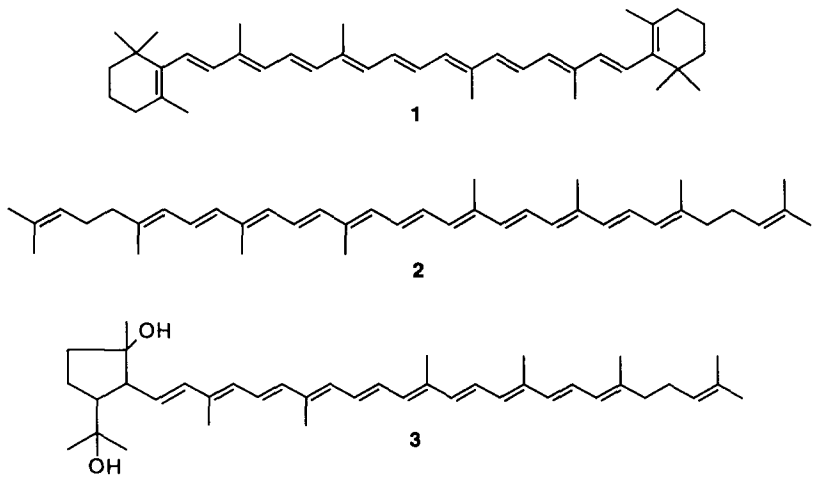
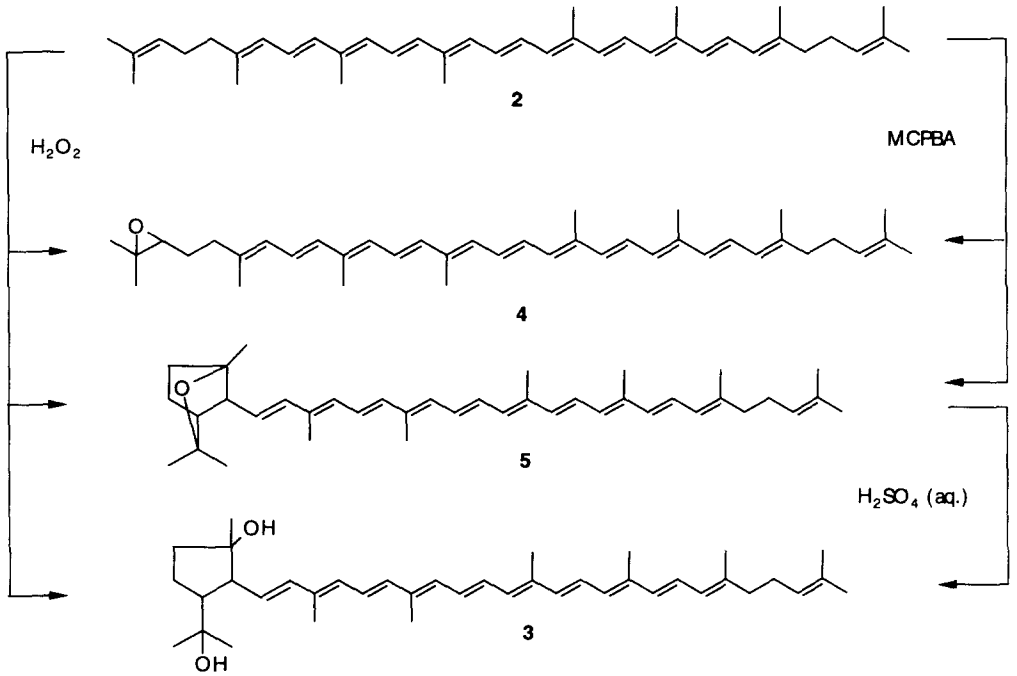


Fig. 1

The biological activities of **3** include the *in vitro* upregulation of the connexin43 gene expression in 10T1/2 cells and human keratinocytes [10], the cancer growth inhibition in human and mouse cells [11] and the *in vitro* growth inhibition of human prostate cancer cells [12].

To the authors knowledge, two synthetic studies on oxidative metabolites of lycopene have been reported [13,14], both of them being partial syntheses starting from lycopene (**2**). Lu *et al.* [13] oxidized lycopene (**2**) with hydrogen peroxide to give, besides 1,2-epoxylycopene (**4**) and 2,6-cyclolycopene-1,5-epoxide (**5**), 2,6-cyclolycopene-1,5-diol (**3**) as a minor compound. Khachik *et al.* [14] prepared 2,6-cyclolycopene-1,5-diol (**3**) by epoxidation of lycopene (**2**) with *m*-chlorperbenzoic acid (MCPBA) to give the epoxides **4** and **5**. The latter was hydrolized subsequently with diluted sulfuric acid to 2,6-cyclolycopene-1,5-diol (**3**) (Scheme 1).

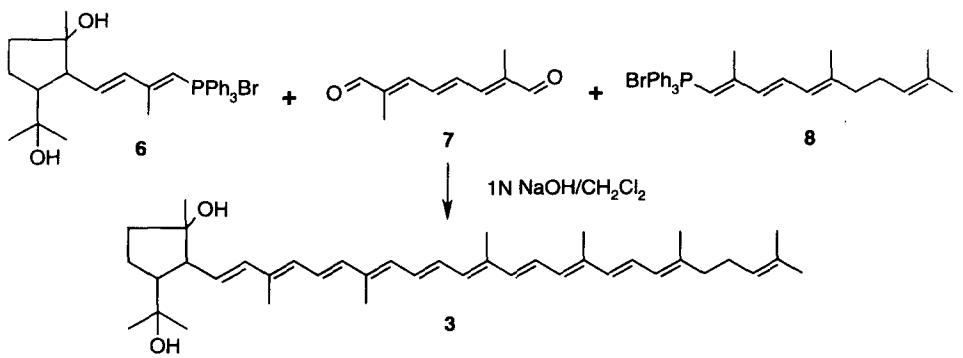


Scheme 1: Partial syntheses of 2,6-cyclolycopene (**3**) from lycopene (**2**)

Results and Discussion

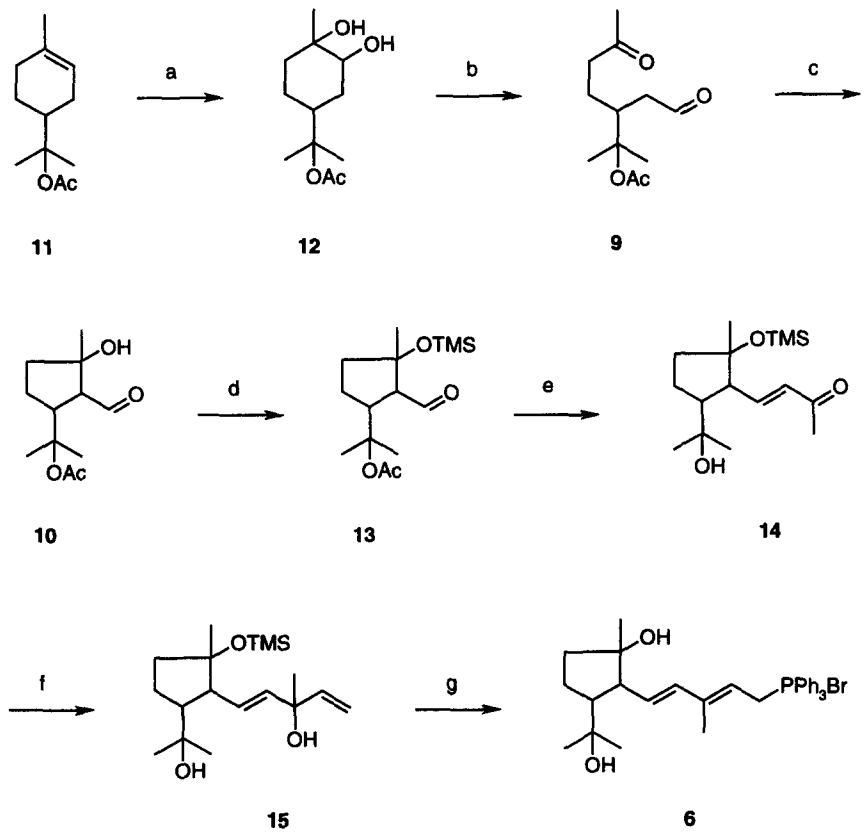
Preparation of the cyclic end group ***6***

For the total synthesis of 2,6-cyclolycopene-1,5-diol the strategy $C_{15} + C_{10} + C_{15} = C_{40}$, which is often used for the synthesis of cyclic carotenoids [15], was selected and the building blocks **6 - 8** were coupled by two successive Wittig olefination reactions (Scheme 2).



Scheme 2: Wittig olefination according to the strategy $C_{15} + C_{10} + C_{15} = C_{40}$

Having at hand 2,7-dimethyl-2,4,6-octatrien-1,8-dial (**7**) and the C_{15}-phosphonium salt **8**, prepared according to Hengartner et al. [16], the cyclic building block **6** with the hitherto unknown five-membered ring moiety was the target molecule. An intramolecular aldol addition of the ketoaldehyde **9** to the formylpentanol **10** with a defined relative stereochemistry at the three asymmetric carbon atoms represented the key step in the synthetic pathway (Scheme 3).



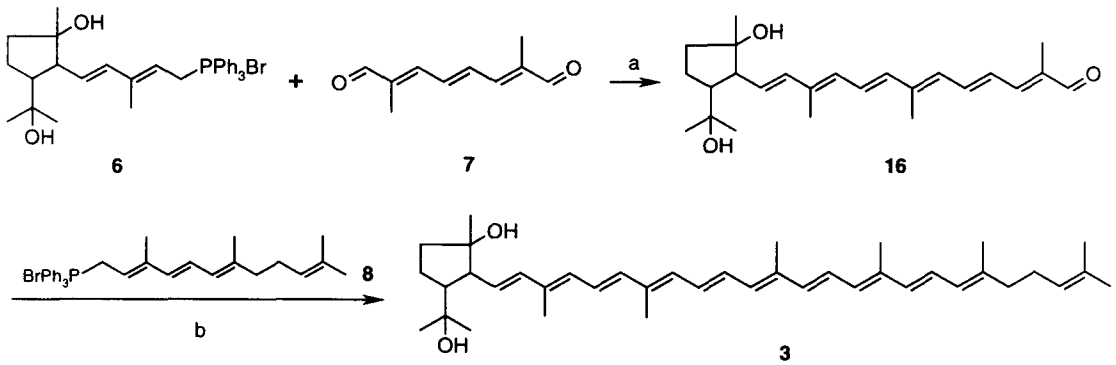
Scheme 3: Synthesis of the cyclic end group **6**

Reagents and Conditions: (a) $KMnO_4$, THF/H_2O, 0°; (b) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0°; (c) piperidine, AcOH, H_2O, THF, r.t.; (d) TMSCl, imidazole, CH_2Cl_2, r.t.; (e) acetone, LDA, THF, -70° - 0°; (f) $CH_2CHMgBr$, THF, -50° - 0°; (g) PPh_3HBr, $CHCl_3$/MeOH, r.t., darkness.

As starting material α-terpinyl acetate (**11**) was chosen and dihydroxylated with aqueous potassium permanganate to the diol **12** which was oxidatively cleaved with lead tetraacetate to the ketoaldehyde **9**. The intramolecular aldol addition, catalyzed by piperidine and acetic acid in the presence of water, gave the formyl cyclopentanol **10** which was protected as the trimethylsilyl ether **13**. The chain elongation by an aldol condensation with acetone and LDA as base under simultaneous cleavage of the acetate group resulted in the α,β-unsaturated ketone **14**. A Grignard reaction with vinylmagnesium bromide to the allylic alcohol **15** and a subsequent conversion with triphenylphosphine hydrobromide gave the deprotected phosphonium salt **16** in 6.5% yield referred to the starting material α-terpinyl acetate (**11**).

Preparation of the carotenoid 2,6-cyclolycopene-1,5-diol (3)

The phosphorus ylid of **6** decomposed rapidly under the basic reaction conditions of the Wittig olefination. Due to the fact that in Wittig reactions the reactivity of the aldehydes correlates inversely with the length of their conjugated polyene chain and considering the instability of the phosphorus ylid, the central building block **7** was first coupled with the phosphonium salt **6** to the C_{25}-apocarotenoid **16**. By using a slight excess (1.2 eq.) of **6**, the mono-condensation product **16** was obtained exclusively, a fact that demonstrates also the difference in reactivity of the aldehydes **7** and **16**. A subsequent Wittig olefination with the end group **8** gave then the desired carotenoid 2,6-cyclolycopene-1,5-diol (**3**), which was isolated as the (all-*E*)-isomer after recrystallization from hexane (Scheme 4).

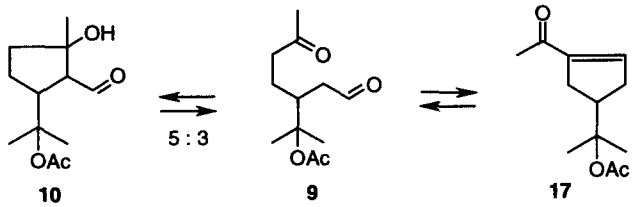


Scheme 4: Coupling of the central C_{10}-building block **7** with the two C_{15}-end groups **6** and **8**.

Reagents and Conditions: (a) 1N NaOH, CH_2Cl_2, r.t; (b) 1N NaOH, CH_2Cl_2, reflux.

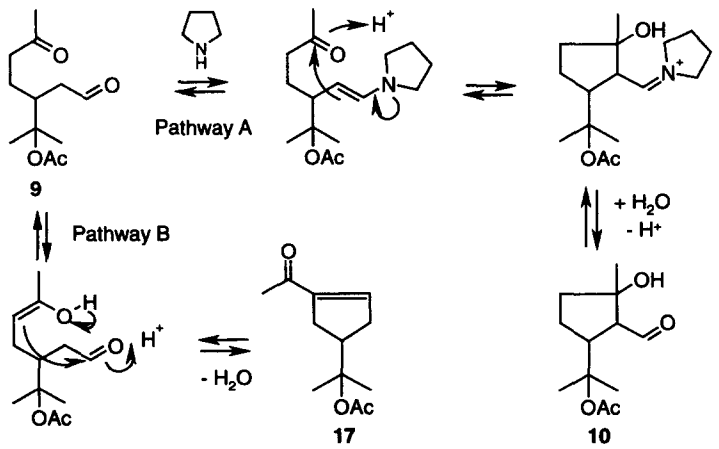
Mechanical and stereochemical consideration of the intramolecular aldol addition

The aldol addition of the ketoaldehyde **9** to the formyl cyclopentol **10** showed to be temperature dependent. When the reaction was carried out at room temperature, an equilibrium between **9** an **10** (ratio ca. 5:3) was observed; by refluxing the mixture, the α,β-unsaturated ketone **17** was the sole product (Scheme 5).



Scheme 5: Intramolecular aldol addition of **9**

These findings can be explained by two different mechanisms which take place at the different reaction temperatures: According to pathway A an enamin is formed at room temperature by the reaction of **9** with piperidine. Upon acid catalysis the enamin attacks the carbonyl group forming the five-membered ring with the iminium substituent, which is readily hydrolized to the aldehyde **10**. When the reaction mixture is refluxed, the aldol addition takes place without the formation of the enamin moiety and according to pathway B the C(5) carbon atom attacks the aldehyde carbonyl group, followed by a dehydration step after the ring closure to give the ketone **17** (Scheme 6).



Scheme 6: Two competing mechanisms for the intramolecular aldol addition of **9**.

During the formation of the cyclopentanol **10** two new stereocenters are formed. As the reaction is an equilibrium, the thermodynamically most favored and least sterically hindered product is formed. This means that the large acetoxymethylethyl-substituent at C(3) and the carbaldehyde at C(2) are in *trans* position, whereas the hydroxy group at C(1) and the carbaldehyde at C(2) are in *cis* position. This relative stereochemical assignment is supported by the coupling constance between H-C(2) and H-C(3) of 9.9 Hz indicating a dihedral angle near 180°. Therefore the two hydrogen atoms and consequently the two substituents are in a *trans* relationship. Additionally the hydroxy group is stabilized by a hydrogen bridge to the carbonyl oxygen of the aldehyde, which favors the *cis* over the *trans* postion of this two substituents (Fig. 2).

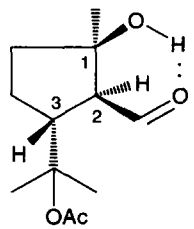


Fig. 2: Relative stereochemistry of the formyl cyclopentanol **10**

Spectroscopic studies of 2,6-cyclolycopene-1,5-diol (3)

The 300 MHz ^{1}H NMR were identified by application of the $^{1}H,^{1}H$ COSY NMR technique which allowed the unambigous assignment of the olefinic and aliphatic ^{1}H signals with the exception of the methyl group. They were identified by comparision with those of literature data [17]. The 75.5 MHz ^{13}C NMR signals were assigned by their $^{1}H,^{13}C$ cross coupling signals, with the exception of the quartenary carbon signals, which have been assigned by comparision with those of literature data [17]. The chemical shifts of the proton and carbon signals are listed in Table 1. The NMR data are in accordance to those of the compound prepared by Khachik by the oxidation of lycopene, and therefore identical with the natural occurring carotenoid, proving its conformation [14].

The UV/Vis spectrum of (all-*E*)-**3** measured in ethyl acetate showed maxima at 433, 459 and 491 nm and a shoulder at 412 nm, which is in accordance with the decaene chromophore. No cis-peak, characteristically 142 nm below the longest-wavelength absorbtion maximum, could be detected, proving, together with the NMR data, the (all-*E*)-configuration of **3** [18]. In petroleum ether the maxima could be observed at 429, 455 and 487 nm, which is at remarkably higher wavelengths than reported by Yokota [9] (430, 451 and 480 nm). This indicates, that the carotenoid isolated from tomato paste was a mixture of (*E*/*Z*)-isomers.

Table 1
^{1}H and ^{13}C NMR data of 2,6-cyclolycopene-1,5-diol (**3**)

Cyclic end group	^{1}H NMR (δ (ppm), J (Hz))	^{13}C NMR (δ (ppm))	Ψ-end group	^{1}H NMR (δ (ppm), J (Hz))	^{13}C NMR (δ (ppm))
C(1)	-	73.1	C(1')	-	131.8
H-C(2)	2.30 (*ddd*, *J* = 17.1, 10.1, 7.0)	54.3	H-C(2')	5.16 (*m*)	123.9
H_2-C(3)	1.53 (*m*) 1.95 (*m*)	25.1	H_2-C(3')	2.12 (*m*)	26.7
H_2-C(4)	1.67 (*m*) 1.79 (*ddd*, *J* = 12.3, 8.4, 3.8)	39.7	H_2-C(4')	2.12 (*m*)	40.2
C(5)	-	82.2	C(5')	-	139.5
H-C(6)	2.23 (*dd*, *J* = 10.1, 9.0)	55.6	H-C(6')	5.94 (*d*, J = 11.0)	125.7
H-C(7)	5.73 (*dd*, *J* = 15.7, 9.0)	129.4	H-C(7')	6.51 (*dd*, *J* = 15.1, 11.0)	124.8
H-C(8)	6.25 (*d*, *J* = 15.7)	138.2	H-C(8')	6.26 (*d*, *J* = 15.1)	135.4
C(9)	-	134.9	C(9')	-	136.3
H-C(10)	6.16 (*d*, *J* = 11.3)	131.5	H-C(10')	6.19 (*d*, *J* = 11.1)	131.6
H-C(11)	6.63 (*dd*, *J* = 14.9, 11.3)	124.6	H-C(11')	6.63 (*dd*, *J* = 15.0, 11.1)	125.2
H-C(12)	6.36 (*d*, *J* = 14.9)	138.0	H-C(12')	6.35 (*d*, *J* = 15.0)	137.3
C(13)	-	136.2	C(13')	-	136.7
H-C(14)	6.23 (*m*)	132.9	H-C(14')	6.23 (*m*)	132.5
H-C(15)	6.63 (*m*)	130.3	H-C(15')	6.63 (*m*)	129.9
H_3-C(16)	1.24 (*s*)	28.5	H_3-C(16')	1.68 (*s*)	25.7
H_3-C(17)	1.18 (*s*)	27.4	H_3-C(17')	1.62 (*s*)	17.7
H_3-C(18)	1.19 (*s*)	26.7	H_3-C(18')	1.82 (*s*)	17.0
H_3-C(19)	1.97 (*s*)	13.1	H_3-C(19')	1.94 (*s*)	12.9
H_3-C(20)	1.98 (*s*)	12.8	H_3-C(20')	1.98 (*s*)	12.8

The electron impact mass spectra showed the molecular ion M^+ at m/e = 570. Further diagnostic signal were detected at m/e= 552 (elimination of water) and at m/e = 478 and 464, which represent the elimination of toluene and xylene from the polyene chain. Their corresponding signals were observed at m/e = 91 and 105. The signal at m/e = 69 is typical for the Ψ-end group and represents the elimination of the terminal isoprenic unit [19].

Summary

The synthesis of (all-*E*)-2,6-cyclolycopene-1,5-diol (**3**), a carotenoid found in human serum and tomato paste, containing a new, five-membered ring end group, was successfully performed according to the strategy $C_{15} + C_{10} + C_{15} = C_{40}$ strategy [20]. The key step was the intramolecular aldol addition of the ketoaldehyde **9** to the formyl cyclopentanol **10**, forming two new stereocenters with defined relative configuration. The carotenoid was fully characterized by ^{1}H-NMR, ^{13}C-NMR, MS and UV/Vis spectra and prove the conformation and relative stereochemistry of the material isolated from natural sources. The design of the

synthetic pathway allows the preparation of the (all-*E*,2*R*,5*R*,6*S*)- and (all-*E*,2*S*,5*S*,6*R*)-isomer starting from optically active α-terpinyl acetate (**11**), which is currently under investigation in our laboratories.

Experimental Part

General. All reactions were carried out under N_2 or Ar. The reagents were purchased from *Fluka AG*, *E. Merck* or *Aldrich*. The solvents were purified according to [34] or purchased in HPLC quality from *Romil*. Flash chromatography (FC): *J.T. Baker* and *E. Merck*, silica gel 60, 0.040-0.063 mm. TLC: *Macherey-Nagel*, DC-Fertigplatten SIL G-25, UV_{254}; Polygram Alox N/ UV_{254}; Polygram CEL 300. M.p.: Tottoli apparatus, open capillary, not corrected. UV/Vis Spectra: Spectrophotometer *Perkin-Elmer* Lambda 6 UV/VIS Spectrophotometer, λ_{max} in nm. IR Spectra (ν, cm^{-1}): *Perkin-Elmer* 1600 Series FTIR. ^1H- and ^{13}C-NMR Spectra (δ, ppm): *Bruker Spectrospin* AC-300 (^1H, 300 MHz and ^{13}C, 75.5 MHz); chemical shifts in ppm rel. to Me_4Si, $CDCl_3$ (δ = 7.27) as reference, *J* in Hz. Assignments marked with an asterix (*) can be interchanged. MS: (m/e (%)): *Varian-MAT* CH-7A spectrometer with direct sample inlet (70 eV).

4-(1-Acetoxy-1-methylethyl)-1-methylcyclohexane-1,2-diol (12). A soln. of $KMnO_4$ (50 g, 316 mmol) in H_2O (1 liter) was added dropwise to a vigorously stirred soln. of α-terpinyl acetate (**11**, 50 g, 255 mmol) in THF (800 ml) at 0°. The mixture was allowed to warm to r.t. and was stirred for 1 h. The brown suspension was filtered over Celite, extracted with AcOEt, the org. phase dried ($MgSO_4$), evaporated and the residue crystallized from AcOEt/hexane. The mother liquor was evaporated and purified by FC (silica gel, AcOEt/hexane 1:1) to give, besides 5.38 g (11%) unchanged **11**, **12** which was crystallized as described above. Both crystalline fractions were dried at 20 torr to yield 33.77 g (65% calculated on consumed material) of white needles. M.p.: 88°. ^1H NMR ($CDCl_3$, 300 MHz)[1]: 3.36 (*dd*, *J* = 11.4, 4.4; H-C(2)); 2.3 (*br.s*, 2 x OH); 2.01 (*m*, H-C(4)); 1.94 (*s*, Ac); 1.81 (*dm*, *J* = 11.4; H-C(5)); 1.67 (*dm*, *J* = 11.4; H-C(3)); 1.40 (*m*, H_2-C(6)); 1.39 (*s*, Me(9)*); 1.38 (*s*, Me(10)*); 1.36 (*m*, H-C(3)); 1.28 (*m*, H-C(5)); 1.23 (*s*, Me(7)). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 170.6 (Ac); 84.6 (C(8)); 75.1 (C(2)); 70.7 (C(1)); 44.4 (C(4)); 37.0 (C(5)); 31.3 (C(3)); 27.1 (C(7)); 23.6 (C(9)*); 23.3 (C(10*); 22.5 (Ac); 21.7 (C(6)). IR ($CHCl_3$): 3620*w*, 3570*w*, 3000*m*, 2930*m*, 1715*s*, 1420*w*, 1365*s*, 1270*s*, 1150*m*, 1115*m*, 1035*m*, 1010*m*. MS: 215 (1, M^+-15), 197 (3), 187 (3), 170 (62), 152 (50), 137 (43), 126 (100), 111 (73), 108 (84), 93 (48), 71 (55), 59 (24), 43 (58).

3-(1-Acetoxy-1-methylethyl)-6-oxo-heptanal (9). To a suspension of **12** (33.77 g, 148 mmol) and water free Na_2CO_3 (34.88 g, 327 mmol) in CH_2Cl_2 (1 liter) at 0° C was added $Pb(OAc)_4$ (93.3 g, 85% with 15% HOAc, 156 mmol) in portions, so that the temp. did not exceed 6° C. The mixture was stirred for 1 h, H_2O (50 ml) added, the suspension allowed to warm to r.t., filtered over Celite, the org. phase separated and the aq. phase extracted with CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), evaporated and purified by FC (silica gel, hexane/AcOEt 6:4) to give 30.14 g (90%) **9** as a white wax. M.p.: 24°. ^1H NMR ($CDCl_3$, 300 MHz): 9.72 (*dd*, *J* = 2.5, 1.8; H-C(1)); 2.58 (*ddd*, *J* = 16.9, 5.8, 2.5; H-C(2)); 2.46 (*m*, H_2-C(5)); 2.44 (*m*, H-C(3)); 2.26 (*ddd*, *J* = 16.9, 5.8, 1.8; H-C(2)); 2.13 (*s*, Me(7)); 1.93 (*s*, Ac)); 1.84 (*m*, H-C(4)); 1.53 (*s*, Me(2')*); 1.42 (*s*, Me-C(1')*); 1.37 (*m*, H-C(4)). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 207.9 (C(6)); 201.6 (C(1)); 170.1 (Ac); 84.4 (C(1')); 45.0 (C(2)); 42.0 (C(5)); 41.9 (C(3)); 30.0 (C(7)); 24.2 (C(4)); 24.1 (C(2')*); 22.4 (Ac); 22.0 (*Me*-C(1')*). IR ($CHCl_3$): 3020*m*, 2810*w*, 2720*w*, 1720*s*, 1370*s*, 1260*s*, 1135*m*, 1015*m*. MS: 228 (1, M^+), 169 (23), 154 (40), 122 (47), 110 (100), 101 (32), 95 (41), 81 (89), 70 (38), 59 (35), 43 (95).

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[1] Assignments according to the numbering of the *p*-menthane skeleton

3-(1-Acetoxy-1-methylethyl)-1-hydroxy-1-methylcyclopentan-2-yl-carbaldehyde (10). A soln. of **9** (11.59 g, 51.1 mmol), piperidine (2.3 ml), acetic acid (2.3 ml) and H_2O (1.15 ml) in THF (250 ml) was stirred for 21.5 h at r.t. and washed twice with 5% Na_2CO_3-soln., twice with 2N HCl-soln. and once with brine. The aq. phase was extracted with TBME and the combined org. phases dried ($MgSO_4$), evaporated and purified by FC (silica gel, hexane/AcOEt 13:7) to give 5.26 g (77% calculated on consumed material) **10** as a colorless oil and 4.76 g (41%) recovered **9**. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.78 (*d*, *J* = 3.3; H-C(6)); 3.04 (*dt*, *J* = 9.9, 6.2; H-C(3)); 2.51 (*dd*, *J* = 9.9, 3.3; H-C(2)); 1.96 - 2.15 (*m*, H-C(4)); 1.92 (*s*, Ac); 1.52 - 1.84 (*m*, H-C(4), H_2-C(5)); 1.48 (*s*, Me(2')); 1.46 (*s*, Me-C(1)); 1.45 (*s*, Me-C(1')). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 205.5 (C(6)); 170.2 (Ac); 83.6 (C(1)*); 83.0 (C(1')*); 61.7 (C(2)); 50.4 (C(3)); 41.7 (C(4)); 27.4 (C(2')*); 25.0 (*Me*-C(1')*); 24.9 (C(5)); 21.8 (*Me*-C(1)); 22.2 (Ac). IR ($CHCl_3$): 3610*w*, 3000*m*, 1720*s*, 1460*w*, 1375*m*, 1270*s*, 1215*s*, 1130*m*, 1020*w*. MS: 228 (1, M^+), 168 (19), 153 (32), 123 (37), 110 (92), 95 (42), 81 (87), 69 (29), 59 (30), 43 (100).

3-(1-Acetoxy-1-methylethyl)-1-methyl-1-trimethylsilyloxycyclopent-2-yl-carbaldehyde (13). A soln. of Me_3SiCl (0.45 ml, 3.56 mmol) in CH_2Cl_2 (5 ml) was added to a soln. of **10** (620 mg, 2.72 mmol) and imidazole (600 mg, 7.5 mmol) in CH_2Cl_2 and the mixture stirred for 17 h at r.t. The soln. was filtered, evaporated and purified by FC (silica gel, hexane/AcOEt 17:3) to give 490 mg (60%) **13** as a white wax. ^{1}H NMR ($CDCl_3$, 300 MHz): 9.45 (*d*, *J* = 4.2; H-C(6)); 2.93 (*dt*, *J* = 9.3, 6.9; H-C(3)); 2.19 (*dd*, *J* = 9.3, 4.2; H-C(2)); 1.90 (*m*, H-C(4)); 1.77 (*s*, Ac), 1.42-1.59 (*m*, H-C(4), H_2-C(5)); 1.33 (*s*, Me(2')*); 1.32 (*s*, Me-C(1)); 1.30 (*s*, Me-C(1')*); -0.02 (*s*, TMS). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 205.1 (C(6)); 170.0 (Ac); 86.0 (C(1)); 83.3 (C(1')); 63.1 (C(2)); 48.9 (C(3)); 41.4 (C(4)); 27.1 (C(2')*); 25.9 (C(5)); 24.6 (*Me*-C(1')*); 22.0 (*Me*-C(1)); 21.8 (Ac); 1.8 (TMS). IR ($CHCl_3$): 2990*m*, 1725*s*, 1460*w*, 1380*m*, 1265*s*, 1215*s*, 1140*m*, 1045*m*. MS: 240 (39), 225 (100), 197 (20), 143 (92), 133 (36), 122 (65), 81 (47), 73 (51), 43 (41).

4-(3-(1-Hydroxy-1-methylethyl)-1-methyl-1-trimethylsilyloxycyclopent-2-yl)-3-buten-2-one (14). BuLi (1.6M in hexane, 1.25 ml, 2 mmol) was added at 0° to a soln. of (*i*-Pr)$_2$NH (275 µl, 2 mmol) in THF (8 ml), the mixture stirred for 30 min and cooled to -70°. Acetone (110 µl, 1.5 mmol) in THF (1 ml) was added, the soln. stirred for 15 min and a soln. of **13** (300 mg, 1 mmol) in THF (1.5 ml) added. The mixture was allowed to warm to 0° within 2 h and sat. NH_4Cl-soln. (10 ml) was carefully added. The org. phase was separated, washed with H_2O and brine, dried ($MgSO_4$) and evaporated. Purification by FC (silica gel, hexane/AcOEt 3:1) gave 210 mg (70%) **14** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 6.83 (*dd*, *J* = 16.2, 9.6; H-C(4)); 6.01 (*d*, *J* = 16.2, H-C(3)); 2.33 (*td*, *J* = 9.9, 5.9; H-C(3')); 2.21 (*s*, Me(1)); 2.16 ('*t*', *J* = 9.6; H-C(2')); 1.98 (*m*, H-C(4'α)); 1.83 (*m*, H-C(5'α)); 1.61 (*m*, H-C(4'β), H-C(5'β)); 1.25 (*s*, Me(2'')*); 1.16 (*s*, Me-C(1')); 1.14 (*s*, Me-C(1'')*); 0.08 (TMS). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 198.7 (C(2)); 152.5 (C(4)); 132.2 (C(3)); 85.8 (C(1')); 72.9 (C(1'')); 56.9 (C(2')); 54.4 (C(3')); 40.7 (C(5')); 28.5 (C(2'')*); 27.8 (*Me*-C(1')); 26.2 (C(1)); 26.0 (*Me*-C(1'')*); 25.4 (C(4)); 2.2 (TMS). IR ($CHCl_3$): 3440*w*, 2980*s*, 2375*w*, 1730*w*, 1675*s*, 1620*m*, 1385*m*, 1255*s*, 1050*m*, 860*s*. MS: 298 (2, M^+), 280 (25), 265 (16), 240 (31), 227 (28), 208 (42), 193 (29), 182 (30), 143 (100), 101 (62), 73 (50), 59 (54), 43 (56).

5-(3-(1-Hydroxy-1-methylethyl)-1-methyl-1-trimethylsilyloxycyclopent-2-yl)-3-methylpenta-1,4-dien-3-ol (15). A soln. of **14** (490 mg, 1.64 mmol) in THF (10 ml) was added dropwise to a cooled soln. of $CH_2CHMgBr$ (1M in Et_2O, 6.6 ml, 6.6 mmol) in THF (30 ml) at -50°. The mixture was stirred for 30 min, $CH_2CHMgBr$ (1M in Et_2O, 3 ml, 3 mmol) added, the soln. allowed to warm to 0° and the reaction quenched with sat. NH_4Cl-soln. (20 ml). The org. phase was separated, washed with brine and evaporated. FC (silica gel, hexane/AcOEt 17:8) gave 190 mg (35%) **15** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 5.91 (*dd*, *J* = 17.3, 10.7; H-C(2)); 5.65 (*dd*, *J* = 15.8, 8.8; H-C(5)); 5.53 (*d*, *J* = 15.8; H-C(4)); 5.18 (*dd*, *J* = 17.3, 1.1; H-C(1)); 4.98 (*dd*, *J* = 10.7, 1.1 H-C(1)); 2.96 (*br.s*, 2 x OH); 2.19 (*m*, H-C(3')); 1.90 (*m*, H-C(2')); 1.81 (*m*, H-C(4'α)); 1.73 (*m*, H-C(5'α)); 1.49 (*m*, H-C(5'β)); 1.38 (*m*, H-C(4'β)); 1.34 (*s*, Me-C(3)); 1.17 (*s*, Me-C(1)); 1.10 (*s*, Me(2''),

Me-C(1'')); 0.08 (TMS). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 144.3 (C(2)); 137.5 (C(4)); 131.3 (C(5)); 112.0 (C(3)); 111.7 (C(1)); 84.6 (C(1')); 73.0 (C(1'')); 56.5 (C(2')); 53.8 (C(3')); 40.2 (C(5')); 28.5 (C(2'')*); 27.5 (*Me*-C(3)); 26.6 (*Me*-C(1'')*); 25.8 (*Me*-C(1)); 25.1 (C(4')); 2.2 (TMS). IR ($CHCl_3$): 3400*s*, 3040*w*, 2970*s*, 1620*w*, 1455*m*, 1380*s*, 1245*s*, 1095*s*, 1040*s*, 835*s*. MS: 326 (1, M^+), 308 (28), 293 (13), 241 (40), 223 (89), 218 (72), 197 (37), 173 (81), 143 (100), 117 (28), 73 (53), 57 (23), 43 (44).

5-(1-Hydroxy-3-(1-hydroxy-1-methylethyl)-1-methylcyclopent-2-yl)-3-methyl-penta-2,4-dienyl-triphenylphosphonium bromide (6). A soln. of **15** (520 mg, 1.6 mmol) and PPh_3HBr (600 mg, 1.74 mmol) in $CHCl_3$/MeOH 1:1 (16 ml) was stirred for 23 h under the exclusion of light, the solvent evaporated and the residue, dissolved in a small amount of CH_2Cl_2, precipitated in ice-cold TBME. The TBME was decanted, the precipitate washed twice with TBME and dried at h.v. to give 1.09 g (100%) crude **6**, which was used without further purification.

(all-*E*)-12'-Apo-1,5-dihydroxy-2,6-cyclolycopen-12'-al (16). To a soln. of **6** (200 mg, 0.36 mmol) and 2,7-dimethyl-2,4,6-octatrien-1,8-dial (**7**, 50 mg, 0.30 mmol) in CH_2Cl_2 (2 ml) was added 1N NaOH (1.5 ml) and the mixture was stirred for 90 min. The soln. was distributed between CH_2Cl_2 and H_2O, the org. phase dried ($MgSO_4$) and purified by FC (silica gel, hexane/ AcOEt 7:3) to give 33 mg (28%) **16** as a mixture of (*E/Z*)-isomers. Orange powder. The (all-*E*)-isomer was obtained by recrystallization from hot hexane. UV/Vis: 410 (AcOEt). ^{1}H NMR ($CDCl_3$, 400 MHz): 9.45 (*s*, H-C(12')); 7.02 (*dd*, *J* = 14.4, 11.9; H-C(15)); 6.95 (*d*, *J* = 11.9; H-C(14')); 6.75 (*dd*, *J* = 15.0, 11.4; H-C(11)); 6.69 (*dd*, *J* = 14.4, 11.9; H-C(15')); 6.37 (*d*, *J* = 15.0; H-C(12)); 6.30 (*d*, *J* = 11.9; H-C(14)); 6.24 (*d*, *J* = 15.7; H-C(8)); 6.16 (*d*, *J* = 11.4; H-C(10)); 5.81 (*dd*, *J* = 15.7, 8.9; H-C(7)); 2.30 (*ddd*, *J* = 19.7, 10.0, 6.9; H-C(2)); *2.24* (*dd*, *J* = 10.0, 8.9; H-C(6)); 2.03 (*s*, Me(20)); 1.99 (*m*, H-C(3α)); 1.96 (*s*, Me(19)); 1.88 (*s*, Me(20')); 1.79 (*ddd*, *J* = 12.3, 8.4, 3.8; H-C(4α)); 1.68 (*ddd*, *J* = 13.1, 10.1, 8.4; H-C(4β)); 1.53 (*dtd*, *J* = 16.1, 6.9, 3.8; H-C(3β), 2 x OH); 1.24 (*s*, Me(18)); 1.18 (*s*, Me(17)*); 1.16 (*s*, Me(16)*). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 194.3 (C(12')); 148.7 (C(14')); 141.5 (C(13)); 137.7 (C(8)); 137.6 (C(15)); 137.03 (C(13')); 136.99 (C(12)); 136.8 (C(9)); 131.1 (C(14)); 130.95 (C(10), C(7)); 127.5 (C(15')); 127.3 (C(11)); 82.2 (C(5)); 73.1 (C(1)); 55.7 (C(6)); 54.4 (C(2)); 40.0 (C(4)); 28.6 (C(17)*); 27.5 (C(16)*); 26.7 (C(18)); 25.1 (C(3)); 13.1 (C(19)); 13.0 (C(20)); 9.6 (C(20')). IR ($CHCl_3$): 3680*w*, 3620*m*, 3460*w*, 3015*s*, 2980*s*, 2415*m*, 1670*m*, 1605*m*, 1530*m*, 1490*m*, 1425*m*, 1215*s*, 1050*s*, 930*m*. MS: 384 (100, M^+), 306 (87), 326 (38), 277 (12), 222 (21), 197 (21), 183 (22), 157 (32), 145 (32), 131 (20), 119 (22), 105 (23), 95 (24), 43 (22).

(all-*E*)-2,6-Cyclolycopene-1,5-diol (3). To a soln. of **16** (59 mg, 0.16 mmol) and **8** [16] (94 mg, 0.17 mmol) in CH_2Cl_2 (5 ml) was added 1N NaOH (1 ml) and the mixture refluxed for 90 min, distributed between AcOEt and H_2O, the org. phase washed with brine, dried (Na_2SO_4), evaporated and purified by FC (silica gel, hexane/AcOEt 2:1) to give 38 mg (43%) **3** as an mixture of (*E/Z*)-isomers. Red powder. The pure (all-*E*)-isomer was obtained by recrystallization from hot hexane. M.p.: 78° decomp. UV/Vis: 491, 459, 433 (AcOEt); 487, 455, 429 (petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): 6.63 (*dd*, *J* = 15.0, 11.1; H-C(11')); 6.63 (*dd*, *J* = 14.9, 11.3; H-C(11)); 6.63 (*m*, H-C(15); H-C(15')); 6.51 (*dd*, *J* = 15.1, 11.0; H-C(7')); 6.36 (*d*, *J* = 14.9; H-C(12)); 6.35 (*d*, *J* = 15.0; H-C(12')); 6.26 (*d*, *J* = 15.1; H-C(8')); 6.25 (*d*, *J* = 15.7; H-C(8)); 6.23 (*m*, H-C(14); H-C(14')); 6.19 (*d*, *J* = 11.1; H-C(10')); 6.16 (*d*, *J* = 11.3; H-C(10)); 5.94 (*d*, *J* = 11.0; H-C(6')); 5.73 (*dd*, J = 15.7, 9.0; H-C(7)); 5.16 (*m*, H-C(2')); 2.30 (*ddd*, *J* = 17.1, 10.1, 7.0; H-C(2)); 2.23 (*dd*, *J* = 10.1, 9.0; H-C(6)); 2.12 (*m*, H_2-C(3'); H_2-C(4')); 1.98 (*s*, Me(20); Me(20')); 1.97 (*s*, Me(19)); 1.95 (*m*, H-C(3α)); 1.94 (*s*, Me(19')); 1.82 (*s*, Me(18')); 1.79 (*ddd*, *J* = 12.3, 8.4, 3.8; H-C(4α)); 1.68 (*s*, Me(16')); 1.67 (*m*, H-C(4β)); 1.62 (*s*, Me(17')); 1.53 (*m*, H-C(3β)); 1.24 (*s*, Me(16)); 1.19 (*s*, Me(18)); 1.18 (*s*, Me(17)). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 139.5 (C(5')); 138.2 (C(8)); 138.0 (C(12)); 137.3 (C(12')); 136.7 (C(13')); 136.3 (C(9')); 135.4 (C(8')); 134.9 (C(9)); 132.9 (C(14)); 132.5 (C(14')); 131.8 (C(1')); 131.6 (C(10')); 131.5 (C(10)); 130.3 (C(15)); 129.9 (C(15')); 129.4 (C(7)); 125.7 (C(6')); 125.2 (C(11')); 124.8 (C(7')); 124.6 (C(11)); 123.9 (C(2')); 82.2 (C(5));

73.1 (C(1)); 55.6 (C(6)); 54.3 (C(2)); 40.2 (C(4')); 39.7 (C(4)); 28.5 (C(16)*); 27.4 (C(17)*); 26.7 (C(3'); C(18)); 25.7 (C(16')); 25.1 (C(3)); 17.7 (C(17')); 17.0 (C(18')); 13.1 (C(19)); 12.9 (C(19')); 12.8 (C(20); C(20')). IR ($CHCl_3$): 3550*m*, 3430*m*, 2980*s*, 2930*s*, 2890*m*, 1715*w*, 1660*w*, 1625*w*, 1590*w*, 1570*w*, 1445*m*, 1385*m*, 1160*m*, 1125*m*, 970*s*, 920*w*. MS: 570 (52, M^+), 552 (2), 478 (14), 464 (12), 223 (19), 209 (25), 159 (52), 145 (62), 133 (36), 105 (62), 91 (43), 69 (31), 55 (20), 43 (100).

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