Molecules **2004**, *9*, 300-322

molecules

ISSN 1420-3049
http://www.mdpi.org

From Labdanes to Drimanes. Degradation of the Side Chain of Dihydrozamoranic Acid.

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Received: 23 February 2004; in revised form: 4 March 2004 / Accepted: 5 March 2004 / Published: 30 April 2004

Abstract: A new route for the degradation of the saturated side chain of dihydrozamoranic acid has been devised, giving an advanced intermediate, compound **14**, useful for the synthesis of insect antifeedants such as warburganal and polygodial.

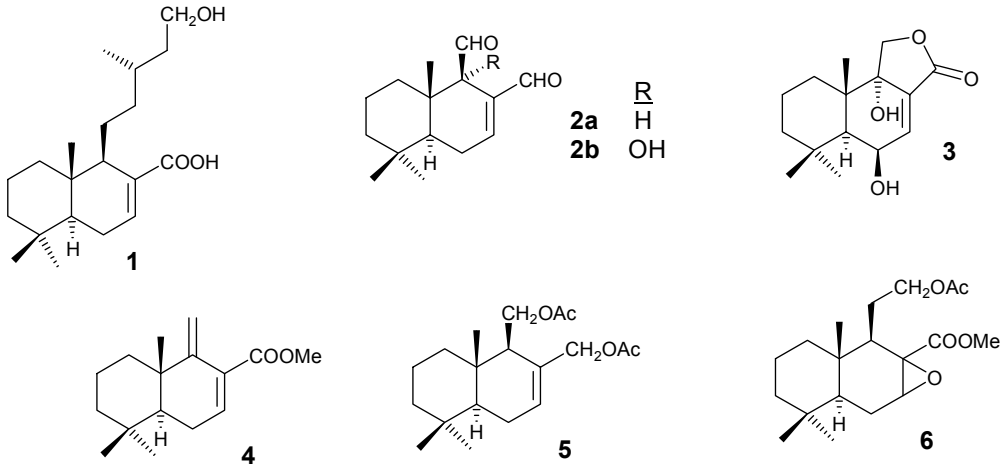
Keywords: Dihidrozamoranic acid, drimane derivatives, antifeedant.

Introduction

One of the main problems of our civilization is the shortage of food, especially in Third World countries. The intensity of the problem will increase as the global caloric demand is likely to double over the next ten years. This may be addressed in two ways; by better distribution of existing resources and by increasing total food supplies. With a rising productive area the number of pests has also increased considerably and thus the use of herbicides and insecticides [1]. Several insect species have developed resistance against agrochemicals causing not only a significant increase in the amount of chemicals used but also in the environmental pollutant level. The strategy used by plants to protect themselves from insect attack is the biosynthesis of secondary metabolites with antifeedant activity.

These natural products are highly specific to some insect species and are completely inactive against other species useful to human beings [2]. Moreover, these compounds are biodegradable and there is no danger of accumulation or environmental pollution [3]. Among the natural antifeedants, azadirachtin isolated from *Azadirachta indica* [4], some clerodane diterpenoids such as jodrellin A and B isolated from *Schutellaria woronowii Juss* [5] and some drimanes such as warburganal (**2b**) isolated from *Warburgia ugandensis* [6] and polygodial (**2a**) isolated from *Polygonum hydropiper* [7] should be highlighted because their specific and high antifeedant activity against Spodoptera species [8], which causes more than 30% crop losses in India [9]. In our lab several bioactive drimanes (Figure 1) have been synthetised starting from zamoranic acid [10].

Figure 1

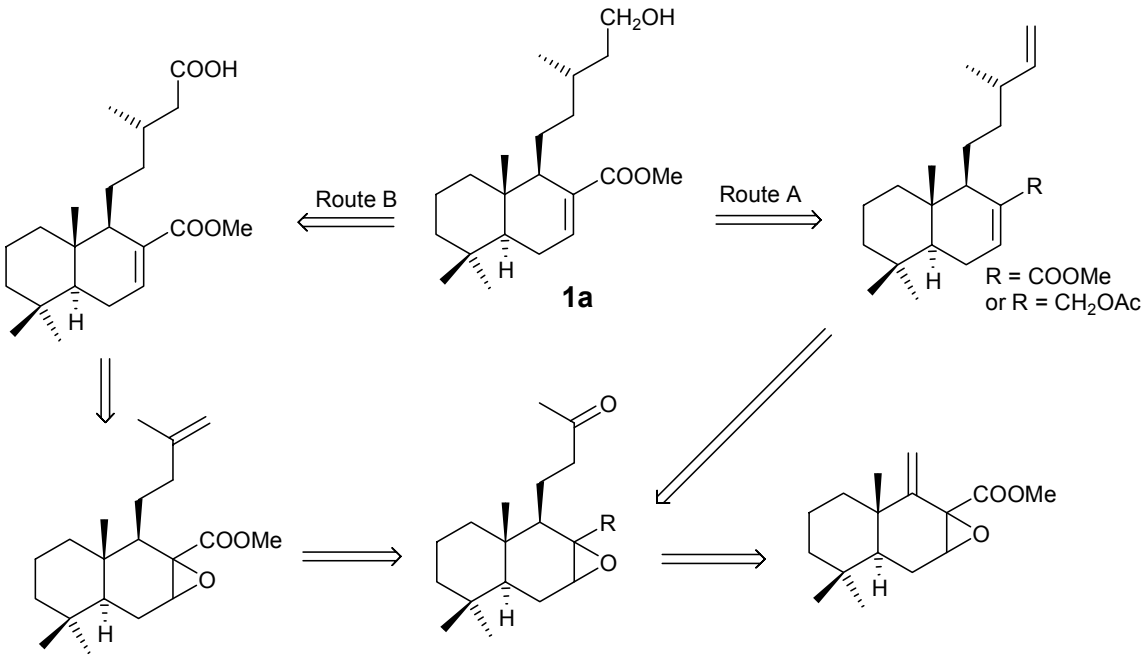


Results and Discussion

Dihydrozamoranic [11] acid (**1**), is a diterpene isolated from *Halimium verticillatum* and *Halimium viscosum*, being a main component in the first case. This compound's only difference with zamoranic acid is the saturation of the side chain. The transformation of this compound into an intermediate readily transformed in turn into natural compounds with biological activity would be of interest. Some of these intermediates are diene **4**, the diacetylderivative **5** [12] and epoxide **6**. The last compound has been transformed by us into poligodial (**2a**), warburganal (**2b**) and pereniporin A (**3**).

Starting from dihydrozamoranic acid methyl ester (**1a**), the retrosynthetic analysis as indicated below (Scheme 1), could be accomplished by two routes. In both cases the main degradation reaction is an elimination of the terminal carbon of the side chain, either by transformation into a double bond or by oxidative decarboxylation of an acid.

Scheme 1

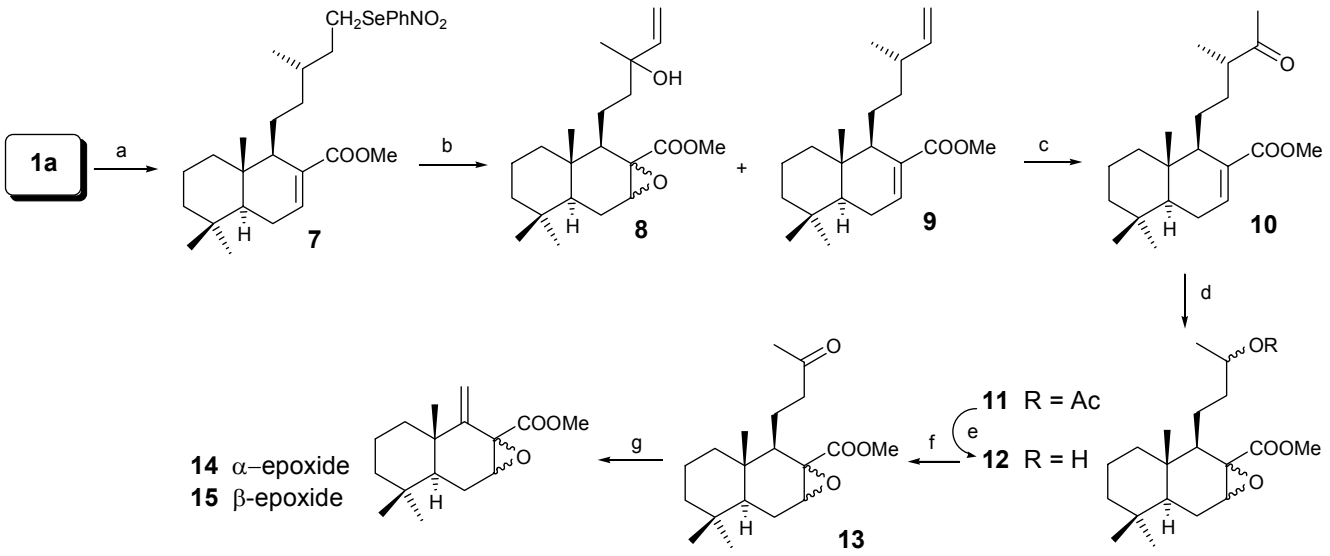


Route A

The first route followed for the degradation of the side chain is shown in Scheme 2. Treatment of **1a** with *o*-nitrophenylselenocyanate (nBu_3P/THF) [13] gave an 87% yield of the nitrophenylselenyl derivative **7**, which with H_2O_2 [14], produced a minor derivative **8** (4%) and compound **9** in 92% yield. Treatment of **9** under Wacker conditions [15] with $CuCl/PdCl_2/O_2$, lead to ketone **10** in 80% yield. Baeyer-Villiger oxidation [16] of **10** with m-CPBA gives **11**, a 1:2 mixture of α and β epoxides, in 95% yield. This compound shows a degradation of the side chain by two carbons.

The hydrolysis of **11** with K_2CO_3/MeOH gives **12** (85% yield), a mixture of epoxy alcohols that by oxidation with CrO_3/Py [17] gave the epoxyketones **13** (82%). As in previous studies, the degradation of the *nor*-derivatives to the drimane skeleton was done by Norrish II type reaction [18]. Photochemical treatment (hυ; λ = 366 nm) of **13** lead to olefins **14** (9.5%) and **15** (22.5%), while a (39%) of **13** was recovered, so the global yield is quite good when the recovery of the starting material is taken into account.

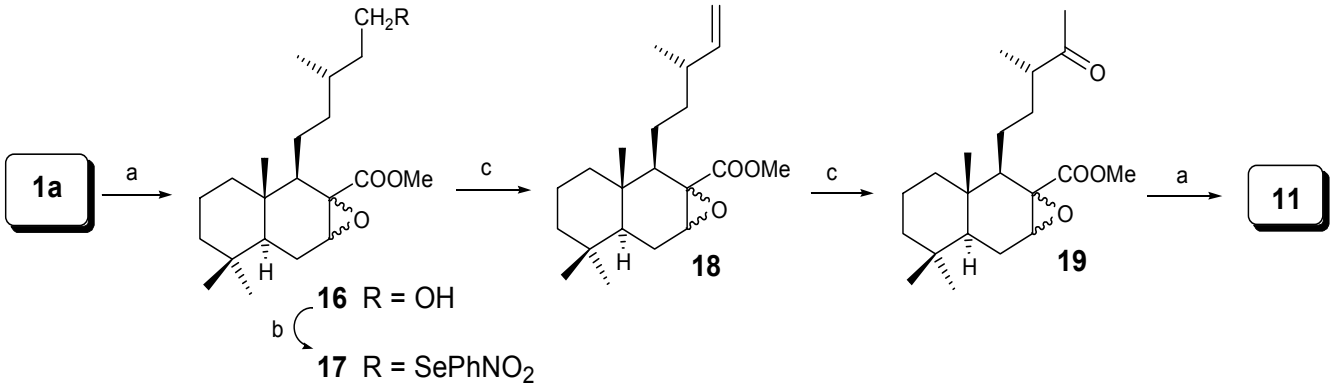
Scheme 2.



Reagents: (a) *o*-$NO_2PhSeCN/nBu_3P/THF$; (b) H_2O_2/TFH; (c) $CuCl/PdCl_2/O_2$/DMF; (d) *m*-$CPBA/CH_2Cl_2$; (e) K_2CO_3/MeOH; (f) CrO_3/Py; (g) Norrish II

The synthesis of compound **11** could be achieved by epoxidation and then degradation, as shown in Scheme 3. Treatment of dihydrozamoranic acid methyl ester (**1a**) with *m*-CPBA led to a 67% yield of the mixture of epoxides **16** in a ratio 3:2 (α:β), which by treatment with *o*-nitrophenylselenocyanate gives the mixture **17** in 75% yield. Oxidation of **17** with H_2O_2 lead to the Δ^{14} olefin **18**, in 86% yield. Wacker oxidation with $CuCl/PdCl_2$ and O_2 gave the corresponding ketone, **19** (80%). Baeyer-Villiger oxidation with *m*-CPBA gave **11** (94% yield).

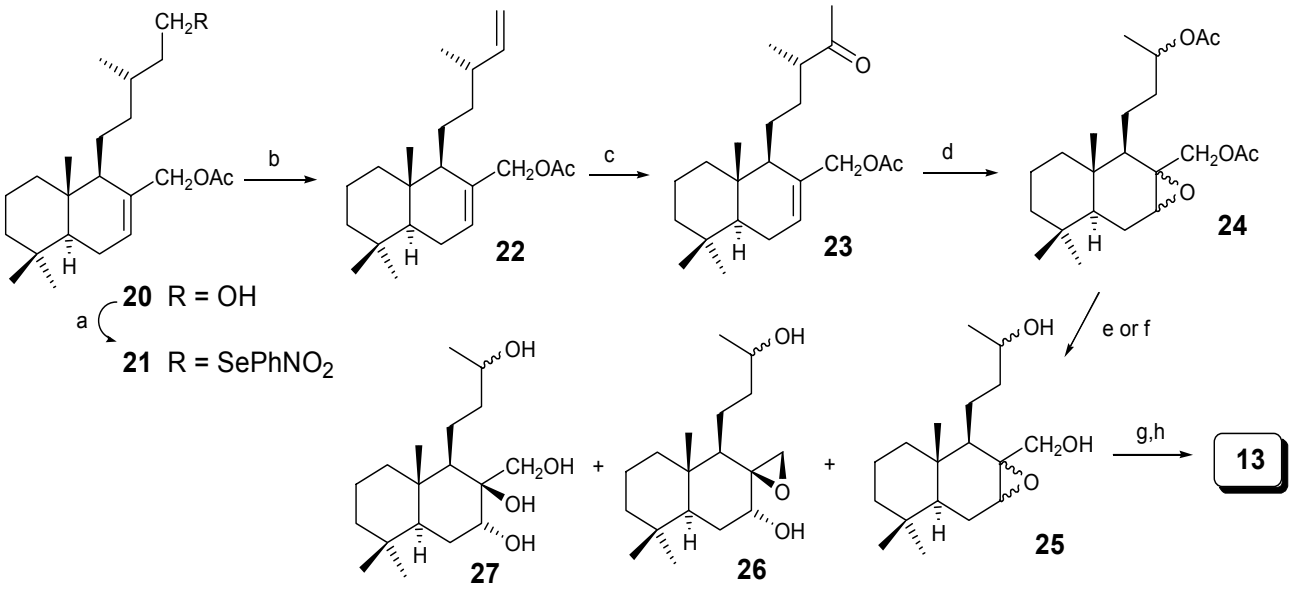
Scheme 3.



Reagents: (a) *m*-$CPBA/CH_2Cl_2$; (b) *o*-$NO_2PhSeCN/nBu_3P/THF$; (c) H_2O_2/THF; (d) $CuCl/PdCl_2/O_2$/DMF.

Compound **13** can also be obtained in a different manner, starting from **20**, a natural compound isolated from *H. verticillatum* and *H. viscosum* [19] (Scheme 4), which in a similar manner as described before was transformed into compound **24**. Hydrolysis of **24** under basic conditions gave **25**, the epoxide of Payne rearrangement [20] **26** and **27** that were separated by CC. Compound **25** was oxidized to give **13**, previously transformed into drimanes **14/15** (Scheme 2).

Scheme 4

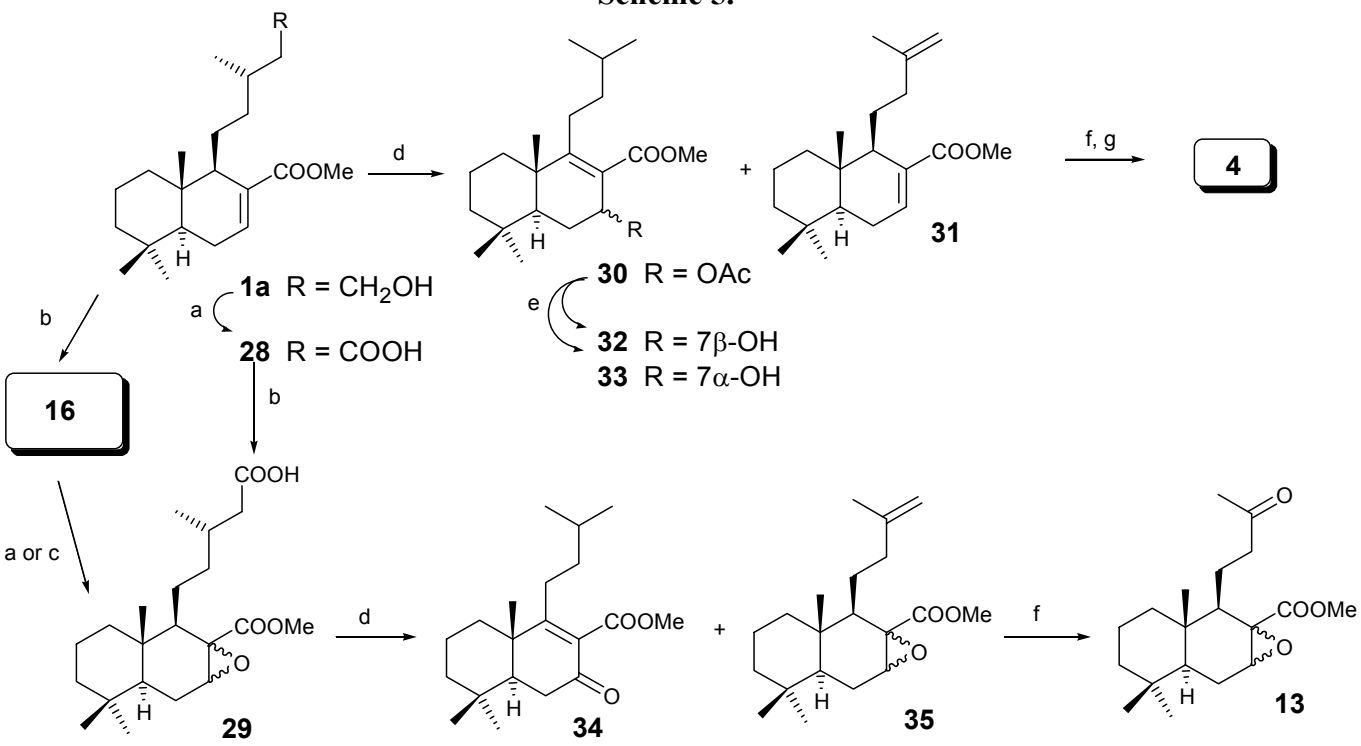


Reagents: (a) *o*-$NO_2PhSeCN/nBu_3P/THF$; (b) H_2O_2/THF; (c) $CuCl/PdCl_2/O_2$/ DMF; (d) *m*-$CPBA/CH_2Cl_2$; (e) K_2CO_3/MeOH; (f) NaOH/MeOH; (g) CrO_3/AcOH; (h) CH_2N_2/ether.

Route B

A second approach is based on the degradation of the side chain by an oxidative decarboxylation process (Scheme 5). The synthesis of the acid group on C-15 and epoxide C-7 can be acheived in two different ways. Oxidation of **1a** with CrO_3/AcOH gives acid **28** in 60% yield, which by treatment with *m*-CPBA lead to the 3:2 mixture of α and β epoxides **29** in 60% yield. Alternatively, treatment of **1a** with *m*-CPBA gives the 3:2 mixture of α and β epoxides **16**, then oxidation with PDC/DMF [21] or CrO_3/AcOH lead to the same 3:2 mixture of α and β epoxides **29**, (in 74% and 56% yields) respectively.

Scheme 5.



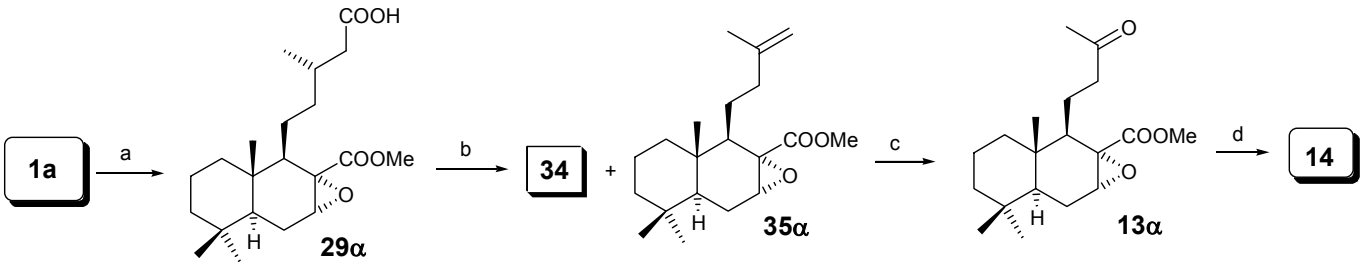
Reagents: (a) CrO_3/AcOH; (b) *m*-CPBA/CH_2Cl_2; (c) PDC/DMF; (d) $(AcO)_4Pb$/ $(AcO)_2Cu$/ Py/C_6H_6; (e) K_2CO_3/MeOH; (f) O_3/CH_2Cl_2; (g) Norrish II

Oxidative decarboxylation of **28** gave **30** and **31** in 40% and 8% yield, respectively. The major component was hydrolysed to give alcohols **32** and **33**. It is very interesting to note that the decarboxylation takes place giving mainly an isobutyl group in the parent compound **30**.

The minor compound **31** was transformed by ozonolysis and Norrish II type reaction into diene **4**, already transformed into active drimanes [12]. As the yield was very poor it was decided to do the same reaction with compound **29**, leading again, to a major component **34** (62%) and a terminal olefin **35** (12%) which was transformed into epoxides **13**.

As we have seen with *m*-CPBA, a mixture of epoxides at C-7 was always obtained. In order to obtain only one epoxide, dihydrozamoranic acid methyl ester (**1a**) was treated with dimethyldioxirane [23], giving selectively only compound **29α** in 45% yield and producing the oxidation of the primary alcohol into the acid at C-15; following the same sequence as in Scheme 6 only compound **14** was obtained.

Scheme 6



Reagents: (a) dimethyldioxirane / acetone; (b) $(AcO)_4Pb/(AcO)_2Cu/Py/C_6H_6$; (c) O_3/ CH_2Cl_2; (d) Norrish II

Conclusions

We have developed a new procedure to obtain drimane **14** from dihydrozamoranic acid, making use of methodology developed in our laboratory [24] that could be useful for further transformations.

Acknowledgments

The authors are grateful to A. Lithgow, Servicio General de Resonancia Magnética Nuclear, Facultad de Ciencias Químicas, Universidad de Salamanca for the NMR spectra.

Experimental

General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra (thin film) were recorded on a MATTSON-GENESIS II FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded 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, on a Bruker WP-200 SY or a Bruker DRX 400 MHz instrument. 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 ionising voltage. Mass spectra are represented at *m/z* (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas). Optical rotations were determined at a digital ADP 220 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. The raw material **1** was isolated from a hexane extract of *Halimium verticillatum* as reported in reference [11].

Reaction of **1a***: Synthesis of methyl 15-o-nitrophenylseleno-7-labden-17-oate* (**7**).

To a solution of **1a** (750 mg, 2.2 mmol) in dry THF (3.3 mL) was added *o*-nitrophenyl-selenocyanate (635.8 mg, 2.8 mmol) and the mixture was stirred under an inert atmosphere for 20 min. at 48ºC. nBu_3P (504.5 mg, 2.5 mmol) was added to the reaction mixture, that was stirred for 48 min., then the solvent was removed and the residue chromatographed (95:5 hexane/EtOAc) yielding 652.5 mg (87%) of **7**; ^{1}H-NMR δ: 8.30 (d, 1H, J=8.2, H-3'), 7.47 and 7.27 (both m, 3H, H-4', H-5' and H-6'), 6.66 (m, 1H, H-7), 3.70 (s, 3H, MeOOC), 2.95 (m, 2H, H-15), 2.15 – 1.30 (m, 11H), 1.22 – 0.90 (m, 6H), 0.98 (d, 3H, J=5.8 Hz, Me-16), 0.92 (s, 3H, Me-19), 0.89 (s, 3H, Me-18) and 0.84 (s, 3H, Me-20); ^{13}C-NMR δ: 39.4 (C-1), 18.4 (c-2), 41.9 (C-3), 32.6 (C-4), 49.3 (C-5), 23.8 (C-6), 137.0 (C-7), 135.2 (C-8), 50.9 (C-9), 36.8 (C-10), 25.6 (C-11), 37.8 (C-12), 34.3 (C-13), 34.7 (C-14), 23.8 (C-15), 19.3 (C-16), 169.6 (C-17), 33.0 (C-18), 21.8 (C-19), 14.3 (C-20), 51.2 (COOMe), 134.0 (C-1'), 146.3 (C-2'), 126.3 (C-3'), 128.9 (C-4'), 133.4 (C-5'), 125.1 (C-6'); IR cm^{-1}: 2925, 1714, 1644, 1590, 1564, 1515, 1332, 1247,1068, 730.

Oxidation of **7** *with* H_2O_2*: Synthesis of methyl 13-hydroxy-7,14-labdadien-17-oate* (**8**) *and methyl 7,14-labdadien-17-oate* (**9**).

To a solution of **7** (600 mg, 1.15 mmol) in THF (6 mL) was added 30% H_2O_2 (0.30 mL, 130 mg, 2.0 mmol) and the mixture was stirred for 12 h. The solvent was evaporated at reduced pressure and the crude product chromatographed eluting with a hexane/EtOAc gradient yielding 24 mg (4%) of **8** (95:5 hexane/EtOAc) and 552 mg (92%) of **9 (**98:2 hexane/EtOAc).

Compound **8**: ^{1}H-NMR δ: 6.69 (m, 1H, H-7), 5.86 (dd, 1H, J=17.4, 10.7, H-14), 5.19 (d, 1H, J=17.4, H-15a), 5.02 (d, 1H, J=17.4, H-15b), 3.69 (s, 3H, COOMe), 2.25 – 1.35 (m, 8H), 1.25 – 0.90 (m, 6H), 1.22 (s, 3H, Me-16), 0.89 (s, 3H, Me-19), 0.85 (s, 3H, Me-18) and 0.80 (s, 3H, Me-20); ^{13}C-NMR δ: 39.3 (C-1), 18.4 (C-2), 41.9 (C-3), 32.6 (C-4), 49.3 (C-5), 22.0 (C-6), 137.4 and 137.6 (C-7, epimers), 135.5 and 135.7 (C-8, epimers), 50.7 and 50.8 (C-9, epimers), 36.9 (C-10), 23.9 (C-11), 42.6 and 42.8 (C-12, epimers), 73.1 (C-13), 144.9 and 145.4 (C-14, epimers), 111.3 and 111.6 (C-15, epimers), 169.5 (C-17), 33.0 (C-18), 21.9 (C-19), 14.2 (C-20), 51.3 (COOMe); IR cm^{-1}: 3446, 3086, 2924, 1717, 1646, 1245,1071, 917; MS *m*/*z* (EI$^+$): 334 (M$^+$, <1%), 316 (4), 284 (19), 249 (15), 248 (79), 233 (28), 203 (15), 192 (29) 175 (25), 124 (15), 109 (56), 105 (16), 91 (24), 81 (33), 79 (34), 77 (15), 71 (100), 69 (28), 67 (20), 59 (15), 55 (45); HRMS (CI) for $C_{21}H_{34}O_3$ (MH$^+$): Calc 334.2508; Found 334.2519.

Compound **9**: ^{1}H-NMR δ: 6.51 (m, 1H, H-7), 5.56 (ddd, 1H, J=17.3, 10.1, 7.3, H-14), 4.82 (dd, 1H, J=17.3 Hz, 2.1 Hz, H-15a), 4.78 (dd, 1H, J=10.1, 2.1 Hz, H-15b), 3.59 (s, 3H, COOMe), 2.15 – 1.65 (m, 4H), 1.60 – 1.25 (m, 6H), 1.20 – 0.90 (m, 5H), 0.87 (d, 3H, J=6.7, Me-16), 0.81 (s, 3H, Me-19), 0.77 (s, 3H, Me-18) and 0.72 (s, 3H, Me-20); ^{13}C-NMR δ: 39.4 (C-1), 18.3 (C-2), 41.9 (C-3), 32.5 (C-

4), 49.2 (C-5), 23.6 (C-6), 136.2 (C-7), 135.4 (C-8), 50.8 (C-9), 36.6 (C-10), 25.7 (C-11), 37.8 (C-12), 38.5 (C-13), 144.4 (C-14), 112.2 (C-15), 20.1 (C-16), 169.3 (C-17), 33.0 (C-18), 21.8 (C-19), 14.2 (C-20), 50.9 (COOMe); $[\alpha]_D^{20}$ - 16.7 (*c* 0.9 in $CHCl_3$); IR cm^{-1}: 3076, 2951, 1722, 1643, 1434, 1246, 1066, 909; MS *m/z* (EI^+) 318 (M^+, 1.8%), 248 (10), 195 (3), 194 (9), 165 (3), 162 (13), 137 (8), 135 (12), 124 (79), 109 (100), 95 (36), 81 (41), 69 (50), 67 (34), 55 (83).

Wacker oxidation of **9**: *Synthesis of methyl 14-oxo-7-labden-17-oate* (**10**).

A solution of $PdCl_2$ (128 mg, 0.72 mmol) and CuCl (3.5 g, 3.6 mmol) in DMF (10 mL) and H_2O (1 mL) was activated for 30 min with O_2. A solution of **9** (1.1 g, 3.6 mmol) in DMF (8 mL) was added and stirred with O_2 atmosphere at room temperature for 36 h. Then to this mixture was added a cooled solution of 3N HCl and the mixture was extracted with CH_2Cl_2 (3 x 30 mL) and washed successively with 10% $NaHCO_3$ and water, dried, filtered, evaporated and chromatographed (9:1 hexane/EtOAc) to give 910 mg (80%) of **10**; ^{1}H-NMR δ: 6.45 (m, 1H, H-7), 3.49 (s, 3H, COOMe), 2.24 (sex, 1H, J=6.8, H-13), 2.00 – 1.60 (m, 4H), 1.91 (s, 3H, Me-15), 1.40 – 0.90 (m, 10H), 0.85 (d, 3H, J=6.8, Me-16), 0.69 (s, 3H, Me-19), 0.65 (s, 3H, Me-18) and 0.60 (s, 3H, Me-20); ^{13}C-NMR δ: 39.0 (C-1), 18.1 (C-2), 41.5 (C-3), 32.3 (C-4), 48.9 (C-5), 23.5 (C-6), 136.8 (C-7), 134.6 (C-8), 50.5 (C-9), 36.4 (C-10), 25.4 (C-11), 34.1 (C-12), 47.6 (C-13), 211.8 (C-14), 27.1 (C-15), 15.6 (C-16), 168.7 (C-17), 32.7 (C-18), 21.5 (C-19), 13.9 (C-20), 50.8 (COOMe); $[\alpha]_D^{20}$ -11.1 (*c* 0.2 in $CHCl_3$); IR cm^{-1}: 2927, 1713, 1645, 1461, 1365, 1254, 1065; MS *m/z* (EI^+) 334 (M^+, <0.8%), 302 (2), 263 (5), 211 (8), 179 (37), 124 (32), 109 (100), 105 (20), 95 (16), 91 (32), 81 (26), 79 (32), 77 (17), 69 (26), 67 (17), 59 (12), 55 (30); HRMS (CI) for $C_{21}H_{34}O_3$ (MH^+): Calcd 334.2508; Found 334.2517.

Baeyer-Villiger reaction and epoxidation of **10** *with m-CPBA: Synthesis of methyl 13-acetoxy-7,8-epoxy-14,15-dinor-labdan-17-oate* (**11**).

To a solution of **10** (334.5 mg, 1.0 mmol) in dry CH_2Cl_2 (5 mL), *m*-CPBA (345.0 mg, 2.0 mmol) was added and the mixture stirred at room temperature. After 12 h, the solvent was removed and ether was added. The organic phase was washed with 40% $Na_2S_2O_3$, 10% Na_2CO_3 and water until neutrality, dried over Na_2SO_4, filtered and evaporated to give **11** (317.8 mg, 95%). ^{1}H-NMR δ: 4.60 (sex, 1H, J=6.1, H-13), 3.53 and 3.51 (two s, 2 x 3H, 2 x COOMe), 3.10 (d, 1H, J=6.2, H-7 β-epoxide), 3.00 (sb, 1H, H-7 α-epoxide), 2.00 – 1.78 (m, 1H), 1.81 and 1.79 (each s, 2 x H, 2 x OOCMe), 1.60 – 1.05 (m, 13H), 0.97 (d, 3H, J=6.1, Me-16), 0.66 and 0.62 (each s, 3 x 3H, Me-18, Me-19 and Me-20); ^{13}C-NMR δ: 38.2 and 40.1 (C-1, isomers), 18.3 and 17.8 (C-2), 41.6 (C-3), 32.6 and 32.7 (C-4 isomers), 45.6 (α-isomer) and 47.1 (β-isomer) (C-5), 20.7 (C-6), 57.5 (α-isomer) and 59.4 (β-isomer) (C-7), 58.8 (α-isomer) and 60.2 (β-isomer) (C-8), 49.1 (β-isomer) and 53.5 (α-isomer) (C-9), 34.7 and 35.6 (C-10 isomers), 22.6 (C-11), 34.9 (C-12), 70.4 (C-13), 21.1 (C-16), 170.2 and 170.7 (C-17 isomers), 32.4 and 33.0 (C-18 isomers), 21.7 (C-19), 14.2 and 14.9 (C-20 isomers), 51.9 and 52.1 (2XCOOMe), 170.2 and 170.7 (2XMeCOO), 19.8 (MeCOO); IR cm^{-1}: 2930, 1731, 1715, 1461, 1251, 1142.

Hydrolysis of **11**: *Synthesis of methyl 13-hydroxy-7α,8α-epoxy-14,15-dinor-labdan-17-oate* (**12α**) and *methyl 13-hydroxy-7β,8β-epoxy 14,15-dinor-labdan-17-oate* (**12β**).

To a solution of **11** (250 mg, 0.68 mmol) in methanol (12 mL) was added K_2CO_3 (150 mg). The reaction mixture was stirred at room temperature for 1 h, water was added and the mixture extracted with ether, washed with 2N HCl and H_2O, dried, filtered and evaporated yielding 212 mg (85%) of **12**.

Compound **12α**: ^{1}H-NMR δ: 3.72 (s, 3H, COOMe), 3.71 (m, 1H, H-13), 3.22 (sb, 1H, H-7), 2.14 (dd, 1H, J=4.3, 14.4, H-6), 1.80 – 1.00 (m, 13H), 1.14 (d, 3H, J=6.1, Me-16), 0.87 (s, 3H,Me-19), 0.86 (s, 3H, 18) and 0.83 (s, 3H, Me-20); ^{13}C-NMR δ: 38.5 (C-1), 18.6 (C-2), 41.8 (C-3), 33.0 (C-4), 45.9 (C-5), 20.1 (C-6), 57.8 (C-7), 59.1 (C-8), 53.8 (C-9), 35.0 (C-10), 21.9 (C-11), 38.3 (C-12), 67.7 (C-13), 23.6 (C-16), 171.1 (C-17), 32.6 (C-18), 21.8 (C-19) 14.6 (C-20), 52.2 (COOMe); $[\alpha]_D^{20}$ + 6.9 (*c* 0.4 in $CHCl_3$); IR cm^{-1}: 3491, 2981, 1732, 1450, 1375, 1167, 1026.

Compound **12β**: ^{1}H-NMR δ: 3.72 (m, 1H, H-13), 3.71 (s, 3H, COOMe), 3.30 (d, 1H, J=6.3, H-7), 2.10 – 0.90 (m, 14H), 1.16 (d, 3H, J=6.2, Me-16); 0.87 (s, 3H, Me-19); 0.84 (s, 3H, Me-18) and 0.82 (s, 3H, Me-20); ^{13}C-NMR δ: 38.5 (C-1), 18.0 (C-2), 41.9 (C-3), 32.9 (C-4), 47.7 (C-5), 21.0 (C-6), 59.7 (C-7), 60.5 (C-8), 49.4 (C-9), 35.9 (C-10), 23.2 (C-11), 40.6 (C-12), 68.1 (C-13), 23.4 (C-16), 172.7 (C-17), 33.2 (C-18), 21.9 (C-19), 15.2 (C-20), 52.3 (COOMe); IR cm^{-1}: 3486, 2985, 1736, 1455, 1371, 1164, 1026.

Oxidation of **12** *with CrO_3/Py: Synthesis of methyl 7α,8α-epoxy-13-oxo-14,15-dinor-labdan-17-oate* (**13α**) *and methyl 7β,8β-epoxy-13-oxo-14,15-dinor-labdan-17-oate* (**13β**).

Pyridine (1 mL) and dry CH_2Cl_2 (3 mL) were placed in a 50 mL Erlenmeyer flask externally cooled with ice. CrO_3 (660 mg, 0.65 mmol) was added in small portions with stirring until a think yellow paste was obtained. This was allowed to reach room temperature and was stirred for 15 min under N_2. Following this **12** (324.0 mg, 1.0 mmol) dissolved in dry CH_2Cl_2 (3 mL) was added and the mixture was stirred vigorously for 1.5 hours. The mixture was filtered and chromatographed on silica-gel, yielding 265.7 mg (82%) of **13**. In some fractions the α isomer is the major compound and in other fractions, it is the β isomer.

Compound **13α**: ^{1}H-NMR δ: 3.62 (s, 3H, COOMe), 3.14 (sb, 1H, H-7), 2.35 – 2.20 (m, 1H, H-6), 2.01 (s, 3H, Me-16), 1.90 – 0.85 (m, 13H), 0.78 (s, 3H, Me-19), 0.77 (s, 3H, Me-18) and 0.73 (s, 3H, Me-20); ^{13}C-NMR δ: 38.1 (C-1), 17.9 (C-2), 41.6 (C-3), 32.7 (C-4), 45.7 (C-5), 18.3 (C-6), 57.5 (C-7), 58.7 (C-8), 53.1 (C-9), 34.8 (C-10), 21.6 (C-11), 42.2 (C-12), 207.6 (C-13), 29.8 (C-16), 170.5 (C-17), 32.4 (C-18), 21.6 (C-19), 14.2 (C-20), 52.2 (COOMe); IR cm^{-1}: 2926, 1732, 1712, 1461, 1282, 1158, 1062, 897.

Compound **13β**: ^{1}H-NMR δ: 3.73 (s, 3H, COOMe), 3.31 (d, 1H, J=6.4, H-7), 2.55 – 2.40 (m, 1H, H-6), 2.11 (s, 3H, Me-16), 2.10 – 0.90 (m, 13H), 0.88 (s, 3H, Me-19), 0.85 (s, 3H, Me-18) and 0.82 (s, 3H, Me-20); ^{13}C-NMR δ: 40.5 (C-1), 18.0 (C-2), 41.9 (C-3), 32.9 (C-4), 46.9 (C-5), 20.9 (C-6), 59.9 (C-7), 60.1 (C-8), 49.4 (C-9), 36.0 (C-10), 20.9 (C-11), 42.6 (C-12), 208.2 (C-13), 29.7 (C-16), 172.7 (C-17), 33.3 (C-18), 21.9 (C-19), 15.2 (C-20), 53.5 (COOMe); IR cm^{-1}: 2950, 1733, 1714, 1275, 1163, 1053.

Norrish type II reaction of **13**: *Synthesis of methyl 7α,8α-epoxy-9-drimen-12-oate* (**14**) *and methyl 7β,8β-epoxy-9-drimen-12-oate* (**15**).

A solution of **13** (250.0 mg, 0.77 mmol) in dry hexane (250 mL) was placed in a quartz flask and a stream of dry N_2 was bubbled through. The solution was irradiated with UV light (Hanau TQ-150, high pressure) for 90 min. Removal of solvent afforded a yellow oil which was purified by chromatography on silica-gel eluting with 98:2 hexane-EtOAc to yield 23.3 mg (9.3%) of **14**, 56.3 mg (22.5%) of **15** and 97.5 mg (39%) of the starting material **13**.

Compound **14**: ^{1}H-NMR δ: 5.25 (s, 1H, H-11a), 5.13 (s, 1H, H-11b), 3.76 (s, 3H, COOMe), 3.50 (t, 1H, J=1.9, H-7), 2.20 (ddd, 1H, J=1.9, 4.3, 15.1 Hz, H-6a), 1.80 (m, 2H, H-6b and H-1), 1.53 (m, 1H), 1.44 – 1.40 (m, 3H), 1.20 (dd, 1H, J=4.3, 13.1 Hz, H-5), 1.12 (m, 1H, H-3), 1.05 (s, 3H, Me-15), 0.90 (s, 3H, Me-14), and 0.85 (s, 3H, Me-13); ^{13}C-NMR δ: 36.4 (C-1), 18.4 (C-2), 41.8 (C-3), 33.0 (C-4), 41.4 (C-5), 22.2 (C-6), 58.5 (C-7), 57.7 (C-8), 150.8 (C-9), 37.0 (C-10), 114.9 (C-11), 170.0 (C-12), 32.8 (C-13), 22.4 (C-14), 20.2 (C-15), 52.6 (COOMe); $[\alpha]_D^{20}$ + 97.8 (*c* 0.5 in $CHCl_3$); IR cm^{-1}: 3098, 1743, 1633, 1373, 1242, 1159, 1047, 902; MS *m/z* (EI$^+$) 264 (M^+, 8%), 263 (3), 249 (49), 232 (26), 217 (35), 205 (22), 189 (46), 175 (29), 161 (74), 154 (30), 147 (59), 135 (88), 121 (69), 107 (87), 105 (92), 91 (100), 79 (80); HRMS (CI) for $C_{16}H_{24}O_3$ (MH^+): Calcd 264.1725; Found 264.1736.

Compound **15:** ^{1}H-NMR δ: 5.33 (s, 1H, H-11a), 5.19 (s, 1H, H-11b), 3.79 (s, 3H, COOMe), 3.57 (d, 1H, J=6.2, H-7), 2.13 (ddd, 1H, J=5.0, 6.2, 15.1 Hz, H-6a), 1.87 (m, 2H, H-6b and H-1), 1.52 – 1.38 (m, 4H), 1.22 (dd, 1H, J=5.0, 13.2, H-5), 1.13 (m, 1H), 1.09 (s, 3H, Me-15), 0.89 (s, 3H, Me-13) and 0.86 (s, 3H, Me-14); ^{13}C-NMR δ: 38.5 (C-1), 18.5 (C-2), 41.8 (C-3), 33.4 (C-4), 48.2 (C-5), 21.3 (C-6), 60.6 (C-7), 60.2 (C-8), 151.1 (C-9), 37.6 (C-10), 115.0 (C-11), 170.0 (C-12), 32.8 (C-13), 21.7 (C-14), 22.7 (C-15), 52.4 (COOMe); $[\alpha]_D^{20}$ + 73.5 (*c* 0.5 in $CHCl_3$); IR cm^{-1}: 3096, 2923, 1744, 1635, 1275, 1244, 1151, 1043, 902; MS *m/z* (EI$^+$) 264 (M^+, 3%), 263 (3), 249 (49), 232 (26), 217 (35), 205 (22), 189 (46), 175 (29), 161 (74), 154 (30), 147 (59), 135 (88), 121 (69), 107 (87), 105 (92), 91 (100), 79 (80); HRMS (CI) for $C_{16}H_{24}O_3$ (MH^+): Calcd 264.1725; Found 264.1737.

Treatment of **1a** *with m-CPBA: Synthesis of methyl 7,8(α+β)epoxy-15-hydroxylabdan-17-oate* (**16**).

Compound **1a** (490 mg, 1.5 mmol) was dissolved in CH_2Cl_2 (10 mL) and *m*-CPBA (380 mg, 2.2 mmol) was added. The mixture was stirred at 40º C and monitored by TLC. After 4 h the reaction was complete and the solvent evaporated. Work-up afforded 480 mg of crude product that after chromatography on silica-gel gave 323 mg (67.3%) of **16** in the 7:3 hexane/EtOAc fractions. ^{1}H-NMR δ: 3.68 (s, 3H, COOMe), 3.64 (m, 2H, H-15), 3.26 (d, 1H, J=6.3, H-7 β-epoxide), 3.18 (sb, 1H, H-7 α-epoxide), 2.09 – 1.88 (m, 3H), 1.82 – 0.90 (m, 14H), 0.89 (d, 3H, J=6.7, Me-16), 0.84 (s each, 2 x 3H, Me-18 and Me-19) and 0.80 (s, 3H, Me-20); ^{13}C-NMR δ (α-epoxide): 38.4 (C-1), 18.0 (C-2), 41.8 (C-3), 32.8 (C-4), 45.7 (C-5), 20.9 (C-6), 57.7 (C-7), 59.0 (C-8), 54.2 (C-9), 35.0 (C-10), 24.6 (C-11), 36.2 (C-12), 30.1 (C-13), 40.5 (C-14), 60.9 (C-15), 19.6 (C-16), 171.4 (C-17), 32.6 (C-18), 21.9 (C-19), 15.2 (C-20), 52.1 (COOMe); ^{13}C-NMR δ (β-epoxide): 39.2 (C-1), 18.6 (C-2), 41.9 (C-3), 33.2 (C-4), 48.4 (C-5), 21.5 (C-6), 59.6 (C-7), 60.7 (C-8), 49.4 (C-9), 35.9 (C-10), 24.6 (C-11), 36.6 (C-12), 29.9 (C-13), 40.5 (C-14), 60.9 (C-15), 19.7 (C-16), 172.7 (C-17), 32.8 (C-18), 21.8 (C-19), 14.6 (C-20), 52.1 (COOMe); IR cm^{-1}: 3445, 1732, 1457, 1283, 1063, 758; HRMS (CI) for $C_{21}H_{36}O_4$ (MH^+): Calcd 352.2614; Found 352.2625.

Reaction of **16**: *Synthesis of methyl 15-o-nitrophenylseleno-7α,8α-epoxylabdan-17-oate* (**17α**) *and methyl 15-o-nitrophenylseleno-7β,8β-epoxylabdan-17-oate* (**17β**)

To a solution of **16** (450 mg, 1.3 mmol) in dry THF (3.0 mL) was added *o*-nitrophenylselenocyanate (363.3 mg, 1.6 mmol) and stirred under inert atmosphere for 20 min at 48º C. n-Bu_3P (322.9 mg, 1.6 mmol) was added to reactional mixture, stirred for 48 min, the solvent was removed at reduced pressure and the residue chromatographed yielding with hexane/EtOAc 95:5, 338.0 mg (75%) of **17**.

Compound **17α**: ^{1}H-NMR δ: 8.27 (d, 1H, J=8.1, H-3'), 7.60 – 7.18 (m, 3H, H-4', H-5' and H-6'), 3.67 (s, 3H, COOMe), 3.21 (sb, 1H, H-7), 2.89 (m, 2H, H-15), 2.24 – 1.90 (m, 3H), 1.85 – 0.90 (m, 14H), 0.94 (d, 3H, J=6.1, Me-16), 0.86 (s each, 2 x 3H, Me-19 and Me-18) and 0.83 (s, 3H, Me-20); ^{13}C-NMR δ: 38.7 (C-1), 18.7 (C-2), 42.0 (C-3), 33.1 (C-4), 46.2 (C-5), 21.7 (C-6), 57.9 (C-7), 59.2 (C-8), 54.7 (C-9), 35.2 (C-10), 22.1 (C-11), 35.0 (C-12), 34.1 (C-13), 35.9 (C-14), 23.9 (C-15), 19.6 (C-16), 171.0 (C-17), 32.7 (C-18), 21.9 (C-19), 14.6 (C-20), 52.2 (COOMe), 134.8 (C-1'), 146.9 (C-2'), 126.5 (C-3'), 129.1 (C-4'), 133.6 (C-5'), 125.3 (C-6'); IR cm^{-1}: 2930, 1740, 1596, 1514, 1331, 715, 711.

Compound **17β**: ^{1}H-NMR δ: 8.29 (d, 1H, J=8.2, H-3'), 7.40 – 7.30 (m, 3H,H-4', H-5' and H-6'), 3.71 (s, 3H, COOMe), 3.32 (d, 1H, J=6.4, H-7), 2.90 (m, 2H, H-15), 2.10 – 1.90 (m, 2H), 1.85 – 0.90 (m, 15H), 1.06 (d, 3H, J=6.1, Me-16), 0.90 (s, 3H, Me-19), 0.85 (s, 3H, Me-18) and 0.85 (s, 3H, Me-20); ^{13}C-NMR ($CDCl_3$) δ: 40.7 (C-1), 18.1 (C-2), 42.0 (C-3), 33.3 (C-4), 48.4 (C-5), 21.1 (C-6), 59.8 (C-7), 60.7 (C-8), 49.5 (C-9), 35.9 (C-10), 24.8 (C-11), 34.9 (C-12), 34.1 (C-13), 36.1 (C-14), 23.9 (C-15),

19.4 (C-16), 172.7 (C-17), 32.9 (C-18), 22.0 (C-19), 15.4 (C-20), 52.3 (COOMe), 134.4 (C-1'), 146.5 (C-2'), 126.5 (C-3'), 129.0 (C-4'), 133.6 (C-5'), 125.3 (C-6'); IR cm^{-1}: 3062, 2929, 1733, 1590, 1513, 1332, 1037, 754.

Oxidation of **17** *with* H_2O_2*: Synthesis of methyl 7,8(α+β)-epoxy-14-labden-17-oate* (**18**).

To a solution of **17** (330.0 mg, 0.61 mmol) in THF (5 mL) was added 30% H_2O_2 (0.07 mL, 42 mg, 1.2 mmol) and the mixture was stirred for 12 h. The solvent was evaporated at reduced pressure and the crude product chromatographed yielding with 98:2 hexane/EtOAc, 284 mg (86%) of **18** as a mixture of epoxides. Data is given for a fraction in which the β-isomer predominates.

Compound **18β**: ^{1}H-NMR δ: 5.63 (ddd, 1H, J=7.7, 10.2, 17.5, H-14), 4.93 (dd, 1H, J=3.1, 17.5, H-15a), 4.91 (dd, 1H, J=3.1, 10.2, H-15b), 3.72 (s, 3H, COOMe), 3.29 (d, 1H, J=6.3, H-7), 2.15 – 1.90 (m, 2H, H-6), 1.85 – 0.98 (m, 13H), 0.96 (d, 3H, J=6.7, Me-16), 0.88 (s, 3H, Me-19) and 0.83 (s each, 2X3H, Me-18 and Me-20); ^{13}C-NMR δ: 40.7 (C-1), 18.1 (C-2), 42.0 (C-3), 32.9 (C-4), 48.0 (C-5), 21.0 (C-6), 59.7 (C-7), 60.6 (C-8), 49.5 (C-9), 35.9 (C-10), 24.9 (C-11), 36.0 (C-12), 38.2 (C-13), 144.3 (C-14), 112.9 (C-15), 20.4 (C-16), 172.7 (C-17), 33.3 (C-18), 22.0 (C-19), 15.3 (C-20), 52.3 (COOMe); IR cm^{-1}: 3074, 2926, 1733, 1649,1460, 1241.

Wacker oxidation of **18**: *Synthesis of methyl 7,8(α+β)-epoxy-14-oxolabdan-17-oate* (**19**).

To a solution of $PdCl_2$ (64 mg, 0.36 mmol) and CuCl (1.7 g, 1.8 mmol) in DMF (8 ml) and H_2O (1 mL) was activated for 30 min with O_2. A solution of **18** (550 mg, 1.8 mmol) in DMF (7 mL) was added and stirred with O_2 atmosphere at room temperature for 36 h. Then the reaction mixture was added a cooled solution of 3N HCl, extracted with CH_2Cl_2 (3 x 30 mL) and washed successively with 10% $NaHCO_3$ and water, dried, filtered, evaporated and chromatographed (eluting with 9:1 hexane/EtOAc) to give 440 mg (80%) of **19.** A fraction collected during this CC was purified to give 4% of the α-isomer of **19**, which was used for characterization purposes.

Compound **19α:** ^{1}H-NMR δ: 3.76 (s, 3H,COOMe), 3.23 (sb, 1H, H-7), 2.47 (sex, 1H, J=6.6, H-13), 2.11 (s, 3H, Me-15), 1.84 – 0.90 (m, 14H), 1.06 (d, 3H, J=6.6, Me-16), 0.86 (s each, 2X3H, Me-19 and Me-18) and 0.84 (s, 3H, Me-20); ^{13}C-NMR δ: 38.5 (C-1), 18.6 (C-2), 41.9 (C-3), 33.0 (C-4), 46.0 (C-5), 21.9 (C-6), 57.8 (C-7), 59.0 (C-8), 54.4 (C-9), 35.1 (C-10), 21.9 (C-11), 32.3 (C-12), 47.4 (C-13), 212.1 (C-14), 28.0 (C-15), 16.4 (C-16), 170.8 (C-17), 32.6 (C-18), 21.9 (C-19), 14.5 (C-20), 52.3 (COOMe); *m/z* (EI^+) 350 (M^+, 10%), 318 (24), 300 (55), 285 (55), 261 (73), 257 (100), 233 (59), 229 (27), 219 (23), 201 (67), 177 (15), 163 (27), 151 (15), 141 (16), 123 (34), 109 (43), 95 (19), 79 (22), 69 (23), 55 (36); $[\alpha]_D^{20}$ + 11.7 (*c* 0.5 in $CHCl_3$); IR cm^{-1}: 2926, 1731, 1718, 1461, 1282, 1158, 769; HRMS (CI) for $C_{21}H_{34}O_4$ (MH^+): Calcd 350.2457; Found 350.2468.

Reaction of **19** *with m-CPBA: Synthesis of* **11**.

Compound **19** (300 mg, 0.86 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and *m*-CPBA (276 mg, 1.6 mmol) was added. The mixture was stirred at 30º C and monitored by TLC. After 5 h the reaction was complete and the solvent evaporated. Work-up afforded 290 mg of crude product that after chromatography on silica-gel gave in the 9:1 hexane/EtOAc fractions 264 mg (88%) of **11** as an epoxide mixture.

Reaction of **20**: *Synthesis of 17-acetoxy-15-o-nitrophenylseleno-7-labdene* (**21**).

To a solution of **20** (450 mg, 1.3 mmol) in dry THF (3.0 mL) was added *o*-nitrophenylselenocyanate (363.3 mg, 1.6 mmol) and the mixture was stirred under an inert atmosphere for 20 min at 48º C. Then n-Bu_3P (322.9 mg, 1.6 mmol) was added to the mixture, which ws stirred for 48 min, then the solvent was removed under reduced pressure and the residue chromatographed (95:5 hexane/EtOAc) yielding 382.5 mg (85%) of **21**. ^{1}H-NMR δ: 8.29 (d, 1H, J=8.2, H-3'), 7.55 – 7.26 (m, 3H, H-4', H-5' and H-6'), 4.57 (d, 1H, J=12.1, H-17a), 4.38 (d, 1H, J=12.1, H-17b), 2.85 (m, 2H, H-15), 2.03 (s, 3H, OOCMe), 2.00 – 0.95 (m, 17H), 0.97 (d, 3H, J=5.7, Me-16), 0.88 (s, 3H, Me-19), 0.85 (s, 3H, Me-18) and 0.75 (s, 3H, Me-20); ^{13}C-NMR δ: 39.0 (C-1), 18.7 (C-2), 42.1 (C-3), 32.9 (C-4), 49.6 (C-5), 23.8 (C-6), 129.1 (C-7), 134.0 (C-8), 52.5 (C-9), 36.7 (C-10), 23.9 (C-11), 38.3 (C-12), 34.4 (C-13), 34.8 (C-14), 23.9 (C-15), 19.4 (C-16), 67.8 (C-17), 33.0 (C-18), 21.8 (C-19), 13.6 (C-20), 170.6 (MeCOO), 21.2 (Me-COO), 134.7 (C-1'), 146.7 (C-2'), 126.4 (C-3'), 129.1 (C-4'), 133.6 (C-5'), 125.2 (C-6'); IR cm^{-1}: 2930, 1733, 1591, 1515, 1332, 1247, 737.

Oxidation of **21** *with* H_2O_2*: Synthesis of 17-acetoxy-7,14-labdadiene* (**22**).

To a solution of **21** (330 mg, 0.61 mmol) in THF (5 mL) was added 30% H_2O_2 (0.07 mL, 42 mg, 1.2 mmol) and this mixure was stirred for 12 h. The solvent was evaporated under reduced pressure and the crude product chromatographed (95:5 hexane/EtOAc) yielding 297 mg (90%) of **22**. ^{1}H-NMR δ: 5.71 (m, 1H, H-7), 5.58 (ddd, 1H, J=7.7, 10.3, 17.1, H-14), 4.89 (dd, 1H, J=2.1, 17.1, H-15a), 4.86 (dd, 1H, J=2.1, 17.1, H-15b), 4.50 (d, 1H, J=12.1, H-17a), 4.30 (d, 1H, J=12.1, H-17b), 1.99 (s, 3H, OOCMe), 1.95 – 0.80 (m, 15H), 0.92 (d, 3H, J=6.7, Me-16), 0.83 (s, 3H, Me-19), 0.80 (s, 3H, Me-18) and 0.69 (s, 3H, Me-20); ^{13}C-NMR δ: 38.9 (C-1), 18.6 (C-2), 42.0 (C-3), 32.8 (C-4), 49.5 (C-5), 23.6 (C-6), 128.5 (C-7), 134.1 (C-8), 52.3 (C-9), 36.6 (C-10), 24.0 (C-11), 38.3 (C-12), 38.5 (C-13), 144.1 (C-14), 112.8 (C-15), 20.4 (C-16), 67.7 (C-17), 32.9 (C-18), 21.7 (C-19), 13.4 (C-20), 170.5 (MeCOO), 21.0 (Me-COO); $[\alpha]_D^{20}$ - 3.9 (*c* 0.5 in $CHCl_3$); IR cm^{-1}: 3076, 1742, 1640, 1240, 911.

Wacker oxidation of **22**: *Synthesis of* **23**.

A solution of $PdCl_2$ (64 mg, 0.34 mmol) and CuCl (1.6 g, 1.6 mmol) in DMF (8 mL) and H_2O (1 mL) was activated for 30 min with O_2. A solution of **22** (520 mg, 1.6 mmol) in DMF (7 mL) was then added and the mixture stirred with an O_2 atmosphere at room temperature for 36 h, then it was added to a cooled solution of 3N HCl, extracted with CH_2Cl_2 (3 x 30 mL) and washed successively with 10% $NaHCO_3$ and water, dried, filtered, evaporated and chromatographed (9:1 hexane/EtOAc) to give 416 mg (80%) of **23**.

Treatment of **23** *with m-CPBA: Synthesis of 13,17-diacetoxy-7,8-epoxy-14,15-dinor-labdane* (**24**).

Compound **23** (300 mg, 0.86 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and *m*-CPBA (276 mg, 1.6 mmol) was added. The mixture was stirred at 40º C and monitored by TLC. After 4 h the reaction was complete and the solvent evaporated. Work-up afforded 290 mg of crude product that after chromatography on silica-gel giving 264 mg (88%) of **24** (as a mixture of epoxides) in the 9:1 hexane/EtOAc fractions. ^{1}H-NMR δ: 4.95 – 4.71 (m, 1H, H-13), 4.20 (d, 1H, J=12.1, H-17a), 4.03 (d, 1H, J=12.1, H-17b), 3.22 (d, 1H, J=6.1, H-7 β-isomer), 3.14 (sb, 1H, H-7 α-isomer), 2.04 and 1.99 (s each, 2X3H, 2X-OOCMe), 1.85 – 0.75 (m, 14H), 1.19 (d, 3H, J=6.2, Me-16), 0.83 (s, 3H, Me-19), 0.82 (s, 3H, Me-18) and 0.72 (s, 3H, Me-20); ^{13}C-NMR δ: 38.0 and 38.4 (C-1, isomers), 18.5 (C-2), 41.9 (C-3), 32.9 (C-4), 45.6 (C-5), 20.3 (C-6), 57.7 (C-7), 58.6 (C-8), 54.1 (C-9), 35.6 (C-10), 22.1 (C-11), 38.0 and 38.4 (C-12, isomers), 70.8 (C-13), 20.8 (C-16), 67.1 (C-17), 32.5 (C-18), 21.8 (C-19), 14.0 (C-20), 170.3 and 170.9 (2 x MeCOO), 21.2 (2 x Me-COO); IR cm^{-1}: 2925, 1724, 1246, 1024.

Hydrolysis of **24**: *Synthesis of 13,17-dihydroxy-7,8-epoxy-14,15-dinor-labdane* (**25**), *7α,13-dihydroxy-7,17-epoxy-14,15-dinor-labdane* (**26)** *and 7α,8β,13,17-tetrahydroxy-14,15-dinor-labdane* (**27**).

Method A: To a solution of **24** (98.5 mg, 0.26 mmol) in methanol (4 mL) was added K_2CO_3 (120 mg). The reaction mixture was stirred at room temperature for 10 h, water was added and the mixture extracted with ether washed with 2N HCl and H_2O, dried, filtered, evaporated and chromatographed yielding 59.1 mg of **25**+**26** (60%), and 29.6 mg of **27** (30%).

Method B: To a solution of **24** (110 mg, 0.29 mmol) was added a solution of 4% NaOH in methanol (6 mL). The reaction mixture was stirred at room temperature for 5 h, water was added and the mixture extracted with ether, washed with 2N HCl and H_2O, dried, filtered, evaporated and chromatographed yielding 33 mg (30%) of **25**, 16.5 mg (15%) of **26** and 36.3 mg (33%) of **27**.

Compound **25**: ^{1}H-NMR δ: 3.83 (d, 1H, J= 12.2, H-17a), 3.70 (m, 1H, H-13), 3.65 (d, 1H, J=12.2 Hz, H-17b), 3.30 (m, 1H, H-7, α and β isomer), 1.90 – 0.90 (m, 14H), 1.42 (d, 3H, J=6.8, Me-16), 0.87 (s, 3H, Me-19) and 0.85 (s each, 2 x 3H, Me-18 and Me-20); ^{13}C-NMR δ: 38.5 and 40.9 (C-1, isomers),

18.0 and 18.4 (C-2, isomers), 41.6 and 41.9 (C-3, isomers), 32.9 (C-4), 45.6 (C-5), 20.4 (C-6), 57.0 (C-7), 58.6 (C-8), 54.3 (C-9), 35.8 (C-10), 22.8 (C-11), 38.5 and 40.9 (C-12 isomer), 67.8 and 67.9 (C-13 isomers), 23.5 and 23.9 (C-16 isomers), 65.4 (C-17), 32.6 and 33.1 (C-18 isomers), 21.6 and 21.9 (C-19 isomers), 13.9 and 14.2 (C-20 isomers); IR cm^{-1}: 3420, 2924, 1474, 1253, 1090, 1070.

Compound **26**: ^{1}H-NMR δ: 3.70 (m, 1H, H-13), 3.34 (t, 1H, J=2.9, H-7), 2.68 (d, 1H, J=4.3, H-17a), 2.44 (d, 1H, J=4.3, H-17b), 1.89 – 0.95 (m, 14H), 1.16 (d, 3H, J=6.7, Me-16), 0.87 (s, 3H, Me-19) and 0.85 (s each, 2X3H, Me-18 and Me-20); ^{13}C-NMR δ: 38.5 and 40.9 (C-1 isomers), 18.0 and 18.4 (C-2 isomers), 41.6 and 41.9 (C-3 isomers), 32.9 (C-4), 46.8 (C-5), 27.7 (C-6), 73.5 (C-7), 61.2 (C-8), 46.9 (C-9), 35.8 (C-10), 22.8 (C-11), 38.5 and 40.9 (C-12 isomers), 67.8 and 67.9 (C-13 isomers), 23.5 and 23.9 (C-16 isomers), 48.6 (C-17), 32.6 and 33.1 (C-18 isomers), 21.6 and 21.9 (C-19 isomers),13.9 and 14.2 (C-20 isomers); IR cm^{-1}: 3420, 2924, 1472, 1252, 1090, 1070.

Compound **27**: ^{1}H-NMR δ: 3.78 – 3.65 (m, 1H, H-13), 3.75 (d, 1H, J=12.0, H-17a), 3.53 (d, 1H, J=12.0, H-17b), 3.17 (sb, 1H, H-7), 1.90 – 1.00 (m, 14H), 1.15 (d, 3H, J=6.4, Me-16), 0.85 (s, 3H, Me-19), 0.83 (s, 3H, Me-19) and 0.80 (s, 3H, Me-20); ^{13}C-NMR δ: 38.7 (C-1), 18.2 (C-2), 42.0 (C-3), 33.1 (C-4), 46.6 (C-5), 25.6 (C-6), 70.7 (C-7), 76.5 (C-8), 50.2 (C-9), 35.8 (C-10), 20.9 (C-11), 42.0 (C-12), 68.6 (C-13), 23.7 (C-16), 66.3 (C-17), 33.1 (C-18), 21.7 (C-19), 15.1 (C-20); IR cm^{-1}: 3420, 1080.

Oxidation of **1a**: *Synthesis of 7-labden-17-methoxycarbonyl-15-oic acid* (**28**).

CrO_3 (620 mg, 6.2 mmol) was added to 90% acetic acid (10.0 mL). After stirring for 15 min, **1a** (1.4 g, 4.17 mmol) in CH_2Cl_2 (10 mL) were added and stirring was continued at 40º C for 40 h. MeOH was added and stirred for 30 min, the solvent removed *in vacuo*. The reaction product was extracted with ether, the ether solution was washed with a solution of 4% NaOH and the pH of the aqueous solution was adjusted to a value of 2 with HCl and the acidic products were recovered by extraction with ether. The solution of the acidic products was dried with anhydrous Na_2SO_4. Solvent removal and chromatography on silica-gel gave 860 mg (60%) of **28** in the 6:4 hexane/EtOAc fractions. ^{1}H-NMR δ: 9.70 (sb, 1H, COOH), 6.62 (m, 1H, H-7), 3.62 (s, 3H, COOMe), 2.42 – 1.70 (m, 4H), 1.68 – 0.90 (m, 13H), 0.94 (d, 3H, J=6.9, Me-16), 0.87 (s, 3H, Me-19), 0.84 (s, 3H, Me-18) and 0.79 (s, 3H, Me-20); ^{13}C-NMR δ: 39.5 (C-1), 18.5 (C-2), 42.0 (C-3), 32.7 (C-4), 49.4 (C-5), 23.9 (C-6), 137.2 (C-7), 135.3 (C-8), 50.9 (C-9), 36.9 (C-10), 25.6 (C-11), 38.1 (C-12), 31.0 (C-13), 41.3 (C-14), 179.7 (C-15), 19.7 (C-16), 170.7 (C-17), 33.1 (C-18), 21.9 (C-19), 14.3 (C-20), 51.3 (COOMe); IR cm^{-1}: 3500 – 2500, 2929, 1710, 1645, 1254.

Epoxidation of **28**: *Synthesis of* **29**.

To a solution of **28** (846 mg, 2.41 mmol) in dry CH_2Cl_2 (5 mL), *m*-CPBA (800 mg, 4.6 mmol) was added and the mixture stirred at 40º C. After 30 h, the solvent was removed and ether was added, the organic phase was washed with 40% $Na_2S_2O_3$, 10% Na_2CO_3 and water to neutrality, dried over Na_2SO_4, filtered and evaporated to give **29** (508 mg, 60%).

Oxidation of **16**: *Synthesis of 7,8(α+β)epoxylabdan-17-methoxycarbonyl-15-oic acid* (**29**).

Method A: CrO_3 (235 mg, 2.3 mmol) was added to 90% acetic acid (5.0 mL). After stirring for 15 min, **16** (330 mg, 0.9 mmol) in CH_2Cl_2 (5 mL) and glacial acetic acid (2 mL) were added and stirring was continued at room temperature for 8 h. MeOH was added and the solvent removed in vacuo. Work-up afforded 320 mg of crude product that after chromatography on silica-gel gave 181.5 mg (55%) of **29** in the EtOAc fractions.

Method B: To a stirred solution of PDC (1.2 mg, 3.3 mmol) in DMF (12.0 mL) was added **16** (340 mg, 1.0 mmol). After 40 h at room temperature the solvent is evaporated, extracted with ether, washed with 7-10 vol of water and dried over Na_2SO_4. The residue was chromatographed on silica-gel affording 889 mg (74%) of **29** in the EtOAc fractions.

Compound **29**: ^{1}H-NMR δ: 3.70 (s, 3H, COOMe), 3.28 (d, 1H, J=6.3, H-7 β), 3.26 (sb, 1H, H-7α), 2.40 – 2.00 (m, 3H), 1.95 – 1.00 (m, 14H), 0.96 (d, 3H, J=6.7, Me-16), 0.88 (s each, 2X3H, Me-18 and Me-19) and 0.85 (s, 3H, Me-20); ^{13}C-NMR δ: 38.6 (C-1), 18.6 (C-2), 42.0 (C-3), 33.0 (C-4), 46.0 (C-5), 21.6 (C-6), 57.8 (C-7), 59.0 (C-8), 54.5 (C-9), 35.1 (C-10), 21.9 (C-11), 36.0 (C-12), 30.6 (C-13), 41.2 (C-14), 178.4 (C-15), 19.8 (C-16), 170.8 (C-17), 32.6 (C-18), 21.8 (C-19), 14.5 (C-20), 52.1 (COOMe); IR cm^{-1}: 3550 – 2500, 1730, 1700, 1089, 758; HRMS (CI) for $C_{21}H_{34}O_5$ (MH^+): Calcd 366.4917; Found 366.4928.

Reaction of **28**: *Synthesis of methyl 15-nor-7(α+β)-acetoxy-8-labden-17-oate* (**30**) *and methyl 15-nor-7,13-labdadien-17-oate* (**31**).

To a solution of **28** (343 mg, 0.98 mmol) in dry C_6H_6 (10 mL) was added dry pyridine (0.1 mL) under a N_2 atmosphere and the mixture was stirred at room temperature. After 15 min, dry $(AcO)_2Cu$ (60 mg, 0.33 mmol) was added and the reaction mixture was heated at 80º C. $(AcO)_4Pb$ (1.280 g, 2.9 mmol) was added in six portions over the next 6 h. The solvent was removed and extracted with ether. The ethereal solution of neutral products was washed with water and dried over Na_2SO_4, filtered and evaporated to give 273 mg of crude mixture that by CC afforded 103.2 mg of **30** and 21.8 mg of **31**.

Compound **30**: ^{1}H-NMR δ: 5.69 (t, 1H, J=8.7, H-7β), 5.68 (m, 1H, H-7α), 3.66 (s, 2 x 3H, 2 x COOMe), 2.60 – 2.00 (m, 4H), 1.98 (s, 2 x 3H, 2 x OOCMe), 1.97 – 1.10 (m, 10H), 1.09 (s, 3H, Me-20, β), 0.97 (s, 3H, Me-20, α), 0.87 (d, 2 x 3H, J=6.9, Me-16), 0.84 (d, 2 x 3H, J=6.9, Me-14) and 0.83 (s, 4 x 3H, Me-18 and Me-19); IR cm^{-1}: 2956, 1733, 1651, 1238.

Compound **31**: ^{1}H-NMR δ: 6.61 (m, 1H, H-7), 4.63 (s, 2H, H-14), 3.69 (s, 3H, COOMe), 2.40 – 1.71 (m, 6H), 1.68 (s, 3H, Me-16), 1.62 – 0.98 (m, 8H), 0.88 (s, 3H, Me-19), 0.85 (s, 3H, Me-18) and 0.81 (s, 3H, Me-20); ^{13}C-NMR ($CDCl_3$) δ: 39.3 (C-1), 18.5 (C-2), 42.0 (C-3), 32.8 (C-4), 49.4 (C-5), 23.8 (C-6), 136.9 (C-7), 135.4 (C-8), 50.7 (C-9), 36.9 (C-10), 26.8 (C-11), 39.4 (C-12), 146.8 (C-13), 109.3 (C-14), 22.5 (C-16), 169.8 (C-17), 33.1 (C-18), 21.9 (C-19), 14.3 (C-20), 51.3 (COOMe); $[\alpha]_D^{20}$ - 19.0 (*c* 0.2 in $CHCl_3$); IR cm^{-1}: 3079, 2960, 1720, 1652, 798.

Reaction of 31 *with* O_3 *and Norrish type II reaction*: *Synthesis of* **5**.

A solution of **31** (100 mg, 0.3 mmol), in CH_2Cl_2 (4 mL) was cooled to –78º C with acetone/Dry Ice. Ozone (about 5.2 g of O_3/h) was bubbled through this solution for 1.5 min. To the cooled reaction mixture Ph_3P (164.5 mg, 0.6 mmol) in CH_2Cl_2 (3 mL) was added and then it was gradually allowed to reach room temperature. The solvent was removed under reduced pressure and the residue chromatographed on silica-gel to give 75 mg (75%) of product. A solution of the reaction product (75 mg, 0.24 mmol) in dry hexane (250 mL) was placed in a quartz flask and a stream of dry N_2 was bubbled through it. The solution was irradiated with UV light (Hanau TQ-150, high pressure) for 2 h. Removal of solvent afforded a yellow oil which was purified by chromatography on silica-gel eluting with 95:5 hexane/EtOAc to yield 37.5 mg (50%) of **5** and 34.2 mg (45%) of the starting material.

Hydrolysis of **30**: *Synthesis of methyl 15-nor-7β-hydroxy-8-labden-17-oate* (**32**) *and methyl 15-nor-7α-hydroxy-8-labden-17-oate* (**33**).

To a solution of **30** (41.4 mg, 0.12 mmol) in methanol (4 mL) was added K_2CO_3 (60 mg). The reaction mixture was stirred at room temperature for 10 h, water was added and the mixture extracted with ether, washed with 2N HCl and H_2O, dried, filtered, evaporated and chromatographed yielding 15.5 mg of **32** and 10.4 mg of **33**.

Compound **32**: ^{1}H-NMR δ: 4.68 (t, 1H, J=8.7, H-7), 3.76 (s, 3H, COOMe), 2.62 (m, 1H), 2.20 – 1.10 (m, 14H), 1.10 (s, 3H, Me-20), 0.90 (s, 3H, Me-19), 0.89 (d, 3H, J=6.8, Me-16), 0.88 (d, 3H, J=6.8, Me-14) and 0.86 (s, 3H, Me-18); ^{13}C-NMR δ: 40.1 (C-1), 18.7 (C-2), 41.4 (C-3), 33.0 (C-4), 49.5 (C-5), 28.4 (C-6), 69.7 (C-7), 128.6 (C-8), 158.5 (C-9), 40.6 (C-10), 26.6 (C-11), 35.9 (C-12), 29.1 (C-13), 22.3 (C-14), 22.3 (C-16), 170.4 (C-17), 33.0 (C-18), 21.7 (C-19), 20.1 (C-20), 51.3 (COOMe); $[\alpha]_D^{20}$ + 38.4 (*c* 0.2 in $CHCl_3$); IR cm^{-1}: 3400, 2940, 1720, 1630, 1460, 1250, 1060; MS *m*/*z* (EI^+) 322 (M^+, 3%), 304 (17), 290 (4), 273 (4), 263 (17), 248 (19), 230 (7), 219 (20), 201 (19), 191 (10), 177

(14), 173 (13), 166 (30), 163 (63), 159 (12), 151 (19), 149 (13), 147 (11), 145 (16), 142 (32), 139 (15), 133 (19), 131 (17), 129 (11), 123 (26), 119 (37), 117 (17), 109 (60), 105 (40), 91 (40), 83 (21), 81 (27), 79 (27), 77 (22), 59 (20), 55 (70), 43 (79), 41 (100); HRMS (CI) for $C_{20}H_{34}O_3$ (MH^+): Calcd 322.2508; Found 322.2520.

Compound **33**: ^{1}H-NMR δ: 4.44 (m, 1H, H-7), 3.76 (s, 3H, COOMe), 2.61 – 2.41 (m, 2H), 1.99 – 1.10 (m, 11H), 0.98 (s, 3H, Me-20), 0.96 (d, 3H, J=6.8, Me-16), 0.88 (d, 3H, J=6.8, Me-14) and 0.86 (s, 2X3H, Me-18 and Me-19); ^{13}C-NMR δ: 40.1 (C-1), 18.9 (C-2), 41.4 (C-3), 33.0 (C-4), 44.9 (C-5), 27.1 (C-6), 65.8 (C-7), 126.3 (C-8), 161.7 (C-9), 41.3 (C-10), 27.2 (C-11), 35.6 (C-12), 29.2 (C-13), 22.3 (C-14), 22.4 (C-16), 170.6 (C-17), 33.1 (C-18), 21.8 (C-19), 18.5 (C-20), 51.4 (COOMe); $[\alpha]_D^{20}$ + 41.4 (*c* 0.3 in $CHCl_3$); IR cm^{-1}: 3450, 2950, 1715, 1620, 1460, 1230, 1100; MS *m*/*z* (EI^+) 322 (M^+, 1%), 304 (17), 263 (17), 248 (16), 234 (17), 233 (100), 219 (25), 201 (28), 191 (15), 177 (16), 167 (10), 164 (18), 163 (98), 159 (15), 149 (11), 147 (11), 145 (18), 133 (20), 121 (19), 119 (48), 117 (17), 105 (40), 95 (23), 91 (46), 83 (24), 81 (22), 79 (25), 77 (23), 69 (50), 67 (22), 55 (55), 43 (73), 41 (92).

Reaction of **29**: *Synthesis of methyl 7-oxo-15-nor-8-labden-17-oate* (**34**) *and methyl 7β,8β-epoxy-15-nor-13-labden-17-oate* (**35β**).

To a solution of **29** (250 mg, 0.68 mmol) in dry C_6H_6 (10 mL) was added dry pyridine (0.1 mL) under a N_2 atmosphere and the mixture was stirred at room temperature. After 15 min, dry $(AcO)_2Cu$ (50 mg, 0.27 mmol) was added and the reaction mixture is heated to 80º C. Over the next 6 h $(AcO)_4Pb$ (774 mg, 1.74 mmol) was added in six portions. The solvent was removed and the residue extracted with ether. The ethereal solution was washed with a solution of 4% NaOH for extraction of the unreacted acid **29** (44.2 mg). The solution of neutral products was washed with water and dried over Na_2SO_4, filtered and evaporated to give 195 mg of a mixture that by CC afforded 155 mg (62%) of **34** and 30 mg (12%) of **35**.

Compound **34**: ^{1}H-NMR δ: 3.76 (s, 3H, COOMe), 2.60 – 2.00 (m, 4H), 1.90 – 1.12 (m, 13H), 1.12 (s, 3H, Me-20), 0.87 (d, 3H, J=7.2, Me-16), 0.86 (s each, 2X3H, Me-18 and Me-19) and 0.85 (d, 3H, J=7.2, Me-14); ^{13}C-NMR δ: 38.9 (C-1), 18.3 (C-2), 41.0 (C-3), 33.2 (C-4), 49.8 (C-5), 34.9 (C-6), 196.4 (C-7), 132.1 (C-8), 167.9 (C-9), 40.5 (C-10), 28.1 (C-11), 34.9 (C-12), 29.0 (C-13), 22.0 (C-14), 22.1 (C-16), 172.7 (C-17), 32.4 (C-18), 21.3 (C-19), 18.3 (C-20), 52.1 (COOMe); $[\alpha]_D^{20}$ + 22.3 (*c* 0.4 in $CHCl_3$); IR cm^{-1}: 2956, 1750, 1667, 1583, 1462, 1348, 1242, 1144, 1095, 1022, 801; MS *m*/*z* (EI^+) 320 (M^+, 0.8%), 288 (25), 273 (14), 245 (100), 217 (41), 189 (27), 175 (29), 161 (25), 149 (32), 135 (23), 121 (22), 109 (39), 91 (31), 79 (22), 77 (17); HRMS (CI) for $C_{20}H_{32}O_3$ (MH^+): Calcd 320.2351; Found 320.2363.

Compound **35β**: ^{1}H-NMR δ: 4.65 (s, 1H, H-14a), 4.63 (s, 1H, H-14b), 3.70 (s, 3H, COOMe), 3.28 (d, 1H, J=6.4, H-7), 2.22 – 0.99 (m, 14H), 1.67 (s, 3H, Me-16), 0.86 (s, 3H, Me-19), 0.83 (s, 3H, Me-19) and 0.81 (s, 3H, Me-20); ^{13}C-NMR δ: 40.5 (C-1), 18.1 (C-2), 42.0 (C-3), 32.9 (C-4), 47.9 (C-5), 25.8 (C-6), 59.7 (C-7), 60.6 (C-8), 49.4 (C-9), 35.9 (C-10), 21.0 (C-11), 37.3 (C-12), 146.0 (C-13), 109.8 (C-14), 22.5 (C-16), 172.5 (C-17), 33.2 (C-18), 22.0 (C-19), 15.3 (C-20), 52.3 (COOMe); IR cm^{-1}: 3070, 2931, 1740, 1650, 1454, 1381, 1283, 1161, 1054, 891, 769; MS *m/z* (EI^{+}) 320 (M^{+}, 0.8%), 281 (8), 243 (7), 234 (9), 219 (49), 207 (23), 193 (20), 135 (26), 123 (44), 109 (100), 95 (65), 93 (43), 81 (83), 79 (45); HRMS (CI) for $C_{20}H_{32}O_3$ (MH^{+}): Calcd 320.2351; Found 320.2362.

Reaction of **35** *with O_3: Synthesis of* **13**.

A solution of **35** (220 mg, 0.69 mmol) in CH_2Cl_2 (6 mL), was cooled to –78º C with acetone/dry ice. Ozone (about 5.2 g of O_3/h) was bubbled through this solution for 8 min. To the cooled reaction mixture Ph_3P (230 mg, 0.90 mmol) in CH_2Cl_2 (6 mL) was added and the mixture was gradually allowed to reach room temperature. The solvent was then removed under reduced pressure and the residue chromatographed on silica-gel affording 16.7 mg (7.6%) of **35** and 158.4 mg (72%) of **13**.

Reaction of **1a** *with dimethyldioxirane: Synthesis of 7α,8α-epoxylabdan-17-methoxycarbonyl-15-oic acid* (**29α**).

To a solution of **1a** (196 mg, 0.58 mmol) in acetone (5 mL) was added dimethyldioxirane (8 mL, 0.1 M). The reaction is carried out at room temperature. After 20 min, the solvent was removed and the residue chromatographed on silica-gel (elution with 7:3 hexane/EtOAc) affording 88.2 mg (45%) of **29α**. ^{1}H-NMR δ: 3.72 (s, 3H, COOMe), 3.22 (sb, 1H, H-7), 2.40 – 1.00 (m, 17H), 0.96 (d, 3H, J=6.7, Me-16), 0.89 (s, 3H, Me-19), 0.88 (s, 3H, Me-18) and 0.85 (s, 3H, Me-20); ^{13}C-NMR δ: 38.6 (C-1), 18.6 (C-2), 42.0 (C-3), 33.0 (C-4), 46.0 (C-5), 21.6 (C-6), 57.8 (C-7), 59.0 (C-8), 54.5 (C-9), 35.1 (C-10), 21.9 (C-11), 36.0 (C-12), 30.6 (C-13), 41.2 (C-14), 178.4 (C-15), 19.8 (C-16), 170.8 (C-17), 32.6 (C-18), 21.8 (C-19), 14.5 (C-20), 52.1 (COOMe); IR cm^{-1}: 3380 – 2600, 1736, 1712, 1437, 1279, 1161, 1054, 755.

Reaction of **29α**: *Synthesis of* **34** *and methyl 7α,8α-epoxy-15-nor-13-labden-17-oate* (**35α**).

To a solution of **29α** (250 mg, 0.68 mmol) in dry C_6H_6 (10 mL) was added dry pyridine (0.1 mL) under a N_2 atmosphere and the mixture was stirred at room temperature. After 15 min, dry $(AcO)_2Cu$ (42 mg, 0.23 mmol) was added and the reaction mixture was heated to 80º C. Over 6 h additional $(AcO)_4Pb$ (882.8 mg, 2.0 mmol) was added in six portions. The solvent was removed and the residue extracted with ether. The ethereal solution was washed with a solution of 4% NaOH to extract the unreacted acid **29α** (25 mg). The solution of neutral products was washed with water and dried over Na_2SO_4, filtered and evaporated to give 220 mg of a mixture that after CC afforded 149 mg (60%) of

34 and 30.1 mg (12%) of **35α**. ^{1}H-NMR δ: 4.71 (s, 1H, H-14a), 4.68 (s, 1H, H-14b), 3.73 (s, 3H, COOMe), 3.23 (sb, 1H, H-7), 2.20 – 1.00 (m, 14H), 1.63 (s, 3H, Me-16), 0.89 (s, 3H, Me-19), 0.87 (s, 3H, Me-18) and 0.85 (s, 3H, Me-20); ^{13}C-NMR δ: 38.5 (C-1), 18.6 (C-2), 42.0 (C-3), 33.0 (C-4), 46.0 (C-5), 22.0 (C-6), 57.8 (C-7), 59.0 (C-8), 53.3 (C-9), 35.3 (C-10), 22.3 (C-11), 36.9 (C-12), 145.2 (C-13), 110.7 (C-14), 22.2 (C-16), 171.0 (C-17), 32.6 (C-18), 21.9 (C-19), 14.6 (C-20), 52.2 (COOMe); IR cm^{-1}: 3073, 2927, 1733, 1649, 1437, 1277, 1053, 886, 768.

Reaction of **35α** *with* O_3*: Synthesis of* **13α**.

A solution of **35α** (100 mg, 0.31 mmol) in CH_2Cl_2 (5 mL), was cooled to –78º C. Ozone (about 5.2 g of O_3/h) was bubbled through this solution for 8 min. To the cooled reaction mixture Ph_3P (158.4 mg, 0.62 mmol) in CH_2Cl_2 (6 mL) was added and the mixture was gradually allowed to reach room temperature. The solvent was then removed under reduced pressure and the residue chromatographed on silica-gel affording 6.0 mg (6%) of **35α** and 72.0 mg (72%) of **13α**.

Norrish type II reaction of **13α**: *Synthesis of* **14**.

A solution of **13α** (100 mg, 0.31 mmol) in dry hexane (250 mL) was placed in a quartz flask and a stream of dry N_2 was bubbled through. The solution was irradiated with UV light (Hanau TQ-150, high pressure) for 90 min. Removal of the solvent afforded a yellow oil which was purified by chromatography on silica-gel eluting with 98:2 hexane/EtOAc, to yield 28.5 mg (28%) of **14** and 40.0 mg (40%) of the starting material **13α**.

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Sample availability: Small amounts (mgs) of the final compounds are available from the authors.