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

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Maslinic acid was obtained from olive-pressing residues, and several derivatives were formed. Rearrangements of 2-tosyloxy-derivatives of methyl maslinate made out by acetolysis. The main product of these rearrangements contained a cyclopentanic A-ring as a result of a concerted 2(3) → 4-*abeo* rearrangement process. Experimental and theoretical (GIAO, B3LYP/6-31G*//MM+) ^{13}C NMR chemical shifts for 20 compounds are given.

Triterpenes are a large family of pentacyclic compounds obtained biosynthetically by cyclization reactions from squalene.[2] Several of these natural products possess biological and pharmacological activities,[3] including possible anti-HIV activity.[4] The oleanolic (3β-hydroxy-12-oleanen-28-oic acid)[5] and maslinic (2α,3β-dihydroxy-12-oleanen-28-oic acid)[5] acids belong to this class of natural products and are widely found in nature.[5] These triterpenoid acids occur, in large amounts, in the solid waste from olive-oil pressing,[4] and our group has developed a procedure for their isolation from these solid waste.[7] Recently, an efficient method to determine hydroxy pentacyclic triterpene acids (HPTAs) in vegetal oils, has been developed.[8] Moreover, it has been shown that virgin olive oil contains similar amounts of oleanolic and maslinic acids, together with traces of ursolic acid. The HPTA concentration is a better-quality index for olive oil than are other indexes such as the variety or the maturity of the olive fruit.[8]

In a previous work,[1] several derivatives were semi-synthesized, mainly from oleanolic acid, and various rearrangements were examined out in the A-ring of this acid, yielding diverse 3(4) → 5-*abeo* products. In the present paper, a wide range of derivatives from the maslinic acid A-ring have been obtained, for which pharmacological properties are being tested. Moreover, solvolysis reactions with the 2-tosyl derivatives of this acid have been performed, to give a high yield of an aldehyde, from a 2(3) → 4-*abeo* rearrangement. The C-3 substituent effects on this rearrangement have also been studied. Finally, the calculated ^{13}C NMR shifts have been compared with the experimental ones.

Several derivatives of methyl maslinate (**1**) were obtained using typical reaction procedures (Fig. 1). Some of these derivatives of methyl maslinate, which contained good leaving groups in the A-ring of the oleanene skeleton, were used for several rearrangements described below. We also used Jones' reagent to oxidise the hydroxyl group at C-3 in compound **2** to obtain the 3-oxoderivative **11**. In a similar manner, the hydroxyl group at C-2 in compound **3** was oxidised to obtain 2-oxoderivative **12**. To obtain oleanene derivatives, including small carbon chains in the A-ring, the oxoderivatives **11** and **12** were treated with triphenylmethylphosphonium bromide and *sec*-butyllithium under the Wittig reaction conditions. The Wittig reaction with the 3-oxoderivative (**11**) yielded products **10**, **13** and **14**. Compound **10**, previously obtained from the oxidation of methyl maslinate, was a side product of this reaction.

Product **6** was treated with AcOK/AcOH for 30 min under reflux to obtain **2** (25%), **3** (15%), **16** (5%), **17** (45%), **18** (5%) and **19** (5%). Products **2**, and **3** were identified as the previously obtained compounds methyl 2α-acetyl maslinate and methyl 3β-acetylmaslinate respectively. The rearrangement proposed in Fig. 4 could explain the formation of these products from the acetolysis of tosyloxy derivative (**6**). Given the *trans*-periplanar arrangement of the tosyloxy group at C-2 and the C-3/C-4 bond, a concerted rearrangement process might have led to the migration of bonds C-3/C-4 to C-2/C-4, to produce compound **17** (pathway *a*). The stereochemistry at C-2 was assigned by comparison of the experimental coupling constants of H-2 with C-1 protons (*J* 7.2 and 10.6Hz) and the values calculated for the two configurations at C-2. The 2(*R*)-epimer was more stable (*E*=72.0 kcal/mol) and had coupling constant values ($J_{2\beta,1\beta}$ 7.2 and $J_{2\beta,1\alpha}$ 10.5Hz) in accordance with experimental values, whereas the values of the constants for the 2(*S*)-epimer (E_2=73.3 kcal/mol) were markedly different (calculated values $J_{2\alpha,1\beta}$ 1.2 and $J_{2\alpha,1\alpha}$ 8.9). Therefore, compound **17** was methyl A-*neo*-3α-formyl-12-oleanen-28-oate.

The possible influence of the functional groups and the stereochemistry of the A-ring on the rearrangement of these pentacyclic triterpenes was checked by solvolysing the 2α-tosyl 3-keto derivative **8** under the same conditions as described for **6** to give **10** (5%), **11** (20%), **12** (35%), **20** (20%), and **21** (5%). As can be seen, in this case an A-ring-contracted compound similar to the aldehyde product **17** previously obtained by A-ring contraction from **6** did not appear.

Because of the presence of the ketone group on C-3, the area around this carbon was flattened; no good *trans*-periplanar disposition was available between the leaving group at C-2 and the C-3/C-4 bond, and thus the concerted rearrangement did not occur.

In order to obtain A-ring-contracted oleanene compounds with different functionality in the cyclopentanic A-ring, we prepared a 3α-ethenyl derivative from the aldehyde compound (**17**) previously formed at high yield. Product **17** was treated with methyltriphenylphosphonium bromide and *sec*-butyllithium, and the ethylene derivative **22** was formed (Figure 7).

Calculations for compounds **2**–**15** and **17**–**22** have been performed by molecular mechanics optimisations, which have been shown to give good geometries. These were followed by single-point evaluations at the B3LYP/6-31G* theoretical level that yields accurate densities. With this methodology, the ^{13}C NMR chemical shifts were calculated, and the numerical results are presented in Tables 1 and 2, in comparison with the experimental values. Both theoretical and experimental data are in good agreement. The largest deviations are observed for the carbonyl carbons (C-28) with deviations up to 16 ppm. However, the δ_c values for methyl groups, within the high field region, match better with deviations < 3 ppm.

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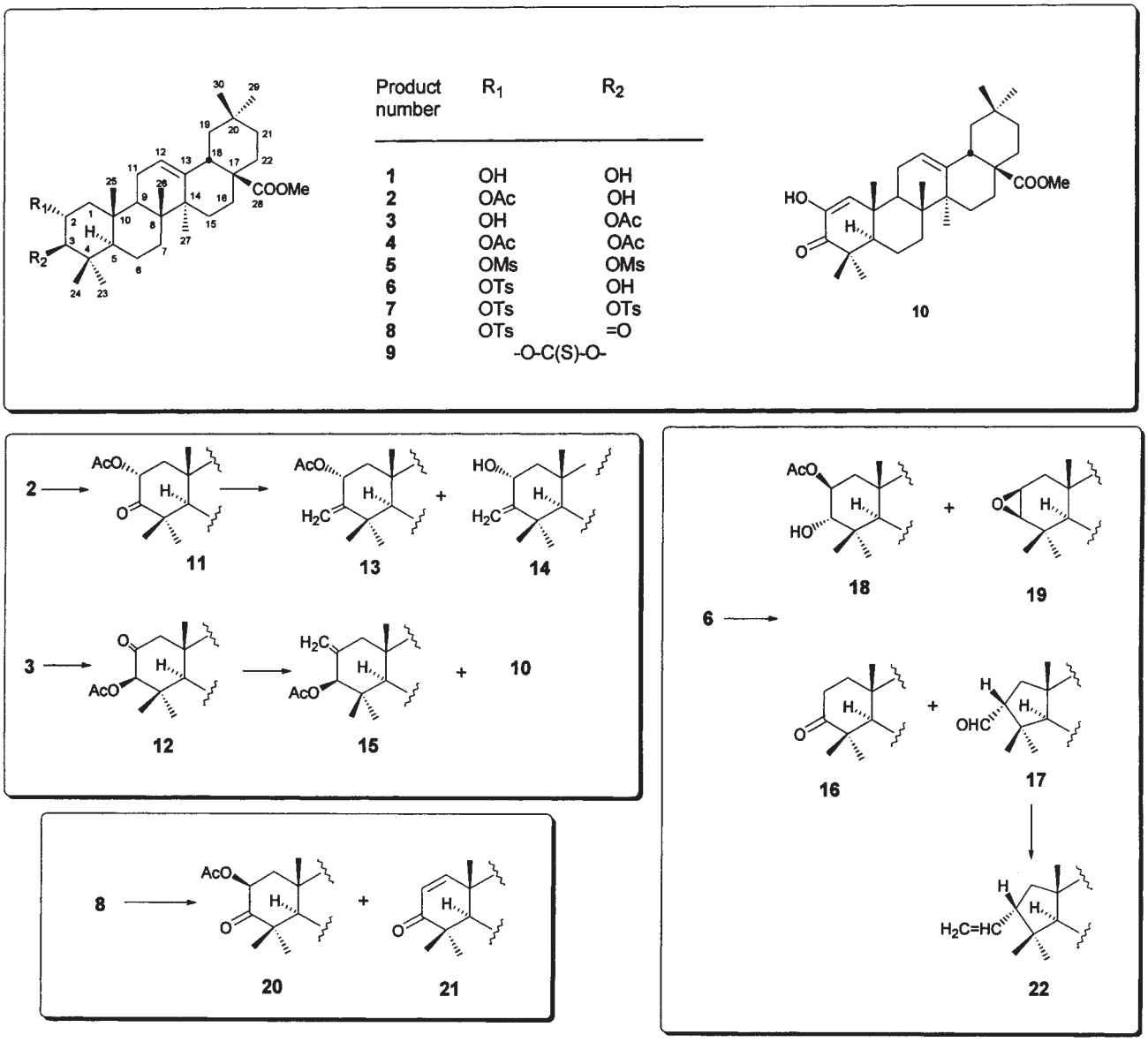

Structure of the different compounds studied together with a schematic reaction path

The utility of the molecular mechanics geometrical optimisations coupled with DFT single-point calculations for the evaluation of the electronic properties of molecules has been tested for several triterpene derivatives, yielding ^{13}C NMR chemical shifts in very good agreement with the experimental ones.

The isolation of maslinic acid in appreciable amounts from the residues of pressed olives enabled us to obtain a wide range of derivatives. Several of these derivatives were subjected to synthetic processes that yielded one main product (**22**) with the A-ring contracted. Similarly, other derivatives have been used to introduce different functional groups in the A-ring, leading to new products.

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