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SYNTHESIS OF (+)-PALITANTIN

Stephen Hanessian*, Yoji Sakito, Daljit Dhanoa and Lucia Baptistella
Department of Chemistry, Université de Montréal
C.P. 6128, Succ. A
Montréal, QC, CANADA, H3C 3J7

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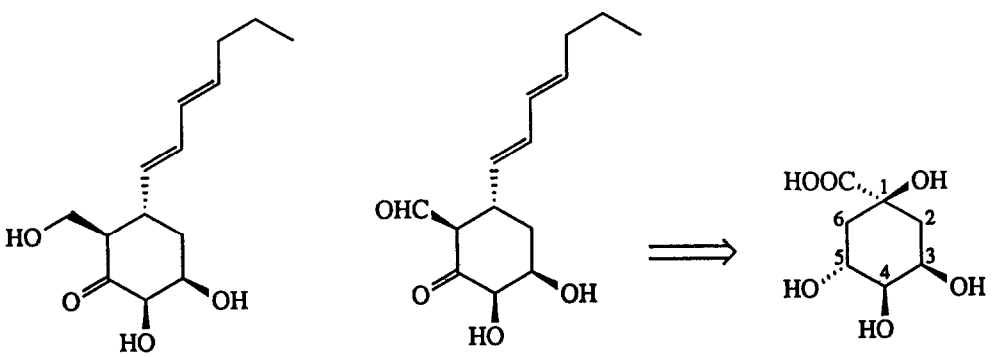
Summary - (-)-Quinic acid was utilized for the synthesis of (+)-palitantin adopting the chiron approach. Pertinent methodology includes stereocontrolled free-radical deoxygenation, functional group adjustments and an α-keto hydroxymethylation reaction.

Palitantin **1** and frequentin **2** are metabolic products isolated from Penicillium palitans[1] and P. frequentans respectively (Figure 1). Frequentin has been shown to have antifungal and antibiotic activity.[2] Its structural correlation with palitantin has been established through chemical transformation.[3] Although the synthesis of **1** in a racemic form was reported by Ichihara and coworkers,[4] the optically active natural isomer has not been synthesized to the best of our knowledge.

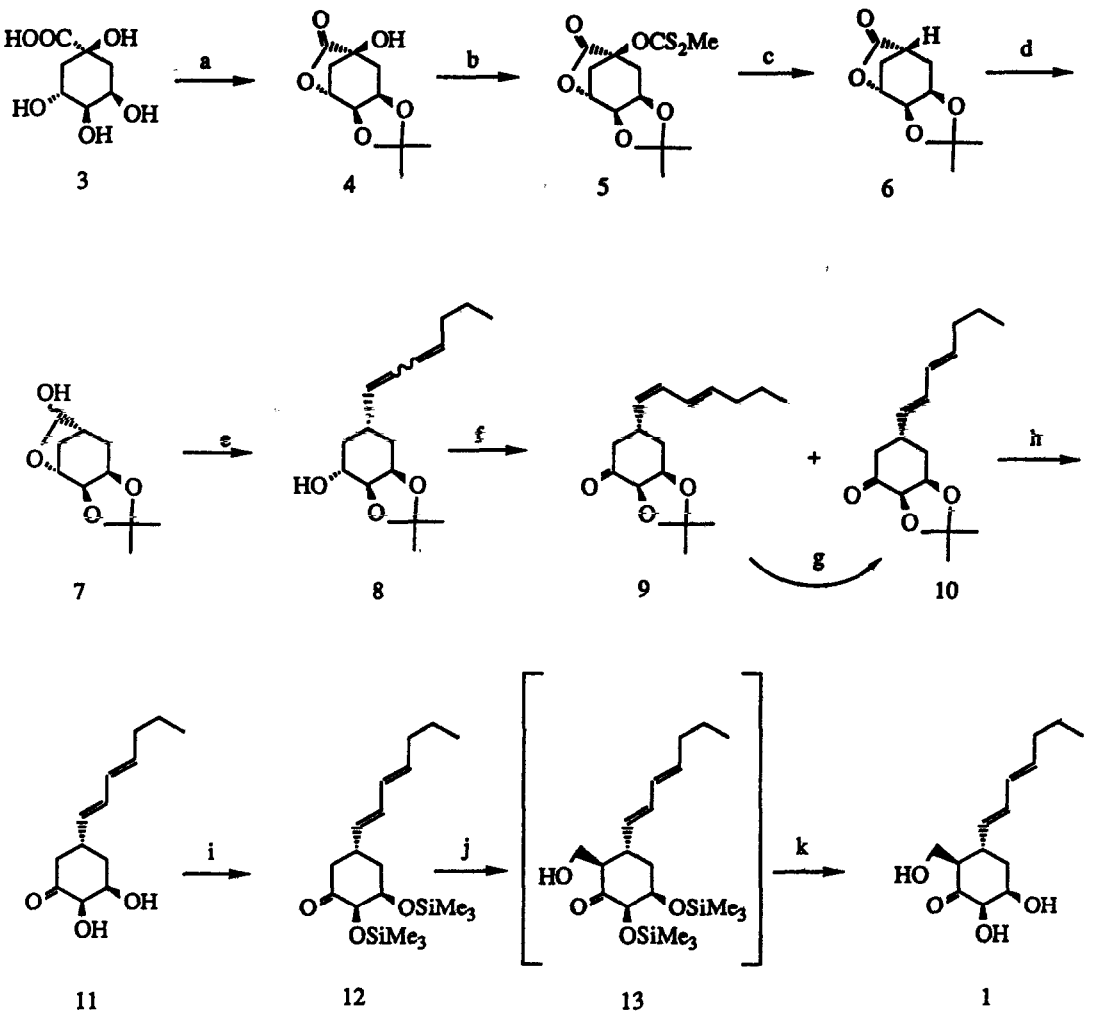
In this paper, we disclose a concise and stereocontrolled synthesis of (+)-palitantin adopting the chiron approach where maximum structural and functional group overlap with an appropriate precursor was sought. Bound disconnection of palitantin and frequentin relates the cyclic carbon skeleton to that of (-)-quinic acid **3**, which is readily available at relatively low cost. The pattern of substitution in **3** makes it an attractive starting material (chiral template) for controlled chemical manipulation and convergence with the intended target. The *cis*-diol group and the carboxyl group of **3** have the desired absolute configuration and disposition. The sites to be modified are at C-1 (deoxygenation, extension), C-5 (oxidation), and C-6 (branching). With this analysis in mind, and convinced by its apparent simplicity, we set out to synthesize (+)-palitantin.

Figure 1



1, Palitantin 2, Frequentin 3, (-)-Quinic acid

Scheme 1



a; acetone, H_2SO_4. b; KH, CS_2, MeI. c; Bu_3SnH, AIBN. d; DIBAL. e; $Ph_3P{=}CHCH{=}CH(CH_2)_2CH_3$

f; PCC. g; I_2. h; 10% H_2SO_4. i; TMSCl, imidazole. j; LiHMDS, TMEDA,CH_2O. k; 10% H_2SO_4

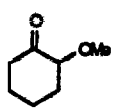
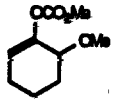
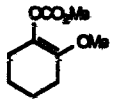
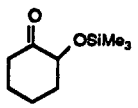
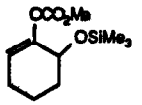
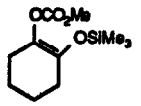
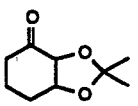
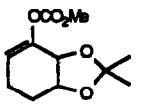
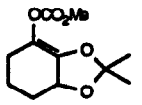
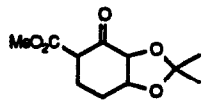
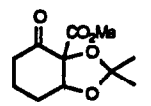
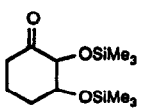
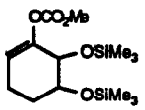
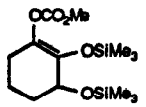
Any blueprint for total or partial synthesis of a target molecule must also take into account the proper "timing" of chemical events so as to satisfy the requirements of functional group compatibility, hence overall efficiency. Since a number of chemical manipulations were required en route to palitantin from quinic acid, we endeavored to minimize the use of protective groups and to use inherent functionality to our advantage. One of the more critical steps was considered to be the deoxygenation of the tertiary hydroxyl group at C-1 while maintaining the relative stereochemistry at the same carbon atom where an α-orientation is needed for the diene chain. Once the latter chain introduced, it was anticipated that conversion of the unprotected hydroxyl group into a ketone and site-selective α-hydroxymethylation of the corresponding enolate would complete the synthesis of (+)-palitantin.

Scheme 1 illustrates the synthesis pathway starting with (-)-quinic acid which was converted to the lactone-acetal derivative **4** according to a published procedure.[5] Deoxygenation of the tertiary alcohol was achieved via the corresponding xanthate derivative **5** by treatment with tributytin hydride in the presence of a catalytic quantity of AIBN[6] to give the deoxy derivative **6** in 73% yield. Thus, the pattern of substitution found in palitantin was expediently achieved in three steps from **3**, with complete stereochemical control in the radical-induced deoxygenation reaction.

Reduction of the lactone with DIBAL gave the corresponding lactol **7** in 78% yield, which was chain-extended via a Wittig reaction to a mixture of dienes **8** (*cis/trans* ratio: 1/4) in 75% yield. Separation of the olefin isomers was not possible at this stage. Oxidation to the ketone **9** with PCC led to a mixture of dienes from which the pure *trans* isomer **10** could be separated by chromatography and obtained in 32% yield. A second fraction was isolated which contained a mixture of unseparated *cis/trans* isomers **9,10** (42:58 ratio) in 42% yield. When this mixture was treated with a 0.1 mole equivalent of iodine in dichloromethane, partial isomerization took place to produce the desired pure *trans* isomer **10** in 52% yield with recovery of 26:74 mixture of the *cis/trans* isomers (22%). The desired *trans* isomer could thus be obtained in 50% overall yield, and the combined *cis/trans* isomers could be recycled. With the desired functionality and oxidation level properly situated, there remained the task of a site-selective hydroxymethylation and deprotection en route to the intended target.

Treatment of the enolate derived from **10** with LiHMDS or KHMDS and formaldehyde in a number of solvents (THF, toluene, DME) led to a preponderance of the undesired regioisomeric hydroxymethylation product. The same trend was also observed when the electrophile was changed to methyl chloroformate or methyl cyanoformate.[7] In light of these unexpected results we looked for precedence in the literature involving the formation of enolates from α-hydroxy or α-alkoxy cycloalkanones. Surprisingly few examples were found involving the desired systems, and none to the best of our knowledge with an O-isopropylidene group as in **10**. The most revealing information was provided by studies conducted by Kowalski et al [8] involving the base-induced enolization of 2-methoxycycloakanones. Thus, 2-methoxycyclohexanone was found to enolize toward the methoxy group only to the extent of 15%, while with 2-methoxycyclopentanone, 30% enolization occurred toward the methoxy group. Complete enolization toward the methoxy group was seen in the case of 2-methoxycyclobutane. In another report,[9] it was found that the direction of enolization of α-adipoin under kinetic deprotonation conditions was toward the methylene group to produce a mixture of enolate dianion and enediolate (85:15). Examples are also available in the aldol reaction of α-silyloxyketones in acyclic systems,[10] but the site-selectivity is not discussed. In another instance, complete enolization toward the α–hydroxy group in α-hydroxy cyclohexanone was observed.[11] In α–methoxyacetone on the other hand, deuterium exchange was faster on the methyl side except in aq.base.[12] Clearly then the effect of ring size and nature of the alkoxy group seem to influence the site-selectivity of enolization.

Table 1

Substrate	ClCOOMe/conditions		NCCOOMe/conditions	
			—	
	85 :	15 (A)		
			—	
	100 :	0 (A)		
				
	25 :	75 (A)	63 :	37 (B) isolated
	63 :	37 (B)		
	43 :	57 (C)		
			—	
	100 :	0 (B)		

Conditions
A: LiHMDS, THF, -78°C
B: LiHMDS, toluene, -78°C
C: LiHMDS, TMEDA, toluene, -78°C

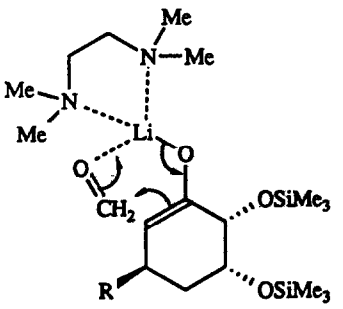
Unless otherwise stated, ratios are based on GC analysis.

We deemed it necessary to study the reaction of some model α-alkoxy cyclohexanones with methyl chloroformate and methylcyanoformate (Table 1). Under the same conditions 2-methoxycyclohexanone and 2-trimethylsilyloxy cyclohexanone led to O-methoxycarbonylation of the enolate formed *toward the methylene group*. However, with 2,3-O-isopropylidene *cis*-2,3-dihydroxycyclohexanone,[13] the major product of acylation was formed from enolization *toward oxygen*. In the latter case, the products with methyl cyanoformate were the isomeric C-methoxycarbonates.

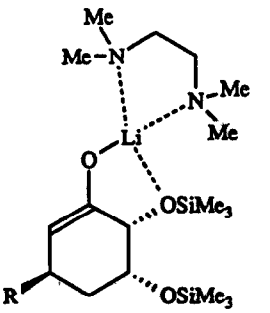
From our own attempts at hydroxymethylation of **10**, it appeared that the desired C-alkylation was disfavored in the constrained bicyclic acetal derivatives of cyclohexanone. This may in fact be due to an enhancement of the kinetic acidity of the α-alkoxy methyl proton due to a favorable conformation in which back bonding from the acetal oxygen to the antibonding σ* methine hydrogen is decreased. When the trimethylsilylated diol was used thus releasing the constraint, enolization took place in the desired sense.

It was therefore decided to attempt hydroxymethylation on a monocyclic O,O'-disubstituted derivative of **10**. Thus, mild acid hydrolysis of the acetal protective group and treatment with trimethylsilyl chloride under the standard conditions gave the bis-O-TMS derivative **12**. With LiHMDS and formaldehyde no reaction was observed at -78°C presumably because of the formation of a stable Li-coordinated enolate. However, with the addition of TMEDA reaction took place with complete consumption of the starting ketone when the temperature reached -35°C to give **13**. One could envisage the formation of a TMEDA coordinated enolate intermediate A which by virtue of its bulk would favor reactivity as well as site-selectivity away from the oxygen substituent as shown in Figure 2. Acid hydrolysis gave palitantin which was isolated in crystalline form, and was shown to be identical to authentic material in all respects.

Figure 2



A



B

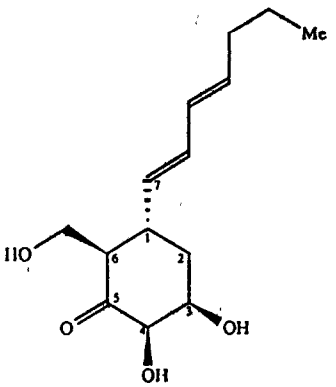
The choice of starting material is an important element in synthesis design which is usually done by visual examination of the target and analysis of various disconnection pathways. The Chiron computer program developed in our laboratory[14] is a powerful tool for such heuristic analysis and stereochemical decoding. The choice of (-)-quinic acid may be an obvious one simply by a visual analysis of palitantin and a mental association with a search for a carbocyclic template. It is of interest that Chiron rapidly perceives a connection with (-)-quinic acid and suggests it as a starting material. The output shown in Figure 3 is the result of a display using the Transformation command where synthetic operations en route to the target are shown as key words. Although, these appear to be somewhat trivial in the scope of the synthesis proper, they provide a global scenario of the required transformations. In that context, the timing and sequence of transformations has relevance particularly

when issues regarding feasibility, compatibility and possible choice of protective group is addressed. Furthermore, seeing the "beginning" and the "end" makes the forward process more focussed and provides an ideal forum for decisions regarding synthesis planning.

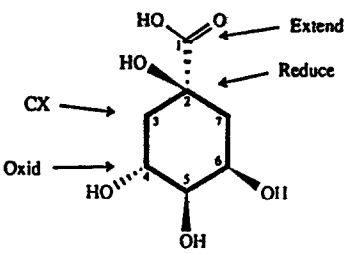
Figure 3

CHIRON PROGRAM ANALYSIS

COMPUTER ASSISTED PRECURSOR SELECTION



PALITANTIN



(-)-Quinic acid
Comm., F=CARBOCYCLIC-BRANCHED
53% # 16, P-M : 1-7/7-2

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker 400 MHz and Varian 300 MHz spectrometers. Infrared spectra were obtained on a Perkin Elmer model 781 spectrometer. Optical rotations were measured at room temperature with a Perkin Elmer model 141 polarimeter. Mass spectra were obtained on a VG-1212 low resolution and Kratos-50 high resolution spectrometers by the EI or CI. Work-up in the usual manner signifies, washing the organic phase with water or dil. hydrochloric acid, washing with aqueous bicarbonate, brine, water, drying ($MgSO_4$) and evaporation to dryness under vacuo. Chromatography was done by the flash column technique.[15]

3,4-O-Isopropylidene quinic acid lactone 1-xanthate, 5 - To a suspension of potassium hydride (35 % dispersion, 503 mg, 4.39 mmol) in dry THF was added a THF solution of 4[5] (625 mg, 2.92 mmol) dropwise at 0°C. Evolution of the hydrogen ceased in 30 min. Carbon disulfide (0.35 mL, 5.8 mmol, 2 eq) was added in one portion at 0°C and the mixture was stirred for 30 min. After adding methyl iodide (0.36 mL, 5.8 mmol, 2 eq), the reaction was complete within 30 min. Aqueous sat. NH_4Cl was added and the reaction mixture was extracted with ether three times. The ethereal layer was washed with aq. sat. NaCl and dried. Evaporation of the solvent and purification of the residue by silica gel column chromatography (hexane: ethyl acetate, 5:2) gave 792 mg (89.2%) of the pure xanthate 5; mp 87-89°C (recryst. from ether/hexane); $[\alpha]_D$ - 7.2° (c 1.12, $CHCl_3$); IR (cm^{-1}) 1795 (C=O) ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm) 1.34 (s, 3H); 1.53 (s, 3H); 2.55 (s, 3H); 2.58-2.60 (m, 2H); 2.68 (d, J=11.6 Hz, 1H); 3.69 (dddd J=11.6, 6.6, 2.4, 1.2 Hz, 1H)); 4.33 (ddd, J=6.0, 2.5, 1.2 Hz, 1H); 4.56 (ddd J=6.0, 5.7, 5.7 Hz, 1H); 4.84 (dd J=6.6, 2.5 Hz, 1H); Anal. calc. for $C_{12}H_{16}O_5S_2$: C,47.35; H, 5.30; S, 21.07. Found C, 47.64; H, 5.45; S, 21.22.

(1S,3R,4R,5R)-3,4-O-Isopropylidene-3,4,5-trihydroxy-1-carboxy cyclohexane 1,5-lactone, 6 - Argon gas was passed through a toluene (10 mL) solution containing 5 (788 mg, 2.59 mmol) and AIBN (20 mg, 0.122 mmol, 4.7 mol%) for 10 min. To this was added tributyltin hydride (0.80 mL, 0.86 g, 2.95 mmol, 1.14 eq) and the mixture was heated quickly at 105°C by immersing the reaction vessel into an oil bath. After 30 min, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate, 2:1) to give crystalline 6 (376 mg, 1.90 mmol, 73.2%), mp 96-98°C (recryst. from ether/hexane); $[\alpha]_D$ -36.2° (c 2.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.33 (s, 3H); 1.51 (s, 3H);

2.09 (ddd, J=15.1, 6.4, 3.2 Hz, 1H); 2.22 (ddddd, J=12.1, 5.6, 5.6, 1.8, 1.7 Hz, 1H); 2.33 (dddd, J=15.1, 7.6, 1.9, 1.8 Hz, 1H); 2.41 (d, J=12.1 Hz, 1H); 2.61 (ddd, J=6.4, 5.6, 1.9 Hz, 1H); 4.33 (ddd, J=6.6, 2.6, 1.7 Hz, 1H); 4.48 (ddd J=7.6, 6.6, 3.2 Hz, 1H); 4.70 (dd, J=5.6, 2.6 Hz, 1H); Anal. calc. for $C_{10}H_{14}O_4$: C, 60.59; H,7.12; Found C, 60.34; H, 7.01.

(1S,3R,4R,5R)-3,4-O-Isopropylidene-3,4,5-trihydroxy cyclohexane-1-carboxaldehyde, 7 - Diisobutylaluminum hydride (1.0M in hexanes; 1.10 mL, 1.10 mmol, 1.35 eq) was added dropwise to a toluene solution (3 mL) of **6** (161 mg, 0.81 mmol) at -78°C and the reaction mixture was stirred for 15 min. Saturated aqueous Na_2SO_4 was added to quench the reaction and the dry ice-acetone bath was removed. Ether was added to the mixture and the ethereal layer was processed in the usual manner. After evaporation of the solvent, the residue was purified by silica gel column chromatography (ethyl acetate) to give **7** (127 mg, 0.63 mmol, 78.3%); IR cm^{-1}, 3420, 2710, 1725 (C=O); $[\alpha]_D$ -86.5° (c 0.96, $CHCl_3$). This product was used as such in the next step.

(2-E)-Heptenyl triphenylphosphonium bromide - To a dichloromethane solution (20 mL) of *trans*-3-hexene-1-ol (3.03 g, 30.3 mmol) and carbon tetrabromide (10.50 g, 31.7 mmol) was added a dichloromethane solution (20 mL) of triphenylphosphine (8.66 g, 33.0 mmol) at 0°C. After 1h the solvent was evaporated and 100 mL of n-hexane was added to the residue. The precipitate was removed by filtration, and the solvent was evaporated to give a crude mixture of *trans*-1-bromo-hex-3-ene and bromoform. To this was added a benzene solution of triphenylphosphine (7.8 g, 29.7 mmol) at room temperature. The reaction solution was stirred overnight (20 h). The precipitate was collected by filtration, dried in a desiccator and used as such. For an alternative preparation see ref. 16.

(1S,3R,4R,5R)-3,4-O-Isopropylidene-3,4,5-trihydroxy-1-(1',3'-E,E and Z,E-1'-heptadienyl) cyclohexane, 8 - To a suspension of the phosphonium bromide (2.23 g, 5.24 mmol, 2.25 eg) in THF (20 mL) was added 3.3 mL of a *n*-BuLi solution (1.6 M in hexanes; 5.28 mmol, 1.01 eq) at 0°C. After 30 min, a THF solution (20 mL) of **7** (465 mg, 2.32 mmol) was added dropwise at 0°C. The mixture was stirred for 1h. Sat. aqueous NH_4Cl solution was added and the mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated and the residue was purified by silica gel column chromatography (hexane: ethyl acetate, 2:1) to give **8** (454 mg, 1.71 mmol, 73.5%) as a 1:4, mixture of *cis/trans* isomers; $[\alpha]_D$ -51.5° (c 0.97, $CHCl_3$); IR (cm^{-1}) 3450, 2930, 1380, 1240, 1220, etc; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm), 0.90 (t, J=7.3 Hz, 3H) 1.10-1.20 (m, 1H) ; 1.37 (s, 3H); 1.37-1.49 (m, 3H); 1.43-1.49 (m, 1H); 1.51 (s, 3H); 1.87-1.93 (m, 1H); 2.04 (td, J=7.0, 7.2 Hz, 2H); 2.10-2.21 (m, 2H); 2.39-2.49 (m, 1H); 3.71-3.80 (m, 2H); 4.31-4.34 (m, 1H); 5.47 (dd, J=14.6, 7.0 Hz, 1H); 5.62 (dt, J=14.4, 7.2 Hz, 1H); 5.89-6.07 (m, 2H). For the Z,E isomer: 0.91 (t, J=7.5 Hz); 1.79-1.85 (m); 2.80-2.90 (m); 5.07 (dd, J=10,10 Hz); 5.53-5.73 (m); 6.23-6.39 (m) etc.. MS calc. for $C_{16}H_{26}O_3$: 266.1882; Found: 266.1870.

(2R,3R,5R)-2,3-O-Isopropylidene-2,3-dihydroxy-5-(1',3'-E,E-1'-heptadienyl)-cyclohexanone, 10 (and the Z,E isomer 9) - To a dichloromethane solution (6 mL) of **8** (161 mg, 0.604 mmol) was added 3Å molecular sieves (200 mg), anhydrous sodium acetate (40 mg, 0.49 mmol) and pyridinium chlorochromate (330 mg, 1.53 mmol, 2.5 eq). After stirring the mixture at room temperature for 15h, ether (20 mL) was added and the ethereal layer was washed with water. After usual processing, the residue was purified by silica gel column chromatography (silica gel ca.75g, hexane: ethyl acetate, 2:1) to give the pure E,E isomer **10** (51.6 mg, 0.195 mmol, 32%) along with a mixture of **10** and the Z,E-isomer **9** to **7** (67.4 mg, 0.255 mmol, 42%, **9:10** ratio 42:58 by NMR). The total yield of **9** and **10** was 74%; for the pure E,E-isomer $[\alpha]_D$ -24.7° (c 1.13, $CHCl_3$); IR (cm^{-1}); 1730 (C=O); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm); 0.91 (t, J= 7.3 Hz, 3H); 1.39 (s, 3H); 1.41 (qt, J=7.3, 7.3 Hz, 2H); 1.44 (s, 3H); 1.83 (ddd, J=15.1, 12.3, 3.5 Hz, 1H); 2.06 (td, J=7.3, 7.2 Hz, 2H); 2.24 (dd, J=13.5, 13.5 Hz, 1H); 2.31 (dddd, J=15.1, 3.2, 2.8, 2.8 Hz, 1H); 2.51 (ddd, J=13.5, 3.2, 2.8 Hz, 1H); 2.81 (m, 1H); 4.28 (d, J=5.2 Hz, 1H); 4.59 (ddd, J=5.2, 3.5, 2.8 Hz, 1H); 5.47 (dd, 14.5, 7.3 Hz, 1H); 5.66 (td, J=7.2, 14.6 Hz, 1H); 5.96-6.09 (m, 2H); MS calc. for $C_{16}H_{24}O_3$: 264.1726; Found: 264.1774.

Isomerization of 9 to 10 - Iodine (6mg, 0.024 mmol) was added to a dichloromethane solution (5 mL) of **9** and **10** (66.0 mg, 0.25 mmol, **9:10** ratio, 42:58) and the solution was stirred for 1 h. The reaction mixture was washed with $Na_2S_2O_3$ solution, the solvent removed by evaporation and the residue was purified by silica gel column chromatography to give the pure *trans* isomer **10** (34.2 mg, 0.13 mmol, 52%), and a mixture of **9** and **10** (14.3 mg, 0.054 mmol, 22%, **9:10** ratio, 26:74).

(2R,3R,5R)-2,3-Dihydroxy-5-(1',3'-E,E-1'-heptadienyl)cyclohexane, 11 - To a solution containing **10** (145 mg, 0.548 mmol) in 2 mL of methanol was added 10% H_2SO_4 (1 mL). After standing for 45 min at room temperature , the reaction mixture was poured into dichloromethane and washed with aq. $NaHCO_3$. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane: ethyl acetate, 1:1) to give the diol **11** (100 mg, 0.446 mmol, 81%); $[\alpha]_D$ + 29.9° (c 0.85, $CHCl_3$); IR (cm^{-1}), 3450, 1720 (C=O); ^1H NMR ($CDCl_3$, 400 MHz, δ ppm); 0.91 (t, J=7.3 Hz, 3H); 1.41 (qt, J=7.3, 7.3 Hz, 2H); 1.75 (ddd, J=14.4, 12.5, 2.0 Hz, 1H); 2.06 (td, J=7.3, 7.1 Hz, 2H); 2.21 (dddd, J=14.4, 3.8, 3.8, 2.7 Hz, 1H); 2.26 (ddd, J=13.6, 12.8, 1.3 Hz, 1H); 2.60 (ddd, J=13.6, 4.2, 2.7 Hz, 1H); 3.00 (ddddd, J=12.8, 12.5, 7.1, 4.2, 3.8 Hz, 1H); 4.15 (dd, J=3.7, 1.3 Hz, 1H); 4.39 (ddd, J=3.8, 3.7, 2.0 Hz, 1H); 5.50 (dd, J=14.5, 7.1 Hz, 1H); 5.66 (td, J=7.1,

14:5 Hz, 1H): 5.93-6.09 (m, 2H); MS calc. for $C_{13}H_{20}O_3$: 224.1413; Found: 224.1418.

(2R,3R,5R)-2,3-Bis-(O-trimethylsilyl)-2,3-dihydroxy-1-(1'3'-E,E-1'-heptadienyl)-cyclohexanone, 12 - To a dichloromethane solution (3 mL) of **11** (54.3 mg, 0.242 mmol) and imidazole (66 mg, 0.97 mmol, 4.0 eq.) was added chlorotrimethylsilane (92 µl, 78 mg, 0.72 mmol, 3.0 eq.) at room temperature and the mixture was stirred for 2 h. The mixture was poured into 20 mL of hexane and washed with water. The organic layer was dried, evaporated, and the residue was purified by means of a short florisil column (hexane:ether, 4:1) to give the disylether **12** as an oil, (82.0 mg, 0.22 mmol, 92%); $[\alpha]_D$ + 41.2° (c 1.09, $CHCl_3$); IR (cm^{-1}), 2960, 1735 (C=O); ^1H NMR ($CDCl_3$; 400 MHz, δ ppm): 0.09 (s, 9H); 0.13 (s, 9H); 0.91 (t, J=7.3 Hz, 3H); 1.41 (qt, J=7.3, 7.3 Hz, 2H); 1.70 (ddd, J=13.0, 12.5, 2.0 Hz, 1H); 1.94 (dddd, J=13.0, 4.0, 4.0, 2.7 Hz, 1H); 2.06 (td, J=7.3, 6.8 Hz, 2H); 2.13 (ddd, J=13.7, 12.5, 1.0 Hz, 1H); 2.46 (ddd, J=13.7, 4.5, 2.7 Hz, 1H); 2.98 (ddddd, J=12.5, 12.5, 7.0, 4.5, 4.0 Hz, 1H); 4.14 (dd, J=3.1, 1.0 Hz, 1H); 4.25 (m, 1H); 5.50 (dd, J=14.1, 7.0 Hz, 1H); 5.64 (td, J=6.8, 14.0 Hz, 1H); 5.90-6.07 (m, 2H). MS calc. for $C_{19}H_{36}O_3Si_2$: 368.2204; Found: 368.2258.

(+)-Pallitantin, 1 - To a mixture of toluene (1 mL) and lithium hexamethyldisilazide (1.0 M in hexanes, 0.23 mL, 0.23 mmol, 2.5 eq/12) was added TMEDA (50 µl, 0.33 mmol) and the mixture was stirred for 10 min at room temperature. To this was added a toluene solution (2.0 mL) of **12** (34.0 mg, 0.092 mmol) at -78°C and the mixture was stirred for 2 h at -78°C. A THF solution of formaldehyde (excess) was added and the temperature was gradually brought up to -35°C. After 15 min, sat. aq. NH_4Cl solution was added to the reaction mixture at -35°C. The mixture was extracted with ether and the organic layer was washed with brine, then processed as usual. The residue was dissolved in MeOH (5.0 mL) and treated with 5.0 mL of 10% H_2SO_4 for 1 h at room temperature. The reaction mixture was extracted with ether and washed with aq. $NaHCO_3$. Evaporation of the solvent and purification of the residue by silica gel column chromatography (chloroform:ethyl acetate:methanol, 4:4:1) gave (+)-pallitantin (13.4 mg, 0.052 mmol, 57%); mp 163-165°C (recrystallized from water); $[\alpha]_{546}$ + 4.4° (c 0.8, $CHCl_3$); reported mp 165°C, $[\alpha]_{546}$ + 4.4° ($CHCl_3$)[1]. ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 0.91 (t, J=7.3 Hz, 3H) 1.42 (qt, J=7.3, 7.3 Hz, 2H); 1.87 (ddd, J=2.0, 12.4, 14.5 Hz, 1H); 2.06 (td, J=7.3, 7.3 Hz, 2H); 2.17 (ddd, J=14.5, 3.8, 3.8 Hz, 1H); 2.41 (td, J=5.0, 10.0 Hz, 1H); 2.85 (dddd, J=12.4, 10.0, 9.1, 3.8 Hz 1H); 3.80 (d, J=5.0 Hz, 2H); 4.22 (dd, J=3.6, 1.1 Hz, 1H); 4.38 (m, 1H); 5.40 (dd, J=14.9, 9.1 Hz 1H); 5.67 (dt, J=14.5, 7.3 Hz, 1H); 6.00 (dd, J=14.5, 10.3 Hz, 1H); 6.12 (dd, J=14.9, 10.3 Hz, 1H).

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REFERENCES

1. J.H. Birkinshaw, H. Raistvick, Biochem. J., 30, 801 (1936); J.H. Birkinshaw, Biochem. J., 51, 271 (1952); K. Bowden, B. Lythgoe, D.J.S. Marsden, J. Chem. Soc., 1662 (1959).
2. P.J. Curtis, H.G. Hemming, W.K. Smith, Nature, 167, 557 (1951).
3. H.P.Sigg, Helv. Chim. Acta, 46, 1061 (1963).
4. A. Ichihara, M. Ubukata, S. Sakamura, Tetrahedron, 36, 1547 (1980); Tetrahedron Lett., 3473 (1977).
5. M. Eberle, D. Arigoni, Helv. Chim. Acta, 43, 1508 (1960);
6. W. Hartwig, Tetrahedron, 39, 2609 (1983); D.H.R. Barton, W. Hartwig, R.S.H. Motherwell, W.B. Motherwell, A. Stange, Tetrahedron Lett., 23, 2019 (1982).
7. L.N. Mander, S.P. Sethi, Tetrahedron Lett., 24, 5425 (1983).
8. C. Kowalski, X. Creary, A.J. Rollin, M.C. Burke, J. Org. Chem., 43, 2601 (1978).
9. S. R. Wilson, M.E. Walters, B. Orbaugh, J. Org. Chem., 41, 378 (1976).
10. See for example, S. Masamune, W. Choy, F.A.J. Kerdesky, B. Imperiali, J.Am.Chem.Soc., 103, 1566 (1981); C.H. Heathcock, M.C. Pirrung, J. Lampe, C.T. Buse, S.D. Young, J. Org. Chem., 46, 2290 (1981).
11. J. Colonge, Y. Vaginay, Bull Soc. Chim. Fr., 3140 (1962).
12. J.Hine, K.G. Hampton, B.C. Menon, J. Am. Chem. Soc., 89, 2664 (1967).
13. F. Becsi, E. Zbiral, Monatsch. Chem., 110, 955 (1979).
14. The Chiron Program, Copyright, 1987. For examples of Chiron analyses, see S. Hanessian, in "Organic Synthesis - An Interdisciplinary Challenges", J. Streith, H. Prinsbach, G. Schill, eds; Blackwell, Boston, U.S.A., 1985, p. 267.
15. W.C. Still, M. Kahn, A. Mitra, J. Org. Chem., 43, 2923 (1978).
16. A. Butenandt, E. Hecker, M. Hopp, W. Koch, Ann., 658, 39 (1962).