Semi-synthesis of triterpene A-ring derivatives from oleanolic and maslinic acids. Theoretical and experimental ^{13}C chemical shifts

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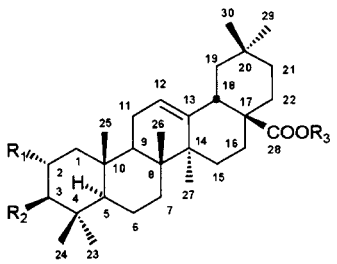
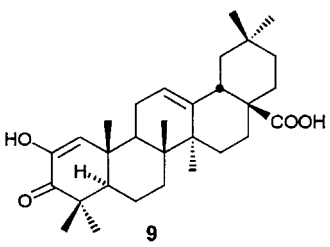
Oleanolic and maslinic acids were isolated from solid waste from olive oil and several derivatives were semi-synthesised using typical reaction procedures. Experimental and theoretical (GIAO, B3LYP/6-31G*//MM+) ^{13}C NMR chemical shifts for 21 compounds are given.

The natural oleanene acids and several closely related derivatives exhibit biological and pharmacological properties. For example, oleanolic and maslinic acids and several of their derivatives have demonstrated significant anti-HIV activities.[4] The pharmacological activities of oleanolic acid were summarised in a recent review.[5] A-ring-cleaved oleanene analogues also show the ability to inhibit the proliferation of nonmalignant cells, and are therefore potential chemopreventive agents for prostate cancer.[6] In the search for synthetic A-ring-contracted triterpene derivatives such as natural musantropic acids,[7] a pinacol rearrangement of ursene-type triterpenes was recently carried out by heating methyl 2α,3β,19α-trihydroxyurs-12-en-oate in the presence of sulphuric acid,[8] although in the present study the products were obtained in low yields. In previous papers, we have reported the rearrangement by solvolysis of tetracyclic *ent*-diterpenoids functionalised at C-12 and/or C-17[9] or C-14.[10] We have shown that when C-12 and C-17 were functionalised, the rearrangement process was more complex, and another nearby group participated in the reaction.



Product number	R_1	R_2	R_3
1	H	OH	H
2	OH	OH	H
3	H	OH	CH_3
4	OH	OH	CH_3
5	H	OAc	H
6	OAc	OAc	H
7	OMs	OMs	H
8	O-C(CH_3)$_2$-O		H
10	H	OAc	CH_3
11	H	OMs	CH_3
12	H	OTs	CH_3
13	H	=O	CH_3



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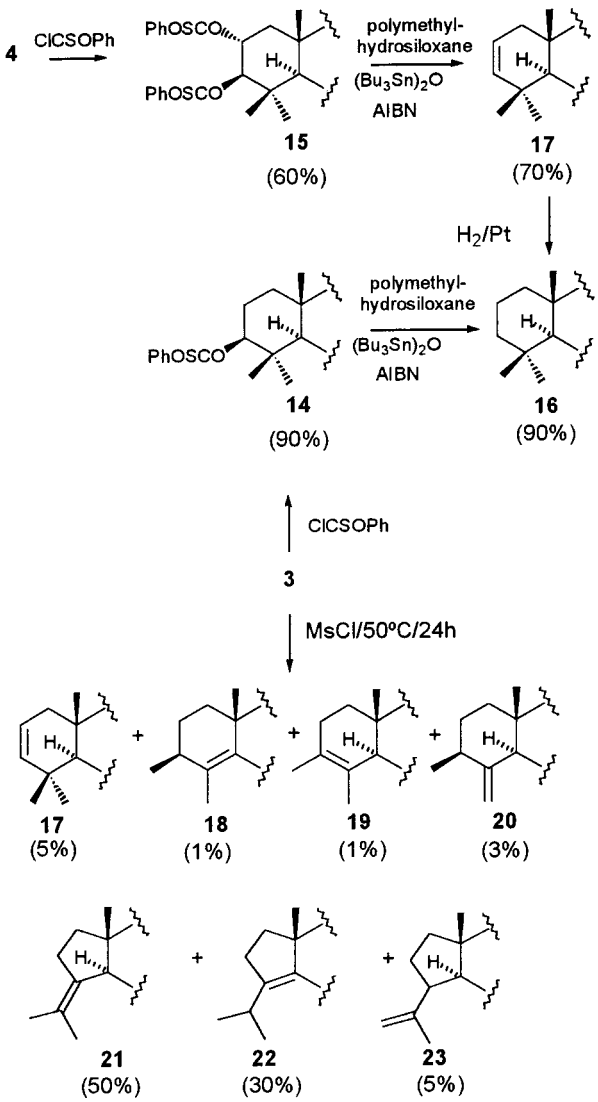

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In the present study, several oleanolic and maslinic acid derivatives are semi-synthetised and characterised (see Scheme). Moreover, deoxygenation of the A-ring of two triterpene acids was also accomplished and the same compound (12-oleanen-28-oic acid) was obtained. We also rearranged methyl oleanate by the solvolysis of derivatives, including mesyloxy group as leaving group in the A-ring. From this reaction, several rearranged compounds with an unsaturated or contracted A-ring were obtained. These new oleanene-type pentacyclic triterpenes were formed in high yields as an appropriate starting material for the semi-synthesis of other modified compounds.

The prolonged treatment of methyl oleanate **3** with MsCl/pyridine at 50 ºC during 24 hours led to a mixture of seven products **17** (5%), **18** (1%), **19** (1%), **20** (3%), **21** (50%), **22** (30%) and **23** (5%) (Figure 3). Four of these products (**17**, **18**, **19**, and **20**) had a six-membered ring, while three of them (**21**, **22** and **23**) had a pentacyclic A-ring as a consequence of a ring contraction. The spectroscopic properties, of **18**, **19** and **20**, indicated that these compounds were the 24(4) → 3-*abeo* ones. Methyl oleanate (**3**) formed its mesyl derivative at C-3 (**11**) and, if treatment with pyridine continued, there was loss of the leaving group, subsequently producing **17** by deprotonation at C-2. Furthermore, a more stable carbocation was formed by methyl migration from C-4 to C-3 and by a loss of C-5 or C-3 or C-23 protons, yielding **18**, **19**, or **20**, respectively, with double bonds between these atoms and C-4. The spectroscopic behaviour of **21**, **22** and **23** indicated that these compounds were 3(4) → 5-*abeo* products and their existence can be explained from a new intermediate obtained by formation of C-3/C-5 bond. To improve the yield of A-ring-contracted compound **21**(80%), we treated methyl oleanate **3** with PCl_5.

The δ_{est} values were estimated by means of a linear regression using 686 points of structures **1**-**17** and **20**-**23** (standard error = 2.978, and correlation coefficient = 0.998):

$$\delta_{est} = 199.62 - 1.084 \cdot \delta_{abs} \quad (1)$$

where δ_{est} are the estimated experimental values and δ_{abs} are the calculated (B3LYP/6-31G*//MM+) absolute ones. The B3LYP/6-31G*/MM+ values were reproduced in good agreement with the experimental ^{13}C NMR chemical shifts for the triterpene series of compounds presented, being a reasonably less time-consuming alternative for the calculation of these shifts (see Figure 4). These calculated ^{13}C shifts were used, together with the 2D experimental spectra for **4**, **8** and **23**, in the correct assignment of the corresponding spectra, and they gave information for the interpretation of some difficult signals. For compounds **18** and **19**, obtained in minor yield and with no experimental spectra available, an estimation of their ^{13}C NMR chemical shifts was made based on a linear regression of **1**–**17** and **20**–**23** δ_C experimental and calculated values, with an accuracy in a *ca* 3 ppm range.

General experimental procedures

Measurements of NMR spectra (300.13 MHz ^1H and 75.47 MHz ^{13}C) were made in $CDCl_3$ (which also provided the lock signal) in a BRUKER AM-300 spectrometer. The assignments of ^{13}C chemical shifts were made with the aid of distortionless enhancement by polarization transfer (DEPT) using a flip angle of 135º. Bruker's programs were used for COSY (45º) and C/H correlation, using HMQC ($J_{C/H}$.~145 Hz) and HMBC ($J_{C/H}$.~9 Hz). One-dimensional NOE-difference experiments were made by irradiation for 4 seconds in series of 8 scans. IR spectra were recorded on a Nicolet 20SX FT-IR spectrometer. High-resolution mass spectra (HRMS) were made in a MICROMASS AUTOSPEC-Q spectrometer (EBE geometry).

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