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TRANSFORMATION OF LABDANES INTO DRIMANES: OBTENTION OF 11-12-DIACETOXY-7-DRIMENE, PRECURSOR OF BIOLOGICALLY ACTIVE DRIMANES.

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Abstract.- The diacetoxy derivative 4, precursor of biologically active drimanes as poligodial and warburganal, was obtained from methyl-14,15-dinor-7-labden-13-oxo-17-oate a major compound isolated from the hexane extract of Halimium viscosum. The mixture 10/11 was obtained by treatment of 3 with m-CPBA and successive treatment with LAH and 2,2 DMP yields 60% of 18, whose oxidation leads to the aldehyde 9. Transformation of the latter into a mixture of enol acetates, ozonolysis and reduction leads to drimane 27, that can readily be converted to 4.

Introduction.- Poligodial 1 and warburganal 2 are examples of drimane sesquiterpenes that have very important biological activities as antifeedants[1], helicocidals[2], antibiotics, antifungal agents[3], anticomplements[4,5], antitumoral agents together with plant-growth regulatory activity[6].

Synthesis of these and similar compounds has been accomplished by the transformation of natural products[4,7,8,9] or by total synthesis, where the decalinic skeleton has been formed by biomimethic polyolefin cyclizations[10,11,12,13] and a metathesis transanular ene sequence[14], Robinson annelations[15] or by Diels-Alder cycloadditions[16,17].

Results and discussion

The diacetoxy derivative 4 has been described[16] as a pivotal compound in the synthesis of 1 and 2, and our aim in this work was to obtain 4 from 3, a nor-diterpene we have recently described as a major component of Halimium viscosum[18] with a biannular system and the stereochemistry of compounds with drimane skeleton.

The retrosynthetic analysis of 4 is shown in scheme I.

Access to 4 can be accomplished by two different approaches. In the first synthesis of the diol 5, the precursor of 4, can be done in two ways: through an intermediate 8, obtained by the Baeyer-Villiger reaction from 3, or by fragmentation of two epimer lactones 6 and 7 which are obtained directly from 3 by reaction with brominating agents.

In an earlier work[4] the transformation of a similar compound 5 to 2 has been reported.

The second strategy consists in obtaining an aldehyde in C-12, compound 9, whose precursor 10 results from reaction of 3 with peracids.

Treatment of 3 with $Br_2/CHCl_3$[19], Br_2/CCl_4[20], and 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane[21] (Scheme II) yields 6 and 7 whose oxidation with $NaIO_4$[22] gives a low yield of 14. Treatment of 14 with LAH furnishes 5.

Treatment of 3 with m-CPBA over short reaction periods provides a mixture of 8, 10/11 and 12/13.

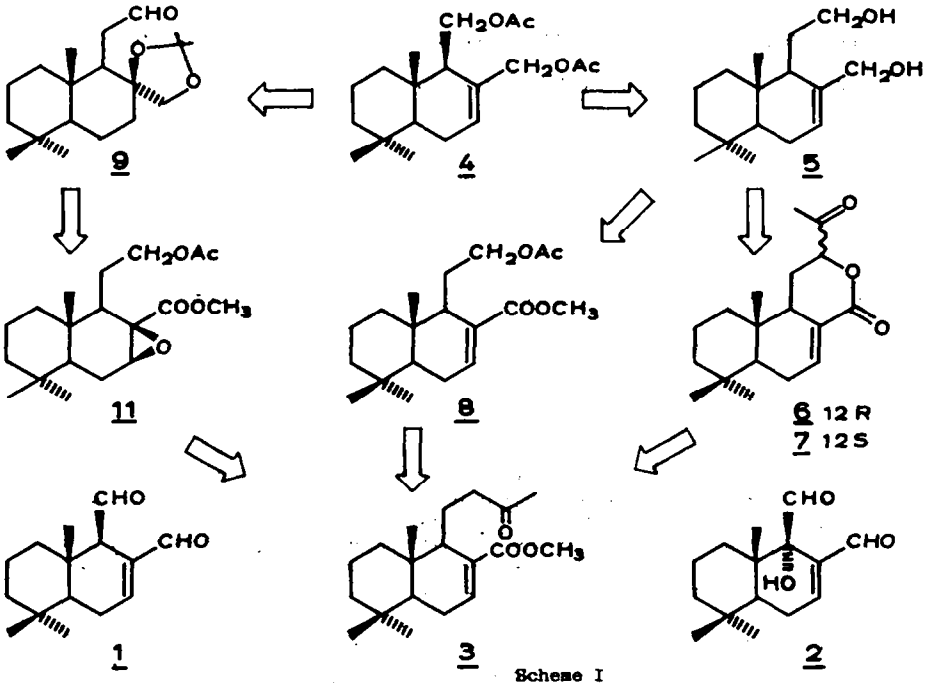
Reduction of 8 with lithium aluminium hydride gives the diol 5 (Scheme II).

The not very promising yields of 8 and 14 have led us to abandon this strategy for the moment and concentrate on the second, as follows.

Treatment of 3 with m-CPBA over long reaction periods give a high yield (95%) of the

mixture 10/11 (Scheme II).

Reduction of 10/11 at room temperature with LAH and later acetylation of the crude mixture gives 15 and 16 at a proportion of 2/3.



Scheme I

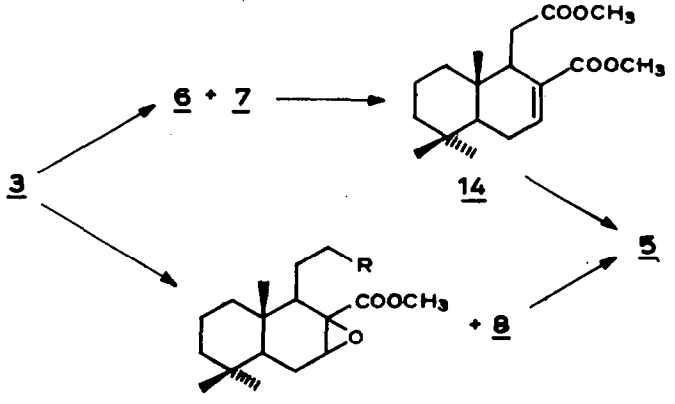
The 8β configuration of the newly formed alcohol 16 was assigned on the basis of its angular methyl ^{1}H NMR shift, in agreement with a cis-1,3-diaxial interaction.

Hydrolysis of 16 gives the desired triol 17, which by treatment with 2,2 DMP/TsOH[23] yields 18, oxidation of the latter with CrO_3/Py[24] gives 9 (Scheme III)

If the crude mixture from the reduction of the mixture 10/11 is treated directly with 2,2 DMP/TsOH a mixture of products that can not be separated by chromatography is obtained.

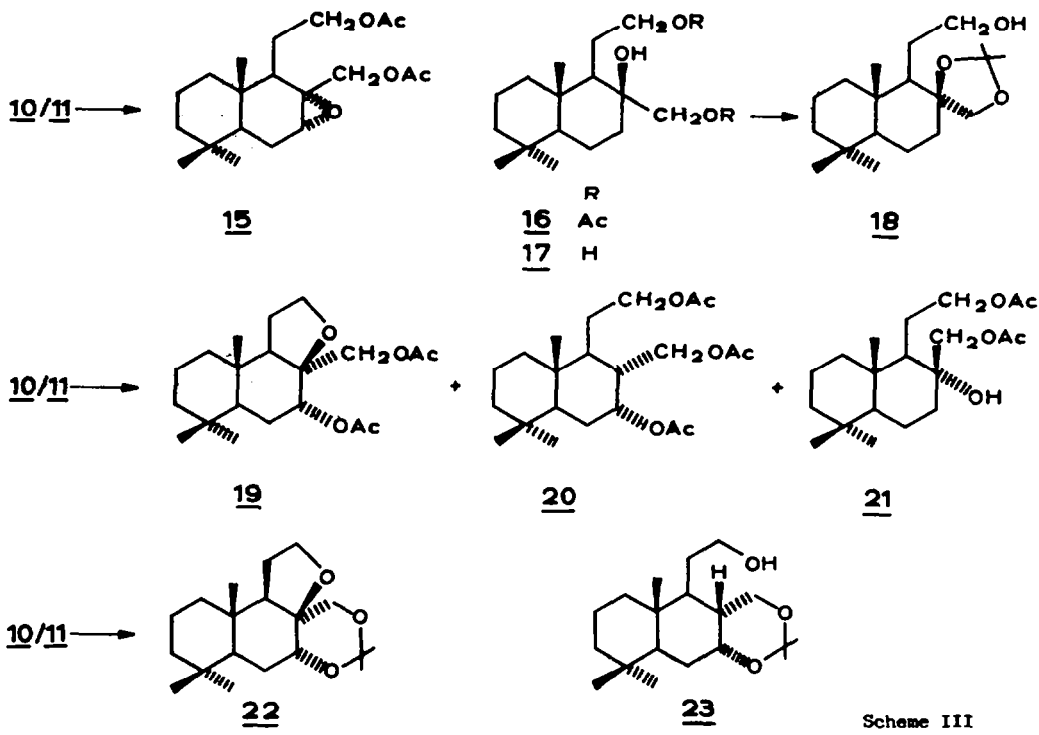
On performing reduction of the mixture 10/11 with LAH and refluxing with THF, followed by acetylation of the crude mixture, 16, 19, 20 and a very small amount of 21 are obtained.

The formation of 16 and 20 can be explained by a trans-diaxial opening of the epoxides



			R
10/11	α/β	epoxy	AcO
12/13	α/β	epoxy	Ac

Scheme II



Scheme III

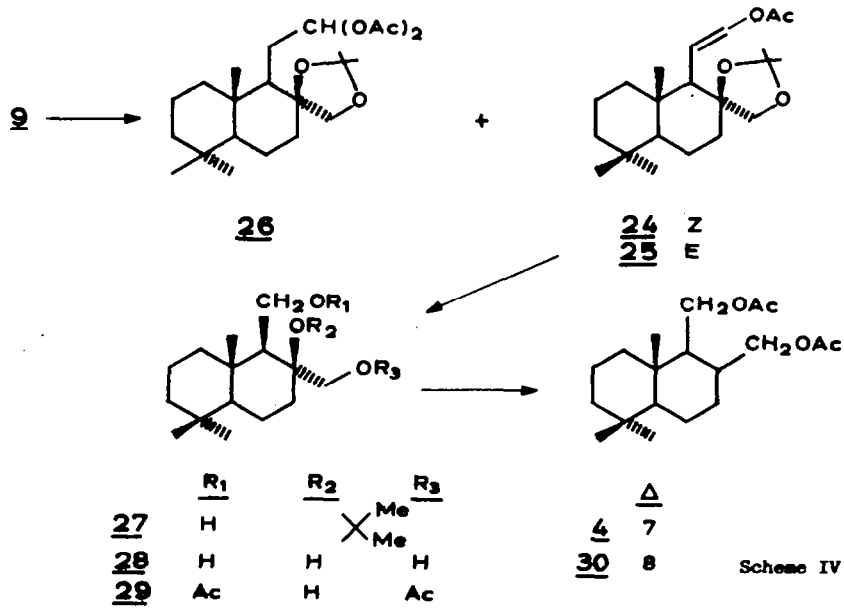
10 and 11 respectively. The formation of 19 from 11 is an intramolecular opening on the epoxide by the hydroxyl group in C-12. The stereochemistry in C-7 of 19 can be established on the basis of the shift and multiplicity of the H-7 signal in the ^{1}H NMR (5.21 ppm, t, J= 5.86 Hz).

If the crude mixture of the reduction of 10/11 with LAH and refluxing with THF is treated directly with 2,2 DMP/TsOH, 22, 23 and 60% of 18 are obtained (Scheme III); the oxidation reaction of 18 gives 9.

Treatment of 9 with Ac_2O/Et_3N/DMAP yields a mixture of configurational isomers 24(Z) and 25 (E) and a very small amount of the acylal 26[25](Scheme IV).

Treatment of 24/ 25 with O_3 and subsequent reduction with LAH[26] provides the drimane 27. A certain amount of 24 is also isolated as non-reacted product.

Hydrolysis of 27 gives 28, which is purified as its acetylderivative 29. Dehydration of 29 using $POCl_3$/Py leads to 4 and 30[16]. (Scheme IV).



Scheme IV

TABLE.- ^{13}C Chemical shifts, in ppm. Assingment based on DEPT experiments.

C	3	4	5	6	7	8	9	11	14	15	16	18	19	20	21	22	23	24	26	27	28	29	30
1	39.3	39.4	39.2	38.4	38.7	39.3	39.6	40.6	37.7	39.6	37.3	39.5	42.0	38.4	39.6	40.9	38.5	39.6	39.6	39.9	38.0	39.8	51.0
2	18.5	18.7	18.7	18.5	18.5	18.6	18.3	18.1	18.6	18.6	18.2	18.4	18.3	18.6	18.5	18.4	18.7	18.5	18.3	18.6	19.0	18.3	18.4
3	42.1	42.1	42.3	41.8	41.9	42.1	41.9	42.1	41.9	42.1	42.0	42.1	42.3	42.0	41.9	42.1	42.2	42.1	42.0	41.9	43.1	41.9	41.6
4	32.8	33.2	33.0	32.9	32.8	32.9	33.5	32.9	32.9	33.0	33.3	33.3	32.8	32.7	33.4	32.5	32.8	33.4	33.3	33.4	34.1	33.4	33.2
5	49.4	49.5	48.7	45.1	48.8	47.6	49.4	45.0	46.9	45.7	51.3	52.9	47.5	41.0	56.1	45.6	42.4	51.7	50.9	55.4	56.2	53.8	51.0
6	24.0	23.7	23.8	23.2	25.3	24.1	40.7	21.1	24.2	22.3	39.3	19.2	27.4	27.1	38.6	25.7	30.8	40.1	39.9	40.0	41.0	38.2	18.8
7	138.0	130.3	138.7	144.2	144.5	138.2	19.2	59.9	139.2	58.2	17.6	40.0	71.4	69.4	19.9	67.6	67.9	18.9	19.1	19.2	19.5	17.6	29.5
8	134.7	133.5	126.5	125.5	125.3	134.6	83.2	60.3	132.8	57.8	73.5	83.7	84.2	44.9	74.0	81.3	38.1	82.2	83.4	82.7	75.8	73.2	141.3
9	50.3	51.1	50.0	48.9	48.9	49.4	55.3	49.5	49.1	50.9	55.7	55.8	54.1	47.5	56.8	52.3	47.1	56.1	55.6	59.2	56.8	55.6	133.5
10	37.0	38.5	36.8	34.6	34.9	36.7	38.7	35.8	36.4	35.7	38.8	39.6	36.4	38.2	38.2	35.5	37.9	39.0	39.4	38.3	39.1	37.5	38.5
11	21.9	62.9	28.4	25.3	25.9	27.6	39.4	26.5	32.9	23.9	23.8	28.2	24.8	26.1	24.2	25.0	28.0	136.8	28.9	59.8	59.3	61.6	59.4
12	45.5	67.8	64.3	81.8	82.9	65.6	202.4	63.7	174.2	65.3	65.5	64.9	65.6	65.0	65.9	64.7	62.1	111.3	91.8	74.8	70.7	71.4	64.5
13	208.9	33.2		206.3	206.5															33.7	34.3	33.6	33.3
14		21.9																		22.0	22.2	20.8	21.6
15		14.4																		15.8	17.1	16.2	20.5
16	29.7			27.1	25.9																		
17	169.2		66.4	164.4	164.2	169.1	74.8	170.1	168.4	67.4	71.1	74.5	66.4	63.6	66.3	67.3	64.8	74.3	74.1				
18	33.1		33.1	32.8	32.9	33.1	33.3	33.2	33.0	32.7	33.4	33.6	33.0	33.0	33.4	33.5	33.2	33.6	33.6				
19	21.9		21.8	21.4	21.5	21.9	21.8	21.9	21.8	22.0	21.8	21.8	21.6	21.5	21.5	21.2	21.6	21.9	21.9				
20	14.1		13.6	13.1	13.4	14.0	15.2	15.3	14.0	14.1	15.1	15.1	16.1	13.1	15.9	14.8	13.3	15.6	15.0				
COOMe	51.3					51.4		52.3	51.5 51.3														
OOCMe		20.9 21.1				21.0		20.9		20.8 20.9	20.8 20.9		21.2 20.9	21.1 20.9 20.8	21.1 21.0			20.7	20.8 20.8			21.7 21.1	20.9 21.1
OOCMe		170.8 170.8				170.9		172.0		170.9 170.2	171.0 170.9		170.9 169.9	170.9 170.8 170.3	171.0 171.0			167.8	169.0 169.0			170.9 170.6	170.9 170.8
$(Me)_2C^{O}_{O}$							109.7					109.6				99.1	98.6	109.5	109.5				
$(Me)_2C^{O}_{O}$							26.4 26.9					26.9 26.9				26.2 22.2	29.9 19.3	27.3 27.3	26.9 26.9				

EXPERIMENTAL

Melting points were determined in a capillary tube in a Buchi apparatus or in a Kofler hotplate apparatus. I.R. spectra were measured as films for oils or as KBr pellets for solids on a Beckman-33-IR spectrophotometer. The 200 MHz ^1H NMR and 50 MHz ^{13}C NMR spectra were determined on a Bruker WP-200-SYspectrometer usually in $CDCl_3$, except otherwise indicated. Chemical shifts in ppm are reported as relative to TMS in the ^1H NMR and to $CDCl_3$ at 77.0 ppm in the ^{13}C NMR . UV absorptions were measured on a digital Varian-8-654 spectrophotometer. Optical rotations were performed in a chloroformic solution except otherwise indicated, with a digital Perkin-Elmer-241- polarimeter.

The raw-material 3, was isolated from a n-hexane extract of Halimium viscosum, as reported in reference 18.

Reaction of 3 with Br_2/ CCl_4.- 0.05 ml of bromine were added to compound 3 (100 mg, 0.33 mmol) in dry CCl_4 (3ml), and the mixture was kept at room temperature overnight. The solvent was eliminated under vacuum, ether was added and the ethereal solution was washed with aqueous $NaHCO_3$ and water, dried and concentrated, yielding 700 mg of a product which was chromatographed on SiO_2. Elution with hexane-AcOEt 90:10 afforded 30 mg (31%) of a lactone 6, and 12 mg (5%) of an epimer 7.

A change in the solvent did not produce alterations in the composition of the crude mixture.

Treatment of 3 with isopropyliden dibromomalonate.- Compound 3 was dissolved (0.77g, 2.52 mmol) in 5ml of CCl_4, and (0.36 mg, 1.28 mmol) of 5,5-Dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane were added. The mixture was heated at 80ºC for 7 hours. The reaction was monitored by ^1H NMR. After evaporating the CCl_4, ether was added and the ethereal solution was washed with aqueous $NaHCO_3$, brine and water until neutral pH was reached. This was dried and concentrated, yielding a crude mixture (775 mg) that was chromatographed on SiO_2 with hexane:AcOEt (90:10) to afford (in order of elution): 6 300 mg (47%) and 7 80 mg (11%).

14,15-dinor-13-oxo-7-labden-12S,17-olide: 6.- Crystalline product, m.p. 97-98ºC (from $CHCl_3$); $[\alpha]_D^{22}$ = -44.7º (c 0.9, $CHCl_3$); ν_{max} (KBr) 1730, 1650, 1370, 1260, 1200, 1100, 980; δ_H ($CDCl_3$) 7.38 (1H, m, 7-H), 4.56 (1H, dd, J= 11.7 , 2.4 Hz, 12-H), 2.33 (3H, s, -OCMe), 0.91 (3H, s), 0.89 (3H, s), 0.75 (3H, s); δ_C ($CDCl_3$) See table.

14,15-dinor-13-oxo-7-labden-12R,17-olide 7.- Crystalline product, m.p. 107-109ºC (from $CHCl_3$); $[\alpha]_D^{22}$ -57.3º (c 0.6, $CHCl_3$); ν_{max} 1720, 1640, 1380, 1270, 1210, 960; δ_H ($CDCl_3$) 7.33 (1H, m, 7-H), 4.88 (1H, m, 12-H), 2.24 (3H, s, OCMe), 0.89 (3H, s), 0.85 (3H, s), 0.74 (3H, s); δ_C ($CDCl_3$) See table.

Oxidation of 6 with $NaIO_4$: 14.- 93 mg (0.32 mmol) of 6 were dissolved in 3 ml of MeOH and 0.18 g (3.2 mmol) of KOH were added. pH was adjusted to 9.5 by addition of 2M HCl. 68 mg (0.32 mmol) of $NaIO_4$ dissolved in 10 ml of water were added in small portions. The pH was kept between 5 and 6 by addition of an aqueous solution NaOH where necessary. Having completed the addition of $NaIO_4$, the mixture was stirred for 4 hours at room temperature. After achieving complete conversion of the substrate, 0.02 ml of $NaSO_2H$ were added to consume the excess of oxidant keeping pH at 5. The mixture was extracted with ether. The ethereal phase was washed with water to neutrality, dried and the solvent eliminated under vacuum, yielding a crude mixture (70 mg) that was esterified by a solution of CH_2N_2 and chromatographed on Silicagel to yield 30 mg of 14 (30%).

Methyl-13,14,15,16-tetranor-7-labden-12,17-dioate 14.- Oily product; $[\alpha]_D^{23}$ -140º (c 0.3, $CHCl_3$); ν_{max} (film) 1750, 1650, 1280, 1240, 1160, 830; δ_H ($CDCl_3$) 6.88 (1H, m, 7-H), 3.70 (3H, s, -COOMe), 2.81 (1H, m, 9-H_a), 2.51 (1H, dd, J= 17.0, 6.4 Hz, 11-H_b), 0.91 (3H, s), 0.89 (3H,s), 0.78(3H, s); δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-7-labden-12,17-diol: 5.- Three milligrams of $LiAlH_4$ (0.08 mmol) in THF (3ml) were added to a solution of 14 (25 mg, 0.08 mmol) in dry THF (3ml) under N_2. The mixture was stirred for 30 min. Following this, THF was added with a few drops of water; the mixture was filtered and evaporated to obtain 18 mg (0.07 mmol) of 5 (90%). Crystalline product, m.p. 90-91ºC (from $CHCl_3$); $[\alpha]_D^{22}$-20.9º (c 2.0, MeOH); ν_{max} 3380, 1470, 1400, 1380, 1060, 1010; δ_H ($CDCl_3$) 5.71 (1H, m, 7-H), 4.28 (1H,d, J= 12.2 Hz, 17-H_a), 3.84 (1H, d, J= 12.2 Hz, 17-H_b), 3.77 (1H,ddd, J= 10.3, 10.3, 5.4 Hz, 12-H_a), 3.60 (1H,ddd, J= 10.3, 8.3, 5.8 Hz, 12-H_b), 0.88 (3H, s), 0.86 (3H, s) 0.76 (3H, s); δ_C ($CDCl_3$) See table.

Reaction of 3 with m-CPBA (I).- Compound 3 (1.11g, 3.63 mmol) was dissolved in dry CH_2Cl_2 (3ml) and m-CPBA (735 mg, purity 85%) was added. The mixture was kept refluxing for 7 hours. The solvent was eliminated and ether was added. The ethereal solution was washed with water, Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue (1.10g) was chromatographed on SiO_2 eluting with hexane:AcOEt (95:5) and contained 570 mg of the initial product (48% conversion), 130 mg (0.40 mmol) of 8 (11%), 60 mg (0.18 mmol) of a mixture 10/11 (5%) (10<<11), and 250 mg (0.74 mmol) of a mixture 12/13 (22%).

Reaction of 3 with m-CPBA (II).- Three grams (85% purity) of m-CPBA was added to a solution of 3 (2.7 g, 8.82 mmol) in 10 ml of dry CH_2Cl_2. The mixture was kept stirred at room temperature for 15 days. 2.7 g (8.4 mmol) of a mixture 10/11 at a proportion 1:1 (95%) were obtained in the same manner as above.

Methyl-13,14,15,16-tetranor-12-acetoxy-7-labden-17-oate: 8.- Colourless oil, $[\alpha]_D^{20}$ -39.2º (c 0.8, $CHCl_3$); ν_{max} (film) 1750, 1730, 1650, 1250, 1150, 1050, 760; δ_H ($CDCl_3$) 6.74 (1H, m, 7-H), 4.29 (1H, ddd, J= 11.0, 10.0, 5.0 Hz, 12-H_a), 4.15 (1H, ddd, J=11.0, 9.0, 7.0 Hz, 12-H_b), 3.87 (3H, s, -COOMe), 2.03 (3H, s, AcO-), 0.90(3H, s), 0.87(3H, s), 0.81 (3H, s); δ_C ($CDCl_3$) See table.

Methyl-13,14,15,16-tetranor-12-acetoxy-7(α/β),8(α/β)-epoxy-17-oate: 10/11.- Colourless oil; ν_{max} (film) 1740, 1240, 1160, 1040, 760; δ_H($CDCl_3$) 4.02 (2H, t, J=7.3 Hz, 12-H), 3.90 (2H, m, 12'-H), 3.71 (3H, s, -COOMe), 3.70 (3H, s, -COOMe), 3.28 (1H, d, J=6.4 Hz, 7-Hα), 3.18 (1H, m, 7-Hβ), 1.98 (6H, s, AcO-), 0.84 (6H, s), 0.80 (6H, s), 0.79 (6H, s).

Methyl-13,14,15,16-tetranor-12-acetoxy-7β-8β-epoxy-labdan-17-oate: 11.- Colourless oil; ν_{max} (film) 1740, 1240, 1160, 1050, 1040, 790, 760; δ_H ($CDCl_3$) 4.02 (2H, t, J= 7.3 Hz. 12-H), 3.70 (3H, s, -COOMe), 3.28 (1H, d, J=6.4 Hz, 7-H), 1.98 (3H, s, AcO-), 0.84 (3H, s), 0.80 (3H, s), 0.79 (3H, s); δ_C ($CDCl_3$) See table.

Methyl-14,15-dinor-7(α/β),8(α/β)-epoxy-13-oxo-labdan-17-oate: 12/13.- Crystalline product; ν_{max} (melting) 1750, 1710, 1370, 1270, 1200, 1160, 1050; 870, 840; δ_H ($CDCl_3$) 3.73 (3H, s, -COOMe), 3.31 (1H, d, J=6.4 Hz, 7-H), 3.24 (1H, m, 7'-H), 2.10 (3H, s, Me-CO), 0.88 (3H, s), 0.87 (3H, s), 0.86 (3H, s), 0.85 (3H, s), 0.84 (3H, s), 0.82 (3H, s).

Reduction of 8 with LAH: 5.- $LiAlH_4$ (13mg, 0.34 mmol) was added to a stirred, ice-cooled solution of 8 (90 mg, 0.28 mmol) in dry ether (3 ml) and the mixture was stirred for 30 min under N_2. The mixture was poured into 5% aq. H_2SO_4-ice and extracted with ether. The ether solution was washed with water, sat. $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed on SiO_2, yielding 70 mg (0.28 mmol) of 5 (100%).

Reduction of mixture 10/11 with LAH (I).- $LiAlH_4$ (20 mg, 0.53 mmol) was added to a solution of 10/11 (82 mg, 0.24 mmol) in dry THF (4ml) and kept stirred at room temperature for 30 min. Following this, THF was added with a few drops of water and the solvent was eliminated under vacuum. The crude mixture was extracted with AcOEt. Evaporation of the solvent afforded 67 mg of crude mixture which was dissolved in dry pyridine (2 ml) and acetylated with Ac_2O (3 ml, 31.8 mmol) at room temperature for 12 hours. Excess Ac_2O was hydrolyzed with ice-water and the product was extracted with ether in the usual way giving, 70 mg of a mixture which was chromatographed on SiO_2 yielding 43 mg of 15 (61.4%) and 12 mg of 16 (17.1%).
Reduction of mixture 10/11 with LAH (II).- $LiAlH_4$ (60 mg, 1.58 mmol) was added to a solution of mixture 10/11 (240 mg, 0.71 mmol) in dry THF (10 ml), under N_2 and the mixture was kept refluxing for 9 hours. In the same manner as described for the previous reduction, a crude mixture (200 mg) was obtained that was dissolved in dry pyridine (3 ml) and was acetylated with Ac_2O (3 ml, 31.8 mmol) at room temperature overnight. The excess of Ac_2O was hydrolyzed with ice-water and the product was extracted with ether in the usual way, giving 240 mg of a mixture of acetylderivatives that were separated by column chromatography on SiO_2 and eluting with hexane:AcOEt (92:8) to afford: 19 (40 mg, 16.7%), 20 (20 mg, 8.3%), 16 (130 mg, 54.2%) and 21 (10 mg, 4.2%).

13,14,15,16-tetranor-12,17-diacetoxy-7α,8α-epoxy-labdane: 15.- Colourless oil, $[\alpha]_D^{22}$ +17.7º (c 0.9, $CHCl_3$), ν_{max} (film) 1740, 1240, 1040; δ_H ($CDCl_3$) 4.21 (1H, d, J=12.2 Hz, 17-H_a), 4.20 (1H, m, 12-Hα) 4.07 (1H, d, J=12.2 Hz, 17-H_b), 4.05(1H, m, 12-H_b), 3.18 (1H, m, 7-H), 2.07 (3H, s, AcO-), 2.05 (3H, s, AcO-), 0.86 (3H, s), 0.85 (3H, s), 0.76 (3H, s). δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-12,17-diacetoxy-8β-labdanol: 16.- Colourless oil, $[\alpha]_D^{20}$ +6.1º (c 1.5, $CHCl_3$); ν_{max} (film) 3500, 1750, 1250, 1040, 980, 930; δ_H ($CDCl_3$) 4.02 (1H, d, J=11.0 Hz, 17-H_a), 4.00 (2H, m, 12-H), 3.84 (1H, d, J=11.0Hz, 17-H_b), 2.10 (3H, s, AcO-), 2.05 (3H, s, AcO-), 0.99(3H, s), 0.89 (3H, s), 0.85 (3H, s); δ_C ($CDCl_3$) See table.

Alkaline hydrolysis of 16: 17.- 51 mg (0.15 mmol) of 16 are saponificated at room temperature with 2 ml (2mmol) of 1M KOH/MeOH for three hours. The usual procedure is followed, yielding 40 mg (0.15 mmol) of 17 (100%), crystalline product, m.p. 183-184ºC (from MeOH); ν_{max} (KBr) 3500, 1120, 1090; δ_H (CD_3OD) 3.40 (2H, m, 12-H), 3.30 (1H, d, J=12.0 Hz, 17-H_a), 3.00 (1H, d, J=12.0 Hz, 17-H_b), 0.97 (3H, s), 0.84 (3H, s), 0.81 (3H, s).

13,14,15,16-tetranor-7α,17-diacetoxy-8β,12-epoxy-labdane: 19.- Colourless oil, $[\alpha]_D^{19}$ -50.0º (c 2.3, $CHCl_3$); ν_{max} (film) 1740, 1240, 1040, 920, 860; δ_H ($CDCl_3$) 5.21 (1H, t, J=5.9 Hz, 7-H), 4.08 (1H, d, J=11.2 Hz, 17-H_a), 4.03 (1H, d, J=11.2 Hz, 17-H_b), 3.91 (2H, m, 12-H), 2.04 (3H, s, AcO-), 2.01 (3H, s, AcO-), 0.92 (3H, s), 0.86 (3H, s), 0.80 (3H, s); δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-7α,12,17-triacetoxy-8-epilabdane: 20.- Colourless oil, $[\alpha]_D^{19}$ -61.5º (c 1.5, $CHCl_3$); ν_{max} (film) 1740, 1240, 1030, 980, 960; δ_H ($CDCl_3$) 5.18 (1H, q, J= 2.9 Hz, 7-H), 4.12 (1H, dd, J=10.8, 4.6 Hz, 17-H_a), 3.96 (1H, dd, J=10.8, 13.0 Hz, 17-H_b), 3.92 (2H, m, 12-H), 2.04 (3H, s, AcO-), 2.02 (3H, s, AcO-), 0.82 (3H, s), 0.79 (3H, s), 0.78 (3H, s); δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-12,17-diacetoxy-8-labdanol: 21.- Colourless liquid, $[\alpha]_D^{21}$ -1.9º (c 0.8, $CHCl_3$); ν_{max} (film) 3500, 1750, 1250, 1050, 980; δ_H ($CDCl_3$) 4.30 (1H, d, J=11.7 Hz, 17-H_a), 4.13 (2H, t, J= 7.8 Hz, 12-H), 4.01 (1H, d, J=11.7 Hz, 17-H_b), 2.11(3H, s, AcO-), 2.04 (3H, s, AcO-), 0.87 (3H, s), 0.81 (3H, s), 0.79 (3H, s); δ_C ($CDCl_3$) See table.

Reaction of the reduction product II with 2,2 DMP.- 2,2 DMP (0.5 ml, 4.09 mmol) and TsOH (3 mg) was added to a suspension of the crude mixture of the reduction II (0.5 g) in dry acetone (5ml). After stirring the mixture at room temperature for 10 hours, 5 mg of $NaHCO_3$ were added and the mixture was filtered and evaporated to obtain 0.55g of reaction product, that was chromatographed

on SiO_2 eluting with hexane:AcOEt (92:8) to afford: 22 (70 mg, 12.7%), 18 (330 mg, 60%) and 23 (45 mg, 8.2%) in order of elution.

13,14,15,16-tetranor-7α,17-isopropylidendioxy-8β,12-epoxy-labdane: 22.- Crystalline product, m.p. 72-73ºC (from $CHCl_3$); $[\alpha]_D^{17}$+10.0º (c 1.0, $CHCl_3$); ν_{max} (film) 1230, 1200, 1080, 1060, 1030, 1000, 970, 900, 840, 720; δ_H ($CDCl_3$) 4.03 (1H, dd, J= 3.9,1.9 Hz, 6-H), 3.77 (1H, ddd, J=8.8, 8.3, 4.9 Hz , 12-H_a), 3.75 (1H, ddd, J=8.8, 8.8, 8.8 Hz, 12-H_b), 3.49 (1H, d, J=12.0 Hz, 17-H_a), 3.41 (1H, d, J=12.0 Hz, 17-H_b), 1.41 (3H, s,-O-C(Me)$_2$-O-), 1.32 (3H, s, -O-C(Me)$_2$-O-), 0.88 (3H, s), 0.86 (3H, s), 0.83 (3H, s); δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-8β,17-isopropylidendioxy-12-labdanol: 18.- Colourless oil, $[\alpha]_D^{19}$+2.3º (c 5.1, $CHCl_3$); ν_{max} (film) 1370, 1260, 1210, 1150, 1050, 1010, 880; δ_H ($CDCl_3$) 3.90 (1H,d, J=8.8 Hz, 17-H_a) 3.59 (2H, m, 12-H), 3.57 (1H, d, J=8.8 Hz, 17-H_b), 1.41 (3H, s, -O-C(Me)$_2$-O-), 1.36 (3H, s, -O-C(Me)$_2$-O-), 0.94 (3H, s), 0.86 (3H, s), 0.84 (3H, s); δ_C ($CDCl_3$) See table.

13,14,15,16-tetranor-7α,17-isopropylidendioxy-8-epi-12-labdanol: 23.- Oily product, $[\alpha]_D^{17}$-26.1º (c 1.0, $CHCl_3$); ν_{max} (film) 3300, 1290, 1240, 1150, 1060, 850; δ_H ($CDCl_3$) 4.15 (1H, q, J=2.4Hz, 7-H), 3.94 (1H, dd, J= 13.1, 2.4 Hz, 17-H_a), 3.90 (1H, dd, J=13.1, 1.9 Hz, 17-H_b), 3.63 (2H, m, 12-H), 1.45 (3H, s, -O!C(Me)$_2$-O-), 1.39 (3H, s, -O-C(Me)$_2$-O-), 0.85 (3H, s), 0.80 (3H, s), 0.78 (3H, s); δ_C ($CDCl_3$) See table.

Oxidation of 18 with CrO_3/Py: 9.- 1 ml of pyridine and dry CH_2Cl_2 (3 ml) were placed in a 50 cc Erlenmeyer flask externally cooled with ice. 662 mg (0.66 mmol) of CrO_3 was added in small portions with stirring until a thick yellow paste was obtained. This was allowed to reach room temperature and was stirred for 15 min. under N_2. Following this 18 (310 mg, 1.00 mmol) dissolved in dry CH_2Cl_2 (2.5 ml) was added and the mixture was stirred vigorously for 1.5 hours. The mixture was filtered and chromatographed on SiO_2, yielding 240 mg (0.78 mmol) of 9, colourless oil, $[\alpha]_D^{22}$ +8.0º (c 1.2, $CHCl_3$); ν_{max} (film) 2720, 1730, 1370, 1260, 1150, 1010, 880; δ_H ($CDCl_3$) 8.75 (1H, s, -CHO), 3.61 (2H, s, 17-H), 2.70 (1H, dd, J=19.5, 3.9 Hz, 11-H_a),2.52 (1H, dd, J=19.5, 4.9 Hz, 11-H_b) 1.43 (3H, s, -O-C(Me)$_2$-O-), 1.34 (3H, s, -O-C(Me)$_2$-O-), 0.93 (3H, s), 0.88 (3H, s), 0.84 (3H, s); δ_C ($CDCl_3$) See table.

Reaction of 9 with Ac_2O/Et_3N/DMAP.- Et_3N (0.4 ml), Ac_2O (0.5 ml, 5.3 mmol) and 7.3 mg of DMAP were added to 230 mg (0.75 mmol) of 9 dissolved in dry THF (4 ml). The mixture was refluxed under N_2 for 42 hours. The solvent was then eliminated under vacuum and the crude was chromatographed on SiO_2, eluting with hexane:AcOEt (95:5) to afford a mixture 24/25 (180 mg, 0.51 mmol) (69%) and 26 (60 mg, 0.15 mmol) (20%).

13,14,15,16-tetranor-8β,17-isopropylidendioxy-12-acetoxy-11(Z/E)-labdene: 24/25.- Colourless oil; ν_{max} (film) 1760, 1670, 1240, 1150, 1050, 910, 790; δ_H ($CDCl_3$) 24(Z): 7.22 (1H, d, J=6.7 Hz, 12-H), 5.06 (1H, dd, J=10.7, 6.7 Hz, 11-H), 3.65 (1H, d, J=8.3 Hz, 17-H_a), 3.56 (1H, d, J=8.3 Hz, 17-H_b), 2.14 (3H, s, AcO-), 1.39 (3H, s, -O-C(Me)$_2$-O-), 1.34 (3H, s, -O-C(Me)$_2$-O-), 0.99 (3H, s), 0.90 (3H, s), 0.87 (3H, s); 25 (E): 6.97 (1H, d, J=12.0 Hz, 12-H), 5.44 (1H, dd, J=12.0, 10.7 Hz, 11-H), 3.64 (1H, d, J=8.0 Hz, 17-H_a), 3.58 (1H, d, J=8.0 Hz, 17-H_b), 1.39 (3H, s, -O-C(Me)$_2$-O-), 1.34 (3H, s, -O-C(Me)$_2$-O-), 0.99 (3H, s), 0.90 (3H, s), 0.87 (3H, s).

13,14,15,16-tetranor-8β,17-isopropylidendioxy-12,12-diacetoxy-labdane: 26.- Colourless liquid, $[\alpha]_D$ +9.0 (c 2.0, $CHCl_3$); ν_{max} (film) 1760, 1240, 1200, 1050, 880; δ_H ($CDCl_3$) 6.75 (1H, dd, J=8.1, 4.4 Hz, 12-H), 4.01 (1H, d, J=8.5 Hz, 17-H_a), 3.56 (1H, d, J=8.5 Hz, 17-H_b), 2.07 (3H, s, AcO-), 2.05 (3H, s, AcO-), 1.38 (3H, s, -O-C(Me)$_2$-O-), 1.35 (3H, s, -O-C(Me)$_2$-O-), 0.92 (3H, s), 0.85 (3H, s), 0.83 (3H, s); δ_C ($CDCl_3$) See table.

Reaction of 24/25 with O_3 and reduction : 27.- A stream of dry O_3 was passed through a solution of 24/25 (180 mg, 0.51 mmol) in CCl_4 (15 ml), cooled at -21ºC, until saturation for 0.5 hours, after which a stream of N_2 was passed and the solution was poured into a suspension of $LiAlH_4$ (76 mg, 2.0 mmol) in dry THF (5 ml) cooled at -21ºC. The mixture was stirred for 30 min. Then THF was added with a few drops of water. The mixture was filtered washing with abundant ether and the filtrate was concentrated in vacuo. The residue (120 mg) was chromatographed on SiO_2, eluting with hexane: AcOEt (92:8) to afford: 25 (50 mg, conversion 73%) and 27 (60 mg, 0.2 mmol)(40%).

8β,12-isopropylidendioxy-11-drimanol: 27.- Crystalline product, m.p. 116-118º (from $CHCl_3$); $[\alpha]_D^{19}$ +5.0º (c 1.1, $CHCl_3$); ν_{max} (film) 3380, 1370, 1260, 1210, 1150, 890; δ_H ($CDCl_3$) 4.23 (1H, d, J= 8.8 Hz, 12-H_a), 3.85 (1H, dd, J=11.8, 6.9 Hz, 11- H_a), 3.77 (1H, dd, J=11.8, 7.3 Hz, 11-H_b), 3.59 (1H, d, J=8.8 Hz, 12-H_b), 1.45 (3H, s, -O-C(Me)$_2$-O-), 1.37 (3H, s, -O-C(Me)$_2$-O-), 0.89 (3H, s), 0.86 (3H, s), 0.83 (3H, s); δ_C ($CDCl_3$) See table.

8β,11,12-drimanetriol: 28.- TsOH (3 mg) was added to a solution of 27 (50 mg, 0.17 mmol) in MeOH (3 ml), and the mixture was stirred at room temperature for 36 hours. The MeOH was eliminated under vacuum; ether was added and the ethereal solution was washed with aqueous 5% $NaHCO_3$ and with water to neutrality, dried (Na_2SO_4), and the solvent eliminated under vacuum, yielding the triol 28 (35 mg, 0.14 mmol, 80%). Colourless oil; ν_{max} (KBr) 3500, 1150, 1050; δ_H (CD_3OD) 3.86 (1H, dd, J=11.4, 4.3 Hz, 11-H_a), 3.77 (1H, dd, J=11.4, 2.8 Hz, 11-H_b), 3.47 (1H, d, J=11.2 Hz, 12-H_a), 3.23 (1H, d, J=11.2 Hz, 12-H_b), 1.05 (3H, s, 15-Me), 0.84 (3H, s), 0.82 (3H, s); δ_C (CD_3OD) See table.

11,12-diacetoxy-8β-drimanol: 29.- 35 mg (0.14 mmol) of 28 dissolved in 2 ml of anhydrous pyridine were acetylated with 1 ml (10.3 mmol) of Ac_2O at room temperature for 12 hours. Ice was added and after one hour the product was recovered in the usual way, yielding after chromatography on SiO_2 and elution with hexane:AcOEt (96:4): 29 (46 mg, 0.14 mmol, 100%). Crystalline product, m.p. 118-120ºC (from $CHCl_3$); $[\alpha]_D^{21}$+18.1º (c 2.0, $CHCl_3$); ν_{max}(melting) 3500, 1740, 1240; δ_H ($CDCl_3$)

4.29 (2H, d, J=3.9 Hz, 11-H), 3.97 (1H, d, J=11.2, 12-H_a), 3.93 (1H, d, J=11.2 Hz, 12-H_b), 2.08 (3H, s, AcO-), 2.01 (3H, s, AcO-), 1.00 (3H, s, 15-Me), 0.88 (3H, s), 0.84 (3H, s); δ_C ($CDCl_3$) See table; (Found. C, 67.0; H 9.4; $C_{19}H_{32}O_5$, requires C, 67.1; H, 9.4%).

Dehydration of 29 with $POCl_3$/Py.- $POCl_3$ (freshly distilled, 0.2 ml, 2.19 mmol) was added to a solution of 29 (29 mg, 0.08 mmol) in anhydrous pyridine (4ml), cooled to 0°C under N_2. Having completed the addition, the mixture was stirred at room temperature for 24 hours. Then ice and ether were added. The ethereal solution was washed with 2M HCl, aqueous 5% $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was eliminated under vacuum, yielding a crude mixture (30 mg) which was chromatographed on SiO_2, eluting with hexane:AcOEt(23:2) to afford: 10 mg of the initial substrate, 15 mg (53%) of 4 and 5 mg (18%) of 30.

11,12-diacetoxy-7-drimene: 4.- Colourless oil; ν_{max} (film) 1750, 1450, 1380, 1360, 970; δ_H ($CDCl_3$) 4.61 (1H, d, J=12.4 Hz, 12-H_a), 4.60 (2H, s, 11-H), 4.49(1H, d, J=12.4 Hz, 12-H_b), 2.04 (3H, s, AcO-), 2.01 (3H, s, AcO-), 1.00 (3H, s), 0.91 (3H, s), 0.88 (3H, s); δ_C ($CDCl_3$) See table. (Found C, 70.7; H, 9.3, requires. C, 70.8; H, 9.3%).

11,12-diacetoxy-8-drimene: 30.- Colourless oil; ν_{max} (film) 1750, 1250, 1030, 970; δ_H ($CDCl_3$) 5.91 (1H, m, 7-H), 4.62 (1H, d, J=12.4 Hz, 12-H_a), 4.47 (1H, d, J=12.4 Hz, 12-H_b), 4.30 (1H, dd, J=10.2, 2.4 Hz, 11-H_a), 4.09 (1H, dd, J=10.2, 5.8 Hz, 11-H_b), 2.03 (3H, s, AcO-), 2.01 (3H, s, AcO-),0.90 (3H, s), 0.89 (3H, s), 0.85 (3H, s); δ_C ($CDCl_3$) See table.

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REFERENCES

1. I. Kubo, I. Miura, M.J. Pettei, Y.W. Lee, F. Pilkiewicz and K. Nakanishi, Tetrahedron Letters, 1977, 52, 4553.
2. A. Marston and K. Hostettman, Phytochemistry, 1985, 24, 639.
3. M. Jalali-Naini, D. Guillerm et J.Y. Lallemand, Tetrahedron, 1983, 39, 749.
4. H. Okawara, H. Nakai and M. Ohno, Tetrahedron Letters, 1982, 23, 1087.
5. Y. Asakawa, T. Takemoto, Y, Fukuyama and T. Sato, Phytochemistry, 1982, 21, 2895.
6. M. Jalali-Naini, D. Guillerm et J.Y. Lallemand, Tetrahedron Letters, 1981, 22, 2995.
7. S.W. Pelletier, S. Lajsic, Y. Otsuka and Z. Djarmati, J.Org. Chem., 1975, 40, 1607.
8. A. Caliezi and H. Schinz, Helv. Chim.Acta, 1950, 33, 1129.
9. S.V. Pelletier, Y. Otsuka, Tetrahedron, 1977, 33, 1021.
10. Y. Kitahara, T. Kato, T. Suzuki, S. Kano and M. Tanemura, J.C.S. Chem. Commun., 1969, 342.
11. M.J. Cortés, I. Razmilic, J.R. Sierra and J. López, Chem and Ind., 1985, 735.
12. T. Nakata, H. Akita, T. Naito and T. Oishi, J.Am. Chem. Soc., 1979, 101, 4400.
13. R.J. Armstrong, F.L. Harris and L. Weiler, Can. J. Chem., 1986, 64, 1002.
14. P. A. Wender and S.L. Eck, Tetrahedron Letters, 1982, 23, 1871.
15. M.P. Bosch, F. Camps, J. Coll, A. Guerrero, T. Tatsuoka and J. Meinwald, J. Org. Chem, 1986, 51, 773.
16. D.M. Hollinshead, S.C. Howell, S.V. Ley, M. Mahon, N. M. Ratcliffe and P.A. Worthington, J. Chem. Soc. Perkin Trans I, 1983, 1579.
17. K. Mori, H Watanabe, Tetrahedron, 1986, 42, 273.
18. J. de Pascual Teresa, J.G. Urones, I. S. Marcos, D. Díez Martín and V. Alvarez, Phytochemistry, 1986, 25, 711.
19. A. Hortmann, D. Darnel and J. Martinelli, J. Org. Chem., 1973, 38, 728.
20. S. Bory, M. Fetizon and P. Laszlo, Bull. Soc. Chim. France., 1963, 2310.
21. R. Bloch, Synthesis, 1978, 140.
22. G.W. Perold, A.J. Hodgkinson, A.S. Howard and P.E.J. Kruger, J. Chem. Soc. Perkin I, 1972, 2457.
23. T.W. Greene, " Protective Groups in Organic Synthesis" Ed. John Wiley 1981.
24. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 1970, 35, 4000.
25. G. Hofle, W. Sleglich and Vorbruggen, Angew. Chem. Ind.Ed. Engl. 1978, 569.
26. C.E. Bishop and P.R. Story, J. Am. Chem. Soc., 1968, 90, 1905.