Epoxides, Cyclic Sulfites, and Sulfate from Natural Pentacyclic Triterpenoids: Theoretical Calculations and Chemical Transformations

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Several triterpenic derivatives, with the A-ring functionalized, were semisynthesized from oleanolic and maslinic acids. The reactivity of sulfites and sulfates in these triterpene compounds was investigated under different reaction conditions. Moreover, contracted A-ring triterpenes (five-membered rings) were obtained, by different treatments of the sulfate. From the epoxide, deoxygenated and halohydrin derivatives were semisynthesized with several nucleophiles. Ozonolysis and Beckmann reactions were used to yield 4-aza compounds, from five-membered ring oleanenedi ene triterpenes. The X-ray structure of sulfate is given and compared with density functional theory geometries. Theoretical 13C and 1H chemical shifts (gauge-invariant atomic orbital method at the B3LYP/6-31G* level) and J_H,H coupling constants were calculated for compounds 5–9 and 34–36, identifying the (R)- or (S)-sulfur and α- or β-epoxide configurations together with 4-aza-3-aza structures.

Introduction

The oleanolic (3β-hydroxy-12-oleanene-28-ol) and maslinic (2α,3β-dihydroxy-12-oleanene-28-ol) acids are natural products widely found in nature, belonging to the pentacyclic triterpeneoid family.1 Recently, our group has reported a method to obtain large amounts of these compounds from olive-pressing residues.2 Both triterpenic acids and some closely related products present interesting pharmacological activities,3 including in vitro anti-inflammatory and antitumor activities and some closely related products present interest- ing pharmacological activities,3 including in vitro anti- inflammatory activities, such as Finasteride11 [5α,17β-N-[(1,1-dimethyl-ethyl)-3-oxo-4-azaastrost-1-ene-17-carbomide], which belongs to the 4-azasteroid structural class of compounds. Finasteride inhibits the enzyme 5α-reductase, which is

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responsible for the conversion of testosterone to dihydro-
testosterone. Therefore, the inhibition of 5α-reductase
lowers the level of dihydrotestosterone. On the other
hand, these male hormones have been linked to prosta-
disorders, hair growth, and pubertal changes. Medicinal
control over hormone systems thus can be advantageous
in treating these disorders. Moreover, other structural
classes of molecules are known to bind to 5α-reductase
including 10- and 6-azasteroids.12

Previous works13 have dealt with the reactivity and
rearrangement of different derivatives of oleanolic and
maslinic acids, reactions which have provided high yields
of several interesting 3(4)-5-abeo and 2(3)-4-abeo prod-
ucts. Recently, our group reported the semisynthesis,
theoretical calculations, and biotransformation of cyclic
sulfites of polyhydroxylated eudesmanes,14 showing that
the sulfites and sulfates are appropriate intermediates
for performing experimental and theoretical studies and,
therefore, for preparing other synthons for fine organic
synthesis.

Theoretical methods of substantial quality can be used
to calculate NMR data using the gauge-invariant atomic
orbital (GIAO) method, yielding data comparable to those
of the experiments,13,14 and helping in the assignment of
orbital (GIAO) method, yielding data comparable to those
synthesis.

Therefore, for preparing other synthons for fine organic
synthesis, especially suitable for a wide range of medium- to large-
sized molecules. Their geometries were comparable with
the X-ray data when available.

Here, we report on the isolation and unequivocal structural
assignments (with the help of the DFT calcula-
tions) of a pair of sulfur-diasteromeric cyclic sulfites
between C-2 and C-3 of maslinic acid. Moreover, from
this sulfite mixture, two possible epoxides between these
positions have been formed, via the corresponding sulfate.
Finally, a sulfate and epoxide reactivity study has been
performed by the nuclophile attack and appropriate
opening of their rings. Thus, several useful A-ring-
contracted compounds and halohydrins were obtained.
In this sense, and from one of the products with a con-
tacted A-ring (in very high yield from methyl oleandate),
we formed an interesting synthon for the A- and B-rings
of the 4-azasteroids.

Results and Discussion

(a) Reactivity. Oleanolic (1) and maslinic (2) acids
were derived from olive-pressing residues by succes-
sive extractions with hexane and ethyl acetate in a Soxhlet
apparatus,2 whereupon these extracts were treated with
etheral diazomethane to obtain methyl oleandate (3)13
and methyl maslinate (4)13 in considerable yields.

The treatment of 4 with thionyl chloride in pyridine
for 5 min yielded a diasteromeric pair of cyclic sulfites
(5, 50%, and 6, 50%) between the hydroxyl groups located
in the A-ring. Thus, several useful A-ring-
contracted compounds and halohydrins were obtained.
In this sense, and from one of the products with a con-
tacted A-ring (in very high yield from methyl oleandate),
we formed an interesting synthon for the A- and B-rings
of the 4-azasteroids.

FIGURE 1. Scheme for the structure of products 1-4, and the formation (from 4) of compounds 5-7.

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ton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J.
R.; Berman, C. J. Med. Chem. 1986, 29, 2298. (b) Sera, G.; Lubrano,
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2000, 653.
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**FIGURE 2.** Semisynthesis of products 8–10 from sulfate 7. Sulfate was then completely oxidized to a cyclic sulfate (their ratios unaltered. The mixture of sulfites had a molecular ion m/z 450 (C_{31}H_{46}O_{2}), indicating the loss of oxygenated functions at C-2 and C-3, showing a molecular mass of m/z 468 as epoxides between C-2 and C-3. These epoxides formed under basic conditions through the attack of the sulfur atom by the OH− group, opening of the sulfate ring from the hydroxyl group at C-2 or C-3, and the subsequent loss of the sulfate group from C-3 or C-2. Compounds 8 and 9 were spectroscopically very similar, making it especially difficult to distinguish between the two epoxide configurations. This distinction made by using theoretical calculations will be discussed in the following sections. In contrast, by Mitsunobu reaction of 4 or its tosyl derivative with MeOH/MeO−Na+, only compound 8 gave high yields (85–95%) (see the Experimental Section). This epoxide 8 was previously formed as a minor product in the rearrangement by acetyloss of the methyl 2α-tosylmaslinate.13b

Moreover, we have proved that sulfate 7 is unstable in the presence of a solid support such as silica gel, and thus decomposes to give an A-ring-contraction compound (10, 50%), as well as other nonisolable dimer products (Figure 2). Compound 10 was formed through an A-ring contraction by a C-3(4) → C-5 rearrangement and the loss of the sulfate group between C-2 and C-3, showing a molecular mass of m/z 450 (C_{31}H_{46}O_{2}), indicating the loss of oxygenated functions at C-2 and C-3. Its structure was deduced from the previous considerations and several mono- and bidimensional NMR experiments.

For the study of the behavior of the cyclic sulfate 7 under nucleophilic substitution conditions, and thus to obtain remarkable deoxygenated and contracted A-ring compounds, several reactions with different nucleophilic reagents were carried out. Therefore, compound 7 was treated with NaN₃ followed by H₂SO₄ at different temperatures, obtaining compounds 11 (40%), 12 (10%), and 13 (15%) (Figure 3). The spectroscopic properties of these products indicated a contracted A-ring due to a 3(4) → 5 rearrangement and diverse functions on this ring. These products were formed because the A-ring contraction occurs beforehand, and the opening and loss of the sulfate group preferably result from a transperiplanar disposition of the C-4–C-5 bond and the C-3–O bonds.

In addition, treatment of 7 with reductive conditions (NaBH₄ or NaBH₃CN in DMF at reflux) yielded comp-

**FIGURE 3.** Semisynthesis of products 11–13 from sulfate 7.

1) NaN₃/DMF/Reflux/1h; 2) H₂SO₄ (20%)
pounds 11 (45%), 12 (25%), 14 (5%), 15 (10%), and 16 (10%) with a five-membered A-ring contraction (Figure 4). The majority products (11 and 12) were also yielded in the above-mentioned azidation reaction. Compounds 14–16 were characterized by their spectroscopic properties and were identified as A-ring-contracted products with one, two, or three double bonds in the A-ring moiety. However, treatment of 7 under more drastic reductive conditions (AlLiH4/THF/rt) gave none of the A-ring-contracted products and only two reduced compounds, 17 (59%) and 18 (38%). Products 17 and 18 were the result of a C-28 carboxymethyl reduction (product 17) and the loss of the sulfate group (product 18) (Figure 5).

On the other hand, to study the reactivity of the epoxy group between C-2 and C-3 for the triterpene and produce A-ring-deoxygenated oleanene compounds, we performed various reduction and halogenation reactions using epoxide 8 as starting material (see the Experimental Section). In this sense, compound 8 was treated with NaBH3CN at different temperatures and times, and therefore, 3 and 4 were formed in variable ratios (Table 1). The reductive treatment was accomplished with AlLiH4 and gave both esters 3 and 4, as well as compounds 19 and 20. From their NMR data, the structures of 19 and 20 were deduced, with the result that compound 19 was eritrodiol15 and 20 was the epoxide with the C-28 carboxymethyl group reduced (Figure 5).

In this way, treatment of epoxide 8 with iodine/triphenylphosphine gave compounds 21–23 in different yields according to the reaction conditions (see Table 2 and Figure 6). Product 2113a had a double bond between C-2 and C-3, resulting from the opening of the oxirane ring, the formation of a secondary carbocation at C-2 or C-3, and the elimination of triphenylphosphine oxide. However, such carbocations can preferably undergo competitive nucleophilic attacks, and thus, iodohydrins 22 and 23 were yielded. Oleandiene compound 21 was also formed by treatment of epoxide 8 with WCl6/n-BuLi as a minor product (8%). From this reaction a C-2α-Cl and C-3β-OH compound, 24 (46%), was also obtained by nucleophilic attack at the C-2α position by a chloride anion of the reagent. Similarly, other halohydrins (24–


27) resulted from the opening of the oxirane ring of 8 by the chloride and bromide anions (Figure 7; see the Experimental Section). In all cases, the oxygenated compound was not found and the halohydrins with the halogen atoms at C-2 in the α configuration were the majority product (chlorohydrin 24 and bromohydrin 26).

On the other hand, acetylation of epoxide 8 caused a new opening of the oxiraner ring, yielding a C-2-acetylated derivative (28, 45%)13a and a C-3-acetylated one (29, 49%)13a (Figure 7). When this oxirane oleane 8 was treated with TFA in DMF, the corresponding 2-formyloxy
(30, 35%) and 3-formyloxy (31, 35%) derivatives were obtained (Figure 7). In this case, the opening of the oxirane ring occurred by a nucleophilic attack of the formyl group from the reagent.

To obtain a considerable quantity of a contracted A-ring product, which served as starting material for later semisynthesis, we treated 3 with phosphorus pentachloride, a strong deoxygenating agent, and thus, products 32 (80%) and 33 (15%) were formed (Figure 8). The main product of this reaction, 32, was a rearranged compound with a pentacyclic A-ring and an isopropyldene group on C-3, whereas product 33 was the C-4=C-5 endo double-bond isomer. These 3(4)=5-abeo products were presumably formed by loss of the oxygenated function on C-3 and by the formation of the C-3=C-5 bond. Subsequently, to degrade the molecule between the C-3=C-4 exo double bond, a selective ozonolysis was carried out on compound 32 using CH₂Cl₂ and pyridine as solvent at −72 °C. In this way, the oxidative deavage yielded the pentacyclic ketone 34 (68%), the C-12=C-13 double bond of diene 32 remaining unchanged (Figure 8).

The structure of ketone 34 was ascertained using its spectroscopic properties, with a molecular mass of m/z 426 (C₂₈H₄₂O₃) that demonstrated a loss of 26 units of mass from 32 by the ozonolysis. On the other hand, in its ¹H NMR spectrum, only five angular methyl groups were recorded (δ 1.16, 0.92, 0.89, 0.79, and 0.77 ppm), and the carbonyl group on C-3 appeared at δ 216.85 ppm in its ¹³C NMR spectrum.

Subsequently, to produce the desired 4-aza compound, we used an oximation and a Beckmann rearrangement. Thus, from pentacyclic ketone 34, only oxime 35 was prepared in very high yield (93%), by treatment with hydroxylamine hydrochloride and pyridine as basic catalyst at 50 °C (Figure 8). Oxime 35 presented a molecular mass of m/z 441 that indicated a molecular formula of

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**TABLE 1.** Reduction of 8 with NaBH₃CN and AlLiH₄ at Different Temperatures

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<th>reducing agent</th>
<th>temp</th>
<th>time (h)</th>
<th>yield (%)</th>
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<td>30 36</td>
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</tr>
<tr>
<td></td>
<td>reflux</td>
<td>1.0</td>
<td>3 4 29 64</td>
</tr>
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</table>

**TABLE 2.** Treatment of 8 with I₂ and PPh₃ in CH₂Cl₂ at Different Temperatures

<table>
<thead>
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<th>temp</th>
<th>yield (%)</th>
</tr>
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<tbody>
<tr>
<td>0 °C</td>
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</tr>
<tr>
<td>rt</td>
<td>80 7</td>
</tr>
<tr>
<td>reflux</td>
<td>83</td>
</tr>
</tbody>
</table>

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**FIGURE 6.** Semisynthesis of products 21–23 from epoxide 8.

**FIGURE 7.** Semisynthesis of products 24–31 from epoxide 8.
was also two possibilities according to the alkyl group located anti with respect to the hydroxyl group, and thus, the 4-aza or the 3-aza derivative could be obtained (Figure 9). When the bond C-3–C-5 was trans with regard to the hydroxyl group of the oxime, this bond migrated toward the N atom and the 4-aza derivative was formed. Contrarily, when the C-2–C-3 bond was anti with respect to the OH, the 3-aza derivative resulted. Taking into account the spectroscopic NMR data published for 3-azasteroids16 and 4-azasteroids 17 and the theoretical calculations (see below), compound 36 presented the structure of a 4-aza derivative. Compound 36 had a molecular mass of m/z 441 in agreement with a molecular formula of C$_{28}$H$_{43}$O$_3$N. Its $^1$H NMR spectrum showed a signal at $\delta$ 5.69 ppm which was interchangeable with that of D$_2$O, being assigned to the proton on the N-4 atom. In its $^{13}$C NMR spectrum the assignments for the A-ring carbon atoms were the following: C-1 ($\delta$ 35.1 ppm), C-2 ($\delta$ 28.5 ppm), C-5 ($\delta$ 61.0 ppm), and C-10 ($\delta$ 36.3 ppm). At $\delta$ 172.5 ppm appeared the carbonyl group on C-3 of the cyclic amide 36.

(b) Geometrical Parameters. Figure 11 (see the Supporting Information) depicts the X-ray structure of sulfate 7, and Table 3 summarizes the experimental and theoretical geometries. The calculated bond lengths were larger than the experimental ones only for the C–C and the terminal S–O bonds, agreeing well with the X-ray data with a maximum deviation for the C–C, C–O, and O–S distances of 0.02, 0.03, and 0.07 Å, respectively. The bond angles showed the largest deviations for the $\angle$OSO angles of ca. 3°.

In addition to compound 7, Figure 10 shows details of the A-ring substructure for the pairs of isomers, the sulfites (5 and 6) and epoxides (8 and 9). The bond lengths, and the atom numbering, are included for comparison.

| TABLE 3. Selected Geometrical Parameters, X-ray and Calculated (at the B3LYP/6-31G*/B3LYP/6-31G* Theoretical Level) Values, for the Sulfate Moiety and the A-Ring Substructure of Compound 7 |
|---|---|---|---|
| bond (Å) | X-ray | B3LYP/6-31G* | angles (deg) | X-ray | B3LYP/6-31G* |
| C-1–C-2 | 1.509 | 1.515 | C-2–C-1–C-10 | 107.6 | 109.6 |
| C-2–C-3 | 1.495 | 1.514 | C-1–C-2–C-3 | 111.3 | 111.4 |
| C-3–C-4 | 1.522 | 1.533 | C-2–C-3–C-4 | 114.9 | 114.1 |
| C-4–C-5 | 1.561 | 1.580 | C-3–C-4–C-5 | 102.4 | 103.2 |
| C-5–C-10 | 1.569 | 1.579 | C-4–C-5–C-10 | 118.7 | 118.2 |
| C-1–C-10 | 1.558 | 1.567 | C-5–C-10–C-1 | 109.3 | 109.4 |
| C-4–C-23 | 1.539 | 1.546 | C-3–C-2–C-4 | 102.1 | 103.1 |
| C-4–C-24 | 1.540 | 1.541 | C-2–C-3–C-4 | 102.0 | 103.6 |
| C-2–O-4 | 1.471 | 1.457 | S–O–4–C-2 | 108.5 | 107.9 |
| C-3–O-3 | 1.483 | 1.455 | S–O–3–C-3 | 107.7 | 108.3 |
| S–O-4 | 1.584 | 1.652 | O-3–S–O-4 | 98.5 | 96.1 |
| S–O-3 | 1.580 | 1.655 | O-1–S–O-4 | 110.5 | 107.6 |
| S–O-1 | 1.404 | 1.450 | O-2–S–O-3 | 110.8 | 107.5 |
| S–O-2 | 1.409 | 1.449 | |

Puckering Parameters for the Five-Membered Ring

| $q_2$ | 0.434 | 0.428 |
| $f$ | 87.8 | 93.2 |

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The most stable conformations of the five- and six-membered rings for compounds 1 and 2 can be determined from the Cremer–Pople puckering parameters\(^\text{(18)}\) (summarized in Table 1 for the five-membered ring and in Supporting Information Table S-3).

The five-membered \(\text{S}–\text{O}–\text{C}–\text{C}–\text{O}\) ring of structures 1–3 presented larger puckering amplitude \((q_2)\) values of ca. 0.43 compared to the 0.39 for a standard cyclopentane ring,\(^\text{(18)}\) the X-ray and theoretical puckering amplitudes of the sulfates being slightly larger than the sulfite values, because of the large volume of the \(\text{S}\) atom. Moreover, the phase angle \((\phi)\) data agreed with an envelope (E) form for the sulfites and a twist (T) form (S at the \(\text{C}_2\) symmetry axis) for the sulfate structures. Sulfite 1 with the \(\text{S}–\text{O}\) bond in the \(\beta\) orientation yielded an \(E\) form at the \(\text{C}-2\) apex, sulfite 2 (\(\alpha\) oriented) being an \(E\) form at the \(\text{C}-3\) apex.

In addition to the five-membered heterocyclic ring of compounds 1–3, these structures presented six-membered rings (A–E). The most stable conformations for these rings were determined from the puckering parameters\(^\text{(18)}\) \((Q\) amplitude and \(\theta\) and \(\phi\) phase angles), yielding a chair form for the \(A\)-, \(B\)-, \(D\)-, and \(E\)-rings, and a half-boat form (at the \(\text{C}-8\) apex) for the \(C\)-ring (due mainly to the double \(\text{C}–\text{C}\) bond for this \(C\)-ring). The \(A\)- and \(B\)-rings showed larger \(Q\) values (ca. 0.58), attributed to the \(A\)-ring substituents, while the \(D\)-ring was less distorted (\(Q\) values ca. 0.50). All the puckering parameters for the six-membered rings remained almost similar for the different structures.

(c) \(^{13}\text{C}\) and \(^{1}\text{H}\) NMR Chemical Shifts and \(^{1}J_{\text{H,H}}\) Coupling Constants. Theoretical chemical shifts \((\delta_{\text{C}}\) and \(\delta_{\text{H}}\)) were calculated, for compounds 5–9 and 34–36, to determine the absolute configuration in sulfite (5 and 6) and epoxide (8 and 9) derivatives, and characterize the products of the oximation and Beckmann rearrangement, compounds 34–36. Moreover, we also included for comparison, with the sulfites, the sulfate 7. Table 4 summarizes the theoretical results (B3LYP/6-31G*/B3LYP/6-31G*) and the experimental data. An entire table (Table S-1) with all the calculated and experimental \(\delta_{\text{C}}\) chemical shifts is given for compounds 5–9 and 34–36 as Supporting Information.

Table 4 shows the corresponding \(\delta_{\text{C}}\) and \(\delta_{\text{H}}\) chemical shifts (calculated and experimental) together with selected \(^{1}J_{\text{H,H}}\) coupling constants only for the \(A\)-ring, where structural and functional changes occurred. Looking at our previous work,\(^\text{13,14}\) the experimental assignments of the chemical shifts were made according to their proximity to the calculated values and the type of carbon (CH/Me, \(\text{CH}_2\), or C). The results gave mean deviation values of ca. 5 and 1 ppm, for the \(\delta_{\text{C}}\) and \(\delta_{\text{H}}\) shifts, respectively. Although this range is still large for a precise determination of the absolute chemical shift values, the theoretical calculations accurately reproduce the trends in the relative shifts from one compound to another, providing a useful tool to characterize natural product derivatives.\(^\text{13,14}\) In this work, we have improved our previous calculations of the chemical shifts using the DFT geometry instead of the molecular mechanics one (i.e., B3LYP/6-31G*/B3LYP/6-31G*).

Compounds 5 and 6 correspond to sulfites with different orientations of the terminal \(\text{S}–\text{O}\) bond. The \(\alpha\) orientation matches an \(R\) configuration on the sulfur atom, the \(\beta\) one matching an \(S\) configuration on the sulfur (see Figure 10). A detailed comparison between the calculated and experimental \(\delta_{\text{C}}\) and \(\delta_{\text{H}}\) values enabled us an unambiguous assignment of both configurations. Moreover, the main differences were found in their \(\delta_{\text{C}}\) shifts for \(\text{C}-2\) and \(\text{C}-3\) atoms. For compound 5, the \(\delta_{\text{C}}\) value of \(\text{C}-2\) was shifted downfield (80.7 ppm) compared to that of compound 6. Furthermore, for compound 6, the \(\delta_{\text{C}}\) value of \(\text{C}-3\) was also shifted downfield in comparison to that of 5 (94.9 and 88.3 ppm, respectively). A similar trend was also noted for the calculated values (77.9 and 73.3 ppm for \(\text{C}-2\), and 91.3 and 86.1 ppm for \(\text{C}-3\); see Table 4). However, the other \(\delta_{\text{C}}\) shifts remained almost unchanged.

In addition, a different configuration on the sulfur atom also affects the \(\delta_{\text{H}}\) shifts, mainly for the closest hydrogens (\(\text{H}-2\) and \(\text{H}-3\)); however, the coupling constants remained almost unchanged due to the similar conformations of the \(A\)-ring in both sulfite products. Thus, compound 5 (with \(\alpha\) and \(R\) configuration) presented the \(\text{H}-3\) near the \(\text{O}\) atom, yielding a larger \(\delta_{\text{H}}\) value (4.0 ppm) than 3.5 ppm for compound 6 (oxygen in the \(\beta\) orientation). Similarly, the \(\text{H}-2\) signal of (5)–6 (\(\beta\) orientation) was shifted downfield (4.6 ppm) compared to that of compound 5, with \(\text{H}-2\) in the \(\beta\) orientation and the oxygen in the \(\alpha\) one (4.1 ppm). This combination of different effects (oxygen in the \(\alpha\) and \(\beta\) orientations together with \(\text{H}-2\) in the \(\beta\) orientation and \(\text{H}-3\) in the \(\alpha\) orientation) yielded a product (5) with similar \(\text{H}-2\) and \(\text{H}-3\) shifts and another (6) with different values.

On the other hand, the theoretical \(^{1}J_{\text{H,H}}\) coupling constants reproduced the experimental data and indi-

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cated that the A-ring remained almost unchanged for both structures.

Therefore, from all the above results, we unambiguously assigned product 5 with an absolute R configuration on the sulfur atom (α orientation), while product 6 corresponded to the S configuration (β orientation) (see Figure 10).

Compound 7, formed from the oxidation of both sulfites 5 and 6 (see Figure 11 in the Supporting Information), presented similar δc shifts except for the C-2 and C-3 atoms (82.9 and 96.0 ppm, respectively), which gave values larger than the sulfite ones.

Another problem in elucidating two configurations arises with both epoxides 8 and 9 (in the α or β orientation). Epoxide 8 was previously characterized as β oriented according to the B3LYP/6-31G*/MM+ chemical shift calculations.13b For a clear assignment of both orientations, we assigned all the 13C shifts for this compound, C-2 and C-5 signals being shifted upfield, δ 24.5 and 55.0 ppm, compared to those of ketone 34. This effect is explained by the electronegativity of the oxygen atom compared to the =CH2 (32) or =NOH (35) group.

All the above experimental trends were accurately reproduced by the theoretical calculations (see Table 4). Oxime 35, by a treatment with PCI5, underwent a Beckmann rearrangement, yielding a six-membered A-ring lactone. As mentioned above (see the Reactivity Section), this rearrangement gave two different structures (3-aza or 4-aza derivatives; see Figure 9), depending on the stereochemistry of the HO–N=C=3–C=5 double bond. However, comparing the experimental 13C spectrum of 36 with the calculated chemical shifts of the 3-aza and 4-aza derivatives (see Table 4), compound 36 corresponded to the 4-aza structure. Thus, focusing on the C-2 and C-5 shifts, the experimental data were in better agreement with the 4-aza structure than with the 3-aza one, those shifts yielding the largest differences with respect to the latter (ca. 10 ppm). Moreover, taking into account the theoretical calculations for compound 36 (in both structures 3-aza and 4-aza) and with our calculations of a 4-azasteroid derivative reported in the literature37 (referred to as compound 13 in that work), the assignments for the C-2 and C-5 shifts were interchanged in ref 17. However, the remaining 13C chemical shifts were in agreement with our theoretical data.

Once the nature of 36 was established as a 4-aza derivative, we concluded that the Beckmann rearrangement was consistent with respect to product 35 with a trans HO–N=C=3–C=5 double bond (E-isomer; see Figure 9), discounting the Z-isomer.

### Concluding Remarks

In this reactivity study of the A-ring of the triterpenic compound, we have prepared two derivatives with a function between the C-2 and C-3 atoms, these being the sulfate 7 and the epoxide 8. The sulfate 7 manifested a clear tendency to be lost after attack with different nucleophilic reagents to form remarkable A-ring-contracted compounds. On the contrary, these contracted compounds with a clear tendency to be lost after attack with different nucleophilic reagents to form remarkable A-ring-contracted compounds. On the contrary, these contracted compounds.

### Table 4. Selected Experimental and Calculated (at the B3LYP/6-31G*/B3LYP/6-31G* theoretical level) NMR 13C and 1H Chemical Shifts (ppm) Together with J_H_H Coupling Constants, for Compounds 5–9 and 34–36

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<th>(S)-6 (β)</th>
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<th>8 (β)</th>
<th>9 (α)</th>
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<th>35</th>
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a Data from ref 13b. b Values calculated for two different structures of this lactone 36, the 3-aza and the 4-aza derivatives. C Methylene carbon type. d Quaternary carbon type.
Melting points were uncorrected, and the optical rotations were measured on a polarimeter at 20°C. All reaction solvents were dried and distilled immediately prior to use; chromatography solvents were distilled prior to use. Commercially available reagents were used without further purification. Silica gel (40–60 μm) was used for flash chromatography. CH₂Cl₂ and CHCl₃ containing increasing amounts of Me₂CO were used as eluents. Analytical plates (silica gel) were rendered visible by spraying with H₂SO₄/AcOH, followed by heating to 120°C.

Isolation of Starting Materials. Oleanolic acid (1) and maslinic acid (2) were isolated from solid wastes resulting from olive oil production, which were macerated and extracted in a Soxhlet apparatus with hexane and ETnAc successively. Hexane extracts were treated with NaOH and acidified with HCl to pH 1. These solutions were mixed with an aqueous solution of NaHSO₃. The mixture was heated to 120°C, rendered visible by spraying with H₂SO₄/AcOH, followed by heating to 120°C.

Formation of Sulfites 5 and 6. Product 4 (1.5 g, 3.1 mmol) was dissolved in 8 mL of pyridine and 25 mL of CH₂Cl₂, and 1.1 mL of Cl₂SO was added. The reaction was maintained with stirring at 0°C for 5 h. The reaction mixture was diluted with water, extracted with CH₂Cl₂, washed with NaOH solution and evaporated at reduced pressure. Chromatography over silica gel yielded 0.97 g of white solid; mp 190°C (80%): white solid; mp 176-178°C; [α]d = 61.1 (c 1, CHCl₃); IR (CHCl₃) 3488, 2947, 2880, 1724, 1461, 1214, 996 cm⁻¹; ¹H NMR (CDCl₃) δ 5.27 (1H, d, J = 3.4, 3.5 Hz, H-12), 4.11 (1H, d, J = 1.6, 14.7 Hz, H-2′), 3.99 (1H, d, J = 10.6 Hz, H-3′), 3.61 (1H, s, COOCH₃), 2.86 (1H, d, J = 13.9 Hz, H-18′), 2.24 (1H, d, J = 4.1, 11.8 Hz, H-1′), 1.14 (3H, s, Me), 1.11 (3H, s, Me), 0.98 (3H, s, Me), 0.92 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.72 (3H, s, Me). For 13C NMR see Table S-1 and spectrum S-2 in the Supporting Information; HRLSIMS m/z calculated for C₃₁H₄₈O₅Na 555.3120, found 555.3121. Data for 6: white solid; mp 176-178°C; [α]d = 54.1 (c 1, CHCl₃); IR (CHCl₃) 3412, 2947, 2875, 757 cm⁻¹; ¹H NMR (CDCl₃) δ 5.28 (1H, d, J = 3.2, 3.4 Hz, H-12), 4.61 (1H, d, J = 10.6, 11.6 Hz, H-2′), 3.61 (1H, s, COOCH₃), 3.46 (1H, d, J = 12.6 Hz, H-3′), 2.86 (1H, d, J = 13.6 Hz, H-18′), 2.25 (1H, d, J = 4.1, 11.7 Hz, H-1′), 1.11 (3H, s, Me), 1.10 (3H, s, Me), 1.04 (3H, s, Me), 0.98 (3H, s, Me), 0.92 (3H, s, Me), 0.89 (3H, s, Me), 0.73 (3H, s, Me); for 13C NMR see Table S-1 and spectrum S-3 in the Supporting Information; HRLSIMS m/z calculated for C₃₁H₄₈O₅Na 555.3120, found 555.3112.

Oxidation with NaO₄/RuCl₃ of Sulfites 5 and 6. NaO₄ (750 mg, 3.6 mmol) and RuCl₃·3H₂O (approximately 5 mg) were added to water (15 mL) to a solution of 5 and 6 (1.3 g) in CH₂Cl₂ (10 mL) and CH₃CN (10 mL). The reaction mixture was stirred at 0°C for 2 h. This mixture was diluted with diethyl ether (50 mL), and the organic layer was washed with water, saturated solution of NaHSO₃ and a NaCl solution and dried over anhydrous Na₂SO₄. The solvent was evaporated at reduced pressure, and the residue was chromatographed to obtain 0.97 g of 7 (80%): white solid; mp 190–192°C; [α]d = 45.1 (c 1, CHCl₃); IR (CHCl₃) 2948, 1724, 1383, 1212 cm⁻¹; ¹H NMR (CDCl₃) δ 5.26 (1H, d, J = 3.6 Hz, H-12), 4.89 (1H, d, d, J = 4.3, 10.4, 11.9 Hz, H-2′), 4.27 (1H, d, J = 10.4 Hz, H-3′), 3.61 (3H, s, COOCH₃), 2.86 (1H, d, J = 4.6, 13.7 Hz, H-18′), 2.20 (1H, d, J = 4.3, 11.8 Hz, H-1′), 1.12 (3H, s, Me), 1.10 (3H, s, Me), 1.06 (3H, s, Me), 0.99 (3H, s, Me), 0.91 (3H, s, Me), 0.90 (3H, s, Me), 0.72 (3H, s, Me); for 13C NMR see Table S-1 and spectrum S-4 in the Supporting Information; HRLSIMS m/z calculated for C₃₁H₄₈O₅Na 571.3151, found 571.3159.
Opening of Sulfate 7 with KOH. Product 7 (63 mg, 0.1 mmol) was dissolved in 5 mL of THF, and 5 mL of MeOH/H₂O (20%) was added. The solution was maintained with stirring at reflux for 30 min. The reaction mixture was washed with diluted HCl solution, extracted with CH₂Cl₂, dried with anhydrous Na₂SO₄, and evaporated at reduced pressure. Chromatography over silica gel yielded 27 mg of 8-(5%) and 26 mg of 9 (10%).

Formation of 8 via Tosylation. Product 8 via tosylation. A solution of NaHCO₃, and dried over anhydrous Na₂SO₄. The solution was evaporated at reduced pressure. Chromatography over silica gel yielded 2.4 g of 8.

Treatment of Cyclic Sulfate 7 on Solid Support. Product 7 (200 mg, 0.4 mmol) and SiO₂ (400 mg, GF 254 type 60, pH 7) were mixed in CH₂Cl₂. The reaction mixture was maintained with stirring at reflux for 3 h, filtered, and evaporated at reduced pressure. Chromatography over silica gel yielded 535 mg of 8 (95%).

Reduction of Sulfate 7 with NaBH₄. Product 7 (100 mg, 0.2 mmol) was dissolved in 5 mL of DMF, and after addition of 10 mg of NaBH₄, the mixture was stirred at reflux for 1 h. Then the suspension was evaporated, and 60 mL of toluene/ethyl ether (3:1) was added, and the solvents were evaporated. The residue was dissolved in ethyl acetate, washed with water, extracted, and evaporated. Chromatography over silica gel yielded 39 mg of 11 (45%), 27 mg of 12 (25%), 4 mg of 14 (5%), 12 mg of 15 (10%), and 14 mg of 16 (10%). Data for 14: yellow solid; mp 84–86 °C; [α]D²⁰ = 66 (c 1, CHCl₃); IR (CHCl₃) 2984, 1725, 1161 cm⁻¹; H NMR (CDCl₃) of δ 1.99 (1H, t, H-1), 3.50 (1H, d, J = 7.5, 10.4 Hz, H-1), 1.34 (1H, m, H-1), 1.19 (3H, s, Me), 0.98 (3H, s, Me), 0.87 (3H, s, Me); for 13C NMR (CDCl₃) see Table S-2 and spectrum S-8 in the Supporting Information; HRLSIMS m/z calc for C₃₁H₄₈O₃Na 491.3501, found 491.3495.

NaBH₄CN, and this mixture was maintained with stirring at 115 °C for 2 h and 30 min. Small amounts of toluene were added, reagitated with 5 mL of THF, with ether, and the residue was extracted with CH₂Cl₂, washed with water, dried over anhydrous Na₂SO₄, and evaporated to give a mixture of compounds. These compounds were chromatographed on a silica gel column to yield the same products of the previous reduction reaction in similar proportions.

**Reduction of Sulfate 7 with AliH₄**

Product 7 (150 mg, 0.3 mmol) was dissolved in 3 mL of THF, 1 mL of a 0.1 M solution of AliH₄ in THF was added, and the mixture was maintained at room temperature for 3 h. This mixture was dissolved with CH₂Cl₂, washed with water, dried with anhydrous Na₂SO₄, and evaporated. Chromatography over silica gel yielded 93 mg of 17 (59%) and 52 mg of 18 (38%). Data for 17: white solid; mp 141–142 °C; [α]D = 48 (c 1, CHCl₃); IR (CHCl₃) 3420, 2949, 1380, 1211 cm⁻¹; ¹H NMR (CDCl₃) δ 5.18 (1H, dd, J = 3.6 Hz, H-12), 4.35 (1H, dd, J = 4.2, 10.7, 12.8 Hz, H-2), 3.60 (3H, s, COOCH₃), 3.32 (1H, dd, J = 10.0 Hz, H-7a), 2.84 (1H, dd, J = 4.2, 13.8 Hz, H-18), 2.41 (1H, dd, J = 4.2, 12.9 Hz, H-3), 1.11 (3H, s, Me), 1.08 (3H, s, Me), 0.94 (3H, s, Me), 0.91 (3H, s, Me), 0.86 (3H, s, Me), 0.82 (3H, s, Me), 0.69 (3H, s, Me); for ¹³C NMR (CDCl₃) see Table S-2 and spectrum S-16 in the Supporting Information; HRLSIMS m/z calc’d for C₃₄H₄₇O₇Na 619.2624, found 619.2628. Data for 23: syrup; [α]D = 66 (c 1, CHCl₃); IR (CHCl₃) 3402, 2943, 1723, 1124 cm⁻¹; ¹H NMR (CDCl₃) δ 2.85 (1H, dd, J = 4.5, 14.4 Hz, H-18), 1.14 (3H, s, Me), 1.12 (3H, s, Me), 1.09 (3H, s, Me), 1.03 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.71 (3H, s, Me); for ¹³C NMR (CDCl₃) see Table S-2 and spectrum S-17 in the Supporting Information; HRLSIMS m/z calc’d for C₃₄H₄₇O₇Na 619.2624, found 619.2623.

**Reduction of 8 with WCl₆ and n-ButLi**

A solution of 160 mg of WCl₆ (0.4 mmol) in 5 mL of THF was cooled at −70 °C, and 0.08 mL of a 1.6 M solution in hexane of n-ButLi (0.8 mmol) was added. The mixture was cooled to room temperature, 100 mg of 8 in 5 mL of THF was added, and the resulting mixture was maintained with stirring at room temperature for 20 min. Then 20 mL of a solution of NaOH (20%) was added and extracted with CH₂Cl₂. The organic layer was washed twice with water, dried with anhydrous Na₂SO₄, and evaporated. The resulting residue was chromatographed on a silica gel column to yield 7 mg of 21 (8%) and 46 mg of 24 (46%): yellow solid; mp 185–187 °C; [α]D = 50 (c 1, CHCl₃); IR (CHCl₃) 3404, 2947, 1724, 1125 cm⁻¹; ¹H NMR (CDCl₃) δ 5.27 (1H, dd, J = 3.6 Hz, H-12), 4.57 (1H, dd, J = 4.3, 10.2, 12.2 Hz, H-2), 3.61 (3H, s, COOCH₃), 3.17 (1H, d, J = 10.2 Hz, H-3), 2.85 (1H, dd, J = 4.5, 13.8 Hz, H-18), 1.12 (3H, s, Me), 1.08 (3H, s, Me), 0.96 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.83 (3H, s, Me), 0.70 (3H, s, Me); for ¹³C NMR (CDCl₃) see Table S-2 and spectrum S-18 in the Supporting Information; HRLSIMS m/z calc’d for C₃₄H₄₇O₇Na 527.3268, found 527.3269.

**Treatment of 8 with NaCl**

To a mixture of 50 mg of 8 (0.1 mmol) in 10 mL of THF and diluted sulfuric acid was added 25 mg of NaCl (0.4 mmol). The resulting mixture was stirred at reflux for 1 h. Then the reaction mixture was neutralized with a diluted solution of NaHCO₃, washed with water, extracted with CH₂Cl₂, and evaporated at reduced pressure. The resulting residue was chromatographed on a silica gel column to yield 45 mg of 24 (89%) and 5 mg of 25 (10%): white solid; mp 151–153 °C; [α]D = 74 (c 1, CHCl₃); IR (CHCl₃) 3393, 2925, 1112 cm⁻¹; ¹H NMR (CDCl₃) δ 5.29 (1H, dd, J = 3.9 Hz, H-12), 4.22 (1H, d, J = 10.6 Hz, H-3), 3.86 (1H, d, J = 4.4, 10.6, 12.4 Hz, H-2), 3.61 (3H, s, COOCH₃), 2.85 (1H, dd, J = 4.1, 13.9 Hz, H-18), 1.12 (3H, s, Me), 1.09 (3H, s, Me), 1.04 (3H, s, Me), 1.02 (3H, s, Me), 0.92 (3H, s, Me), 0.87 (3H, s, Me), 0.86 (3H, s, Me); for ¹³C NMR (CDCl₃) see Table S-2 and spectrum S-19 in the Supporting Information; HRLSIMS m/z calc’d for C₃₄H₄₇O₇Na 527.3268, found 527.3270.

**Treatment of 8 with KBr**

To a mixture of 50 mg of 8 (0.1 mmol) in 10 mL of THF and diluted sulfuric acid was added 50 mg of KBr (0.4 mmol). The resulting mixture was stirred at reflux for 1 h. Then the reaction mixture was neutralized with a diluted solution of NaHCO₃, washed with water, extracted with CH₂Cl₂, and evaporated at reduced pressure. Chromatography over silica gel column yielded 47 mg of 26 (85%) and 8 mg of 27 (15%): Data for 26: white solid; mp 170–172 °C; [α]D = 23 (c 1, CHCl₃); IR (CHCl₃) 3356, 2931, 1609, 1117 cm⁻¹; ¹H NMR (CDCl₃) δ 5.26 (1H, dd, J = 3.6 Hz, H-12), 4.35 (1H, ddd, J = 4.3, 10.4, 12.4 Hz, H-2), 3.61 (3H, s, COOCH₃), 2.73 (1H, dd, J = 2.0, 10.4 Hz, H-3), 2.85 (1H, dd, J = 4.4, 13.9 Hz, H-18), 1.91 (3H, s, Me), 1.10 (3H, s, Me), 0.96 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.83 (3H, s, Me), 0.70 (3H, s, Me); for ¹³C NMR (CDCl₃) see Table S-2 and spectrum S-20 in the Supporting Information; HRLSIMS m/z calc’d for C₃₄H₄₇O₇Na 527.3268, found 527.3270.
and spectrum S-20 in the Supporting Information; HRLSIMS m/z calc for C$_{32}$H$_{40}$O$_{5}$Na 537.3556, found 537.3555. Data for 33: white solid; mp 72–74 °C; [a]$_D^{10}$ = 74 (c 1, CHC1$_3$); IR (CHC1$_3$) 2947, 1739, 1161, 755 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 5.32 (1H, dd, J = 3.4 Hz, H-12), 3.61 (3H, s, COOCH$_3$), 2.87 (1H, dd, J = 4.5, 14.0 Hz, H-18)$^\alpha$, 1.16 (3H, s, Me), 0.92 (3H, s, Me), 0.89 (3H, s, Me), 0.79 (3H, s, Me), 0.77 (3H, s, Me); for $^{13}$C NMR see Table S-1 and spectrum S-24 in the Supporting Information; HRLSIMS m/z calc for C$_{32}$H$_{40}$O$_{5}$Na 449.3032, 449.3029 found.

**Oximation of Ketone 34.** A 45 mg sample of 34 (0.11 mmol) was dissolved in 2 mL of pyridine, and 14 mg (0.20 mmol) of hydroxylamine hydrochloride was added, whereupon this mixture was stirred at 50 °C for 30 min. Then the solvent was evaporated to toulene, and the resulting residue was washed with a diluted solution of HCl, and CHCl$_3$, dried over anhydrous Na$_2$SO$_4$, and finally evaporated at reduced pressure and purified over silica gel to yield 45 mg (93%) of 35: mp 131–133 °C; [a]$_D^{10}$ = 74 (c 1, CHC1$_3$); IR (CHC1$_3$) 3292, 2948, 1725, 1162, 756 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 5.29 (1H, dd, J = 3.5 Hz, H-12), 3.61 (3H, s, COOCH$_3$), 2.86 (1H, dd, J = 4.1, 13.9 Hz, H-18)$^\alpha$, 1.15 (3H, s, Me), 0.91 (3H, s, Me), 0.88 (3H, s, Me), 0.77 (3H, s, Me), 0.73 (3H, s, Me); for $^{13}$C NMR see Table S-1 and spectrum S-25 in the Supporting Information; HRLSIMS m/z calc for C$_{34}$H$_{44}$O$_{5}$Na 464.3141, found 464.3143.

**Beckmann Rearrangement of 35 with PCl$_3$.** Product 35 (25 mg, 0.06 mmol) was dissolved in 3 mL of diethyl ether, and 50 mg of PCl$_3$ (0.24 mmol) was added. This suspension was maintained at room temperature for 15 min. After evaporation at reduced pressure, the resulting residue was washed with water, extracted with CHCl$_3$, dried over Na$_2$SO$_4$, evaporated, and purified, yielding 18 mg (70%) of 36: mp 134–136 °C; [a]$_D^{10}$ = 72 (c 1, CHC1$_3$); IR (CHC1$_3$) 2947, 1726, 1666, 754 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 5.69 (1H, brs, N$_2$), 5.31 (1H, dd, J = 3.6 Hz, H-12), 3.621 (3H, s, COOCH$_3$), 2.98 (1H, dd, J = 3.4, 11.4 Hz, H-5), 2.87 (1H, dd, J = 4.1, 13.8 Hz, H-18)$^\alpha$, 1.13 (3H, s, Me), 0.93 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.87 (3H, s, Me), 0.71 (3H, s, Me); for $^{13}$C NMR see Table S-1 and spectrum S-26 in the Supporting Information; HRLSIMS m/z calc for C$_{36}$H$_{46}$O$_{5}$Na 464.3141, found 464.3145.

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**Supporting Information Available:** Table S-1 with the calculated and experimental $\delta_c$ chemical shifts for compounds 5–9 and 34–36 (PDF); $^{13}$C spectra for all new compounds 5–7, 9–18, 20, 22–27, 30, and 31 (PDF); and 34–36 (PDF), Table S-2 with the experimental $\delta_c$ chemical shifts for compounds 10–18, 20, 22, 23–27, 30, and 31 (PDF), X-ray data of compound 7 (CIF file), Table S-3 with the puckering parameters of the five- and six-membered rings of compounds 5–7 (PDF), and Figure 11 with the X-ray structure of compound 7 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.