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CHEMISTRY OF 7-LABDEN-3β,15-DIOL (I): HOMOCHIRAL SYNTHESIS OF FREGENEDADIOL

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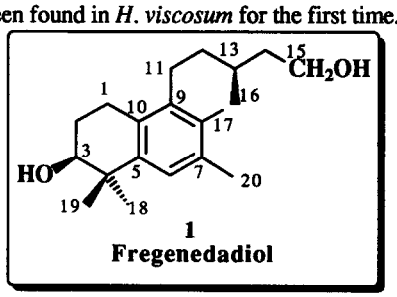
Abstract: *7-labden-3β,15-diol was transformed into its diacetyl or dimethoxy derivatives. By double bond isomerization, allylic oxidation and dehydrogenation the diacetyl derivative was transformed into a dienone that was aromatized with good yield by methyl loss to afford 3β,15-diacetoxy-20-nor-5,7,9-labdatrien-7-ol. An analog procedure was used to transform the dimethoxy derivative into 3β,15-dimethoxy-20-nor-5,7,9-labdatrien-7-ol. The triflate of the latter was transformed by a cross-coupling reaction into fregenedadiol dimethyl ether that was demethylated to afford fregenedadiol.*

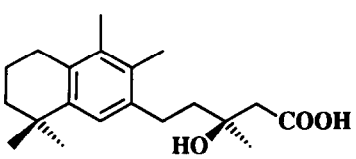
Studies on the chemical composition of *Halimium viscosum* (Wilk) P. Silva, collected in the West of the Iberian Peninsula have demonstrated the existence of three different chemotypes for this species.[1] These chemotypes have been named in relation to the plant collection sites: La Fregeneda (Salamanca, Spain), Villarino de los Aires (Salamanca) and Valparaíso (Zamora, Spain). The hexane extracts of *H. viscosum* essentially contains bicyclic and tricyclic diterpenes. The diterpenic fraction of *H. viscosum* (La Fregeneda) contains labdane,[2] *ent*-halimane,[3] tormesane,[1,4] tormesolane,[5] and fregenedane compounds.[6] The same fraction from *H. v.* (Valparaíso) contains only labdane[7], valparane,[8] valparolane,[9] while the one from *H. v.* (Villarino de los Aires) contains only labdane[10] and *ent*-halimane compounds.[11] The compounds belonging to tormesane, tormesolane, fregenedane, valparane and valparolane classes have been found in *H. viscosum* for the first time.

Fregenedadiol **1** is a bicyclic diterpene isolated from *H. viscosum* (La Fregeneda). This compound presents a new carbon skeleton called fregenedane.[6]

Formally, this skeleton can be considered as a new kind of rearranged labdane with an aromatized B ring. Only two rearranged labdanes with an aromatized B ring have been described to date: chrysolic acid **2**[12] and a hydroxy derivative **3**[13] but these compounds differ in the substitution pattern on ring B compare to fregenedadiol.



1
Fregenedadiol



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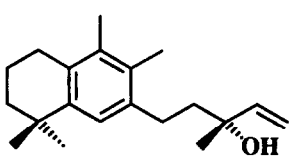

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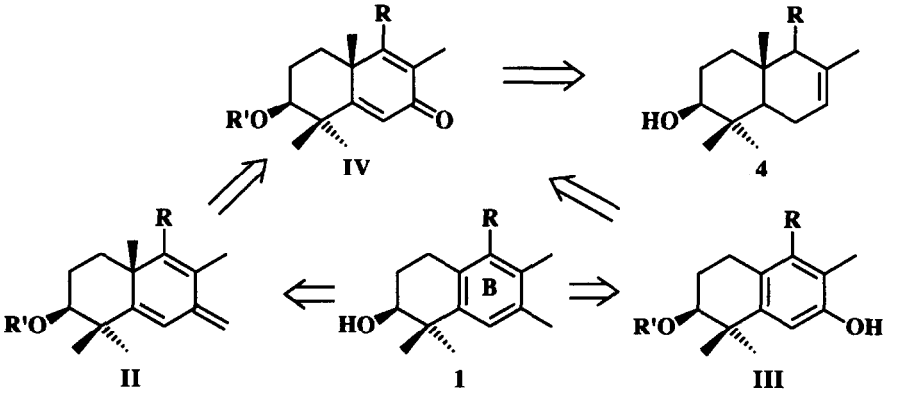
In the present work we report the synthesis of fregenedadiol in order to confirm its structure. It is also the first synthesis reported so far of rearranged labdanes with an aromatic B ring.

In the hexane extract of *H. viscosum* compounds **1** and **4** are found, as well as other unsaturated 3β-hydroxylabdanes,[2] this suggested that compound **1** is formed biosynthetically by a rearrangement. Assuming that the stereochemical integrity is maintained at C-3 and C-13, 7-labden-3β-15-diol **4**, one of the main components of the extract from which fregenedadiol was isolated, is used as our starting material.

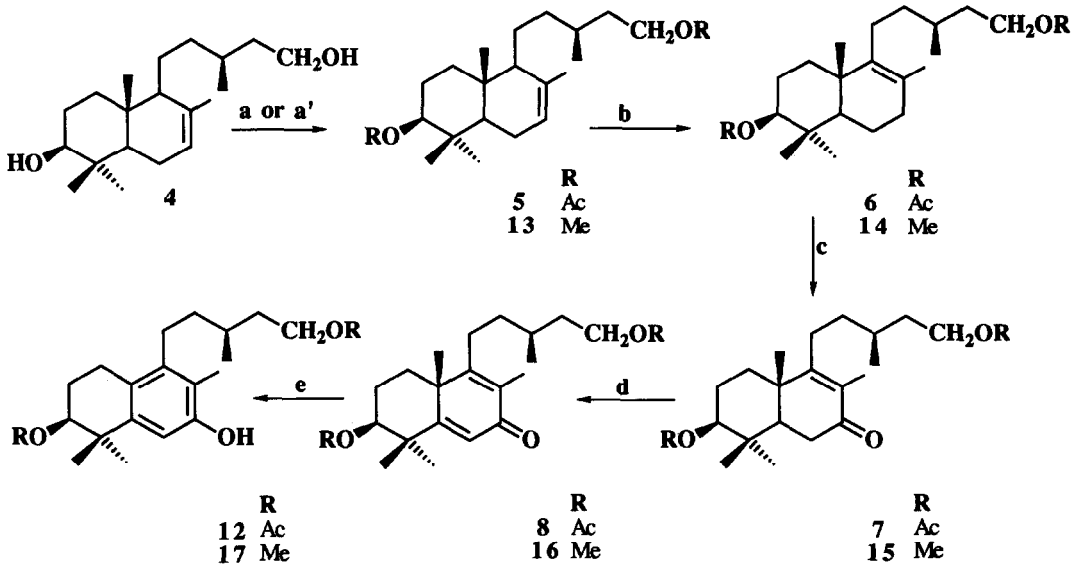
The retrosynthetic analysis is shown in the following scheme (Scheme 1):



Scheme 1.

Different routes are possible to obtain **1**: One considers the aromatization of the triene (**II**) with loss of the methyl group; another is based on a cross–coupling reaction with the phenol (**III**) or alternatively a Birch reduction of **III**, methylation and rearomatization of ring B.

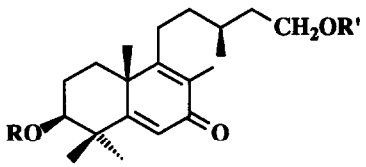
Treatment of compound **4** with Ac_2O/Py afforded the acetyl derivative **5**, that was isomerized by heating it with a catalytic amount of I_2 to **6**. Oxidation of the latter with Na_2CrO_4 afforded enone **7**, that is transformed into dienone **8** by treatment with SeO_2 (Scheme 2).



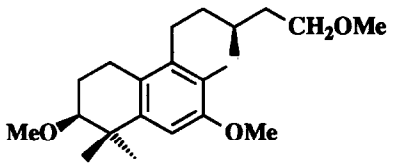
Scheme 2. a) Ac_2O/Py; a') MeI/NaH; b) I_2/C_6H_6; c) Na_2CrO_4; d) SeO_2; e) Zn/HOAc

To obtain the triene **II** from dienone **8**, it is necessary to protect the hydroxyl groups at C-3 and C-15 with different protecting groups than the acetoxyl groups. Deprotection of **8** gave diol **9** that was treated with TBDMSCl under different reaction conditions[14] to afford **10**.

However, the protection of both hydroxyl groups under the same reaction conditions is only possible when **9** is treated with TBDMSTf[15] affording **11**, that was then transformed into the unmanageable triene **II** (R = $CH_2CH_2CH(Me)CH_2CH_2OTBDMS$, R' = TBDMS) either by treatment with MeLi or MeMgI.[16] The triene was detected spectroscopically but it is unuseful for synthetic purposes due to its high decomposition rate.



	R	R'
9	H	H
10	H	TBDMS
11	TBDMS	TBDMS



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Therefore, we turned our attention to the second alternative route. Aromatization of dienones, similar to **8**, in order to obtain phenols, has been attempted in triterpenes with a lanostane skeleton[17] and steroids[18]. The yields for this are variable and in many cases very disappointing. However in our case refluxing **8** in acetic acid with zinc, gave the phenol **12** in excellent yield (93%) (Scheme 2).

The proposed structure for **12** (3β,15–diacetoxy–20–*nor*–5,7,9–labdatrien–7–ol) is in agreement with the spectroscopic data (IR, ^1H, ^{13}C NMR, H–C CORR). Long range heteronuclear correlation experiments helped to confirm the substitution pattern on the aromatic ring (Table 1).

Table 1. Long range H-C Correlations for compound **12**.

H	δ_C	δ_H	Correlated Carbon
6	152.9	6.67	4, 7, 8, 10
16	19.4	1.04	13, 14
17	11.3	2.18	7, 8, 9
18	29.9	1.27	3, 4, 5, 19
19	26.1	1.27	3, 4, 5, 18

The three bond correlation observed for the aromatic hydrogen (H-6) and the quaternary carbon that beared the gem–dimethyl group demonstrates the substitution pattern on the aromatic ring.

As mentioned before the acetoxyl groups are not suitable to achieve the substitution of the phenolic hydroxyl group of **12** by a methyl group. However, use of methoxyl groups allows this transformation through the intermediate dienone **16** (Scheme 2). Thus, treatment of **4** with MeI in the presence of NaH afforded the dimethyl derivative **13** as the major product. The configuration at C-3 of **13** was established by comparison with the spectral data of 15–acetoxy–3β–methoxy–7-labdene obtained from 15–acetoxy–7-labden–3β–ol by methylation with CH_2N_2 on silica gel.[2] **13** was then isomerized with a catalytic amount of I_2 in refluxing benzene to **14** in quantitative yield. The latter was then oxidized with Na_2CrO_4 to give the enone **15**. Treatment of this with SeO_2 yielded the desired intermediate **16**.

Another route, instead of the cross–coupling reaction, to obtain fregenedadiol dimethyl ether **21** from **17**, is the Birch reduction of the trimethyl ether **18** to afford, after methylation and rearomatization of ring B, compound **21**.

Table 1. ^{13}C NMR data ($CDCl_3$, 50.3 MHz)

C	1	4	5	6	7	8	9	13	14	15	16	17	18	19	20	21
1	24.3	36.8	37.0	37.6	35.9	31.0	31.4	37.4	37.9	36.4	31.3	24.2	24.2	24.1	23.9	24.9
2	27.1	27.5	23.9	24.2	23.7	23.2	26.7	22.3	22.7	22.4	21.9	22.2	22.1	21.7	21.5	22.17
3	76.4	79.2	81.1	81.0	79.8	67.9	76.5	89.0	88.8	87.7	86.3	84.8	84.9	84.4	84.0	84.9
4	39.1	38.7	37.6	38.7	40.5	41.5	44.1	38.7	38.9	40.7	41.5	39.2	39.5	39.3	39.3	39.1
5	141.6	49.8	49.8	51.3	49.3	168.9	171.5	50.3	51.7	49.8	170.9	143.7	143.2	143.7	144.8	138.6
6	126.2	23.6	23.3	18.8	33.9	125.0	124.7	23.4	18.8	34.3	124.7	110.8	106.7	115.7	117.1	126.0
7	134.7	122.0	121.8	33.7	199.3	186.3	187.2	122.1	33.9	199.9	187.0	152.3	156.2	147.9	147.6	142.4
8	132.1	135.4	135.3	125.8	130.1	130.1	130.2	135.3	125.6	129.9	130.4	119.9	122.5	124.6	125.8	130.2
9	138.7	55.4	55.2	140.1	167.2	163.4	164.9	55.5	140.6	167.8	164.2	140.3	140.0	140.6	141.9	134.4
10	129.9	37.4	36.5	37.8	37.7	43.7	43.1	36.9	38.9	38.7	44.1	124.8	124.8	129.2	133.1	131.8
11	27.2	24.5	24.4	25.6	27.3	27.9	28.2	24.4	25.7	27.4	27.3	27.3	27.3	27.4	27.5	27.3
12	36.5	39.7	39.6	34.9	34.6	35.2	35.9	39.9	35.2	34.8	35.9	36.3	56.3	36.1	35.9	36.4
13	30.6	30.6	30.7	31.1	31.1	31.1	30.8	30.9	31.1	31.3	29.7	30.9	30.9	30.9	30.9	30.9
14	39.9	39.9	35.3	35.5	35.3	35.8	39.4	36.4	36.6	36.2	36.4	36.6	36.6	36.5	36.5	36.6
15	61.2	61.2	62.9	63.0	62.7	62.5	60.7	71.2	71.3	70.9	70.9	71.2	71.2	71.1	71.1	71.2
16	19.5	19.8	19.6	19.4	19.2	19.2	19.4	19.8	19.4	19.4	19.5	19.5	19.5	19.5	19.4	19.5
17	15.2	21.9	21.8	20.3	11.3	10.9	11.1	21.9	20.2	11.3	11.1	11.2	11.2	12.0	12.5	15.1
18	29.4	27.9	27.8	28.1	27.4	27.2	27.4	28.0	28.2	27.6	27.3	29.6	29.7	29.7	30.1	29.6
19	25.3	15.1	16.2	16.6	16.2	25.8	25.5	15.8	16.3	15.8	25.7	25.8	25.9	25.8	25.9	25.9
20	20.9	13.7	13.6	19.4	18.4	23.2	22.1	13.6	19.5	18.3	22.9	–	–	–	–	20.9
MeO								58.5	58.6	58.6	58.6	58.5	55.8	58.6	58.7	58.6
MeO								57.5	57.5	57.6	57.7	57.2	57.2	57.1	57.3	51.2
MeO													58.8			
MeCOO			21.2	21.2	21.2	20.9										
MeCOO			20.9	20.9	21.0	20.7										
MeCOO			170.7	170.8	171.1	170.0										
MeCOO			170.7	170.8	170.8	170.1										
TfO													121.8q			
$MeCH_2O$														16.1		
$MeCH_2O$														16.2		
$MeCH_2O$														64.2		
$MeCH_2O$														64.4		

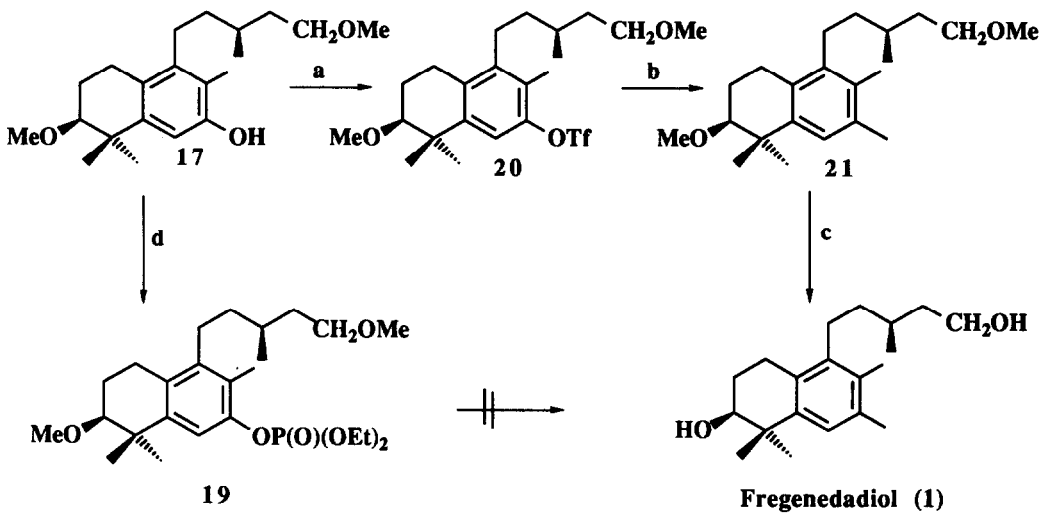
17 was treated with MeI in the presence of K_2CO_3 to obtain **18**. However, several attempts to reduce **18** under different reaction conditions with Lithium in liquid ammonia failed and the substrate was recovered untransformed. A few cases of hindered methyl ethers that cannot be reduced under Birch conditions are described in the literature.[19]

The transformation of the phenol **17** into fregenedadiol dimethyl ether requires the substitution of the aromatic hydroxyl by a methyl group. This could be carried out by a Palladium catalyzed cross-coupling of the phenol ester (as phosphate or triflate).

Reaction of **17** with NaH and $(EtO)_2P(O)Cl$ afforded the phosphate **19** in a 73% yield. However, all attempts to carry out the "cross-coupling" on this substrate failed using the following reagents: $MeMgI/Ni(acac)_2$ in Et_2O or THF; $Me_3SiCH_2MgCl/Ni(acac)_2$ in Et_2O or THF[20]; $Me_3Al/NiCl_2(dppp)$ in Et_2O or THF. Interestingly, all of them worked on our model system (β-naftol).

Modification of **17** was required and reaction with triflic anhydride in collidine afforded the triflate **20**[21] in 71% yield. Heating the triflate **20** at 140°C in DMF with Me_4Sn and catalytic $(Ph_3P)_2PdCl_2$[22] gave compound **21** in a 75% yield. Spectroscopic data for **21** (IR, ^1H and ^{13}C NMR, HRMS) are identical with the 3β,15-fregenedadiol dimethylether.

Demethylation of **21** with Me_3SiCl/NaI[23] afforded **1** ($[\alpha]_D = -11.0$) which is identical in all respect to fregenedadiol ($[\alpha]_D = -11.3$). (Scheme 3).



Scheme 3. a) $(TfO)_2O$, b) $Me_4Sn/Pd(II)$, c) TMSCl/NaI, d) $(EtO)_2P(O)Cl$

Consequently, the structure of **1** is determined in addition to its absolute configuration.

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EXPERIMENTAL

IR spectra were measured as films for oils on a Beckman-33-IR spectrophotometer. The 200 MHz ^1HNMR and 50 MHz ^{13}C NMR spectra were determined on a Bruker WP-200-SY spectrometer. Chemical shifts are given in ppm and coupling constants in Hertz.The NMR spectra are referenced in $CDCl_3$to the residual $CHCl_3$ at 7.26 ppm for ^1H and 77.0 ppm for ^{13}C, respectively, unless otherwise stated. The mass spectra were obtained on a VG-TS 250 spectrometer at 70eV and at suitable temperature in each case. Optical rotations were performed in a

chloroformic solution except where otherwise indicated, with a digital Perkin-Elmer-241 polarimeter. Melting points were determined in a Kofler hot plate apparatus and are uncorrected.

7-labdene-3β,15-diol: **4.** Compound **4** was isolated from *n*-hexane extract of *Halimium viscosum*, as reported in reference.[2] mp 111-112°C; $[\alpha]_D$= –5.2 (c 1.1, $CHCl_3$); ν_{max} (film) 3340, 1640, 1060, 1020, 1000, 960, 910 and 810 cm^{-1}; δ_H 5.35 (1H, s, H-7), 3.63 (2H, m, H-15), 3.20 (1H, m, H-3), 1.64 (3H, s, Me-17), 0.94, 0.82 and 0.72 (3H, s ea, Me-18, Me-19 and Me-20); δ_C: see table 1; EIMS 70 eV, *m/z* (rel. int.): 308[M^+] (15), 290(16), 275(12), 208(65), 207(64), 190(36), 189(70), 135(57), 121(100), 107(74), 83(26), 81(57) and 69(19).

Acetylation of **4**: **5** (*3β,15 diacetoxy-7-labdene*). Compound **4** (5.42 g, 17.59 mmol) was acetylated with Ac_2O/Pyridine (6ml/5ml) at room temperature overnight. The reaction mixture was poured into ice-water and extracted with ether, The ethereal extract was washed with 2N HCl, 6% $NaHCO_3$ and H_2O, dried over Na_2SO_4. Removed of the solvent afforded **5** (6.62 g, 97%) as a colourless oil. ν_{max} (film) 3020, 1740, 1640 and 1240 cm^{-1}; δ_H 5.32 (1H, s, H-7), 4.43 (1H, m, H-3), 4.04 (2H, t, J= 6.8, H-15), 1.98 (6H, s, $MeCO_2$), 1.61 (3H, s, Me-17), 0.87 (3H, s, Me-18), 0.87 (3H, d, J= 6.9, Me-16), 0.80 (3H, s, Me-19), 0.73 (3H, s, Me-20). δ_C: see table 1.

Isomerization of **5**: **6** (*3β,15-diacetoxy-8-labdene*). I_2 (120 mg, 0.95 mmol) was added to a solution of **5** (6.62 g, 16.89 mmol) in dry benzene (100 ml) under argon. The solution was heated under reflux for 95 hours until complete conversion is attained (monitored by ^1H NMR spectroscopy). The mixture was diluted with benzene (200 ml) and washed with 20% $NaHSO_3$ and water, dried (Na_2SO_4) and evaporated to yield **6** (6.22 g, 94%) as a colourless oil. ν_{max} (film) 1740, 1240, 1030 cm^{-1}; δ_H 4.45(1H, dd, J_1=11.1 and J_2= 4.8, H-3), 4.08 (2H, m, H-15), 2.04 (3H, s, $MeCO_2$), 2.01 (3H, s, $MeCO_2$), 1.53 (3H, s, Me-17), 0.92 (3H, d, J= 6.4, Me-16), 0.95, 0.87 and 0.86 (3H, s ea, Me-18, Me-19 and Me-20). δ_C: see table 1.

Oxidation of **6** *with* Na_2CrO_4: **7** (*3β,15-diacetoxy-7-oxo-8-labdene*). To a solution of **6** (5.96 g, 15.20 mmol) in dry benzene (50 ml), Na_2CrO_4 (7.10 g, 42.83 mmol), NaOAc (5.44 g, 42.83 mmol), Ac_2O (40 ml) and glacial acetic acid (40 ml) were added. The reaction mixture was stirred at 60°C for 24 hours, then the reaction was quenched with ice-water, extracted with ether and the ether extracts washed with $NaHCO_3$ and water, dried over Na_2SO_4, filtered and the solvent was removed, the residue was chromatographed on silica gel to yield **7** (3.70 g, 60%). $[\alpha]_D$ +26.2 (c 0.7, $CHCl_3$). UV λ_{max} : 246 nm (log ε: 4.11). ν_{max} (film)1750, 1680, 1615, 1250 cm^{-1}; δ_H 4.49 (1H, dd, J_1= 10.7 and J_2= 4.3, H-3), 4.07 (2H, t, J= 6.4, H-15), 2.03 (3H, s, $MeCO_2$), 2.01(3H, s, $MeCO_2$), 1.71 (3H, s, Me-17), 1.06 (3H, s, Me-20), 0.96 (3H, d, J= 6.4, Me-16), 0.93 and 0.85(3H, s ea, Me-18 and 19). δ_C: see table 1.

Oxidation of **7** *with* SeO_2: **8** (*3β,15-diacetoxy-7-oxo-5,8-labdadiene*). Glacial acetic acid (2 ml) and SeO_2 (3.24 g, 29.10 mmol) were added to a solution of **7** (1.99, 3.62 mmol) in *t*-BuOH (40 ml), the mixture was stirred at 100°C for 23 hours. After that, the solution was concetrated and ice-water was added, extracted with bencene, filtered through a pad of Celite and removed the solvent. Column chromatography of the residue on silica gel afforded **8** (1.49 g, 75%). UV λ_{max}: 249 nm (log ε: 4.27). ν_{max} (film) 1740, 1650, 1615, 1595 cm^{-1}; δ_H 6.35 (1H, s, H-6), 4.53 (1H, m, H-3), 4.15 (2H, t, J= 6.4, H-15), 2.09 (3H, s, $MeCO_2$), 2.05 (3H, s, $MeCO_2$), 1.88 (3H, s, Me-17), 1.35 (3H, s, Me-20), 1.29 and 1.18 (3H, s ea, Me-18 and Me-19), 0.98 (3H, d, J= 6.8, Me-16). δ_C: see table 1.

Alcaline hydrolisis of **8**: **9** (*7-oxo-5,8 labdadiene-3β,15 diol*). Compound **8** (238 mg, 0.59 mmol) was treated with K_2CO_3 (130 mg, 0.59 mmol) in MeOH (5 ml). The mixture was stirred for 2 hours at room

temperature. Usual work-up afforded **9** (178 mg, 94%). ν_{max} (film) 3300, 1650, 1615, 1595 cm^{-1}; δ_H 6.25 (1H, s, H-6), 3.62 (2H, t, J= 6.4, H-15), 3.30 (1H, m, H-3), 1.79 (3H, s, Me-17), 1.25 (3H, s, Me-20), 1.21 and 1.14 (3H, s ea., Me-18 and Me-19), 0.90 (3H, d, J= 6.8, Me-16).δ_C: see table 1. EIMS 70 eV, *m/z* (rel. int.): 320[M^+] (22), 233(8), 220(29), 205(48), 187(37), 175(28), 159(20), 149(50), 135(26), 127(49),120(25), 105(30), 81(39), 69(59), and 57(100).

Reaction of **9** *with TBDMSCl*: **10**. To a solution of compound **9** (107 mg, 0.34 mmol) in CH_2Cl_2 (5 ml), Et_3N (0.2 ml), TBDMSCl (129 mg, 0.86 mmol) and DMAP (10 mg) were added. The reaction mixture was stirred for 17 hours at room temperature. After that, H_2O was added and extracted with ether, washed with 2N HCl, 6% $NaHCO_3$ and H_2O, and dried over Na_2SO_4. Removal of the solvent afforded **10** (132 mg, 89%). ν_{max} (film) 3450, 1650, 1615, 1595, 1250, 1100, 850 cm^{-1}; δ_H 6.36 (1H, s, H-6), 3.66 (2H, m, J_1= 1.95 and J_2= 6.35, H-15), 3.34 (1H,m, H-3), 1.86 (3H, s, Me-17), 1.33 and 1.30(3H, s ea, Me-18 and Me-19), 1.23 (3H, s, Me-20), 0.96 (3H, d, J= 6.8, Me-16), 0.89 (18H, s, Me_3-C-Si), 0.06 (12H, s, Me_3-C-Si). **10** was also obtained as follows: To a solution of **9** (115 mg, 0.36 mmol) in CH_2Cl_2 (5 ml), imidazole (10 mg, 0.15 mmol), TBDMSCl (155mg, 1.03 mmol) and DMF (2ml) were added. The reaction mixture was heated under reflux for 18 hours. After that, water was added, extracted with ether and dried over Na_2SO_4. Removal of the solvent afforded **10** (140 mg, 90 %).

Reaction of **9** *with TBDMSTf* **11.** To a solution of compound **9** (216 mg, 0.68 mmol) in CH_2Cl_2 (5 ml), Et_3N (0.9 ml) and TBDMSTf (0.3 ml) were added under argon at -14°C . The reaction mixture was stirred at 0°C for 3 hours, then cooled to -14°C, and water was added carefully, extracted with ether, washed with brine and water and dried over Na_2SO_4. Removal of the solvent afforded **11** (137 mg, 36.8%). ν_{max} (film) 1650, 1615, 1595, 1250, 1100, 850 cm^{-1}; δ_H 6.33 (1H, s, H-6), 3.64 (2H, m, J_1= 6.8 and J_2= 1.9, H-15), 3.28 (1H, dd, J_1= 4.9 and J_2= 11.2, H-3), 1.87 (3H, s, Me-17), 1.31 and 1.20 (3H, s ea, Me-18 and Me-19), 1.17 (3H, s, Me-20), 0.95 (3H, d,J=6.8, Me-16), 0.90 (18H, s, Me_3-C-Si), 0.04 (12 H, s, Me_3-C-Si).

Reaction of **11***with MeLi:* **II.** MeLi (0.6 ml of 1.6M solution in ether, 0.96 mmol) was added to a solution of **11** (137 mg, 0.25 mmol) in dry ether (5 ml) at -78°C under argon. The solution was stirred for 1 hour, then the mixture was allowed to warm at room temperature and stirred for 1 hour, then the mixture was cooled to -21°C, quenched with NH_4Cl and extracted with ether, washed with brine and H_2O and dried over Na_2SO_4. Removal of the solvent afforded 3β,15-di-*tert*-butyldimethylsilyloxy–7–methylen–labda–5,8–diene, **II** (103 mg, 75 %). ν_{max} (film) 1490, 1360, 1350, 1250, 1090, 890, 850, 760 cm^{-1}; δ_H 6.24 (1H, s, H-6), 4.88 and 4.70 (1H, s ea), 3.65 (2H, dt, J_1= 6.8 and J_2= 1.9, H-15), 3.26 (1H, dd, J_1= 4.9 and J_2= 11.2, H-3),1.83 (3H,s, Me-17), 1.19, 1.18 and 1.12 (3H, s ea, Me-18, Me-19 and Me-20), 0.94 (3H, d, J= 6.8, Me-16), 0.90 (18H, s, Me_3-C-Si), 0.05 (12H, s, Me_3-C-Si).

Aromatization of **8**: **12** *(3β,15-diacetoxy-20-*nor*–labda-5,7,9-trien-7-ol).* Zn (4.30 g, 64.78 mmol) was added to a solution of **8** (170 mg, 0.43 mmol) in glacial acetic acid (50 ml), under argon, and stirred at 120°C for 8 hours. The Zn was filtered off carefully, washed with ether, and the organic phase washed with 6% $NaHCO_3$ and water, dried (Na_2SO_4). The solvent was removed and the residue chromatographed on silica gel (20% EtOAc-Hexane) to afford **12** (153 mg, 93%) ν_{max} (film)3440, 1730, 1600, 1240 cm^{-1}; δ_H 6.67 (1H, s, H-6), 4.94 (1H, dd, J_1= 4.4 and J_2= 6.3, H-3), 4.15 (2H, t, J= 6.8, H-15), 2.19 (3H, s, Me-17), 2.09 (6H, s, $MeCO_2$), 1.27 (6H, s, Me-18, Me-19), 1.04 (3H, d, J= 6.3, Me-16). EIMS 70 eV, *m/z* (rel. int.): 390[M^+] (28), 330(100), 255(15), 201(32), 185(48), 173(15), 159(13), 149(21), 83(10), 55(16), 43(56).

Methylation of **4**: **13** *(7-labdene-3β,15-diol dimetylether).* To a solution of **4** (2.62 g, 8.5 mmol) in dry ether was carefully added NaH (60% dispersion in mineral oil) (6.12 g, 255 mmol) under argon. The reaction mixture was stirred at 40°C for 30 min. Then MeI (5 ml) was added, the resulting mixture was heated at 40°C for

an additional 70 hours. After that, ice/water was added and two hours later the mixture was extracted with EtOAc. The organic phases were washed with 2N HCl, brine and water, dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel to give **13** (2.18 g, 76%) as a colourless oil, ν_{max} (film) 1190, 1110 and 940 cm^{-1}; δ_H 5.37 (1H, br s, H-7), 3.38 (2H, t, J= 6.5, H-15), 3.34 (3H, s, MeO), 3.31 (3H, s, MeO), 2.65 (1H, dd, J_1=3.8 and J_2=11.3, H-3), 1.66 (3H, s, Me-17), 0.94, 0.82 and 0.75 (3H, s ea, Me-18, Me-19 and Me-20), 0.90 (3H, d, J=6.5, Me-16); δ_C see table 1.

Isomerization of **13**: **14** *(8-labdene-3β,15-diol dimethylether).*I_2 (20 mg, 0.08 mmol) was added to a solution of **5** (1.41 g, 4.19 mmol) in dry benzene under argon. The solution was heated under reflux for 94 hours until complete conversion is achieved (monitored by ^1H NMR spectroscopy). The mixture was diluted with benzene and washed with 20% $NaHSO_3$ and water, dried (Na_2SO_4) and evaporated to yield **14** (1.34 g, 95%) as a colourless oil ν_{max} (film) 1190, 1110 and 940 cm^{-1}; δ_H 3.40 (2H, t, J=6.5, H-15), 3.36 (3H, s, MeO), 3.32 (3H, s, MeO), 2.66 (1H, dd, J_1=4.3 and J_2=11.3, H-3), 1.54 (3H, s, Me-17), 0.91 (3H, d, J=6.4, Me-16), 0.98, 0.93 and 0.77 (3H, s ea, Me-18, Me-19 and Me-20); δ_C see table 1.

Oxidation of **14** *with* Na_2CrO_4: **15** *(7-oxo-8-labdene-3β,15-diol dimethylether).* To a solution of **14** (1.29 g, 3.84 mmol) in dry benzene, Na_2CrO_4 (2.35 g, 8.99 mmol), NaOAc (1.33 g, 16.2 mmol), Ac_2O and glacial acetic acid (12 ml) were added. The reaction mixture was stirred at 60°C for 4 hours, then the reaction was quenched with ice-water, extracted with ether and the ether extracts washed with $NaHCO_3$ and water, dried over Na_2SO_4, filtered and the solvent was removed to yield **15** (1.24 g, 92%) as a colourless oil, ν_{max} (film) 1670, 1610, 1190, 1110, 900, 870 and 850 cm^{-1}; δ_H 3.41 (2H, t, J=6.5, H-15), 3.37 (3H, s, MeO), 3.33 (3H, s, MeO), 2.71 (1H, dd, J_1= 3.8 and J_2= 10.8, H-3), 0.95 (3H, d, J= 6.5, Me-16),1.06, 0.97 and 0.85(3H,s ea, Me-18, Me-19 and,Me-20); δ_C see table 1.

Oxidation of **15** *with* SeO_2: **16** *(7-oxo-5,8-labdadien-3β,15-diol dimethylether).*Glacial acetic acid (2ml) and SeO_2 (2.39 g, 3.62 mmol) were added to a solution of **15** (1.26, 3.62 mmol) in *t*-BuOH (32 ml), the mixture was stirred at 100°C for 5 hours. After that the solution was concetrated and ice-water was added, extracted with ether. The ethereal phases were washed with 6% $NaHCO_3$, brine and water, dried over Na_2SO_4. Evaporation of the solvent gave **16** (1.03 g, 82%) as a colourless oil, ν_{max} (film) 1650, 1615, 1595, 1190 and 1110 cm^{-1}; δ_H 6.32 (1H, s, H-6), 3.40 (2H, t, J=7.0, H-15), 3.38 (3H, s, MeO), 3.32 (3H, s, MeO), 2.74 (1H, dd, J_1=3.8 and J_2=11.3, H-3), 1.86 (3H, s, Me-17), 1.31 (3H, s, Me-20), 1.25 (3H, s ea, Me-18 and Me-19), 0.96 (3H, d, J=6.5, Me-16); δ_C see table 1.

Aromatization of **16**: **17** *(3β,15-dimethoxy-20-*nor*–labda-5,7,9-trien-7-ol).* Zn (10g, 15.3 mmol) was added to a solution of **16** (1.12 g, 3.27 mmol) in glacial acetic acid (100 ml), under argon, and stirred for at 120°C for 5 hours. The Zn was filtered off carefully, washed with ether, and the organic phase washed with 6% $NaHCO_3$ and water, dried (Na_2SO_4). The solvent was removed and the residue chromatographed on silica gel (20% EtOAc-Hexane) to afford **17** (0.975 g, 91%) as a colourless oil, $[\alpha]_D$ +66.0 (c 1.1, $CHCl_3$); ν_{max} (film) 3380, 1600 and 1110 cm^{-1} ; δ_H 6.65 (1H, s, H-6), 3.46 (2H, t, J=7.0, H-15), 3.43 (3H, s, MeO), 3.37 (3H, s, MeO), 3.15 (1H, dd, J_1=2.7 and J_2=8.6, H-3), 2.16 (3H, s, Me-17), 1.29 and 1.24 (3H, s ea, Me-18 and Me-19), 1.02 (3H, d, J=6.5, Me-16); δ_C see table 1. EIMS 70 eV, *m/z* (rel. int.): 334[M^+](47), 302(35), 255(8), 219(18), 203(38), 187(100), 185(49), 161(48), 121(36), 81(51) and 69(73).

Methylation of **17**: **18** *(20-*nor*-5,7,9-labdatriene-3β,7,15-triol trimethylether).* To a solution of **17**(61 mg, 8.5 mmol) in dry ether was carefully added NaH (60% dispersion in mineral oil) (6.12 g, 255 mmol) under argon. The reaction mixture was stirred at 40°C for 30 min. Then MeI (5 ml) was added, the resulting mixture was heated at 40°C for an additional 70 hours. After that, ice/water was added and two hours later the mixture

was extracted with EtOAc. The organic phases were washed with 2N HCl, brine and water, dried over Na_2SO_4 and evaporated in vacuo. The residue was chromatographed on silica gel to give **18** (2.18 g, 76%). ν_{max} (film) 1600 and 1110 cm^{-1} ; δ_H 6.71 (1H, s, H-6), 3.61 (3H, s, MeO), 3.46 (2H, t, J= 6.8, H-15), 3.45 (3H, s, MeO), 3.44 (3H, s, MeO), 3.17 (1H, dd, J_1=2.9 and J_2=9.3, H-3), 2.16 (3H, s, Me-17), 1.35 and 1.29 (3H, s ea, Me-18 and Me-19), 1.03 (3H, d, J=6.8, Me-16); δ_C see table 1 1. EIMS 70 eV, *m/z* (rel. int.): 348[M^+](38), 316(20), 256(10), 216(10), 201(15), 149(14), 111(23), 97(40), 83(52), 69(80) and 55(100).

Reaction of **17** *with diethyl chlorophosphate:* **19**. Compound **17** (147 mg, 0.80 mmol) was solved in dry THF (5 ml), and NaH (60% dispersion in mineral oil) (94 mg, 3.90 mmol) was added under argon. The reaction mixture was stirred at room temperature for 30 min. Then $(EtO)_2P(O)Cl$ (0.1 ml) was added and the mixture stirred for 21 hours. After that, the mixture was extracted with ether. The combined organic layers were washed with 4% NaOH and water, dried (Na_2SO_4). Evaporation of the solvent gave a crude mixture which after purification by chromatography on silica gel eluting with 20% EtOAc-*n*-hexane afforded **19** (112 mg, 73%) as a colourless oil, ν_{max} (film) 1600, 1580, 1270, 1110, 1030, 970, 880 and 810 cm^{-1} ; δ_H 7.10 (1H, s, H-6), 4.19 (4H, m, $\underline{CH_2}$-CH_3), 3.41 (2H, t, J=6.5, H-15), 3.41 (3H, s, MeO), 3.34 (3H, s, MeO), 3.11 (1H, dd, J_1=2.7 and J_2=8.6, H-3), 2.19 (3H, s, Me-17), 1.34 (6H, t, J=7.0, CH_2-$\underline{CH_3}$), 1.28 and 1.25 (3H, s ea, Me-18 and Me-19), 1.00 (3H, d, J=6.45, Me-16); δ_C see table 1.

Reaction of **17** *with triflic anhydride:* **20**. Collidine (0.5 ml) and triflic anhydride (0.2 ml) were added to a solution of **15** (82 mg, 0.24 mmol) in dry DCM (2 ml) and stirred for 2 hours. Then water was added and extracted with ether. The ethereal phase was washed with a saturated solution of Cu_2SO_4, dried (Na_2SO_4). After removal of the solvent, the crude mixture was cromatographed on silica gel (10% EtOAc-*n*-hexane) to yield **20** (78 mg, 71%) as a colourless oil, ν_{max} (film) 1640, 1570, 1220, 1150, 1120, 1040 and 850 cm^{-1}; δ_H 7.04 (1H, s, H-6), 3.45 (2H, t, J=6.8, H-15), 3.45 (3H, s, MeO), 3.43 (3H, s, MeO), 3.17 (1H, dd, J_1=2.9 and J_2=7.8, H-3), 2.25 (3H, s, Me-17), 1.28 and 1.27 (3H, s ea, Me-18 and Me-19), 1.02 (3H, d, J=6.4, Me-16); δ_C see table 1.

Reaction of **20** *with* Me_4Sn: **21** *(3β,15-fregenedadiol dimethylether).* To a solution of **20** (45 mg, 0.10 mmol), $(Ph_3P)_2PdCl_2$ (6 mg), Ph_3P (24 mg, 0.10 mmol), anhydride LiCl (31 mg, 0.73 mmol, heated for 3 hours at 100°C and 0.1 mm Hg) and 2,6-Di–*t*–butyl-4-methyl-phenol (one crystal) in freshly distilled DMF (3 ml). Then Me_4Sn (0.2 ml) was added and the reaction mixture was heated at 140°C, under argon, for two hours. The reaction was quenched with water and extracted with ether. The ethereals phases were washed with 2N HCl and a saturated solution of KF, dried (Na_2SO_4). Removed the solvent, the crude mixture was cromatographed on silicagel (5% EtOAc-*n*-hexane) to afford **21** (25mg, 75%) and starting material (6 mg), $[\alpha]_D$ +6.0 (c 0.6, $CHCl_3$); ν_{max} (film) 1480, 1370 and 1110 cm^{-1}; δ_H 7.01 (1H, s, H-6), 3.45 (2H, t, J=6.5, H-15), 3.43 (3H, s, MeO), 3.36 (3H, s, MeO), 3.15 (1H, dd, J_1=2.7 and J_2=8.6, H-3), 2.26 (3H, s, Me-17), 2.18 (3H, s, Me-20), 1.32 and 1.26 (3H, s ea, Me-18 and Me-19), 1.02 (1H, d, J=6.5, Me-16); δ_C see table 1. EIMS 70 eV, *m/z* (rel. int.): 332 [M^+](30), 300(71), 285(14), 253(17), 200(42), 185(100), 157(30), 143(18), 115(21), 97(15), 83(38) and 69(43).

Demethylation of **21**: **1** *(fregenedadiol).* To a solution of **21** (39 mg, 0.12 mmol) in acetonitrile (10 ml) was added NaI (280 mg, 1.87mmol) and TMSCl (0.2 ml) at room temperature and the solution was stirred under argon. One hour later the reaction was worked up as usual. The ethereal phase was washed with $Na_2S_2O_3$, brine and water. By preparative cromatography **1** (18 mg, 0.06mmol) was obtained.

$[\alpha]_D$ -11.0.(c 0.7, $CHCl_3$) (literature:[6] $[\alpha]_D$ -11.3 (c 0.5, $CHCl_3$)). ν_{max} (film) 3430, 3040, 1620, 1580, 1380, 1360, 1080, 1020 and 895 cm^{-1} ; δ_H 7.05 (1H, s, H-6), 3.74 (2H, m, H-15), 3.72 (1H, m, H-3), 2.86 (2H, m, H-1), 2.63 (2H, m, H-11), 2.27 (3H, s, Me-17), 2.20 (3H, s, Me-20), 1.33 and 1.30 (3H, s, each one, Me-18 and Me-19), 1.04 (3H, d, J=6.4, Me-16); δ_C see table 1.

References and Notes.

1. Urones, J.G., Marcos, I.S., Garrido, N.M., Pascual, J. de and San Feliciano, A.M. *Phytochemistry* **1989**, *28*, 183-187.
2. a.- Pascual, J. de, Urones, J.G., Basabe, P., Carrillo, H., Muñoz, M.A.G.and Marcos, I.S. *Phytochemistry* **1985**, *24*, 791-794. b.-Urones, J.G.,Marcos, I.S., Basabe, P., Garrido, N.M. *Phytochemistry* **1988**, *27*, 501-504. c.- Urones, J.G., Marcos, I.S., Garrido, N.M., Basabe, P. *Phytochemistry* **1990**, *29*, 2927-2930.
3. Pascual Teresa, J. de, Urones, J.G., Carrillo, H., Muñoz, M.A.G. *An. Quim.* **1979**, *75*, 140-143.
4. Urones, J.G., Marcos, I.S., Garrido, N.M. *Phytochemistry* **1990**, *29*, 3243-3246.
5. Urones, J.G., Marcos, I.S., Garrido, N.M. *Phytochemistry* **1990**, *29*, 2585-2589.
6. Urones, J.G., Marcos, I.S., Garrido, N.M., Moro, R.F. *Phytochemistry* **1990**, *29*, 3042-3044.
7. a.- Urones, J.G., Marcos, I.S., Basabe, P., Sexmero, M.J., Diez, D., Garrido, N.M.and Prieto, J.E.S. *Tetrahedron* **1990**, *46*, 2495-2502. b.-Pascual, J. de, Urones, J.G., Marcos, I.S., Diez, D., Alvarez, M. V.*Phytochemistry* **1986**, *25*, 711-713. c.-Urones, J.G., Marcos, I.S., Diez, D, Brito Palma, F.M.S., Rodilla, J.S. *Phytochemistry* **1987**, *26*, 3037-3040.
8. a.- Urones, J.G., Marcos, I.S., Basabe, P., Alonso, C.A., Diez, D, Garrido, N.M., Oliva, I.M., Rodilla, J.S., Slawin, A.M.Z., Williams, D.J. *Tetrahedron Letters* **1990**, *31*, 4501-4504. b.- Urones, J.G., Basabe, P., Marcos, I.S., Alonso, C.A., Oliva, I.M., Garrido, N.M., Diez, D, Lithgow, A.M. *Tetrahedron Letters* **1992**, *33*, 5269-5272.
9. Urones, J.G., Marcos, I.S., Basabe, P., Alonso, C.A., Diez, D., Garrido, N.M., Oliva, I.M. *Tetrahedron Letters* **1990**, *31*, 5665-5668.
10. I.Mateos Oliva. M. Sc. Thesis. Facultad de Química. Universidad de Salamanca. 1988.
11. a.- Urones, J.G, Marcos, I.S., Sexmero, M.J., Basabe, P., Lithgow, A.M. *Phytochemistry* **1990**, *29*, 3597-3600. b.- Urones, J.G., Marcos, I.S., Sexmero, M.J., Basabe, P., Lithgow, A.M. *Phytochemistry* **1990**, *29*, 1247-1251. c.- Urones, J.G., Pascual Teresa, .J de, Marcos, I.S., Martin, D.D., Garrido, N.M., Alfayate Guerra, R. *Phytochemistry* **1987**, *26*, 1077-1079.
12. Timmermann, B.N., Hoffmann, J.J., Jolad, S.D., Schram, K.H.Y., Klenck, R.E., Bates, R.B. *J.Org.Chem.* **1982**, *47*, 4114-4116.
13. Zdero, C., Bohlmann, F., Niemeyer, H.M. *Phytochemistry* **1991**, *30*, 3689-3691.
14. a.- Olah, G.A., Balaram, G.B.G., Narang, S.C., Malhotra, R. *J.Org.Chem.* **1979**, *44*, 4272-4275. b.- Ley, S.V., Santafianos, D. Blaney, W.M. Simmonds, S. J. *Tetrahedron Lett.* **1987**, *28*, 221-224.
15. Hanessian, S., Roy, P.J., Petrini, M., Hodges, P.J., Di Fabio, R., Carganico, G. *J.Org.Chem.* **1990**, *55*, 5766-5777.
16. Colombo, M.I., Zinczuck, J., Bacigaluppo, J.A., Somoza, C., Rúveda, E.A. *J.Org.Chem.* **1990**, *55*, 5631-5639.
17. a.- Tsuda, K., Ohki, E., Suzuki, J., Shimizu, H. *Chem.Pharm.Bull.* **1961**, *9*, 131-138. b.- Barton, D.H.R., Thomas, B.R. *J.Chem.Soc.* **1953**, 1842-1847.
18. Djerassi, C., *Steroid Reactions* Ed. Holden-Day. San Francisco, **1963**, Vol. I, pag 267.
19. Trost, B.M., Fleming, I., *Comprehensive Organic Synthesis*. Ed. Pergamon Press. Oxford. **1991**, vol 8, pag. 489.
20. Hayashi, T., Katsuro, Y., Okamoto, Y., Kumada, M. *Tetrahedron Letters* **1981** *22*, 4449-4452.
21. Saá, J.M., Dopico, M., Martorell, G., Garcia-Raso, A. *J.Org. Chem.* **1990**, *55*, 991-995.
22. Saá, J.M., Martorell, G., Garcia-Raso, A. *J.Org. Chem.* **1992**, *57*, 678-685.
23 Olah, G.A.; Narang, S.C.; Balaram Gupta, B.G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247-1251.