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

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Abstract: Three drimanes, polygodial (2), allicyanal acetate (3) and 7-oxo-8,12-drimer-11-1al (5), and two homodrimanes, 13,14,15,16-tetrnorlabd-7-en-12,17-dial (6) and 7-oxo-13,14,15,16-tetrnorlabd-8(17)-en-12-1al (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 NH2 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-cysteine 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, allicyanal 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-dicarboxyl derivatives, structurally related to the active drimanes, were prepared. Thus, 7-oxo-8,12-drimer-11-1al (5), 13,14,15,16-tetrnorlabd-7-ene-12,17-dial (6) and 7-oxo-13,14,15,16-tetrnorlabd-8(17)-en-12-1al (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 NH2 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®, 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.

\[ \text{Scheme 1} \]

(i) OsO₄/NaIO₄, PhOH, 45°C, 6h, 73%. (ii) Ac₂O, Et₃N, 4-DMAP, THF, reflux, 18h, 89%. (iii) TBSCI, 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 Me₂S 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 LiAlH₄, 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 acetooxyacid 15 (scheme 2).

![Scheme 2](image_url)

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 NaBH₄ (scheme 3). Dehydration regioselectivity has been studied in 18. The treatment of 18 with POCl₃ in pyridine, or with MsCl, Et₃N and DMAP in dichloromethane, gives equimolecular mixtures of the isomers Δ⁷, Δ⁸ and Δ⁸,¹². However the use of SnCl₄ in dichloromethane allows the transformation of 18 into drimeryl 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 reported¹³ (scheme 3).
The acetoxyalcohol 18 can be transformed through its O-acetyl derivative into albicyanil 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).

Polygodial (2) was synthesized from 3, by a five-step sequence. The oxidation of 3 with ScO\(_2\) and BuO\(_2\)OH in dichloromethane, allows the regio and diastereoselective hydroxylation at the 7\( \alpha \) 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).

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), whereas in the present study although polygodial (2) and 5 showed slight antifeedant 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 S3, 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 CHCl₃ as solvent (concentration expressed in cg·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 CDCl₃ as solvent and TMS or residual protic solvent CHCl₃ (δ_H = 7.25 ppm) as internal reference. ¹³C 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 (δ 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 carryed 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'Bu (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 O₃ in 10 litres of O₂/h). Compound I was isolated from flowerheads of *Salvia sclarea* L.

**Reaction of 1 with OsO₄-NaIO₄**

To a stirred solution of 1 (2 g, 6.5 mmol), iPrOH (40 ml) and H₂O (7.5 ml), 7.7 g (36.3 mmol) of NaIO₄ and 8.2 ml (0.065 mmol) of 0.2% OsO₄ 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'Bu (50 ml) and washed with H₂O (3 x 50 ml). The recombined organic layers were dried over anhydrous Na₂SO₄ and evaporated to afford a crude (1.87 g) that by column chromatography yielded 8α-acetoxy-13,14,15,16-tetranor-12-labdadienal (8) (1.4 g, 73%, 7.3 H-E): colourless crystals; [α]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-C₁₀), 0.83 (3 H, s, Meβ-C₄), 0.86 (3 H, s, Meα-C₄), 1.48 (3 H, s, Meβ-C₈), 1.85 (3 H, s, AcO-C₈), 9.64 (1 H, dd, 3.4, 1.8, H₁₂); ¹³C NMR (75 MHz): 39.81 (CH₂, C₁), 18.27 (CH₂, C₂), 41.57 (CH₂, C₃), 33.11 (C, C₄), 55.59 (CH, C₅), 19.73 (CH₂, C₆), 40.28 (CH₂, C₇), 86.08 (C, C₈), 53.59 (CH, C₉), 38.44 (C, C₁₀), 38.95 (CH₂, C₁₁), 202.42 (CH, C₁₂), 22.52 (CH₃, C₁₇), 33.25 (CH₃, C₁₈), 21.31 (CH₃, C₁₉), 15.88 (CH₃, C₂₀), 20.06 (CH₃, AcO-C₈), 169.66 (C, AcO-C₈).

**Enol acetates 9a-b**

A stirred mixture of 8 (1.06g, 3.60 mmol), THF (19 ml), Et₃N (1.8 ml), Ac₂O (2.3 ml) and DMAP (32 mg) was refluxed for 18 h under argon. The solvent was evaporated and the residue solved in Et₂O (25 ml) and washed with sat. NaHCO₃ solution (3 x 20 ml) and H₂O (3 x 20 ml). The organic phase was dried over anh. Na₂SO₄, 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-C₁₀), 0.85 (3 H, s, Me₃-C₄), 0.87 (3 H, s, Meα-C₄), 1.42 (3 H, s, Meβ-C₈), 2.44 (1 H, d, 12.8, 3.3, 3.3, H₇eq); 9a: 1.90 (3 H, s, AcO-C₈), 2.10 (3 H, s, AcO-C₁₂), 2.34 (1 H, d, 11.1, H₉), 5.38 (1 H, dd, 12.2, 11.1, H₁₁), 7.00 (1 H, d, 12.2, H₁₂); 9b: 1.82 (3 H, s, AcO-C₈), 2.14 (3 H, s, AcO-C₁₂), 3.08 (1 H, d, 11.0, H₉), 4.90 (1 H, dd, 11.0, 6.7, H₁₁), 7.11 (1 H, d, 6.7, H₁₂); ¹³C NMR (75 MHz): 9a: 40.76 (CH₂, C₁), 18.37 (CH₂, C₂), 41.86 (CH₂, C₃), 33.28 (C, C₄), 55.17 (CH, C₅), 20.01 (CH₂, C₆), 38.26 (CH₂, C₇), 85.38 (C, C₈), 52.68 (CH, C₉), 37.91 (C, C₁₀), 110.31 (CH, C₁₁), 137.92 (CH, C₁₂), 22.86 (CH₃, C₁₇), 33.33 (CH₃, C₁₈), 21.55 (CH₃, C₁₉), 16.05 (CH₃, C₂₀), 20.86 (CH₃, AcO-C₈), 168.08 (C, AcO-C₈), 21.32 (CH₃, AcO-C₁₂), 170.38 (C, AcO-C₁₂); 9b: 39.95 (CH₂, C₁), 18.37 (CH₂, C₂), 41.86 (CH₂, C₃), 33.28 (C, C₄), 55.01 (CH, C₅), 20.10 (CH₂, C₆), 38.08 (CH₂, C₇), 85.72 (C, C₈), 55.01 (CH, C₉), 38.42 (C, C₁₀), 110.45 (CH, C₁₁), 136.67 (CH, C₁₂), 22.86 (CH₃, C₁₇), 33.33 (CH₃, C₁₈), 21.44 (CH₃, C₁₉), 15.62 (CH₃, C₂₀), 20.86 (CH₃, AcO-C₈), 168.08 (C, AcO-C₈), 21.32 (CH₃, AcO-C₁₂), 170.38 (C, AcO-C₁₂).

**8α,12,12-triaxetoxy-13,14,15,16-tetranorlabdane (II):** 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-C₁₀), 0.81 (3 H, s, Meβ-C₄), 0.85 (3 H, s, Meα-C₄), 1.47 (3 H, s, Meβ-C₈), 1.98 (3 H, s, AcO-C₈), 2.06 (3 H, s, AcO-C₁₂), 2.09 (3 H, s, AcO-C₁₂), 2.62 (1 H, dt, 12.6, 3.3, 3.3, H₇eq), 6.97 (1 H, dd, 7.2, 5.6, H₁₂); ¹³C NMR (75 MHz): 39.56 (CH₂, C₁), 18.33 (CH₂, C₂), 41.67 (CH₂, C₃), 33.20 (C, C₄), 55.39 (CH, C₅), 19.86 (CH₂, C₆), 38.45 (CH₂, C₇), 86.76 (C, C₈), 52.60 (CH, C₉), 38.87 (C, C₁₀), 29.72 (CH₂, C₁₁), 91.63 (CH, C₁₂), 22.93 (CH₃, C₁₇), 33.29 (CH₃, C₁₈), 21.45 (CH₃, C₁₉), 15.67 (CH₃, C₂₀), 20.97 (CH₃, AcO-C₇), 170.26 (C, AcO-C₈), 20.71 (CH₃, AcO and AcO-C₁₂), 169.22 (C, AcO-C₁₂), 169.08 (C, AcO-C₁₂).

**Silyl enol ethers 10a-b**

To a stirred solution of 8 (1.176 g, 4 mmol) and TBSCI (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 silica gel 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-butylidemethylsilyloxy-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⁺, 0.5), 349 (100); ¹H NMR (300 MHz): 0.12 (6 H, s, 2Me-Si), 0.77 (3 H, s, Me-C₁₀), 0.86 (6 H, s, Me₃-C₄ and Me₃-C₄), 0.91 (9 H, s, tert-butyl-Si), 1.40 (3 H, s, Me₃-C₈), 1.88 (3 H, s, AcO-C₈), 2.23 (1 H, d, 11.1, H₉), 2.40 (1 H, dt, 12.7, 3.4, 3.4, H₇eq), 4.94 (1 H, t, 11.1, H₁₁), 6.14 (1 H, d, 11.1, H₁₂); ¹³C NMR (75 MHz): 40.62 (CH₂, C₁), 18.32 (CH₂, C₂), 41.82 (CH₂, C₃), 33.12 (C, C₄), 56.36 (CH, C₅), 19.91 (CH₂, C₆), 38.03 (CH₂, C₇), 86.00 (C, C₈), 55.15 (CH, C₉), 37.92 (C, C₁₀), 106.47 (CH, C₁₁), 142.76 (CH, C₁₂), 22.85 (CH₃, C₁₇), 33.19 (CH₃, C₁₈), 21.44 (CH₃, C₁₉), 15.97 (CH₃, C₂₀), 21.37 (CH₃, AcO-C₈), 170.12 (C, AcO-C₈), 14.00 (2 x CH₃-Si), 25.67 (3 x CH₃-C-Si).

* These assignments may be interchanged.
# These assignments may be interchanged.
8α-acetoxy-12-α-butyldimethylsiloxy-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-C4), 0.86 (6 H, s, Meα-C4 and Me-C10), 0.91 (9 H, s, Me-1", Me-2" and Me-3"), 1.41 (3 H, s, Meβ-C8), 1.81 (3 H, s, AcO-C8), 2.97 (1 H, d, 10.6, H9), 4.36 (1 H, dd, 10.6, 6.4, H11), 6.31 (1 H, d, 6.4, H12).

Oxidations of the enol derivatives 9-10

i) Ozonolysis of 9a-b and further reduction with Me₂S

A solution of 9a-b (1.0 g, 3 mmol) in MeOH (70 ml) was slowly bubbled with a O₂/O₂ mixture at -78°C for 1.5 h. Then Me₂S (10 ml) was added and the mixture stirred for 2 h. The solvent was evaporated and the residue filtered through silica gel, affording a crude that on chromatographic column yielded 9b (248 mg, 24%, 98.2% H-E), 12 (378 mg, 46%, 95.5% and 94.6% H-E), 14 (21 mg, 2%, 93.7% H-E) and 15 (135 mg, 15%, 1.1% H-E).

8α-Acetoxy-11-driman-11-one (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-C4), 0.83 (3 H, s, Meα-C4), 1.13 (3 H, s, Me-C10), 1.74 (3 H, s, Meβ-C8), 1.98 (3 H, s, AcO-C8), 1.88 (3 H, s, AcO-C12), 2.43 (1 H, d, 3.7, H9), 9.93 (1 H, d, 3.7, H11).

Methyl 8α-acetoxy-11-drimanate (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-C4), 0.85 (3 H, s, Meα-C4), 1.13 (3 H, s, Me-C10), 1.69 (3 H, s, Meβ-C8), 1.88 (3 H, s, AcO-C8), 2.51 (1 H, dt, 12.7, 3.4, H5), 2.75 (1 H, s, H9), 3.62 (3 H, s, MeO-C11); 13C NMR (75 MHz): 39.72 (CH2, C1), 18.23 (CH2, C2), 41.78 (CH2, C3), 33.06 (CH, C4), 55.11 (CH, C5), 20.13 (CH2, C6), 38.78 (CH2, C7), 85.17 (CH, C8), 63.40 (CH, C9), 38.56 (CH, C10), 172.54 (C, C11), 22.60 (CH3, C12), 33.23 (CH3, C13), 21.28 (CH3, C14), 15.26 (CH3, C15), 20.90 (CH3, AcO-C8), 169.85 (C, AcO-C8), 50.88 (CH3, MeO-C11).

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-C4), 0.86 (3 H, s, Meα-C4), 1.14 (3 H, s, Me-C10), 1.71 (3 H, s, Meβ-C8), 1.92 (3 H, s, AcO-C8), 2.56 (1 H, dt, 12.7, 3.4, H5), 2.80 (1 H, s, H9); 13C NMR (75 MHz): 29.74 (CH2, C1), 18.24 (CH2, C2), 41.74 (CH2, C3), 33.09 (CH, C4), 55.07 (CH, C5), 20.11 (CH2, C6), 38.74 (CH2, C7), 85.00 (CH, C8), 63.04 (CH, C9), 38.44 (CH, C10), 22.65 (CH3, C12), 33.25 (CH3, C13), 21.29 (CH3, C14), 15.23 (CH3, C15), 20.84 (CH3, AcO-C8), 169.97 (C, AcO-C8).

When the reaction was carried out in ethyl acetate, 9-epi-8α-acetoxy-11-driman-11-one (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 C8-Me and C10-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 Me₂S

A solution of 10a-b (500 mg, 1.3 mmol) in MeOH (20 ml) - CH₂Cl₂ (20 ml) was ozonized for 1 h, under the above reaction conditions, and the residue stirred with Me₂S (5 ml) for 2 h. 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 LiAlH₄

When the reaction was carried out in the same conditions described in i), but treating with LiAlH₄ (228 mg, 6 mmol) as reducing agent for 4 h, diols 16 (459 mg, 63%) and 17 (190 mg, 24%) were obtained.
8α,11-Drimanediol (16): colourless crystals; [α]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-C4 and Me-C10), 0.86 (3 H, s, Meα-C4), 1.32 (3 H, s, Meβ-C8), 1.86 (1 H, dt, 12.3, 3.2, 3.2, Heq), 3.90 (2 H, d, 6.8, H11, H11'); ¹³C NMR (75 MHz): 39.99 (CH2, C1), 18.58 (CH2, C2), 41.67 (CH2, C3), 33.24 (C, C4), 55.90 (CH, C5), 20.14 (CH2, C6), 44.27 (CH2, C7), 75.00 (C, C8), 60.50 (CH, C9), 37.49 (C, C10), 61.00 (CH2, C11), 24.24 (CH3, C12), 33.52 (CH3, C13), 21.60 (CH3, C14), 15.99 (CH3, C15).

13,14,15,16-tetranor-8α,12-labdane diol (17): colourless crystals; [α]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-C10 and Meβ-C4), 0.85 (3 H, s, Meα-C4). 1.16 (3 H, s, Meβ-C8), 1.87 (1 H, dt, 12.2, 3.1, Heq), 3.42 (1 H, dt, 10.3, 6.9, H12), 3.75 (1 H, dt, 10.3, 4.3, H12'); ¹³C NMR (75 MHz): 39.31 (CH2, C1), 18.38 (CH2, C2), 41.87 (CH2, C3), 33.24 (C, C4), 55.99 (CH, C5), 20.42 (CH2, C6), 44.15 (CH2, C7), 72.94 (C, C8), 59.22 (CH, C9), 38.93 (C, C10), 27.85 (CH2, C11), 63.98 (CH2, C12), 24.56 (CH3, C17), 33.28 (CH3, C18), 21.48 (CH3, C19), 15.29 (CH3, C20).

iv) Ozonolysis of 10a-b and further reduction with LiAlH4

Following the above conditions, the ozonolysis mixture was treated with LiAlH4 (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 OsO₄-NaIO₄

A mixture of 9a-b (1 g, 3 mmol), t-BuOH (20 ml), H₂O (4 ml), NaIO₄ (32 g, 15 mmol) and 0.2% OsO₄ 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 H₂O-Et₂O and extracted with Et₂O (3 x 40 ml). The organic phase was dried over anh. Na₂SO₄ 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 OsO₄-NaIO₄

A mixture of 10a-b (500 mg, 1.3 mmol), t-BuOH (10 ml), H₂O (2 ml), NaIO₄ (14 g, 6.5 mmol) and 0.2% OsO₄ 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 NaBH₄ (50 mg, 1.3 mmol) for 30 h, yielded 18 (356 mg, 95%, 1:1 H-E): colourless crystals; [α]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-C10), 0.85 (3 H, s, Meβ-C4), 0.87 (3 H, s, Meα-C4), 1.17 (3 H, s, Meβ-C8), 1.88 (1 H, dt, 12.5, 3.3, Heq), 2.03 (3 H, s, AcO-C9), 4.23 (1 H, dd, 11.8, 5.3, H11), 4.33 (1 H, dd, 11.8, 4.4, H11'); ¹³C NMR (75 MHz): 39.71 (CH2, C1), 18.36 (CH2, C2), 41.70 (CH2, C3), 33.17 (C, C4), 55.70 (CH, C5), 20.26 (CH2, C6), 43.93 (CH2, C7), 72.63 (C, C8), 59.94 (CH,
Drimenyl acetate (4)
To a stirred solution of 18 (100 mg, 0.35 mmol) in CH₂Cl₂ (36 ml), SnCl₄ (0.42 ml) was added dropwise at -19°C under argon for 5 min. The mixture was diluted with CH₂Cl₂ (30 ml) and poured into ice. The organic phase was washed with H₂O, dried over anh. Na₂SO₄ and evaporated to afford 4 (23 mg, 61%) : [α]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-C₄), 0.81 (3 H, s, Me-C₁₀), 0.89 (3 H, s, Meα-C₄), 1.65 (3 H, s, Me-C₈), 2.00 (3 H, s, Me-C₈), 3.78-4.37 (2 H, m, H₈ and H₁₁), 5.40-5.60 (1 H, m, H₇).

8α,11-Diacetoxydrimane (21)
A stirred mixture of 18 (1.5 g, 5.3 mmol), THF (20 ml), Et₃N (1.1 ml), Ac₂O (0.7 ml) and DMAP (50 mg) was refluxed under argon for 18 h. After evaporating the solvent, the residue was dissolved in Et₂O (25 ml) and washed with sat. NaHCO₃ solution (3 x 20 ml). The organic phase was dried over anh. Na₂SO₄ and the solvent evaporated to afford a crude reaction that by column chromatography yielded 21 (1.6 g, 92%, 95.5-92.8% E-E). IR (nujol): 1725, 1240, 1070 cm⁻¹; MS m/z (rel. int.): 324 (2), 264 (10), 123 (30), 109 (43); °H NMR (400 MHz): 0.79 (3 H, s, Me-C₁₀), 0.88 (3 H, s, Meβ-C₄), 0.90 (3 H, s, Meα-C₄), 1.42 (3 H, Me-C₈), 1.94 (3 H, s, AcO-C₈), 2.02 (3 H, s, AcO-C₁₁), 2.48 (1 H, dt, 12.3, 3.2, 3.2, H₇eq), 4.11 (1 H, dd, 11.7, 5.5, H₁₁), 4.27 (1 H, dd, 11.7, 3.0, H₁₁').

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 dissolved in Et₂O (50 ml) and washed with 2N HCl solution (3 x 30 ml), sat. NaHCO₃ solution (3 x 50 ml) and H₂O (50 ml). The organic phase was dried over anh. Na₂SO₄, filtered and evaporated yielding a crude reaction (321 mg, 99%) that after being chromatographed on 20% AgNO₃/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); °H NMR (80 MHz): 0.81 (3 H, s, Meβ-C₄), 0.85 (3 H, s, Meα-C₄), 0.94 (3 H, s, Me-C₁₀), 1.61 (3 H, s, Me-C₈), 2.02 (3 H, s, AcO-C₁₁), 4.56 (2 H, s, H₁₁ and H₁₁').

Albicanyl acetate (3): oil; [α]D: +22° (c, 0.37); IR (neat): 1730, 1650, 1248, 901 cm⁻¹; MS m/z (rel. int.): 264 (2), 123 (37), 43 (100); °H NMR (300 MHz): 0.78 (3 H, s, Me-C₁₀), 0.86 (3 H, s, Meβ-C₄), 0.88 (3 H, s, Meα-C₄), 2.01 (3 H, s, AcO-C₁₁), 2.41 (1 H, dd, 13.0, 4.5, 3.0, H₇eq), 4.18 (1 H, dd, 11.0, 9.0, H₁₁), 4.34 (1 H, dd, 11.0, 4.0, H₁₁'), 4.51 (1 H, d, 1.0, H₁₂), 4.85 (1 H, d, 1.0, H₁₂).

11-t-Butyldimethylsilyloxy-8α-drimanol (23)
A mixture of 16 (300 mg, 1.25 mmol), CH₂Cl₂ (6.2 ml), Et₃N (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 CH₂Cl₂ (25 ml) and washed with H₂O (3 x 25 ml). The organic phase was washed with 2N HCl solution (3 x 30 ml), sat. NaHCO₃ (3 x 50 ml) and H₂O (50 ml), and dried over anh. Na₂SO₄. 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); H NMR (80 MHz): 0.03 (6 H, s, Me2 and Me2), 0.68 (3 H, s, Me-C10), 0.78 (15 H, s, Mea and Meb-C4, Me"), 1.20 (3 H, s, Me-C8), 3.63-4.13 (2 H, m, H11 and H11').

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

The reaction of a mixture of 23 (440 mg, 1.2 mmol), THF (4.7 ml), Et3N (0.26 ml), Ac2O (0.16 ml) and DMAP (12 mg), under the same conditions as for 18, yielded 24 (413 mg, 87%): H NMR (80 MHz): 0.03 (6 H, s, Me1 and Me2), 0.78 (3 H, s, Me-C10), 0.85 (12 H, s, Meb-C4, Me", Me", Me3"), 0.88 (3 H, s, Mea-C4), 1.39 (3 H, s, Me-C8), 1.93 (3 H, s, AcO-C8), 3.55-3.95 (2 H, m, H11 and H11').

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 H NMR (80 MHz) spectrum revealed.

11-Acetoxy-8(12)-drimen-7α-ol (27)

To a stirred mixture of ScO2 (222 mg, 2 mmol), CH2Cl2 (3 ml) and 3M isooctane t-BuOOH solution (3 ml, 9 mmol), a solution of 3 (1g, 3.8 mmol) in CH2Cl2 (30 ml) was slowly added under argon. After stirring for 4 h at room temperature, the mixture was diluted with CH2Cl2 (30 ml) and washed with H2O (3 x 25 ml). The organic phase was dried over anh. Na2SO4 and evaporated to yield 27 (955 mg, 88%): colourless crystals; [α]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); H NMR (300 MHz): 0.71 (3 H, s, Me-C10), 0.78 (3 H, s, Meb-C4), 0.86 (3 H, s, Mea-C4), 1.99 (3 H, s, AcO-C11), 2.54-2.56 (1 H, m, H9), 4.16 (1 H, dd, 11.3, 8.7, H11), 4.30 (1 H, dd, 11.3, 4.3, H11'), 4.36 (1 H, t, 2.7, H7eq), 4.63 (1 H, s, H12), 5.04 (1 H, s, H12'); C NMR (75 MHz): 38.85 (CH2, C1), 19.20 (CH2, C2), 41.95 (CH2, C3), 33.06 (C, C4), 47.20 (CH, C5), 30.61 (CH2, C6), 73.74 (CH, C7), 148.21 (C, C8), 49.40 (CH, C9), 39.22 (C, C10), 61.41 (CH2, C11), 110.45 (CH2, C12), 33.39 (CH3, C13), 20.36 (CH3, C14), 14.23 (CH3, C15), 20.85 (CH3, AcO-C11), 171.39 (C, AcO-C11).

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. Na2SO4 and evaporated to afford 28 (1.1 g, 74%): H NMR (80 MHz): 0.65 (3 H, s, Me-C10), 0.70 (3 H, s, Me-C4), 0.76 (3 H, s, Meb-C4), 1.93 (3 H, s, AcO-C11), 2.88 (3 H, s, MsO-C7), 3.90-4.40 (2 H, m, H11, H11'), 4.88 (1 H, s, H12), 5.10-5.36 (2 H, m, H12' H7eq).

Solvolysis of 28

To a stirred solution of 28 (950 mg, 2.6 mmol) in acetone (27 ml) and H2O (20 ml), NaAcO (506 mg) was added and the mixture refluxed for 2 h. After evaporating the acetone it was extracted with Et2O (3 x 20 ml). Organic layers were dried over Na2SO4 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); H NMR (300 MHz): 0.82 (3 H, s, Me-C10), 0.86 (3 H, s, Meb-C4),
0.89 (3 H, s, Meα-C4), 2.05 (3 H, s, AcO-C11), 3.97 (1 H, d, 11.5, H12), 4.09-4.20 (2 H, m, H11, H11'), 4.37 (1 H, dd, 11.5, 3.3, H12'), 5.84 (1 H, dt, 12.0, 12.0, 3.3, H7); 13C NMR (75 MHz): 39.40 (CH2-C1), 18.57 (CH2-C2), 41.85 (CH2-C3), 32.79 (C-C4), 49.39 (CH-C5), 23.28 (CH2-C6), 126.40 (CH, C7), 136.02 (C-C8), 50.47 (CH, C9), 35.67 (C-C10), 63.10 (CH2-C11), 65.93 (CH2-C12), 33.06 (CH3-C13), 21.76 (CH3-C14), 14.30 (CH3-C15), 20.99 (CH3, AcO-C11), 170.71 (C, AcO-C11).

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 H2O-Et2O and extracted with Et2O (3 x 30 ml). Combined organic phases were dried over anh. Na2SO4 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); 1H NMR (400 MHz): 0.75 (3 H, s, Me-C10), 0.87 (3 H, s, Meβ-C4), 0.89 (3 H, s, Meα-C4), 3.65 (1 H, dd, 11.0, 8.0, H11), 3.89 (1 H, dd, 11.0, 1.5, H11'), 3.95 (1 H, d, 12.0, H12), 4.32 (1 H, d, 12.0, H12'), 5.76 (1 H, t, 2.6, H7); 13C NMR (100 MHz): 39.33 (CH2-C1), 18.69 (CH2-C2), 41.77 (CH2-C3), 32.99 (C-C4), 49.42 (CH, C5), 23.59 (CH2-C6), 127.23 (CH, C7), 136.92 (C-C8), 54.39 (CH, C9), 35.61 (C-C10), 61.26 (CH2-C11), 67.26 (CH2-C12), 33.21 (CH3-C13), 21.93 (CH3-C14), 14.52 (CH3-C15).

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); 1H NMR (300 MHz): 0.62 (3 H, s, Me-C10), 0.73 (3 H, s, Meβ-C4), 0.81 (3 H, s, Meα-C4), 2.38 (1 H, d, 3.5, H9), 3.65 (1 H, t, 10.2, H11), 3.80 (1 H, dd, 10.2, 3.5, H11'), 4.30 (1 H, t, 2.6, H7eq), 4.55 (1 H, s, H12), 5.06 (1 H, s, H12); 13C NMR (75 MHz): 38.89 (CH2-C1), 19.29 (CH2-C2), 42.04 (CH2-C3), 33.06 (C-C4), 47.44 (CH, C5), 30.38 (CH2-C6), 73.63 (CH, C7), 148.44 (C-C8), 53.22 (CH, C9), 39.16 (C-C10), 58.33 (CH2-C11), 109.92 (CH2-C12), 33.39 (CH3-C13), 21.60 (CH3-C14), 14.43 (CH3-C15).

Polygodial (2)

To a stirred 2M solution of (CICO)2 in CH2Cl2 (0.23 ml, 0.45 mmol) a solution of DMSO (0.07 ml, 0.91 mmol) in CH2Cl2 (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 CH2Cl2 (0.5 ml) was added and the mixture allowed to stir for 15 min. Then, Et3N (0.14 ml, 1.0 mmol) was added and the mixture stirred at room temperature for 5 min. It was diluted with CH2Cl2 (10 ml) and washed with H2O (3 x 10 ml). The organic phase was dried over anh. Na2SO4 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); 1H NMR (300 MHz): 0.93 (3 H, s, Meβ-C4), 0.96 (3 H, s, Meα-C4), 0.97 (3 H, s, Me-C10), 7.14 (1 H, dd, 6.0, 3.0, 3.0, H7), 9.47 (1 H, s, H12), 9.54 (1 H, d, 5.0, H11); 13C NMR (75 MHz): 39.52 (CH2-C1), 17.98 (CH2-C2), 41.68 (CH2-C3), 33.09 (C-C4), 48.92 (CH, C5), 25.18 (CH2-C6), 154.21 (CH, C7), 139.25 (C-C8), 60.25 (CH, C9), 36.82 (C-C10), 201.85 (CH, C11), 193.16 (CH, C12), 33.09 (CH3-C13), 21.93 (CH3-C14), 15.24 (CH3-C15).
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-C₄), 0.89 (3 H, s, Meα-C₄), 0.92 (3 H, s, Me-C₁₀), 5.93 (1 H, s, H₁₂), 6.31 (1 H, s, H₁₂), 9.63 (1 H, s, 5.0, H₁₁).

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-C₁₀), 0.80 (3 H, s, Meβ-C₄), 0.88 (3 H, s, Meα-C₄), 2.38 (2 H, d, 2.0, H₁₁ and H₁₁'), 4.36 (1 H, s, H₁₇), 4.78 (1 H, s, H₁₇), 9.58 (1 H, t, 3.0, H₁₂).

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), NaBH₄ (194 mg, 5.1 mmol) was added, and the mixture allowed to stir at room temperature for 30 min. After evaporating, the residue was dissolved in Et₂O (50 ml) and washed with 2N HCl (3 x 50 ml), sat. NaHCO₃ solution (3 x 50 ml) and H₂O (50 ml). The organic layer was dried over anhyd. Na₂SO₄ and evaporated to yield the corresponding alcohol (1.1 g, 93%, 6.4 and 1:1 H-E), which after treating with Ac₂O (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-C₁₀), 0.81 (3 H, s, Meβ-C₄), 0.88 (3 H, s, Meα-C₄), 2.03 (3 H, s, AcO-C₁₂), 3.86-4.3 (1 H, m, H₁₂), 4.16-4.22 (1 H, m, H₁₂'), 4.53 (1 H, s, H₁₇), 4.83 (1 H, s, H₁₇); ¹³C NMR (100 MHz): 39.10 (CH₂, C₁), 19.39 (CH₂, C₂), 42.17 (CH₂, C₃), 33.62 (C, C₄), 55.55 (CH, C₅), 24.36 (CH₂, C₆), 38.17 (CH₂, C₇), 148.09 (C, C₈), 53.11 (CH, C₉), 39.46 (C, C₁₀), 23.19 (CH₂, C₁₁), 64.42 (CH₂, C₁₂), 106.65 (CH₂, C₁₇), 33.62 (CH₃, C₁₈), 21.75 (CH₃, C₁₉), 14.41 (CH₃, C₂₀), 21.07 (CH₃, AcO-C₇), 171.08 (C, AcO-C₇).

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-C₁₀), 0.80 (3 H, s, Meβ-C₄), 0.89 (3 H, s, Meα-C₄), 2.04 (3 H, s, AcO-C₁₂), 3.97 (1 H, dt, 10.7, 7.7, 7.7, H₁₂), 4.15 (1 H, dq, 10.7, 8.0, 4.6, H₁₂), 4.33 (1 H, t, 2.9, H₇αq), 4.69 (1 H, s, H₁₇), 5.01 (1 H, s, H₁₇); ¹³C NMR (100 MHz): 39.50 (CH₂, C₁), 19.27 (CH₂, C₂), 41.99 (CH₂, C₃), 33.04 (C, C₄), 47.50 (CH, C₅), 30.74 (CH₂, C₆), 73.75 (CH, C₇), 149.35 (C, C₈), 47.08 (CH, C₉), 38.69 (C, C₁₀), 22.77 (CH₂, C₁₁), 63.78 (CH₂, C₁₂), 109.56 (CH₂, C₁₇), 33.19 (CH₃, C₁₈), 21.45 (CH₃, C₁₉), 13.34 (CH₃, C₂₀), 21.02 (CH₃, AcO-C₁₂), 171.29 (C, AcO-C₇).

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-C10), 0.78 (3 H, s, Meβ-C4), 0.86 (3 H, s, Meα-C4), 2.01 (3 H, s, AcO-C12), 2.93 (3 H, s, MS-CN-C7), 3.35-4.30 (2 H, m, H12 and H12'), 5.00 (1 H, s, H17), 5.20-5.38 (2 H, m, H7eq and H17').

Solvolysis of 34

To a stirred solution of 34 (1.2 g, 3.2 mmol) in acetone (60 ml) and H2O (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-C10), 0.83 (3 H, s, Meβ-C4), 0.85 (3 H, s, Meα-C4), 3.57 (1 H, dd, 9.6, 5.2 H2), 3.74 (1 H, q, 9.6, H12), 3.81 (1 H, d, 12.1, H17), 4.26 (1 H, d, 12.1, H12'), 5.69 (1 H, t, 2.7, H7); ¹³C NMR (75 MHz): 39.01 (CH2, C1), 18.61 (CH2, C2), 42.12 (CH2, C3), 32.85 (C, C4), 49.83* (CH, C5), 23.68 (CH2, C6), 126.38 (CH, C7), 138.44 (C, C8), 48.55* (CH, C9), 36.69 (C, C10), 28.04 (CH2, C11), 64.05 (CH2, C12), 66.10 (CH2, C13), 32.98 (CH3, C18), 21.71 (CH3, C19), 13.48 (CH3, C20).

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-C10), 0.78 (3 H, s, Meβ-C4), 0.86 (3 H, s, Meα-C4), 1.61 (1 H, td, 13.2, 13.2, 2.8, H6ax), 1.82 (1 H, dr, 13.2, 2.8, 2.8, H6eq), 3.56 (1 H, td, 10.7, 10.7, 4.9 H12), 3.63 (1 H, ddd, 10.7, 6.3, 4.1, H12'), 4.34 (1 H, t, 2.8, H7eq), 4.60 (1 H, t, 1.5, H17), 5.03 (1 H, s, H17'); ¹³C NMR (75 MHz): 38.77 (CH2, C1), 19.32 (CH2, C2), 42.08 (CH2, C3), 33.06 (C, C4), 47.66 (CH, C5), 26.29 (CH2, C6), 73.99 (CH, C7), 149.05 (C, C8), 46.31 (CH, C9), 39.50 (C, C10), 31.31 (CH2, C11), 60.81 (CH2, C12), 109.75 (CH2, C13), 33.26 (CH3, C18), 21.51 (CH3, C19), 14.46 (CH3, C20).

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-C10), 0.87 (3 H, s, Meβ-C4), 0.89 (3 H, s, Meα-C4), 2.30 (1 H, dd, 17.5, 2.5 H11), 2.46 (1 H, ddd, 17.8, 9.1, 2.3, H11'), 6.84 (1 H, quintuplet, 5.0, 2.5, 2.5, H7), 9.27 (1 H, s, H17), 9.81 (1 H, dd, 2.3, 0.7, H12); ¹³C NMR (100 MHz): 38.19 (CH2, C1), 18.27 (CH2, C2), 41.69 (CH2, C3), 32.80 (C, C4), 49.03 (CH, C5), 25.25 (CH2, C6), 154.45 (CH, C7), 141.61 (C, C8), 43.06 (CH, C9), 35.46 (C, C10), 40.27 (CH2, C11), 200.88 (CH, C12), 194.56 (CH, C17), 32.80 (CH3, C18), 21.57 (CH3, C19), 14.08 (CH3, C20).

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); \textsuperscript{1}H NMR (400 MHz): 0.82 (3 H, s, Me-C\textsubscript{10}), 0.88 (3 H, s, Me\textsubscript{\beta}-C\textsubscript{4}), 0.89 (3 H, s, Me\textsubscript{\alpha}-C\textsubscript{4}), 2.31 (1 H, dd, 17.5, 14.1, 4.9 H\textsubscript{11}), 2.51 (1 H, ddd, 17.5, 9.4, 2.7, H\textsubscript{12}), 4.34 (1 H, t, 2.8, H\textsubscript{eq}), 4.49 (1 H, d, 2.5, H\textsubscript{17}), 5.91 (1 H, d, 2.5, H\textsubscript{17}), 9.74 (1 H, d, 2.7, H\textsubscript{12}); \textsuperscript{13}C NMR (100 MHz): 38.23 (CH\textsubscript{2}, C\textsubscript{1}), 18.77 (CH\textsubscript{2}, C\textsubscript{2}), 41.52 (CH\textsubscript{2}, C\textsubscript{3}), 33.51 (C, C\textsubscript{4}), 51.29 (CH, C\textsubscript{5}), 40.51 (CH\textsubscript{2}, C\textsubscript{6}), 201.90 (C, C\textsubscript{7}), 147.33 (C, C\textsubscript{8}), 49.21 (CH, C\textsubscript{9}), 40.98 (CH\textsubscript{2}, C\textsubscript{11}), 201.52 (CH, C\textsubscript{12}), 120.28 (CH\textsubscript{2}, C\textsubscript{17}), 33.52 (CH\textsubscript{3}, C\textsubscript{18}), 20.85 (CH\textsubscript{3}, C\textsubscript{19}), 14.21 (CH\textsubscript{3}, C\textsubscript{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 10 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.\textsuperscript{17} IC\textsubscript{50} (µg/ml) are shown in the table.

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<th>Compound</th>
<th>P-388</th>
<th>A-549</th>
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<th>MEL-28</th>
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<td>2.5</td>
</tr>
</tbody>
</table>

**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 typhimurium* 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\textsuperscript{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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