Tetrahedron Vol. 47, No 23, pp 3829-3844, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

SYNTHESIS OF (–)-AURICULARIC ACID AND ITS C-4 EPIMER THE ABSOLUTE CONFIGURATION OF AURICULARIC ACID

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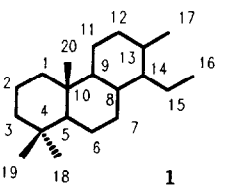
(*Received in UK* 18 *December* 1990)

Abstract: A synthesis of (-)-auricularic acid (2a) starting from methyl (+)-13-oxo-podocarp-8(14)-en-19-oate (3a) and a synthesis of its C-4 epimer (2b) starting from methyl (+)-13-oxopodocarp-8(14)-en-18-oate (3b) are described. The absolute configuration of natural auricularic acid is stablished as (4R, 5S, 8S, 9R, 10S, 14S).

INTRODUCTION

The cleistanthanes are a small group of diterpenes isolated from various plant families and whose structures are based on the 14-ethyl-13-methyl podocarpane skeleton (**1**).[1a] Most members of the group are characterized by the presence of an aromatic C-ring.[1b,c] Recently, a series of nonaromatic cleistanthanes have been discovered,[1d,e] the most significant of which, auricularic acid, was isolated from *Pogostemon auricularis* Hassk (Lamiaceae) by Prakash and coworkers[1f,g] in 1986.



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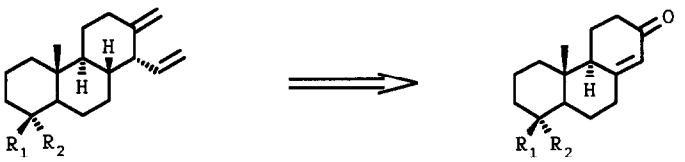
The structure **(2b)** [cleistanth-13(17),15-dien-18-oic acid] for auricularic acid was proposed originally on the basis of degradative and spectroscopic studies.[1f] However, we have recently shown that the properties of **(2b)** differ from those reported for the natural product and we have proposed,

by comparison of the ^{13}C NMR spectra of various abietane and podocarpane type diterpenoids[2] with that of auricularic acid, that this is an epimer at C-4 of (**2b**), necessitating its reformulation as cleistanth-13(17),15-dien-19-oic acid (**2a**).

In this paper, we describe the synthesis of (**2a**) which provides synthetic confirmation for the structure of auricularic acid. In addition, we report full experimental details concerning the preparation of (**2b**), the epimer at C-4 of auricularic acid.

RESULTS AND DISCUSSION

For the synthesis of (**2a**) and (**2b**), ketones (**3a**) and (**3b**), respectively, appeared to be the ideal precursors, since they possess the required tricyclic skeleton with the necessary functional groups for building up the two-carbon side chain with the required stereochemistry at C-14 and for the transformation of the C-13 carbonyl group into the exo-methylene moiety.



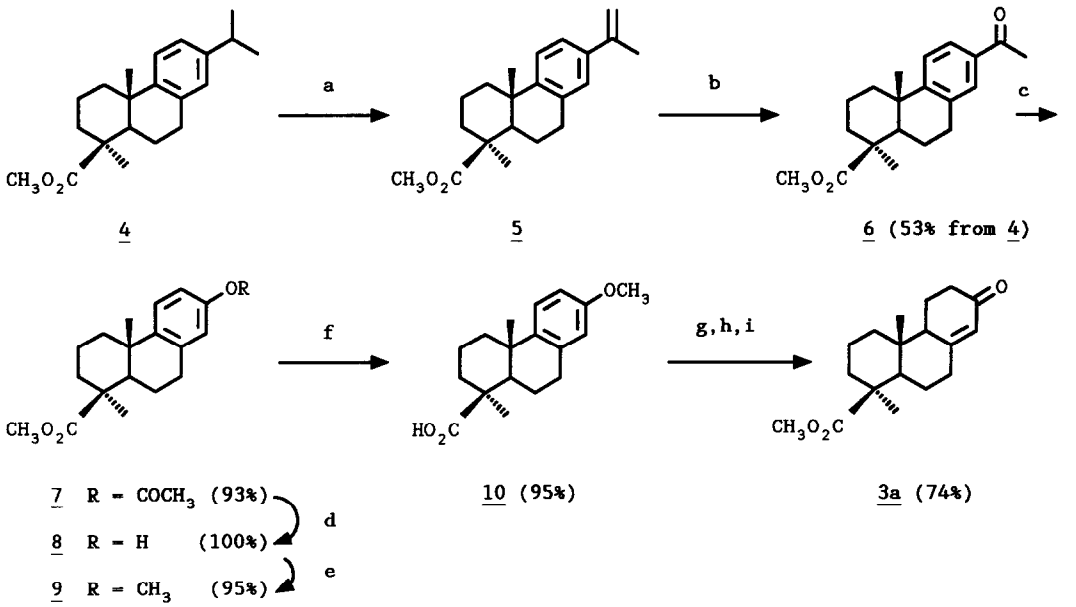
2a $R_1 = CO_2H$; $R_2 = CH_3$ 3a $R_1 = CO_2CH_3$; $R_2 = CH_3$

2b $R_1 = CH_3$; $R_2 = CO_2H$ 3b $R_1 = CH_3$; $R_2 = CO_2CH_3$

Both ketones could be obtained in optically active form from natural sources. Thus, the ketone (**2b**) was obtained from colophony or abietic acid, in five steps in *ca.* 24% overall yield[3] and the ketone (**2a**) was prepared from callistrisic acid (isolated from sandarac resin)[4] in *ca.* 33% overall yield, following the sequence outline in Scheme I.

Regioselective dehydrogenation of the isopropyl group of methyl callistrisate (**4**) was achieved using the same procedure used by us for identical functionalization of the isopropyl group of methyl dehydroabietate.[5] Thus, heating a solution of (**4**) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) under reflux in dry benzene gave a mixture of starting material (**4**) (41%) and (**5**) (57%). Since their chromatographic separation was difficult, the mixture of (**4**) and (**5**) was treated with potassium permanganate in the heterogeneous two-phase water-benzene system and the phase-tranfer agent methyltrioctylammonium chloride.[6] Under these conditions a mixture of products was obtained from which the methyl ketone (**6**) was isolated, after column chromatography, in an overall yield (two steps) of 53% based on recovered (**4**). Baeyer-Villiger oxidation of (**6**) using *m*-chloroperbenzoic acid in dichloromethane gave the acetate (**7**) in excellent yield. Treatment of (**7**) with sodium methoxide in methanol to effect methanolysis of (**7**) to the corresponding phenol (**8**) was followed by methylation with lithium hydroxide and methyl iodide in DMF to furnish the methyl ether (**9**) in 95%. In order to avoid partial reduction of the 18-carbomethoxy moiety in the subsequent Birch reduction, the

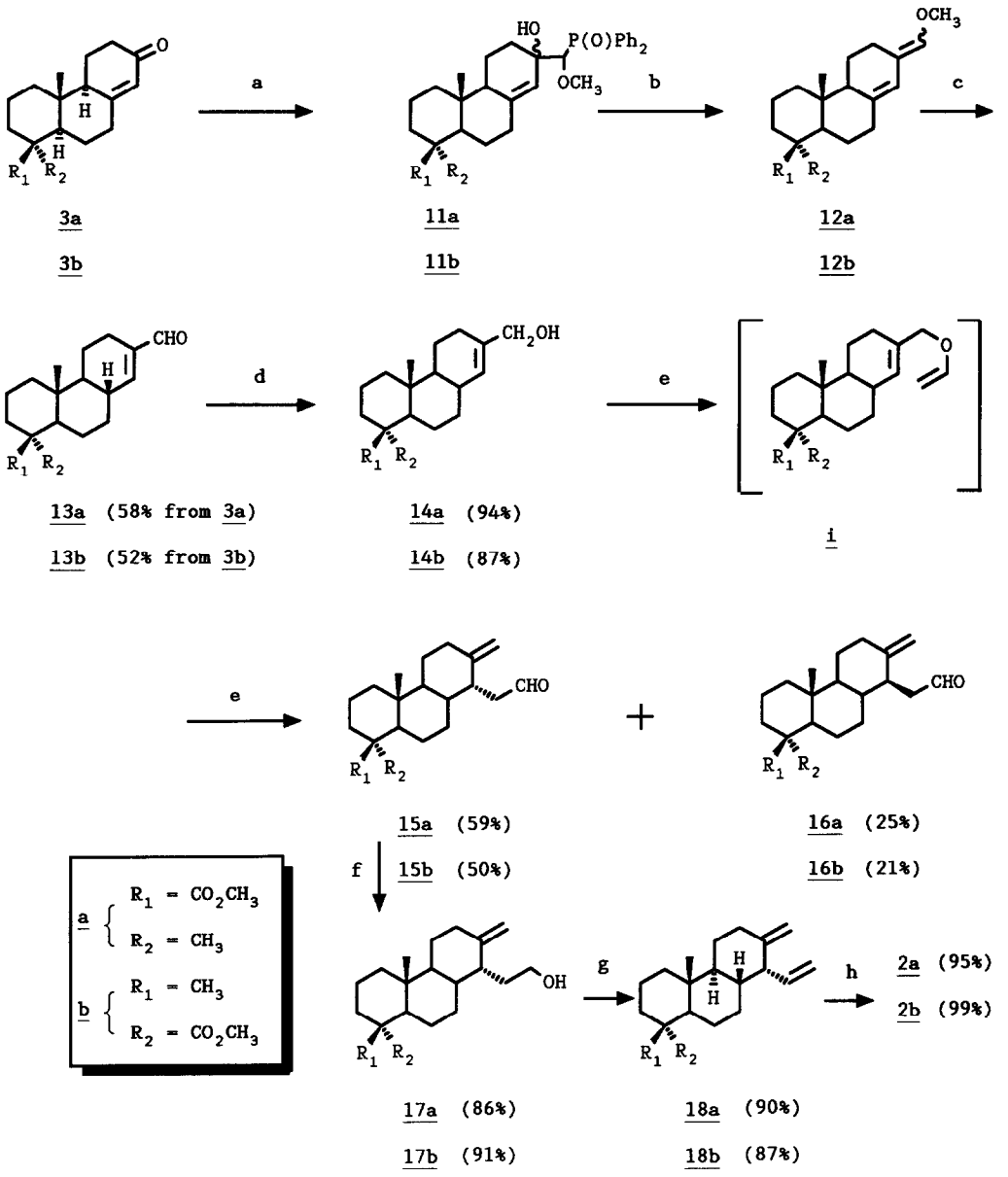
hindered C-4 axial methyl ester group of (**9**) was hydrolyzed with lithium iodide in refluxing collidine[7] to give the acid (**10**) in 95% yield. Finally, Birch reduction of the aromatic ring of (**10**) with lithium in liquid ammonia-THF and *t*-butanol, followed by acid treatment and re-esterification with ethereal diazomethane furnished the α,β-unsaturated enone ester (**3a**) in 74% overall yield (three steps) which was identical in every respect with that prepared early by Cambie from podocarpic acid.[8]



Scheme I. *Reagents and conditions:* (a) DDQ, benzene, ref.; (b) $KMnO_4$, benzene-H_2O, 0°C; (c) MCPBA, CH_2Cl_2, rt; (d) $NaOCH_3$, CH_3OH, rt; (e) i: LiOH, DMF, rt. ii: CH_3I, 0°C to rt; (f) NaI, collidine, ref.; (g) Li, liq. NH_3, THF-*t*-BuOH; (h) HCl, CH_3OH, ref.; (i) CH_2N_2, ether.

With the supply of podocarpenones (**3a**) and (**3b**) in hand, we turned our attention to their transformation into target compounds (**2a**) and (**2b**), respectively. It was envisaged that the required cleistanthane framework would be efficiently and stereoselectively generated by a sequence employing as key transformation a classical Claisen rearrangement[9] of an allyl vinyl ether such as (**i**) (see Scheme II).

This approach, which parallels the preparation of (**2a**) and (**2b**), begins with the one carbon homologation of enones (**3**) into the corresponding α,β-unsaturated aldehydes (**13**).[10] Thus, treatment of (**3a**) and (**3b**) with the lithium derivative of α-methoxymethyldiphenylphosphine oxide[11] at -78°C afforded adducts (**11a**) and (**11b**), respectively, in high yield, together with an small amount of unreacted enone (**3**). Treatment of these adducts with sodium hydride in dimethylformamide at room



Scheme II. *Reagents and conditions:* (a) $Ph_2P(O)CHLiOMe$, THF, -78°C; (b) NaH, DMF, rt; (c) HCO_2H, 0°C; (d) $NaBH_4$, MeOH, 0°C; (e) $Hg(OAc)_2$, $EtOCH=CH_2$, 195°C; (f) NaBH4, MeOH; (g) i: *o*-$NO_2PhSeCN$, Bu_3P, THF, 0°C. ii: H_2O_2-*t*-BuOOH; (h) NaSePh, HMPT, THP, ref.

temperature completed the Horner-Wittig reaction to give vinyl ethers **(12)** [a mixture of the *E*- and *Z*-isomers in a 6:4 ratio, as shown by the integration of the vinyl proton (14-H) at 5.87 ppm (*E*-isomer) and 6.23 ppm (*Z*-isomer) in the ^{1}H NMR spectrum], which although apparently obtained in a pure form (^{1}H NMR and TLC) were isolated in only 60 % yield after silica gel column chromatography of the crude reaction mixture. On account of this chromatographic instability, these vinyl ethers **(12)** were not isolated but hydrolysed directly with aqueous formic acid (see experimental section) to the desired homologous aldehyde **(13)**. In this manner we were able to realize a 50-60% overall yield of α,β-unsaturated aldehydes **(13a)** and **(13b)**. The conditions of this hydrolysis were somewhat critical to ensure a good yield of the α,β-unsaturated aldehyde **(13)** and most standard conditions used to hydrolyse vinyl ethers gave very poor yields of **(13)**, even when chromatographically pure **(12)** was used.

The next step was the reduction of aldehydes **(13a)** and **(13b)** with sodium borohydride in methanol to furnish allylic alcohols **(14a)** (94% yield) and **(14b)** (87% yield), respectively. When these allylic alcohols **(14)** were subjected to equilibration with excess ethyl vinyl ether and *in situ* Claisen rearrangement of the intermediate vinyl ether **(i)**, the aldehydes **(15)** and **(16)** were formed in a ratio of 7:3. These two aldehydes were inseparable by conventional chromatography but they could be easily separated by column chromatography on $AgNO_3$-silica gel or preparative HPLC, and their stereochemistries unambiguosly assigned on the basis of the magnitude of the J-value of the signal due to the 14-H proton. In the case of **(15a)** and **(15b)** the 14β-H signal was observed at 2.80 ppm as a multiplet which collapsed to a doublet with J 3.5-3.9 Hz when the 15-H protons were irradiated; this vicinal coupling constant is consistent with an axial-equatorial orientation of 8α- and 14β-hydrogens that stablishes the α-(axial) orientation of the acetaldehyde residue. Additional evidence confirming these stereochemical assignments was found in the ^{13}C NMR spectra of these compounds; of particular significance is the different shift of C-9 in each pair of C-14 epimers [**(15a)**/**(15b)** *vs* **(16a)**/**(16b)**] which resonates 7.2 ppm upfield in the 14β-H isomers **(15)** compared with the 14α-H isomers **(16)** due to the γ-effect exerted by the axially oriented C-15.

With the desired C-4 epimeric cleistanthane frameworks in hand, the final stage of this work was the conversion of the C-14 acetaldehyde residue to the required ethylene moiety. To this end, aldehydes **(15a)** and **(15b)** were reduced with sodium borohydride to give alcohols **(17a)** (86% yield) and **(17b)** (91% yield), respectively. The C15-C16 double bond was introduced by dehydration of the primary alcohol using Grieco's method.[12] Thus, treatment of **(17a)** and **(17b)** with *o*-nitrophenyl selenocyanate and tri-*n*-butylphosphine in tetrahydrofuran gave the corresponding selenides, which were immediately oxidized to give olefins **(18a)** and **(18b)**, respectively, after elimination of the selenoxide moiety. Some difficulties were encountered in this step. Thus, when the oxidation was effected under standard conditions using an excess of hydrogen peroxide, substantial epoxidation of the exocyclic double bond was observed, while no oxidation was observed when *t*-butylhydroperoxide was used as oxidising agent. This difficulty was overcome by employing an equivalent of hydrogen peroxide and excess *t*-butylhydroperoxide.[13] Under these conditions the desired olefins **(18a)** and **(18b)** were obtained in 90% and 87% yield, respectively.

The spectroscopic data of (**18a**) are in agreement with those reported for the methyl ester of natural auricularic acid. Thus, the synthesis of (**18a**) chemically confirms the structure of auricularic acid and the axial orientation of the carboxyl group at C-4 in this compound.

Although the ^{13}C NMR spectra of (**18a**) and its C-4 epimer (**18b**) are essentially identical (see table II), they differ significantly in the shielding of C-5 and Me-4; these carbons resonate at 6.65 and 11.93 ppm downfield, respectively, in (**18a**) compared with (**18b**), a phenomenon which is characteristic of the different stereochemistry at C-4 in this type of structures.

A significant feature of the ^{1}H NMR spectra of (**18a**) and (**18b**) is their temperature-dependence. Thus, while the expected spectrum is observed for (**18a**) at room temperature (See experimental part), several signals are duplicated at higher temperatures. Specifically, two partly overlapped double double doublets (ddd) centred at 6.01 ppm [(J 16.6, 10.1 and 9.0 Hz) and (J 18.1, 9.1 and 9.0 Hz) can be observed for H-15 at 40°C in the aproximate ratio 85:15, which increases at higher temperature. This observation is consistent with the existence of two rotamers around the C14-C15 bond above room temperature. A similar temperature-dependent phenomenon is observed for (**18b**), which exhibits, even at room temperature, two partly overlapped ddd for H-15 [(J 17.6, 9.4 and 8.7 Hz) and (J 14.7, 12.2 and 8.7 Hz)] with an intensity ratio of *ca.* 85:15, which suggests that in this case the two rotational isomers coexist at lower temperature than in the case of (**18a**). In the case of (**18b**) only one rotamer is observed at temperatures below about 0°C.

Molecular mechanics calculations[14] were performed on (**18a**) and (**18b**) in order to obtain a fairly detailed indication of the structure of both rotamers and the potential energy diagram for their interconversion. The dihedral driver option in PCMODEL was employed, changing systematically the torsional angle H14-C14-C15-H15 in 10° steps.† The graphical representation of the final results is shown in Figure 1. As can be seen, there are two energy barriers to rotation (which can be attributed to the steric interaction of 16-H with 7α- and 12α-hydrogens) and two minimum energy conformations (rotamers) located at H14-C14-C15-H15 dihedral angles of 175° and -39° (See Figure 2). Although the calculated energy difference between both minima [2.65 and 2.55 Kcal/mol for (**18a**) and (**18b**), respectively] is too great to reproduce‡ the experimental populations found by ^{1}H NMR, the results obtained give at least a qualitative idea what the distribution between the two rotamers is and, in agreement with the experimental data, they predict a greater energy difference between the two conformations for (**18a**) than for (**18b**). This small but significant energy difference (about 100 cal/mol) allows to estimate that the rotamer distribution found for (**18b**) at room temperature would be reached by (**18a**) at a temperature *ca.* 12°C higher, a prediction which appears to correlate reasonably well with the experimental data.

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† *The starting geometry for each of these dihedral driver calculations was previously minimized assuming that the A, B, and C rings adopt a chair like conformation. Possible different conformations of the C ring were initially analyzed but they were not considered in the futher calculations, because they lead to geometries higher in energy (ca. 5 Kal/mol).*

‡ *Assuming a Boltzmann distribution without entropy effects.*

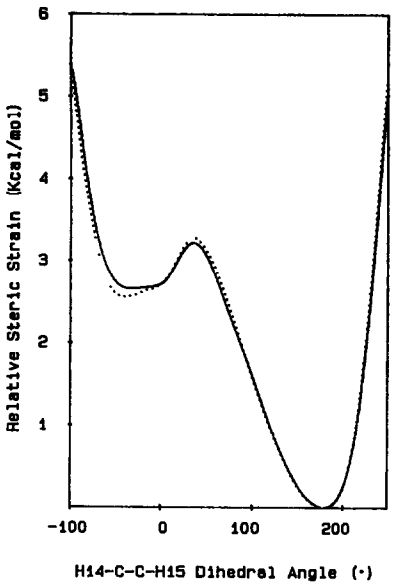

Figure 1. Energy profile for rotation of the 14α-vinyl group in **(18a)** (full line) and its C-4 epimer **(18b)** (dotted line).

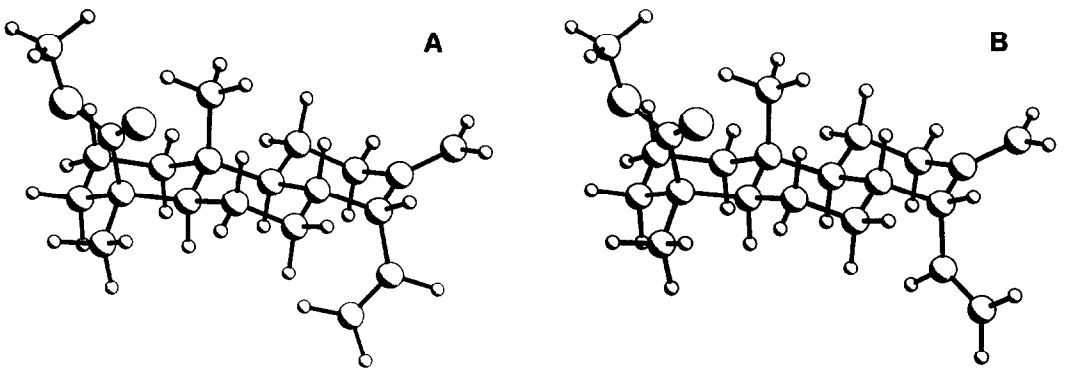

Figure 2. Computer-generated PLUTO representation of minimum energy conformations obtained from force field calculations of **(18a)**, which correspond to H14-C-C-H15 dihedral angles of -39° **(A)** and 175° **(B)**.

Finally, in order to compare the physical data of synthetic **(2a)** with those of the natural auricularic acid, in particular its optical rotation, we proceeded to the hydrolysis of the ester moiety of **(18a)**. The standard conditions used for the cleavage of hindered esters with the phenyl selenide anion were used.[15] Thus, treatment of **(18a)** with sodium phenyl selenide in tetrahydrofuran-hexamethylphosphoramide at reflux produced the acid **(2a)** in 94.5% yield [the C-4 epimeric **(18b)** was hydrolysed in the same manner as **(18a)** in nearly quantitative yield].

The physical and spectroscopic data found for **(2a)** are in agreement with those reported for the natural auricularic acid isolated from *Pogostemon auricularis*. The sole discrepancy was found in the

optical rotation {[α]D -12° for **(2a)** *vs* [α]D +15.2° for natural auricularic acid}. The discrepancy found in the sign of the optical rotation showed that we had synthesized the enantiomer of the natural product. Therefore, the acid **(2a)** and the natural auricularic acid possess antipodal stereochemistry and, consequently, the latter has the (4R, 5S, 8S, 9R, 10S, 14S) absolute configuration. This result is not totally unexpected since cleisthantane diterpenes of both antipodal series are known.[16]

Table I. ^{13}C Chemical shifts (δ) and assignments for compounds 4-10.

	4	**5**	**6**	**7**	**8**	**9**	**10**
C-1	37.67	37.66	37.37	37.49	37.56	37.58	37.26
C-2	19.95	19.96	19.73	19.81	19.90	19.91	19.84
C-3	39.36	39.34	38.97	39.30	39.51	39.50	39.44
C-4	43.93	44.00	43.85	43.85	43.93	43.86	43.83
C-5	52.88	52.85	52.34	52.53	52.90	52.87	52.91
C-6	21.02	21.01	20.67	20.70	20.86	20.91	20.81
C-7	32.07	32.14	31.85	31.86	32.01	32.21	32.13
C-8	134.99	135.10	135.61	136.81	136.85	136.59	136.53
C-9	145.56	142.96	153.48	145.49	140.33	140.40	140.40
C-10	38.12	38.31	38.77	38.17	37.83	37.81	38.02
C-11	125.45	125.49	125.62	126.65	126.83	126.62	126.53
C-12	123.98	123.07	125.82	118.80	113.25	112.17	112.22
C-13	145.41	138.20	134.32	148.01	153.08	156.95	157.03
C-14	126.76	126.01	129.18	121.12	114.74	112.90	113.01
C-15	33.39	147.44					
C-16	23.92	111.62					
C-17	23.92	21.73					
C-18	28.51	28.53	28.33	28.40	28.49	28.46	28.63
C-19	177.85	177.87	177.48	177.63	178.35	177.82	184.45
C-20	22.95	22.87	22.63	22.93	23.00	22.95	23.11
$CO_2\underline{C}H_3$	51.13	51.22	51.15	51.12	51.38	51.17	
$CO\underline{C}H_3$			26.36	21.00			
CO			197.81	169.53			
OCH_3						55.00	55.01

Table II. ^{13}C Chemical shifts (δ) for compounds 2a, 3a, 13a-18a and their related C-4 epimers.

	2a	2b	3a	3b	13a	13b	14a	14b	15a	15b	16a	16b	17a	17b	18a	18b
C-1	37.91	38.44	37.76	37.95	38.08	37.45	38.30	37.55	38.13	38.49	38.06	38.22	38.11	38.59	38.20	38.54
C-2	19.41	17.98	19.36	17.65	19.28	17.80	19.42	17.90	19.47	17.96	19.50	18.08	19.44	18.01	19.50	18.06
C-3	39.64	36.94	39.31	36.52	38.62	36.84	38.81	36.91	39.70	36.87	39.35	36.87	39.71	36.87	39.69	36.94
C-4	43.87	47.35	43.95	46.94	43.86	47.35	43.99	47.51	43.97	47.54	43.87	47.48	43.90	47.61	43.96	47.65
C-5	56.22	49.36	55.02	47.85	55.93	49.58	56.37	49.91	56.32	49.60	55.85	49.28	56.39	49.66	56.22	49.57
C-6	23.13	24.16	23.59	23.78	23.65	24.49	23.72	24.55	23.26	24.08	23.23	24.13	23.42	24.30	23.26	24.17
C-7	32.61	31.60	36.30	34.84	33.34	32.48	34.70	33.80	32.34	31.32	33.29	32.49	31.97	30.97	32.64	31.65
C-8	40.82	40.60	164.75	164.40	37.44	37.33	35.79	35.62	40.66	40.44	42.56	42.46	41.20	41.05	40.85	40.64
C-9	48.73	49.11	50.44	51.28	52.28	52.86	52.94	53.44	48.05	48.71	55.26	55.87	47.88	48.63	48.70	49.39
C-10	37.66	36.40	39.86	38.06	36.97	36.04	36.93	35.95	37.52	36.56	37.49	36.53	37.44	36.54	37.44	36.56
C-11	27.31	26.72	20.52	20.07	20.76	20.28	21.79	21.22	27.04	26.44	27.45	27.02	27.38	26.84	27.30	26.76
C-12	31.45	31.22	36.52	36.39	22.57	22.36	27.05	26.76	30.64	30.38	36.81	36.71	30.59	30.41	31.45	31.26
C-13	152.24	152.36	199.69	199.20	140.16	140.14	136.45	136.38	150.60	150.56	151.01	151.04	152.63	152.76	152.26	152.40
C-14	54.70	54.66	125.50	125.80	155.93	155.56	128.53	128.07	43.27	43.02	43.29	44.01	45.72	45.66	54.71	54.67
C-15	137.69	137.69							41.74	41.69	43.80	43.34	28.86	28.99	137.70	137.77
C-16	115.74	115.91							202.99	202.71	203.25	203.26	61.92	61.99	115.71	115.86
C-17	106.45	106.36							108.03	108.03	105.67	105.84	107.03	107.08	106.40	106.34
C-18	29.01	185.67	28.78	178.50	28.56	178.86	28.67	179.27	28.86	179.29	28.69	179.27	28.86	179.44	28.86	179.44
C-19	184.28	16.59	177.28	16.73	177.56	16.38	177.96	16.42	177.91	16.91	177.80	16.68	178.01	16.96	178.02	16.93
C-20	12.82	14.15	14.05	15.24	12.13	14.07	12.38	14.30	12.88	14.37	12.70	14.46	12.85	14.40	12.68	14.20
$CO_2\underline{C}H_3$			51.27	51.74	51.04	51.67	51.06	51.69	51.15	51.85	51.09	51.86	51.06	51.83	51.10	51.85
CHO					194.12	193.98										
CH_2OH							66.96	66.75								

EXPERIMENTAL PART

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were recorded in Perkin-Elmer 281 spectrometer. ^{1}H and ^{13}C NMR spectra were measured at 200.13 and 50.32 MHz, respectively, at room temperature using a Bruker AC-200 spectrometer; the carbon type (methine, methylene, methyl, or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a HP 5938A instrument and microanalyses were performed by Servicio de Semimicroanálisis del CSIC (Barcelona). Optical rotations were measured with a Schmidt + Haensch Polartronic-D polarimeter. Gas chromatography was carried out on a Konick KNK-3000, using helium as carrier gas (1/8-in. diameter, 2 m column packed with 5% EGA on Chromosorb W AW; 250°C injector and detector temperature; flow rate 30 ml/min). Chromatography refers to flash chromatography and was performed on Merck silica gel 60 (230-400 mesh). Commercially available chemicals were used as obtained without futher purification, except for solvents, which were purified and dried before use by standard methods. All reactions involving reagents or other moisture-sensitive reactants were executed under an atmosphere of dry argon using oven-dried glassware. The tricyclic enone **(3b)** was obtained from abietic acid or commercial colophony following the procedure previously described by us.[3]

Reaction of (+)-Methyl callistrisate (4) with DDQ. A stirred solution of **(4)** (6.0 g, 19.1 mmol) and DDQ (4.8 g, 20.9 mmol) in dry benzene (420 ml) was heated under reflux for 135 min. The reaction mixture was cooled in an ice-water bath, diluted with hexane (420 ml) and filtered to recover the 2,3-dichloro-5,6-dicyanohydroquinone formed. The filtrate was washed with 10% aqueous NaOH solution and brine, dried (Na_2SO_4), and concentrated to give an oily residue, which was purified by flash chromatography with hexane-ethyl acetate (9:1) as eluant to give a mixture of unreacted methyl callistrisate **(4)** and *methyl abieta-8,11,13,15-tetraen-19-oate* **(5)** (4.74 g, 79%). GLC analysis (220°C column temperature) showed two major peaks with retention times of 5.70 and 7.20 min, corresponding to **(4)** (41%) and **(5)** (57%), respectively. An analytical sample of **(5)** was obtained from the above mixture by preparative HPLC on a μ-Porasil column using hexane-ethyl acetate (95:5) as eluant. Compound **(5)** was a solid, m.p. 118-120°C (from MeOH); $[\alpha]_D$ +139° (c 2.6, $CHCl_3$); ν_{max} (film KBr) 3070, 3010, 1710, 1620, 885, 875, and 830 cm^{-1}; δ_H ($CDCl_3$) 7.1-7.3 (3H, m, Ar protons), 5.31 (1H, s, H-16), 5.00 (1H, s, H-16'), 3.65 (3H, s, CO_2CH_3), 2.82 (2H, m, H-7α,β), 1.52 (1H, dd, J 12 and 2 Hz, H-5α), 1.26 (3H, s, 4-CH_3), 1.02 (3H, s, 10-CH_3); δ_C see table I.

Methyl (+)-13-Acetylpodocarpa-8,11,13-trien-19-oate (6). To a solution of the mixture of **(4)** and **(5)** [5.112 g, containing 2.91 g of **(5)**, 9.34 mmol] in benzene (106 ml) was added methyltrioctylammoniumchloride (527 mg of an 88% ethanolic solution, 1.05 mmol) in water (71 ml). The mixture was immersed in an ice bath and stirred vigorously (mechanical stirring). Solid $KMnO_4$ (4.277 g, 27 mmol) was added in small portions over 3 h. After stirring for about 1.5 h at 0°C, concentrated HCl was added followed by $NaHSO_3$ until decolourization. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated to give an oily residue, which was purified by column chromatography on silica gel (hexane-ethyl acetate 9:1 to 7:3) to give unreacted **(4)** (2.20 g) and **(6)** [2.04 g, 34% from **(4)**; 53% considering recovered **(4)**] as a solid, m.p. 103-104°C

(from hexane-ether) [lit.,[8] 102-103°C]; $[\alpha]_D$ +176° (c 0.8, $CHCl_3$); ν_{max} (KBr) 1710, 1670, 1600, 1560 and 840 cm^{-1}; δ_H ($CDCl_3$) 7.68 (1H, dd, J 8.2 and 1.8, H-12), 7.61 (1H, d, J 1.8 Hz, H-14), 7.32 (1H, d, J 8.2 Hz, H-11), 3.65 (3H, s, CO_2CH_3), 2.97 (1H, ddd, J 17, 6 and 2 Hz, H-7β), 2.79 (1H, ddd, J 17, 12 and 6 Hz, H-7α), 2.54 (3H, s, CH_3CO), 1.52 (1H, dd, J 12 and 2 Hz, H-5α), 1.27 (3H, s, 4-CH_3), 1.02 (3H, s, 10-CH_3); δ_C see table I; m/z (relative intensity) 315 (M^+ + 1, 5), 314 (M^+, 22), 299 (18), 283 (3), 241 (10), 240 (33), 239 (100), 197 (10), 173 (11) and 128 (12); found: C, 76.15; H, 8.42%. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%.

Methyl (+)-13-Acetoxypodocarpa-8,11,13-trien-19-oate (7). A mixture of **(6)** (4.00 g, 12.7 mmol) and m-chloroperbenzoic acid (MCPBA) (5.17 g of 85% purity, 25.5 mmol) in $CHCl_3$ (46 ml) was stirred in the dark at 0°C for 3 days. The solid formed was filtered off. The filtrate was diluted with ether and was washed successively with saturated aqueous $NaHSO_3$, 10% aqueous $NaHCO_3$, and brine, and the organic layer was dried and concentrated to yield a yellowish residue which was chromatographed on silica gel (hexane-ethyl acetate 9:1 as eluant) to give **(7)** (3.916 g, 93%) as a solid, m.p. 140-141°C (from hexane-ethyl acetate); $[\alpha]_D$ +125° (c 1.3, $CHCl_3$); ν_{max} (KBr) 1750, 1710, 1600, 1210 and 815 cm^{-1}; δ_H ($CDCl_3$) 7.22 (1H, d, J 8.7 Hz, H-11), 6.80 (1H, dd, J 8.7 and 2.6 Hz, H-12), 6.72 (1H, d, J 2.6 Hz, H-14), 3.64 (3H, s, CO_2CH_3), 2.80 (m, 2H, H-7α,β), 2.25 (3H, s, $OCOCH_3$), 1.51 (1H, dd, J 12 and 2 Hz, H-5α), 1.25 (3H, s, 4-CH_3), 1.00 (3H, s, 10-CH_3); δ_C see table I; m/z (relative intensity) 331 (M^+ + 1, 4), 330 (M^+, 19), 315 (7), 289 (11), 288 (59), 273 (83), 241 (10), 213 (100), 175 (14) and 147 (14); found: C, 72.67; H, 7.98%. $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%.

Methyl (+)-13-Hydroxypodocarpa-8,11,13-trien-19-oate (8). The acetate **(7)** (3.490 g, 10.57 mmol) was added with stirring to 0.85M sodium methoxide in methanol (36 ml) at 0°C. After stirring for 30 min at room temperature the mixture was poured into 10% hydrochloric acid and extracted with dichloromethane. The organic phase was washed with water and brine. Drying (Na_2SO_4) and evaporation of the solvent afforded **(8)** (3.046 g, 100%) which was used in the next step without further purification. M.p. 156-157°C (from hexane-ethyl acetate) [lit.,[8] 145-147°C]; $[\alpha]_D$ +130° (c 1.5, $CHCl_3$); ν_{max} (KBr) 3400, 1690, 1600, 1500, 1240, 1225, 1190 and 1150 cm^{-1}; δ_H ($CDCl_3$) 7.10 (1H, d, J 8.6 Hz, H-11), 6.60 (1H, dd, J 8.6 and 2.8 Hz, H-12), 6.48 (1H, d, J 2.8 Hz, H-14), 4.60 (1H, br s, OH), 3.64 (3H, s, CO_2CH_3), 2.78 (2H, m, H-7α,β), 1.50 (1H, dd, J 12 and 2 Hz, H-5α), 1.25 (3H, s, 4-CH_3), 0.98 (3H, s, 10-CH_3); δ_C see table I; m/z (relative intensity) 289 (M^+ + 1, 5), 288 (M^+, 29), 274 (12), 273 (64), 213 (100), 185 (4) and 157 (16); found: C, 74.55; H, 8.34%. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%.

Methyl (+)-13-Methoxypodocarpa-8,11,13-trien-19-oate (9). A solution of phenol **(8)** (3.364 g, 11.7 mmol) and powdered lithium hydroxide monohydrate (765 mg, 18.21 mmol) in dimethylformamide (13.5 ml) was stirred for 3 h at 50°C and then cooled in an ice-water bath. After addition of dimethyl sulfate (3.18 ml) stirring was continued for 30 min at room temperature. The mixture was poured into water and extracted with hexane. The combined extracts were washed successively with 5% HCl solution, 10% $NaHCO_3$ solution, and brine. Removal of the solvent after drying gave a white residue that was purified by chromatography (hexane-ethyl acetate 9:1, as eluant) to give **(9)** (3.347 g, 95%) as a solid; m.p. 103-103.5°C (from MeOH) [lit.,[17] 105-107°C]; $[\alpha]_D$ +227° (c 0.7, $CHCl_3$); ν_{max}

(KBr) 3040, 1715, 1600, 1570 and 800 cm^{-1}; δ_H ($CDCl_3$) 7.17 (1H, d. J 8.7 Hz, H-11), 6.69 (1H, dd, J 8.7 and 2.8 Hz, H-12), 6.54 (1H, d, J 2.8 Hz, H-14), 3.74 (3H, s, OCH_3), 3.64 (3H, s, CO_2CH_3), 2.80 (2H, m, H-7α,β), 1.51 (1H, dd, J 12 and 2 Hz, H-5α), 1.25 (3H, s, 4-CH_3), 0.99 (3H, s, 10-CH_3); δ_C see table I; m/z (relative intensity) 303 ($M^+ + 1$, 8), 302 (M^+, 41), 288 (15), 287 (95), 255 (5), 228 (15) and 227 (100); found: C, 75.21; H, 8.67%. $C_{19}H_{26}O_3$ requires C, 75.46; H, 8.67%.

(+)-13-Methoxypodocarpa-8,11,13-trien-19-oic acid (10). A solution of **(9)** (2.318 g, 7.7 mmol) in anhydrous 2,4,6-collidine (37 ml) containing LiI (9.536 g, 56.1 mmol, of LiI trihydrate previously flame-dried at 0.1 mmHg) was refluxed under argon for 3 h. The cooled brown solution was poured into 6N hydrochloric acid and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated to give a brown residue which was chromatographed (hexane-ethyl acetate 8:2, as eluant) to give the acid **(10)** (2.100 g, 95%) as a white solid; m.p. 129-130°C (from MeOH); $[\alpha]_D$ +145° (c 0.9, $CHCl_3$); ν_{max} (KBr) 2300-2500, 1690, 1605, 1500, 1245 and 1030 cm^{-1}; δ_H ($CDCl_3$) 7.14 (1H, d, J 8.8 Hz, H-11), 6.68 (1H, dd, J 8.8 and 2.6 Hz, H-12), 6.53 (1H, d, J 2.6 Hz, H-14), 3.74 (3H, s, OCH_3), 2.80 (m, 2H, H-7α,β), 1.32 (3H, s, 4-CH_3), 1.08 (3H, s, 10-CH_3); δ_C see table I; m/z (relative intensity) 289 ($M^+ + 1$, 6), 288 (M^+, 32), 274 (16), 273 (100), 227 (47), 187 (5) and 171 (18).

Methyl (+)-13-Oxopodocarp-8(14)-en-19-oate (3a). The acid **(10)** (2.486 g, 8.6 mmol) in a mixture of tetrahydrofuran (10.5 ml) and t-butanol (10.5 ml) was added to liquid ammonia (30 ml). Lithium (1.205 g, 172 mmol) was added during 30 min to the reaction mixture at -78C. The blue mixture was stirred at the same temperature for 6 h, isoprene (8 ml) and solid NH_4Cl were successivaly added and the ammonia was evaporated. The residue was poured into 10% hydrochloric acid and extracted with dichloromethane. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated to give a brown oil (2.418 g) which was dissolved in MeOH (50 ml) and concentrated hydrochloric acid (20 ml). The mixture was refluxed for 30 min, poored into water, and extracted with dichloromethane. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue (2.37 g) was dissolved in ether and treated with ethereal diazomethane (50 ml). After 15 min the solution was evaporated to dryness and the residue was chromatographed (hexane-ethyl acetate 8:2, as eluant) to afford the enone **(3a)** [1.855 g, 74% from **(10)**] as a solid; m.p. 119-120°C (from hexane-ethyl acetate) [lit.,[18] 116-117°C; lit.,[8] 114.5-116°C]; $[\alpha]_D$ +49° (c 1.5, $CHCl_3$) [lit.,[8] +49.5°]; ν_{max} (KBr) 3010, 1705, 1670, 1610 and 850 cm^{-1}; δ_H ($CDCl_3$) 5.86 (1H, br s, H-14), 3.62 (3H, s, CO_2CH_3), 2.53 (1H, ddd, J 15, 4 and 2 Hz, H-12β), 1.37 (1H, dd, J 12 and 3 Hz, H-5α), 1.22 (3H, s, 4-CH_3), 0.62 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 291 ($M^+ + 1$, 8), 290 (M^+, 31), 231 (14), 230 (6), 215 (6), 181 (27), 121 (78), 110 (100) and 91 (29); found: C, 74.40; H, 9.22%. $C_{18}H_{26}O_3$ requires C, 74.45; H, 9.02%.

Methyl (-)-13-Formylpodocarp-13-en-19-oate (13a). To a stirred slurry of methoxymethyl-diphenylphosphine oxide (1.83 g, 7.4 mmol) in THF (10 ml) at -20°C was added, dropwise via syringe, lithium diisopropylamide (LDA) [from diisopropylamine (1.08 ml, 7.1 mmol) and butyl-lithium (4.01 ml of a 1.6M solution in hexane, 6.4 mmol) in THF (10 ml)]. The mixture was stirred at 0°C for 15 min and then cooled to -78°C and the ketone **(3a)** (1.475 g, 5.1 mmol) in THF (7.5 ml) was added dropwise. After 1.45 h at -78°C, the reaction was quenched by the addition of saturated ammonium

chloride solution and the product was isolated by extraction with dichloromethane. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by chromatography on silica gel using hexane-ethyl acetate (3:7) as eluant to give unreacted **(3a)** (133 mg, 9%) and *Methyl 13-Hydroxy-13-(1-diphenylphosphinoyl-1-methoxymethyl)podocarp-13-en-19-oate* **(11a)** (2.423 g, 89%) as a white foam.

To a stirred slurry of prewashed sodium hydride (500 mg, 55% dispersion in oil, 11.5 mmol) in DMF (5 ml) at room temperature was added, dropwise via syringe, alcohol **(11a)** (2.423 g, 4.5 mmol) in DMF (15 ml). After 1 h the reaction was cooled at 0°C and was quenched by cautious addition of water (4.1 ml). After hydrogen evolution had ceased, formic acid (37 ml) was added and the mixture was stirred for 3 days at 0°C. Water was added and the aqueous layer extracted with benzene. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated. Chromatography of the residue (hexane-ethyl acetate 8:2 as eluant) afforded the aldehyde **(13a)** [811 mg, 59% from **(11a)**] as a solid; m.p. 103-104°C (from hexane-ethyl acetate); $[\alpha]_D$ -0.5° (c 1.2, $CHCl_3$); ν_{max} (KBr) 3010, 1715, 1665, 1635, 1230, 1190 and 1160 cm^{-1}; δ_H ($CDCl_3$) 9.38 (1H, s, CHO), 6.46 (1H, br s, H-14), 3.62 (3H, s, CO_2CH_3), 1.15 (3H, s, 4-CH_3), 0.65 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 305 ($M^+ + 1$, 4), 304 (M^+, 24), 245 (9), 244 (10), 182 (8), 161 (9), 136 (100) and 123 (62); found: C, 74.94; H, 9.30%. $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27%.

Methyl (+)-13-Formylpodocarp-13-en-18-oate (13b). Enone **(3b)** (1.49 g, 5.14 mmol) was converted into aldehyde **(13b)** (812 mg, 52%) in the same way as described above for **(13a)**; An amorphous solid; $[\alpha]_D$ +2.7° (c 4.4, $CHCl_3$); ν_{max} (KBr) 3015, 1725, 1680,1665, 1640, 1385 and 1250 cm^{-1}; δ_H ($CDCl_3$) 9.39 (1H, s, CHO), 6.46 (1H, br s, H-14), 3.63 (3H, s, CO_2CH_3), 1.17 (3H, s, 4-CH_3), 0.87 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 305 ($M^+ + 1$, 8), 304 (M^+, 32), 275 (1), 260 (8), 245 (18), 216 (2.5) and 123 (100).

Methyl (+)-13-Hydroxymethylpodocarp-13-en-19-oate (14a). Sodium borohydride (311 mg, 8.2 mmol) was added to a solution of **(13a)** (640 mg, 2.1 mmol) in MeOH (19 ml) at 0°C. The solution was stirred for 30 min at 0°C, poured into water and extracted with dichloromethane. The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane-ethyl acetate 6:4, as eluant) to give the alcohol **(14a)** (605 mg, 94%) as an oil that solidified on standing; m.p. 64-65°C (from hexane-ethyl acetate); $[\alpha]_D$ +22° (c 0.8, $CHCl_3$); ν_{max} (KBr) 3100-3600, 1720, 1230, 1165 and 1150 cm^{-1}; δ_H ($CDCl_3$) 5.38 (1H, br s, H-14), 3.92 and 3.99 (1H each, two d, J 13 Hz, H-15), 3.61 (3H, s, CO_2CH_3), 1.14 (3H, s, 4-CH_3), 0.62 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 307 ($M^+ + 1$, 6), 306 (M^+, 28), 291 (11), 247 (35), 215 (15), 181 (20), 180 (40), 121 (100) and 91 (34); found: C, 74.22; H, 9.86%. $C_{19}H_{30}O_3$ requires C, 74.47; H, 9.87%.

Methyl (+)-13-Hydroxymethylpodocarp-13-en-18-oate (14b). Aldehyde **(13b)** (700 mg, 2.30 mmol) was reduced with sodium borohydride in the same way as described for **(13a)**. The alcohol **(14b)** (613 mg, 87%) was obtained as an oil; $[\alpha]_D$ +14° (c 3.3, $CHCl_3$); ν_{max} (film) 3600-3000, 1715 and 1235 cm^{-1}; δ_H ($CDCl_3$) 5.34 (1H, br s, H-14), 3.90 and 4.00 (1H each, two d, J 13 Hz, H-15), 3.62

(3H, s, CO_2CH_3), 1.15 (3H, s, 4-CH_3), 0.84 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 307 ($M^+ + 1$, 3), 306 (M^+, 14), 291 (17), 247 (17), 215 (14), 181 (13), 180 (12) and 121 (100).

Methyl (+)-16-Oxo-5α,14β-cleistanth-13(17)-en-19-oate (15a) and 14α-Epimer (16a). A sealed Craig tube containing alcohol **(14a)** (100 mg, 0.33 mmol), mercuric acetate (freshly recrystallized from absolute ethanol in the presence of a catalytic amount of acetic acid; 6 mg, 0.019 mmol), and ethyl vinyl ether (distilled from sodium before use; 1.3 ml) under argon was placed in an oil bath at 195°C, and the temperature maintained between 190-200°C for 30 min. The tube was cooled, the solvent was evaporated and the residue was chromatographed on silica gel with hexane-ethyl acetate (7:3) as eluant to give a mixture of the aldehyde **(15a)** and its 14α-epimer **(16a)** (101 mg, 93%) as a colourless oil. The mixture of the two isomeric aldehydes was separated by column chromatography on 25% $AgNO_3$-silica gel with hexane-ethyl acetate 98:2 as eluant:

Aldehyde **(15a)** (64 mg, 59%; less mobile isomer); an oil; $[\alpha]_D$ +13° (c 0.4, $CHCl_3$); ν_{max} (film) 3060, 2800, 2710, 1715, 1635, 1155 and 890 cm^{-1}; δ_H ($CDCl_3$) 9.60 (1H, dd, J 3.5 and 1.9 Hz, CHO), 4.66 (1H, br s, H-17), 4.61 (1H, m, H-17'), 3.60 (3H, s, CO_2CH_3), 2.82 (1H, m, H-14), 2.49 (1H, ddd, J 15.5, 5.4 and 1.9 Hz, H-15), 2.30 (1H, ddd, J 15.5, 9.7 and 3.5, H-15'), 1.15 (3H, s, 4-CH_3), 0.59 (3H, s, 10-CH_3); δ_C see table **II**; m/z (relative intensity) 333 ($M^+ + 1$, 3), 332 (M^+, 14), 314 (10), 290 (56), 288 (39), 273 (19), 272 (28), 256 (28), 180 (48), 121 (100) and 91 (74); found: C, 75.61; H, 9.83%. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%.

Aldehyde **(16a)** (26.8 mg, 25%; more mobile isomer); m.p. 117-118°C (from hexane-ether); $[\alpha]_D$ +21° (c 1.1, $CHCl_3$); ν_{max} (KBr) 3080, 2715, 1720, 1645, 1160 and 895 cm^{-1}; δ_H ($CDCl_3$) 9.72 (1H, dd, J 2.3 and 1.8, CHO), 4.70 (1H, br s, H-17), 4.39 (1H, br s, H-17'), 3.60 (3H, s, CO_2CH_3), 2.63 (1H, ddd, J 17, 5.1 and 1.8 Hz, H-15), 2.50 (1H, ddd, J 17, 7.7 and 2.3 Hz, H-15'), 1.15 (3H, s, 4-CH_3), 0.59 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 333 ($M^+ + 1$, 4), 332 (M^+, 15), 314 (12), 290 (23), 288 (31), 273 (20), 272 (36), 256 (22), 180 (35), 121 (100) and 91 (70); found: C, 75.63; H, 9.91%. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%.

Methyl (-)-16-Oxo-5α,14β-cleistanth-13(17)-en-18-oate (15b) and 14α-Epimer (16b). In almost the same manner as above, Claisen rearrangement of the allyl vinyl ether derived from **(14b)** (100 mg, 0.33 mmol) afforded a mixture of aldehydes **(15b)** and **(16b)** (92 mg, 85 %) which were separated by preparative HPLC on a μ-Porasil column, with hexane-ethyl acetate (9:1) as eluant, to give pure 14β-isomer **(15b)** (54 mg, 50%) and 14α-isomer **(16b)** (23 mg, 21%).

Aldehyde **(15b)**: an oil; $[\alpha]_D$ -24° (c 3.5, $CHCl_3$); ν_{max} (film) 3070, 2720, 1730, 1720, 1650 and 900 cm^{-1}; δ_H ($CDCl_3$) 9.58 (1H, dd, J 3.5 and 1.7 Hz, CHO), 4.66 (1H, m, H-17), 4.61 (1H, m, H-17'), 3.63 (3H, s, CO_2CH_3), 2.80 (1H, m, H-14β), 2.52 (1H, ddd, 15.6, 5.3 and 1.7 Hz, H-15), 2.32 (1H, ddd, J 15.6, 9.7 and 3.5 Hz, H-15'), 1.16 (3H, s, 4-CH_3), 0.82 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 333 ($M^+ + 1$, 2), 332 (M^+, 7), 290 (23), 231 (13), 159 (33), 121 (100).

Aldehyde **(16b)**: an oil; $[\alpha]_D$ -12° (c 1.5, $CHCl_3$); ν_{max} (film) 3080, 2710, 1725, 1650 and 900 cm^{-1}; δ_H ($CDCl_3$) 9.69 (1H, dd, J 2.8 and 1.7 Hz, CHO), 4.71 (1H, br s, H-17), 4.40 (1H, br s, H-17'), 3.63 (3H, s, CO_2CH_3), 2.48 (1H, ddd, J 16.5, 7.5 and 2.8 Hz, H-15), 2.59 (1H, ddd, J 16.5, 5.6 and 1.7 Hz, H-15'), 1.14 (3H, s, 4-CH_3), 0.80 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 333 ($M^+ + 1$, 2), 332 (M^+, 7), 288 (10), 231 (8), 159 (25), 121 (96), 91 (64), 79 (65), 55 (82) and 41 (100).

Methyl (+)-16-Hydroxy-5α,14β-cleistanth-13(17)-en-19-oate (17a). This compound was obtained in the same way that compound (**14a**), by treatment for 45 min of aldehyde (**15a**) (195 mg, 0.59 mmol) in MeOH (12.5 ml) with sodium borohydride (123 mg, 3.2 mmol). An oil (169 mg, 86%); $[\alpha]_D$ +19° (c 0.4, $CHCl_3$); ν_{max} (film) 3100-3600, 3050, 1720, 1640, 1150 and 880 cm^{-1}; δ_H ($CDCl_3$) 4.58 (2H, br s, H-17), 3,58 (3H, s, CO_2CH_3), 3.50 (2H, m, H-16), 1.13 (3H, s, 4-CH_3), 0.56 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 335 (M^+ + 1, 1), 334 (M^+, 4), 319 (3), 290 (30), 275 (10), 231 (11), 215 (4), 180 (36) and 121 (100); found: C, 75.52; H, 10.10%. $C_{21}H_{34}O_3$ requires C, 75.41; H, 10.25%.

Methyl (-)-16-Hydroxy-5α,14β-cleistanth-13(17)-en-18-oate (17b). In the same manner as above, (**15b**) (100 mg, 0.30 mmol) was converted to (**17b**) (92 mg, 91%); $[\alpha]_D$ -24° (c 2.5, $CHCl_3$); ν_{max} (film) 3650-3000, 3070, 1725, 1650 and 895 cm^{-1}; δ_H ($CDCl_3$) 4.61 (2H, br s, H-17), 3.64 (3H, s, CO_2CH_3), 3.55 (2H, m, H-16), 1.16 (3H, s, 4-CH_3), 0.81 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 335 (M^+ + 1, 0.5), 334 (M^+, 2), 290 (21), 275 (8), 231 (14), 180 (29), 121 (100) and 91 (56).

Methyl (-)-5α,14β-Cleistanth-13(17),15-dien-19-oate (18a). To a stirred and cooled solution of (**17a**) (70.5 mg, 0.21 mmol) and *o*-nitrophenyl selenocyanate (190 mg ,0.84 mmol)[12] in THF (37 ml) was added dropwise tri-*n*-butylphosphine (208 μl, 0.84 mmol) at 0°C. The mixture was stirred for 30 min at 0°C and *t*-butylhydroperoxide (80%, 0.528 ml, 4.2 mmol, 20 equiv) was added followed by 30% H_2O_2 (24 μl, 0.21 mmol). After stirring for 1 h at room temperature, the mixture was poured into saturated $NaHCO_3$ solution and extracted with ether. The ethereal layer was washed with 5% $Na_2S_2O_3$ solution, 10% Na_2CO_3 solution and brine, dried (Na_2SO_4) and concentrated. The residual brown oil was chromatographed on silica gel with hexane-ethyl acetate (95:5) as eluant to give *(-)-methyl auricularate* (**18a**) (60 mg, 90%); $[\alpha]_D$ -7° (c 0.4, $CHCl_3$); ν_{max} (film) 3060, 1720, 1645, 1625, 1150, 905 and 880 cm^{-1}; δ_H ($CDCl_3$) 6.01 (1H, ddd, J 16.7, 10.1 and 9.2 Hz, H-15), 5.00 (1H, dd, J 16.7 and 2.2 Hz, H-16), 4.98 (1H, dd, J 10.1 and 2.2 Hz, H-16'), 4.62 (1H, d, J 2.6 Hz, H-17), 4.53 (1H, m, H-17'), 3.60 (3H, s, CO_2CH_3), 2.80 (1H, dd, J 9.2 and 4.3 Hz, H-14β), 1.14 (3H, s, 4-CH_3), 0.59 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 317 (M^+ + 1, 6), 316 (M^+, 25), 301 (8), 257 (18), 241 (12), 148 (26), 121 (45) and 83 (100); found: C, 79.42; H, 10.35%. $C_{21}H_{32}O_2$ requires C, 79.70; H, 10.19%.

Methyl (-)-5α,14β-Cleistanth-13(17),15-dien-18-oate (18b). In almost the same manner as above, (**17b**) (60 mg, 0.18 mmol) was converted to (**18b**) (49 mg, 87%); $[\alpha]_D$ -52° (c 1.5, $CHCl_3$); ν_{max} (film) 3070, 1730, 1650, 1635, 895 and 920 cm^{-1}; δ_H ($CDCl_3$, -20°C) 6.02 (1H, ddd, J 16.3, 9.8 and 9.0 Hz, H-15), 5.00 (1H, dd, J 16.3 and 1.8 Hz, H-16), 4.99 (1H, dd, J 9.8 and 1.8 Hz, H-16'), 4.62 (1H, d, J 2.2 Hz, H-17), 4.53 (1H, m, H-17'), 3.62 (3H, s, CO_2CH_3), 2.78 (1H, dd, J 9.0 and 4.3 Hz, H-14β), 2.16 (2H, m, H-12), 1.12 (3H, s, 4-CH_3), 0.78 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 317 (M^+ + 1, 6), 316 (M^+, 26), 301 (6), 257 (21), 241 (28), 187 (9), 161 (22), 121 (100) and 73 (93).

(-)-5α,14β-Cleistanth-13(17),15-dien-19-oic acid (2a). A mixture of diphenyl diselenide (74 mg, 0.24 mmol), sodium (11 mg, 0.48 mmol) and THF (0.5 ml) was sonicated at 50°C until all the sodium had disappeared (*ca.* 4 h). The yellowish suspension obtained was cooled and HMPA (0.25 ml) was added followed by a solution of (**18a**) (30 mg, 0.1 mmol) in THF (0.5 ml). The reaction mixture was then heated under reflux overnight, poured into 5% hydrochloric acid and extracted with dichloromethane. The organic layer was washed with water and brine, dried (Na_2SO_4) and

concentrated to give a reddish oil which was chromatographed on silica gel. Elution with hexane-ethyl acetate (8:2) gave *(-)-auricularic acid* (**2a**) (27.1 mg, 94.5%) as a white solid; m.p. 214-216°C (from MeOH) [lit.,[1g] 220°C]; $[\alpha]_D$ -12° (c , 0.2, $CHCl_3$) [lit.,[1g] +15.2°]; ν_{max} (KBr) 3600-2200, 3070, 3060, 3010, 1680, 1645, 1630, 1265, 910 and 880 cm^{-1}; δ_H ($CDCl_3$) 11.2 (1H, br s, COOH), 6.02 (1H, ddd 16.7, 10.1 and 9.1, H-15), 5.01 (1H, dd, 16.7 and 2.2 Hz, H-16), 4.99 (1H, dd, J 10.1 and 2.2 Hz, H-16'), 4.62 (1H, d, J 2.5, H-17), 4.56 (1H, m, H-17'), 2.80 (1H, dd, J 9.1 and 4.5 Hz, H-14β), 1.20 (3H, s, 4-CH_3), 0.69 (3H, s, 10-CH_3); δ_C see table II; m/z (relative intensity) 303 (M^+ + 1, 12), 302 (M^+, 58), 287 (26), 257 (14), 175 (9), 148 (29), 134 (45) and 79 (100).

(-)-5α,14β-Cleistanth-13(17),15-dien-18-oic acid (2b). In the same manner as above, (**18b**) (20 mg, 0.063 mmol) was converted to (**3b**) (18.9 mg, 99%); m.p. 167-170°C (from EtOH-H_2O); $[\alpha]_D$ -48° (c 1.5, $CHCl_3$); ν_{max} (KBr) 3600-2200, 3065, 3010, 1690, 1645, 1630, 1280, 910 and 880 cm^{-1}; δ_H ($CDCl_3$, only the signals corresponding to the main rotamer are given) 6.01 (1H, ddd, J 17.5, 9.4 and 9.2 Hz, H-15), 5.02 (1H, dd, J 17.5 and 1.8 Hz, H-16), 5.01 (1H, dd, J 9.4 and 1.8 Hz, H-16'), 4.62 (1H, d, J 2.5 Hz, H-17), 4.52 (1H, m, H-17'), 2.78 (1H, dd, J 9.2 and 4.3 Hz, H-14β), 2.15 (2H, m, H-12), 1.15 (3H, s, 4-CH_3), 0.82 (3H, s, 10-CH_3); δ_C see table II.

Acknowledgements: Finantial support from CICYT (Grant N° PB86-0578) is gratefully acknowledged. We also thank Dr D. Craig for manuscript revision.

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