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SYNTHESIS OF BIOLOGICALLY ACTIVE DRIMANES FROM (-)-SCLAREOL

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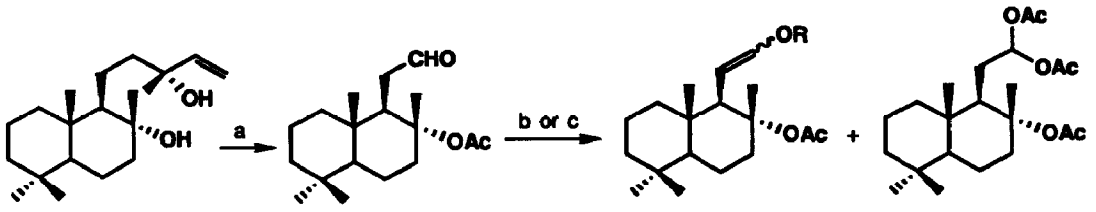
Key Words: Sclareol, drimane, osmium tetroxide, ozonolysis.

Abstract: *The enantiospecific synthesis of drimenyl acetate (8), a key intermediate in the synthesis of biologically active drimanes, and albicanyl acetate (14), potent fish antifeedant, from sclareol (1), are described. Also a short and efficient synthesis of polygodial (22), from albicanyl acetate (14), is shown.*

A number of drimane sesquiterpenes showing interesting biological activity occur in nature.[1] Because of this, different procedures for their preparation have been described.[2] In this paper the synthesis of drimenyl acetate (**8**) and albicanyl acetate (**14**) from sclareol are presented. Albicanyl acetate is a potent fish antifeedant [3] and has been used by the authors in the synthesis of polygodial (**22**).[1]

The oxidation of sclareol (**1**) with osmium tetroxide-sodium periodate leads to the acetoxyaldehyde **2** in 73% yield, which besides being an intermediate in the synthesis of Ambrox®,[4] can be transformed into drimenyl acetate (**8**) in three simple steps in high overall yield. **8** has been used in the preparation of polygodial (**22**),[5] warbuganal (**23**)[6] and ugandensidial (**24**).[7] The treatment of **2** with *tert*-butyldimethylsilyl chloride in dichloromethane, gives quantitative yields of the corresponding silyl enol ethers (**3a** and **3b**),[8] which after ozonolysis and subsequent reduction with sodium borohydride, lead to the acetoxyalcohol **6** in 95% yield (schemes 1 and 2).

Scheme 1

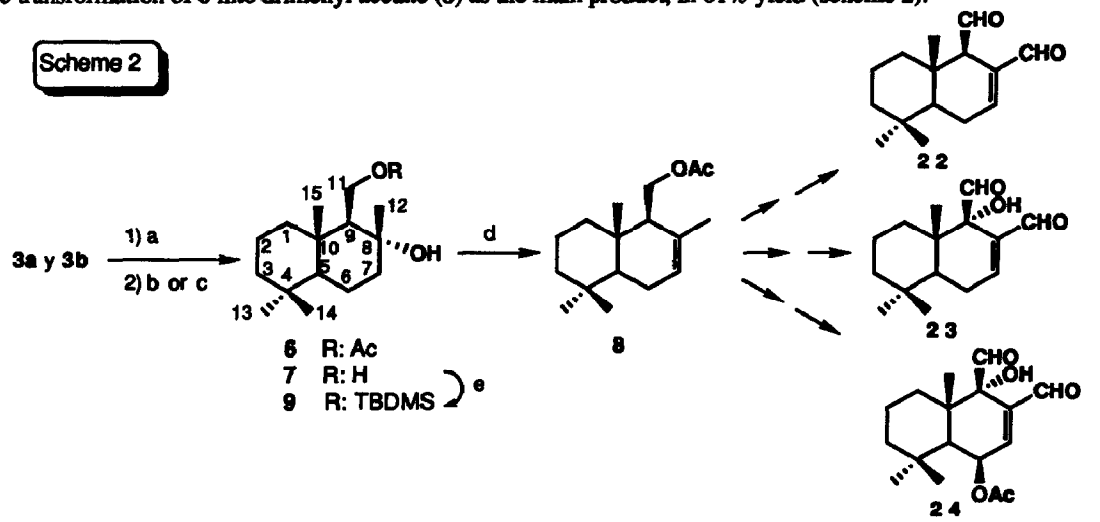


1 **2** **3a** R: TBDMS (E) **3b** R: TBDMS (Z) **4a** R: Ac (E) **4b** R: Ac (Z) **5**

a) $OsO_4/NaIO_4$, Pr^iOH, 45°C, 6 h, 73%; b)Cl-TBDMS, HNa, THF, -78°C, 4 h, 99%; c) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18 h, 89%.

The use of the silyl enol ethers **3a** and **3b** improves considerably the yield of this transformation in comparison with the use of the corresponding enol acetates (**4a** and **4b**),[9] with which the yield is 64%. This is because the triacetate **5**[10] is obtained in the acetylation step, and the ozonolysis produces the stereospecific degradation of the enol acetate *E* (**4a**), while the isomer *Z* (**4b**) remains unaltered. The dehydration of the acetoxyalcohol **6** with $POCl_3$ in Py, and MsCl, Et_3N, DMAP in dichloromethane is not regioselective and gives equimolar mixtures of the isomers Δ^7, Δ^8 y $\Delta^{8,12}$. However the use of $SnCl_4$ in dichloromethane allows the transformation of **6** into drimenyl acetate (**8**) as the main product, in 61% yield (scheme 2).

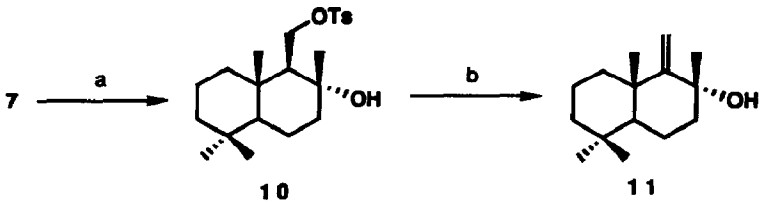
Scheme 2



a) O_3, $MeOH/CH_2Cl_2$, -78°C, 1 h; b) $NaBH_4$, MeOH, rt, 30 min, 95%; c) $LiAlH_4$,MeOH, rt, 40 min, 95%; d) Cl_4Sn, CH_2Cl_2, -19°C, dropwise 30 min, 61%; e) Cl-TBDMS, 4-DMAP, Et_3N, CH_2Cl_2, rt, 2 h, 99%.

The silyl derivatives **3a** and **3b** can be employed as precursors for other drimanes of interest, such as (+)-drim-9(11)-en-8-ol (**11**), isolated from the fungus *Aspergillus oriyzae*[11] which is used in the manufacture of certain Japanese drinks such as "sake", "tamari" and "shoyu". The ozonolysis of mixture **3a** and **3b**, and subsequent reduction with lithium aluminium hydride gives 95% of the diol **7**, as shown in scheme 2, whose transformation to **11** has been previously described[12] (scheme 3).

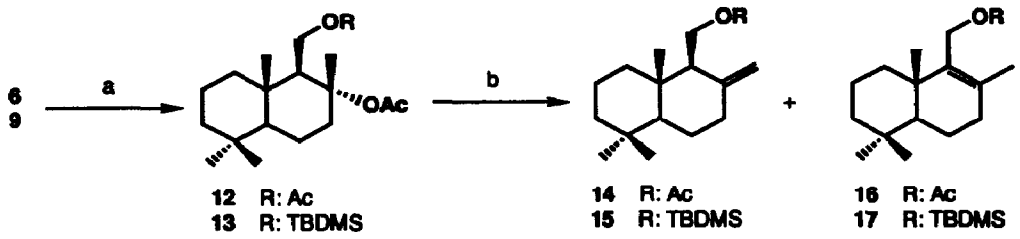
Scheme 3



a) TsCl, Py, 4-DMAP; b) NaI, Zn.

The acetylation of **6** gives the diacetate **12** in 92% yield, which converts almost quantitatively into an equimolecular mixture of **14** and **16** by heating with collidine. The elimination of acetate can be regioselective to $\Delta^{8,12}$ using the silyl derivative **13** instead of the corresponding diacetate **12**, in which case the ratio of **15**:**17** is 2:1 (scheme 4).

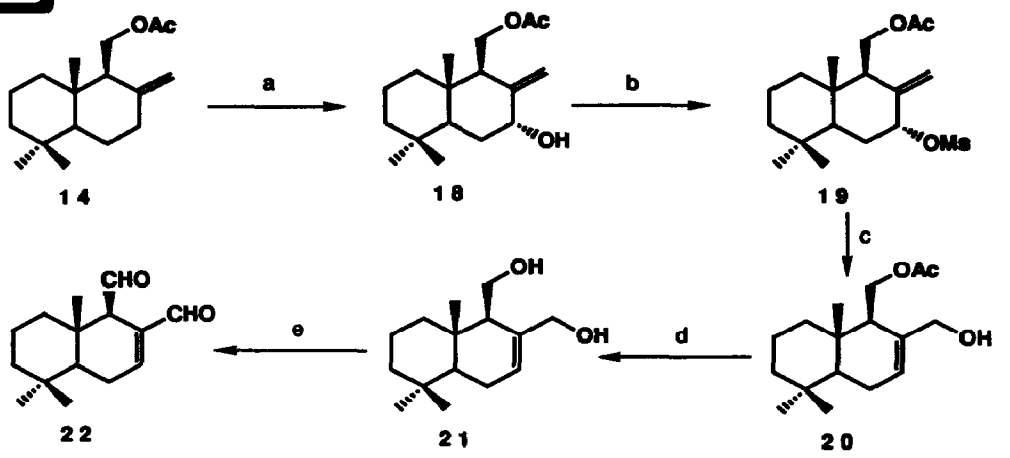
Scheme 4



a) Ac_2O, Et_3N, 4-DMAP, THF, reflux, 18 h, 92%; b) collidine, reflux, 8 h, 99%.

The oxidation of albicanyl acetate (**14**) with SeO_2 and Bu^tOOH in dichloromethane, allows the regio and diastereoselective hydroxylation at the 7α position, yielding **18** in 85%. By the treatment of **18** with MsCl in Py and further solvolysis of the mesylate **19**, a 67% of **20** is obtained, which saponifies to give the diol **21**. This is converted in polygodial (**22**) (92%) by oxidation with Swern's reagent (scheme 5).

Scheme 5



a) SeO_2, Bu^tOOH, CH_2Cl_2, rt, 4 h, 85%; b) MsCl, Py, rt, 30 min, 98%; c) NaOAc, H_2O, acetone, reflux, 2 h, 69%; d) KOH/MeOH 2N, 2 h, 95%; e) $(ClCO)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C, 15 min, 92%.

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8- *8α-acetoxy-12-t-buthyldimethylsilyloxy-13,14,15,16-tetranorlabd-11E/Z-ene* (**3a**, **3b**) (4:1): ^{1}H-NMR (80 MHz): signals asignable to **3b** 0.11 (6 H), 0.73 (3 H), 0.86 (6 H), 0.91 (9 H), 1.41 (3 H), 1.81 (3 H), 2.97 (1 H, *d*, 10.6), 4.36 (1 H, *dd*, 10.6, 6.4), 6.31(1 H, *d*, 6.4,).

The recrystallisation in methanol of the mixture of silyl enol ethers allows purification to the isomer **3a**: ^{1}H-NMR (300 MHz): 0.12 (6 H), 0.77 (3 H), 0.86 (6 H), 0.91 (9 H), 1.40 (3 H), 1.88 (3 H), 2.23 (1 H, *d*, 11.1), 2.40 (1 H, *dt*, 12.7, 3.4, 3.4), 4.94 (1 H, *t*, 11.1), 6.14 (1 H, *d*, 11.1); ^{13}C-NMR (75 MHz): 38.03 (C_1), 18.32 (C_2), 41.82 (C_3), 33.12 (C_4), 56.36 (C_5), 19.91 (C_6), 40.62 (C_7), 86.00 (C_8), 55.15 (C_9), 37.92 (C_{10}), 106.47 (C_{11}), 142.76 (C_{12}), 22.85 (C_{17}), 33.19 (C_{18}), 21.44 (C_{19}), 15.97 (C_{20}), 21.37 (AcO-C_8), 170,12 (AcO-C_8), 14.01 (C_1'y C_2'), 25.67 (C_1", C_2" y C_3").

9- *8α,12-diacetoxy-13,14,15,16-tetranorlabd-11(E/Z)-ene* (**4a**, **4b**) (3:1): IR (film): 1757, 1725, 1668, 1253, 940, 886, 803 cm^{-1}; ^{1}H-NMR (300 MHz): signals asignable to **4a** and **4b** 0.78 (3 H), 0.85 (3 H), 0.87 (3 H), 1.42 (3 H), 2.44 (1 H, *dt*, 12.8, 3.3, 3.3), signals asignable to **4a** 1.90 (3 H), 2.10 (3 H), 2.34 (1 H, *d*, 11.1), 5.38 (1 H, *dd*, 12.2, 11.1), 7.00 (1 H, *d*, 12.2), signals asignable to **4b** 1.82 (3 H), 2.14 (3 H), 3.08 (1 H, *d*, 11.0), 4.90 (1 H, *dd*, 11.0, 6.7), 7.11 (1 H, *d*, 6.7); ^{13}C-NMR (75 MHz): isomer **4a** 40.76 (C_1), 18.37 (C_2), 41.86 (C_3), 33.28 (C_4), 55.17 (C_5), 20.01 (C_6), 38.26 (C_7), 85.38 (C_8), 52.68 (C_9), 37.91 (C_{10}), 110.31 (C_{11}), 137.92 (C_{12}), 22.86 (C_{17}), 33.33 (C_{18}), 21.55 (C_{19}), 16.05 (C_{20}), 168,12 (AcO-C_8), 170,38 (AcO-C_{12}), isomer **4b** 39.95 (C_1), 18.37 (C_2), 41.86 (C_3), 33.28 (C_4), 56.69 (C_5), 20.10 (C_6), 38.08 (C_7), 85.72 (C_8), 52.01 (C_9), 38.42 (C_{10}), 110.45 (C_{11}), 136.67 (C_{12}), 22.86 (C_{17}), 33.33 (C_{18}), 21.44 (C_{19}), 15.62 (C_{20}), 168,12 (AcO-C_8), 178,38 (AcO-C_{12}).

10- *8α,12,12-triacetoxy-13,14,15,16-tetranorlabdane* (**5**) : ^{1}H-NMR (300 MHz): 0.77 (3 H), 0.81 (3 H), 0.85 (3 H), 1.47 (3 H), 1.98 (3 H), 2.06 (3 H), 2.09 (3 H), 2.62 (1 H, *dt*, 12.6, 3.3, 3.3,), 6.97 (1 H, *dd*, 7.2, 5.6,); ^{13}C-NMR (75 MHz): 39.56 (C_1), 18.33 (C_2), 41.67 (C_3), 33.20 (C_4), 56.39 (C_5), 19.86 (C_6), 38.45 (C_7), 86.76 (C_8), 52.60 (C_9), 38.87 (C_{10}), 29.72 (C_{11}), 91.63 (C_{12}), 21.93 (C_{17}), 33.29 (C_{18}), 21.45 (C_{19}), 15.67 (C_{20}), 20.97* (AcO-C_8), 170,26 (AcO-C_8), 20.71* (AcO y AcO'-C_{12}), 169,22# (AcO-C_{12}), 169,80# (AcO'-C_{12}).

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* These assignments may be interchanged.
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