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$BF_3 \cdot Et_2O$-catalyzed rearrangement of 7-epimeric 3β,7-diacetoxy-9β,11β-epoxy-5α-lanostanes. Formation of novel 19(10→9β)*abeo*- and 19(10→9β),30(14→8α)bis-*abeo*-lanostane derivatives☆

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Dedicated to the memory of Dr. Oliver E. Edwards

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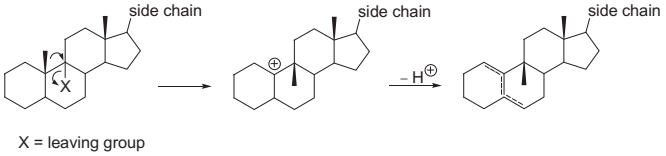
ABSTRACT

The boron trifluoride etherate catalyzed reaction of 7-epimeric 3β,7-diacetoxy-9β,11β-epoxy-5α-lanostanes **1** and **2** in acetic anhydride resulted in the formation of a series of skeletally rearranged products, mainly 19(10→9β)*abeo*-lanostanes. 19(10→9β),30(14→8α)Bis-*abeo*-lanostane derivative **5** possessing a novel type of the triterpene skeleton was formed as the major product in the reaction of 7α-epimer **2**. The direction and extent of rearrangements of 9β,11β-epoxides **1** and **2** depends on the configuration of the 7-acetoxy group. The structures of the new compounds were determined on the basis of spectroscopic methods, mainly ^1H and ^{13}C NMR. The structure of compound **5** was confirmed by single-crystal X-ray diffraction.

1. Introduction

19(10→9β)*Abeo*-5α-lanostane (5α-cucurbitane) constitutes the basic skeleton of cucurbitacins, highly oxygenated natural tetracyclic triterpenes of plant origin.[1–4] The 19(10→9β)*abeo*-steroids are synthetically available from the reaction of 9-substituted steroid derivatives in which scission of the C(9)-X (X=leaving group) bond is followed by the migration of the 10β-methyl group to C-9 (Scheme 1).[5,6] In triterpenes, Lewis acid catalyzed reaction of 9,11-epoxylanostanes resulted in the synthesis of compounds having a cucurbit-5-ene[7,8] and a protost-13(17)-ene[9] skeleton as the major products. By this approach compounds closely related to natural cucurbitacin, bryogenin,[8] and to steroid antibiotic, fusidic acid,[10] have been synthesized.



Scheme 1.

The 19(10→9β)*abeo*-lanost-1(10)-ene and the corresponding 5(10)-ene derivatives have also been obtained under Westphalen dehydration conditions from 11-oxo- or 11α-acetoxy-9α-hydroxy-5α-lanostane derivatives, some of them bearing additional 7-oxo- and 7-acetoxy groups.[11,12] However, the compounds possessing a double bond in position 5, characteristic for natural cucurbitacins, have not been found among the products of those rearrangements.

In reactions of 9,11-epoxy-7-oxo-5α-lanostane derivatives, the 7-carbonyl group effectively suppressed formation of the transient carbocationic center at C-8.[8,13] Thus, the migration of C-19 to C-9[8] or C-18 to C-12[13] was the dominant process in the reaction of 7-oxo-9β,11β- or 7-oxo-9α,11α-epoxides, respectively, carried out in acetic anhydride. The 9α,11α-epoxides of 5α-lanostane and 4β-demethyl-5α-lanostane, which were not substituted at C-7 rearranged to compounds possessing the protost-13(17)-ene[9] or the fusid-13(17)-ene[10] skeleton, respectively. Therefore, it appears that, beside the solvent used, configuration of C-9 and functionalization at C-7 of the 9,11-epoxylanostane are important factors in these transformations. The results reported by us[8,10,13,14] and other groups[11,15,16] prompted our further studies to better understand the structural requirements and factors involved in the reactions of 5α-lanostane derivatives proceeding via a C-9 carbocation intermediate. In this respect the investigation of the rearrangement of the 9β,11β-epoxy-5α-lanostane derivative bearing no 7-oxo group appeared particularly interesting.

The attempts to prepare 3-substitiuted 9β,11β-epoxy-5α-lanostane lacking a substituent in position 7 were unsuccessful.[15,17] The

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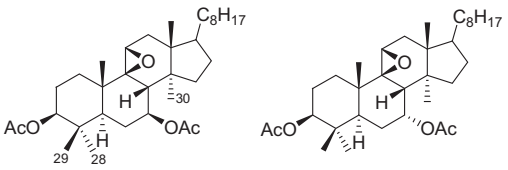
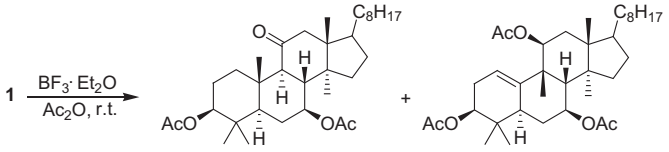
other interesting substrates, 3β,7β- and 3β,7α-diacetoxy-9β,11β-epoxy-5α-lanostane, **1**, and **2**, respectively, could be prepared from the respective 7-oxo derivative.[18] Since acetic anhydride was found previously as the solvent of choice for the effective skeletal rearrangement of steroid epoxides,[8,10,13,14] the studies of reactions of epoxides **1** and **2** in that solvent were undertaken and are reported.



1 **2**

2. Results and discussion

The boron trifluoride etherate catalyzed reaction of 7β-acetoxy-9β,11β-epoxide **1** carried out in acetic anhydride at room temperature gave two products (Scheme 2) isolated by chromatography. The major compound (63% yield) was identified as already known 11-ketone **3**[18] by comparing its ^{1}H and ^{13}C NMR spectra with those of the original sample. The second product, obtained in 26% yield, was a compound, which was shown to have the 5α-cucurbitane skeleton. Structure **4** was assigned from the analysis of NMR spectra. The ^{1}H NMR spectrum displayed three signals for the acetoxyl groups at δ_H 2.01, 1.99, and 1.98. The four other characteristic low-field signals at δ_H 5.70, 5.59, 5.07, and 4.66 were ascribed to protons H-1, H-11α, H-7α, and H-3α, respectively. The placement of the double bond in position 1(10) was evident from the analysis of the ^{1}H–^{1}H COSY spectrum, in which the spin system of four protons in positions 1, 2α, 2β, and 3α was detected. Proton H-1 correlated with H-5α (δ_H 2.17) and gave cross peaks with H-2β (δ_H 1.89) and H-2α (δ_H 2.42), while these two signals gave cross peaks with H-3α. In addition, the ^{1}H–^{1}H COSY correlation of H-11α with H-12β (δ_H 1.67) and H-12α (δ_H 1.81) and also of H-7α with H_2-6 (δ_H 1.44 and 2.17) and H-8β (δ_H 2.00) was observed. The resemblance of the ^{1}H NMR spectrum of **4** and that of its 7α epimer, compound **9** (vide infra), was evident. The ^{13}C NMR spectrum of **4** displayed 36 signals, among them all characteristic low-field signals attributable to three acetoxyl carbonyl groups and two remaining sp^2 carbon atoms (see Experimental).

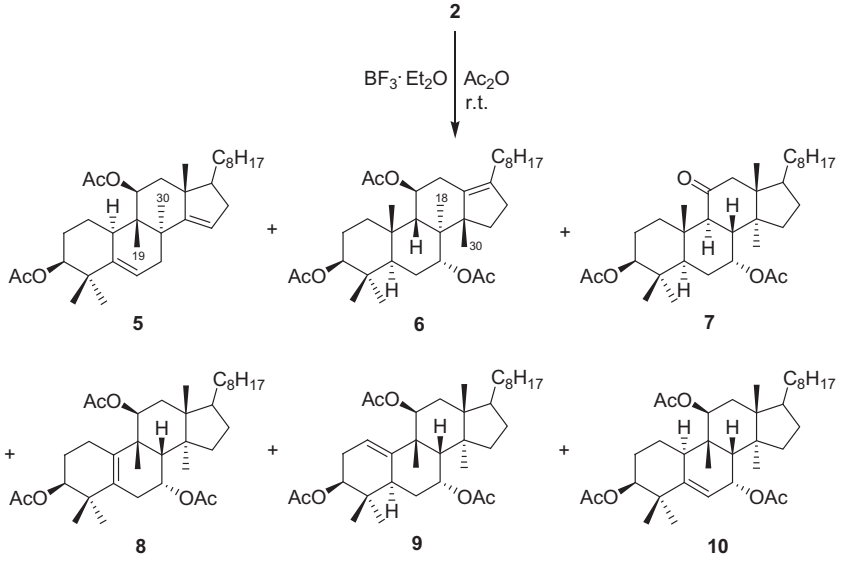


Scheme 2.

A far more interesting result was obtained when 7α-acetoxy-9β,11β-epoxide **2** was subjected to the same reaction conditions (Scheme 3). The reaction of epoxide **2** afforded a complicated mixture of several products (TLC monitoring). The compounds were separated by a combination of column and preparative thin layer chromatography. After tedious separation four novel compounds **5**, **6**, **8**, and **9** were isolated and characterized in addition to the two known substances **7** and **10**. The compounds are described in the order of their increasing polarity.

The less polar compound was the most abundant product, isolated in 23% yield. It was identified as 3β,11β-diacetoxy-19(10→9β),30(14→8α)bis-*abeo*-lanosta-5,14-diene **5**. The ^{1}H NMR spectrum of **5** in $CDCl_3$ showed the presence of signals indicating two acetoxyl groups (δ_H 2.08 and 2.03) and two vinylic protons (narrow signal at δ_H 5.52). The signal of H-11α appeared at δ_H5.09 as a characteristic doublet (J=7.14 Hz). The narrow signal of H-3α at δ_H 4.49 (t, J=2.7 Hz) indicated the inversion of configuration[8] at C-10 thus implying the migration of the 10-methyl group to position 9β. This was confirmed by the analysis of 2D ^{1}H NMR spectra (vide infra). The ^{13}C NMR spectrum displayed 34 signals, among them all relevant low-field signals: two acetate carbonyl carbon atoms at δ_C 170.5 and 170.3 and four remaining sp^2 carbon atom signals (δ_C 162.5, 141.5, 121.6, and 118.3) pointing to the presence of two trisubstituted C–C double bonds, which were not conjugated, as indicated by the lack of absorption above 220 nm in the UV spectrum. The unusual *abeo*-cucurbitane skeleton, as in compound **5**, could be identified by the analysis of 2D NMR data, including COSY, TOCSY and HETCOR experiments.

In the ^{1}H–^{1}H COSY and TOCSY spectra of **5**, recorded for a solution in C_6D_6, proton H-3α (δ_H 4.88) displayed a correlation with H_2-2 (δ_H 1.85 and 1.65), H_2-1 (δ_H 1.68 and 1.40), and with H_3-28 (δ_H 0.83), while H-10α(δ_H 2.10) gave cross peaks with H_2-1 and H-2 (δ_H 1.85) thus confirming the six proton spin system of ring A. Proton H-11α (δ_H 5.38) correlated with H_2-12 (δ_H 2.36 and 2.30) and with



Scheme 3.

H-10α. The signal of vinylic protons H-6 and H-15 (both at δ_H 5.51), correlated with H_2-7 and H_2-16, which gave a multiplet at δ_H 2.0–2.35. In the ^1H–^1H COSY 90–45 spectrum of **5** (in C_6D_6), the signals of methyl groups H_3-19 (δ_H 1.37), H_3-30 (δ_H 1.32), and H_3-18 (δ_H 0.97) gave cross peaks with H-10α, H_2-7 (δ_H 2.33 and 2.24), and H_2-12, respectively.

Although structure **5** for the major product appeared well justified, further confirmation was obtained by single-crystal X-ray analysis. Figure 1 shows a perspective view of molecule **5**. The conformation of the four-ring system can be described as close to chair(A)/sofa(B)/half-chair(C)/half-chair(D). The ring junctions are quasi-*cis* (A/B), *trans* (B/C), and quasi-*cis* (C/D). Both acetoxy substituents are in axial positions at C-3 and C-11. The presence of two carbon–carbon double bonds is confirmed by their lengths of 1.317(8)Å for C-5–C-6 and 1.334(7)Å for C-14–C-15.

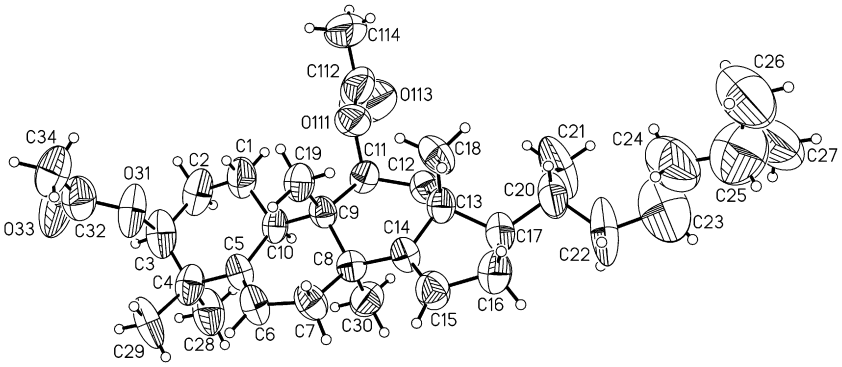


Figure 1. Anisotropic ellipsoid representation of **5**.[19] The ellipsoids are drawn at 30% probability level.

The second product of the reaction of epoxide **2** was 3β,7α,11β-triacetoxy-5α-protost-13(17)-ene (**6**), isolated in 16% yield. This unusual and rather unexpected structure resulting from the extensive rearrangement of **2** was established through detailed analysis of the NMR spectra. The presence of three acetoxyl groups and a tetrasubstituted C–C double bond was evidenced by the relevant signals in the ^1H and ^{13}C NMR spectra (see Experimental). The other characteristic low-field signals were those of protons in the allylic position: H-12α (quartet at δ_H 2.92), H-20 (multiplet at δ_H2.44) and of H_2-16 (multiplet at δ_H 2.15). For the placement of the double bond in position 13(17) decoupling experiments were crucial because they showed the coupling of proton H-20 with the protons of methyl group CH_3-21 (δ_H 0.96) and of proton H-11α (δ_H 4.94) with H-12α. The ^1H and ^{13}C NMR spectra of compound **6** correlated well with the spectral data reported for diacholestenes[20] and those obtained for 3β-benzoyloxy-11α-acetoxy-5α,9β-protost-13(17)-ene synthesized by us previously.[10,14]

The third product was obtained as a crystalline compound in 9.5% yield. The ^1H and ^{13}C NMR spectra (see Experimental) showed signals indicating the presence of two acetoxyl groups and a signal of a carbonyl carbon at δ_C 211.5. Thus, the compound was assumed to be ketone **7**, a product of a 1,2-hydrogen shift in epoxide **2**. This was confirmed by the comparison of the ^1H and ^{13}C NMR spectra of **7** with those of the original sample[18] and the literature data.[11]

The minor product, 3β,7α,11β-triacetoxy-cucurbit-5(10)-ene (**8**), was isolated as a crystalline compound in 4.5% yield. The ^1H NMR spectrum showed a signal of H-8β as a characteristic doublet at δ_H 2.52 (J=6.9 Hz), which was also observed in the spectra of the other 19(10→9β)*abeo*-7α-acetoxylanostene derivatives (vide infra). The low-field signals of 3α, 11α, and 7β protons in the ^1H NMR spectra and all the relevant signals in the ^{13}C NMR spectra indicated the presence of three acetoxyl groups (see Experimental). The tetrasubstituted carbon–carbon double bond was indicated by signals at δ_C 133.7 and 132.5 in the ^{13}C NMR spectrum. In the ^1H–^1H TOCSY spectrum of **8**, starting from the H-3α spin system of H_2-2, H_2-1 and H_2-6 was observed. Thus 11α-H gave a correlation with methylene protons H_2-12 (δ_H1.68 and 1.77), while H-7β (δ_H5.56) correlated with H-8β and H_2-6 (δ_H2.45 and 2.32). The structure of compound **8** was confirmed by the X-ray analysis of crystals obtained from solution in heptane.[21]

The next more polar product of the reaction also had a rearranged carbon skeleton, as indicated by the presence of NMR signals ascribed to three acetoxyl groups and a trisubstituted double bond. Three acetate methyl group signals were observed at δ_H2.06, 2.01 and 1.96, and four other characteristic signals were found in the low-field region of the ^1H NMR spectrum at δ_H 5.49, 5.40, 5.08, and 4.68. These were ascribed to protons H-1, H-11α, H-7β and H-3α, respectively. The location of the double bond in position 1(10) of the lanostane was deduced from the five proton spin system of the ring A detected in the ^1H–^1H COSY NMR spectrum. Vinylic proton H-1 displayed cross peaks with proton H-5α (δ_H2.38) and also with H_2-2 (δ_H2.19 and 2.30). In turn, these two signals correlated with proton H-3α. The signal of H-7β gave three cross peaks with H_2-6 (δ_H 1.75 and 2.52) and with proton H-8β (δ_H 2.39). Accordingly, H-11α gave cross peaks with H-12β (δ_H1.43) and H-12α (δ_H 2.35). The structure of this compound was assigned as 3β,7α,11β-triacetoxy-5α-cucurbit-1(10)-ene (**9**) and was finally confirmed by X-ray analysis of suitable crystals obtained from solution in heptane.[21]

The most polar product of the rearrangement of **2** was isolated in approx. 10% yield. The compound was identified as 3β,7α,11β-triacetoxy-10α-cucurbit-5-ene (**10**) whose spectroscopic data (^1H and ^{13}C NMR, IR, MS) were in full agreement with those of the original compound reported by us in an earlier paper.[8]

The total isolated yield of the four compounds possessing a cucurbitane or a 30(14→8α)*abeo*-cucurbitane skeleton formed from epoxide **2** under the rearrangement conditions was approx. 47%. The other skeletally rearranged compound was that having protostane skeleton **6**.

Rearrangements of steroids and triterpenes initiated by the formation of a carbocatonic center in the molecule are usually complex reactions affording mixtures of products of similar polarity. Carbocationic intermediates are postulated in these multi-step rearrangements, although some degree of concertedness at any step of the reaction may not be excluded. The intermediate carbocationic species involved in the rearrangement are of similar energy (Fig. 2), as was shown by semiempirical calculations (PM3, CAChe Fujitsu). This explains the formation of a considerable amount of protostane derivative **6** together with the series of products having the 19(10→9β)*abeo*-lanostane skeleton. As far as we know, this is the first example of skeletal rearrangement proceeding via a C-9 carbocationic intermediate in which a series of 1,2-shifts of methyl or hydride occurs in both directions, that is, toward ring A and ring D of the triterpene starting from the electron deficient central carbon atom.

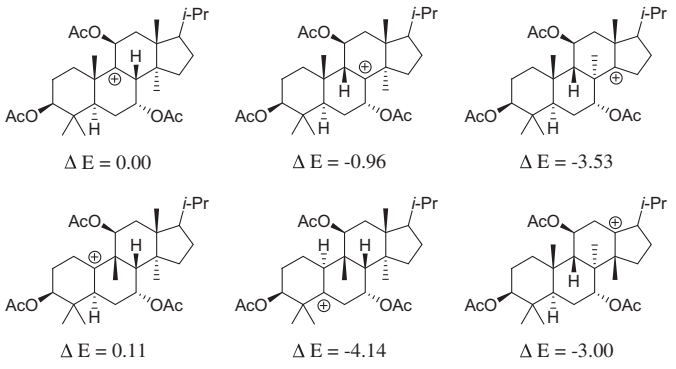


Figure 2. Relative energy of transient carbocations postulated in the rearrangement of epoxide **2** (CAChe Fujitsu, PM3; for simplicity side chain C_8H_{17} was replaced by *i*-Pr group).

In the reactions of epoxide **1** and **2**, the original *cis* relationship between the 9β-oriented leaving group and the migrating C-19 and H-8β requires that the rupture of the C(9)–O bond must precede the migration step. This may imply that the steric interaction of the 10-methyl group with the 11β-substituent, which develops in the process of carbocation formation at C-9 is responsible for the effective 1,2-shift of C-19 toward C-9. The intriguing fact is that in the Westphalen-type dehydration of 3β,11β-diacetoxy-9α-hydroxy-5α-lanostane derivatives bearing additional 7α-acetoxyl, 7β-acetoxyl or 7-oxo groups no product resulting from the migration of C-19 to C-9 was identified.[11] It appears therefore that in the reaction of epoxide **2**, the interaction of the bulky complex of epoxidic oxygen and $BF_3\cdot Et_2O$–Ac_2O[8] with the 10β-methyl group along with the 1,3-diaxial repulsion of that methyl with 4β-methyl directs the migration of the 10β-methyl to C-9, as shown in Figure 3.

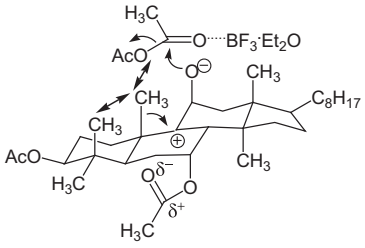


Figure 3. Plausible interactions in the transient C-9 carbocation derived from epoxide **2**.

In general, electron-withdrawing groups destabilize incipient carbocationic centers by the $-I$ effect. However, it is quite conceivable that in the reaction of epoxide **2** the axial 7α-acetoxy group participates in the stabilization of the 'transient C-9 carbocation' by dipole–dipole interaction (Fig. 2). In consequence, transition state compression which facilitates methyl migration along with the neighboring group effect is responsible for the net result of the reaction of **2**. Epoxide **1**, in which additional stabilization by the 7β-acetoxyl is not possible for steric reasons, gave mainly 9α-11-oxo compound **3**, the product of a most likely concerted 1,2-hydride shift.

The rearrangement of epoxide **2** leading to compounds **5**, **6**, **8**, and **9** is a domino type reaction[22] involving sequential 1,2-shifts of methyl or hydride. It is assumed that 19(10→9β),30(14→8α)bis-*abeo*-lanostane derivative **5** is formed from the allylic acetate **10**, which undergoes further rearrangement under the reaction conditions. This was confirmed when **10** was treated with $BF_3\cdot Et_2O$ in acetic anhydride. The ^1H NMR spectrum of the crude product of this reaction showed signals characteristic of compound **5**, in particular that at δ_H 5.52 and a signal of H-11α at δ_H5.08 (d, J=7.14 Hz). To the best of our knowledge, a compound possessing the *abeo*-cucurbitane skeleton as in **5** has not been reported in the literature.

The *results* of this and previous studies show that the 9β-configuration of the 9,11-epoxy-5α-lanostane derivatives is essential for the effective migration of the 10-methyl group to C-9, i.e., formation of the cucurbitane derivatives in reactions carried out in acetic anhydride being a polar medium with high dielectric constant. In steroidal or triterpene 9α,11α-epoxides, effective 10-methyl migration was observed only if additional allylic stabilization of the incipient carbocation $C(10)^+$ by the Δ^5-double bond was present.[5,23] Moreover, substitution at C-7 of the lanostane epoxide is another important factor. The 7-oxo-, 7β-, and 7α-acetoxy groups clearly influenced the extent and direction of the rearrangement of 9β,11β-epoxylanostane derivatives.

3. Conclusion

In summary, the $BF_3\cdot Et_2O$-catalyzed reaction of the two 7-epimeric 3β,7-diacetoxy-9β,11β-epoxy-5α-lanostanes **1** and **2** carried out in acetic anhydride gave strikingly different results. While the reaction of 7β-acetoxyepoxide **1** gave mainly 11-ketone **3**, a product resulting from the 1,2-hydride shift, the reaction of 7α-acetoxy epimer **2** resulted in the formation of a set of skeletally rearranged compounds clearly indicating the importance of the stereochemistry of the C-7 acetoxy group in these reactions. It is postulated that the steric compression of the 10-methyl group and the sterically feasible stabilization of the original carbocation $C(9)^+$ by the 7α-acetoxyl group are responsible for an extensive rearrangement of epoxide **2** resulting in formation of 19(10→9β)*abeo*-lanostane derivatives. In the reaction of epoxide **2**, compound **5** possessing a new type of the teriterpene skeleton, 30(14→8α)*abeo*-cucurbitane, was found as the major product. In compliance with our earlier findings, the importance of acetic anhydride acting simultaneously as a polar solvent and the reagent was again confirmed, as was the presence and stereochemistry of substituents in position 7 of 9,11-epoxylanostanes. The structures of the new compounds were assigned on the basis of spectroscopic data, mostly ^1H and ^{13}C NMR and supported by the analysis of spin systems detected in the two-dimensional NMR spectra. The single-crystal X-ray analysis of compounds **5**, **8**, and **9** confirmed the validity of our structural assignments.

4. Experimental

4.1. General

Mp values were determined on a Kofler hot-stage apparatus and are uncorrected. IR Spectra were determined with an FTIR Bruker FS 113 V spectrophotometer for solutions in chloroform or as KBr pellets. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 300 VT spectrometer (300 and 75.5 MHz, respectively) and Bruker Avance-DRX 600 spectrometer (600 and 151 MHz, respectively) operating in the Fourier transform mode using solutions in deuteriochloroform. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane as the internal standard. The DEPT technique was used for the assignment of multiplicity of carbon signals in ^{13}C NMR spectra. COSY and HETCOR experiments were performed using standard VARIAN pulse sequences. The additivity rules and comparison with data reported for compounds of similar structure were helpful for signal assignment. Electron impact (ionization energy of 70 eV) and FAB mass spectra were recorded with an AMD 402 or AMD 604 spectrometer. Solvents were dried and distilled according to standard procedures. Reactions progress and purity of compounds were monitored by TLC using precoated aluminum-backed silica plates (E. Merck, no. 5554). Silica gel 60 (Merck 70–230 mesh, no. 7734) was used for flash chromatography and silica gel (E. Merck, no. 13895) for preparative TLC separation.

4.2. Reaction of epoxide 1 with $BF_3 \cdot Et_2O$ in acetic anhydride

To a solution of epoxide **1** (712 mg, 1.3 mmol) in acetic anhydride (50 ml), $BF_3 \cdot Et_2O$ (0.9 ml) was added at room temperature and the mixture was stirred for 3 min under argon. Pyridine (0.9 ml) and benzene (100 ml) were added and the solution was washed with H_2O, brine, $NaHCO_3$ (5%), and H_2O. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a crude product as an oil (713 mg), which was chromatographed on silica gel column (80:1) with chloroform as the eluent and rechromatographed on preparative TLC plates with benzene–ethyl acetate 30:1 as the eluent. The combined pure fractions gave the ketone **3** (452 mg, 63%) and compound **4** (188 mg, 26%).

*4.2.1. Ketone **3**.* Ketone **3** was identified on the basis of its physicochemical data (mp 173–174 °C, lit.[18] mp 170–173.5 °C) and comparison of ^1H and ^{13}CNMR spectra with those of the original sample.[18]

*4.2.2. 3β,7β,11β-Triacetoxy-5α-cucurbit-1(10)-ene (**4**).* Oil. IR ($CHCl_3$): ν 3025, 2956, 2935, 2400, 1722, 1468, 1369, 1254, 1023 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.70 (br s, 1H, H-1), 5.59 (br s, 1H, H-11α), 5.07 (t, J=9.06 Hz, 1H, H-7α), 4.66 (dd, J_1=6.84, J_2=9.81 Hz, 1H, H-3α), 2.42 (m, 1H, H-2α), 2.17 (m, 2H, H-5 and H-6), 2.01 (s, 3H, CH_3COO), 1.99 (s, 3H, CH_3COO), 1.98 (s, 3H, CH_3COO), 1.89 (m, 1H, H-2β), 1.81 (m, 1H, H-12α), 1.67 (m, 1H, H-12β), 1.44 (m, 1H, H-6), 1.04, 0.89, 0.85, 0.78, 0.79, 0.77, 0.76, 0.70 methyl groups; ^{13}C NMR ($CDCl_3$): δ 170.8 (CH$_3$*C*OO), 170.4 (CH$_3$*C*OO), 170.1 (CH$_3$*C*OO), 141.2 (C-10), 117.4 (C-1), 76.5 (C-3), 75.1 (C-11), 71.5 (C-7), 51.3 (C-5), 49.1 (C-17), 48.9 (C-14), 44.1 (C-13), 43.1 (C-8), 42.4 (C-9), 39.3 (C-24), 36.4 (C-4), 36.3 (C-12), 36.2 (C-22), 36.1 (C-20), 33.3 (C-15), 30.9 (C-28), 29.4 (C-2), 27.9 (C-25), 27.2 (C-16), 25.6 (C-6), 24.1 (C-23), 23.9 (C-19) 22.8 (C-26), 22.4 (C–27), 21.5 (*C*H$_3$COO), 21.4 (*C*H$_3$COO), 21.1 (*C*H$_3$COO), 18.9 (C-30), 18.6 (C-21), 17.2 (C-18), 13.8 (C-29); MS (EI): m/z (%) 526 (3)(M^+–60), 466(10), 406 (31), 391 (25), 207 (17), 169 (100); HRMS calcd for $C_{34}H_{54}O_4$ (M^+–60): 526.4022; found 526.4039.

4.3. Reaction of epoxide 2 with $BF_3 \cdot Et_2O$ in acetic anhydride

To a solution of epoxide **2** (1.996 g, 3.64 mmol) in acetic anhydride (310 ml), $BF_3 \cdot Et_2O$ (2.02 ml) was added at room temperature and the mixture was stirred for 6 min under argon. The solution was poured on ice, pyridine (20 ml) was added and the reaction products were extracted with chloroform. The organic layer was washed with H_2O, brine, $NaHCO_3$ (5%), and H_2O, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a crude product as an oil (1.971 g). This was separated on silica gel column with a mixture of benzene–ethyl acetate of increasing polarity as the eluent. The mixed fractions were rechromatographed on preparative plates of silica gel with benzene–ethyl acetate 30:1 as the eluent. The following compounds were isolated:

*4.3.1. 3β,11β-Diacetoxy-30(14→8α)abeo-cucurbita-5,14-diene (**5**).* Yield 451 mg (23%), white needles; mp 167–168 °C (methanol). IR (KBr): ν_{max} 1732, 1462, 1381, 1370, 1245 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.52 (m, $W_{1/2}$=9.3 Hz, 2H, H-6, and H-15), 5.09 (d, J=7.14 Hz, 1H, H-11α), 4.69 (t, J=2.74 Hz, 1H, H-3α), 2.08 (s, 3H, CH_3COO), 2.03 (s, 3H, CH_3COO), 1.11, 1.08, 1.07, 0.96 (methyl groups), 0.87 (d, J=6.59 Hz, 6H, CH_3-26 and CH_3-27), 0.82 (d, J=6.59 Hz, 3H, CH_3-21); ^1H NMR (C_6D_6): δ 5.51 (br s, 2H, H-6, and H-15), 5.38 (d, J=6.87 Hz, 1H, H-11α), 4.88 (br s, 1H, H-3α), 1.76 (s, 3H, CH_3COO), 1.67 (s, 3H, CH_3COO), 1.37 (s, 3H, CH_3-19), 1.32 (s, 3H, CH_3-30), 1.11 (s, 3H, CH_3-29), 0.97 (s, 3H, CH_3-18), 0.91 (d, J=6.59 Hz, 6H, CH_3-26, and CH_3-27), 0.83 (s, 3H, CH_3-28); ^{13}C NMR ($CDCl_3$): δ 170.5 (CH$_3$*C*OO), 170.3 (CH$_3$*C*OO), 162.5 (C), 141.6 (C), 121.6 (CH) 118.3 (CH), 78.5 (CH), 77.4 (C and CH), 63.7 (CH), 45.4 (C), 44.6 (CH and CH$_2$), 40.2 (C), 40.0 (C), 39.6 (CH$_2$), 35.7 (two CH$_2$), 34.8 (CH$_2$), 33.6 (CH), 28.5 (CH), 28.3 (CH$_3$), 28.1 (CH$_3$), 25.6 (CH$_2$), 25.2 (CH$_3$), 24.0 (CH$_2$), 22.9 (CH$_3$), 22.6 (CH$_3$), 22.0 (CH$_3$), 21.3 (CH$_3$), 19.8 (CH$_2$), 19.7 (CH$_3$), 18.5 (CH$_3$), 16.5 (CH$_3$); MS (EI): m/z (%) 466 (80), 391 (100), 233 (47), 159 (36), 43 (56); HRMS calcd for $C_{32}H_{51}O_2$: 467.3889; found 467.3869.

*4.3.2. 3β,7α,11β-Triacetoxy-protost-13(17)-ene (**6**).* Oil, 314 mg (16% yield). IR ($CHCl_3$): ν_{max} 1715, 1370, 1245, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.21 (1H, br s, H-7β), 4.94 (m, 1H, H-11α), 4.53 (dd, J_1=5.94, J_2=10.38 Hz, 1H, H-3α), 2.93 (dd, J_1=14.01, J_2=6.60 Hz, 1H, H-12), 2.44 (dd, J_1=14.00, J_2=7.14 Hz, 1H, H-20), 2.15 (m, 2H, H-12, and H-16), 2.05 (s, 3H, CH_3COO), 2.04(s, 3H, CH_3COO), 2.03 (s, 3H, CH_3COO), 1.15, 1.12, 1.04, 0.86, 0.84, 0.83, 0.81 (methyl groups), 0.96 (d, J=6.87 Hz, CH_3-21); ^{13}C NMR ($CDCl_3$): δ ($CDCl_3$): 170.7 (CH$_3$*C*OO), 170.1 (CH$_3$*C*OO), 169.9 (CH$_3$*C*OO), 139.0 (C, C-17), 134.3 (C, C-13), 80.1 (CH), 73.2 (CH), 72.6 (CH), 56.4 (C, C-14), 49.8 (CH), 43.9 (CH), 39.1 (CH$_2$, C-24), 38.1 (C), 37.8 (C, C-10), 35.8 (CH$_2$), 35.7 (C), 32.8 (CH$_2$), 31.9 (CH, C-20), 31.6 (CH$_2$, C-15), 29.6 (CH$_2$, C-16), 29.2 (CH$_2$), 28.8 (CH$_3$), 28.0 (CH), 26.9 (CH$_2$), 25.5 (CH$_2$), 24.9 (CH$_2$), 24.7 (CH$_3$), 22.7 (two CH$_3$), 21.9 (two CH$_3$), 21.7 (CH$_3$), 21.3 (CH$_3$), 20.0 (CH$_3$), 17.1 (CH$_3$), 15.9 (CH$_3$); MS (EI): m/z (%) 586 (2), 526 (99), 467 (100), 353 (24), 43.0 (76); HRMS calcd for $C_{36}H_{58}O_6$: 586.4233; found 586.4207.

*4.3.3. 3β,7α-Diacetoxy-5α-lanostan-11-one (**7**).* Yield 188 mg (9.5%), white solid; mp 191–194 °C (methanol); lit.[18] mp 192–194 °C. IR, ^1H and ^{13}C NMR spectra were identical with those of the original sample.[11,18]

*4.3.4. 3β,7α,11β-Triacetoxy-cucurbit-5(10)-ene (**8**).* Yield 87 mg (4.5%), white solid; mp 95–96 °C (heptane). IR ($CHCl_3$): ν_{max} 1724, 1253, 1028 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.56 (dt, J_1=6.32, J_2=9.47 Hz, 1H, H-7β), 5.48 (br s, 1H, H-11α), 4.60 (dd, J_1=10.99, J_2=3.30 Hz, 1H, H-3α), 2.52 (d, J=6.9 Hz, 1H, H-8β), 2.46 (m, 1H, H-6), 2.32 (m, 2H, H-1, and H-6), 2.16 (m, 1H, H–1), 2.04 (s, 3H, CH_3COO), 2.05 (s, 3H, CH_3COO), 2.06 (s, 3H, CH_3COO), 1.13, 1.01, 0.95, 0.874, 0.870, 0.85, 0.84, 0.82 (methyl groups); ^{13}C NMR ($CDCl_3$): δ 171.1 (CH$_3$*C*OO), 171.0 (CH$_3$*C*OO), 170.6 (CH$_3$*C*OO), 133.7 (C, C-5), 132.7 (C, C-10), 77.4 (CH, C-3), 73.7 (CH, C-11), 70.3 (CH, C-7), 49.5 (CH), 48.4 (C), 45.6 (C), 44.1 (C), 43.1 (CH), 39.3 (CH$_2$), 38.3 (C), 37.1 (CH$_2$), 36.3 (CH$_2$), 35.8 (CH), 35.2 (CH$_2$), 29.3 (CH$_2$), 28.3 (CH$_2$), 27.8 (CH), 27.6 (CH$_3$), 25.2 (CH$_2$), 23.91 (CH$_2$), 23.86 (CH$_2$), 23.67 (CH$_3$), 22.7 (CH$_3$), 22.4 (CH$_3$), 21.57 (CH$_3$), 21.49 (CH$_3$), 21.18 (CH$_3$), 21.14 (CH$_3$), 18.6 (CH$_3$), 18.2 (CH$_3$), 17.2 (CH$_3$); MS (FAB): m/z (%) 526 (M^+–60) (20), 468 (32), 467 (100), 407 (82), 187 (51), 173 (61), 133 (72); HRMS calcd for $C_{34}H_{54}O_4$: 526. 4022; found 526.4050.

*4.3.5. 3β,7α,11β-Triacetoxy-5α-cucurbit-1(10)-ene (**9**).* Yield 213 mg (11%), white solid; mp 135–137 °C (heptane). IR ($CHCl_3$): ν_{max} 1721 (C=O), 1371, 1255, 1028, 930 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.49 (br s, 1H, H-1), 5.40 (t, J=8.5 Hz, 1H, H-11α), 5.08 (dd, J_1=16.8, J_2=9.3 Hz, 1H, H-7β), 4.68 (dd, J_1=6.7, J_2=2.7 Hz, 1H, H-3α), 2.52 (dd, J_1=9.5, J_2=22.3 Hz, 1H, H-6), 2.39 (d, J=6.87 Hz, 1H, H-8β), 2.38 (m, 1H, H-5α), 2.35 (m, 1H, H-12α), 2.30 (m, 1H, H-2α), 2.19 (m, 1H, H-2β), 2.06 (s, 3H, CH_3COO), 2.01 (s, 3H, CH_3COO), 1.96 (s, 3H, CH_3COO), 1.75 (dd, J_1=10.1, J_2=22.7 Hz, 1H, H-6), 1.43 (m, 1H, H-12β), 1.39, 1.25, 1.04, 0.94, 0.88, 0.87, 0.85, 0.82 (methyl groups); ^{13}C NMR ($CDCl_3$): δ 170.9 (CH$_3$*C*OO), 170.4 (CH$_3$*C*OO), 170.2 (CH$_3$*C*OO), 140.3 (C, C-10), 117.1 (CH, C-1), 75.5 (CH, C-3), 71.9 (CH), 71.4 (CH) 51.5 (CH, C-5), 47.9 (CH, C-17), 47.7 (C), 46.6 (C), 43.3 (C), 39.4 (CH$_2$), 39.2 (CH$_2$), 38.7 (CH), 36.5 (CH$_2$), 36.3 (CH$_2$), 36.1 (CH), 34.8 (C), 30.0 (CH$_2$), 29.8 (CH$_2$), 29.0 (CH$_2$), 27.9 (CH), 26.7 (CH$_3$), 24.2 (CH$_2$), 22.8 (CH$_3$), 22.5 (CH$_3$), 22.1 (two CH$_3$), 21.6 (CH$_3$), 21.3 (CH$_3$), 21.0 (two CH$_3$), 18.3 (CH$_3$), 14.1 (CH$_3$); MS (EI): m/z (%) 526 (M–60)(6) 484 (10); 466 (M–120)(46), 451 (59), 406 (30), 391 (100), 187 (84), 145 (29), 95

(49), 43 (67), 18 (91); HRMS calcd for $C_{34}H_{54}O_4$: 526.4022; found 526.3996.

*4.3.6. 3β,7α,11β-Triacetoxy-cucurbit-5-ene (**10**).* Oil, 198 mg (10% yield). IR ($CHCl_3$): ν_{max}1722, 1375, 1255, 1027 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.78 (d, J=6.6 Hz, 1H, H-7β), 5.32 (br s, $W_{1/2}$=9.0 Hz, 1H, H-6), 5.10 (br s, $W_{1/2}$=12.0 Hz, 1H, H-11α), 4.66 (br s, $W_{1/2}$=9.6 Hz, 1H, H-3α), 2.42 (d, J=7.08 Hz, 1H, H-8β), 2.15 (d, J=10.5 Hz, 1H, H-10α), 2.01 (s, 3H, C*H*$_3$COO), 1.98 (s, 3H, C*H*$_3$COO), 1.94 (s, 3H, C*H*$_3$COO), 1.90 (m, 1H, H-12), 1.80 (m, 1H, H-12), 1.74 (m, 2H, H_2-2), 1.37 (m, 1H, H-1), 1.02, 1.01, 1.00 (methyl groups), 0.94 (d, J=13,7 Hz, 3H, H-21), 0.879, 0.80, 0.79, 0.78 (methyl groups); ^{13}C NMR ($CDCl_3$): δ 170.7 (CH_3COO), 170.4 (CH_3COO), 170.3 (CH_3COO), 143.0 (C, C-5), 121.0 (CH, C-6), 78.1 (CH, C-3), 73,8 (CH), 71.2 (CH), 49.2 (CH, C-17), 47.8 (C), 46.1 (C), 44.9 (CH), 40.8 (C), 39.8 (C), 39.4 (CH and CH_2), 36.4 (CH_2), 35.9 (CH_2), 35.8 (CH), 35.3 (CH_2), 28.4 (CH_2), 28.0 (CH), 26.6 (CH_2), 26.3 (CH_3), 24.7 (CH_3), 24.0 (CH_2), 22.8 (CH_3), 22.6 (CH_2), 22.5 (two CH_3), 21.8 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 18.9 (CH_3), 18.3 (CH_3), 17.4 (CH_3); MS (EI): m/z (%) 585 (2), 527 (M-60)(17), 543 (18), 484 (19), 467 (20), 407 (40), 173 (79), 421 (90), 119 (100); HRMS calcd for $C_{34}H_{54}O_4$: 526.4022; found 526.4015.

4.4. Treatment of compound 10 with $BF_3 \cdot Et_2O$ in acetic anhydride

To a solution of compound **10** (19.4 mg) in acetic anhydride (1.5 ml), $BF_3 \cdot Et_2O$ (20 μl) was added at room temperature and the mixture was stirred for 3 min under argon. The solution was poured on ice, pyridine (0.1 ml) was added and the product was extracted with benzene. The solution was washed with H_2O, brine, $NaHCO_3$ (5%, 2×), and H_2O. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give a crude product as an oil (14 mg) whose ^1H NMR spectrum showed signals characteristic of compound **5** at δ_H 5.52 (H-6 and H-15) and 5.10 (d, J=7.14 Hz, H-11α).

4.5. X-ray analysis of compound 5

$C_{34}H_{54}O_4$ Colorless needles, crystal size 0.04,0.04,0.3 mm, monoclinic, C2, a=21.395(4)Å, b=6.1790(12)Å, c=24.892(5)Å, β=102.31(3)°, V=3215.1(11)Å^3, Z=4, ρ_{calcd}=1.09 Mg m^{-3}, F(000)=1160, μ=0.07 mm^{-1}, 17,586 reflections measured ($2\theta_{max}$=50°), 3121 independent reflections (R_{int}=0.107). Final $R1(I>2\sigma(I))$=0.057, wR_2(all reflections)=0.131, S=1.07, largest diff. peak and hole 0.25 and −0.19e Å^{-3}. Diffraction data were collected on a KUMA KM4CCD diffractometer,[24] using graphite-monochromated MoK_α radiation (λ=0.71073 Å) at room temperature. The unit-cell parameters were determined by the least squares fit of the positions of the 2263 most intense reflections chosen from the whole experiment. The Lorentz-polarization and absorption corrections were applied.[24] The structures were solved by direct methods with SIR92 program[25] and refined by full-matrix least squares on F^2 using SHELXL-97.[26] Scattering factors incorporated in SHELXL-97 were used. Non-hydrogen atoms were refined anisotropically, hydrogen atoms were located in the idealized positions and refined as a 'riding model'.

Crystallographic data (excluding structure factors) for the structural analyses have been deposited with the Cambridge Crystallographic Data Center, No. CCDC-728670. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336 033, e-mail:deposit@ccdc.cam.ac.uk, or web: www.ccdc.cam.ac.uk.

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