Tetrahedron Vol. 44, No 16, pp. 5139 to 5144, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

STEREOCONTROLLED SYNTHESIS OF (3S,4S,5S)-3-ALKYL-4-HYDROXY-5-METHYL-2(3H)-DIHYDROFURANONES AND DERIVATIVES. CONFIGURATIONAL ASSIGNMENT OF SOME CLINOSTEMON MAHUBA AND PLEXAURA FLAVA METABOLITES.

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(*Received in UK* 6 *June* 1988)

Abstract.- Absolute and relative configuration has been assigned to some metabolites from mahuba tree and the coral Plexaura flava, by enantio- and diastereocontrolled synthesis of (3S,4S,5S)-3-alkyl-4-hydroxy-5-methyl-2(3H)-dihydrofuranones and their acetyl derivativatives, (S)-lactic acid being used as chiral precursor.

INTRODUCTION

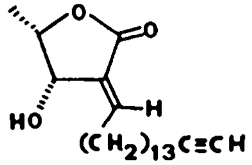
The 4-hydroxy-5-methyl-2(3H)-dihydrofuranone structure and its O-acetyl derivative, both substituted at C-3 by alkyl or alkylidene chains of variable lenght, are widespread in several kinds of metabolites from rather different natural sources. For instance, isodihydromahubynolide B, 1, and isodihydromahubanolide B, 2, are polyketide metabolites isolated from the trunk wood of Clinostemon mahuba, a tree from the estuary of the Amazon, and they give compound 3 by hydrogenation.[1] (Chart 1). On the other hand, the Gorgonian coral Plexaura flava produces unusual lipid metabolites with structures having the relative configuration shown in 4, 6-8, among other products.[2]

The relative configurations of these metabolites have been assigned in some cases by means of stereocontrolled chemical transformations, e.g. pyrolytic cis-elimination of acetic acid in 4 to give 9.[1] However, more frequently NMR data, mainly coupling constants between vicinal protons, have been used.[1,2] Concerning absolute configuration, no assignment has been reported for the Gorgonian metabolites, and the (4S,5S) configuration has been tentatively given to 1 and 2 by analogy with other known closely related products.[1]

We have recently demonstrated that coupling constants in such kind of lactones are influenced by both the relative disposition of the protons (configuration) and the more stable molecular conformation.[3] Moreover, sometimes J(cis) and J(trans) values are too close to be distinguished. Therefore, we have prepared compounds 3-6 from (S)-lactic acid as a suitable chiral precursor, and we have compared the coupling constants of the synthesized products with those described for the isolated metabolites and derivatives. In a similar way, a correlation between optical rotations of both synthetic and natural products has been established. As a result, absolute and relative configurations of these compounds have been determined unambigously.

RESULTS AND DISCUSSION

Our synthetic procedure is based on stereoselective alkylation at the C-3 position in (4S,5S)-4-hydroxy-5-methyldihydro-2(3H)-furanone, 14.[4] This product is easily obtained from commercial ethyl (S)-lactate, 11, by the method described by Brandange and coworkers[5] (Scheme 1). Thus,-



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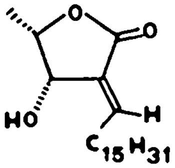

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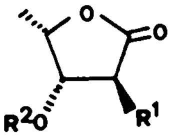
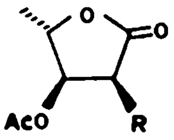


R^1	R^2	
$C_{16}H_{33}$	H	**3**
$C_{16}H_{33}$	Ac	**4**
$C_{14}H_{29}$	H	**5**
$C_{14}H_{29}$	Ac	**6**



R	
$C_{16}H_{33}$	**7**
$C_{14}H_{29}$	**8**

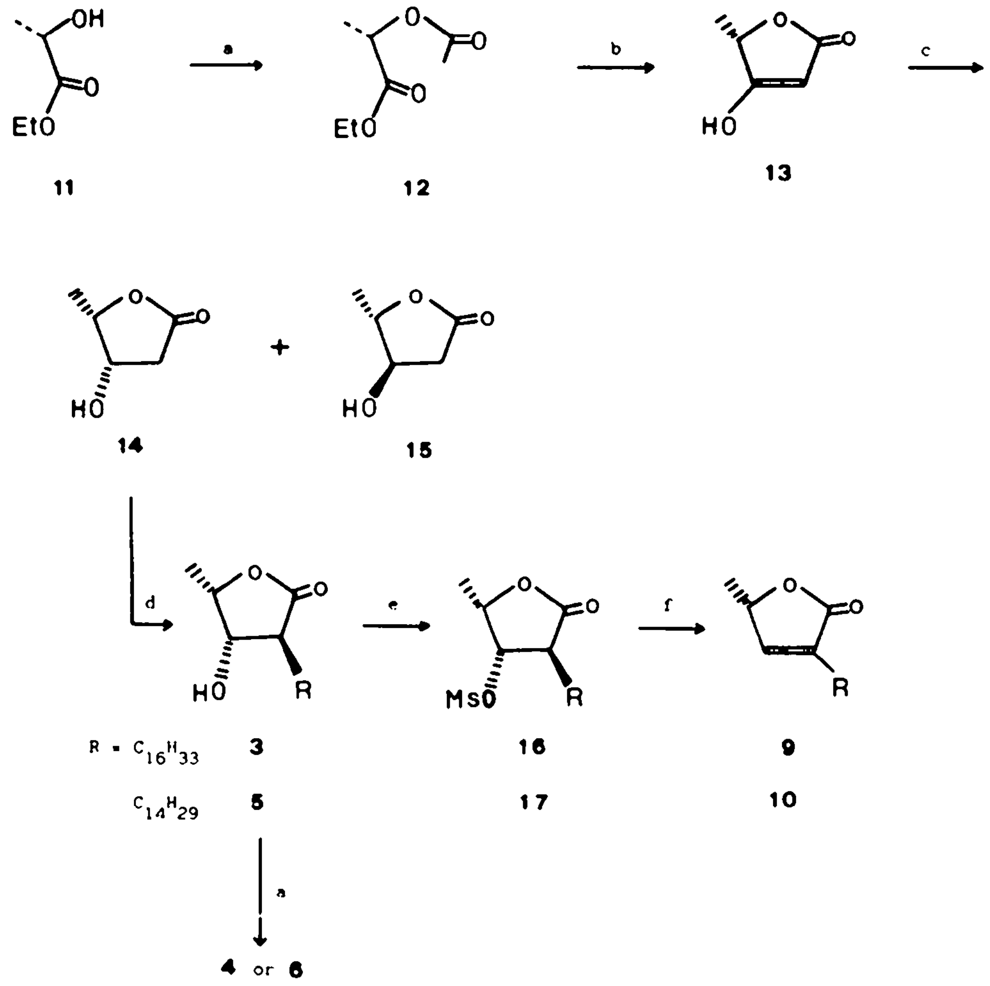
Chart 1

acetylation of 11, followed by treatment with the bulky base lithium bis(trimethylsilyl)amide gave (S)-γ-methyltetronic acid, 13, without epimerization of the chiral center. Subsequent hydrogenation of 13 at 60 psi pressure, using 5% Rh/C as catalyst,[6] afforded a 85:15 mixture of hydroxylactones 14 and 15, respectively, that were isolated by column chromatography. The lithium enolate of the major isomer 14 was alkylated with hexadecyl iodide, giving 3 that was acetylated to afford compound 4. The homologous side-chain compound 5 and its acetyl derivative 6 were prepared by the same procedure, using tetradecyl iodide as alkylating agent.

Attempts to epimerize lactone 3 at C-4 in order to prepare isomer 7 failed since the mesyl derivative 16 gave butenolide 9, (Scheme 1) along with recovered starting material, when treated with tetrabutylammonium acetate under several conditions of temperature and time. This reagent was successfully utilized for hydroxyl epimerization in mild conditions.[7] However, β-elimination processes in related lactones have been described by several authors,[8] the remarkable acidity of the proton at the α-carbonyl position in 16 accounting for the observed elimination prior to a substitution process. In the same manner, the mesylate 17 lead to butenolide 10.

Compound 9 had also been synthesizad by elimination of acetic acid in the acetate 4 prepared from mahuba lactones 1 and 2.[1] Since optical rotations measured for this product, obtained by the two ways, agree fair (see experimental part), the (5S) configuration can be assigned to 1 and 2.

Table 1 shows the values of J's and optical rotations measured for compounds 3–6, synthesized in this work, and those described in the literature for the natural metabolites and derivatives 3–8, 18, and 19. Some slight discrepances are observed in J's, even between the values reported in references 1 and 2 (Entry 2, Table 1). Nevertheless, arguments to assign a (trans,cis) disposition of the substituents in the natural products are the following. Very different J's are found in lactones with (cis,trans) (entries 5,6) and (trans,trans) (entries 7,8) configurations and



a: Ac_2O, pyridine; b: $(Me_3Si)_2NLi$; c: H_2, 5% Rh/C, 60 psi; d: 1)LDA, 2)RI, R = $C_{16}H_{33}$ or $C_{14}H_{29}$; e: MsCl, pyridine; f: Bu_4NOAc.

Scheme 1

R	
$C_{:6}H_{33}$	18
$C_{14}H_{29}$	19

R	
$C_{16}H_{33}$	4a
$C_{14}H_{29}$	6a

Chart 2

all these values are in good accordance with those obtained by theoretical calculations.[3] Furthermore, in the case of mahuba derivatives 3, 4 and 9, physical constants (optical rotations, mp's) are in good agreement. Therefore, the (4S,5S) absolute configuration is confirmed for the natural products 1 and 2.

Table 1. Vicinal coupling constants and optical rotations measured in this work for compounds 3–6 and described in the literature for compounds 3–8, 18 and 19.

				Measured J's[a]		Described J's (ref)		Measured $[\alpha]_D$	Described $[\alpha]_D$
Entry	Compound	R^1	R^2	$J_{3,4}$	$J_{4,5}$	$J_{3,4}$	$J_{4,5}$		
(1)	3	$C_{16}H_{31}$	H	3.6	4.9	b	b	-38.0[c]	-37.7[c] (1)
(2)	4	$C_{16}H_{31}$	Ac	2.9	4.9	3.5(1,2)	5.0(1),5.6(2)	-32.9[d]	+31.9[d] (2)
(3)	5	$C_{14}H_{29}$	H	3.4	4.9	-	--	-43.2[d]	--
(4)	6	$C_{14}H_{29}$	Ac	2.9	4.9	3.5 (2)	5.6 (2)	-35.3[d]	+36.1[d] (2)
(5)	7	$C_{16}H_{31}$	Ac	---	---	6.0 (2)	--	-----	-32.5[d] (2)
(6)	8	$C_{14}H_{31}$	Ac	---	---	6.0 (2)	--	-----	-36.6[d] (2)
(7)	18[e]	$C_{16}H_{31}$	H	---	---	8.6 (1)	7.6 (1)	-----	-9.6[c] (2)
(8)	19[e]	$C_{14}H_{29}$	H	---	---	8.6 (9)	7.0 (9)	-----	+11.5[f] (9)

[a] 80 MHz. [b] Signal described as a multiplet (ref 1). [c] In dioxane. [d] In dichloromethane. [e] See Chart 2. [f] In chloroform.

Metabolites from Plexaura Flava are described as oils and optical rotation magnitudes agree with those measured for the synthetic compounds but are of opposite sign, showing that the (3R,4R,5R) is the absolute configuration of the natural metabolites 4a and 6a (Chart 2). The elimination product 9 (the enantiomer is shown) was also obtained from pyrolysis of 6a, but nor [α] neither mp are reported in this case.[2]

In conclusion, we provide herein an easy synthetic way to prepare (3S,4S,5S)-3-alkyl-4-hydroxy-5-methyl-2(3H)-dihydrofuranones and (S)-3-alkyl-5-methyl-2(5H)-furanones; moreover the absolute and relative configurations of metabolites 1, 2, 4a and 6a have been unequivocally established.

EXPERIMENTAL SECTION

Melting points have been determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained on a Propol polarimeter, model Dr. Kernchen. Distillation of small amounts were effected on a rotational distillator Büchi, model KRV 65/30 (only external or oven temperature given). The 70 eV electron impact mass spectra were recorded on a Hewlett-Packard spectrometer, model 1310. The 80 MHz pmr and 20 MHz cmr spectra were recorded on a Bruker spectrometer model WP 80 SY, from chloroform-d solutions; chemical shifts are given in parts per million relative to TMS (δ scale). Microanalyses were performed at the Instituto de Química Bio-Orgànica, C.S.I.C., Barcelona.

(4S,5S)-4-Hydroxy-5-methyldihydro-2(3H)-furanone, 14.

(S)-γ-Methyltetronic acid, 13[5] (250 mg, 2.2 mmol) in ethyl acetate (10 ml) was hydrogenated at 60 psi pressure and room temperature, in the presence of 5% Rh/C (50 mg) as catalyst. The catalyst was filtered and washed with ethyl acetate, and the solvent was removed from the filtrate at reduced pressure. The residue was chromatographed on silica gel (mixtures of hexane-ethyl acetate as eluents) affording 190 mg (76 % yield) of hydroxylactone 14 and 30 mg (13% yield) of the isomer 15. Physical and spectral characteristics of the major product 14 agree with those described for this compound in ref 4.

(3S,4S,5S)-3-Hexadecyl-4-hydroxy-5-methyldihydro-2(3H)-furanone, 3

To a stirred solution of diisopropylamine (0.4 ml, 2.85 mmol) in anhydrous THF (3.5 ml) cooled at -78° under argon, 2 ml (3.2 mmol) of a 1.6 M solution of butillithium in hexane were added. After 30 min hydroxylactone 14 (150 mg, 1.3 mmol) in 2.5 ml of THF was added. After stirring for 45 min a solution of 1-iodohexadecane (545 mg, 1.5 mmol) and HMPA (1.5 ml) in THF (3 ml) was dropped. The mixture was stirred at -78° for 20 min and at -35° for 5 h. Then 2 M hydrochloric acid (3.5 ml) was added at -35° and the mixture was allowed to reach r.t. and then extracted with methylene chloride. The combined organic layers were successively washed with 5 ml of 10 % aq sodium thiosulfate and 5 ml of sat aq NaCl. After drying over sodium sulfate the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (mixtures of hexane-ether as eluents), to give 233 mg (53 %) yield of compound 3 as a solid, m.p. 74-75° (from ethyl acetate); $\{\alpha\}^{20}_{D}$ -38.0° (c 1.42, dioxane). (Lit[1] m.p. 88-90°; $\{\alpha\}^{24}_{D}$ -37.3° (dioxane)); ir (KBr) 3540, 3500-3140 (broad), 2940, 2870, 1750, 1730, 1465, 1370, 1210, 1140, 1060 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 30H); 1.40 (d, J 6.5 Hz, 3H); 1.97 (broad s, 1H); 2.53 (m, 1H); 4.18 (dd, J 4.9 Hz, J' 3.6 Hz, 1H); 4.62 (dq, J 6.5 Hz, J' 4.9 Hz, 1H); cmr 13.8, 14.0, 22.6, 27.2, 28.4, 29.3, 29.4, 29.5, 29.7, 31.9, 49.2, 73.8, 78.8, 178.5; ms, m/e 341 (M+1, 5.9), 340 (M, 21.7), 323 (3.9), 129 (63.3), 116 (100.0), 111 (18.7), 99 (28.2), 85 (10.5), 71 (7.5), 57 (58.7), 55 (22.2), 43 (31.1), 41 (19.1).

(3S,4S,5S)-3-Tetradecyl-4-hydroxy-5-methyldihydro-2(3H)-furanone, 5.

Compound 5 was prepared as described above for 3, using 1-iodotetradecane as alkylating agent; m.p. 67-68° (from ethyl acetate-hexane); $\{\alpha\}^{20}_{D}$ -43.2° (c 1.2, methylene chloride), ir (KBr) 3540, 3500-3140 (broad), 2940, 2870, 1750, 1730, 1465, 1370, 1210, 1140, 1060 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 26H), 1.40 (d, J 6.6 Hz, 3H); 1.78 (broad s, 1H); 2.52 (m, 1H); 4.19 (dd, J 4.9 Hz, J' 3.4 Hz, 1H); 4.62 (dq, J 6.6 Hz, J' 4.9 Hz, 1H); cmr 13.8, 14.0, 22.6, 27.2, 28.4, 29.3, 29.4, 29.6, 31.9, 49.2, 73.8, 78.7, 178.4; ms, m/e 312 (M, 11.2), 295 (3.4), 129 (52.8), 116 (100.0), 111 (20.5), 99 (33.3), 71 (12.0), 57 (68.5), 55 (31.3), 43 (45.1), 41 (26.7). Anal. Calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 72.75; H, 11.98.

(3S,4S,5S)-3-Hexadecyl-4-O-acetyl-5-methyldihydro-2(3H)-furanone, 4.

A solution of hydroxylactone 3 (86 mg, 0.2 mmol) and acetic anhydride (270 mg, 2.6 mmol) in anhydrous pyridine (3 ml) was stirred at room temperature for 18 hours. The reaction mixture was poured dropwise into ice-water (50 ml) with stirring and the resulting solution was extracted with four 15 ml portions of ethyl acetate . The combined organic layers were washed with 5 % hydrochloric acid (20 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (95:5 hexane-ethyl acetate as eluent) to afford 90 mg (93 % yield) of acetate 4; m.p. 42.0-43.5°, $\{\alpha\}^{15}_{D}$ -32.9° (c 1.6, methylene chloride). (Lit[2] $\{\alpha\}^{20}_{D}$ 31.9° (c 1.3, methylene chloride) for the enantiomer, described as an oil; lit[1] m.p. 62-64°, not optical rotation given); ir (chloroform) 2940, 2860, 1770, 1740, 1465, 1380, 1240, 1060 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 30 H); 1.33 (d, J 6.5 Hz, 3H); 2.10 (s, 3H); 2.56 (m, 1H); 4.75 (dq, J 6.5 Hz, J' 4.9 Hz, 1H); 5.16 (dd, J 4.9 Hz, J' 2.8 Hz, 1H); cmr 14.0, 14.2, 20.6, 22.6, 27.0, 28.5, 29.3, 29.5, 29.7, 31.9, 47.0, 75.5, 76.6, 170.0, 176.4; ms, m/e 382 (M, 0.7), 323 (11.1), 322 (11.5), 158 (26.9), 99 (23.4), 57 (18.9), 55 (15.7), 43 (100), 41 (20.0).

(3S,4S,5S)-3-Tetradecyl-4-O-acetyl-5-methyldihydro-2(3H)-furanone, 6.

Acetate 6 was prepared in a simmilar manner than described above for compound 4; m.p. 30-32°; $\{\alpha\}^{20}_{D}$ -35.3° (c 1.9, methylene chloride). (Lit[2] $\{\alpha\}^{20}_{D}$ 36.1° (c 1.9, methylene chloride) for the enantiomer, described as an oil); ir (chloroform) 2940, 2860, 1770, 1740, 1465, 1380, 1240, 1060 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 26 H); 1.32 (d, J 6.6 Hz, 3H); 2.10 (s, 3H); 2.56 (m, 1H); 4.75 (dq, J 6.6 Hz, J' 4.9 Hz, 1H); 5.16 (dd, J 4.9 Hz, J' 2.8 Hz, 1H); cmr 14.0, 14.1, 20.5, 22.6, 26.9, 28.5, 29.1, 29.2, 29.4, 29.5, 31.8, 46.9, 75.5, 76.5, 169.9, 176.3; ms, m/e 355 (M+1, 0.9), 295 (2.5), 294 (1.7), 158 (9.0), 99 (13.8), 57 (14.9), 55 (14.8), 43 (100.0), 41 (23.2).

(S)-3-Hexadecyl-5-methyl-2(5H)-furanone, 9 through mesylate 16.

To a stirred solution of hydroxylactone 3 (145 mg, 0.4 mmol) in anhydrous methylene chloride (1.5 ml) under argon, a solution of mesyl chloride (490 mg, 4.3 mmol) and anhydrous pyridine (340 mg, 4.3 mmol) in methylene chloride (0.6 ml) was added over a 5 min period, and the mixture was stirred for 48 h. Then the mixture was diluted with methylene chloride and washed successively with water (20 ml), 5 % hydrochloric acid (2 x 15 ml) and sat aq NaCl (2 x 20 ml), and dried over anhydrous sodium sulfate. The solvent was removed at reduced pressure and the residue was chromatographed on silica gel (mixtures of hexane-ethyl acetate as eluents) to give 137 mg (77 % yield) of (3S,4S,5S)-3-hexadecyl-4-O-mesyl-5-methyldihydro-2(3H)-furanone, 16; m.p. 52-53°; $\{\alpha\}^{21}_{D}$ -30.0 (c 1.6, chloroform); ir (chloroform) 2940, 2870, 1775, 1470, 1350, 1185, 960 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 30H); 1.45 (d, J 6.3 Hz, 3H); 2.82 (m, 1H); 3.08 (s, 3H); 4.77 (dq, J 6.3 Hz, J' 4.8 Hz, 1H); 5.05 (dd, J 4.8 Hz, J' 2.5 Hz, 1H); cmr 13.9, 14.4, 22.5, 26.8, 28.2, 29.1, 29.2, 29.6, 31.8, 38.6, 47.4, 76.4, 80.5, 175.1; ms, m/e 418 (M, 17.5), 382 (10), 334 (20.0), 323 (31.1), 194 (60.4), 111 (37.5), 99 (100), 81 (28.3), 69 (33.7), 57 (60.8), 43 (69.6).

To a stirred solution of mesylate 16 (43 mg, 0.1 mmol) in dry acetone (1 ml) under argon, a solution of tetrabutylammonium acetate (35 mg, 0.1 mmol) in acetone (0.5 ml) was added over a 5 min period. After stirring for 25 min the reaction mixture was poured into water (5 ml) and extracted with three 10 ml portions of ether. The combined organic layers were washed with water (5 ml) and sat aq NaCl (6 ml), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (mixtures of hexane-ethyl acetate as eluents) to give 23 mg (70 % yield) of furanone 9; m.p. 64.5–65.5° (from ethyl acetate-hexane); $\{\alpha\}^{21}_{D}$ 26.7° (c 1.3, dioxane). (Lit[1] m.p. 60–61°; $\{\alpha\}^{24}_{D}$ 27.1° (dioxane)); ir (chloroform) 2950, 2870, 1750, 1655, 1470, 1330, 1095, 1040 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 28 H); 1.40 (d, J 6.7 Hz, 3H); 2.13–2.40 (complex abs, 2H); 4.99 (m, 1H); 6.97 (m, 1H); cmr 14.0, 19.1, 22.6, 25.1, 27.4, 29.1, 29.3, 29.5, 29.6, 31.9, 77.3, 134.4, 148.7, 173.7; ms, m/e 323 (M+1, 22.1, 322 (M, 94.7), 112 (80.5), 97 (22.8), 95 (28.5), 81 (21.4), 67 (40.4), 55 (52.5), 43 (100), 41 (63.6).

(S)-3-Tetradecyl-5-methyl-2(5H)-furanone, 10.

Furanone 10 was prepared in a similar manner than described above for compound 9; m.p. 57–58° (from ethyl acetate-hexane); $\{\alpha\}^{23}_{D}$ 27.7° (c 2.3, methylene chloride; ir (chloroform) 2950, 2870, 1750, 1655, 1470, 1330, 1095, 1040 cm^{-1}; pmr 0.88 (t, J 6.0 Hz, 3H); 1.27 (complex abs, 24 H); 1.40 (d, J 6.7 Hz, 3H); 2.11–2.40 (complex abs, 2H); 4.99 (m, 1H); 6.97 (m, 1H); cmr 14.0, 19.1, 22.6, 25.1, 27.4, 29.1, 29.3, 29.6, 31.8, 77.2, 134.3, 148.7, 173.7; ms, m/e 294 (M, 5.6), 112 (26.4), 97 (8.6), 95 (18.9), 81 (20.3), 67 (41.6), 55 (49.7), 43 (96.5), 41 (100). Anal. Calcd. for $C_{19}H_{34}O_2$: C, 77.50; H, 11.64. Found: C, 77.62; H, 11.36.

Acknowledgement.- Financial support from "Dirección General de Investigación Científica y Técnica" (projet PB-0320) is gratefully acknowledged.

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