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Synthesis of Biologically Active Drimanes and Homodrimanes from (-)-Sclareol.

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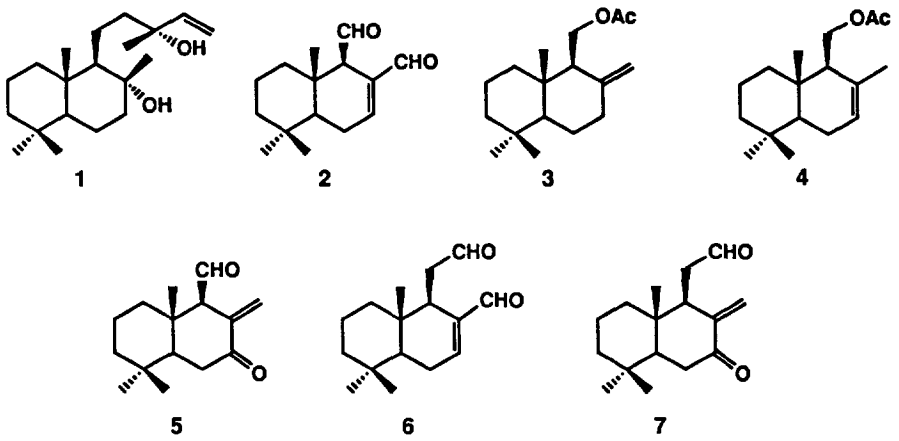
Abstract: Three drimanes, polygodial (2), albicanyl acetate (3) and 7-oxo-8,12-drimen-11-al (5), and two homodrimanes, 13,14,15,16-tetranorlabd-7-en-12,17-dial (6) and 7-oxo-13,14,15,16-tetranorlabd-8(17)-en -12-al (7), were synthesized from (-)-sclareol (1), and their antifeedant, antitumor and antimicrobial properties tested. In most cases, 6 and 7 were found to be more active than 2.

INTRODUCTION

The wide variety of biological activities of some drimane sesquiterpenes [1] has greatly stimulated the development of general synthetic routes to this class of compounds.[2] There have been a number of studies [3-6] on the mode of action of sesquiterpene drimane antifeedants, such as polygodial (**2**). A reactive enedial functionality, which blocks insect chemoreceptors, is a common feature in these compounds. Based on kinetic data, Kubo [5] and Ma [6] proposed that the enedial functionality reacts with a receptor SH group in a Michael-addition fashion. Sodano et al [4] suggested that it is an NH_2 group of the receptor which reacts with the enedial group to form a pyrrole. Lam et al [3b] isolated a pyrrole derivative, formed from reacting L-cisteine methyl ester with muzigadial, an antifeedant drimane, which supports Sodano's hypothesis.

In this paper enantiospecific syntheses of drimenyl acetate (**4**), a key intermediate in the synthesis of bilogically active drimanes, albicanyl acetate (**3**), a potent fish antifeedant, together with the well-known polygodial (**2**) from sclareol (**1**) are described.[7] Moreover, in order to confirm hypotheses for antifeedant activity based on the formation of heterocyclic species by reactions with chemoreceptor proteins, some 1,4- and 1,5-dicarbonylderivatives, structurally related to the active drimanes, were prepared. Thus, 7-oxo-8,12-drimen-11-al (**5**), 13,14,15,16-tetranorlabd-7-ene-12,17-dial (**6**) and 7-oxo-13,14,15,16-tetranorlabd-8(17)-en-12-al (**7**) were synthesized from sclareol (**1**) and their antifeedant, antitumor and antimicrobial properties compared with those of polygodial (**2**). In the present study, the homodrimanes **6** and **7**, which may interact with the NH_2 group yielding pyridine derivatives, showed significantly more antifeedant activity than polygodial (**2**) and its isomer **5**. Furthermore, since these compounds are easier to prepare than the related drimane it is suggested that their application could be more advantageous.

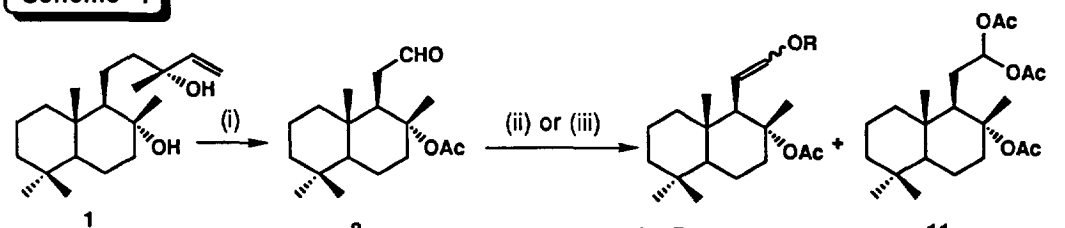


RESULTS AND DISCUSSION

The oxidation of sclareol (**1**) with osmium tetroxide-sodium periodate leads to good yields of the acetoxyaldehyde **8**, which, besides being an intermediate in the synthesis of Ambrox®,[8] can be transformed into further biologically active drimanes and homodrimanes.

The synthesis of drimanes involves the shortening of the side chain of **8**, by oxidative degradation of the corresponding enol derivatives. The preparation of the enol acetates from **8** (scheme 1) leads to a mixture of the isomers **9a**, **9b** (ratio E/Z 3:1), and the triacetate **11**. The treatment of **8** with *tert*-butyldimethylsilyl chloride in dichloromethane gives quantitative yields of the corresponding silyl enol ethers **10a** and **10b**.

Scheme 1



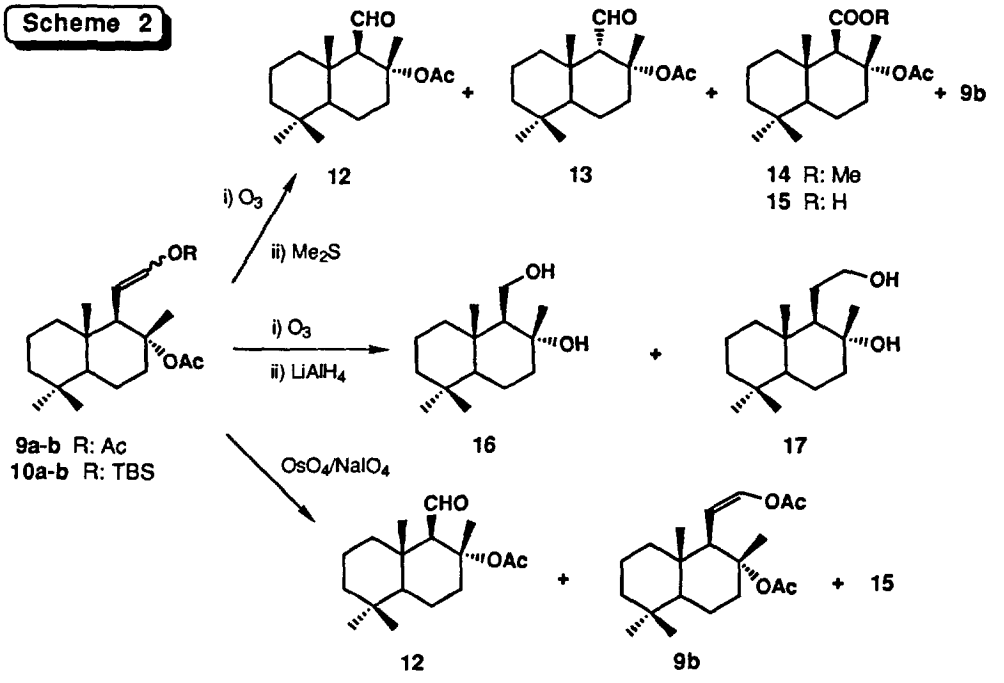
1 8 **9a** R: Ac (E) **9b** R: Ac (Z) **10a** R: TBS (E) **10b** R: TBS (Z) 11

(i) $OsO_4/NaIO_4$, $PrOH$, 45°C, 6h, 73%. (ii) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18h, 89%. (iii) TBSCl, NaH, THF, -78°C, 4h, 99%.

The oxidative degradation of enol derivatives **9** and **10** was carried out using several oxidizing reagents. In most cases, the use of the silyl enol ethers **10a-b** considerably improved the overall yield from the degradation of **8** in comparison with the use of the corresponding enol acetates (**9a** and **9b**). These derivatives

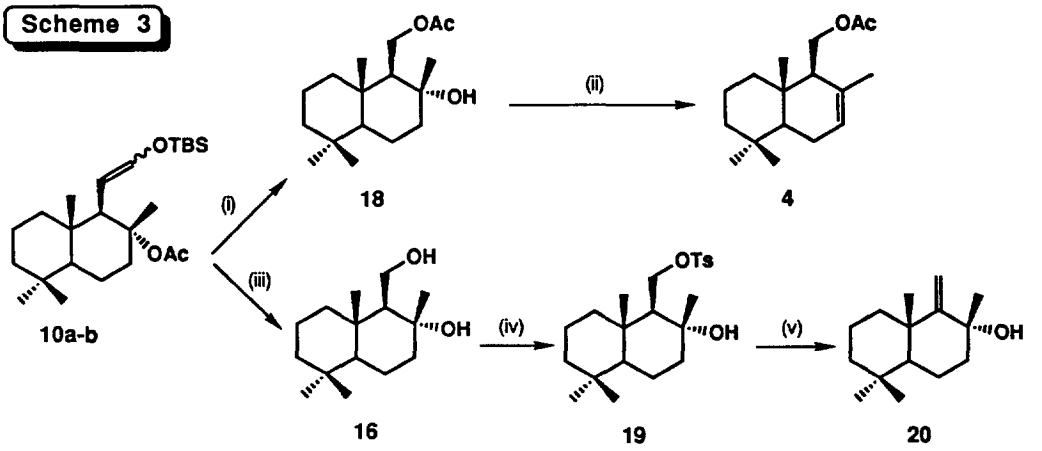
are obtained at smaller yields and oxidation causes the stereospecific degradation of the enol acetate E (**9a**), while the isomer Z (**9b**) remains unaltered. Thus, the ozonolysis of **9a** and **9b**, with Me_2S as reducing agent, gives as many as four products: the drimane aldehyde **12**, its C-9 epimer **13** and the over-oxidation compounds **14** and **15**, **9b** being recovered. Epimerization at C-9 is observed when ethyl acetate or methylene chloride are used as solvents and can be prevented by using MeOH or adding pyridine. Under optimum conditions the ozonolysis of **9a-b** gives **12** at 46% yield. Under the same reaction conditions, 93% of **12** is obtained from **10a-b**. The diols **16** (63%) and **17** (24%) are obtained by the reductive ozonolysis of **9a-b**, using $LiAlH_4$, while **16** (95%) is the only product obtained from **10a-b**. Oxidation of the enol derivatives with osmium-tetroxide-sodium periodate was also carried out. In this case also the enol acetate Z (**9b**) remains unaltered, whereas **10a-b** yields the aldehyde **12** and acetoxyacid **15** (scheme 2).

Scheme 2



Taking into account the above results, reductive ozonolysis of the silyl enol ethers **10a-b** was the degradation method chosen for preparing the biologically active drimanes. Thus, acetoxyalcohol **18** is obtained at high yields by ozonolysis of **10a-b** followed by further reduction with $NaBH_4$ (scheme 3). Dehydration regioselectivity has been studied in **18**. The treatment of **18** with $POCl_3$ in pyridine, or with MsCl, Et_3N and DMAP in dichloromethane, gives equimolecular mixtures of the isomers Δ^7, Δ^8 and $\Delta^{8,12}$. However the use of $SnCl_4$ in dichloromethane allows the transformation of **18** into drimenyl acetate (**4**), which has been used as an intermediate in the synthesis of several biologically active drimanes.[9-11] Other relevant drimanes can also be prepared from silyl enol ethers **10a-b**. The synthesis of (+)-drim-9(11)-en-8-ol (**20**) (previously having been isolated from the fungus *Aspergillus oryzae* [12]) from diol **16**, has been previously reported [13] (scheme 3).

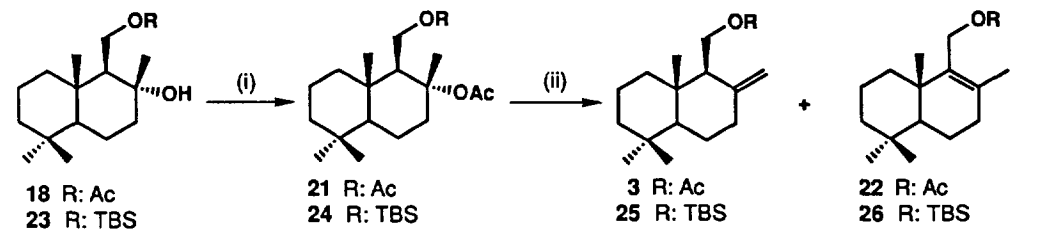
Scheme 3



(i) O_3, $MeOH/CH_2Cl_2$, -78°C, 1h; $NaBH_4$, MeOH, rt, 30 min., 95%. (ii) $SnCl_4$, CH_2Cl_2, -19°C, dropwise 30 min., 61%. (iii) O_3, $MeOH/CH_2Cl_2$, -78°C, 1h; $LiAlH_4$, THF, rt, 40 min., 95%. (iv) TsCl, 4-DMAP. (v) NaI, Zn.

The acetoxyalcohol **18** can be transformed through its O-acetylderivative into albicanyl acetate (**3**), a potent fish antifeedant. The acetylation of **18** gives the diacetate **21** at 92% yield, which converts almost completely into an equimolecular mixture of **3** and **22** by heating with collidine. The elimination of acetate can be regioselective to $\Delta^{8,12}$ using the silyl derivative **24** instead of the corresponding diacetate **21**, in which case the ratio of compounds **25** and **26** is 2:1 respectively (scheme 4).

Scheme 4



18 R: Ac
23 R: TBS

21 R: Ac
24 R: TBS

3 R: Ac
25 R: TBS

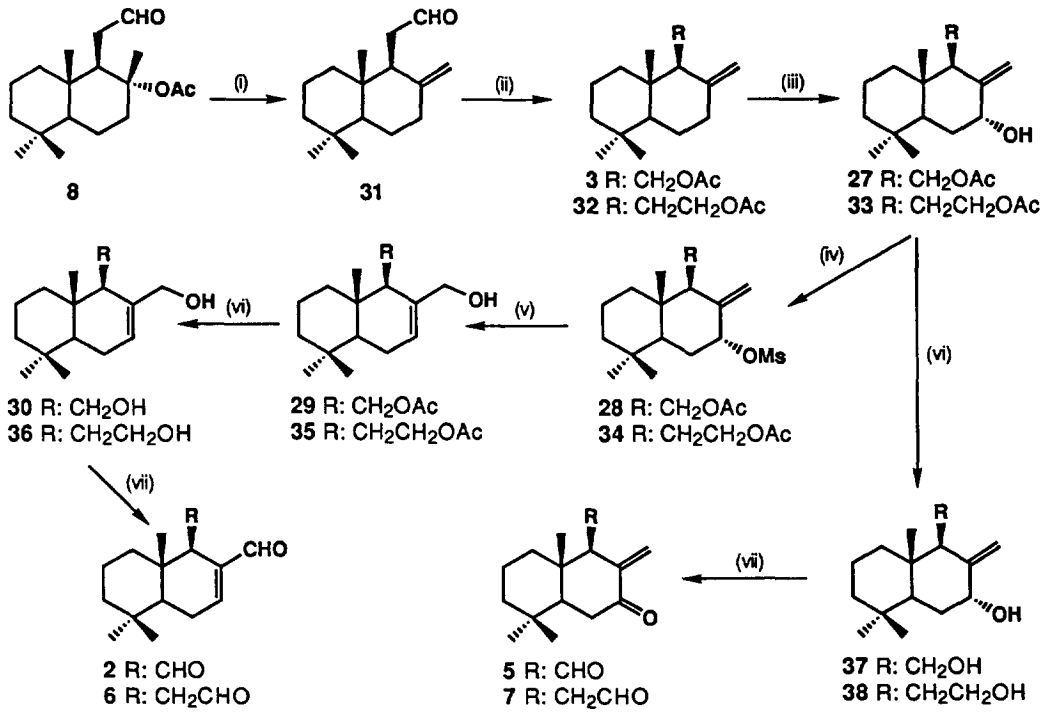
22 R: Ac
26 R: TBS

(i) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18h, 92%. (ii) Collidine, reflux.

Polygodial (**2**) was synthesized from **3**, by a five-step sequence. The oxidation of **3** with SeO_2 and Bu^tOOH in dichloromethane, allows the regio and diastereoselective hydroxylation at the 7α position, yielding 85% of **27**. By the treatment of **27** with MsCl in Py and further solvolysis of the mesylate **28**, a 67% of **29** is obtained, which saponifies to give the diol **30**. This is converted into polygodial (**2**) (92%) by oxidation with Swern's reagent.[14] The intermediate acetoxyalcohol **27** was transformed into the drimane **5**, at a very good yield, by saponification and further oxidation (scheme 5).

In a similar way, the homodrimanes **6** and **7** were prepared from the albicanyl acetate homologue **32**. The regioselective deacetylation of **8** gave **31**, which after reduction and acetylation yielded **32** (scheme 5).

Scheme 5



(i) Collidine, 170°C, 8h, 60 %. (ii) $NaBH_4$, MeOH, rt, 30 min, 93 %; Ac_2O, Py, rt, 2 h, 94 %. (iii) t-BuOOH, SeO_2, CH_2Cl_2, rt. (iv) MsCl, Py, rt. (v) NaAcO, acetone-H_2O, reflux. (vi) 2N KOH/MeOH, rt. (vii) $(ClCO)_2$/DMSO, CH_2Cl_2, Et_3N, -78°C, 15 min.

Some of the biological activities of compounds **2**, **5**, **6** and **7** were tested. The behavioural bioassay against *Spodoptera littoralis* revealed that **6** and **7** elicited positive dose-dependent responses and at 100 ppm both showed significantly more antifeedant activity than **2** or **5**. Overall, the insects behavioural responses to the compounds were very variable. In earlier studies polygodial (**2**) had shown potent antifeedant activity against *S.littoralis* at 100 ppm (Antifeedant Index 63 +/- 13.21),[15] whereas in the present study although polygodial (**2**) and **5** showed slight antifedant activity at 10 ppm, the activity was lost at the higher concentration, 100 ppm. Antitumor activity of **2**, **6** and **7** was tested against four cell lines. In these tests **6** was found to be slightly less active than **2**, whereas **7** showed more activity than **2** only against human lung carcinoma. Antimicrobial activity tests against ten different microorganisms were also performed for compounds **2**, **6** and **7**. Polygodial (**2**) was only found to be active against *Saccharomyces cerevisiae* S 3,[16] whereas its homologue **6** was also active against another three microrganisms. **7** only showed activity against *Pseudomonas aeruginosa*.

In conclusion, the above results suggest that isomerization of the enedial functional group of polygodial does not significantly increase the activity of the compound, whereas the presence of 1,5-dicarbonyl groups does increase the biological activity of the compounds.

EXPERIMENTAL

Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter with a 1 dm microcell, using $CHCl_3$ as solvent (concentration expressed in $cg \cdot cm^{-3}$). IR spectra were obtained on Perkin-Elmer Models 782 and 983G spectrometers with samples between sodium chloride plates or as potassium bromide pellets. ^1H NMR spectra were recorded on Bruker WP 80 SY (80 MHz), Bruker AM 300 (300 MHz) and Bruker ARX 400 (400 MHz) spectrometers using $CDCl_3$ as solvent and TMS or residual protic solvent $CHCl_3$ (δ_H= 7.25 ppm) as internal reference. ^{13}C NMR spectra were run at 20 MHz and 75 MHz on Bruker WP 80 SY and Bruker AM 300 instruments. Chemical shifts are in ppm (d scale) and the coupling constants are in Hertz. Carbon substitution degrees were established by DEPT pulse sequence. MS were recorded on a Hewlett-Packard 5988A spectrometer using an ionizing voltage of 70 eV. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70-230 mesh) and by flash column on Merck silica gel 60 (230-400 mesh) using hexane-MeO^tBu (H-E) mixtures of increasing polarity. Ozonization reactions were carried out with a mixture of ozone-oxygen provided by an oxygen-feed Fischer apparatus (8.3 mmol of O_3 in 10 litres of O_2/h). Compound **1** was isolated from flowerheads of *Salvia sclarea* L.

Reaction of 1 with OsO_4-$NaIO_4$

To a stirred solution of **1** (2 g, 6.5 mmol), ^{i}PrOH (40 ml) and H_2O (7.5 ml), 7.7 g (36.3 mmol) of $NaIO_4$ and 8.2 ml (0.065 mmol) of 0.2% OsO_4 aq. solution were added for 5 min. The mixture was further stirred for 6 h at 45° C. After filtering and removing the solvent, the crude was diluted in MeO^tBu (50 ml) and washed with H_2O (3 x 50 ml). The recombined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford a crude (1.87 g) that by column chromatography yielded *8α-acetoxy-13,14,15,16-tetranor-12-labdanal* (**8**) (1.4 g, 73%, 7:3 H-E): colourless crystals; $[\alpha]_D$: -30.7° (*c*, 0.1); IR (nujol): 2870, 1724, 1246 cm^{-1}; MS m/z (rel. int): 295 ($M+1^+$,1), 251 (100); ^1H NMR (300 MHz): 0.77 (3 H, *s*, Me-C_{10}), 0.83 (3 H, *s*, Meβ-C_4), 0.86 (3 H, *s*, Meα-C_4), 1.48 (3 H, *s*, Meβ-C_8), 1.85 (3 H, *s*, AcO-C_8), 9.64 (1 H, *dd*, 3.4, 1.8, H_{12}); ^{13}C NMR (75 MHz): 39.81 (CH_2, C_1), 18.27 (CH_2, C_2), 41.57 (CH_2, C_3), 33.11 (C, C_4), 55.59 (CH, C_5), 19.73 (CH_2, C_6), 40.28 (CH_2, C_7), 86.08 (C, C_8), 53.59 (CH, C_9), 38.44 (C, C_{10}), 38.95 (CH_2, C_{11}), 202.42 (CH, C_{12}), 22.52 (CH_3, C_{17}), 33.25 (CH_3, C_{18}), 21.31 (CH_3, C_{19}), 15.88 (CH_3, C_{20}), 20.06 (CH_3, AcO-C_8), 169,66 (C, AcO-C_8).

Enol acetates 9a-b

A stirred mixture of **8** (1.06g, 3.60 mmol), THF (19 ml), Et_3N (1.8 ml), Ac_2O (2.3 ml) and DMAP (32 mg) was refluxed for 18 h under argon. The solvent was evaporated and the residue solved in Et_2O (25 ml) and washed with sat. $NaHCO_3$ solution (3 x 20 ml) and H_2O (3 x 20 ml). The organic phase was dried over anh. Na_2SO_4, filtered and evaporated to dryness to afford a crude (1.21 g) that on chromatographic column yielded a mixture of **9a** and **9b** (1.08 g, 89%, E/Z 3:1 98:2 H-E) and **11** (29 mg, 2%, 96:4 and 95:5 H-E).

8α,12-diacetoxy-13,14,15,16-tetranor-11(E/Z)-labdene (**9a** and **9b**): oil; IR (neat): 1757, 1725, 1668, 1253, 940, 886, 803 cm^{-1}; MS m/z (rel. int.): 336 (M^+, 2), 217 (100); ^1H NMR (300 MHz): signals assigned to **9a** and **9b** 0.78 (3 H, *s*, Me-C_{10}), 0.85 (3 H, *s*, Meβ-C_4), 0.87 (3 H, *s*, Meα-C_4), 1.42 (3 H, *s*, Meβ-C_8), 2.44 (1 H, *dt*, 12.8, 3.3, 3.3, H_{7eq}); **9a**: 1.90 (3 H, *s*, AcO-C_8), 2.10 (3 H, *s*, AcO-C_{12}), 2.34 (1 H, *d*, 11.1, H_9), 5.38 (1 H, *dd*, 12.2, 11.1, H_{11}), 7.00 (1 H, *d*, 12.2, H_{12}); **9b**: 1.82 (3 H, *s*, AcO-C_8), 2.14 (3 H, *s*, AcO-C_{12}), 3.08 (1 H, *d*, 11.0, H_9), 4.90 (1 H, *dd*, 11.0, 6.7, H_{11}), 7.11 (1 H, *d*, 6.7, H_{12}); ^{13}C NMR (75 MHz): **9a**: 40.76 (CH_2, C_1), 18.37 (CH_2, C_2), 41.86 (CH_2, C_3), 33.28 (C, C_4), 55.17 (CH, C_5), 20.01 (CH_2, C_6), 38.26 (CH_2, C_7), 85.38 (C, C_8), 52.68 (CH, C_9), 37.91 (C, C_{10}), 110.31 (CH, C_{11}), 137.92 (CH, C_{12}), 22.86 (CH_3, C_{17}), 33.33 (CH_3, C_{18}), 21.55 (CH_3, C_{19}), 16.05 (CH_3, C_{20}), 20.86 (CH_3, AcO-C_8), 168.08 (C, AcO-C_8), 21.32 (CH_3, AcO-C_{12}), 170.38 (C, AcO-C_{12}); **9b**: 39.95 (CH_2, C_1), 18.37 (CH_2, C_2), 41.86 (CH_2, C_3), 33.28 (C, C_4), 55.01 (CH, C_5), 20.10 (CH_2, C_6), 38.08 (CH_2, C_7), 85.72 (C, C_8), 55.01 (CH, C_9), 38.42 (C, C_{10}), 110.45 (CH, C_{11}), 136.67 (CH, C_{12}), 22.86 (CH_3, C_{17}), 33.33 (CH_3, C_{18}), 21.44 (CH_3, C_{19}), 15.62 (CH_3, C_{20}), 20.86 (CH_3, AcO-C_8), 168.08 (C, AcO-C_8), 21.32 (CH_3, AcO-C_{12}), 170.38 (C, AcO-C_{12}).

8α,12,12-triacetoxy-13,14,15,16-tetranorlabdane (**11**): oil; IR (neat): 1769, 1746, 1729, 1252 cm^{-1}; MS m/z (rel. int.): 217 (100); ^1H NMR (300 MHz): 0.77 (3 H, *s*, Me-C_{10}), 0.81 (3 H, *s*, Meβ-C_4), 0.85 (3 H, *s*, Meα-C_4), 1.47 (3 H, *s*, Meβ-C_8), 1.98 (3 H, *s*, AcO-C_8), 2.06 (3 H, *s*, AcO-C_{12}), 2.09 (3 H, *s*, AcO'-C_{12}), 2.62 (1 H, *dt*, 12.6, 3.3, 3.3, H_{7eq}), 6.97 (1 H, *dd*, 7.2, 5.6, H_{12}); ^{13}C NMR (75 MHz): 39.56 (CH_2, C_1), 18.33 (CH_2, C_2), 41.67 (CH_2, C_3), 33.20 (C, C_4), 55.39 (CH, C_5), 19.86 (CH_2, C_6), 38.45 (CH_2, C_7), 86.76 (C, C_8), 52.60 (CH, C_9), 38.87 (C, C_{10}), 29.72 (CH_2, C_{11}), 91.63 (CH, C_{12}), 22.93 (CH_3, C_{17}), 33.29 (CH_3, C_{18}), 21.45 (CH_3, C_{19}), 15.67 (CH_3, C_{20}), 20.97* (CH_3, AcO-C_8), 170,26 (C, AcO-C_8), 20.71* (CH_3, AcO and AcO'-C_{12}), 169,22# (C, AcO-C_{12}), 169,08# (C, AcO'-C_{12}).

Silyl enol ethers 10a-b

To a stirred solution of **8** (1.176 g, 4 mmol) and TBSCl (764 mg, 5.2 mmol) in THF (30 ml), NaH (384 mg, 16 mmol) was added at -78°C under argon. The mixture was further stirred at room temperature for 4 h. Then it was filtered through silicagel and the solvent evaporated, affording a mixture of **10a** and **10b** (1.50 g, 99%, E/Z 4:1, 99:1 H-E), which after crystallization in MeOH yielded **10a**.

8α-acetoxy-12-t-butyldimethylsilyloxy-13,14,15,16-tetranor-11E-labdene (**10a**): colourless crystals;IR (nujol): 1727, 1653, 1252, 1081, 971, 837 cm^{-1}; MS m/z (rel. int.): 409 ($M+1^+$, 0.5), 349 (100); ^1H NMR (300 MHz): 0.12 (6 H, *s*, 2Me-Si), 0.77 (3 H, *s*, Me-C_{10}), 0.86 (6 H, *s*, Meβ-C_4 and Meα-C_4), 0.91 (9 H, *s*, *ter*-butyl-Si), 1.40 (3 H, *s*, Meβ-C_8), 1.88 (3 H, *s*, AcO-C_8), 2.23 (1 H, *d*, 11.1, H_9), 2.40 (1 H, *dt*, 12.7, 3.4, 3.4, H_{7eq}), 4.94 (1 H, *t*, 11.1, H_{11}), 6.14 (1 H, *d*, 11.1, H_{12}); ^{13}C NMR (75 MHz): 40.62 (CH_2, C_1), 18.32 (CH_2, C_2), 41.82 (CH_2, C_3), 33.12 (C, C_4), 56.36 (CH, C_5), 19.91 (CH_2, C_6), 38.03 (CH_2, C_7), 86.00 (C, C_8), 55.15 (CH, C_9), 37.92 (C, C_{10}), 106.47 (CH, C_{11}), 142.76 (CH, C_{12}), 22.85 (CH_3, C_{17}), 33.19 (CH_3, C_{18}), 21.44 (CH_3, C_{19}), 15.97 (CH_3, C_{20}), 21.37 (CH_3, AcO-C_8), 170.12 (C, AcO-C_8), 14.00 (2 x CH_3-Si), 25.67 (3 x CH_3-C-Si).

* These assignments may be interchanged.
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8α-acetoxy-12-t-butyldimethylsilyloxy-13,14,15,16-tetranor-11Z-labdene (**10b**): IR (nujol): 1725, 1655, 1250, 1083, 965 cm^{-1};MS m/z (rel int.): 409 (1), 408 (0.5), 393 (2), 349 (100);^1H NMR (80 MHz): 0.11 (6 H, *s*, Me-1' and Me-2'), 0.77 (3 H, *s*, Meβ-C_4), 0.86 (6 H, *s*, Me$_\alpha$-C_4 and Me-C_{10}), 0.91 (9 H, *s*, Me-1", Me-2" and Me-3"), 1.41 (3 H, *s*, Meβ-C_8), 1.81 (3 H, *s*, AcO-C_8), 2.97 (1 H, *d*, 10.6, H_9), 4.36 (1 H, *dd*, 10.6, 6.4, H_{11}), 6.31(1 H, *d*, 6.4, H_{12}).

Oxidations of the enol derivatives 9-10

i) Ozonolysis of **9a-b** and further reduction with Me_2S

A solution of **9a-b** (1.0 g, 3 mmol) in MeOH (70 ml) was slowly bubbled with a O_3/O_2 mixture at -78°C for 1.5 h. Then Me_2S (10 ml) was added and the mixture stirred for 2h. The solvent was evaporated and the residue filtered through silicagel, affording a crude that on chromatographic column yielded **9b** (248 mg, 24%, 98:2 H-E), **12** (378 mg, 46%, 95:5 y 94:6 H-E), **14** (21 mg, 2%, 93:7 H-E) and **15** (133 mg, 15%, 1:1 H-E).
8α-Acetoxy-11-drimanal (**12**): IR (nujol): 2830, 1723, 1235 cm^{-1}; MS m/z (rel. int.): 281 (1), 220 (13); ^1H NMR (80 MHz): 0.78 (3 H, *s*, Meβ-C_4), 0.83 (3 H, *s*, Me$_\alpha$-C_4), 1.13 (3 H, *s*, Me-C_{10}), 1.74 (3 H, *s*, Meβ-C_8), 1.98 (3 H, *s*, AcO-C_8), 1.88 (3 H, *s*, AcO-C_{12}), 2.43 (1 H, *d*, 3.7, H_9), 9.93 (1 H, *d*, 3.7, H_{11}).
Methyl 8α-acetoxy-11-drimanoate (**14**): IR (neat): 1723, 1255, 1163, 1017, 941 cm^{-1}; MS m/z (rel. int.): 251 (100); ^1H NMR (300 MHz): 0.79 (3 H, *s*, Meβ-C_4), 0.85 (3 H, *s*, Me$_\alpha$-C_4), 1.13 (3 H, *s*, Me-C_{10}), 1.69 (3 H, *s*, Meβ-C_8), 1.88 (3 H, *s*, AcO-C_8), 2.51 (1 H, *dt*, 12.7, 3.4, 3.4, H_{7eq}), 2.75 (1 H, *s*, H_9), 3.62 (3 H, *s*, MeO-C_{11}); ^{13}C NMR (75 MHz): 39.72 (CH_2, C_1), 18.23 (CH_2, C_2), 41.78 (CH_2, C_3), 33.06 (C, C_4), 55.11 (CH, C_5), 20.13 (CH_2, C_6), 38.78 (CH_2, C_7), 85.17 (C, C_8), 63.40 (CH, C_9), 38.56 (C, C_{10}), 172.54 (C, C_{11}), 22.60 (CH_3, C_{12}), 33.23 (CH_3, C_{13}), 21.28 (CH_3, C_{14}), 15.26 (CH_3, C_{15}), 20.90 (CH_3, AcO-C_8), 169.85 (C, AcO-C_8), 50.88 (CH_3, MeO-C_{11}).
8α-Acetoxy-11-drimanoic acid (**15**): IR (nujol): 3300-2500, 1724, 1240, 880 cm^{-1}; MS m/z (rel. int.): 297 ($M+1^+$, 0.6), 237 (100); ^1H NMR (300 MHz): 0.80 (3 H, *s*, Meβ-C_4), 0.86 (3 H, *s*, Me$_\alpha$-C_4), 1.14 (3 H, *s*, Me-C_{10}), 1.71 (3 H, *s*, Meβ-C_8), 1.92 (3 H, *s*, AcO-C_8), 2.56 (1 H, *dt*, 12.7, 3.4, 3.4, H_{7eq}), 2.80 (1 H, *s*, H_9); ^{13}C NMR (75 MHz): 39.74 (CH_2, C_1), 18.24 (CH_2, C_2), 41.74 (CH_2, C_3), 33.09 (C, C_4), 55.07 (CH, C_5), 20.11 (CH_2, C_6), 38.74 (CH_2, C_7), 85.00 (C, C_8), 63.04 (CH, C_9), 38.44 (C, C_{10}), 22.65 (CH_3, C_{12}), 33.25 (CH_3, C_{13}), 21.29 (CH_3, C_{14}), 15.23 (CH_3, C_{15}), 20.84 (CH_3, AcO-C_8), 169.97 (C, AcO-C_8).

When the reaction was carried out in ethyl acetate, *9-epi-8α-acetoxy-11-drimanal* (**13**), besides the above compounds, was obtained as a 1:1 mixture with **12**. The ^1H NMR (80 MHz) spectrum of this mixture showed the C_8-Me and C_{10}-Me signals at 2.00 and 1.30 ppm, respectively, and the aldehydic proton at 10.0 ppm.

ii) Ozonolysis of **10a-b** and further reduction with Me_2S

A solution of **10a-b** (500 mg, 1.3 mmol) in MeOH (20 ml) - CH_2Cl_2 (20 ml) was ozonized for 1h, under the above reaction conditions, and the residue stirred with Me_2S (5 ml) for 2h. Following the same work-up described for **9a-b** the aldehyde **12** (349 mg, 93%) was obtained.

iii) Ozonolysis of **9a-b** and further reduction with $LiAlH_4$

When the reaction was carried out in the same conditions described in i), but treating with $LiAlH_4$ (228 mg, 6mmol) as reducing agent for 4 h, diols **16** (459 mg, 63%) and **17** (190 mg, 24%) were obtained.

8α,11-Drimanediol (**16**): colourless crystals; $[\alpha]_D$: +1.6° (*c*, 0.63); IR (nujol): 3360, 1076, 1053, 1023, 1015, 994, 940, 913 cm^{-1}; MS m/z (rel. int.): 240 (0.5), 164 (60), 123 (60), 109 (79), 82 (72), 95 (84), 69 (72), 43 (100); ^1H NMR (300 MHz): 0.77 (6 H, *s*, Meβ-C_4 and Me-C_{10}), 0.86 (3 H, *s*, Meα-C_4), 1.32 (3 H, *s*, Meβ-C_8), 1.86 (1 H, *dt*, 12.3, 3.2, 3.2, H_{7eq}), 3.90 (2 H, *d*, 6.8, H_{11}, $H_{11'}$); ^{13}C NMR (75 MHz): 39.99 (CH_2, C_1), 18.58 (CH_2, C_2), 41.67 (CH_2, C_3), 33.24 (C, C_4), 55.90 (CH, C_5), 20.14 (CH_2, C_6), 44.27 (CH_2, C_7), 75.00 (C, C_8), 60.50 (CH, C_9), 37.49 (C, C_{10}), 61.00 (CH_2, C_{11}), 24.24 (CH_3, C_{12}), 33.52 (CH_3, C_{13}), 21.60 (CH_3, C_{14}), 15.99 (CH_3, C_{15}).

13,14,15,16-tetranor-8α,12-labdanediol (**17**): colourless crystals; $[\alpha]_D$: -15° (*c*, 0.39); IR (nujol): 3242, 1273, 1155, 1085, 1052, 915 cm^{-1}; MS m/z (rel. int.): 252 (0.4), 236 (3), 221 (5), 177 (26), 151 (18), 123 (17), 109 (43), 95 (49), 69 (62), 67 (44), 43 (100); ^1H NMR (300 MHz): 0.77 (6 H, *s*, Me-C_{10} and Meβ-C_4), 0.85 (3 H, *s*, Meα-C_4), 1.16 (3 H, *s*, Meβ-C_8), 1.87 (1 H, *dt*, 12.2, 3.1, H_{7eq}), 3.42 (1 H,*dt*, 10.3, 6.9, H_{12}), 3.75 (1 H, *dt*, 10.3, 4.3, $H_{12'}$); ^{13}C NMR (75 MHz): 39.31 (CH_2, C_1), 18.38 (CH_2, C_2), 41.87 (CH_2, C_3), 33.24 (C, C_4), 55.99 (CH, C_5), 20.42 (CH_2, C_6), 44.15 (CH_2, C_7), 72.94 (C, C_8), 59.22 (CH, C_9), 38.93 (C, C_{10}), 27.85 (CH_2, C_{11}), 63.98 (CH_2, C_{12}), 24.56 (CH_3, C_{17}), 33.28 (CH_3, C_{18}), 21.48 (CH_3, C_{19}), 15.29 (CH_3, C_{20}).

iv) Ozonolysis of **10a-b** and further reduction with $LiAlH_4$

Following the above conditions, the ozonolysis mixture was treated with $LiAlH_4$ (50 mg, 1.3 mmol) for 30 h. After the usual work-up **16** (243 mg, 95%) was obtained.

v) Reaction of **9a-b** with OsO_4-$NaIO_4$

A mixture of **9a-b** (1g, 3mmol), *t*-BuOH (20 ml), H_2O (4 ml), $NaIO_4$ (32 g, 15 mmol) and 0.2% OsO_4 aq. solution (2.4 ml, 0.03 mmol) was stirred at 45°C under argon for 22 h. After filtering and removing the solvent, the residue was fractionated into H_2O-Et_2O and extracted with Et_2O (3 x 40 ml). The organic phase was dried over anh. Na_2SO_4 and the solvent evaporated affording a crude that on chromatographic column yielded **9b** (23%), **12** (48%) and **15** (18%).

vi) Reaction of **10a-b** with OsO_4-$NaIO_4$

A mixture of **10a-b** (500 mg, 1.3 mmol), t-BuOH (10 ml), H_2O (2 ml), $NaIO_4$ (14 g, 6.5 mmol) and 0.2% OsO_4 aq. solution (2.1 ml, 0.026 mmol) was stirred at 45°C under argon for 22 h. After working-up as it was described in v) the aldehyde **12** (207 mg, 57%) and the acetoxyacid **15** (131 mg, 34%) were obtained.

***11-Acetoxy-8α-drimanol* (18)**

The ozonolysis of **10a-b** under the same reaction conditions described in ii) and further treatment of the ozonides mixture with $NaBH_4$ (50 mg, 1.3 mmol) for 30 h, yielded **18** (356 mg, 95%, 1:1 H-E): colourless crystals; $[\alpha]_D$: -8.5° (*c*, 0.39); IR (neat): 3458, 1736, 1242 cm^{-1}; MS m/z (rel. int.): 283 ($M+1^+$,0.6), 251 (10), 51 (100); ^1H NMR (300 MHz): 0.79 (3 H, *s*, Me-C_{10}), 0.85 (3 H, *s*, Meβ-C_4), 0.87 (3 H, *s*, Meα-C_4), 1.17 (3 H, *s*, Meβ-C_8), 1.88 (1 H, *dt*, 12.5, 3.3, H_{7eq}), 2.03 (3 H, *s*, AcO-C_8), 4.23 (1 H,*dd*, 11.8, 5.3, H_{11}), 4.33 (1 H, *dd*, 11.8, 4.4, $H_{11'}$); ^{13}C NMR (75 MHz): 39.71 (CH_2, C_1), 18.36 (CH_2, C_2), 41.70 (CH_2, C_3), 33.17 (C, C_4), 55.70 (CH, C_5), 20.26 (CH_2, C_6), 43.93 (CH_2, C_7), 72.63 (C, C_8), 59.94 (CH,

C_9), 38.08 (C, C_{10}), 62.55 (CH_2, C_{11}), 24.55 (CH, C_{12}), 33.44 (CH_3, C_{13}), 21.52 (CH_3, C_{14}), 15.78 (CH_3, C_{15}), 21.26 (CH_3, AcO-C_{11}), 171.31 (C, AcO-C_{11}).

***Drimenyl acetate* (4)**

To a stirred solution of **18** (100 mg, 0.35 mmol) in CH_2Cl_2 (36 ml), $SnCl_4$ (0.42 ml) was added dropwise at -19°C under argon for 5 min. The mixture was diluted with CH_2Cl_2 (30 ml) and poured into ice. The organic phase was washed with H_2O, dried over anh. Na_2SO_4 and evaporated to afford **4** (23 mg, 61%) : $[\alpha]_D$: +9.7° (*c*, 0.7); IR (neat): 1735,1660, 1240 cm^{-1}; MS m/z (rel. int.): 264 (0.5), 123 (36), 109 (52), 43 (100); ^1H NMR (80 MHz): 0.78 (3 H, *s*, Meβ-C_4), 0.81 (3 H,*s*, Me-C_{10}), 0.89 (3H, *s*, Meα-C_4), 1.65 (3 H, *s*, Me-C_8), 2.00 (3 H, *s*, AcO-C_{11}), 3.78-4.37 (2 H, *m*, H_{11} and $H_{11'}$), 5.40-5.60 (1 H, *m*, H_7).

***8α,11-Diacetoxydrimane* (21)**

A stirred mixture of **18** (1.5 g, 5.3 mmol), THF (20 ml), Et_3N (1.1 ml), Ac_2O (0.7 ml) and DMAP (50 mg) was refluxed under argon for 18 h. After evaporating the solvent, the residue was solved in Et_2O (25 ml) and washed with sat. $NaHCO_3$ solution (3 x 20 ml). The organic phase was dried over anh. Na_2SO_4 and the solvent evaporated to afford a crude reaction that by column chromatography yielded **21** (1.6 g, 92%, 95:5-92:8 H-E): IR (nujol): 1725, 1240, 1070 cm^{-1}; MS m/z (rel. int.): 324 (2), 264 (10), 123 (30), 109 (43); ^1H NMR (400 MHz): 0.79 (3 H, *s*, Me-C_{10}), 0.88 (3 H, *s*, Meβ-C_4), 0.90 (3 H, *s*, Meα-C_4), 1.42 (3 H, Meβ-C_8), 1.94 (3 H, *s*, AcO-C_8), 2.02 (3 H, *s*, AcO-C_{11}), 2.48 (1 H, *dt*, 12.3, 3.2, 3.2, H_{7eq}), 4.11(1 H, *dd*, 11.7, 5.5, H_{11}), 4.27 (1 H, *dd*, 11.7, 3.0, $H_{11'}$).

Pyrolysis of 21

A stirred solution of **21** (450 mg, 1.4 mmol) in collidine (12 ml) was refluxed for 8 h. After removing the solvent by distillation, the residue was solved in Et_2O (50 ml) and washed with 2N HCl solution (3 x 30 ml), sat. $NaHCO_3$ solution (3 x 50 ml) and H_2O (50 ml). The organic phase was dried over anh. Na_2SO_4, filtered and evaporated yielding a crude reaction (321 mg, 99%) that after being chromatographed on 20% $AgNO_3$/silicagel afforded **22** (118 mg, 32%) and **3** (109 mg, 30%).

11-Acetoxy-8-drimene (**22**): oil; IR (neat): 1740, 1664, 1237 cm^{-1}; MS m/z (rel. int.): 264 (1), 204 (3), 123 (25), 109 (65), 43 (100); ^1H NMR (80 MHz): 0.81 (3 H, *s*, Me$_b$-C_4), 0.85 (3 H, *s*, Me$_a$-C_4), 0.94 (3 H, *s*, Me-C_{10}), 1.61 (3 H, *s*, Me-C_8), 2.02 (3 H, *s*, AcO-C_{11}), 4.56 (2 H, *s*, H_{11} and $H_{11'}$).

Albicanyl acetate (**3**): oil; [a]$_D$: +22° (*c*, 0.37); IR (neat): 1730, 1650, 1248, 901 cm^{-1}; MS m/z (rel. int.): 264 (2), 123 (37), 43 (100); ^1H NMR (300 MHz): 0.78 (3 H, *s*, Me-C_{10}), 0.86 (3 H, *s*, Me$_b$-C_4), 0.88 (3 H, *s*, Me$_a$-C_4), 2.01 (3 H, *s*, AcO-C_{11}), 2.41 (1 H, *ddd*, 13.0, 4.5, 3.0, H_{7eq}), 4.18 (1 H, *dd*, 11.0, 9.0, H_{11}), 4.34 (1 H, *dd*, 11.0, 4.0, $H_{11'}$), 4.51 (1 H, *d*, 1.0, H_{12}), 4.85 (1 H, *d*, 1.0, H_{12}).

***11-t-Butyldimethylsilyloxy-8α-drimanol* (23)**

A mixture of **16** (300 mg, 1.25 mmol), CH_2Cl_2 (6.2 ml), Et_3N (0.22 ml), TBSCl (207 mg, 1.37 mmol) and DMAP (11 mg, 0.1 mmol) was stirred at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (25 ml) and washed with H_2O (3 x 25 ml). The organic phase was washed with 2N HCl solution (3 x 30 ml), sat. $NaHCO_3$ (3 x 50 ml) and H_2O (50 ml), and dried over anh. Na_2SO_4. After evaporating the solvent **23** (411 mg, 93%) was obtained: oil; IR (neat): 3433, 1086, 836 cm^{-1}; MS m/z (rel. int.): 336 (10), 123 (52),

109 (31); ^{1}H NMR (80 MHz): 0.03 (6 H, *s*, Me_1' and Me_2'), 0.68 (3 H, *s*, Me-C_{10}), 0.78 (15 H, *s*, Me_a and Me_b-C_4, Me_1", Me_2", Me_3"), 1.20 (3 H, *s*, Me_b-C_8), 3.63-4.13 (2 H, *m*, H_{11} and H_{11}').

***8α-Acetoxy-11-t-butyldimethylsilyloxydrimane* (24)**

The reaction of a mixture of **23** (440 mg, 1.2 mmol), THF (4.7 ml), Et_3N (0.26 ml), Ac_2O (0.16 ml) and DMAP (12 mg), under the same conditions as for **18**, yielded **24** (413 mg, 87%) : ^{1}H NMR (80 MHz): 0.03 (6 H, *s*, Me_1' and Me_2'), 0.78 (3 H, *s*, Me-C_{10}), 0.85 (12 H, *s*, Me_b-C_4, Me_1", Me_2", Me_3"), 0.88 (3 H, *s*, Me_a-C_4), 1.39 (3 H, *s*, Me_b-C_8), 1.93 (3 H, *s*, AcO-C_8), 3.55-3.95 (2 H, *m*, H_{11} and H_{11}').

Pyrolysis of 24

A solution of **24** (240 mg, 0.6 mmol) in collidine (6 ml) was refluxed for 8 h. After working-up as it was described for compound **21**, a crude reaction (161 mg) was obtained. It consisted of a 2:1 mixture of **25** and **26**, as its ^{1}H NMR (80 MHz) spectrum revealed.

***11-Acetoxy-8(12)-drimen-7α-ol* (27)**

To a stirred mixture of SeO_2 (222 mg, 2 mmol), CH_2Cl_2 (3 ml) and 3M isooctane t-BuOOH solution (3 ml, 9 mmol), a solution of **3** (1g, 3.8 mmol) in CH_2Cl_2 (30 ml) was slowly added under argon. After stirring for 4 h at room temperature, the mixture was diluted with CH_2Cl_2 (30 ml) and washed with H_2O (3 x 25 ml). The organic phase was dried over anh. Na_2SO_4 and evaporated to yield **27** (955 mg, 88%) : colourless crystals; $[\alpha]_D$: -38.8 (*c*, 0.44); IR (neat): 3458, 1735, 1645, 1259, 902 cm^{-1}; MS m/z (rel. int.): 280 (2), 123 (52), 43 (100); ^{1}H NMR (300 MHz): 0.71 (3 H, *s*, Me-C_{10}), 0.78 (3 H, *s*, Me_β-C_4), 0.86 (3 H, *s*, Me_α-C_4), 1.99 (3 H, *s*, AcO-C_{11}), 2.54-2.56 (1 H, *m*, H_9), 4.16 (1 H, *dd*, 11.3, 8.7, H_{11}), 4.30 (1 H, *dd*, 11.3, 4.3, H_{11}'), 4.36 (1 H, *t*, 2.7, H_{7eq}), 4.63 (1 H, *s*, H_{12}), 5.04 (1 H, *s*, H_{12}'); ^{13}C NMR (75 MHz): 38.85 (CH_2, C_1), 19.20 (CH_2, C_2), 41.95 (CH_2, C_3), 33.06 (C, C_4), 47.20 (CH, C_5), 30.61 (CH_2, C_6), 73.74 (CH, C_7), 148.21 (C, C_8), 49.40 (CH, C_9), 39.22 (C, C_{10}), 61.41 (CH_2, C_{11}), 110.45 (CH_2, C_{12}), 33.39 (CH_3, C_{13}), 20.36 (CH_3, C_{14}), 14.23 (CH_3, C_{15}), 20.85 (CH_3, AcO-C_{11}), 171.39 (C, AcO-C_{11}).

***7α-Methanesulfonyl-11-acetoxy-8(12)-drimene* (28)**

A mixture of **27** (1g, 3.5 mmol), pyridine (6.5 ml) and MsCl (0.55 ml) was stirred at room temperature for 30 min. The mixture was acidified with 2N HCl solution and extracted with AcOEt (3 x 30 ml). Combined organic phases were dried over anh. Na_2SO_4 and evaporated to afford **28** (1.1 g, 74%) : ^{1}H NMR (80 MHz): 0.65 (3 H, *s*, Me-C_{10}), 0.70 (3 H, *s*, Me_β-C_4), 0.76(3 H, *s*, Me_α-C_4), 1.93 (3 H, *s*, AcO-C_{11}), 2.88 (3 H, *s*, MsO-C_7), 3.90-4.40 (2 H, *m*, H_{11}, H_{11}'), 4.88 (1 H, *s*, H_{12}), 5.10-5.36 (2 H, *m*, H_{12}' H_{7eq}).

Solvolysis of 28

To a stirred solution of **28** (950 mg, 2.6 mmol) in acetone (27 ml) and H_2O (20 ml), NaAcO (506 mg) was added and the mixture refluxed for 2 h. After evaporating the acetone it was extracted with Et_2O (3 x 20 ml). Organic layers were dried over Na_2SO_4 and evaporated to yield a crude reaction (498 mg) that by column chromatography afforded **27** (199 mg, 27%, 75:25 H-E) and **29** (513 mg, 69%, 73:27 H-E).

11-Acetoxy-7-drimen-12-ol (**29**): IR (neat): 3450, 1732, 1663, 1250, 895 cm^{-1}; MS m/z (rel. int.): 281 (1), 220 (2), 123 (60), 110 (45), 43 (100); ^{1}H NMR (300 MHz): 0.82 (3 H, *s*, Me-C_{10}), 0.86 (3 H, *s*, Me_β-C_4),

0.89 (3 H, *s*, Me$_\alpha$-C$_4$), 2.05 (3 H, *s*, AcO-C$_{11}$), 3.97 (1 H, *d*, 11.5, H$_{12}$), 4.09-4.20 (2 H, *m*, H$_{11}$, H$_{11}$'), 4.37 (1 H, *dd*, 11.5, 3.3, H$_{12}$'), 5.84 (1 H, *dt*, 12.0, 12.0, 3.3, H$_7$); ^{13}C NMR (75 MHz): 39.40 (CH$_2$, C$_1$), 18.57 (CH$_2$, C$_2$), 41.85 (CH$_2$, C$_3$), 32.79 (C, C$_4$), 49.39 (CH, C$_5$), 23.28 (CH$_2$, C$_6$), 126.40 (CH, C$_7$), 136.02 (C, C$_8$), 50.47 (CH, C$_9$), 35.67 (C, C$_{10}$), 63.10 (CH$_2$, C$_{11}$), 65.93 (CH$_2$, C$_{12}$), 33.06 (CH$_3$, C$_{13}$), 21.76 (CH$_3$, C$_{14}$), 14.30 (CH$_3$, C$_{15}$), 20.99 (CH$_3$, AcO-C$_{11}$), 170.71 (C, AcO-C$_{11}$).

***7-Drimene-11,12-diol* (30)**

To a stirred solution of **29** (400 mg, 1.4 mmol) in MeOH (4 ml) a 2N KOH-MeOH solution (4 ml) was added and the mixture kept at room temperature for 10 min. After removing the solvent, the residue was fractionated into H$_2$O-Et$_2$O and extracted with Et$_2$O (3 x 30 ml). Combined organic phases were dried over anh. Na$_2$SO$_4$ and evaporated to yield **30** (329 mg, 98%): colourless crystals; IR (KBr): 3620, 3420, 1665, 1460, 1440, 1370, 1040, 990 cm^{-1}; MS m/z (rel. int.): 238 (0.5), 190 (11), 124 (27), 119 (19), 109 (100), 95 (21), 91 (21), 81 (30), 69 (27); ^{1}H NMR (400 MHz): 0.75 (3 H, *s*, Me-C$_{10}$), 0.87 (3 H, *s*, Me$_\beta$-C$_4$), 0.89 (3 H, *s*, Me$_\alpha$-C$_4$), 3.65 (1 H, *dd*, 11.0, 8.0, H$_{11}$), 3.89 (1 H, *dd*, 11.0, 1.5, H$_{11}$'), 3.95 (1 H, *d*, 12.0, H$_{12}$), 4.32 (1 H, *d*, 12.0, H$_{12}$'),5.76 (1 H, *t*, 2.6, H$_7$); ^{13}C NMR (100 MHz): 39.33 (CH$_2$, C$_1$), 18.69 (CH$_2$, C$_2$), 41.77 (CH$_2$, C$_3$), 32.99 (C, C$_4$), 49.42 (CH, C$_5$), 23.59 (CH$_2$, C$_6$), 127.23 (CH, C$_7$), 136.92 (C, C$_8$), 54.39 (CH, C$_9$), 35.61 (C, C$_{10}$), 61.26 (CH$_2$, C$_{11}$), 67.30 (CH$_2$, C$_{12}$), 33.21 (CH$_3$, C$_{13}$), 21.93 (CH$_3$, C$_{14}$), 14.52 (CH$_3$, C$_{15}$).

***8(12)-Drimene-7α,11-diol* (37)**

Following the above procedure **27** (150 mg, 0.5 mmol) was transformed into **37** (116 mg, 97%): IR (nujol): 3580, 1643, 1070, 900 cm^{-1}; MS m/z (rel. int.): 238 (1), 220 (10), 124 (30), 109 (100); ^{1}H NMR (300 MHz): 0.62 (3 H, *s*, Me-C$_{10}$), 0.73 (3 H, *s*, Me$_\beta$-C$_4$), 0.81 (3 H, *s*, Me$_\alpha$-C$_4$), 2.38 (1 H, *d*, 3.5, H$_9$), 3.65 (1 H, *t*, 10.2, H$_{11}$), 3.80 (1 H, *dd*, 10.2, 3.5, H$_{11}$'), 4.30 (1 H, *t*, 2.6, H$_{7eq}$), 4.55 (1 H, *s*, H$_{12}$), 5.06 (1 H, *s*, H$_{12}$'); ^{13}C NMR (75 MHz): 38.89 (CH$_2$, C$_1$), 19.29 (CH$_2$, C$_2$), 42.04 (CH$_2$, C$_3$), 33.06 (C, C$_4$), 47.44 (CH, C$_5$), 30.38 (CH$_2$, C$_6$), 73.63 (CH, C$_7$), 148.44 (C, C$_8$), 53.22 (CH, C$_9$), 39.16 (C, C$_{10}$), 58.33 (CH$_2$, C$_{11}$), 109.92 (CH$_2$, C$_{12}$), 33.39 (CH$_3$, C$_{13}$), 21.60 (CH$_3$, C$_{14}$), 14.43 (CH$_3$, C$_{15}$).

***Polygodial* (2)**

To a stirred 2M solution of (ClCO)$_2$ in CH$_2$Cl$_2$ (0.23 ml, 0.45 mmol) a solution of DMSO (0.07 ml, 0.91 mmol) in CH$_2$Cl$_2$ (0.1 ml) was added at -78°C under argon, and the mixture stirred at low temperature for 2 min and at room temperature for 5 min. After cooling at -78°C, a solution of **30** (500 mg, 2.1 mmol) in CH$_2$Cl$_2$ (0.5 ml) was added and the mixture allowed to stir for 15 min. Then, Et$_3$N (0.14 ml, 1.0 mmol) was added and the mixture stirred at room temperature for 5 min. It was diluted with CH$_2$Cl$_2$ (10 ml) and washed with H$_2$O (3 x 10 ml). The organic phase was dried over anh. Na$_2$SO$_4$ and filtered through a silicagel column. After removing the solvent **2** (459 mg, 92%) was obtained . IR (neat): 2870, 2850, 2710, 1720, 1680, 1645 cm^{-1}; MS m/z (rel. int.): 234 (3), 218 (1), 191 (8), 121 (26), 109 (100); ^{1}H NMR (300 MHz): 0.93 (3 H, *s*, Me$_\beta$-C$_4$), 0.96 (3 H, *s*, Me$_\alpha$-C$_4$), 0.97 (3 H, *s*, Me-C$_{10}$), 7.14 (1 H, *ddd*, 6.0, 3.0, 3.0, H$_7$), 9.47 (1 H, *s*, H$_{12}$), 9.54 (1 H, *d*, 5.0, H$_{11}$); ^{13}C NMR (75 MHz): 39.52 (CH$_2$, C$_1$), 17.98 (CH$_2$, C$_2$), 41.68 (CH$_2$, C$_3$), 33.09 (C, C$_4$), 48.92 (CH, C$_5$), 25.18 (CH$_2$, C$_6$), 154.21 (CH, C$_7$), 139.25 (C, C$_8$), 60.25 (CH, C$_9$), 36.82 (C, C$_{10}$), 201.85 (CH, C$_{11}$), 193.16 (CH, C$_{12}$), 33.09 (CH$_3$, C$_{13}$), 21.93 (CH$_3$, C$_{14}$), 15.24 (CH$_3$, C$_{15}$).

***7-Oxo-8(12)-drimen-11-al* (5)**

Oxidation of **37** (110 mg, 0.4 mmol) with Swern's reagent in the same conditions as for **30**, yielded **5** (87 mg, 91%) : oil; IR (neat): 2852, 1724, 1681, 978 cm^{-1}; MS m/z (rel. int.): 234 (100), 206 (12), 205 (50), 135 (85); ^1H NMR (300 MHz): 0.87 (3 H, *s*, Meβ-C_4), 0.89 (3 H, *s*, Meα-C_4), 0.92 (3 H, *s*, Me-C_{10}), 5.93 (1 H, *s*, H_{12}), 6.31 (1 H, *s*, H_{12}'), 9.63 (1 H, *s*, 5.0, H_{11}).

***13,14,15,16-Tetranor-8(17)-labden-12-al* (31)**

A solution of **8** (500 mg, 1.7 mmol) in collidine (4 ml) was refluxed for 8 h. After working-up as it was described for **21**, **31** (238 mg, 60%) was obtained.IR(neat): 2825, 1721, 1642 cm^{-1}; MS m/z (rel. int.): 234 (2), 123 (30), 109 (45); ^1H NMR (80 MHz): 0.68 (3 H, *s*, Me-C_{10}), 0.80 (3 H, *s*, Meβ-C_4), 0.88 (3 H, *s*, Meα-C_4), 2.38 (2 H, *d*, 2.0, H_{11} and H_{11}'), 4.36 (1 H, *s*, H_{17}), 4.78 (1 H, *s*, H_{17}'), 9.58 (1 H, *t*, 3.0, H_{12}).

***12-Acetoxy-13,14,15,16-tetranor-8(17)-labdene* (32)**

To a stirred solution of **31** (1.2 g, 5.1 mmol) in MeOH (30 ml), $NaBH_4$ (194 mg, 5.1 mmol) was added, and the mixture allowed to stir at room temperature for 30 min. After evaporating, the residue was solved in Et_2O (50 ml) and washed with 2N HCl (3 x 30 ml), sat. $NaHCO_3$ solution (3 x 50 ml) and H_2O (50 ml). The organic layer was dried over anh. Na_2SO_4 and evaporated to yield the corresponding alcohol (1.1 g, 93%, 6:4 and 1:1 H-E), which after treating with Ac_2O (10 ml) in pyridine (10 ml) at room temperature for 2 h afforded **32** (1.2 g, 94%) : IR (neat): 1730, 1648, 1250, 899 cm^{-1}; Ms m/z (rel. int.): 278 (1), 218 (2), 123 (70), 43 (100); ^1H NMR (400 MHz): 0.68 (3 H, *s*, Me-C_{10}), 0.81 (3 H, *s*, Meβ-C_4), 0.88 (3 H, *s*, Meα-C_4), 2.03 (3 H, *s*, AcO-C_{12}), 3.86-4.3 (1 H, *m*, H_{12}), 4.16-4.22 (1 H, *m*, H_{12}'), 4.53 (1 H, *s*, H_{17}), 4.83 (1 H, *s*, H_{17}'); ^{13}C NMR (100 MHz): 39.10 (CH_2, C_1), 19.39 (CH_2, C_2), 42.17 (CH_2, C_3), 33.62 (C, C_4), 55.55 (CH, C_5), 24.36 (CH_2, C_6), 38.17 (CH_2, C_7), 148.09 (C, C_8), 53.11 (CH, C_9), 39.46 (C, C_{10}), 23.19 (CH_2, C_{11}), 64.42 (CH_2, C_{12}), 106.65 (CH_2, C_{17}), 33.62 (CH_3, C_{18}), 21.75 (CH_3, C_{19}), 14.41 (CH_3, C_{20}), 21.07 (CH_3, AcO-C_7), 171.08 (C, AcO-C_7).

***12-Acetoxy-13,14,15,16-tetranor-8(17)-labden-7α-ol* (33)**

Oxidation of **32** (1.1 g, 4 mmol) with Swern's reagent in the same reaction conditions as for **30**, yielded **33** (1.0 g, 84%, 1:1 H-E) : IR (neat): 3458, 1735, 1645, 1259, 902 cm^{-1}; Ms m/z (rel. int.): 294 (1), 276 (2),234 (37),123 (89); ^1H NMR (400 MHz): 0.65 (3 H, *s*, Me-C_{10}), 0.80 (3 H, *s*, Meβ-C_4), 0.89 (3 H, *s*, Meα-C_4), 2.04 (3 H, *s*, AcO-C_{12}), 3.97 (1 H, *dt*, 10.7, 7.7, 7.7, H_{12}), 4.15 (1 H, *qd*, 10.7, 8.0, 4.6, H_{12}'), 4.33 (1 H, *t*, 2.9, H_{7eq}), 4.69 (1 H, *s*, H_{17}), 5.01 (1 H, *s*, H_{17}'); ^{13}C NMR (100 MHz): 39.50 (CH_2, C_1), 19.27 (CH_2, C_2), 41.99 (CH_2, C_3), 33.04 (C, C_4), 47.50 (CH, C_5), 30.74 (CH_2, C_6), 73.75 (CH, C_7), 149.35 (C, C_8), 47.08 (CH, C_9), 38.69 (C, C_{10}), 22.77 (CH_2, C_{11}), 63.78 (CH_2, C_{12}), 109.56 (CH_2, C_{17}), 33.19 (CH_3, C_{18}), 21.45 (CH_3, C_{19}), 13.34 (CH_3, C_{20}), 21.02 (CH_3, AcO-C_{12}), 171. 29 (C, AcO-C_{12}).

***7α-Methanesulfonyl-12-acetoxy-13,14,15,16-tetranor-8(17)-labdene* (34)**

A mixture of **33** (1 g, 3.4 mmol), pyridine (6 ml) and MsCl (0.53 ml) was stirred at room temperature for 2.5 h. After working-up as it was described for **27**, **34** (1.2 g, 96%) was obtained. ^1H NMR (80 MHz):

0.66 (3 H, *s*, Me-C_{10}), 0.78 (3 H, *s*, Meβ-C_4), 0.86 (3 H, *s*, Meα-C_4), 2.01 (3 H, *s*, AcO-C_{12}), 2.93 (3 H, *s*, MsO-C_7), 3.75-4.30 (2 H, *m*, H_{12} and $H_{12'}$), 5.00 (1 H, *s*, H_{17}), 5.20-5.38 (2 H, *m*, H_{7eq} and $H_{17'}$).

Solvolysis of 34

To a stirred solution of **34** (1.2 g, 3.2 mmol) in acetone (60 ml) and H_2O (30 ml), NaAcO (684 mg) was added, and the mixture refluxed for 3 h. After working-up as it was described for **28**, a 1:2 mixture (767 mg, 82%, 6:4 H-E) of **33** and **35** was obtained.

Saponification of 33 and 35

The mixture (767 mg, 2.6 mmol) of **33** and **35** was saponified under the same reaction conditions as for **29**, yielding **36** (298 mg, 46%, 4:6 H-E) and **38** (228 mg, 35%, 4:6 and 3:7 H-E).

13,14,15,16-Tetranor-7-labdene-12,17-diol (**36**): IR (nujol): 3250, 1667, 1050, 895 cm^{-1}; MS m/z (rel. int.): 252 (13), 219 (15), 201 (10), 175 (12), 123 (100), 95 (58), 69 (62), 41 (69); ^1H NMR (80 MHz): 0.73 (3 H, *s*, Me-C_{10}), 0.83 (3 H, *s*, Meβ-C_4), 0.85 (3 H, *s*, Meα-C_4), 3.57 (1 H, *td*, 9.6, 9.6, 5.2 H_{12}), 3.74 (1 H, *q*, 9.6, $H_{12'}$), 3.81 (1 H, *d*, 12.1, H_{17}), 4.26 (1 H, *d*, 12.1, $H_{17'}$), 5.69 (1 H, *t*, 2.7, H_7); ^{13}C NMR (75 MHz): 39.01 (CH_2, C_1), 18.61 (CH_2, C_2), 42.12 (CH_2, C_3), 32.85 (C, C_4), 49.83* (CH, C_5), 23.68 (CH_2, C_6), 126.38 (CH, C_7), 138.44 (C, C_8), 48.55* (CH, C_9), 36.69 (C, C_{10}), 28.04 (CH_2, C_{11}), 64.05 (CH_2, C_{12}), 66.10 (CH_2, C_{17}), 32.98 (CH_3, C_{18}), 21.71 (CH_3, C_{19}), 13.48 (CH_3, C_{20}).

13,14,15,16-Tetranor-8(17)-labdene-7α,12-diol (**38**) (35%): IR (nujol): 3550, 1645, 1065, 892 cm^{-1}; MS m/z (rel. int.): 252 (9), 219 (9), 201 (7), 175 (8), 123 (100), 95 (55), 69 (65), 67 (63), 43 (26); ^1H NMR (300 MHz): 0.63 (3 H, *s*, Me-C_{10}), 0.78 (3 H, *s*, Meβ-C_4), 0.86 (3 H, *s*, Meα-C_4), 1.61 (1 H, *td*, 13.2, 13.2, 2.8, H_{6ax}), 1.82 (1 H, *dt*, 13.2, 2.8, 2.8, H_{6eq}), 3.56 (1 H, *td*, 10.7, 10.7, 4.9 H_{12}), 3.63 (1 H, *ddd*, 10.7, 6.3, 4.1, $H_{12'}$), 4.34 (1 H, *t*, 2.8, H_{7eq}), 4.60 (1 H, *t*, 1.5, H_{17}), 5.03 (1 H, *s*, $H_{17'}$); ^{13}C NMR (75 MHz): 38.77 (CH_2, C_1), 19.32 (CH_2, C_2), 42.08 (CH_2, C_3), 33.06 (C, C_4), 47.66 (CH, C_5), 26.29 (CH_2, C_6), 73.99 (CH, C_7), 149.05 (C, C_8), 46.31 (CH, C_9), 39.50 (C, C_{10}), 31.31 (CH_2, C_{11}), 60.81 (CH_2, C_{12}), 109.75 (CH_2, C_{17}), 33.26 (CH_3, C_{18}), 21.51 (CH_3, C_{19}), 13.46 (CH_3, C_{20}).

13,14,15,16-Tetranor-7-labdene-12,17-dial **(6)**

Oxidation of **36** (100 mg, 0.4 mmol) with Swern's reagent in the same reaction conditions as for **30**, yielded **6** (91 mg, 91%) : IR (neat): 2867, 2722, 1721, 1681, 1641 cm^{-1}; MS m/z (rel. int.): 248 (4), 220 (2), 189 (73); ^1H NMR (400 MHz): 0.71 (3 H, *s*, Me-C_{10}), 0.87 (3 H, *s*, Meβ-C_4), 0.89 (3 H, *s*, Meα-C_4), 2.30 (1 H, *dd*, 17.8, 2.5 H_{11}), 2.46 (1 H, *ddd*, 17.8, 9.1, 2.3, $H_{11'}$), 6.84 (1 H, *quintuplet*, 5.0, 2.5, 2.5, H_7), 9.27 (1 H, *s*, H_{17}),9.81 (1 H, *dd*, 2.3, 0.7, H_{12}); ^{13}C NMR (100 MHz): 38.19 (CH_2, C_1), 18.27 (CH_2, C_2), 41.69 (CH_2, C_3), 32.80 (C, C_4), 49.03 (CH, C_5), 25.25 (CH_2, C_6), 154.45 (CH, C_7), 141.61 (C, C_8), 43.06 (CH, C_9), 35.46 (C, C_{10}), 40.27 (CH_2, C_{11}), 200.88 (CH, C_{12}), 194.56 (CH, C_{17}), 32.80 (CH_3, C_{18}), 21.57 (CH_3, C_{19}), 14.08 (CH_3, C_{20}).

7-Oxo-13,14,15,16-tetranor-8(17)-labden-12-al **(7)**

38 (100 mg, 0.4 mmol) was transformed into **7** (90 mg, 90%) by treating with Swern's reagent under the above reaction conditions. IR (neat): 2725, 1719, 1689, 1638 cm^{-1}; MS m/z (rel. int.): 249 (3), 221 (6),

* These assignments may be interchanged.

123 (100); ^{1}H NMR (400 MHz): 0.82 (3 H, *s*, Me-C_{10}), 0.88 (3 H, *s*, Meβ-C_4), 0.89 (3 H, *s*, Meα-C_4), 2.31 (1 H, *dd*, 17.5, 14.1, 4.9 H_{11}), 2.51 (1 H, *ddd*, 17.5, 9.4, 2.7, H_{11}'), 4.34 (1 H, *t*, 2.8, H_{7eq}), 4.49 (1 H, *d*, 2.5, H_{17}), 5.91 (1 H, *d*, 2.5, H_{17}'), 9.74 (1 H, *d*, 2.7, H_{12}); ^{13}C NMR (100 MHz): 38.23 (CH_2, C_1), 18.77 (CH_2, C_2), 41.52 (CH_2, C_3), 33.51 (C, C_4), 51.29 (CH, C_5), 40.51 (CH_2, C_6), 201.90 (C, C_7), 147.33 (C, C_8), 49.21 (CH, C_9), 40.98 (CH_2, C_{11}), 201.52 (CH, C_{12}), 120.28 (CH_2, C_{17}), 33.52 (CH_3, C_{18}), 20.85 (CH_3, C_{19}), 14.21 (CH_3, C_{20}).

Biological activities

Antifeedant screening

The insect bioassays,with 10 replications per concentration per compound, were carried out under MAFF licence No. PHF 1020/10 issued under Import and Export Order (Plant Health Great Britain) 1980 and Plant Pests Order (Great Britain) 1980. Antifeedant Index (((C-T)/(C-T) x 100; mean +/- sem) was calculated on the amount eaten of treated (T) and control glass-fibre discs (C). At 100 ppm the antifeedant activity per compound was **2**(7.4 +/- 15.09), **5** (18.5 +/- 15.3), **6** (51.7 +/- 13.22)* and **7** (43.7 +/- 3.09)* (* = significant antifeedant activity; Wilcoxon matched pairs test, $P<0.05$). At 10 ppm the compounds were less active: **2** (24.9 +/- 7.0), **5** (40.2 +/- 13.32), **6** (-17.9 +/- 9.39) and **7** (-10 +/- 17.19).

Antitumoral screening

The antitumor activity of **2**, **6** and **7** were assayed against cells P-388, A-549, HT-29 and MEL-28, following the method reported by Bergeron et al.[17] IC_{50} (μg/ml) are shown in the table.

	IC_{50} (μg/ml)			
Compound	P-388	A-549	HT-29	MEL-28
2	1.2	2.5	2.5	2.5
6	2.5	2.5	5.0	5.0
7	1.2	1.2	2.5	2.5

Antimicrobial screening

The antimicrobial activity of **2**, **6** and **7**, with the minimal inhibitory concentration (MIC, μg/ml) given in parentheses, were tested against Gram positive bacteria (*Enterococcus faecalis* OGIX: **2** (>100), **6** (>100) and **7** (>100); *Bacillus subtilis* CECT 397: **2** (>100), **6** (100) and **7** (>100); *Staphylococcus aureus* ATCC 8: **2** (>100), **6** (100) and **7** (>100)); Gram negative (*Salmonella tiphymurium* LT 2 : **2** (>100), **6** (>100) and **7** (>100); *Proteus sp.* : **2** (>100), **6** (>100) and **7** (>100); *Pseudomonas aeruginosa* : **2** (>100), **6** (100) and **7** (100)) and yeasts (*Saccharomyces cerevisiae* S 3 : **2** (100), **6** (100) and **7** (>100); *Candida albicans* CECT 1394: **2** (>100), **6** (>100) and **7** (>100);*Cryptococcus neoformans* CECT 1075 : **2** (>100), **6** (>100) and **7** (>100)).

The microorganisms were obtained from the Microbiology Department, Faculty of Sciences, University of Granada. The minimal inhibitory concentration (MIC) was measured in 1 ml of nutrient broth (tryptose broth ADSA-MICRO for bacteria, and USP ADSA-MICRO Sabouraud medium for yeasts) containing the sample at the required concentration. The test tubes were inoculated with 10^4 cells of the microorganism and

incubated at 28 °C (24 h for bacteria and 48 h for fungi). The test tubes were then examined, taking as MIC the least concentration showing no turbidity.

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