Pergamon

Tetrahedron 57 (2001) 713–723

TETRAHEDRON

Synthesis of (+)-limonidilactone and 12-*epi*-limonidilactone

Isidro S. Marcos,* Rosalina F. Moro, Santiago Carballares and Julio G. Urones

Dpto. Química Orgánica Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de la Merced s/n, 37008 Salamanca, Spain

Received 29 June 2000; revised 26 October 2000; accepted 8 November 2000

Abstract—The synthesis of (+)-limonidilactone from zamoranic acid is described. This synthesis has allowed the absolute configuration for the natural product (−)-limonidilactone be established. The synthesis of 12-*epi*-limonidilactone is also realized. In addition, a solid compound, which possesses a carbonyl group, has been isolated and identified as a hydrate stabilized by three hydrogen bonds.

1. Introduction

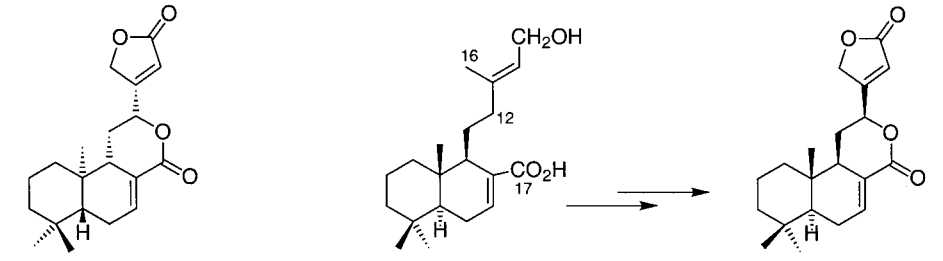
(−)-Limonidilactone[1,2] is a labdane diterpene recently isolated from *Vitex limonidifolia* by A. Suksramarn et al. These workers established its relative configuration based on spectroscopic and X-ray diffraction experiments, but the authors in their work did not determined if the compound belonged to the normal or antipode labdane series.

In this paper, we report the synthesis of compound **3** from the natural product **2**, zamoranic acid,[3] a bicyclic diterpene with a labdane skeleton, which has been transformed into many different compounds which possess interesting biological activities.[4] After comparison of the spectroscopic data, melting point and $[\alpha]_D$ of compound **3** with the natural (−)-limonidilactone **1**, we can be sure that both are enantiomers, thus the configuration for **1** is established, as shown in Scheme 1, corresponding to the *ent*-labdanes series.

2. Results and discussion

In order to synthesis limonidilactone **3** from zamoranic acid **2**, functionalisation of C-12 and C-16 with stereochemical control at C-12 is required to form the δ-lactone with the C-17 carboxylic group.

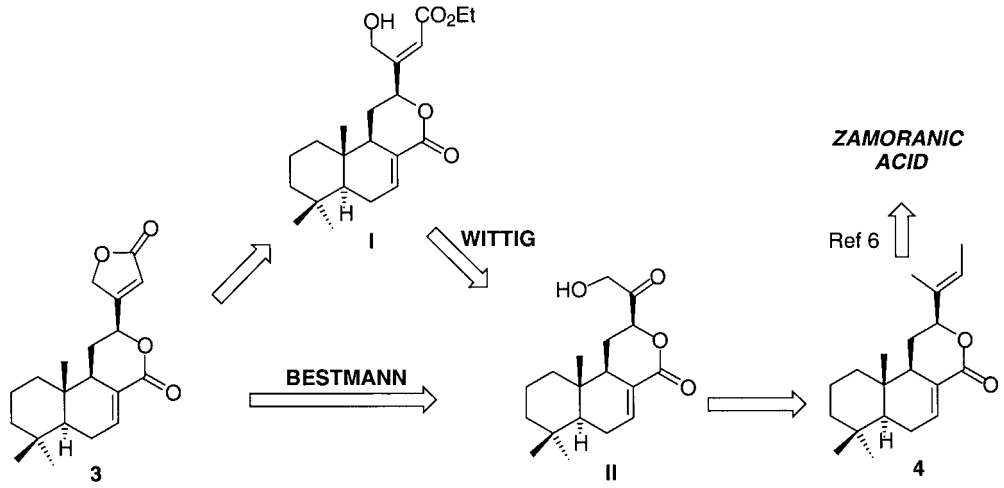
Scheme 2 shows the retrosynthesis for compound **3** from zamoranic acid through intermediate **II**, by reaction of this with Bestmann ketene[5] giving a γ-lactone. Alternatively C-14 and C-15 could be introduced by a Wittig reaction giving the intermediate **I** followed by lactonization (Scheme 2).



Scheme 1.

Keywords: limonidilactone; zamoranic acid; diterpenes; absolute configuration.
* Corresponding author. Tel.: +34-923-294474; fax: +34-923-294574; e-mail: ismarcos@gugu.usa1.es

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01057-7



Scheme 2.

Both routes go through hydroxyketone **II**, which can be formed from lactone **4**, whose synthesis has been already described.[6]

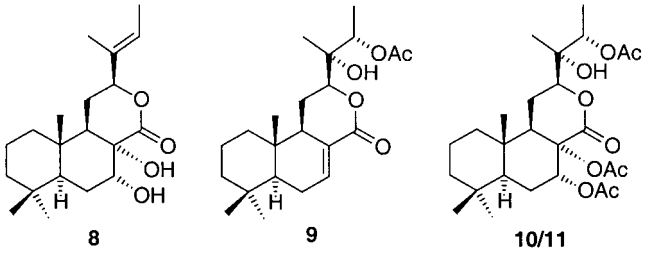
2.1. Synthesis of methyl ketones 6 and 7

Compounds **4** and its epimer on C-12, **5** were obtained in one single step from zamoranic in a very good yield.[6] Transformation of δ-lactone **4** into compound **II** was achieved by Δ^{13} cleavage to form methylketone **6** and subsequent α-oxidation with respect to the carbonyl group (Scheme 3).

We firstly tried oxidation of Δ^{13} in compound **4** by treatment with OsO_4/NMO, yielding compound **8** (29%) and a mixture of products separated after acetylation (Ac_2O/Py, r.t.) and identified as **9** (22%), **10** (8%) and **11** (8%). The less polar compound was identified as **8** and the stereochemistry for H-7 was establishes as β because of its coupling constants.

Diastereomers **10** and **11** were easily separated by CC and identified by its spectroscopic data ^{1}H, ^{13}C NMR.

Both of them show three acetoxy groups, two of them are secondary and the other one is tertiary. The position of the last was established by long range heteronuclear correlation (HMBC).

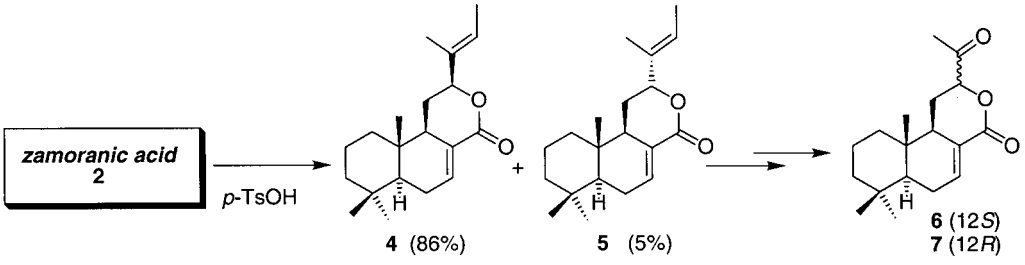


Compound **9** is the expected *cis* hydroxylated product at Δ^{13}, however it was obtained in a low yield. Therefore we decided to carry out the oxidation of **4** with *m*-CPBA.

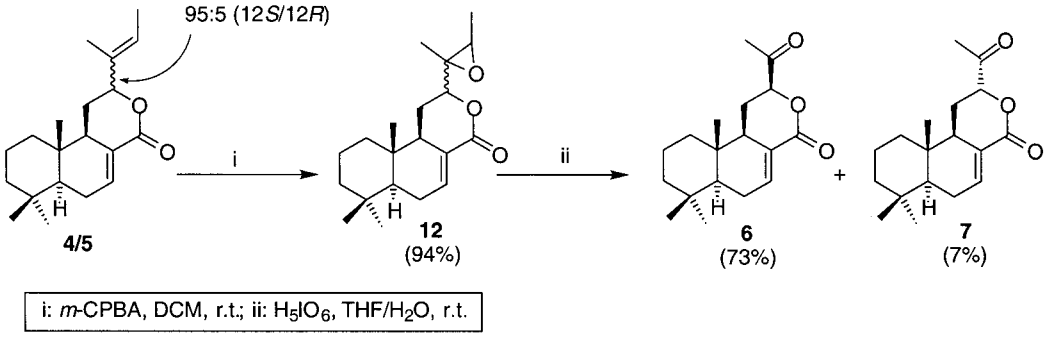
The mixture **4/5** (95:5) was treated with *m*-CPBA at room temperature giving the epoxide derivative **12**; subsequent treatment of these with H_5IO_6 afforded the methylketone **6** in a very good yield and its epimer **7** (Scheme 4). Configuration at C-12 was established by ^{1}H NMR.[6]

Intermediate **II** requires the C-16 oxidation of methylketone **6**. A first attempt through the function of silylenolether[7] and further oxidation with *m*-CPBA gave the undesired compound **13**, resulting from the abstraction of the more acidic proton H-12 (Scheme 5).

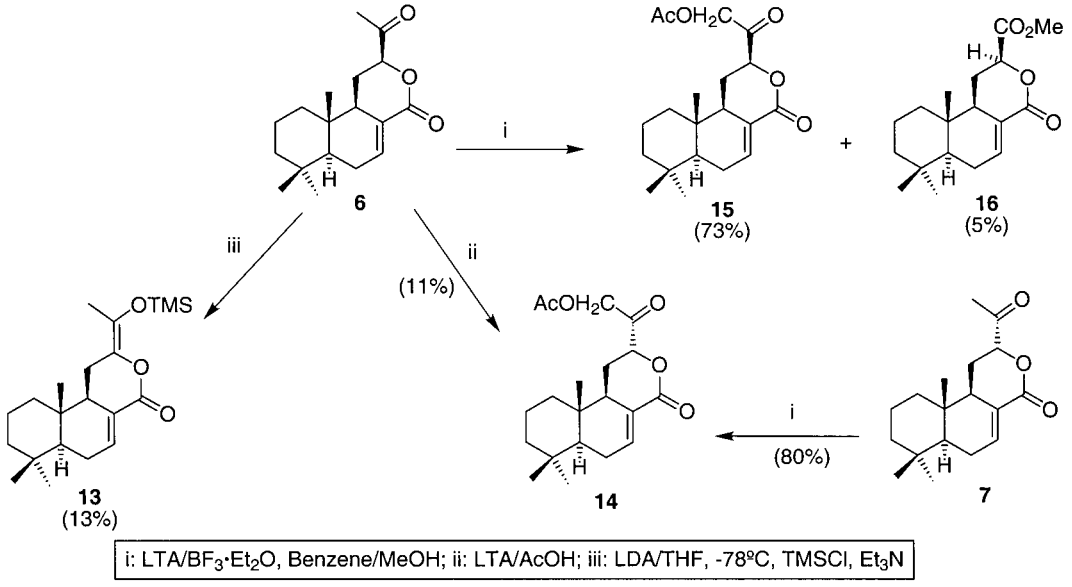
A second attempt was carried out using LTA (lead tetra-acetate)/AcOH[8], giving **14**, in a low yield. We proved that



Scheme 3.



Scheme 4.



Scheme 5.

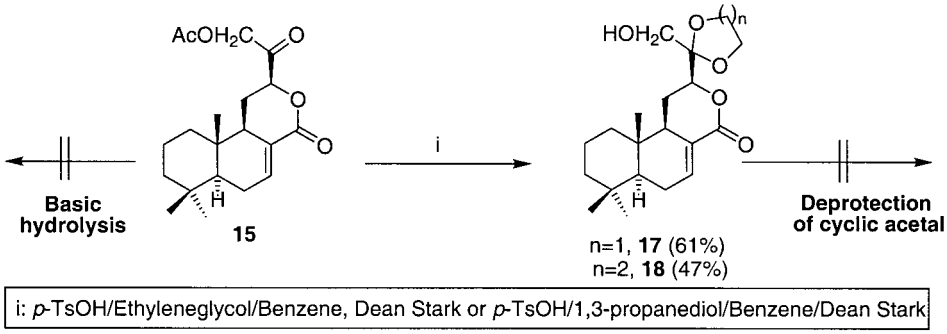
epimerization has taken place on C-12 caused by the different multiplicity observed for H-12 in ^{1}H NMR.

Finally, when the oxidation reaction of **6** was performed with LTA in the presence of a Lewis acid[9] ($BF_3{\cdot}Et_2O$), compounds **15** and **16** were obtained. The same reaction conditions for methylketone **7** afforded **14** in an excellent yield, without epimerization on C-12 (Scheme 5).

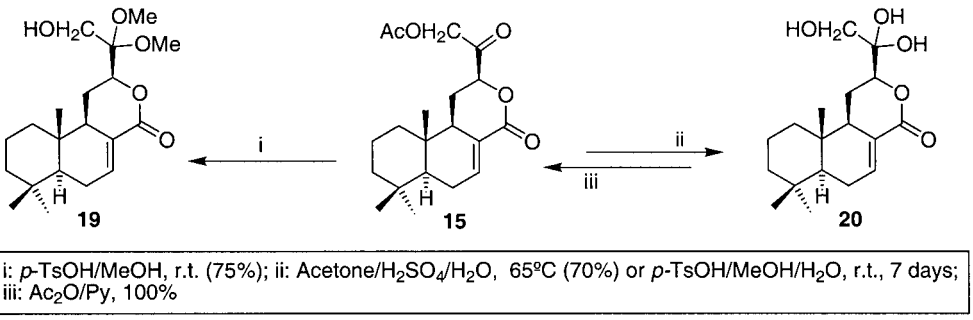
Compound **16** occurred as a minor product by cleavage of C12–C13 with LTA (excess) present in the reaction medium and subsequent acid esterification.

2.2. Hydrolysis of the acetoxy group at C-16

Basic hydrolysis of the acetoxy group in compound **15** (K_2CO_3/MeOH or KOH/MeOH) were not successful, giving only decomposition of the starting material because of the easy ring-opening under alkaline reaction conditions.



Scheme 6.



Scheme 7.

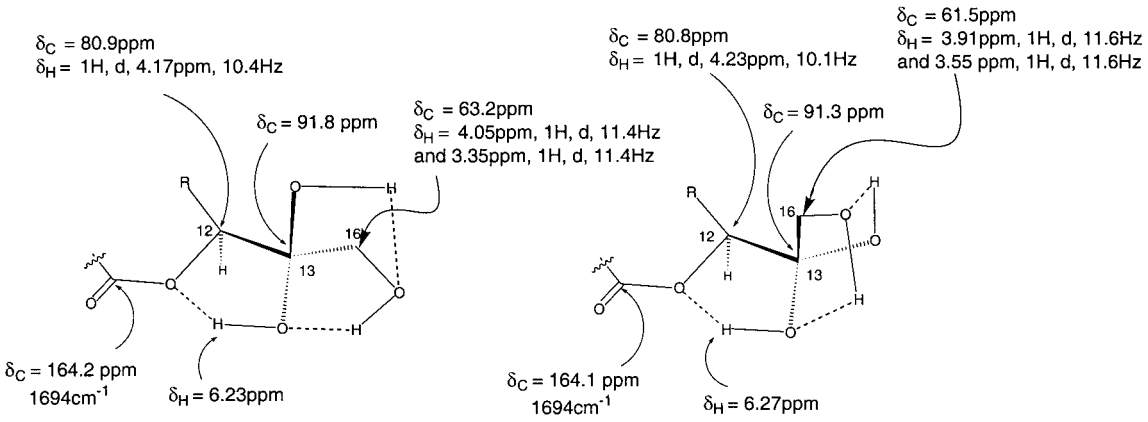
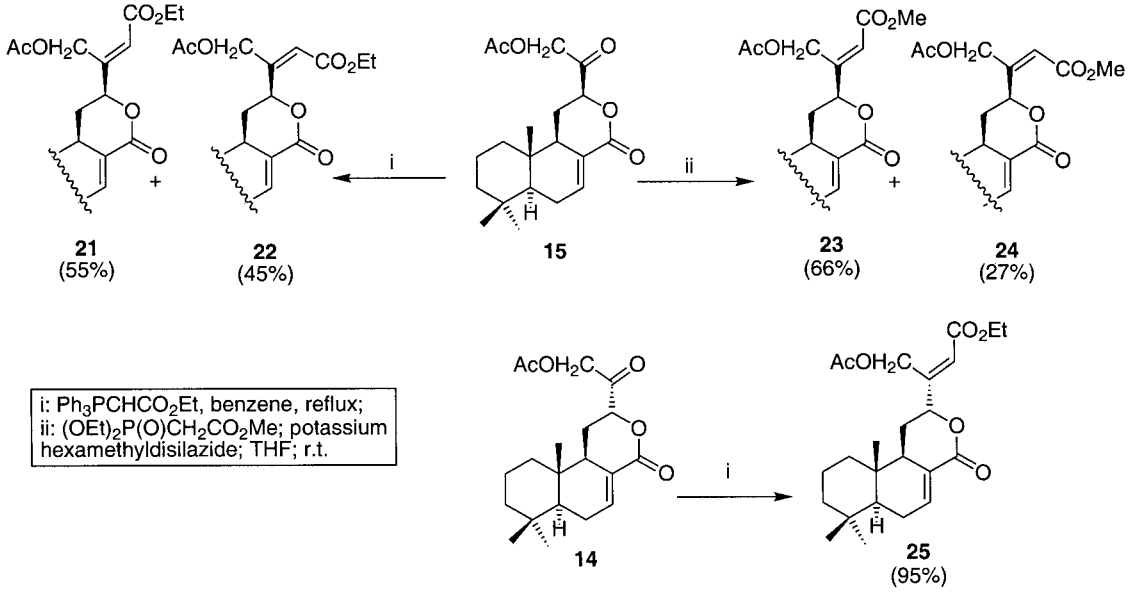


Figure 1.

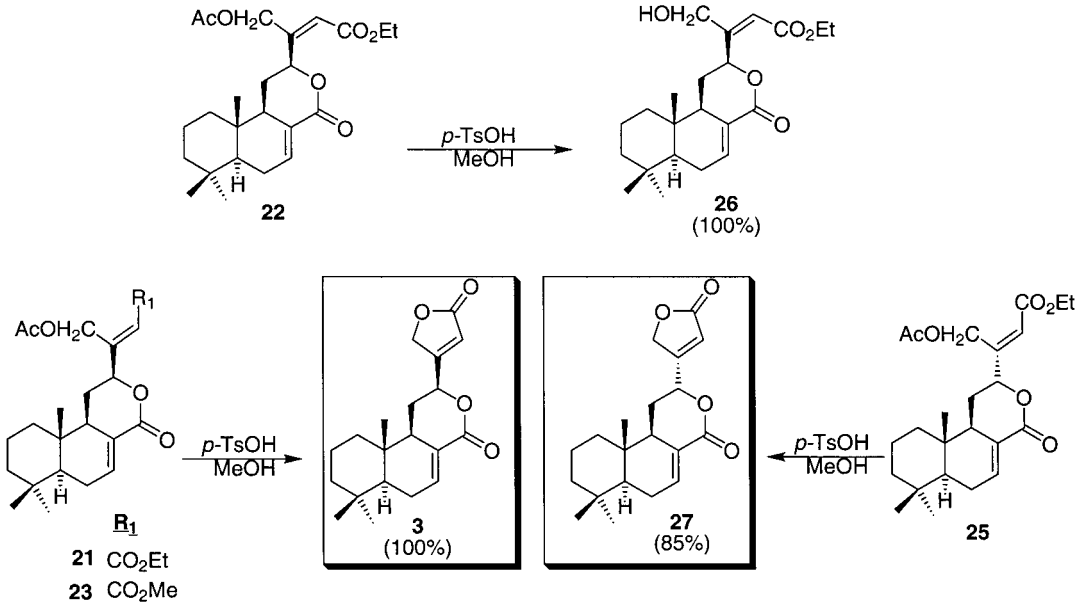
To avoid the interaction with the carbonyl group, protection of **15** by reaction with *p*-TsOH and ethyleneglycol or 1,3-propanediol, afforded acetals **17** and **18**, respectively; also with hydrolysis of the acetoxy group (Scheme 6).

However, the deprotection reaction of compounds **17** and **18** under several reaction conditions (*p*-TsOH/ketone, PPTS/ketone, HCl/ketone, Amberlyst-15/ketone), gave only decomposition products, when the temperature was increased up to 65–70°C.

Attempts to hydrolyse **15** with *p*-TsOH/MeOH at room temperature afforded **19**, but once the hydroxyl group at C-16 occurred, the carbonyl group cannot be deprotected. In order to avoid the formation of the dimethylacetal, compound **15** was treated with *p*-TsOH/MeOH/H_2O at



Scheme 8.



Scheme 9.

room temperature over 7 days, giving **20** as a white amorphous solid, only soluble in DMSO. This compound is also obtained in the treatment of **15** with acetone/H_2SO_4/H_2O at 60°C. Acetylation of **20** under usual conditions (Ac_2O/Py, r.t.) led quantitatively to **15**. Careful analysis of spectrocopic data indicated the structure shown in Scheme 7 for compound **20**.

The orientation of α,α'-dioxocarbonyl of **20** allows the formation of three hydrogen bonds that stabilize the hydrate. Its ^{1}H and ^{13}C NMR show signals corresponding to the more stable 'isomers' that can be formed because of the three hydrogen bonds (see Fig. 1).[10]

2.3. Wittig reaction and lactonization

Because all the attempts to form an α-hydroxylcarbonyl from **15** failed, we decided to introduce carbons C-14 and C-15 through a Wittig type reaction.[11] Treatment of **15** with $Ph_3P{=}CHCO_2Et$ afforded compounds **21** and **22** but a better ratio *E/Z* was obtained in the Horner–Wadsworth–Emmons reaction of **15**, giving **23** and **24**. The Wittig reaction of **14** epimer led to compound **25** in an excellent yield (Scheme 8).

Acid hydrolysis of **22** led to the hydroxyderivative **26**, where the unfavourable *Z* stereochemistry avoids intramolecular cyclization. Under the same reaction conditions, **21** and **23** afforded (+)-limonidilactone **3**; while **25** gave 12-*epi*-limonidilactone **27** (Scheme 9).

All the spectrocopic and physical properties for compound **3** are in agreement with those reported for (−)-limonidilactone in literature, nevertheless the opposite sign for the specific rotation between **3** and (−)-limonidilactone **1** led us to the conclusion that synthetic compound **3** and the natural product, (−)-limonidilactone are enantiomers. $[\alpha]_D^{20°C}$ (compound **3**)=+14.2 (c, 1.4 in $CHCl_3$); $[\alpha]_D^{25°C}$ (lit.)[1]=−23.8 (c, 0.12 in $CHCl_3$).

3. Experimental

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT ir spectrophotometer. ^{1}H and ^{13}C NMR spectra were performed in deuterochloroform and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, at a Bruker WP-200 SY and a Bruker DRX 400 MHz. Chemical shifts are reported in δ, ppm and coupling constants (*J*) are given in Hz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as *m/z* (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas). Optical rotations were determined at a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane were distilled from calcium hydride under an Ar atmosphere.

3.1. Reaction of zamoranic acid 2, with *p*-TsOH: 4 and 5

To a solution of zamoranic acid **2** (380 mg, 1.19 mmol) in benzene (11 ml) was added at room temperature *p*-TsOH (380 mg, 2.0 mmol) under stirring. After 24 h, the solution was diluted with Et_2O, washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed under vacuum to afford 380 mg of crude material that was cromatographed (Hex/AcOEt 95:5) to give δ-lactone **4** (310 mg, 86%) and δ-lactone **5** (18 mg, 5%).

3.1.1. 7,13*E*-Labdadien-17,12*S*-olide: 4. Rf (Hex/AcOEt 8:2)=0.34; ν_{max}^{film}: 2926, 1717, 1643, 1298, 1122, 1078 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.32 (1H, m, H-7), 5.60 (1H, q, *J*=7.0 Hz, H-14), 4.60 (1H, dd, *J*=2.2

and 13.6 Hz, H-12), 1.64 (3H, s, Me-16), 1.62 (3H, d, J=7.0 Hz, Me-15), 0.90, 0.88 and 0.75 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 165.5 (C-17), 142.1 (C-7), 134.1 (C-8), 126.2 (C-13), 122.8 (C-14), 84.4 (C-12), 49.3 (C-5), 48.9 (C-9), 41.9 (C-3), 38.6 (C-1), 34.7 (C-10), 32.7 (C-4), 32.7 (C-18), 27.4 (C-11), 25.1 (C-6), 21.4 (C-19), 18.5 (C-2), 13.3 (C-20), 13.0 (C-15), 11.4 (C-16); MS *m/z* (relative intensity): 302 (M^+,15), 204 (10), 179 (12), 151 (18), 137 (22), 109 (35), 89 (58), 69 (58), 59 (100).

3.1.2. 7,13*E*-Labdadien-17,12*R*-olide: 5. Rf (Hex/AcOEt 8:2)=0.33; ν_{max}^{film}: 2926, 1723, 1643, 1458, 1368, 1254, 1010 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.23 (1H, m, H-7), 5.45 (1H, q, J=6.3 Hz, H-14), 4.82 (1H, broad s, H-12), 1.66 (3H, s, Me-16), 1.60 (3H, d, J=6.3 Hz, Me-15), 0.91, 0.88 and 0.77 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 166.5 (C-17), 142.0 (C-7), 132.8 (C-8), 126.7 (C-13), 120.8 (C-14), 80.4 (C-12), 49.0 (C-9), 43.8 (C-5), 42.0 (C-3), 38.5 (C-1), 34.5 (C-10), 32.8 (C-4), 32.8 (C-18), 25.1 (C-6), 24.4 (C-11), 21.5 (C-19), 18.6 (C-2), 13.5 (C-15), 13.1 (C-16), 13.1 (C-20); HRMS calcd for $C_{20}H_{30}O_2$: 302.2246; found: 302.2229.

3.2. Oxidation of 4 with OsO_4/NMO: 9, 10 and 11

To a solution of δ-lactone **4** (74 mg, 0.25 mmol) in *t*-BuOH/THF/H_2O (10:3:1), was added 4-methylmorpholine *N*-oxide (NMO) (36 mg, 0.27 mmol) and OsO_4 (2.5% in *t*-BuOH, 5 μl). The solution stirred and checked by TLC during 15 h, then Na_2SO_3 aq. sat. was added and the solution stirred for 1/2 h, diluted with Et_2O, washed with HCl 7%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent evaporated at low vacuum to give, after chromatography (Hex/AcOEt 8:2), compound **4** (15 mg, 20%), **8** (24 mg, 29%) and a mixture of compounds that were separated after acetylation (Ac_2O/Py) and identified as compounds **9** (20 mg, 22%), **10** (11 mg, 9%) and **11** (10 mg, 8%).

3.2.1. 7*R*,8*R*-Dihydroxy-13*E*-labden-17,12*S*-olide: 8. Rf (Hex/AcOEt 8:2)=0.16; m.p.=169–170°C; ν_{max}^{nujol}: 3381, 1738, 1468, 1377, 1240, 1209, 1154, 1074, 1051, 980, 947, 912, 890, 816, 783, 721, 685 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** 5.61 (1H, q, J=6.5 Hz, H-14), 5.32 (1H, dd, J=4.8 and 11.3 Hz, H-12), 4.45 (1H, q, J=4.3 Hz, H-7), 3.69 (1H, s, –OH); 2.65 (1H, d, J=4.3 Hz, –OH), 1.71 (3H, s, Me-16), 1.64 (3H, d, J=6.5 Hz, Me-15), 0.89, 0.83 and 0.82 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 172.7 (C-17), 133.7 (C-13), 123.1 (C-14), 81.6 (C-12), 72.5 (C-8), 68.1 (C-7), 51.0 and 46.4 (C-5 and C-9), 41.8 (C-3), 39.6 (C-1), 37.9 (C-10), 33.0 (C-18), 32.8 (C-4), 26.8 and 26.1 (C-6 and C-11), 21.5 (C-19), 18.2 (C-2), 13.7, 13.1 and 11.5 (C-15, C-16 and C-20); MS *m/z* (relative intensity): 354 ($M+NH_4^+$, 100), 337 ($M+H^+$, 75), 319 (30), 292 (9), 275 (9), 235 (10), 210 (4), 195 (7), 175 (4), 168 (4), 154 (5), 109 (6), 95 (5), 81 (4).

3.2.2. 14-Acetoxy-13-hydroxy-7-labden-17,12*S*-olide: 9. Rf (Hex/AcOEt 6:4)=0.46; ν_{max}^{film}: 2928, 2868, 1738, 1642, 1469, 1424, 1371, 1246, 1202, 1121, 1053, 953, 918, 745 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** 7.32 (1H, m, H-7), 5.17 and 5.14 (1H, q each one, J=6.5 Hz, H-14 and H-14′), 4.25 and 4.17 (1H, dd each one, J=2.1 and 11.4 Hz, H-12 and H-12′), 2.09 and 2.07 (1Me, s ea, OAc and OAc′), 1.16 (2Me, m, Me-15 and Me-16), 0.91, 0.86 and 0.76 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; MS *m/z* (relative intensity): 396 ($M+NH_4^+$, 100), 379 ($M+H^+$, 50), 248 (20), 148 (10), 109 (10), 73 (10), 61 (16), 44 (12).

3.2.3. 7*R*,8*R*,14-Triacetoxy-13-hydroxy-17,12*S*-labdanolide: 10. Rf (Hex/AcOEt 6:4)=0.30; ν_{max}^{film}: 3472, 2930, 2872, 1759, 1738, 1464, 1373, 1250, 1229, 1119, 1078, 1044, 953, 779, 737 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 6.00 (1H, t, J=3.8 Hz, H-7), 5.20 (1H, q, J=6.5 Hz, H-14), 4.49 (1H, dd, J=5.9 and 11.3 Hz, H-12), 2.10, 2.08 and 2.00 (3Me, s, 3xOAc), 1.23 (3H, d, J=6.5 Hz, Me-15), 1.13 (3H, s, Me-16), 0.86, 0.84 and 0.79 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 170.9, 169.3, 168.3 and 167.7 (C-17 and 3xO*C*OMe), 78.8 (C-12), 76.4 and 75.5 (C-14 and C-8), 73.4 and 68.4 (C-14 and C-7), 47.3 (C-9), 46.9 (C-5), 41.7 (C-3), 39.6 (C-10), 39.2 (C-1), 33.1 (C-18), 32.5 (C-4), 25.1 (C-6), 21.5 (C-19), 21.4 (3xOCO*Me*), 20.3 (C-11), 17.9 (C-15 and C-2), 15.1 (C-20), 12.5 (C-16); MS *m/z* (relative intensity): 514 ($M+NH_4^+$, 100), 472 (40), 454 (6), 426 (9), 412 (10), 396 (40), 379 (15), 324 (4), 308 (4), 289 (5), 264 (4), 246 (10), 218 (4), 148 (7), 131 (6), 109 (6), 60 (4), 44 (5).

3.2.4. 7*R*,8*R*,14-Triacetoxy-13-hydroxy-17,12*S*-labdanolide: 11. Rf (Hex/AcOEt 6:4)=0.21; ν_{max}^{film}: 3470, 2928, 2870, 1759, 1464, 1373, 1252, 1231, 1165, 1119, 1045, 953, 737 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)**: 5.96 (1H, t, J=3.8 Hz, H-7), 5.00 (1H, q, J=6.5 Hz, H-14), 4.37 (1H, dd, J=5.9 and 11.3 Hz, H-12), 2.10, 2.09 and 2.00 (3Me, s, 3xOAc), 1.30 (3H, s, Me-16), 1.19 (3H, d, J=6.5 Hz, Me-15), 0.85, 0.83 and 0.79 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: 170.2, 169.6 and 168.5 (3xO*C*OMe), 167.9 (C-17), 78.3 (C-12), 77.0 (C-8), 75.1 (C-13), 72.1 (C-14), 68.1 (C-7), 46.9 (C-9), 46.7 (C-5), 41.5 (C-3), 39.4 (C-1), 39.0 (C-10), 33.1 (C-18), 32.4 (C-4), 25.0 (C-11), 21.4 (C-19), 21.1 (3xOCO*Me*), 20.0 (C-6), 18.4 (C-16), 17.8 (C-2), 15.0 (C-15), 12.5 (C-20); MS *m/z* (relative intensity): 514 ($M+NH_4^+$, 50), 472 (30), 437 (4), 396 (20), 379 (10), 340 (25), 323 (30), 303 (70), 293 (100), 264 (4), 246 (6), 124 (11), 109 (15), 81 (84).

3.3. Oxidation of 4/5 with *m*-CPBA: 12

To a solution of the mixture of compounds **4/5** (67 mg, 95:5, 0.22 mmol) in DCM (2.2 ml) was added *m*-CPBA (50 mg, 0.29 mmol) and the solution was stirred at room temperature. After 2.5 h, $Na_2S_2O_3$ 10% aq. was added and the resulting solution was stirred for 5 min; the mixture was diluted and extracted with Et_2O, washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4) and the solvent evaporated in vacuum to give the mixture of epoxides **12** (66 mg, 94%).

3.3.1. 13,14-Epoxy-7-labden-17,12-olide: 12. Rf (Hex/AcOEt 6:4)=0.27; ν_{max}^{film}: 2874, 1720, 1714, 1643, 1462, 1371, 1269, 1242, 1188, 1146, 1121, 1038, 984, 872, 745 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.33 (1H, m, H-7), 3.71 and 4.05 (1H, dd, J=2.2 and 11.8 Hz, H-12 and H-12′), 3.13 and 3.00 (1H, q, J=5.4 Hz, H-14 and

H-14′), 1.34–1.28 (2Me, m, J=5.4 Hz, Me-15, Me-16 and Me-15′ and Me-16′), 0.92, 0.68 and 0.79 (3Me, s ea, Me-18, Me-19 and Me-20 and Me-18′, Me-19′ and Me-20′) ppm; MS *m/z* (relative intensity): 336 ($M+NH_4^+$, 100), 319 ($M+H^+$, 100), 301 (9), 275 (15), 217 (4), 212 (25), 124 (20), 109 (24), 95 (4), 58 (4), 44 (4).

3.4. Reaction of 12 with H_5IO_6: 6 and 7

To a solution of compound **12** (410 mg, 1.29 mmol) in THF/H_2O (9 ml/4 ml), was added at room temperature H_5IO_6 (760 mg, 3.32 mmol) and the solution stirred for 24 h. After this time, the mixture was diluted with Et_2O and washed with water, Na_2SO_3 10%, water and brine, dried (Na_2SO_4) and the solvent evaporated at low vacuum to give the crude material that was chromatographed on silicagel (Hex/AcOEt 8:2) to give compounds **6** (270 mg, 73%) and **7** (27 mg, 7%).

3.4.1. 13-Oxo-14,15-dinor-7-labden-17,12*S*-olide: 6. Rf (Hex/AcOEt 7:3)=0.31; $[\alpha]_D^{20°C}=-44.7$ (c, 0.90 in $CHCl_3$); m.p.=97–99°C; ν_{max}^{film}: 2928, 1730, 1719, 1642, 1458, 1422, 1364, 1227, 1198, 1123, 1036, 974, 955, 876, 669 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$):** 7.38 (1H, m, H-7), 4.57 (1H, dd, J=2.7 and 11.8 Hz, H-12), 2.34 (3H, s, MeCO), 0.91, 0.89, 0.75 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 206.1 (C-13), 164.0 (C-17), 144.1 (C-7), 125.4 (C-8), 82.7 (C-12), 48.8 (C-9), 48.7 (C-5), 41.7 (C-3), 38.6 (C-1), 34.8 (C-10), 32.8 (C-4), 32.8 (C-18), 25.7 (C-16), 25.2 (C-6), 25.0 (C-11), 21.4 (C-19), 18.5 (C-2), 13.3 (C-20); HRMS calcd for $C_{18}H_{26}O_3$: 290.1882; found: 290.1875.

3.4.2. 13-Oxo-14,15-dinor-7-labden-17,12*R*-olide: 7. Rf (Hex/AcOEt 7:3)=0.20; $[\alpha]_D^{20°C}=-57.3$ (c, 0.60 in $CHCl_3$); m.p.=107–109°C; ν_{max}^{film}: 1723, 1643, 1462, 1443, 1389, 1244, 1188, 1146, 1123, 1080, 1036, 986, 914, 745 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.36 (1H, m, H-7), 4.90 (1H, dd, J=2.7 and 4.9 Hz, H-12), 2.28 (3H, s, MeCO), 0.91, 0.88 and 0.77 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; MS *m/z* (relative intensity): 308 ($M+NH_4^+$, 100), 291 ($M+H^+$, 70), 280 (4), 264 (10), 247 (15), 230 (4), 217 (5), 124 (4), 109 (7), 95 (4), 58 (3); **^{13}C NMR (50 MHz, $CDCl_3$)**: 206.3 (C-13), 164.4 (C-17), 144.1 (C-7), 125.5 (C-8), 81.8 (C-12), 48.9 (C-9), 45.1 (C-5), 41.8 (C-3), 38.4 (C-1), 34.6 (C-10), 32.9 (C-4), 32.8 (C-18), 27.1 (C-16), 25.3 (C-6), 23.2 (C-11), 21.4 (C-19), 18.5 (C-2), 13.1 (C-20).

3.5. Reaction of 6 with LDA/TMSCl: 13

To a solution of diisopropylamine (0.12 ml) in THF (2 ml) cooled at −78°C was added *n*-BuLi (0.5, 1.6 M in hexane). The resulting solution was brought up to −25°C and then recooled to −78°C. To this solution of lithiumdiisopropylamide was added, dropwise and with stirring, compound **6** (80 mg, 0.28 mmol) in THF (2 ml). Meanwhile, a quenching solution, prepared from 5 ml THF, triethylamine (0.50 ml) and chlorotrimethylsilane (2 ml) was centrifuged to remove any of the insoluble triethylamine hydrochloride. By use of a syringe, this chlorotrimethylsilane solution (1.3 ml) was added to a cold solution of the lithium enolate. After 15 min, the resulting mixture was diluted with Et_2O and washed with NH_4Cl sat. aq., water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed in low vacuum to give, after chromatography (Hex/AcOEt 9:1), compound **13** (13 mg, 13%).

3.5.1. 13-Trimethylsilyloxy-14,15-dinor-7,12-labdadien-17,12-olide: 13. Rf (Hex/AcOEt 7:3)=0.68; ν_{max}^{film}: 2938, 2866, 1723, 1699, 1643, 1454, 1424, 1368, 1196, 1123, 1086, 1013, 845, 743, 700, 681 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.35 (1H, m, H-7), 2.85 (1H, dd, J=3.8 and 13.4 Hz, H-11), 1.90 (3H, s, Me-16), 0.93, 0.89 and 0.80 (3Me, s ea, Me-18, Me-19 and Me-20), 0.12 (3Me, s, TMS) ppm.

3.6. Reaction of 6 with LTA/AcOH: 14

To a solution of compound **6** (68 mg, 0.23 mmol) in AcOH (3 ml) was added, at room temperature, LTA (290 mg, 0.65 mmol) and the solution heated to 75°C. After 24 h, all the starting material had disappeared (detected by TLC). The mixture was diluted with Et_2O and washed with $NaHCO_3$ 5%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent evaporated to give, after chromatography (Hex/AcOEt 8:15), compound **14** (9 mg, 11%).

3.6.1. 16-Acetoxy-13-oxo-14,15-dinor-7-labden-17,12*R*-olide: 14. Rf (Hex/AcOEt 7:3)=0.15; $[\alpha]_D^{20°C}=-27.0$ (c, 0.81 in $CHCl_3$); ν_{max}^{film}: 2926, 1742, 1726, 1640, 1462, 1414, 1389, 1271, 1229, 1202, 1142, 1121, 1101, 1030, 739, 691, 669 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.40 (1H, m, H-7), 5.05 (1H, m, H-12), 4.95 and 4.83 (1H, d ea, J=17.2 Hz, CH_2OAc), 2.19 (3H, s, –OAc), 0.91, 0.88 and 0.77 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 201.8 (C-13), 170.0 (O*C*OMe), 164.0 (C-17), 144.8 (C-7), 125.3 (C-8), 80.7 (C-12), 67.1 (C-16), 48.6 (C-9), 44.7 (C-5), 41.8 (C-3), 38.2 (C-1), 34.6 (C-10), 32.8 (C-4 and C-18), 25.3 and 23.8 (C-6 and C-11), 21.5 (C-19), 20.3 (OCO*Me*), 18.5 (C-2), 13.1 (C-20); MS *m/z* (relative intensity): 366 ($M+NH_4^+$, 45), 349 ($M+H^+$, 20), 324 (100), 308 (60), 291 (30), 280 (14), 247 (16), 164 (10), 124 (11), 109 (12), 73 (30), 61 (68), 44 (52).

3.7. Reaction of 7 with LTA/BF_3: 14

To a solution of compound **7** (64 mg, 0.22 mmol) in benzene (3 ml), MeOH (142 μl) and LTA (133 mg, 0.30 mmol) was added, dropwise at room temperature and under an Ar atmosphere, BF_3Et_2O (442 μl); the solution was maintained at this temperature and monitored by TLC. After 6 h, the solution was diluted with Et_2O, washed with water and brine, dried (Na_2SO_4 anhydrous) and the solvent evaporated to give, after chromatography (Hex/AcOEt 85:15), compound **14** (61 mg, 80%).

3.8. Reaction of 6 with LTA/BF_3: 15 and 16

To a solution of compound **6** (896 mg, 3.09 mmol) in benzene (42 ml) was added MeOH (1.99 ml), LTA (1868 mg, 4.20 mmol) and the solution was treated dropwise with BF_3Et_2O (6.2 ml) under an Ar atmosphere. The solution was kept at this temperature for 4 h, after which the solution was diluted with Et_2O and washed with water, brine

and dried (Na_2SO_4 anhydrous); the solvent was removed at low vacuum to give, after chromatography (Hex/AcOEt 7:3), compounds **15** (784 mg, 73%) and **16** (47 mg, 5%).

3.8.1. 16-Acetoxy-13-oxo-14,15-dinor-7-labden-17,12*S*-olide: 15. Rf (Hex/AcOEt 7:3) = 0.22; $[\alpha]_D^{20°C}=-43.2$ (c, 0.52 in $CHCl_3$); m.p.=106–108°C; ν_{max}^{film}: 2928, 1738, 1726, 1642, 1462, 1443, 1422, 1371, 1248, 1184, 1121, 1096, 1053, 1011, 974, 914, 839, 737 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.39 (1H, m, H-7), 5.13 and 5.00 (1H, d ea, *J*=18.3 Hz, CH_2OAc), 4.77 (1H, dd, *J*=2.2 and 11.8 Hz, H-12), 2.17 (3H, s, –OAc), 0.92, 0.89 and 0.76 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 200.7 (C-13), 170.0 (*O*COMe), 163.5 (C-17), 144.9 (C-7), 125.2 (C-8), 82.3 (C-12), 66.1 (C-16), 48.9 and 48.8 (C-5 and C-9), 41.2 (C-3), 38.7 (C-1), 34.9 (C-10), 32.8 (C-4 and C-18), 25.3 (C-6 and C-11), 21.4 (C-19), 20.3 (OCOMe), 18.5 (C-2) 13.3 (C-20); MS *m/z* (relative intensity): 366 ($M+NH_4^+$, 8), 352 (4), 338 (5), 324 (100), 307 (20), 264 (9), 247 (10), 124 (5), 109 (9); Anal. calcd. for $C_{20}H_{28}O_5$: C, 68.96%; H, 8.05%; found: C, 69.03%; H, 8.32%.

3.8.2. Methyl 17,12*S*-olide-14,15,16-trinor-7-labden-13-oato: 16. Rf (Hex/AcOEt 7:3)=0.27; $[\alpha]_D^{20°C}=+34.1$ (c, 0.27 in $CHCl_3$); m.p.=114–116°C, ν_{max}^{film}: 2926, 1763, 1726, 1642, 1460, 1441, 1368, 1248, 1213, 1130, 1098, 1020, 945, 928, 741 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$):** 7.39 (1H, m, H-7), 4.68 (1H, dd, *J*=2.4 and 12.0 Hz, H-12), 3.79 (3H, s, –OMe), 0.90, 0.88 and 0.74 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: 169.4 (C-13), 163.7 (C-17), 144.3 (C-7), 124.8 (C-8), 76.5 (C-12), 52.6 (OMe), 48.5 (C-5 and C-9), 41.6 (C-3), 38.5 (C-1), 34.6 (C-10), 32.7 (C-4 and C-18), 25.7 and 25.1 (C-11 and C-6), 21.3 (C-19), 18.3 (C-2), 13.2 (C-20); HRMS calcd for $C_{18}H_{26}O_4$: 306.1831; found: 306.1838.

3.9. Reaction of 15 with ethyleneglycol/*p*-TsOH: 17

To a solution of compound **15** (92 mg, 0.27 mmol) in benzene (6 ml) was added ethyleneglycol (254 μl) and a catalytic amount of *p*-TsOH (2 mg) and the solution was refluxed in a Dean Stark apparatus. After 3 h, the mixture was cooled and diluted with Et_2O, washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed to give a colourless oil that was chromatographed (Hex/AcOEt 6:4), affording compound **17** (58 mg, 61%).

3.9.1. 13-Ethylenedioxy-16-hydroxy-14,15-dinor-7-labden-17,12*S*-olide: 17. Rf (Hex/AcOEt 6:4)=0.04; ν_{max}^{film}: 3445, 2924, 1721, 1642, 1462, 1422, 1391, 1269, 1250, 1198, 1125, 1080, 1040, 949, 883, 745 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.27 (1H, m, H-7), 4.44 (1H, dd, *J*=1.8 and 11.1 Hz, H-12), 4.05 (4H, m, CH_2O), 3.71 and 3.61 (1H, d ea, *J*=11.7 Hz, CH_2OH), 0.88, 0.85 and 0.72 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 165.2 (C-17), 143.2 (C-7), 126.0 (C-8), 108.5 (C-13), 79.6 (C-12), 66.6 and 66.2 (OCH_2CH_2O), 63.2 (C-16), 48.9 and 48.5 (C-9 and C-5), 42.0 (C-3), 38.8 (C-1), 34.6 (C-10), 32.9 (C-18 and C-4), 25.2 (C-6), 22.1 (C-11), 21.5 (C-19), 18.6 (C-2), 13.5 (C-20).

3.10. Reaction of 15 with 1,3-propanediol/*p*-TsOH: 18

To a solution of compound **15** (50 mg, 0.15 mmol) in benzene (3 ml) was added 1,3-propanediol (240 μl) and *p*-TsOH (5 mg) and the resulting solution was refluxed in a Dean Stark apparatus. After 12 h, the mixture was cold and diluted with Et_2O, washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed to give a colourless oil that was chromatographed (Hex/AcOEt 1:1), affording compound **18** (25 mg, 47%).

3.10.1. 16-Hydroxy-13-propylenedioxy-14,15-dinor-7-labden-17,12*S*-olide: 18. Rf (Hex/AcOEt 3:7)=0.16; $[\alpha]_D^{20°C}=-3.3$ (c, 0.33 in $CHCl_3$); m.p.=50–52°C; ν_{max}^{film}: 3441, 2928, 1757, 1736, 1638, 1458, 1424, 1389, 1368, 1248, 1200, 1098, 968, 745 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.31 (1H, m, H-7), 4.42 (1H, dd, *J*=2.2 and 11.3 Hz, H-12), 4.10-3.90 (6H, m, H-16 and CH_2O–CH_2–), 0.92, 0.89 and 0.77 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 164.9 (C-17), 143.0 (C-7), 126.4 (C-8), 97.1 (C-13), 80.2 (C-12), 60.6 and 60.2 (OCH_2CH_2-CH_2O), 57.8 (C-16), 49.1 (C-9), 48.8 (C-5), 42.1 (C-3), 38.8 (C-1), 34.9 (C-10), 32.7 (C-4 and C-18), 25.0 (C-6 and $OCH_2CH_2CH_2O$), 21.5 (C-19), 21.3 (C-11), 18.6 (C-2), 13.5 (C-20).

3.11. Reaction of 15 with *p*-TsOH (MeOH): 19

To a solution of compound **15** (50 mg, 0.15 mmol) in MeOH (2 ml) was added at room temperature *p*-TsOH (150 mg) and the solution maintained with vigorously stirring for 4 days. The resulting mixture was diluted with Et_2O and washed with water, $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed to give after chromatography (Hex/AcOEt 7:3) compound **19** (40 mg, 75%).

3.11.1. 16-Hydroxy-13-dimethoxy-14,15-dinor-7-labden-17,12*S*-olide: 19. Rf (Hex/AcOEt 1:1)=0.25; $[\alpha]_D^{20°C}=-8.0$ (c, 1.1 in $CHCl_3$); m.p.=113–115°C; ν_{max}^{film}: 3410 (broad), 2926, 1705, 1640, 1458, 1439, 1387, 1368, 1344, 1267, 1252, 1088, 1051, 988 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.31 (1H, m, H-7), 4.42 (1H, dd, *J*=1.6 and 9.7 Hz, H-12), 3.78 (2H, m, CH_2OH), 3.46 (1H, d, *J*=1.6 Hz, –OH), 3.34 (2Me, s, OMe), 0.91, 0.88 and 0.75 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 164.9 (C-17), 143.4 (C-7), 126.1 (C-8), 99.3 (C-13), 78.8 (C-12), 61.5 (C-16), 49.8 and 49.5 (C-9 and C-5), 49.0 (2xOMe), 42.0 (C-3), 38.7 (C-1), 34.9 (C-10), 32.9 (C-4 and C-18), 25.3 (C-6), 23.0 (C-11), 21.5 (C-19), 18.6 (C-2), 13.5 (C-20).

3.12. Reaction of 15 with *p*-TsOH (MeOH/H_2O): 20

To a solution of compound **15** (44 mg, 0.13 mmol) in MeOH/H_2O (1:2, 3 ml) was added *p*-TsOH (20 mg) and the resulting solution was stirred at room temperature. The solution was checked by TLC and after 6 days all the starting material had disappeared, the white solid was filtered and washed with Et_2O affording compound **20** (29 mg, 70%).

3.12.1. 13,13,16-Trihydroxy-14,15-dinor-7-labden-17,12*S*-olide: 20. ν_{max}^{nujol}: 3341, 2728, 2679, 1694, 1638, 1262, 1250, 1194, 1152, 1127, 1086, 1013, 936, 721, 665 cm^{-1}; **^{1}H NMR (400 MHz, DMSO-d_6)**: 7.09 (1H, m, H-7), 6.27 and 6.23 (1H, s ea, interchanging for deuterium, OH and OH′), 4.23 (1H, d, J=10.1 Hz, H-12), 4.17 (1H, d, J=10.4 Hz, H-12′), 4.05 and 3.35 (1H, d ea, J=11.4 Hz, $-CH_2OH$), 3.91 and 3.55 (1H, d ea, J=11.6 Hz, $-CH_2OH'$), 0.87 and 0.85 (2Me, s ea, Me-18, Me-19 and Me-18′ and Me-19′), 0.68 (1Me, s, Me-20) and 0.67 (1Me, s, Me-20′) ppm; **^{13}C NMR (100 MHz, DMSO-d_6):** 164.2 and 164.1 (C-17), 141.9 (C-7), 126.4 and 126.3 (C-8), 91.9 and 91.3 (C-13), 80.9 and 80.8 (C-12), 63.2 and 61.5 (C-16), 48.1 (C-9), 47.5 and 47.2 (C-5), 41.4 (C-3), 37.9 and 37.8 (C-1), 34.2 (C-10), 32.7 (C-4), 32.5 (C-18), 24.6 (C-6), 21.3 (C-19), 21.0 and 20.1 (C-11), 18.2 and 18.1 (C-2), 13.1 (C-20); HRMS calcd for $C_{18}H_{28}O_5$: 324.1937; found: 324.1929.

3.13. Reaction of 20 with Ac_2O/Py: 15

A solution of compound **20** (25 mg) in pyridine (100 μl) and Ac_2O (60 μl) was stirred at room temperature for 24 h. Then ice was added, the solution stirred for 1/2 h and diluted with Et_2O, the organic layer was washed with HCl 10% and water, dried (Na_2SO_4 anhydrous) and the solvent removed in low vacuum to give compound **15** (26 mg).

3.14. Reaction of 15 with Ph_3PCHCO_2Et: 21 and 22

To a solution of compound **15** (80 mg, 0.24 mmol) in benzene (4.7 ml) was added, at room temperature, Ph_3PCHCO_2Et (174 mg, 0.48 mmol). The solution was heated to 80°C for 30 min, cooled and diluted with Et_2O. The organic layer was washed with water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed in a low vacuum to give a pale yellow oil that was chromatographed (Hex/AcOEt 85:15) to give compounds **21** (44 mg, 45%) and **22** (54 mg, 55%).

3.14.1. Ethyl 16-acetoxy-17,12S-olide-7,13*E*-labdadien-15-oate: 21. Rf (Hex/AcOEt 7:3)=0.27; ν_{max}^{film}: 2928, 1746, 1719, 1642, 1443, 1370, 1316, 1235, 1186, 1150, 1121, 1036, 976, 945 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.38 (1H, m, H-7), 6.25 (1H, s, H-14), 5.39 and 5.13 (1H, d ea, J=14.0 Hz, CH_2OAc), 4.87 (1H, d broad, J=8.6 Hz, H-12), 4.19 (2H, q, J=7.0 Hz, OEt), 2.08 (3H, s, OAc), 1.28 (3H, t, J=7.0 Hz, OEt); 0.92, 0.90 and 0.75 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 170.2 (O*C*OMe), 165.4 and 164.6 (C-17 and C-15), 150.4 (C-13), 143.9 (C-7), 125.6 (C-8), 120.1 (C-14), 78.2 (C-12), 60.6 (C-16), 60.0 (O*C*H_2CH_3), 49.5 and 49.0 (C-9 and C-5), 41.9 (C-3), 38.7 (C-1), 34.9 (C-10), 32.9 (C-18), 32.7 (C-4), 28.8 (C-11), 25.3 (C-6), 21.5 (C-19), 20.7 (OCO*Me*), 18.6 (C-2), 14.2 (OCH_2CH_3), 13.4 (C-20).

3.14.2. Ethyl 16-acetoxy-17,12*S*-olide-7,13*Z*-labdadien-15-oate: 22. Rf (Hex/AcOEt 7:3)=0.31; $[\alpha]_D^{20°C}$=+62.0 (c, 0.40 in $CHCl_3$); ν_{max}^{film}: 2926, 1750, 1719, 1643, 1458, 1424, 1389, 1371, 1316, 1229, 1188, 1121, 1080, 1013, 876 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.36 (1H, m, H-7), 6.08 (1H, d broad, J=11.3 Hz, H-12), 5.89 (1H, q, J=2.2 Hz, H-14), 4.92 (1H, dd, J_{AB}=16.7 Hz and J_{AX}=2.2 Hz, CH_2OAc), 4.82 (1H, dd, J_{BA}=16.7 Hz and J_{BX}=2.2 Hz, CH_2OAc), 4.17 (2H, q, J=7.0 Hz, OEt), 2.13 (3H, s, OAc), 1.30 (3H, t, J=7.0 Hz, OEt), 0.91, 0.89, 0.76 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 169.9 (O*C*OMe), 165.2 and 164.7 (C-17 and C-15), 153.5 (C-13), 143.7 (C-7), 125.8 (C-8), 116.4 (C-14), 77.0 (C-12), 62.3 (C-16), 60.6 (O*C*H_2CH_3), 49.4 and 49.0 (C-9 and C-5), 42.0 (C-3), 38.5 (C-1), 34.9 (C-10), 32.9 (C-4), 32.7 (C-18), 27.9 (C-11), 25.3 (C-6), 21.4 (C-19), 20.7 (OCO*Me*), 18.6 (C-2), 14.2 (OCH_2CH_3), 13.4 (C-20).

3.15. Reaction of 15 with $(EtO)_2P(O)CH_2CO_2Me$: 23 and 24

To a solution of $(EtO)_2P(O)CH_2CO_2Me$ (46 mg, 3 equiv.) in THF (1 ml) was added, at 0°C, a solution of KHMDS (0.5 M in toluene, 310 μl) and the solution was continuously vigorously stirred. After 5 min, compound **15** (26 mg, 0.078 mmol) in THF (2 ml) was added. The solution was maintained at this temperature for 20 min and NH_4Cl sat. aq. was added, the mixture was diluted with Et_2O, washed with water and brine, dried (Na_2SO_4 anhydrous) and the solvent evaporated to give a yellow oil that was chromatographed (Hex/AcOEt 85:15) affording compounds **23** (21 mg, 66%) and **24** (8 mg, 27%).

3.15.1. Methyl 16-acetoxy-17,12*S*-olide-7,13*E*-labdadien-15-oate: 23. Rf (Hex/AcOEt 7:3)=0.20; ν_{max}^{film}: 2928, 2868, 1748, 1717, 1458, 1437, 1373, 1319, 1236, 1186, 1152, 1121, 1082, 1034, 974, 743 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.37 (1H, m, H-7), 6.24 (1H, s broad, H-14), 5.38 and 5.10 (1H, d ea, J=14.5 Hz, CH_2OAc), 4.86 (1H, d broad, J=10.2 Hz, H-12), 3.73 (3H, s, –OMe), 2.08 (3H, s, –OAc), 0.91, 0.89 and 0.74 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; HRMS calcd for $C_{23}H_{32}O_6$: 404.2199; found: 404.2193.

3.15.2. Methyl 16-acetoxy-17,12*S*-olide-7,13*Z*-labdadien-15-oate: 24. Rf (Hex/AcOEt 7:3)=0.25; ν_{max}^{film}: 2957, 1750, 1719, 1373, 1229, 1154, 1121, 1080 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.36 (1H, m, H-7), 6.06 (1H, d broad, J=10.7 Hz, H-12), 5.86 (1H, s broad, H-14), 4.93 and 4.81 (1H, dd ea, J=2.2 and 16.7 Hz, CH_2OAc), 3.73 (3H, s, –OMe), 2.12 (3H, s, –OAc), 0.92, 0.89 and 0.76 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; HRMS calcd for $C_{23}H_{32}O_6$: 404.2199; found: 404.2206.

3.16. Reaction of 14 with Ph_3PCHCO_2Et: 25

A solution of compound **14** (50 mg, 0.15 mmol) was dissolved in benzene (3 ml) and Ph_3PCHCO_2Et (110 mg, 0.30 mmol) was added at room temperature. The solution was heated to 65°C for 1 h. After this time, all the starting material had converted to a less polar compound (checked by TLC). The resulting mixture was cooled and filtered over Celite®, washed with Et_2O, the solvent was removed at low vacuum and the resulting oil was chromatographed (Hex/AcOEt 7:3) affording compound **25** (59 mg, 95%).

3.16.1. Ethyl 16-acetoxy-17,12*R*-olide-7,13*E*-labdadien-15-oate: 25. Rf (Hex/AcOEt 7:3)=0.30; $[\alpha]_D^{20°C}$=−48.8 (c, 0.6 in $CHCl_3$); ν_{max}^{film}: 2926, 1748, 1723, 1645, 1464,

1387, 1368, 1331, 1314, 1273, 1223, 1144, 1086, 1032, 976, 918, 737, 694 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.30 (1H, m, H-7), 6.00 (1H, t, *J*=1.6 Hz, H-14), 5.46 (1H, d, *J*=14.0 Hz, H-16), 5.19 (1H, m, H-12), 4.91 (1H, ddd, *J*=1.1, 1.6 and 14.0 Hz, H-16), 4.17 (2H, dq, *J*=1.1 and 7.0 Hz, O*CH*$_2$CH$_3$), 2.08 (3H, s, OAc); 1.28 (3H, t, *J*=7.0 Hz, OCH$_2$*CH*$_3$), 0.90, 0.87 and 0.77 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 170.0 (O*C*OMe), 165.1 (C-17 and C-15), 150.6 (C-13), 143.6 (C-7), 126.0 (C-8), 120.7 (C-14), 76.8 (C-12), 60.7 (O*C*H$_2$CH$_3$), 59.9 (C-16), 48.8 (C-9), 44.0 (C-5), 41.9 (C-3), 38.5 (C-1), 34.6 (C-10), 32.8 (C-18 and C-4), 25.2 and 24.6 (C-11 and C-6), 21.4 (C-19), 20.7 (OCO*Me*), 18.5 (C-2), 14.1 (OCH$_2$*C*H$_3$), 13.4 (C-20).

3.17. Reaction of 22 with *p*-TsOH: 26

Compound **22** (13 mg, 0.031 mmol) was dissolved in MeOH (1 ml) at room temperature and *p*-TsOH (25 mg) was added. The solution was stirred at this temperature for 5 h, after which all the starting material had converted to a more polar compound (checked by TLC). The solution was diluted with Et_2O and washed with $NaHCO_3$ 5%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent evaporated to give compound **26** (12 mg, 100%) as a white solid crystalline.

3.17.1. Ethyl 16-hydroxy-17,12*S*-olide-7,13*Z*-labdadien-15-oate: 26. Rf (Hex/AcOEt 7:3)=0.13; $[\alpha]_D^{20°C}=-81.6$ (c, 0.77 in $CHCl_3$); m.p.=149–151°C; ν_{max}^{film}: 3428 (broad), 2924, 1709, 1640, 1462, 1443, 1381, 1258, 1231, 1211, 1148, 1047, 1013, 978, 872 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.37 (1H, m, H-7), 6.13–6.02 (2H, m, H-14 and H-12), 4.52 (1H, dd, *J*=1.6 and 16.7 Hz, CH_2OH), 4.35 (1H, dd, *J*=1.6 and 16.7 Hz, CH_2OH), 4.17 (2H, q, *J*=7.0 Hz, OEt), 1.29 (3H, t, *J*=7.0 Hz, OEt), 0.92, 0.89 and 0.74 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 165.7 (C-17 and C-15), 157.9 (C-13), 144.2 (C-7), 125.8 (C-8), 115.9 (C-14), 78.0 (C-12), 62.0 (C-16), 60.4 (O*C*H$_2$CH$_3$), 49.4 (C-9), 48.9 (C-5), 41.9 (C-3), 38.5 (C-1), 34.8 (C-10), 32.8 (C-18 and C-4), 28.3 (C-11), 25.3 (C-6), 21.4 (C-19), 18.5 (C-2), 14.2 (OCH$_2$*C*H$_3$), 13.4 (C-20); HRMS calcd for $C_{21}H_{30}O_5$: 362.2093; found: 362.2088.

3.18. Reaction of 21 with *p*-TsOH: (+)-limonidilactone, 3

A solution of compound **21** (13 mg, 0.03 mmol) in MeOH (1.5 ml) was added, at room temperature, to *p*-TsOH (50 mg) and the solution heated at 50°C for 1 h. The mixture was cooled and diluted with Et_2O, the organic layer was washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent removed at low vacuum to give compound **3** (10 mg, 100%) as a white solid crystalline.

3.18.1. (+)-limonidilactone: 3. Rf (Hex/AcOEt 7:3)=0.11; $[\alpha]_D^{20°C}=+14.2$ (c, 1.4 in $CHCl_3$); m.p.=225−228°C; ν_{max}^{nujol}: 2928, 1790, 1740, 1713, 1638, 1352, 1248, 1171, 1146, 1171, 1146, 1088, 1030, 893, 862, 743, 721, 683 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$)**: 7.41 (1H, td, *J*=2.4 and 4.8 Hz, H-7), 6.08 (1H, q, *J*=1.7 Hz, H-14), 5.21 (1H, d broad, *J*=11.1 Hz, H-12), 4.95 (2H, dd, *J*=0.8 and 1.7 Hz, CH_2O), 2.43 and 2.15 (2H, m, H-6), 2.37 (1H, m, H-9), 2.06 (1H, ddd, *J*=2.2, 3.4 and 13.0 Hz, H-11$_\alpha$), 1.80 (1H, d broad, *J*=12.6 Hz, H-1$_\beta$), 1.56 (2H, m, H-2), 1.63 (1H, ddd, *J*=12.0, 13.0 and 13.0 Hz, H-11$_\beta$), 1.51 (1H, m, H-3$_\beta$), 1.34 (1H, dd, *J*=11.9 and 4.8 Hz, H-5), 1.21 (1H, ddd, *J*=4.3, 12.6 and 12.6 Hz, H-3$_\alpha$), 1.09 (1H, ddd, *J*=4.5, 12.6 and 12.6 Hz, H-1$_\alpha$), 0.93 (3H, s, Me19), 0.91 (3H, s, Me-18) and 0.78 (3H, s, Me-20) ppm; **^{13}C NMR (100 MHz, $CDCl_3$)**: 172.4, 166.9 and 163.8 (C-17, C-15 and C-13), 145.2 (C-7), 124.6 (C-8), 116.2 (C-14), 74.8 (C-12), 70.6 (C-16), 48.9 (C-9), 48.7 (C-5), 41.7 (C-3), 38.7 (C-1), 34.8 (C-10), 32.8 (C-18 and C-4), 28.1 and 25.6 (C-11 and C-6), 21.3 (C-19), 18.4 (C-2), 13.4 (C-20); Anal. calcd. for $C_{20}H_{26}O_4$: C, 72.72%; H, 7.88%; found: C, 72.60%; H, 8.12%.

3.19. Reaction of 25 with *p*-TsOH: 27

A solution of compound **25** (32 mg, 0.08 mmol) in MeOH (2 ml) was added, at room temperature, to *p*-TsOH (15 mg) and the resulting mixture heated at 50°C for 2 h. The solution was cooled and diluted with Et_2O, and the organic layer washed with $NaHCO_3$ 10%, water and brine, dried (Na_2SO_4 anhydrous) and the solvent was removed at low vacuum to give, after chromatography (Hex/AcOEt 7:3), compound **27** (21 mg, 85%).

3.19.1. 12-epi-limonidilactone: 27. Rf (Hex/AcOEt 6:4)=0.15; $[\alpha]_D^{20°C}=-67.6$ (c, 1.4 in $CHCl_3$); m.p.=157–159°C; ν_{max}^{film}: 2928, 1782, 1755, 1723, 1640, 1458, 1445, 1389, 1370, 1350, 1279, 1256, 1209, 1132, 1086, 1038, 914, 887, 864 cm^{-1}; **^{1}H NMR (200 MHz, $CDCl_3$)**: 7.35 (1H, m, H-7), 6.05 (1H, q, *J*=1.7 Hz, H-14), 5.43 (1H, m, H-12), 4.83 (2H, dd, *J*=1.1 and 1.7 Hz, CH_2O), 0.91, 0.89 and 0.80 (3Me, s ea, Me-18, Me-19 and Me-20) ppm; **^{13}C NMR (50 MHz, $CDCl_3$)**: 172.1, 167.2 and 164.0 (C-17, C-15 and C-13), 144.9 (C-7), 125.1 (C-8), 117.2 (C-14), 73.8 (C-12), 70.7 (C-16), 48.8 (C-9), 44.6 (C-5), 41.7 (C-3), 38.6 (C-1), 34.6 (C-10), 32.8 (C-4), 32.7 (C-18), 25.8 and 25.2 (C-11 and C-6), 21.4 (C-19), 18.4 (C-2), 13.3 (C-20); HRMS calcd for $C_{20}H_{26}O_4$: 330.1831; found: 330.1827.

Acknowledgements

The authors thank the CICYT for financial support (QFN 95-4705) and the Spanish Ministerio de Educación y Cultura for a doctoral fellowship to M. S. C.

References

1. Aphaijitt, S.; Nimgirawath, K.; Suksamrarn, A.; Tooptakong, U. *Aust. J. Chem.* **1995**, *48*, 133–137.
2. Hanson, J. R. *Nat. Prod. Rep.* **1997**, *14*, 246.
3. Urones, J. G.; Pascual, T. J.; Marcos, I. S.; Díez, D.; Garrido, N. M.; Guerra, R. A. *Phytochemistry* **1987**, *26*, 1077.
4. (a) Urones, J. G.; Marcos, I. S.; Basabe, P.; Gómez, P. M.; Lithgow, A.; Díez, D.; Garrido, N. M. *Tetrahedron* **1995**, *51*, 1845. (b) Urones, J. G.; Díez, D.; Gómez, P. M.; Marcos, I. S.; Basabe, P.; Moro, R. F. *J. Chem. Soc. Perkin Trans 1* **1997**, 1815. (c) Urones, J. G.; Díez, D.; Gómez, P. M.; Marcos, I. S.;

Basabe, P.; Moro, R. F. *Nat. Prod. Letters* **1998**, *11*, 145. (d). Urones, J. G.; Marcos, I. S.; Basabe, P.; Sexmero, M. J.; Diez, D.; Garrido, N. M.; Prieto, J. E. S. *Tetrahedron* **1990**, *46*, 2495.

5. (a) Bestmann, H. J. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 349. (b) Bestmann, H. J.; Sandemier, D. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 634. (c) Bestmann, H. J.; Sandemeier, D. *Angew. Chem.* **1975**, *87*, 630. (d) Nickisch, K.; Klose, W.; Bohlmann, F. *Chemische Berichte* **1980**, *113*, 2038.
6. (a) Marcos, I. S.; Moro, R. F.; Carballares, S.; Urones, J. G. *Tetrahedron Letters* **1999**, *40*, 2615. (b) Marcos, I. S.; Moro, R. F.; Carballares, S.; Urones, J. G. *Synlett* **2000**, 541.
7. (a) Rubottom, G. M.; Grubber, J. M. *J. Org. Chem.* **1978**, *43*, 1599. (b) Rubottom, G. M.; Vázquez, M. A.; Pelegrina, D. R. *Tetrahedron Letters* **1974**, 4319. (c) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
8. (a) Cavill, G. W. K.; Solomon, D. H. *Aust. J. Chem.* **1960**, *13*, 121. (b) Hanessian, S.; Beaulieu, P. *Tetrahedron Letters* **1986**, *27*, 5071.
9. (a) Petitt, G. R.; Herald, C. L.; Yardley, Y. P. *J. Org. Chem.* **1970**, *35*, 1389. (b) Habermahl, G.; Haff, A. Z. *Naturfosch, Teil B* **1968**, *23*, 880. (c) Yoshii, E.; Koizumi, T.; Ikeshima, H.; Ozaki, K.; Hayashi, I. *Chem. Pharm. Bull.* **1975**, *23*, 2496. (d) Cocker, J. D.; Henbest, H. B.; Phillipps, G. H.; Slater, G. P.; Thomas, D. A. *J. Chem. Soc.* **1965**, 6.
10. March, J. *Advanced Organic Chemistry & Reactions, Mechanisms and Structure*, 3rd Ed; John Wiley and Sons: New York, 1985, pp 783.
11. (a) Maryahoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Heron, B. M. *Heterocycles* **1995**, *41*, 2357. (c) Trost, B. M., Fleming, I. A. *Comprehensive Organic Synthesis*; Pergamon Press, New York, Wiley-Interscience, 1991, 1, pp 755.