Tetrahedron Vol. 49, No. 28, pp. 6251-6262, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
© 1993 Pergamon Press Ltd

Synthesis of *Ambrox*® from Communic Acids

Alejandro F. Barrero,* Joaquín Altarejos, Enrique J. Alvarez-Manzaneda, José M. Ramos and Sofía Salido

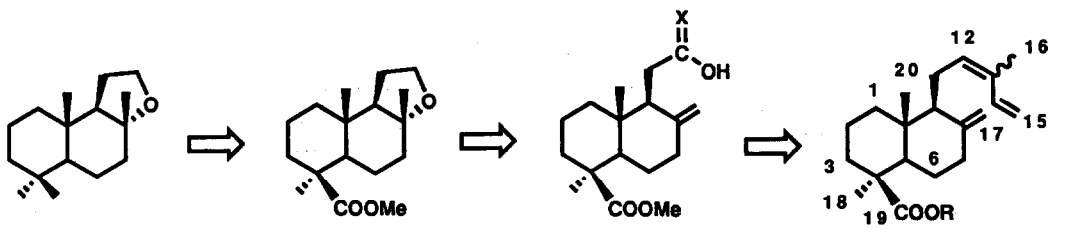
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Granada,
18071 Granada (Spain)

(*Received in UK* 28 *April* 1993)

Abstract: Two routes for preparing *Ambrox*® (**1**) from the methyl esters of *trans*-communic acid (**2b**) and/or *cis*-communic acid (**3b**), *via* selective degradation of their side chains, stereoselective formation of the tetrahydrofurane ring, and reduction of the axial methoxycarbonyl group, are described.

INTRODUCTION

Ambergris is a metabolic product found in the gut of some blue sperm whales (*Physeter macrocephalus* L.).[1] After several years of aging, *ambergris* is then used in perfumery as a valuable ingredient of many fine fragrances because of its unique scent and fixative properties. One of the constituents of the *ambergris* tincture[2] is the labdane-like tricyclic epoxide *ambrox*® (**1**)# which possesses a powerful amber-type aroma. As a consequence of the growing demand for ambergris-type odorants coupled with the almost complete worldwide ban on whaling, *ambrox* became probably the commercially most important synthetic equivalent of the scarce natural *ambergris*. For this reason, several syntheses of (-)-ambrox, since initially prepared in 1950,[3] have been developed. Most of them use diterpene-type starting materials such as sclareol,[4] manoyl oxide,[5] abietic acid,[6] levopimaric acid[7] and labdanolic acid.[8] Furtherly, diverse total syntheses of (±)-ambrox employ biogenetic-type cyclizations from farnesic or monocyclofarnesic acids or derivatives of these.[9]



1 **9** **6:** X=O **14:** X=H_2 **2a:** R=H, Δ^{12E} **2b:** R=Me, Δ^{12E} **3a:** R=H, Δ^{12Z} **3b:** R=Me, Δ^{12Z}

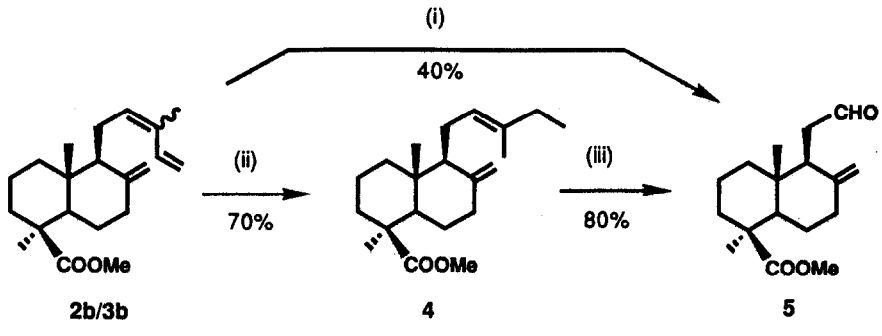
Scheme 1

Registered trade-mark of Firmenich S.A. for (-)-8α,12-epoxy-13,14,15,16-tetranorlabdane.

In this paper we report the use of the *trans*- and *cis*-communic acids (**2a**, **3a**), as a new natural source for preparing (-)-ambrox (**1**). Communic acids are found in many species of the Cupresaceae family and they are the main components of non-polar extracts of species of the genus *Juniperus*.[10] For example, methyl *trans*-communate (**2b**) has been directly crystallized from diazomethane-treated acid fractions of hexane extracts of *Juniperus sabina* L. wood.[11] This fact, along with their structural features (*trans*-decalin juntion, β side chain and a diene system proned to be cleaved on the C_{12}-C_{13} bond), converts **2b** and **3b** in good chiral synthons for the synthesis of (-)-ambrox (**1**).

RESULTS AND DISCUSSION

The scheme developed starts from both methyl *trans*- (**2b**) or *cis*-communate (**3b**), or a mixture of them, and performs first the selective degradation of the side chain, followed by the stereoselective formation of the tetrahydrofurane ring, and then the reduction of the methoxycarbonyl group (scheme 1). In previous work,[12] we described the appropriated cleavage of the C_{12}-C_{13} bond of compound **2b**; thus, the two methods followed here consisted (a) in the carefully controlled ozonolysis of **2b** and/or **3b** at low temperature to give aldehyde **5** (40%) and recovered starting material (40%), which can be re-used to afford good total conversions of **2b/3b** into **5** (60-70%), or (b) in the Δ^{14} selective hydrogenation of **2b** with diimide (70%), followed by the relatively more profitable C_{12}-C_{13} degradation of the resulting 14,15-hydrogenated derivative (**4**) with the OsO_4-$NaIO_4$ system (Scheme 2). Therefore, we concluded that these results were promising enough to attempt the conversion of these substrates into (-)-ambrox (**1**).

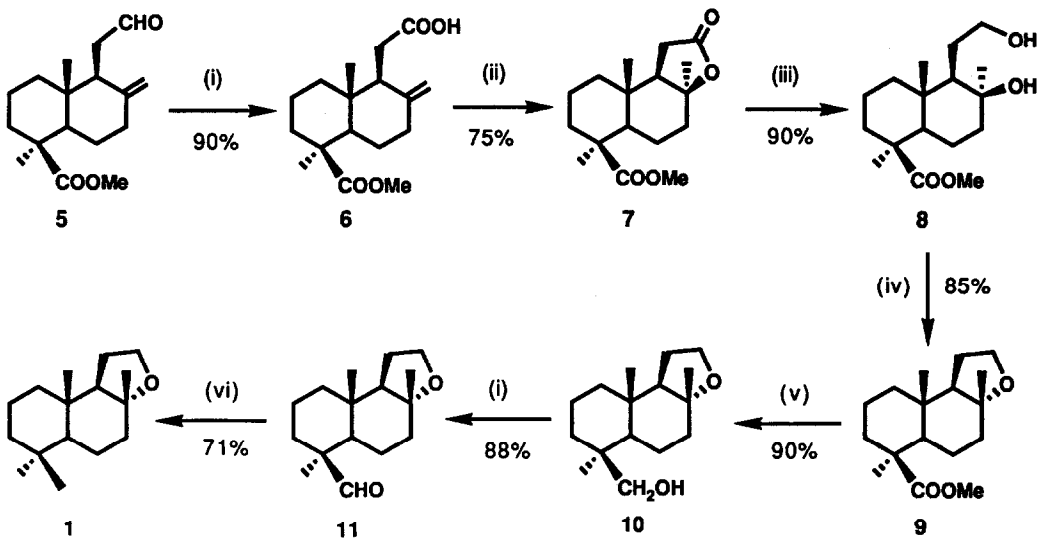


Scheme 2

(i) O_3, CH_2Cl_2, -78°C, Me_2S. (ii) N_2H_4•H_2O, EtOH, 30% H_2O_2, 0°C. (iii) $NaIO_4$, 0.2% OsO_4, *t*-BuOH, H_2O, r.t., 60 h.

The ***route 1*** starts with the oxidation of **5** with the *Jones reagent* to give the acid **6**, which is cyclizated with *p*-TsOH to the γ-lactone **7** (scheme 3). The stereochemistry at C-8 for compound **7** was established on the basis of the deshielded δ value for C-17 in ^{13}C NMR (29.33 ppm). In order to avoid the required chromatographic separation of **5** from the unaltered starting material we also performed the *Jones* oxidation of the ozonolysis crude of **3b** to give a mixture of **6** and **3b**, from which **6** was directly isolated in 35-40% yield by washing with aq. NaOH.[13] The tetrahydrofurane ring (**9**), with adequated stereochemistry at C-8, was prepared

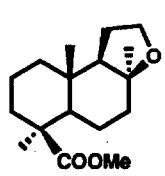
by treating lactone **7** with $LiAlH_4$ at room temperature, and cyclization of the resulting diol **8** in CH_3NO_2 at room temperature, using 0.3 eq. of *p*-TsOH. The choice of the *p*-TsOH/CH_3NO_2 system was made on the basis of the best results found by Büchi and Wüest to accomplish the dehydration of a related diol.[15] However, in our case we observed the temperature is crucial to get the desired configuration at C-8; thus, when the reaction was carried out at 70-90°C, contrary to them, a mixture of **9** and **12** was obtained in a *ca.* 1.5:1 ratio,[16] whereas at room temperature, **9** was almost exclusively formed (20:1 ratio, estimated by ^1H NMR).



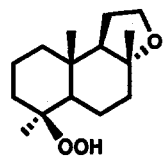
Scheme 3

(i) *Jones reagent*, acetone, 0°C. (ii) *p*-TsOH, toluene, reflux, 1h. (iii) $LiAlH_4$, THF, r.t., 1h. (iv) *p*-TsOH, CH_3NO_2, r.t., 3h. (v) $LiAlH_4$, THF, reflux, 1.5h. (vi) $N_2H_4 \cdot H_2O$, KOH, triethylene glycol, reflux, 1h.

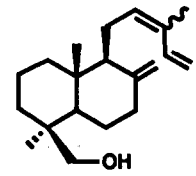
The conversion of the hindered methoxycarbonyl group into methyl group was accomplished in three steps (scheme 3): (a) reduction of the ester **9** with $LiAlH_4$ on refluxing, (b) oxidation of alcohol **10** with the *Jones reagent*,[17] and (c) treatment of the resulting aldehyde **11** in the *Huang-Minlon* conditions.[18b,c] This sequence was chosed as more convenient than the reduction with $LiAlH_4$ of the tosyl (or mesyl) derivative of alcohol **10** since it has failed with closely related axial esters.[19] As for aldehyde **11**, our first attempts to isolate it by chromatography on SiO_2 were unsuccessful because it decomposed during the elution. Instead of, hydroperoxide **13** was eluted, which can be explained by a radical mechanism[20] as reported in similar axial diterpene aldehydes.[21] The lability of aldehyde **11** was overcome by crystallization of the crude reaction in MeOH-H_2O mixtures.



12

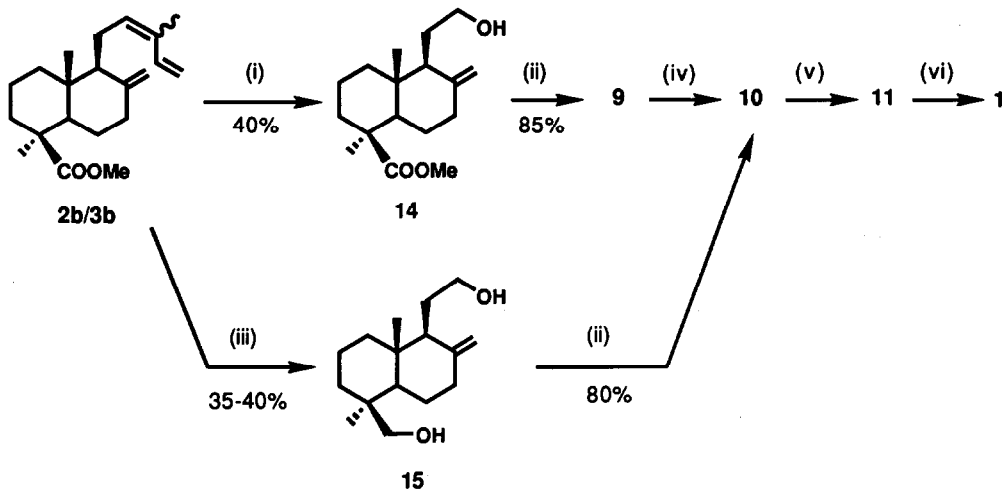


13



16

When the hydroxylolefin **14** was treated in the same reaction conditions as for **8**, with *p*-TsOH in CH_3NO_2 at room temperature, only compound **9** was formed (scheme 4). This finding evidently opened a shorter and more efficient approach to (-)-ambrox from communic acids. Therefore, ***route 2*** (scheme 4) comprised the preparation of **14** by reductive ozonolysis of **2b/3b**, using $LiAlH_4$ as reducing agent of the ozonides mixture, subsequent cyclization of **14** with *p*-TsOH in CH_3NO_2 (85% yield), and the aforementioned sequence (scheme 3) for converting **9** into **1**. Further, this route was shortened by the direct conversion of **2b/3b** into diol **15** (scheme 4) by refluxing with $LiAlH_4$ the ozonides crude reaction, followed by its cyclization to **10** under the same established conditions (80%). The reductive ozonolysis of **2b/3b**, at room temperature or on refluxing, to give **14** or **15**, respectively, in 35-40% yield, also allowed the recovering of unaltered starting material or **16** (35-40%), in each case, that can again be recycled.



Scheme 4

(i) O_3, CH_2Cl_2, -78°C; $LiAlH_4$, THF, r.t. (ii) *p*-TsOH, CH_3NO_2, r.t., 1-1.2 h.
(iii) O_3, CH_2Cl_2, -78°C; $LiAlH_4$, THF, reflux. (iv)-(vi) As for scheme 3.

Taking into account the above mentioned influence of the temperature in the stereoselective cyclization of **8** into **9**, we also studied that temperature effect on the reaction of **14** with *p*-TsOH in CH_3NO_2. Thus, the reaction performed at room temperature afforded almost exclusively compound **9** (detected in the crude reaction in 95%; entry 1 in table 1. Isolated as pure **9** in 85% yield; scheme 3) whereas *iso*-ambrox **12** was the unique cyclizated

product formed (**9** was not detected in the crude) when the reaction mixture was refluxed (entry 2 in table 1). In order to clarify the influence of the nitromethane[22] in these cyclizations we replaced it by other solvents as nitropropane (entry 4) or dichloromethane (entry 5) performing both essays at room temperature. These only resulted in the decreasing of the formation rate of **9**, appreciable loss of stereoselectivity in the cyclization being not observed, which mean that the real stereoselective cyclization control is due to the reaction temperature and

Table 1

Entry	14[a] (mmol)	9[a] (mmol)	*p*-TsOH (mmol)	$Hg(OAc)_2$ (mmol)	RNO_2[b] (ml)	CH_2Cl_2 (ml)	THF (ml)	Temp.	Time	9[c]	12[c]
1	2.32		3.42		60			r.t	1h	95	-
2	0.13		0.21		3			70-90°C	1h	-	50
3		0.26	0.42		3			70-90°C	1h	-	50
4	0.16		0.25		5			r.t	24h	95	-
5	0.12		0.19			2		r.t.	7h	90	-
6		0.12	0.19			2		reflux	1.5h	-	30
7	0.15			0.22			2	r.t.	2h	-	70
8	0.71			0.86			5	reflux	0.8h	5	85

[a] Starting materials. [b] CH_3NO_2 for entries 1-3; Pr-NO_2 for entry 4. [c] ^1H NMR estimated percentages for **9** or **12**, detected in the crude reaction.

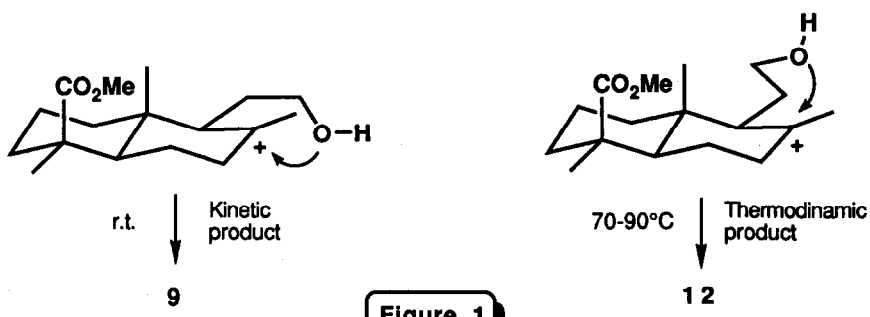


Figure 1

not to the solvent. Both compounds **9** and **12** seems to be formed through the corresponding HO-C_{12} attack on the same tertiary C-8 carbenium intermediate (figure 1). We also carried out the conversion of **9** into isomer **12** by refluxing with *p*-TsOH in CH_3NO_2 (entry 3) or CH_2Cl_2 (entry 6), which agrees with the statement[3] that the *trans*-fused tetrahydrofuran ring (**9**) is the kinetic isomer (favoured at room temperature) and the *cis*-fused ring (**12**) the thermodynamic one (preferred at higher temperatures). In order to determine the behaviour of **14** with alternative cyclization agents, the treatment with mercury (II) salts was tried. In all cases, the reaction of **14** with

$Hg(OAc)_2$ in THF, either at room temperature (entry 7) or at reflux (entry 8), followed by reduction with $NaBH_4$, yielded preferentially the *iso*-ambrox derivative **12**. However, the replacement of THF by CH_3NO_2 (with $Hg(OAc)_2$ or $Hg(F_3CCO_2)_2$) led to complicated reaction mixtures.

EXPERIMENTAL

Melting points were determined using a Reichert type Kofler microscope and are uncorrected. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter with a 1 dm microcell, using $CHCl_3$ as solvent (concentration expressed in $cg \cdot cm^{-1}$): IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between sodium chloride plates or as potassium bromide pellets. ^1H NMR spectra were recorded on Bruker WP 80 SY (80 MHz) and Bruker AM 300 (300 MHz) spectrometers using $CDCl_3$ as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H=7.25 ppm) as internal reference. ^{13}C NMR spectra were run at 20 MHz and 75 MHz on Bruker WP 80 SY and Bruker AM 300 instruments. Chemical shifts are in ppm (δ scale) and the coupling constants are in hertz. Carbon substitution degrees were established by DEPT pulse sequence. MS spectra were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70-230 mesh) and by flash column on Merck silica gel 60 (230-400 mesh) using hexane-Et_2O (H-E) mixtures of increasing polarity. Ozonization reactions were carried out with a mixture of ozone-oxygen provided by an oxygen-feed Fischer apparatus (10 liters of O_2 per hour are equivalent to 8.3 mmol of O_3). Compound **2b** was isolated from diazomethane-treated acide fractions of wood of *Juniperus sabina* L. and *Juniperus oxycedrus* L.[11] and the mixture of **2b** and **3b** from berries of *Juniperus communis* L.[24] Compound **5** was prepared by ozonolysis of methyl *trans*-communate (**2b**) and/or methyl *cis*-communate (**3b**).[12]

Methyl Labda-8(17),12*E*-dien-19-oate (4)

To a stirred solution of **2b** (540 mg, 1.71 mmol), EtOH (30 ml), and $N_2H_4 \cdot H_2O$ (2.1 ml, 43 mmol), 3.1 ml of 30% H_2O_2 (27.4 mmol) were slowly added for 15 min at 0°C. The mixture was further stirred for 30 min at room temperature. Then it was fractionated in H_2O-Et_2O mixture and extracted with Et_2O (3x20 ml). The combined organic layers were washed with sat. $FeSO_4$ aq. solution (4x10ml) and brine (10 ml) yielding a crude reaction (500 mg) that after being chromatographed on 20% $AgNO_3$/silica gel afforded **4** (380 mg, 70%, 98:2 H-E): oil; $[\alpha]_D$ +42.5° (*c* 1.00); IR (neat): ν 3081,1644, 888 ($C=CH_2$), 1680, 819 (C=CH), 1725, 1228, 1153 (CO_2Me); ^1H NMR (300 MHz): δ 0.52 (3H, *s*, Me-10), 0.93 (3H, *t*, 7.5, Me-14), 1.17 (3H, *s*, Me-4), 1.59 (3H, *br s*, Me-13), 1.94 (2H, *br q*, 7.5, H-14), 3.61 (3H, *s*, MeO-19), 4.47 (1H, *br s*, H-17), 4.82 (1H, *d*, 1.5, H'-17), 5.02 (1H, *qt*, 6.4, 1.2, H-12); ^{13}C NMR (75 MHz): δ 39.27 (C-1), 20.01 (C-2), 38.28 (C-3), 44.31 (C-4), 56.31 (C-5), 26.09 (C-6), 38.62 (C-7), 148.25 (C-8), 56.64 (C-9), 40.15 (C-10), 22.75 (C-11), 123.58 (C-12), 136.08 (C-13), 32.38 (C-14), 12.81 (C-15), 16.02 (C-16) , 107.35 (C-17), 28.86 (C-18), 177.82 (C-19), 12.62 (C-20), 51.05 (C-21); MS *m/z* (rel. int.): 318 (M^+, 29%), 303 (M^+-CH_3, 49), 261 (62), 259 (M^+-CO_2Me, 76), 258 (M^+-HCO_2Me, 30), 243 (51), 229 (25), 201 (64), 175 (M^+-HCO_2Me-C_6H_{11}, 100), 161 (29), 121 (79), 107 (41), 105 (35), 91 (40), 79 (38), 55 (57).

Reaction of 4 with OsO_4-$NaIO_4$ to give 5

A mixture of **4** (160 mg, 0.503 mmol), *t*-BuOH (6 ml), H_2O (2 ml), $NaIO_4$ (252 mg, 1.178 mmol) and 0.2% OsO_4 aq. solution (0.55 ml, 0.0043 mmol) was stirred at room temperature under argon for 60 h. The mixture was fractionated in Et_2O-H_2O and extracted with Et_2O (3x10 ml), and the combined organic layers washed with sat. K_2CO_3 (2x10 ml) and H_2O (10 ml). The organic phase was dried over anh. Na_2SO_4 and the solvent evaporated to afford a crude reaction (180 mg) that by column chromatography yielded *methyl 12-oxo-13,14,15,16-tetranor-labd-8(17)-en-19-oate* (**5**) (112 mg, 80%, 98:2 H-E): oil; $[\alpha]_D$ +18.5° (*c* 1.15); IR (neat): ν 3080, 1644, 893 (C=CH_2), 2716, 1721 (CHO), 1721, 1228, 1186, 1155 (CO_2Me); ^1H NMR (300 MHz): δ 0.51 (3H, *s*, Me-10), 1.18 (3H, *s*, Me-4), 3.60 (3H, *s*, MeO-19), 4.37 (1H, *br s*, H-17), 4.81 (1H, *s*, H'-17), 9.61 (1H, *dd*, 2.8, 1.4, H-12); ^{13}C NMR (75 MHz): δ 39.41 (C-1), 19.80 (C-2), 37.90 (C-3), 44.22 (C-4), 55.97 (C-5), 25.64 (C-6), 38.08 (C-7), 147.97 (C-8), 50.22 (C-9), 39.46 (C-10), 39.83 (C-11), 203.03 (C-12), 108.05 (C-17) 28.71 (C-18), 177.45 (C-19), 12.84 (C-20), 51.22 (C-21); MS *m/z* (rel. int.): 278 (M^+, 3%), 260 (M^+-H_2O, 2), 235 (4), 234 (9), 219 (M^+-CO_2Me, 5), 218 (M^+-HCO_2Me, 9), 181 (7), 175 (9), 121 (100), 109 (28), 91 (23), 81 (22), 69 (15), 55 (13), 43 (9), 41 (16).

Methyl 12-hydroxy-12-oxo-13,14,15,16-tetranorlabd-8(17)-en-19-oate (6)

To a stirred solution of **5** (1.85 g, 6.65 mmol) in acetone (20 ml), a 2.67 M solution of *Jones reagent* was added dropwise at 0°C till starting material disappeared. After filtering and removing the solvent, the residue was fractionated into H_2O-Et_2O and extracted with Et_2O (3x20 ml). Organic layers were washed with 5% NaOH solution (3x20 ml) and the resulting alkaline phases were acidified with 10% HCl solution and extracted into Et_2O (3x20 ml). The brine-washed organic layers finally yielded **6** (1.76 g, 90%): white crystalls; m.p. 127-8°C (MeOH); $[\alpha]_D$ +11.8° (*c* 1.13); IR (KBr): ν 3400-2500, 1710 (shoulder) (CO_2H), 3080, 1646, 891 (C=CH_2), 1721, 1229, 1154 (CO_2Me); ^1H NMR (80 MHz): δ 0.54 (3H, *s*, Me-10), 1.20 (3H, *s*, Me-4), 3.61 (3H, *s*, MeO-19), 4.55 (1H, *br s*, H-17), 4.81 (1H, *br s*, H'-17); MS *m/z* (rel. int.): 294 (M^+, 2%), 277 (M^+-OH, 0.2), 249 (M^+-CO_2H, 0.7), 235 (M^+-CH_2CO_2H, 5), 234 (M^+-HCO_2Me, 9), 175 (6), 181 (8), 149 (77), 121 (100), 109 (29), 105 (18), 93 (20), 91 (21), 83 (25), 55 (24), 43 (19), 41 (21).

Methyl 8β,12-epoxy-12-oxo-13,14,15,16-tetranorlabdan-19-oate (7)

A stirred solution of **6** (1.65 g, 5.61 mmol) and *p*-TsOH (0.4 g, 2.11 mmol) in toluene (50 ml) was refluxed for 1 h. After washing the mixture with 15% NaOH solution (2x20 ml), toluene was evaporated yielding a crude reaction that after crystallization in hexane afforded **7** (1.24 g, 75%): white crystals; m.p. 125-7°C (hexane); $[\alpha]_D$ +7.3° (*c* 1.00); IR (KBr): ν 1719, 1229, 1144 (CO_2Me), 1765, 1176, 927 (γ-lactone); ^1H NMR (300 MHz): δ 0.71 (3H, *s*, Me-10),1.19 (3H, *s*, Me-4), 1.30 (3H, *s*, Me-8), 1.76 (1H, *d*, 7.5, H-9), 2.36 (1H, *d*, 17.7, H-11), 2.75 (1H, *dd*, 17.7, 7.5, H'-11), 3.61 (3H, *s*, MeO-19); ^{13}C NMR (75 MHz): δ 41.06 (C-1), 18.71 (C-2), 37.81 (C-3), 43.60 (C-4), 53.60* (C-5), 19.50 (C-6), 35.83 (C-7), 85.32 (C-8), 53.11* (C-9), 36.40 (C-10), 32.89 (C-11), 177.45 (C-12), 29.33 (C-17), 28.62 (C-18), 177.60 (C-19), 13.55 (C-20), 51.37

* These assignments may be interchanged.

(C-21); MS *m/z* (rel. int.): 294 (M^+, 1%), 279 (M^+-CH_3, 4), 250 (1), 235 (M^+-CH_3-CO_2, 3), 234 (M^+-HCO_2Me, 2), 219 (M^+-CH_3-HCO_2Me, 4), 180 (6), 179 (5), 121 (18), 85 (66), 83 ($C_4H_3O_2^+$, 100), 47 (10).

Methyl 8β,12-dihydroxy-13,14,15,16-tetranorlabdan-19-oate (8)

To a stirred solution of **7** (1.00 g, 3.40 mmol) in THF (25 ml) was added $LiAlH_4$ (0.18 g, 4.74 mmol). After stirring for 2 h at room temperature, the mixture was diluted with Et_2O (20 ml), acidified with 10% HCl solution and extracted with Et_2O (3x30 ml). The organic phase was washed with 10% $NaHCO_3$ solution, dried over anh. Na_2SO_4 and evaporated to afford a reaction mixture (0.97 g) that by column chromatography yielded **8** (0.91 g, 90%, 9:1 H-E): white crystals; m.p. 130-2°C (hexane); $[\alpha]_D$ +15.9° (*c* 1.00); IR (KBr): ν 3361, 1096, 1077, 1052, 1033 (OH), 1723, 1231, 1153 (COOMe); ^1H NMR (300 MHz): δ 0.78 (3H, *s*, Me-10), 1.13 (3H, *s*, Me-8), 1.16 (3H, *s*, Me-4), 3.55 (1H, *td*, 9.9, 6.9, H-12), 3.62 (1H, *td*, 9.9, 6.0, H'-12), 3.62 (3H, *s*, MeO-19); ^{13}C NMR (75 MHz): δ 39.52 (C-1), 18.74 (C-2), 38.00 (C-3), 43.88 (C-4), 56.62 (C-5), 19.72 (C-6), 42.34 (C-7), 72.51 (C-8), 53.89 (C-9), 38.82 (C-10), 28.73 (C-11), 64.77 (C-12), 30.68 (C-17), 28.66 (C-18), 177.76 (C-19), 13.05 (C-20), 51.20 (C-21); MS *m/z* (rel. int.): 298 (M^+, 4%), 283 (M^+-CH_3, 2), 280 (M^+-H_2O, 2), 239 (M^+-CO_2Me, 10), 235 (M^+-H_2O-C_2H_4OH, 11), 228 (16), 210 (19), 179 (13), 169 (24), 121 (48), 109 ($C_8H_{13}^+$, 76), 95 (45), 84 ($C_5H_8O^+$, 84), 67 ($C_5H_7^+$, 44), 55 (58), 49 (77), 43 (100).

Cyclization of diol 8. Methyl 8α,12-epoxy-13,14,15,16-tetranorlabdan-19-oate (9)

A stirred mixture of **8** (0.80 g, 2.68 mmol), *p*-TsOH (0.17 g, 0.90 mmol) and CH_3NO_2 (50 ml) was kept at room temperature for 3 h. It was diluted with Et_2O (30 ml), washed with 15% $NaHCO_3$ solution, dried over anh. Na_2SO_4 and evaporated to afford a residue (0.75 g) which was crystallized from a MeOH/H_2O mixture to yield **9** (0.64 g, 85%): white crystals; m.p. 61-3°C (MeOH/H_2O); $[\alpha]_D$ +11.1° (*c* 1.00); IR (KBr): ν 1716, 1235, 1187, 1150 (COOMe), 1025, 1005, 975 (ether); ^1H NMR (300 MHz): δ 0.65 (3H, *s*, Me-10), 1.07 (3H, *s*, Me-8), 1.17 (3H, *s*, Me-4), 3.63 (3H, *s*, MeO-19), 3.81 (1H, *q*, 8.4, H-12), 3.89 (1H, *td*, 8.4, 3.9, H'-12); ^{13}C NMR (75 MHz): δ 40.28 (C-1), 18.88 (C-2), 38.36 (C-3), 43.62 (C-4), 57.26 (C-5), 22.25 (C-6), 39.64 (C-7), 79.58 (C-8), 59.76 (C-9), 36.64 (C-10), 22.75 (C-11), 64.86 (C-12), 20.71 (C-17), 28.74 (C-18), 177.60 (C-19), 12.49 (C-20), 51.15 (C-21); MS *m/z* (rel. int.): 265 (M^+-CH_3, 100%), 221 (M^+-CO_2Me, 5), 205 (M^+-CH_3-HCO_2Me, 16), 187 (6), 175 (M^+-HCO_2Me-C_2H_4O, 8), 161 (4), 135 (9), 121 (32), 97 (51), 91 (22), 83 (7), 79 (25), 67 (28), 59 (36), 55 (29), 43 (47).

8α,12-epoxy-13,14,15,16-tetranorlabdan-19-ol (10)

A stirred mixture of **9** (0.60 g, 2.15 mmol), THF (20 ml) and $LiAlH_4$ (0.238 g, 6.27 mmol) was refluxed for 1.5 h. Following the same work-up used to prepared **8**, alcohol **10** (0.488 g, 90%) was obtained: white crystals; m.p. 120-2°C (hexane); $[\alpha]_D$ -27.7° (*c* 1.00); IR (KBr): ν 3461, 1036 (OH), 1085, 991, 937 (ether); ^1H NMR (300 MHz): δ 0.81 (3H, *s*, Me-10), 0.96 (3H, *s*, Me-4), 1.04 (3H, *s*, Me-8), 3.48 (1H, *dd*, 10.9, 0.8, H-19), 3.67 (1H, *d*, 10.9, H'-19), 3.79 (1H, *q*, 8.4, H-12), 3.89 (1H, *td*, 8.4, 3.9, H'-12); ^{13}C NMR (75 MHz): δ 40.04 (C-1), 18.01 (C-2), 36.19 (C-3), 38.36 (C-4), 57.77 (C-5), 20.96 (C-6), 40.04 (C-7), 79.78 (C-8), 60.22 (C-9), 36.08 (C-10), 22.74 (C-11), 64.92 (C-12), 20.93 (C-17), 27.17 (C-18), 65.27 (C-19),

15.29 (C-20); MS *m/z* (rel. int.): 252 (M^+, 1.3%), 237 (M^+-CH_3, 81), 221 (M^+-CH_2OH, 5), 219 (M^+-CH_3-H_2O, 9), 209 (6), 207 (8), 191 (4), 163 (4), 153 ($C_{10}H_{17}O^+$, 2), 147 (5), 135 (153$^+$-H_2O, 12), 123 (14), 111 (24), 97 ($C_6H_9O^+$, 97), 85 ($C_5H_9O^+$, 28), 81 (34), 67 (39), 55 (48), 43 (100).

8α,12-epoxy-13,14,15,16-tetranorlabdan-19-al (11)

To a stirred solution of **10** (0.45 g, 1.79 mmol) in acetone (6 ml) a 2.67 M solution of *Jones reagent* was added dropwise at 0°C till starting material disappeared. The mixture was filtered, evaporated and extracted with Et_2O (3x10 ml). Organic layers were dried over anh. Na_2SO_4 and evaporated to yield **11** (0.393 g, 88%): white crystals; m.p. 85-8°C (MeOH/H_2O); $[\alpha]_D$ -23.0° (*c* 1.00); IR (KBr): ν 2680, 1716 (CHO), 1076, 996, 976, 918 (ether); ^1H NMR (300 MHz): δ 0.68 (3H, *s*, Me-10), 0.99 (3H, *s*, Me-4), 1.07 (3H, *s*, Me-8), 3.80 (1H, *q*, 8.6, H-12), 3.88 (1H, *td*, 8.6, 3.5, H'-12), 9.75 (1H, *s*, H-19); ^{13}C NMR (75 MHz): δ 39.58* (C-1), 18.12 (C-2), 34.75 (C-3), 48.07 (C-4), 57.19 (C-5), 20.41 (C-6), 39.39* (C-7), 79.35 (C-8), 59.32 (C-9), 36.60 (C-10), 22.72 (C-11), 64.85 (C-12), 20.95 (C-17), 24.22 (C-18), 205.23 (C-19), 13.70 (C-20); MS *m/z* (rel. int.): 235 (M^+-CH_3, 100%), 222 (M^+-CO, 1), 217 (M^+-CH_3-H_2O, 10), 207 (M^+-CH_3-CO, 4), 189 (M^+-CH_3-CO-H_2O, 4), 177 (3), 163 (7),137 (7), 123 (29), 107 (20), 97 ($C_6H_9O^+$, 45), 84 ($C_5H_8O^+$, 31), 81 (30), 67 (32), 55 (44), 49 (33), 43 (76), 41 (45).

8α,12-epoxy-13,14,15,16-tetranorlabdane (Ambrox®) (1)

A mixture of **11** (0.38 g, 1.52 mmol), N_2H_4•H_2O (0.48 g, 9.59 mmol), powdered KOH (1.91 g, 34 mmol) and triethylene glycol (13 g) was refluxed under argon for 1 h. The mixture was acidified with 10% HCl solution, extracted with Et_2O (3x20 ml) and the combined extracts were washed with brine, dried over anh. Na_2SO_4 and evaporated to yield a crude reaction (0.32 g) which was crystallized from a MeOH/H_2O mixture to afford **1** (0.254 g, 71%): white crystals; m.p. 74-76°C (MeOH/H_2O); $[\alpha]_D$ -22.1° (*c* 0.68); IR (KBr): ν 1083, 1006, 978, 915 (ether); ^1H NMR (300 MHz): δ 0.81 (3H, *s*, Meβ-4 or Me-10), 0.82 (3H, *s*, Me-10 or Meβ-4), 0.86 (3H, *s*, Meα-4), 1.07 (3H, *s*, Me-8), 3.81 (1H, *q*, 8.3, H-12), 3.90 (1H, *td*, 8.3, 4.3, H'-12); ^{13}C NMR (75 MHz): δ 39.95* (C-1), 18.39 (C-2), 42.43 (C-3), 33.06 (C-4), 57.25 (C-5), 20.64 (C-6), 39.73* (C-7), 79.91 (C-8), 60.11 (C-9), 36.18 (C-10), 22.62 (C-11), 64.97 (C-12), 21.13 (C-17), 33.58 (C-18), 21.13 (C-19), 15.03 (C-20); MS *m/z* (rel. int.): 236 (M^+, 2%), 221 (M^+-CH_3, 100), 205 (5), 203 (4), 177 (3), 137 ($C_{10}H_{17}^+$, 15), 109 (5), 97 (13), 81 (7), 67 (6), 55 (5), 43 (8).

Methyl 8β,12-epoxy-13,14,15,16-tetranorlabdan-19-oate (12)

To a stirred suspension of $Hg(OAc)_2$ (273 mg, 0.86 mmol) in THF (3 ml) was added a solution of **14** (200 mg, 0.71 mmol) in THF (2 ml). The mixture was refluxed for 0.8 h under argon. It was cooled to room temperature and then a solution of $NaBH_4$ (17 mg, 0.45 mmol) in 3M NaOH (17 ml) was added. After stirring for 1h at room temperature it was extracted with Et_2O (3x10 ml). Combined organic phases were dried on anh.

* These assignments may be interchanged.

Na_2SO_4, filtered and evaporated to dryness to afford a residue (170 mg) that on chromatographic column yielded **12** (140 mg, 70%, 95:5 H-E): white crystals; m.p. 56-60°C (MeOH-H_2O); $[\alpha]_D$ +42.6° (*c* 1.00); IR (KBr): ν 1715, 1229, 1194, 1154 (CO_2Me), 1090, 1029, 993 (ether); ^1H NMR (300 MHz): δ 0.69 (3H, *s*, Me-10), 1.03 (3H, *s*, Me-8), 1.18 (3H, *s*, Me-4), 3.60 (3H, *s*, MeO-19), 3.69 (1H, *q*, 8.4, H-12), 3.80 (1H, *td*, 8.4, 3.7, H'-12); ^{13}C NMR (75 MHz): δ 41.45 (C-1), 19.00 (C-2), 38.28 (C-3), 43.81 (C-4), 54.47 (C-5), 19.77 (C-6), 36.36 (C-7), 81.04 (C-8), 55.91 (C-9), 36.36 (C-10), 26.79 (C-11), 64.76 (C-12), 27.83 (C-17), 28.71 (C-18), 178.06 (C-19), 13.78 (C-20), 51.19 (C-21); MS *m/z* (rel. int.): 280 (M^+, 0.4%), 265 (M^+-CH_3, 100), 233 (M^+-CH_3-CH_3OH, 7), 221 (M^+-CO_2Me, 5), 205 (M^+-CH_3-HCO_2Me, 19), 187 (7), 175 (M^+-HCO_2Me-C_2H_4O, 2), 161 (5), 135 (4), 121 (40), 97 (50), 91 (15), 83 (51), 79 (16), 67 (13), 59 (8), 55 (11), 43 (11).

Methyl 12-hydroxy-13,14,15,16-tetranorlabd-8(17)-en-19-oate (14)

A solution of **2b** and/or **3b** (2.0 g, 6.33 mmol) in CH_2Cl_2 (150 ml) was slowly bubbled with a O_3/O_2 mixture at -78°C for 3.5 h. The solution was flushed with argon and most of the solvent was evaporated under vacuum at room temperature. The residue was solved in THF (30 ml) and $LiAlH_4$ (0.312 g, 8.23 mmol) was added in portions for 0.4 h. The mixture was allowed to stir for 1.5 h at room temperature, then it was diluted with Et_2O (50 ml), acidified with 10% HCl solution and extracted with Et_2O (3x30 ml). The ether phase was washed with sat. $NaHCO_3$ solution, dried over anh. Na_2SO_4 and evaporated to afford a crude reaction (1.86 g) that by column chromatography yielded starting material (0.802 g, 40%, 99:1 H-E) and **14** (0.709 g, 39.5%, 8:2 H-E): white crystals; m.p. 91-3°C (MeOH/H_2O); $[\alpha]_D$ +37.1° (*c* 1.00); IR (KBr): ν 3355, 1047 (OH), 3079, 1641, 890 (C=CH_2), 1722, 1230, 1156 (COOMe); ^1H NMR (300 MHz): δ 0.48 (3H, *s*, Me-10), 1.15 (3H, *s*, Me-4), 3.46 (1H, *dt*, 10.1, 7.1, H-12), 3.58 (3H, *s*, MeO-19), 3.68 (1H, *ddd*, 10.1, 7.7, 4.5, H'-12), 4.51 (1H, *br s*, H-17), 4.81 (1H, *d*, 1.3, H'-17); ^{13}C NMR (75 MHz): δ 39.03 (C-1), 19.86 (C-2), 38.13 (C-3), 44.25 (C-4), 56.20 (C-5), 26.09 (C-6), 38.57 (C-7), 148.17 (C-8), 51.96 (C-9), 39.91 (C-10), 27.14 (C-11), 62.21 (C-12), 106.40 (C-17), 28.73 (C-18), 177.69 (C-19), 12.53 (C-20), 51.09 (C-21); MS *m/z* (rel. int.): 280 (M^+, 2%), 265 (M^+-CH_3, 1), 249 (M^+-CH_2OH, 1), 221 (M^+-CO_2Me, 7), 220 (M^+-HCO_2Me, 12), 181 ($C_{11}H_{17}O_2^+$, 5), 180 ($C_{11}H_{16}O_2^+$, 6), 161 (7), 149 (8), 133 (8), 121 ($C_9H_{13}^+$, 100), 107 (23), 93 (25), 91 (34), 81 (23), 79 (32), 67 (21), 55 (19), 41 (18).

12,19-Dihydroxy-13,14,15,16-tetranorlabd-8(17)-ene (15)

A solution of **2b** and/or **3b** (2.0 g, 6.33 mmol) in CH_2Cl_2 (200 ml) was ozonizated as for compound **14** to afford a residue that was treated with $LiAlH_4$ (720 mg, 18.9 mmol) in portions for 0.5 h at room temperature. The mixture was then refluxed for 1h and following the work-up described for compound **14**, the crude reaction obtained (1.86 g) was column chromatographed to afford **15** (735 mg, 40%, 1:1 H-E) and **16** (744 mg, 40%, 6:4 H-E).

(**15**): white crystals; m.p. 73-5°C (hexane); $[\alpha]_D$ +16.3° (*c* 0.50); IR (KBr): ν 3300, 1054, 1028 (OH), 3082, 1641, 891 (C=CH_2); ^1H NMR (300 MHz): δ 0.64 (3H, *s*, Me-10), 0.96 (3H, *s*, Me-4), 3.37 (1H, *dd*, 10.9, 1.1, H-19), 3.49 (1H, *dt*, 10.2, 7.1, H-12), 3.70 (1H, *ddd*, 10.2, 7.5, 4.7, H'-12), 3.73 (1H, *d*, 10.9, H'-19), 4.52 (1H, *d*, 1.3, H-17), 4.80 (1H, *d*, 1.3, H'-17); ^{13}C NMR (75 MHz): δ 38.93* (C-1), 18.93 (C-2), 35.33

* These assignments may be interchanged.

(C-3), 39.25 (C-4), 56.20 (C-5), 24.32 (C-6), 38.47* (C-7), 148.26 (C-8), 52.83 (C-9), 38.82 (C-10), 27.09 (C-11), 62.35 (C-12), 106.65 (C-17), 27.03 (C-18), 64.97 (C-19), 15.26 (C-20); MS *m/z* (rel. int.): 252 (M^+, 0.5%), 237 (M^+-CH_3, 0.4), 234 (M^+-H_2O, 0.7), 221 (M^+-CH_2OH, 6), 203 (M^+-CH_2OH-H_2O, 3), 177 (M^+-C_2H_4OH-CH_2O, 6), 149 (43), 121 (13), 107 (14), 95 (22), 86 (65), 84 (100), 51 (30), 49 (80).
(**16**): ^1H NMR (80 MHz): δ 0.69 (3H, *s*, Me-10), 0.97 (3H, *s*, Me-4), 1.80 (3H, *br s*, Me-13), 3.40 (1H, *d*, 10, H-19), 3.77 (1H, *d*, 10, H'-19), 4.46 (1H, *br s*, H-17), 4.80 (1H, *br s*, H'-17), 4.87 (1H, *br d*, 10, H-15, *E* isomer), 5.03 (1H, *br d*, 17, H'-15, *E* isomer), 5.27 (1H, *br t*, 7, H-12, *Z* isomer), 5.40 (1H, *br t*, 7, H-12, *E* isomer), 6.32 (1H, *dd*, 17, 10, H-14, *E* isomer), 6.80 (1H, *dd*, 17, 10, H-14, *Z* isomer).

Cyclization of alcohol 14 to give 9

A stirred mixture of **14** (0.65 g, 2.32 mmol), *p*-TsOH (0.65 g, 3.42 mmol) and CH_3NO_2 (60 ml) was kept at room temperature for 1 h. After working-up as done for diol **8**, the crude reaction (0.60 g) was crystallized from a MeOH/H_2O mixture to yield **9** (0.552 g, 85%).

Cyclization of diol 15 to give 10

A mixture of **15** (0.03 g, 0.12 mmol), *p*-TsOH (0.03 g, 0.18 mmol) and CH_3NO_2 (4 ml) was allowed to stir at room temperature for 1.2 h. Following the same work-up as for diol **8**, compound **10** was obtained (0.024 g, 80%).

ACKNOWLEDGEMENTS

We wish to thank to the *Junta de Andalucía* for the financial support.

REFERENCES AND NOTES

1. Ohloff, G. The Fragrance of Ambergris. In *Fragrance Chemistry;* Theimer, E. T. Ed.; Academic Press: New York, 1982; pp. 535-573.
2. Mookherjee, B. D.; Patel, R. R. In *Proceedings of the 7th. Int. Congr. Essent. Oils*; Kyoto, 1977; p. 479.
3. (a) Stoll, M.; Hinder, M., *Helv. Chim. Acta* **1950**, *33*, 1251-1261.
   (b) Hinder, M; Stoll, M., *ibid.* 1308-1312.
4. (a) Decorzant, R.; Vial, C.; Näf, F.; Whitesides, G. M., *Tetrahedron* **1987**, *43*, 1871-1879.
   (b) Christenson, P. A., *ibid.* **1988**, *44*, 1925-1932.
   (c) Coste-Manière, I. C.; Zahra, J. P.; Waegell, B., *Tetrahedron Lett.* **1988**, *29*, 1017-1020, and references cited therein.
   (d) Martres, P.; Perfetti, P.; Zahra, J.-P.; Waegell, B.; Giraudi, E.; Petrzilka, M., *Tetrahedron Lett.* **1993**, *34*, 629-632.
5. Cambie, R. C.; Joblin, K. N.; Preston, A. F., *Aust. J. Chem.* **1971**, *24*, 583-591.
6. Koyama, H.; Kaku, Y.; Ohno, M., *Tetrahedron Lett.* **1987**, *28*, 2863-2866.

7. Nishi, Y.; Ishihara, H., *J. Jpn. Oil Chem. Soc.* **1989**, *38*, 276-279.
8. Urones, J. G.; Basabe, P.; Marcos, I. S.; González, J. L.; Jiménez, V.; Sexmero, M. J.; Lithgow, A. M., *Tetrahedron* **1992**, *48*, 9991-9998, and references cited therein.
9. (a) Sell, C., *Chem. Ind.* **1990**, 516-520, and references cited therein.
   (b) Snowden, R. L.; Linder, S., *Tetrahedron Lett.* **1991**, *32*, 4119-4120.
   (c) Snowden, R. L.; Eichenberger, J.-C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H., *J. Org. Chem.* **1992**, *57*, 955-960.
10. Pascual Teresa, J. de; San Feliciano, A.; Miguel del Corral, J. M.; Barrero, A. F., *Phytochemistry* **1983**, *22*, 300-301.
11. Barrero, A. F.; Sánchez, J. F.; Altarejos, J., *Ars Pharmaceutica* **1987**, *28*, 449-457.
12. Barrero, A. F.; Sánchez, J. F.; Altarejos, J., *Tetrahedron Lett.* **1989**, *30*, 5515-5518.
13. This was the method more convenient to get **6** since the oxidative ozonolysis of **3b** with H_2O_2 (ref. 14) afforded **6** in lower yields.
14. Henne, A. L.; Hill, P., *J. Am. Chem. Soc.* **1943**, *65*, 752-754.
15. Büchi, G. H.; Wüest, H., *Helv. Chim. Acta* **1989**, *72*, 996-1000.
16. Both isomers can be easily distinguished by their ^{13}C NMR data, specially those for C-17 (**9**: δ 20.71; **12**: δ 27.83).
17. Although alcohol **10** was properly converted into aldehyde **11** in 4 h with 2 equivalents of piridinium dichromate in CH_2Cl_2 (ref. 18a), its separation from the chromium salts by elution through SiO_2 or $MgSO_4$ pads gave more decomposed material than in the *Jones* oxidation.
18. (a) Corey, E. J.; Schmidt, G., *Tetrahedron Lett.* **1979**, *5*, 399.
    (b) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301-3303.
    (c) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Zaragozá, R. J., *J. Org. Chem.* **1989**, *54*, 5123-5125.
19. Traverso, G.; Fringuelli, F.; Taticchi, A.; Mancini, V.; De Giuli, G., *Gazz. Chim. Ital.* **1969**, *99*, 411-421.
20. (a) Caputo, R.; Mangoni, L.; Revitere, L.; Laccanino, R., *Tetrahedron Lett.* **1971**, 3731-3734.
    (b) Tanaka, U.; Nihashi, S.; Yanagisama, T.; Nikaido, S.; Shibata, S., *Tetrahedron* **1972**, *28*, 4523-4529.
    (c) Do Khac Manh, D.; Bastard, J.; Fetizon, M., *J. Nat. Prod.* **1983**, *46*, 262-268.
21. Grande, M.; Mancheño, B.; Sánchez, M. J., *Phytochemistry* **1991**, *30*, 1977-1982.
22. The role attributed in the literature (ref. 23) to the nitromethane in the stereoselective conversion at 75-85°C of a related diol of **8** (methyl group instead the methoxycarbonyl group) into the corresponding analog of **9**, is to reduce the double bond formation subsequent to the dehydration of HO-C_8.
23. Büchi, G. H.; Wüest, H., **Eur. Pat. Appl. EP 170, 995** (1986).
24. Pascual Teresa, J. de; San Feliciano, A.; Barrero, A. F., *An. Quím.* **1973**, *69*, 1065-1067.