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

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Received December 10, 2002

Several triterpenic derivatives, with the A-ring functionalized, were semisynthesized from oleanolic and maslinic acids. The reactivities of sulfites, sulfate, and epoxides in these triterpene compounds were investigated under different reaction conditions. Moreover, contracted A-ring triterpenes (five-membered rings) were obtained, by different treatments of the sulfate **7**. From the epoxide **8**, deoxygenated and halohydrin derivatives were semisynthesized with several nucleophiles. Ozonolysis and Beckmann reactions were used to yield 4-aza compounds, from five-membered ring olanediene triterpenes. The X-ray structure of sulfate **7** is given and compared with density functional theory geometries. Theoretical ^{13}C and ^{1}H chemical shifts (gauge-invariant atomic orbital method at the B3LYP/6-31G*//B3LYP/6-31G* level) and $^{3}J_{H,H}$ 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 or 3-aza structures.

Introduction

The oleanolic (3*β*-hydroxy-12-oleanen-28-oic) and maslinic (2α,3*β*-dihydroxy-12-oleanen-28-oic) acids are natural products widely found in nature, belonging to the pentacyclic triterpenoid 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-HIV activity.[4] Cyclic sulfites and sulfates of *vic*-diols are considered to be activated and have been used for a variety of nucleophilic displacement reactions.[5] Such sulfates are obtained by catalytic oxidation of cyclic sulfites following Sharpless's procedure.[6] The significant role of cyclic sulfates in organic synthesis is due to their reactivity and stereochemical properties. On the other hand, epoxides and halohydrins have found broad use as synthetic intermediates in organic synthesis,[7] especially in synthesizing many bioactive compounds.[8] Deoxygenating epoxides is a very useful reaction to yield olefins, and a great variety of reagents effective in this transformation have been reported.[9] Moreover, the triterpenes with the A-ring contracted are natural compounds isolated from various parts of several plants.[10] These triterpenoids are important synthons for semisynthesis of A-ring-modified derivatives showing biological activities, such as Finasteride[11] [5α,17*β*-*N*-(1,1,dimethylethyl)-3-oxo-4-azaandrostan-1-ene-17-carboxamide], which belongs to the 4-azasteroid structural class of compounds. Finasteride inhibits the enzyme 5α-reductase, which is

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10.1021/jo026832s CCC: $25.00
Published on Web 05/16/2003

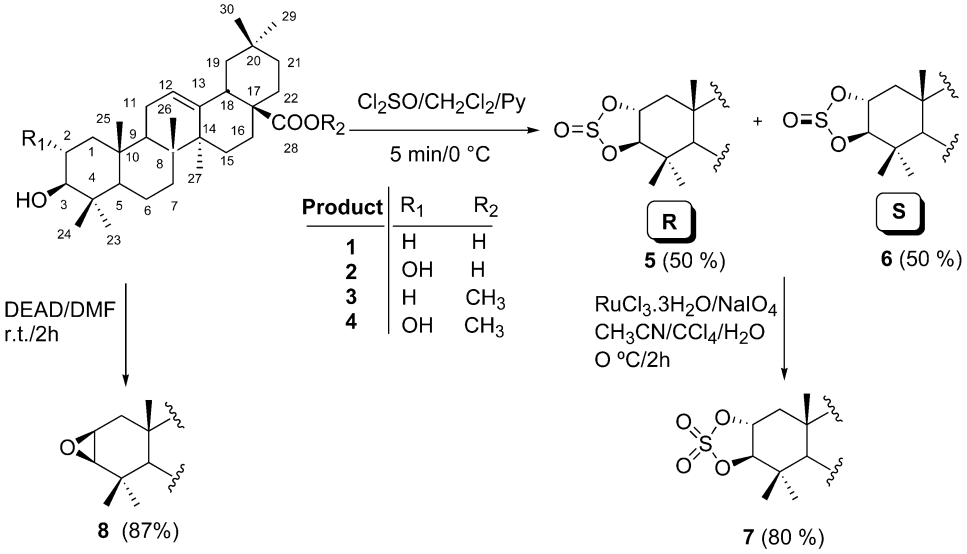

FIGURE 1. Scheme for the structure of products **1**−**4**, and the formation (from **4**) of compounds **5**−**7**.

responsible for the conversion of testosterone to dihydrotestosterone. Therefore, the inhibition of 5α-reductase lowers the level of dehydrotestosterone. On the other hand, these male hormones have been linked to prostate 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 works[13] 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* products. 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 chemical shifts for natural product derivatives. In this sense, the density functional theory (DFT) methods are 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 calculations) 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 nucleophilic 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 contracted A-ring (in very high yield from methyl oleanolate), 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 successive extractions with hexane and ethyl acetate in a Soxhlet apparatus,[2] whereupon these extracts were treated with ethereal diazomethane to obtain methyl oleanate (**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 at C-2 and C-3 of the A-ring of methyl maslinate (Figure 1). These compounds showed different physical properties, however, with identical molecular ion peaks of *m*/*z* 532 ($C_{31}H_{48}O_5S$). On the other hand, the diasteromer sulfites **5** and **6** presented different ^{1}H and ^{13}C NMR chemical shifts mainly for the A-ring atoms. Thus, in **5**, the lesser polar sulfite, H-2β was detected at δ 4.11 ppm (1H, ddd, $J_1 = 4.1$ Hz, $J_2 = 10.6$ Hz, $J_3 = 14.7$ Hz), while, in **6** (more polar), this proton appeared at δ 4.61 ppm (1H, ddd, $J_1 = 4.0$ Hz, $J_2 = 10.6$ Hz, $J_3 = 11.8$ Hz). However, H-3α was more shifted in **6** (δ 3.99 ppm, 1H, d, $J = 10.6$ Hz) than in **5** (δ 3.46 ppm, 1H, d, $J = 10.6$ Hz). In terms of ^{13}C NMR spectra, the main differences

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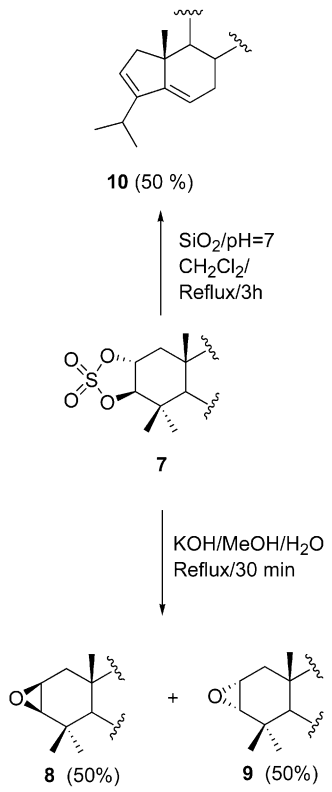

FIGURE 2. Semisynthesis of products **8**−**10** from sulfate **7**.

were again in the chemicals shifts at C-2 (δ 80.7 ppm in **5** and δ 74.5 ppm in compound **6**) and C-3 (δ 88.3 ppm in **5** and δ 94.9 ppm in **6**). These spectroscopic data were inadequate to distinguish between the pair of sulfites and, therefore, to establish the arrangement of the S=O bond in the A-ring. A full assignment of the arrangement, and consequently the absolute sulfur configuration in each compound, will be made below from spectroscopic and geometric properties. The stability of the two sulfites was verified by dissolving the mixture in different solvents (CH_2Cl_2, CH_3CN) and maintaining it at reflux for 8 h. Similarly, this stability was tested under acidic conditions (acid resin, Amberlite IRC-50, pH 5−6, or HCl solution, pH 2, in CH_3CN, at reflux for 4 h) or on a solid support (silica gel GF254, pH 7, CH_2Cl_2, at reflux for 4 h). In all cases, both sulfites remained unchanged and their ratios unaltered. The mixture of sulfites **5** and **6** was then completely oxidized to a cyclic sulfate (**7**) using $RuCl_3/NaIO_4$ (Figure 1). Sulfate **7** had a molecular ion peak (*m*/*z* 548) 16 *m*/*z* units higher than those of the related sulfites. In its ^{1}H NMR spectrum the H-2β and H-3α signals appeared at δ 4.89 ppm (1H, ddd, $J_1 = 4.3$ Hz, $J_2 = 10.4$ Hz, $J_3 = 11.9$ Hz) and at δ 4.27 ppm (1H, d, $J = 10.4$ Hz), respectively. The accurate geometry in the sulfate and A-rings will be discussed and clearly established in the following sections of this paper.

The reactivity of sulfate **7** was also tested, first, by treatment with HCl solution (pH 2) in THF at reflux for 2 h, and remains unaltered. However, treatment of **7** with $KOH/MeOH/H_2O$ at reflux for 30 min yielded compounds **8**[13b] (50%) and **9** (50%) (Figure 2). Products **8** and **9** were identified with the same molecular mass (*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 acetolysis 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-contracted 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 NaN_3 followed by H_2SO_4 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 ($NaBH_4$ or $NaBH_3CN$ in DMF at reflux) yielded com-

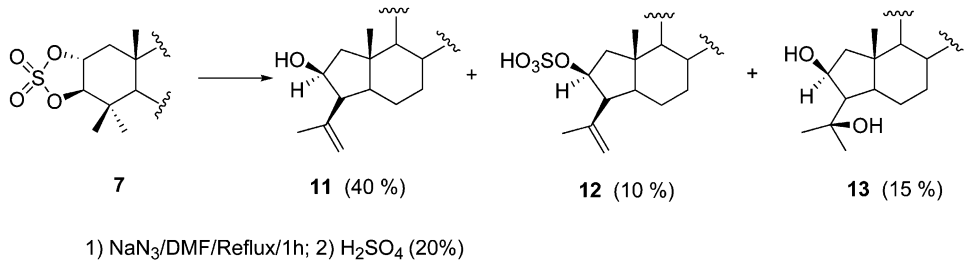

FIGURE 3. Semisynthesis of products **11**−**13** from sulfate **7**.

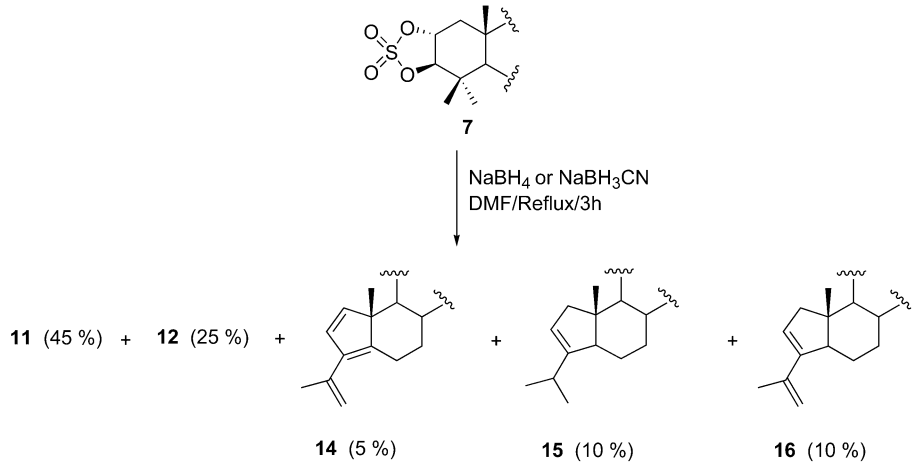

FIGURE 4. Semisynthesis of products **14**−**16** from sulfate **7**.

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 ($AlLiH_4$/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 $NaBH_3CN$ at different temperatures and times, and therefore, **3** and **4** were formed in variable ratios (Table 1). The reductive treatment was accomplished with $AlLiH_4$ 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 eritrodiol[15] 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 **21**[13a] 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 WCl_6/*n*-BuLi as a minor product (8%). From this reaction a C-2α-Cl and C-3*β*-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**).

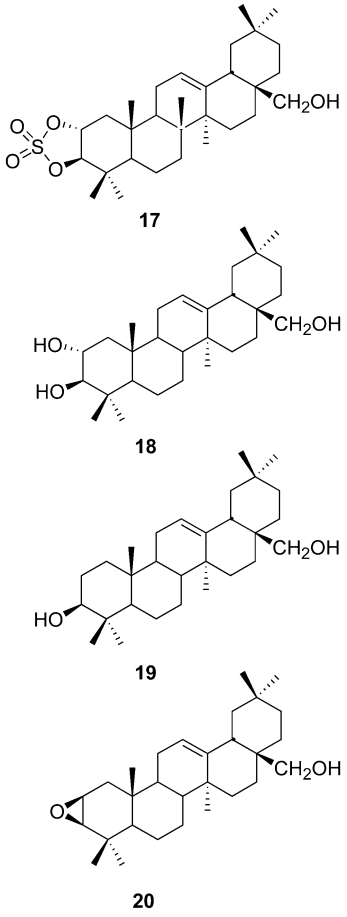

FIGURE 5. Structures of products **17**−**20**.

On the other hand, acetolysis of epoxide **8** caused a new opening of the oxirane ring, yielding a C-2-acetylated derivative (**28**, 45%)[13a] and a C-3-acetylated one (**29**, 49%)[13a] (Figure 7). When this oxirane oleanene **8** was treated with TFA in DMF, the corresponding 2-formyloxy

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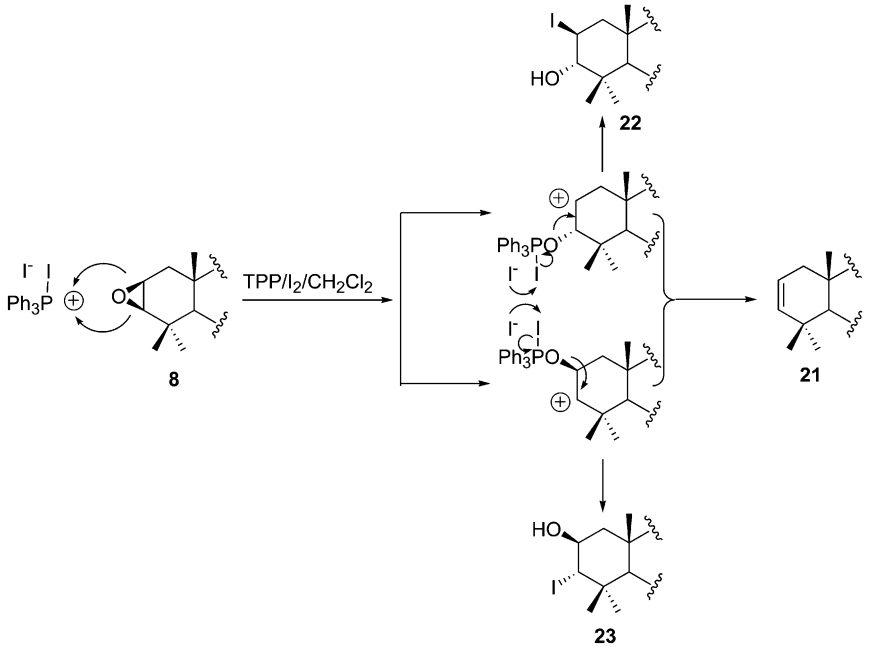

FIGURE 6. Semisynthesis of products **21**−**23** from epoxide **8**.

TABLE 1. Reduction of 8 with $NaBH_3CN$ and $AlLiH_4$ at Different Temperatures

			yield (%)			
reducing agent	temp	time (h)	**3**	**4**	**19**	**20**
$NaBH_3$**CN**	0 °C	2.5	30	36		
	rt	2.5	53	37		
	reflux	2.5	43	57		
$AlLiH_4$	rt	1.5		9	38	53
	reflux	1.0	3	4	29	64

TABLE 2. Treatment of 8 with I_2 and PPh_3 in CH_2Cl_2 at Different Temperatures

	yield (%)		
temp	**21**	**22**	**23**
0 °C		81	19
rt	13	80	7
reflux	17	83	

(**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%)[13a] and **33** (15%)[13a] were formed (Figure 8). The main product of this reaction, **32**, was a rearranged compound with a pentacyclic A-ring and an isopropylidene 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 CH_2Cl_2 and pyridine as solvent at −72 °C. In this way, the oxidative cleavage yielded the pentacyclic ketone **34** (68%), the C-12═C-13

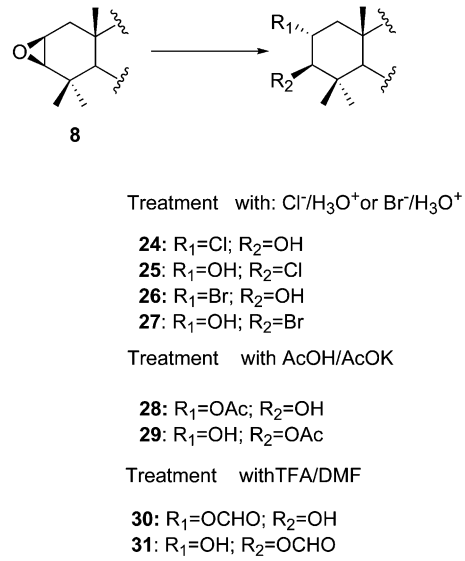

FIGURE 7. Semisynthesis of products **24**−**31** from epoxide **8**.

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 ($C_{28}H_{42}O_3$) that demonstrated a loss of 26 units of mass from **32** by the ozonolysis. On the other hand, in its ^{1}H 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 ^{13}C 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

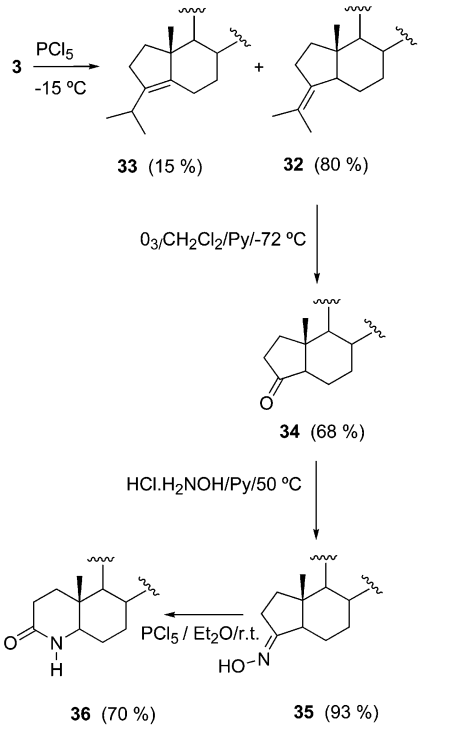

FIGURE 8. Semisynthesis of products **32**−**36** from **3**.

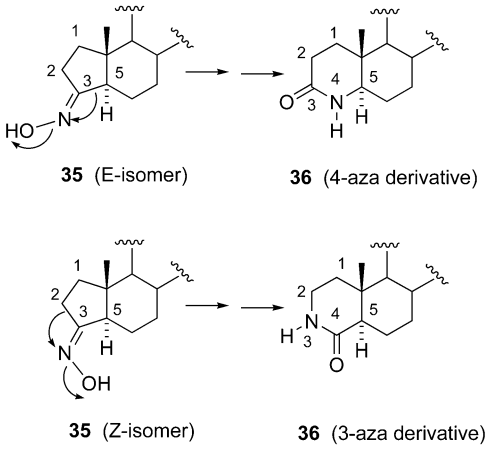

FIGURE 9. Formation of 3-aza or 4-aza compounds, from oxime **35**, by Beckmann rearrangement.

$C_{28}H_{43}O_3N$. Moreover, its ^{1}H NMR spectrum showed only as significant signals five methyl groups at δ 1.15, 0.91, 0.88, 0.77, and 0.73 ppm and a double doublet at δ 5.29 ppm corresponding to H-12. Furthermore, in its ^{13}C NMR spectrum a signal appeared at δ 166.10 ppm assigned to C-3, which supported the C-3═N double bond of the oxime.

Finally, to expand the A-ring including the N atom, thereby obtaining the lactam function in this ring, we treated the oxime **35** with PCl_5 in diethyl ether at rt (Figure 8), yielding compound **36**. However, depending on the *Z*−*E* isomerism of the C═N double bond of the oxime **35**, two different lactamic compounds were formed (Figure 9). In the Beckmann rearrangement, the group that migrates displayed an *anti* orientation to the hydroxyl group, and this is often used as a method for determining the oxime configuration. In this case, there were 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-azasteroids[16] 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 $C_{28}H_{43}O_3N$. Its ^{1}H NMR spectrum showed a signal at δ 5.69 ppm which was interchangeable with that of D_2O, 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 (δ 35.1 ppm), C-2 (δ 28.5 ppm), C-5 (δ 61.0 ppm), and C-10 (δ 36.3 ppm). At δ 172.5 ppm appeared the carbonyl group on C-3 of the cyclic amide **36**.

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−O-4	102.1	103.1
C-4−C-24	1.540	1.541	C-2−C-3−O-3	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			

(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 ∠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.

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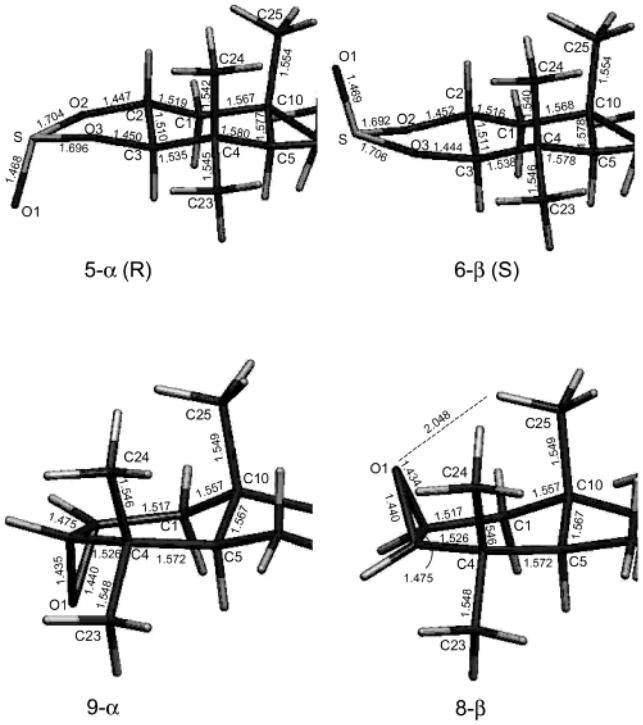

FIGURE 10. Details of the structure for the A-ring of sulfites **5** and **6**, and epoxides α and *β*.

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[18] (summarized in Table 1 for the five-membered ring and in Supporting Information Table S-3).

The five-membered S−O−C−C−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,[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 S atom. Moreover, the phase angle (ϕ) data agreed with an *envelope* (E) form for the sulfites and a *twist* (T) form (S at the C_2 symmetry axis) for the sulfate structures. Sulfite 1 with the S−O bond in the *β* orientation yielded an E form at the C-2 apex, sulfite 2 (α oriented) being an E form at the 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[18] (Q amplitude and θ and ϕ phase angles), yielding a *chair* form for the A-, B-, D-, and E-rings, and a *half-boat* form (at the C-8 apex) for the C-ring (due mainly to the double C═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}C and ^{1}H NMR Chemical Shifts and $^{3}J_{H,H}$ Coupling Constants. Theoretical chemical shifts (δ_C and δ_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 δ_C chemical shifts is given for compounds **5**−**9** and **34**−**36** as Supporting Information.

Table 4 shows the corresponding δ_C and δ_H chemical shifts (calculated and experimental) together with selected $^{3}J_{H,H}$ coupling constants only for the A-ring, where structural and functional changes occurred. Looking at our previous work,[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, CH_2, or C). The results gave mean deviation values of ca. 5 and 1 ppm, for the δ_C and δ_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.[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 S═O bond. The α orientation matches an *R* configuration on the sulfur atom, the *β* one matching an *S* configuration on the sulfur (see Figure 10). A detailed comparison between the calculated and experimental δ_C and δ_H values enabled us an unambiguous assignment of both configurations. Moreover, the main differences were found in their δ_C shifts for C-2 and C-3 atoms. For compound **5**, the δ_C value of C-2 was shifted downfield (80.7 ppm) compared to 74.5 ppm for **6**. Furthermore, for compound **6**, the δ_C value of 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 C-2, and 91.3 and 86.1 ppm for C-3; see Table 4). However, the other δ_C shifts remained almost unchanged.

In addition, a different configuration on the sulfur atom also affects the δ_H shifts, mainly for the closest hydrogens (H-2 and 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 α and *R* configuration) presented the H-3 near the O atom, yielding a larger δ_H value (4.0 ppm) than 3.5 ppm for compound **6** (oxygen in the *β* orientation). Similarly, the H-2 signal of (*S*)-**6** (*β* orientation) was shifted downfield (4.6 ppm) compared to that of compound **5**, with H-2 in the *β* orientation and the oxygen in the α one (4.1 ppm). This combination of different effects (oxygen in the α and *β* orientations together with H-2 in the *β* orientation and H-3 in the α orientation) yielded a product (**5**) with similar H-2 and H-3 shifts and another (**6**) with different values.

On the other hand, the theoretical $^{3}J_{H,H}$ coupling constants reproduced the experimental data and indi-

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TABLE 4. Selected Experimental and Calculated (at the B3LYP/6-31G*//B3LYP/ 6-31G* theoretical level) NMR ^{13}C and ^{1}H Chemical Shifts (ppm) Together with $^{3}J_{H,H}$ Coupling Constants, for Compounds 5−9 and 34−36

	C	(*R*)-**5** (α)		(*S*)-**6** (*β*)		**7**		**8** (*β*)		**9** (α)		**34**		**35**		**36**		
	type	exptl	calcd	exptl	calcd	exptl	calcd	exptl[a]	calcd	exptl	calcd	exptl	calcd	exptl	calcd	exptl	calcd,[b] 4-aza	calcd,[b] 3-aza
C-1	CH_2	42.1	42.6	41.2	41.7	40.9	40.9	38.4	38.4	40.0	41.5	36.5	37.4	37. 9	39.0	35.1	37.8	38.0
C-2	CH	80.7	77.9	74.5	73.3	82.9	77.0	54.4	54.2	52.7	51.2	32.4[c]	34.7[c]	24.5[c]	26.7[c]	28.5[c]	29.7[c]	40.3
C-3	CH	88.3	86.1	94.9	91.3	96.0	89.9	61.0	60.0	61.7	60.2	216.8[d]	203.6[d]	166.1[d]	156.6[d]	172.5[d]	157.4[d]	
C-4	C	38.2	40.8	38.7	41.3	38.4	40.2	32.4	35.6	32.5	35.6							159.8
C-5	CH	56.2	56.7	55.9	56.6	55.5	56.2	52.2	51.3	46.1	47.2	61.8	60.6	55.0	55.2	61.0	61.4	51.2
C-6	CH_2	17.9	21.1	17.9	21.0	17.8	20.8	19.7	22.9	18.9	21.9	16.8	20.2	18.4	21.4	24.6	27.9	20.5
C-9	CH	47.9	50.1	48.0	50.2	47.8	50.0	47.8	47.9	47.0	47.9	46.2	47.7	45.3	46.9	42.6	44.1	
C-10	C	40.3	43.2	40.6	43.5	39.7	43.0	36.9	40.3	36.1	39.6	40.4	43.3	42.0	45.8	36.3	39.2	38.9
C-23	Me	28.6	29.4	28.5	29.4	28.1	28.9	30.4	30.2	28.2	28.3							
C-24	Me	16.3	18.1	16.3	17.9	16.1	17.7	20.6	22.7	22.3	23.3							
C-25	Me	17.2	19.2	17.2	19.1	17.1	19.1	16.7	19.0	17.9	19.8	14.6	16.0	14.1	15.7	11.8	13.8	
H-2		4.1	3.9	4.6	4.7	4.9	4.5	3.2	3.2	3.2	3.0							
H-3		4.0	4.0	3.5	3.3	4.3	3.8	2.8	2.8	2.8	2.7							
$J_{1\alpha,2}$		14.7	11.3	11.8	11.2	11.9	11.2	2.0	2.9	3.9	1.3							
$J_{1\beta,2}$		4.1	4.3	4.0	4.5	4.3	4.6	2.0	3.5	3.9	8.4							
$J_{2,3}$		10.6	9.3	10.6	9.4	10.4	9.3	4.0	7.4	3.9	7.4							

[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.

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 δ_C 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 epoxides, in this work, the calculations were improved with DFT geometries instead of molecular mechanics ones (B3LYP/6-31G*//B3LYP/6-31G*). According mainly to the δ_C values at the C-1, C-2, and C-5 atoms, the compounds with a *β* orientation yielded an upfield shift for the C-2 and C-5 atoms together with a downfield one for C-1. However, neither the ^{1}H shifts nor the $^{3}J_{H,H}$ coupling constants clearly differentiated between the α and *β* orientations in this case.

Following the above trends from the δ_C chemical shifts, we assigned the *β* orientation to product **8** and the α orientation to product **9**.

On the other hand, from **3**, by a treatment with PCl_5 and further ozonolysis of the main product **32**, the ketone **34** was obtained. This compound **34** presented a five-membered contracted A-ring differing from the previous triterpenes (six-membered A-ring). With the help of the calculated NMR chemical shifts, and according to the type of carbons (CH/Me, CH_2, or C), we managed to assign all the ^{13}C shifts for this compound, C-2 and C-5 being the main characteristic signals for this five-membered A-ring, which were shifted downfield (*δ* 32.4 and 61.8 ppm compared to *δ* 28.7 and 55.9 ppm, respectively, in compound **32**). Moreover, oxime **35**, obtained from ketone **34**, yielded the same trends as diene **32**, the 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 $=CH_2$ (**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 PCl_5, 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 ^{13}C 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 literature[17] (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 ^{13}C 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), discarding 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

products were not obtained from the epoxide **8** (but rather their opening led to the halohydrins by preferential opening of C-2 and deoxygenated derivatives). Moreover, from the main A-ring-contracted compound **32** of the above-mentioned rearrangement, 4-azasteroid synthons for the A- and B-rings were prepared.

In the previous section, some doubts about the clear differentiation between the sulfite and epoxide isomers were presented, as well as the geometry of the aforementioned sulfate, which has been solved in the following section of this work by the help of theoretical calculations and X-ray data.

Experimental Section

Computational Details. In the first step, structures **5**−**9** and **34**−**36** were fully optimized at the HF/3-21G*//HF/3-21G* theoretical level within the Gaussian 98 package of programs.[19] Moreover, frequency calculations were performed at the same level of theory to test the nature of the stationary points, yielding no imaginary frequency (true minima), for all the structures **5**−**9**. In the second step, the HF/3-21G*//HF/3-21G* geometries were optimized using the density functional theory (B3LYP functional[20] with the 6-31G* basis set). Finally, the ^{1}H and ^{13}C NMR chemical shifts were also calculated with the Gaussian 98 program[19] by means of the GIAO method,[21] using the tetramethylsilane (TMS) ^{1}H and ^{13}C signals as reference, at the B3LYP/6-31G*//B3LYP/6-31G* theoretical level (the reference value of ^{13}C is δ 189.77 ppm, and that of ^{1}H is δ 32.18 ppm). The $^3J_{H,H}$ coupling constants were estimated with the Haasnoot−Altona equation.[22] Drawing the X-ray structure of **7** was performed with the Ortep-3 program.[23]

General Methods. Measurements of NMR spectra (300.13 MHz (^{1}H) and 75.47 MHz (^{13}C)) were made in $CDCl_3$ (which also provided the lock signal) in a 300 MHz 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 135° and with a two-dimensional NMR experiment. Bruker's programs were used for COSY (45°) and C/H correlation. One-dimensional NOE difference experiments were done by irradiation for 4 s in a series of eight scans. IR spectra were recorded on an FTIR spectrometer. High-resolution mass spectra were obtained with a spectrometer with EBE geometry.

X-ray data were collected on a diffractometer equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The single crystals of compound **7** were obtained by recrystallization from a mixture of methanol and methylene chloride (1:1), and the structure was determined and refined using the SHELXTL program package.[24]

Melting points were uncorrected, and the optical rotations were measured on a polarimeter at 20°. 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. CH_2Cl_2 and $CHCl_3$ containing increasing amounts of Me_2CO were used as eluents. Analytical plates (silica gel) were rendered visible by spraying with H_2SO_4/AcOH, followed by heating to 120 °C.

Isolation of Starting Materials. Oleanolic acid (**1**)[1,2] and maslinic acid (**2**)[1,2] were isolated from solid wastes resulting from olive oil production, which were macerated and extracted in a Soxhlet apparatus with hexane and EtOAc successively. Hexane extracts were a mixture of oleanolic acid and maslinic acid (80:20), whereas this relationship was 20:80 for the EtOAc extracts. Both products were purified from these mixtures by CC over silica gel, eluting with a $CHCl_3$/MeOH or CH_2Cl_2/acetone mixture of increasing polarity. **1** and **2** were transformed into the corresponding methyl esters with ethereal CH_2N_2 or NaOH/Ime, and thus, methyl 3β-hydroxy-12-oleanen-28-oate (**3**)[13] and methyl 2α,3β-dihydroxy-12-oleanen-28-oate (**4**)[13] were obtained.

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 CH_2Cl_2, and 1.1 mL of Cl_2SO was added. The reaction was maintained with stirring at 0 °C for 5 min. The reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated aqueous $KHSO_4$, neutralized with saturated aqueous $NaHCO_3$, dried with anhydrous Na_2SO_4, and evaporated at reduced pressure. Chromatography over silica gel yielded 1.65 g (99%) of **5** (50% ee) and **6** (50% ee). Data for **5**: white solid; mp 176−178 °C; $[\alpha]^{25}_D$ = 61 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3488, 2948, 2880, 1724, 1461, 1214, 996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.27 (1H, dd, *J* = 3.4, 3.5 Hz, H-12), 4.11 (1H, ddd, *J* = 4.1, 10.6, 14.7 Hz, H-2β), 3.99 (1H, d, *J* = 10.6 Hz, H-3α), 3.61 (3H, s, COO*CH*$_3$), 2.86 (1H, dd, *J* = 4.5, 13.9 Hz, H-18β), 2.24 (1H, dd, *J* = 4.1, 11.8 Hz, H-1β), 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 ^{13}C NMR see Table S-1 and spectrum S-2 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_5$SNa 555.3120, found 555.3121. Data for **6**: white solid; mp 111−113 °C; $[\alpha]^{25}_D$ = 54 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3412, 2947, 2867, 1725, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.28 (1H, dd, *J* = 3.2, 3.4 Hz, H-12), 4.61 (1H, ddd, *J* = 4.0, 10.6, 11.8 Hz, H-2α), 3.61 (3H, s, COO*CH*$_3$), 3.46 (1H, d, *J* = 10.6 Hz, H-3 α), 2.86 (1H, dd, *J* = 4.5, 13.6 Hz, H-18β), 2.25 (1H, dd, *J* = 4.0, 11.7 Hz, H-1β), 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 ^{13}C NMR see Table S-1 and spectrum S-3 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_5$SNa 555.3120, found 555.3112.

Oxidation with $NaIO_4$/$RuCl_3$ of Sulfites 5 and 6. $NaIO_4$ (750 mg, 3.6 mmol) and $RuCl_3 \cdot 3H_2O$ (approximately 5 mg) in water (15 mL) were added to a solution of **5** and **6** (1.3 g) in CCl_4 (10 mL) and CH_3CN (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, a saturated solution of $NaHCO_3$, and a NaCl solution and dried over anhydrous Na_2SO_4. 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; $[\alpha]^{25}_D$ = 45 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2948, 1724, 1383, 1212 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.26 (1H, dd, *J* = 3.6 Hz, H-12), 4.89 (1H, ddd, *J* = 4.3, 10.4, 11.9 Hz, H-2β), 4.27 (1H, d, *J* = 10.4 Hz, H-3α), 3.61 (3H, s, COO*CH*$_3$), 2.86 (1H, dd, J_1 = 4.6, 13.7 Hz, H-18β), 2.20 (1H, dd, *J* = 4.3, 11.8 Hz, H-1β), 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 ^{13}C NMR see Table S-1 and spectrum S-4 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_6$SNa 571.3151, found 571.3159.

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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/H_2O (70%) containing KOH (20%) was added. The reaction was maintained with stirring at reflux for 30 min. The reaction mixture was washed with diluted HCl solution, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and evaporated at reduced pressure. Chromatography over silica gel yielded 27 mg of **8**[13b] (50%) and 26 mg of **9** (50%): white solid; mp 200−202 °C; $[\alpha]^{25}_D = 45$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2948, 1726, 1161 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.29 (1H, dd, $J = 3.6$ Hz H-12), 3.61 (3H, s, COOCH_3), 3.17 (1H, ddd, $J = 3.9$ Hz, H-2β), 2.85 (1H, dd, $J = 4.4$, 14.1 Hz, H-18β), 2.78 (1H, $J = 3.9$ Hz, H-3β), 1.08 (6H, s, Me), 0.99 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.81 (3H, s, Me), 0.69 (3H, s, Me); for ^{13}C NMR see Table S-1 and spectrum S-5 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_3Na$ 491.3501, found 491.3500.

Formation of 2β,3β-Epoxide 8 by Mitsunobu Reaction. Product **4** (3 g, 6 mmol) was dissolved in 20 mL of DMF, and 4.7 g (18 mmol) of PPh_3 was added. The reaction mixture was maintained with stirring at 0 °C, and then a solution of 2.8 g of diethyl azodicarboxylate (DEAD) (18 mmol) in 2 mL of DMF was added. This mixture was stirred at reflux for 2 h, and then 120 mL of toluene/diethyl ether (3:1) was added to remove DMF, with evaporation at reduced pressure. The residue was extracted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4, and evaporated at reduced pressure. The residue was chromatographed to obtain 2.4 g of **8** (87%).

Formation of 8 via Tosylation. Product **4** (3.4 g, 6.9 mmol) was dissolved in 25 mL of pyridine, and 3.4 g of TsCl (14 mmol) was added. The reaction mixture, after being maintained with stirring at room temperature for 3 h, was washed with a diluted HCl solution to remove pyridine, extracted with CH_2Cl_2, washed with water plus a saturated solution of $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was chromatographed to provide 1.9 g of a 2α-tosyl derivative (42%). After this monotosylate (600 mg) was dissolved in 10 mL of anhydrous MeOH, 125 mg of Na (5 mmol) in 10 mL of anhydrous MeOH was added, and the mixture was stirred at reflux for 1 h. Afterward, 1 mL of glacial AcOH 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 535 mg of **8** (95%).

Treatment of Cyclic Sulfate 7 on Solid Support. Product **7** (200 mg, 0.4 mmol) and SiO_2 (400 mg, GF_{254} type 60, pH 7) were mixed in CH_2Cl_2. The reaction mixture was maintained with stirring at reflux for 3 h, filtered, and evaporated at reduced pressure. Chromatography over silica gel yielded 100 mg (50%) of **10**: syrup; $[\alpha]^{25}_D = 88$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2948, 1725, 1161, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.24 (1H, dd, $J = 0.0$, 10.2 Hz, H-2), 5.45 (1H, dd, $J = 0.0$, 10.0 Hz, H-6), 5.45 (1H, dd, $J = 2.1$ Hz, H-12), 3.62 (3H, s, COOCH_3), 2.87 (1H, dd, $J_1 = 3.7$, 13.7 Hz, H-18β), 2.75 (1H, h, $J = 6.8$ Hz, H-4), 1.07 (3H, s, Me), 0.97 (3H, d, $J = 6.9$ Hz, Me), 0.95 (3H, d, $J = 6.8$ Hz, Me), 0.91 (6H, s, Me), 0.88 (3H, s, Me), 0.87 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-6 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{46}O_2Na$ 473.3395, found 473.3387. This type of reaction was also carried out with basic and neutral alumina under the same above-mentioned conditions and proportions, but no changes were detected. Moreover, this reaction was carried out with SiO_2 (GF_{254} type 60, pH 7) in the same proportions and under acidic conditions with HCl at pH 2. Thus, product **7** (50 mg) was dissolved in CH_2Cl_2, and a pH 2 HCl solution was added. The reaction mixture was maintained at reflux for 8 h, and a low proportion of **10** (5%) was observed by TLC.

Opening of Sulfate 7 with NaN_3. Product **7** (250 mg, 0.5 mmol) was dissolved in 10 mL of DMF, and 175 mg of NaN_3 (2.7 mmol) in 15 mL of DMF and 15 mL of an aqueous H_2SO_4 solution (20%) were added. The mixture was maintained with stirring for 30 min. Then it was neutralized with a saturated solution of $NaHCO_3$, washed with water, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and evaporated at reduced pressure. The resulting residue was chromatographed on a silica gel column to yield 93 mg of **11** (40%), 25 mg of **12** (10%), and 36 mg of **13** (15%). Data for **11**: white solid; mp 95−97 °C; $[\alpha]^{25}_D = 42$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3371, 2949, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.28 (1H, dd, $J = 3.4$ Hz, H-12), 4.83 (1H, br s, H-23), 4.80 (1H, br s, H-23), 4.52 (1H, ddd, $J =$ 4.5, 8.0, 12.6 Hz, H-2α), 3.61 (3H, s, COOCH_3), 2.84 (1H, dd, $J = 4.2$, 13.9 Hz, H-18β), 2.53 (1H, dd, $J = 4.5$, 11.4 Hz, H-1α), 2.12 (1H, dd, $J = 8.0$, 11.4 Hz, H-1β), 1.79 (3H, s, Me), 1.15 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.84 (3H, s, Me), 0.72 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-7 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_3Na$ 491.3501, found 491.3493. Data for **12**: white solid; mp 72−73 °C; $[\alpha]^{25}_D = 21$ (*c* 1, $CHCl_3$); IR 3396, 2948, 1726, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, s, HO_3SO-), 5.53 (1H, ddd, $J = 4.3$, 7.5, 11.9 Hz, H-2α), 5.27 (1H, dd, $J = 3.5$ Hz, H-12), 4.87 (1H, br s, H-23), 4.85 (1H, br s, H-23), 3.61 (3H, s, COOCH_3), 2.84 (1H, dd, $J = 4.6$, 13.6 Hz, H-18β), 2.74 (1H, dd, $J = 4.3$, 11.4 Hz, H-1α), 2.29 (1H, dd, $J = 7.5$, 11.4 Hz, H-1β), 1.78 (3H, s, Me), 1.15 (3H, s, Me), 0.91 (6H, s, Me), 0.89 (3H, s, Me), 0.72 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-8 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_6SNa$ 571.7724, found 571.7720. Data for **13**: syrup; $[\alpha]^{25}_D = 50$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3318, 2933, 1723, 1159, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.28 (1H, dd, $J = 3.5$ Hz, H-12), 4.23 (1H, m, H-2α), 3.61 (3H, s, COOCH_3), 2.84 (1H, dd, $J = 4.1$, 14.0 Hz, H-18β), 1.29 (3H, s, Me), 1.19 (3H, s, Me), 1.12 (3H, s, Me), 1.02 (3H, s, Me), 0.91 (3H, s, Me), 0.88 (3H, s, Me), 0.73 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-9 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{50}O_4Na$ 509.3607, found 509.3608.

Reduction of Sulfate 7 with $NaBH_4$. Product **7** (100 mg, 0.2 mmol) was dissolved in 5 mL of DMF, and after addition of 10 mg of $NaBH_4$, 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. The residue was extracted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, and finally evaporated at reduced pressure. 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; $[\alpha]^{25}_D = 66$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2948, 1725, 1162, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.30 (2H, br s, H-1 and H-2), 5.33 (1H, dd, $J = 3.6$ Hz, H-12), 4.97 (1H, br s, H-23), 4.96 (1H, br s, H-23), 3.64 (3H, s, COOCH_3), 2.00 (3H, s, Me), 1.03 (3H, s, Me), 0.97 (3H, s, Me), 0.94 (3H, s, Me), 0.91 (3H, s, Me), 0.87 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-10 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{44}O_2Na$ 471.3239, found 471.3236. Data for **15**: white solid; mp 71−73 °C; $[\alpha]^{25}_D = 7$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2927, 1628, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.30 (1H, dd, $J = 3.6$ Hz, H-12), 5.20 (1H, dd, $J = 3.7$ Hz, H-2), 4.97 (1H, br s, H-23), 4.96 (1H, br s, H-23), 3.62 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 4.3$, 13.6 Hz, H-18β), 1.19 (3H, s, Me), 0.99 (6H, d, $J = 6.8$ Hz, Me), 0.92 (3H, s, Me), 0.87 (3H, s, Me), 0.82 (3H, s, Me), 0.80 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-11 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{48}O_2Na$ 475.3552, found 475.3555. Data for **16**: syrup; $[\alpha]^{25}_D = 107$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2947, 1726, 1161, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.67 (1H, dd, $J = 3.0$, 5.2 Hz, H-2), 5.30 (1H, dd, $J = 3.5$ Hz, H-12), 4.97 (1H, br s, H-23), 4.83 (1H, br s, H-23), 3.61 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 3.9$, 13.7 Hz, H-18β), 1.87 (3H, s, Me), 1.19 (3H, s, Me), 0.91 (3H, s, Me), 0.88 (3H, s, Me), 0.87 (3H, s, Me), 0.80 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-12 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{46}O_2Na$ 473.3395, found 473.3396.

Reduction of Sulfate 7 with $NaBH_3CN$. To a solution of 200 mg of **7** (0.4 mmol) in 7 mL of DMF was added 40 mg of

$NaBH_3CN$, and this mixture was maintained with stirring at 115 °C for 2 h and 30 min. Small amounts of toluene were added to remove DMF, with evaporation at reduced pressure, and the residue was extracted with CH_2Cl_2, washed with water, dried over anhydrous Na_2SO_4, 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 $AlLiH_4$. Product **7** (150 mg, 0.3 mmol) was dissolved in 3 mL of THF, 1 mL of a 0.1 M solution of $AlLiH_4$ in THF was added, and the mixture was maintained at room temperature for 3 h. This mixture was diluted with CH_2Cl_2, washed with water, dried with anhydrous Na_2SO_4, 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; $[\alpha]^{25}_D = 48$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3420, 2949, 1380, 1211 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 (1H, dd, $J = 3.6$ Hz, H-12), 4.90 (1H, ddd, $J = 4.2$, 10.4, 11.2 Hz, H-2), 4.28 (1H, d, $J = 10.4$ Hz, H-3α), 3.52 (1H, d, $J = 10.9$ Hz, H-28), 3.19 (1H, d, $J = 10.9$ Hz, H-28), 2.23 (1H, dd, $J = 4.2$, 11.8 Hz, H-1α), 1.16 (3H, s, Me), 1.12 (3H, s, Me), 1.10 (3H, s, Me), 1.00 (3H, s, Me), 0.95 (3H, s, Me), 0.88 (3H, s, Me), 0.87 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-13 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{30}H_{48}O_5SNa$ 543.3120, found 543.3129. Data for **18** (38%): white solid; mp 137−139 °C; $[\alpha]^{25}_D = 115$ (*c* 1, $CHCl_3$); IR 3385, 2947, 1460, 1046 ($CHCl_3$) cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 5.18 (1H, dd, $J = 3.6$ Hz, H-12), 3.68 (1H, ddd, $J = 4.5$, 9.5, 11.3 Hz, H-2β), 3.54 (1H, d, $J = 11.0$ Hz, H-28) 3.19 (1H, d, $J = 11.0$ Hz, H-28), 2.99 (1H, d, $J = 9.5$ Hz, H-3), 1.15 (3H, s, Me), 1.02 (3H, s, Me), 0.98 (3H, s, Me), 0.92 (3H, s, Me), 0.87 (3H, s, Me), 0.86 (3H, s, Me), 0.81 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-14 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{30}H_{50}O_3Na$ 481.3658, found 481.3656.

Reductive Opening of Epoxide 8 with $NaBH_3CN$. Product **8** (150 mg, 0.3 mmol) was dissolved in 9 mL of THF, and 120 mg of $NaBH_3CN$ (1.8 mmol) was added. A solution of 0.3 mL of CF_3COOH in 6 mL of THF was added, and the resulting mixture was stirred at several temperatures for different times. Trifluoroacetic acid was neutralized with $NaHCO_3$, and the mixture was washed with water, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and evaporated. Chromatography over silica gel yielded different products (**3** and **4**) in different amounts (see Table 1).

Reductive Opening of Epoxide 8 with $AlLiH_4$. Product **8** (150 mg, 0.3 mmol) was dissolved in 1 mL of a 0.1 M solution of $AlLiH_4$ in THF, and the mixture was maintained with stirring under different conditions (Table 1). After 1 h, the reaction mixture was evaporated at reduced pressure, and the resulting residue was chromatographed on a silica gel column to obtain **3**, **4**, **19**,[15] and **20** in different quantities (see Table 1). Data for **20**: syrup; $[\alpha]^{25}_D = 98$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3417, 2948, 2867, 756 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 5.19 (1H, dd, $J = 3.6$ Hz, H-12), 3.52 (1H, d, $J = 10.8$ Hz, H-28), 3.22 (1H, dd, $J = 2.0$, 3.9 Hz, H-2α), 3.19 (1H, d, $J = 10.8$ Hz, H-28), 2.81 (1H, dd, $J = 4.0$ Hz, H-3α), 1.13 (3H, s, Me), 1.07 (3H, s, Me), 1.07 (3H, s, Me), 0.99 (3H, s, Me), 0.91 (3H, s, Me), 0.87 (3H, s, Me), 0.86 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-15 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{30}H_{48}O_2Na$ 463.3552, found 463.3544.

Opening of 8 with I_2 and PPh_3. To a mixture of 51 mg of I_2 (0.2 mmol), 53 mg of triphenylphosphine (0.2 mmol), and 7 mL of CH_2Cl_2 was added a solution of product **8** (150 mg, 0.3 mmol) in 3 mL of CH_2Cl_2. The resulting mixture was stirred for 30 min at different temperatures (Table 2). When the reaction was finished, the mixture was washed with a diluted solution of $Na_2S_2O_3{\cdot}5H_2O$, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated. Depending on the conditions (see Table 2), chromatography over silica gel yielded different amounts of **21**,[13a] **22**, and **23**. Data for **22**: syrup; $[\alpha]^{25}_D = 22$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3424, 2946, 1722, 1162, 756 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 5.26 (1H, dd, $J = 3.6$ Hz, H-12), 4.57 (1H, ddd, $J = 4.2$, 10.7, 12.8 Hz, H-2β), 3.60 (3H, s, COOCH_3), 3.32 (1H, dd, $J = 3.4$, 10.7 Hz, H-3α), 2.84 (1H, dd, $J = 4.2$, 13.8 Hz, H-18β), 2.41 (1H, dd, $J = 4.2$, 12.9 Hz, H-1β), 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 ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-16 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{49}O_3INa$ 619.2624, found 619.2628. Data for **23**: syrup; $[\alpha]^{25}_D = 66$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3402, 2943, 1723, 1124 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (1H, dd, $J = 3.6$ Hz, H-12), 4.73 (1H, d, $J = 4.8$ Hz, H-3α), 4.01 (1H, ddd, $J = 4.8$, 9.4, 10.5 Hz, H-2β), 3.61 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 4.5$, 14.4 Hz, H-18β), 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 ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-17 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{49}O_3INa$ 619.2624, found 619.2623.

Reduction of 8 with WCl_6 and *n*-BuLi. A solution of 160 mg of WCl_6 (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*-BuLi (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 CH_2Cl_2. The organic layer was washed twice with water, dried with anhydrous Na_2SO_4, 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; $[\alpha]^{25}_D = 50$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3404, 2947, 1724, 1125 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 5.27 (1H, dd, $J = 3.6$ Hz, H-12), 4.57 (1H, ddd, $J = 4.3$, 10.2, 12.2 Hz, H-2β), 3.61 (3H, s, COOCH_3), 3.17 (1H, d, $J = 10.2$ Hz, H-3α), 2.85 (1H, dd, $J = 4.5$, 13.8 Hz, H-18β), 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 ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-18 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{49}O_3ClNa$ 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 $NaHCO_3$, washed with water, extracted with CH_2Cl_2, and evaporated at reduced pressure. The resulting residue was chromatographed on a silica gel column to provide 45 mg of **24** (89%) and 5 mg of **25** (10%): white solid; mp 151−153 °C; $[\alpha]^{25}_D = 74$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3395, 2925, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (1H, dd, $J = 3.9$ Hz, H-12), 4.22 (1H, d, $J = 10.6$ Hz, H-3α), 3.86 (1H, ddd, $J = 4.4$, 10.6, 12.4 Hz, H-2β), 3.61 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 4.1$, 13.9 Hz, H-18β), 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), 0.89 (3H, s, Me), 0.71 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-19 in the Supporting Information; HRLSIMS *m*/*z* calcd for $C_{31}H_{46}O_3ClNa$ 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), and the resulting mixture was maintained at reflux for 1 h. Then the reaction mixture was neutralized with a diluted solution of $NaHCO_3$, washed with water, extracted with CH_2Cl_2, and evaporated at reduced pressure. Chromatography over silica gel yielded 47 mg of **26** (85%) and 8 mg of **27** (15%). Data for **26**: white solid; mp 170−172 °C; $[\alpha]^{25}_D = 23$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3356, 2931, 1609, 1117 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 5.26 (1H, dd, $J = 3.6$ Hz, H-12), 4.35 (1H, ddd, $J = 4.3$, 10.4, 12.4 Hz, H-2β), 3.61 (3H, s, COOCH_3), 3.27 (1H, dd, $J = 2.0$, 10.4 Hz, H-3α), 2.85 (1H, dd, $J = 4.5$, 13.9 Hz, H-18β), 1.12 (3H, s, Me), 1.09 (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 ^{13}C NMR ($CDCl_3$) see Table S-2

and spectrum S-20 in the Supporting Information; HRLSIMS *m/z* calcd for $C_{31}H_{49}O_3BrNa$ 571.2763, found 571.2757. Data for **27**: white solid; mp 72−74 °C; $[\alpha]^{25}_D = 74$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3462, 2947, 1723, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.29 (1H, dd, $J = 3.6$ Hz, H-12), 4.49 (1H, d, $J = 10.9$ Hz, H-3α), 3.97 (1H, ddd, $J = 4.4$, 10.9, 12.3 Hz, H-2β), 3.61 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 3.9$, 13.7 Hz, H-18β), 1.12 (3H, s, Me), 1.09 (6H, s, Me), 1.05 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.71 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-21 in the Supporting Information; HRLSIMS *m/z* calcd for $C_{31}H_{49}O_3BrNa$ 571.2763, found 571.2762.

Acetolysis of 8. Product **8** (100 mg. 0.2 mmol) was dissolved in 4 mL of a solution of AcOK/AcOH (0.5 N), and this mixture was maintained with stirring at reflux for 3 h. The reaction was neutralized with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and evaporated. The resulting residue was chromatographed on a silica gel column to yield 48 mg of **28**[13a] (45%) and 42 mg of **29**[13a] (40%).

Treatment of 8 with TFA/DMF. Product **8** (100 mg, 0.2 mmol) was dissolved in 10 mL of DMF, 0.2 mL of trifluoroacetic acid was added, and the resulting mixture was maintained at reflux for 2 h. The reaction mixture was neutralized with a saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, and evaporated. The products were chromatographed on a silica gel column to provide 33 mg of **30** (32%) and 36 mg of **31** (34%). Data for **30**: white solid; mp 110−112 °C; $[\alpha]^{25}_D = 15$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2947, 1724, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, s, *H*COO-), 5.26 (1H, dd, $J = 3.6$ Hz, H-12), 5.03 (1H, ddd, $J = 4.4$, 10.6 Hz, H-2β), 3.61 (3H, s, COOCH_3), 3.23 (1H, d, $J = 10.6$ Hz, H-3α), 2.85 (1H, dd, $J = 4.7$, 13.8 Hz, H-18β), 1.11 (3H, s, Me), 1.05 (3H, s, Me), 1.02 (3H, s, Me), 0.91 (3H, s, Me), 0.88 (3H, s, Me), 0.86 (3H, s, Me), 0.71 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-22 in the Supporting Information; HRLSIMS *m/z* calcd for $C_{32}H_{50}O_5Na$ 537.3556, found 537.3555. Data for **31**: white solid; mp 211−213 °C; $[\alpha]^{25}_D = 24$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3415, 2947, 1725, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.26 (1H, s, *H*COO−), 5.28 (1H, dd, $J = 3.7$ Hz, H-12), 4.53 (1H, d, $J = 9.9$ Hz, H-3α), 3.84 (1H, ddd, $J = 4.3$, 9.9, 12.1 Hz, H-2β), 3.61 (3H, s, COOCH_3), 2.85 (1H, dd, $J = 4.5$, 13.9 Hz, H-18β), 1.12 (3H, s, Me), 0.99 (3H, s, Me), 0.91 (6H, s, Me), 0.89 (3H, s, Me), 0.88 (3H, s, Me), 0.71 (3H, s, Me); for ^{13}C NMR ($CDCl_3$) see Table S-2 and spectrum S-23 in the Supporting Information; HRLSIMS *m/z* calcd for $C_{32}H_{50}O_5Na$ 537.3556, found 537.3555.

Treatment of 3 with PCl_5. Product **3** (870 mg, 1.8 mmol) was dissolved in 50 mL of Cl_4C_2, and 1.125 mg of PCl_5 (5.4 mmol) was added. The resulting mixture was maintained with stirring at −15 °C for 25 min. Then the mixture was washed with water, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and evaporated at reduced pressure. The obtained products were chromatographed over silica gel with $AgNO_3$ (10%) to obtain 651 mg (80%) of **32**[13a] and 122 mg (15%) of **33**.[13a]

Ozonolysis of 32. Product **32** (220 mg, 0.5 mmol), after being dissolved in 15 mL of CH_2Cl_2 and 1.5 mL of pyridine, was stirred at −72 °C and passed through an O_3 flow, <0.1 L/min (50% O_2/50% O_3). After 20 min, 1.5 mL of Me_2S was added to reduce excess ozone. This mixture was maintained with stirring and meanwhile was cooled for 3 h. Then it was evaporated and purified over silica gel, yielding 146 mg (68%) of **34**: mp 129−131 °C; $[\alpha]^{25}_D = 12$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2947, 1739, 1161, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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-18β), 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* calcd for $C_{28}H_{42}O_3Na$ 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 with toluene, and the resulting residue was washed with a diluted solution of HCl, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and finally evaporated at reduced pressure and purified over silica gel to yield 45 mg (93%) of **35**: mp 131−133 °C; $[\alpha]^{25}_D = 74$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3292, 2948, 1725, 1162, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 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-18β), 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* calcd for $C_{28}H_{43}O_3NNa$ 464.3141, found 464.3143.

Beckmann Rearrangement of 35 with PCl_5. Product **35** (25 mg, 0.06 mmol) was dissolved in 3 mL of diethyl ether, and 50 mg of PCl_5 (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 CH_2Cl_2, dried with Na_2SO_4, evaporated, and purified, yielding 18 mg (70%) of **36**: mp 134−136 °C; $[\alpha]^{25}_D = 72$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2947, 1726, 1666, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.69 (1H, br s, N*H*), 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-18β), 1.13 (3H, s, Me), 0.93 (3H, s, Me), 0.91 (3H, s, Me), 0.89 (3H, s, Me), 0.81 (3H, s, Me); for ^{13}C NMR see Table S-1 and spectrum S-26 in the Supporting Information; HRLSIMS *m/z* calcd for $C_{28}H_{43}O_3NNa$ 464.3141, found 464.3145.

Acknowledgment. This work was supported by a grant from the Comisión Interministerial de Ciencia y Tecnología and by a project from the Ministerio de Educación y Cultura (No. PM98-0213). Computing time was provided by the Universidad de Granada. We thank David Nesbitt for reviewing the language of the original English manuscript.

Supporting Information Available: Table S-1 with the calculated and experimental δ_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**, **31**, and **34**−**36** (PDF), Table S-2 with the experimental δ_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.

JO026832S