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Degradation of triterpenic compounds from olive-pressing residues. Synthesis of *trans*-decalin type chiral synthons

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Abstract—Three *seco*-C-ring triterpenic compounds were obtained from oleanolic or maslinic acids from olive-mill solid wastes by photochemical and chemical reactions. From these oleantriene compounds, different remarkable sesquiterpene and *nor*-sesquiterpene fragments such as 3β-hydroxydrimenol (**13**) and epoxydecalone (**16**) were achieved through oxidative cleavages of the double bonds in the opened C-ring.

1. Introduction

Oleanenes form a wide group of triterpenes, characterized by a 4,4,10-trimethyl substituted *trans*-decalin system with the hydrogen on C-9 in an α disposition. Pentacyclic triterpenes are readily available from different resources[1] in nature and could be useful as starting material for the synthesis of other remarkable decalins.[2] Oleanolic and maslinic acids are olean-12-ene compounds present in considerable proportion (0.4 and 0.8% in weight, respectively) in solid residues from olive-oil production.[3] Our research group has previously established a relatively problem-free extraction process that renders large amounts[4] of both acid products, enabling the exploitation of the above-mentioned triterpenic compounds as suitable starting material for the semisynthesis of other biologically or chemically useful compounds.

In addition, isomerization reactions of optically excited molecules have a notable interest in photochemistry. Photochemical interconversions of provitamin D_2, lumisterol, previtamin D_2 and tachysterol have been known for many years,[5] while photochemical and thermal transformations of some pentacyclic triterpenoids, such as methyl dehydroursolate, have also been studied by Barton et al.[6] A triene, resembling preergocalciferol (previtamin D_2), was obtained and thermally isomerized to another exocyclic triene, similar in structure to ergocalciferol (vitamin D_2). In addition, currently synthetic efforts towards drimane sesquiterpenes or related compounds are very important within the scientific community due to their significant biological activities.[7] In this sense, to obtain suitable chiral synthons is highly advantageous for the synthesis of these products. Currently, the aforementioned semisynthetic processes are based on the degradation of rarer and more expensive high terpenes such as sclareol, some abietic acids, and glycyrrhetinic acid.[8]

In the present paper, we describe the process of obtaining three different trienes **7** or **8**, **9** and **10** with similar structures to previtamin D_2, tachysterol and vitamin D_2, respectively, from oleanolic or maslinic acids isolated from olive-mill solid wastes. This semisynthetic process was carried out by means of an efficient reaction sequence including photochemical and chemical-isomerization reactions. In addition, we present the semisynthesis of drimane-related fragments, such as 3β-hydroxydrimenol (**13**)[9] and epoxydecalone (**16**), through different oxidative cleavages of the double bonds situated in the opened C ring of above-mentioned oleantrienes.

2. Results and discussion

Oleanolic acid (3β-hydroxy-12-oleanen-28-oic acid) (**1**) and maslinic acid (2α,3β-dihydroxy-12-oleanen-28-oic acid) (**2**) were isolated from olive-pressing residues following an extraction process established by us.[4] Both acids were esterificated with an ethereal solution of diazomethane to provide the corresponding methyl ester compounds **3** and **4**. Acetylation of these esters with Ac_2O/Py at reflux and subsequent treatment with

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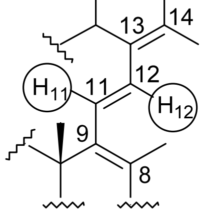
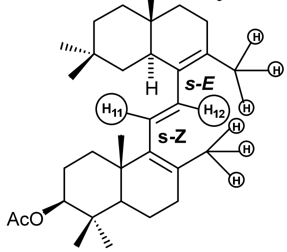
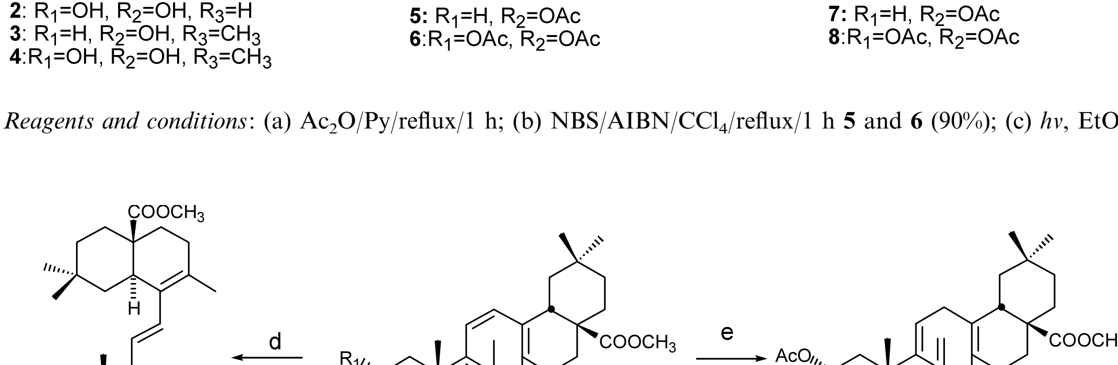
NBS/AIBN in CCl$_4$ gave acetylated dienes **5**[10] and **6** in an excellent yield (90%) (Scheme 1). It was noticeable that a bromination/dehydrobromination between C-9 and C-11 had occurred in this treatment, giving rise to a conjugated double bond in the C ring of the triterpenic compounds. Irradiation[11] of the homodienes **5** or **6**, rendered the trienes **7**[12] or **8** (95%), respectively (Scheme 1). This C-ring opening took place by a conrotatory photochemical electrocyclic reaction similar to those that happened between ergosterol and previtamin D.[5,13] Thus, *trans*-disposition between Me on C-8 (C-26) and Me on C-14 (C-27) allowed an antarafacial reaction of the 6π electron system, which permitted the cleavage of C-8/C-14 bond and thus rendered trienes **7** and **8**. These trienes (**7** and **8**) were chromatographically separated, purified and characterized. Products **7** and **8** were independently treated with different oxidative reagents (ozone, OsO$_4$/NaIO$_4$, Cl$_3$Ru/NaIO$_4$), and it was verified that the central double bond (C-11/C-12 double bond) was not affected. However, a mixture of various epoxy or methylketone compounds were isolated as result of oxidation of the other double bonds. Consequently, we isomerized compounds **7** and **8** to trienes **9**[14] and **10**, respectively (Scheme 2). This behavior had no synthetic value and hence, to attempt to cut the molecule, the *cis*-triene **7** was isomerized to the *trans*-triene **9** by treatment with I$_2$ in hexane in acceptable yield (60%) (Scheme 2). This isomerization was noted mainly by comparison of ^{1}H and ^{13}C NMR data (see References). Thus, compounds **7** and **8** were *cis*-trienes and had moderately high coupling constants (12.9 and 12.6 Hz, respectively). However, compound **9**, a *trans*-triene, presented similar shifts for H-11 and H-12, but had the highest coupling constant (16.2 Hz). Furthermore, compound **9** had lower ^{13}C NMR shifts for C-12 and C-11 (123.0 and 132.4 ppm, respectively) than did compounds **7** and **8** (δ around 127 and 134 ppm). However, when the *trans* disposition of the central double bond was fixed between C$_{11}$ and C$_{12}$, there were four possible stereochemical dispositions double bond systems between C$_9$ and C$_{11}$ or C$_{12}$ and C$_{13}$. By NOE experiments, we confirmed that one of the ethylenic protons was located between the two allylic methyls and therefore only two of these dispositions were possible. Finally, using HMBC and HMQC experiments we could differentiate between both possibilities and so we deduced that triene **9** had a S$_{9,11}$ *Z* S$_{12,13}$ *E* disposition (see the enclosed figures).





On the other hand, when *cis*-triene was isolated and irradiated again according to the above-described conditions[11] during an extra time of 30 min, exocyclic

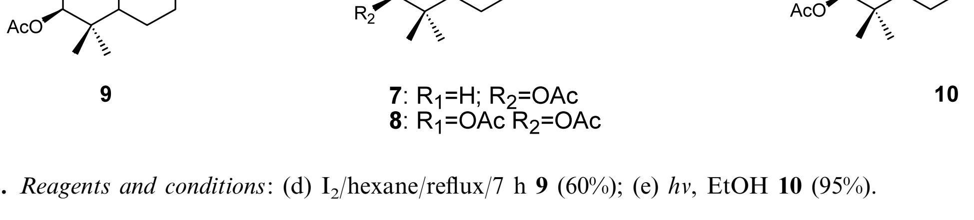


1: R$_1$=H, R$_2$=OH, R$_3$=H
2: R$_1$=OH, R$_2$=OH, R$_3$=H
3: R$_1$=H, R$_2$=OH, R$_3$=CH$_3$
4:R$_1$=OH, R$_2$=OH, R$_3$=CH$_3$

5: R$_1$=H, R$_2$=OAc
6:R$_1$=OAc, R$_2$=OAc

7: R$_1$=H, R$_2$=OAc
8:R$_1$=OAc, R$_2$=OAc

Scheme 1. *Reagents and conditions*: (a) Ac$_2$O/Py/reflux/1 h; (b) NBS/AIBN/CCl$_4$/reflux/1 h **5** and **6** (90%); (c) *hν*, EtOH **7** and **8** (95%).

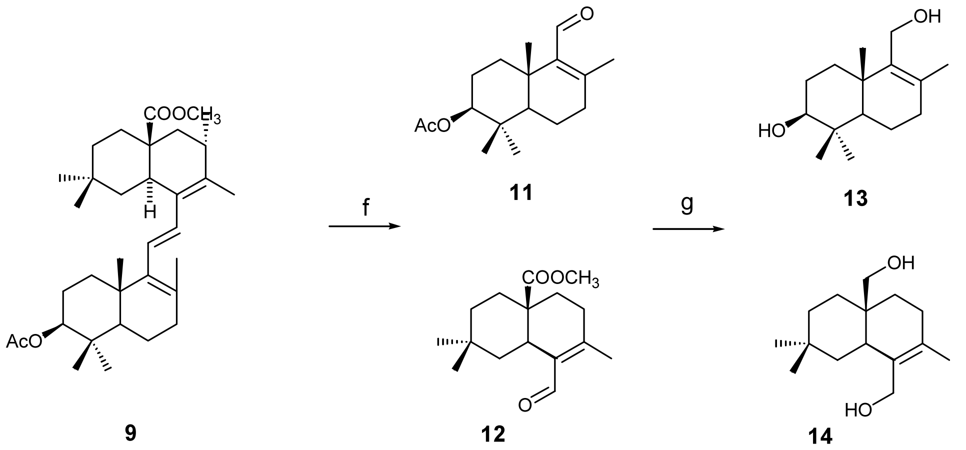


9

7: R$_1$=H; R$_2$=OAc
8: R$_1$=OAc R$_2$=OAc

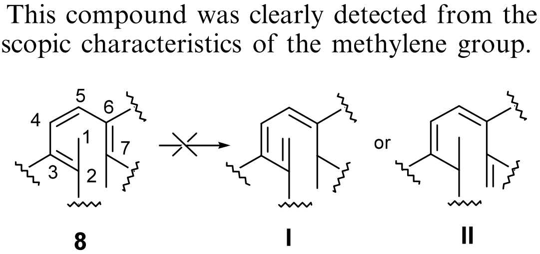
10

Scheme 2. *Reagents and conditions*: (d) I$_2$/hexane/reflux/7 h **9** (60%); (e) *hν*, EtOH **10** (95%).



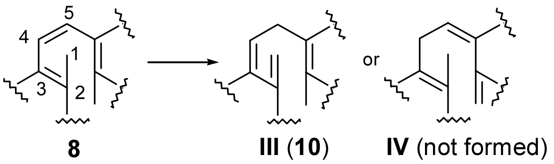
Scheme 3. *Reagents and conditions*: (f) $Cl_3Ru/NaIO_4$/acetone/H_2O (5:1)/rt/30 min **11** and **12** (50%); (g) $AlLiH_4$/THF/reflux/1 h **13** and **14** (95)%.

triene **10** was obtained in very high yield (95%) (Scheme 2). This compound was clearly detected from the spectroscopic characteristics of the methylene group.



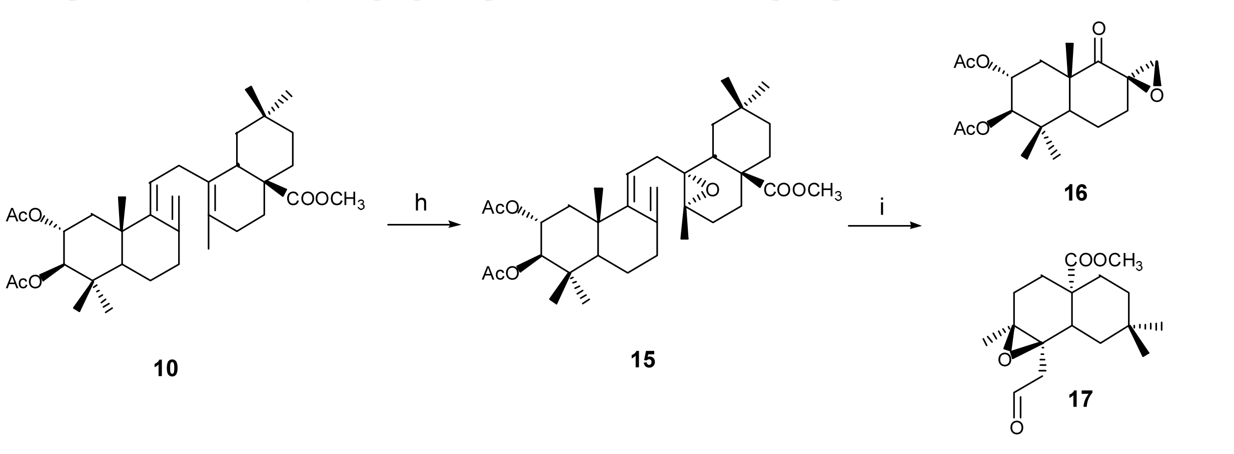
[1,7]H-sigmatropic shift

Hypothetically, in this triene **8**, [1,7]H and/or [1,5]H sigmatropic transpositions could occur, which would give trienes **I** and **II** or **III** and **IV**, respectively. However, only triene **III** (product **10**) was experimentally obtained. Therefore, in this case, a spontaneous or photochemical [1,7]H sigmatropic rearrangement did not occur as in the transformation of provitamin D_2 to vitamin D_2,[5,13] because C-26 and C-27 methyls distorted the molecular conformation, thus impeding any antarafacial or suprafacial migration between 1 and 7 positions of the H sigmatropic shift. Moreover, the molecular disposition allowed only the [1,5]H displacement that gave triene **III** (compound **10**) through a suprafacial migration between one hydrogen from C-26 methyl group (on C-8) to C-12. Thus, the result was a new triene system with two conjugated double bonds between C-8/C-26 and C-9/C-11 and another isolated double bond between C-13 and C-14 atoms (product **10**).



[1,5]H-sigmatropic shift

We found *trans*-triene (**9**) to be a very labile compound in ozonolysis and other oxidative cleavage transformations that we performed. These treatments yielded complex mixtures of fragmented and oxidized compounds, which were difficult to separate. However, treatment of triene **9** with $Cl_3Ru/NaIO_4$ in acetone/H_2O at room temperature for 30 min resulting in a mixture of two aldehydic sesquiterpenes (**11** and **12**), one of which (**11**)



Scheme 4. *Reagents and conditions*: (h) MCPBA/CH_2Cl_2/−40°C/12 h **15** (60%); (i) $O_3/CH_2Cl_2/(CH_3)_2S$/−80°C/5 min **16** and **17** (75)%.

was a promising 3β-acetoxy-8-drimen-11-al (with apple like odor). These sesquiterpene fragments were immediately reduced with $AlLiH_4$ to give two dihydroxylic sesquiterpenes **13**[9] and **14** (Scheme 3). It was noteworthy that compound **13** had structure of 8-drimenol and therefore was an appropriate synthon to obtain other drimane related compounds. Moreover, to minimize undesirable oxidative cleavages, we protected exocyclic triene **10** at the C-13/C-14 double bond by previous epoxidation, and thus 13α,14α-epoxide **15** was formed (60%) together with 15% of the β-isomer (Scheme 4). Ozonization in CH_2Cl_2 of the epoxydiene **15** at −80°C for 5 min rendered two fragments, one with a 14-carbon skeleton (**16**) and the other with a 16-carbon skeleton (**17**) as result of the C-9/C-11 double-bond rupture (Scheme 4). It was noticeable that compound **16**[15] is an adequate ketoepoxy synthon to obtain drimane and ambra oxide related compounds.

Acknowledgements

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11. Irradiated in a borosilicate or quartz flasks using a 125 W high-pressure Hg street lamp with the outermost glass shell removed, in ethanol.
12. ^1H and ^{13}C NMR data for **7**: $[\alpha]_D^{25}=+157$ (*c* 1, $CHCl_3$); (300 MHz, $CDCl_3$) ^1H NMR: δ 5.90 (d, 1H, $J=12.8$ Hz, H-12), 5.80 (d, 1H, $J=12.8$ Hz, H-11), 4.52 (dd, 1H, $J_1=5.0$ Hz, $J_2=11.3$ Hz, H-3), 3.62 (s, 3H, methyl of carboxymethyl group), 2.79 (dd, 1H, $J_1=3.9$ Hz, $J_2=12.7$ Hz, H-18), 2.04 (s, 3H, methyl of acetoxy group), 1.48, 1.27, 1.10, 0.89, 0.88, 0.88 and 0.85 (s, 3H each, methyl groups); ^{13}C NMR: δ 16.75 (C-24), 18.77 (C-6), 20.85 (C-27), 21.43 (C-26), 21.54 (methyl of acetoxy group), 22.00 (C-25), 22.68 (C-16), 24.36 (C-2), 25.02 (C-30), 28.28 (C-23), 29.83 (C-7), 30.76 (C-20), 32.91 (C-22), 33.00 (C-29), 34.14 (C-15), 34.14 (C-21), 35.54 (C-1), 37.15 (C-18), 37.93 (C-4), 38.58 (C-10), 43.09 (C-19), 45.41 (C-17), 50.63 (C-5), 51.72 (methyl of carboxy methyl group), 81.01 (C-3), 127.31 (C-12), 127.97 (C-14), 129.73 (C-8), 132.90 (C-11), 134.47 (C-13), 137.79 (C-9), 171.11 (carbonyl of carboxymethyl group), 178.40 (C-28).
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14. ^1H and ^{13}C NMR data for **9**: $[\alpha]_D^{25}=+80$ (*c* 1, $CHCl_3$); (300 MHz, $CDCl_3$) ^1H NMR: δ 6.15 (d, 1H, $J=16.2$ Hz, H-11), 5.94 (d, 1H, $J=16.2$ Hz, H-12), 4.48 (dd, 1H, $J_1=4.5$ Hz, $J_2=11.4$ Hz, H-3), 3.59 (s, 3H, methyl of carboxymethyl group), 3.11 (dd, 1H, $J_1=3.3$ Hz, $J_2=13.1$ Hz, H-18), 2.03 (s, 3H, methyl of acetoxy group), 1.65, 1.62, 1.02, 0.98, 0.87, 0.87 and 0.86 (s, 3H each, methyl groups); ^{13}C NMR: δ 16.80 (C-24), 18.63 (C-6), 19.05 (C-27), 20.47 (C-26), 21.39 (methyl of acetoxy group), 21.44 (C-25), 22.43 (C-16), 24.08 (C-30), 24.23 (C-2), 28.09 (C-23), 30.65 (C-7), 30.90 (C-20), 32.12 (C-22), 32.92 (C-18), 33.28 (C-29), 33.64 (C-15), 34.14 (C-21), 36.20 (C-1), 37.90 (C-4), 37.90 (C-10), 42.20 (C-19), 45.70 (C-17), 50.67 (C-5), 51.69 (methyl of carboxymethyl group), 80.97 (C-3), 123.02 (C-12), 126.76 (C-14), 129.52 (C-8), 131.41 (C-11), 132.42 (C-13), 141.31 (C-9), 171.05 (carbonyl of carboxymethyl group), 178.21 (C-28).
15. ^1H and ^{13}C NMR data for **16**: $[\alpha]_D^{25}=-12$ (*c* 1, $CHCl_3$); (300 MHz, $CDCl_3$) ^1H NMR: δ 5.13 (ddd, 1H, $J_1=4.5$ Hz, $J_2=10.3$ Hz, $J_3=12.1$ Hz, H-2), 4.73 (d, 1H, $J=10.3$

Hz, H-3), 3.25 (d, 1H, $J=5.2$ Hz, H-11), 2.59 (d, 1H, $J=5.2$ Hz, H-11), 2.18 (dd, 1H, $J_1=4.7$ Hz, $J_2=13.5$ Hz, H-1), 1.99 and 2.06 (s, 3H each, methyls of acetoxy groups), 0.95, 1.05 and 1.36 (s, 3H each, methyl groups); ^{13}C NMR ($CDCl_3$): δ 18.01 (C-13), 18.31 (C-14), 18.59 (C-6), 20.92 y 21.12 (methyls of acetoxy groups), 28.31 (C-12), 31.51 (C-7), 37.34 (C-1), 40.18 (C-4), 49.82 (C-5), 49.93 (C-10), 50.09 (C-11), 57.69 (C-8), 69.04 (C-2), 79.50 (C-3), 170.45 y 170.67 (carbonyls of acetoxy groups), 207.87 (C-9).