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Structure Determination and Mechanism of Formation of a *seco*-Moreliane Derivative Supported by Computational Analysis

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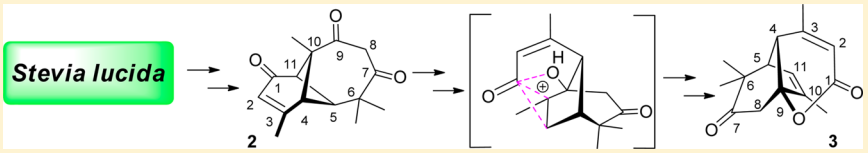
Supporting Information



ABSTRACT: Basic hydrolysis of a dichloromethane extract of *Stevia lucida* yielded (4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-dihydroxylongipin-2-en-1-one (**1**), which was oxidized and subjected to acidic conditions to generate the new *seco*-moreliane derivative **3**. The structure of **3** was established based on NMR data interpretation and confirmed computationally. A plausible mechanism for the carbocationic rearrangement of the trione **2** to the *seco*-moreliane **3** was supported by DFT computations.

Sesquiterpenoids of the longipinane series are a small family of compounds that are restricted to very few groups of plants. The most prominent feature of these compounds is the presence of a cyclobutane ring in their molecular structure. The potential release of the annular strain conferred by the four-membered ring makes these compounds important substrates for the generation of new carbocyclic skeletons through molecular rearrangements (Figure 1). So far, there have been nine new skeletons obtained by chemical (moreliane,[1] arteagane,[2] quirogane,[3] jiquilpane,[4] uruapane,[5] meridane,[6] and uladane[6]) and photochemical (pingilonane[7] and patzcuarane[8]) pathways. The first molecular rearrangement carried out on a longipinane derivative led to the moreliane structure (Scheme 1). The mechanism established for the formation of this compound is a Wagner−Meerwein rearrangement that involves migration of one bond of a cyclobutane ring in a concerted process with the departure of a leaving group[9] (i.e., with the antiperiplanar C−C bond migrating; Scheme 1). Reported herein is the generation of the new *seco*-moraliene derivative **3** through an unusual carbocationic ketone-to-ester transformation. The compound structure elucidation and the mechanistic proposal were fully supported by DFT (density functional theory) computational analysis.

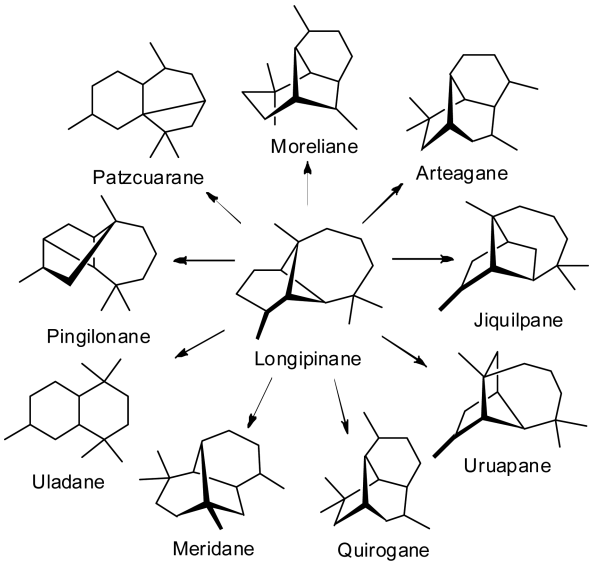
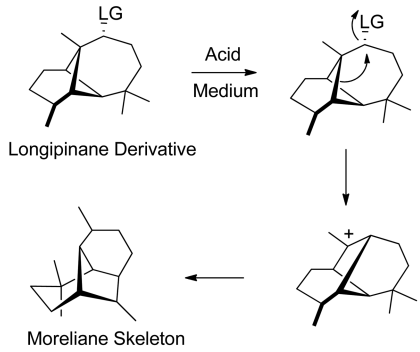


Figure 1. New sesquiterpene skeletons generated by longipinane rearrangements.

Scheme 1. Mechanism Established for the Formation of Moreliane[9]



LG: Leaving group (generally a protonated hydroxy group)

The uncrushed leaves and stems of *Stevia lucida* Lag. (Asteraceae) (about 7.0 kg) were extracted with dichloro-

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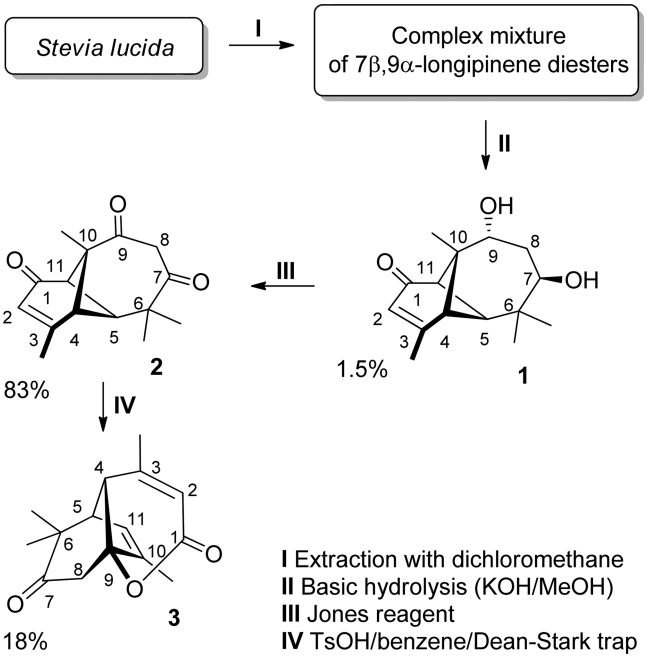
methane at room temperature for 10 min. The crude extract (about 900 g) was found to contain complex mixtures of 7β,9α-dihydroxylongipinene diesters.[11] In order to reduce the number of individual components, the crude dichloromethane extract was hydrolyzed with concentrated KOH/MeOH, by boiling under reflux for 30 min (Scheme 2). Upon completion of the hydrolysis, about 14 g of a white solid was recovered and purified by recrystallization with dichloromethane. The crystalline product was identified as (4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-dihydroxylongipin-2-en-1-one (**1**). In previous research, this compound was obtained by a similar procedure from *Stevia salicifolia*, and its ^{1}H and ^{13}C NMR data were acquired in $CDCl_3$ and $(CD_3)_2CO$, respectively.[10] In the present study, the 1D and 2D NMR data of the diol **1** were measured in C_5D_5N.

Scheme 2. General Procedure to Obtain the *seco*-Moreliane Derivative 3



The ^{1}H NMR spectrum of compound **1** exhibited four three-proton singlets. Two of these, with very similar chemical shifts (δ_H 1.16 and 1.18), were attributed to the *gem*-dimethyl group [>C(CH_3)$_2$ (H-13 and H-14)] and were characterized in the HMBC spectrum through the correlations C-13 ↔ H-14 ↔ C-6 ↔ H-13 ↔ C-14. The singlet at δ_H 1.33 was assigned to an angular methyl group [>C−CH_3 (H-15)], and the downfield-shifted broad singlet at δ_H 1.95 was attributed to an allyl methyl group [=C−CH_3 (H-12)], because it showed a ^{1}H−^{1}H COSY long-range coupling correlation with a slightly broadened signal [δ_H 5.96; apparently a narrow quartet, $J_{2,12}$ = 1.6 Hz, =CH (H-2)]. Analysis of these latter data revealed the presence of a trisubstituted double bond, and the ^{13}C NMR chemical shift of its carbons [δ_C 123.0, =CH (C-2); δ_C 171.7, =C< (C-3)] indicated that it is conjugated to a ketone [δ_C 204.0, =C−C=O (C-1)]. This α,β-unsaturated ketone corresponds to cyclohexenone in structure **1** (Scheme 2). In the ^{1}H−^{1}H COSY spectrum was observed the AMX spin system of a cyclobutane ring [δ_H 3.62, d, $J_{4,11}$ = 6.8 Hz, (H-11) ↔ δ_H 2.66, d, $J_{4,11}$ = 6.8 Hz, (H-4) ↔ δ_H 2.43, s, (H-5)]. Finally, the geminal protons to hydroxy groups on the cycloheptane ring were observed as two doublets of doublets [δ_H 4.54, dd, $J_{7,8}$ = 11.6 and 2.0 Hz, >CH−OH (H-7); 4.01, dd, $J_{8,9}$ = 3.8 and 2.9 Hz, >CH−OH (H-9)] from their respective coupling with the C-8 methylene diastereotopic protons [multiplets at δ_H 2.64 and δ_H 2.39, >CH_2 (H-8α and H-8β)].

Treatment of compound **1** with Jones reagent (Scheme 2) generated triketone **2**, for which the formation was confirmed by the disappearance of the oxymethine proton signals (H-7 and H-9) in its ^{1}H NMR spectrum and the detection of two new ketone carbonyl peaks [δ_C 203.1, >C=O (C-7) and 202.4, >C=O (C-9)] in the ^{13}C NMR spectrum. It is important to note that the diastereotopic C-8 methylene protons located between the two carbonyls were strongly deshielded [δ_H 3.85, d, $J_{8,8'}$ = 11.0 Hz, (H-8) ↔ δ_H 4.30, d, $J_{8',8}$ = 11.0 Hz, (H-8′)].

Table 1. NMR Data of Compounds 1−3[a]

	δ_C (100 MHz)				δ_H (400 MHz, *J* values in Hz)			
position	**1**	**2**	**3** (exp)	**3** (calcd)	**1**	**2**	**3** (exp)	**3** (calcd)
1	204.0	200.2	162.6	161.2				
2	123.0	122.5	118.8	120.0	5.96 (q, 1.6)	5.87 (s)	5.92 (dq, 2.0, 1.4)	5.74 (dq, 2.1, 1.3)
3	171.7	169.8	158.5	155.5				
4	49.3	50.0	51.2	52.6	2.66 (d, 6.8)	2.78 (d, 6.8)	3.07 (s)	3.05
5	62.7	63.1	50.0	50.9	2.43 (s)	2.55 (s)	2.66 (d, 3.0)	2.60 (d, 3.3)
6	39.0	49.6	48.8	49.0				
7	69.1	203.1	211.4	212.5	4.54 (dd, 11.6, 2.0)			
8	40.6	57.9	47.2	48.7	H-8/H-8′ 2.64 (m)	H-8/H-8′	H-8/H-8′	H-8/H-8′
					2.39 (m)	3.85 (d, 11.0)	2.87 (d, 17.1)	2.97 (d, 18.5)
						4.30 (d, 11.0)	2.79 (d, 17.1)	2.77 (d, 18.5)
9	73.3	202.4	87.3	86.6	4.01 dd (3.8, 2.9)			
10	57.9	65.11	144.6	148.5				
11	53.8	56.9	124.9	124.8	3.62 d (6.8)	3.37 (d, 6.8)	5.59 (dq, 3.0, 1.7)	5.50 (dq, 3.3, 1.6)
12	23.2	24.0	20.8	21.4	1.95 (d, 1.6)	2.09 (s)	1.91 (t, 1.2)	1.98 (t, 1.3)
13	27.1	23.3	26.3	25.4	1.16 (s)	1.18 (s)	1.24 (s)	1.26
14	18.4	23.6	25.8	23.8	1.18 (s)	1.22 (s)	1.11 (s)	1.18
15	22.5	17.3	12.2	13.5	1.33 (s)	1.21 (s)	1.66 (d, 1.7)	1.84 (d, 1.6)

[a]Data for **1** were measured in C_5D_5N. Data for **2** and **3** were measured in $CDCl_3$. Chemical shifts (δ) are in ppm, relative to trimethylsilane.

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The remaining NMR signals were not significantly changed (Table 1). Additionally, the oxidation of both hydroxy groups of compound **1** was corroborated by the peak observed in the HREIMS at m/z 246.1278. This peak is consistent with the loss of four hydrogen atoms by the oxidation of the two hydroxy groups of compound **1**. The presence of the enolized form of tricetone **2** was not detected from its spectroscopic data.

Triketone **2** and *p*-toluenesulfonic acid were dissolved in benzene and refluxed for 1 h in a Dean–Stark trap (Scheme 2). After this, the solvent was removed under reduced pressure to provide a mixture of compounds, which were purified by preparative thin-layer chromatography on silica gel plates, eluted with dichloromethane. The molecular formula of compound **3**, $C_{15}H_{18}O_3$, was determined by 1D NMR and MS data and revealed seven unsaturation degrees, and, of these, a ketone [δ_C 211.4, >C=O (C-7)], an ester [δ_C 162.6, –O–C=O (C-1)], and two double bonds [δ 118.8, =CH (C-2); 5.92, =CH, dq, $J_{2,12}$ = 2.0, 1.4 Hz (H-2); 158.5, =C< (C-3); 144.6, =C< (C-10); 124.9, =CH (C-11); 5.59, =CH, dq, $J_{5,11,15}$ = 3.0, 1.7 Hz (H-11)] were deduced from the NMR data; therefore this compound was assigned with necessarily a tricyclic structure. According to the NMR data, both double bonds were trisubstituted, and each was found to contain a methyl group [δ 20.8, $-CH_3$ (C-12); 1.91, t, $J_{2,12}$ = 1.2 Hz (H-12); 12.2, $-CH_3$ (C-15); 1.66, d, $J_{11,15}$ = 1.7 Hz (H-15)]. Moreover, the chemical shifts revealed that one double bond is conjugated to a carbonyl group. Comparative analysis of the 1D NMR spectra of compound **3** versus those of its precursor **2** (Table 1) showed five significant changes; these were (1) a new trisubstituted olefinic system that contained a methyl group was detected (HMBC correlations: C-10 ↔ H-15 ↔ C-11); (2) the characteristic longipinane signals of the cyclobutane ring disappeared ["*cis*" *W*-coupling (H-4 ↔ H-11)]; (3) the ketone carbonyl peak of the system $\Delta^{2,3}$-cyclohexen-1-one (C-1) was profoundly shielded with its new chemical shift corresponding to an ester group (HMBC correlations: C-3 ↔ H-12 ↔ C-2/H-2 ↔ C-1); (4) the ketone carbonyl peak C-9 disappeared and also a typical ^{13}C NMR peak corresponding to an oxygenated tertiary carbon was detected, indicating that it belongs to an ester group [δ_C 87.3, >C–O (C-9)]; and (5) the ketone carbonyl peak C-7 was deshielded and the methylene protons located in the α-position to the ketone were shielded [δ_H 2.87, d, $J_{8,8'}$ = 17.1 Hz (H-8) ↔ δ_H 2.79, d, $J_{8',8}$ = 17.1 Hz (H-8′)]. This corroborated the fact that the ketone at the β-position (C-9) had disappeared (HMBC correlations: C-7 ↔ H-8/H-8′ ↔ C-9/H-8/H-8′ ↔ C-10). Finally, signals of a *gem*-dimethyl group were preserved without any significant changes. The peak detected in the HREIMS (m/z 246.1262) suggests that compound **3** is an isomer of its precursor (**2**). This strengthened the hypothesis that **3** is a molecular rearrangement product from **2**. After detailed analysis of the above-mentioned and the data provided by the 2D NMR spectra (Figure 2), it was established that compound **3** is (4*R*,5*S*,9*S*)-1,11-*seco*-oxomorelian-2,10-dien-9,1-olide (**3**).

Calculations of NMR chemical shifts are becoming more reliable and offer a practical tool in structure and configurational assignments.[12] Proton–proton coupling constants have been more challenging, although with the approach of Bally and Rablen for the scaling of Fermi contacts[13] and the rff (relativistic force field) method[14] developed by one of us (A.G.K.), reliable *J* values can now be obtained in a reasonable time. The rff method uses multiparametric scaling of Fermi contacts based on NBO hybridization parameters to obtain

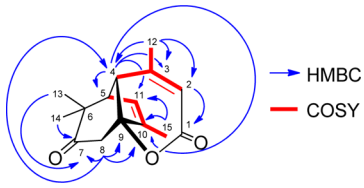
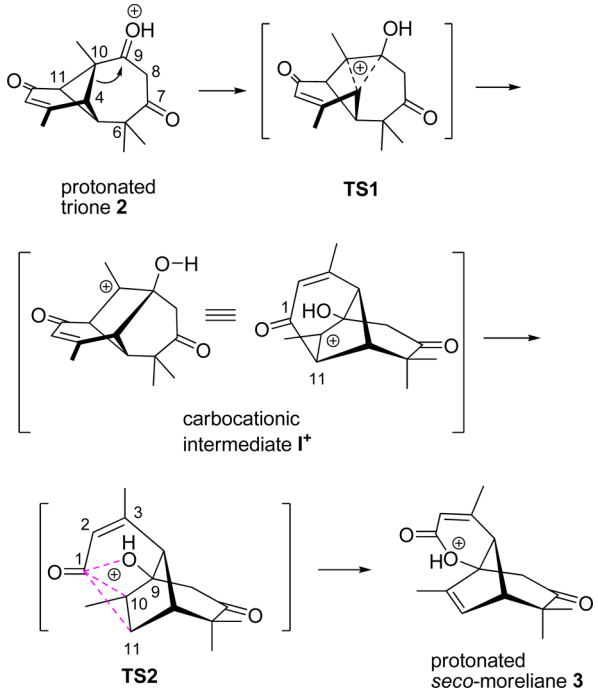


Figure 2. $^1H–^1H$ COSY and HMBC correlations of compound **3**.

accurate nuclear spin–spin coupling constants. These methods augment the existing methods for calculations of NMR chemical shifts, providing a synergistic and comprehensive computational tool for structure elucidation. As Table 1 shows, the calculated NMR chemical shifts and nuclear spin–spin coupling constants for **3** matched the experimental data. These computational results leave no doubt that the above structural hypothesis for *seco*-moreliane **3** is correct. A mechanistic rationale for the acid-catalyzed rearrangement of **2** to **3** is shown in Scheme 3. Acyl shifts were observed in the past

Scheme 3. Plausible Mechanism for Acid-Catalyzed Rearrangement of Triketone 2 into *seco*-Moreliane 3



during carbocationic rearrangements and were investigated computationally with common DFT functionals such as B3LYP, providing critical mechanistic insights even with modest basis sets, e.g., 6-31+G(d,p).[15] We suggest that the reaction is initiated by cyclobutane ring expansion in the protonated trione **2**, generating the carbocationic intermediate $\mathbf{I}^+$, which, in turn, rearranges via transition state **TS2** into the protonated *seco*-moreliane **3**. This last rearrangement is unusual. Computations at the B3LYP/6-311+G(d) level of DFT theory[16] with zero-point energy (ZPE) corrections show that **TS2** is a low-lying transition state, only 2.5 kcal/mol above $\mathbf{I}^+$, which can be interpreted as the vinyl acylium carbocation ($-C_3=C_2-C_1\equiv O^+$), hovering over the C-10/C-11 double bond. An instructive finding was that the C-9 hydroxy group is participating in stabilization of this electron-depleted species. The migrating carbon C-1 was positioned above C-10 (at 2.69

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Å), being almost equidistant from C-11 (2.97 Å) and from the oxygen of C-9 (−C_9−OH) (3.03 Å; see Figure 3). A

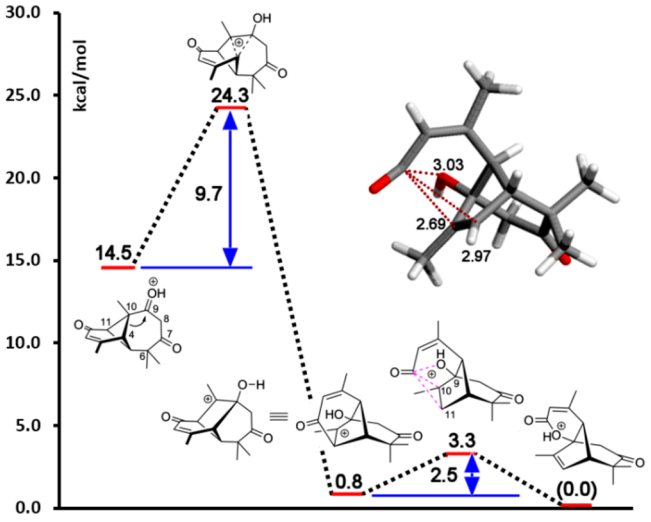

Figure 3. ZPE-corrected B3LYP/6-311+G(d) energies (relative kcal/mol).

dissociative mechanism with intermediate formation of the carboxylic acid and subsequent esterification cannot be ruled out. However, such pivoted gliding of the C-3/C-2/C-1 (−C_3=C_2−C_1≡O^+) arm on the π-density of the double bond, from the departure point, C-11, via C-10 and onto the hydroxy group, presents a plausible alternative.

In conclusion, we have described a new sesquiterpenoid moreliane derivative, *seco*-moreliane **3**, obtained in several experimentally simple steps from a leaf and stem extract of *S. lucida*. The structure of this unprecedented tricyclic lactone was determined by experimental NMR spectroscopy and confirmed computationally. A plausible nondissociative mechanism for the acid-catalyzed formation of **3** has been proposed, which involves an unusual low-lying transition state with the migrating acyl cation coordinated to both the double bond and the lone pair of the allylic alcohol moiety.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined with a Fisher-Johns instrument and are uncorrected. Optical rotations were measured in $CHCl_3$ on a 60 Hz Steeg and Reuter polarimeter. UV spectra were obtained in a PerkinElmer Lambda 3B spectrophotometer, using 1 cm thick quartz cells and methanol (Merck-Uvasol) as solvent. IR spectra were recorded on a PerkinElmer FT-1725X spectrophotometer as KBr pellets. ^{1}H, ^{13}C, and two-dimensional NMR spectra were acquired with a Bruker-Avance DRX-400 instrument, using $CDCl_3$ or C_5D_5N as solvent. Mass spectra were recorded on a Hewlett-Packard mass spectrometer, model 5930A (70 eV). TLC plates were developed on 0.25 mm layers of silica gel PF 254 (Merck), and spots were visualized by spraying with a mixture $CH_3COOH/H_2O/H_2SO_4$ (20:4:1) and then heating with an air flow at 100 °C for a few seconds. Plates for preparative thin-layer chromatography were prepared by suspending fluorescent silica gel HF 254 (Merck) in distilled water (1:2, w/w) and then spreading the mixture on glassware. The plates were activated at 120 °C for 24 h.

Plant Material. The leaves and stems of *Stevia lucida* were collected on July 15, 2008, at Páramo de la Negra, Municipio Rivas Dávila, Estado Mérida, Venezuela. The plant was identified by Eng. Juan Carmona Arzola, Department of Pharmacognosy and Organic Medicaments, Faculty of Pharmacy and Bioanalysis, University of Los Andes. A voucher specimen (JM Amaro-Luis & P. Chacón-Morales, No. 2332) was deposited at the Herbario MERF of this faculty.

Extraction and Isolation. The dried uncrushed leaves and stems (ca. 7.0 kg) were extracted with dichloromethane at room temperature for 10 min. The obtained solution was filtered and concentrated in vacuo in a rotary evaporator at a temperature not exceeding 40 °C, to produce a crude extract (ca. 900 g), containing complex mixtures of 7β,9α-dihydroxylongipinene diesters. In order to obtain fewer products, the dichloromethane extract was hydrolyzed with KOH (400 g)/MeOH by boiling under reflux for 30 min. Upon completion of the reaction, about 14 g of a white solid was recovered and purified by recrystallization with dichloromethane. Compound obtained was identified as (4*R*,5*S*,7*R*,9*R*,10*R*,11*R*)-7,9-dihydroxylongipin-2-en-1-one (**1**): mp 174−175 °C (dichloromethane); $[\alpha]_D$ +42 (*c* 0.33, methanol)]; UV (MeOH) λ_{max} (log ε) 251 (0.6) nm; IR (KBr) ν_{max} 3528, 3332, 2956, 1669, 1615, 1061, 1024, 951, 844 cm^{-1}; ^{1}H and ^{13}C NMR data (C_5D_5N), Table 1; HREIMS *m*/*z* 232.1470 [M − H_2O]$^-$ was assigned to a fragment generated by the successive loss of one water molecule from the molecular ion (calcd for $C_{15}H_{20}O_2$, 232.1463).

(4*R*,5*S*,10*R*,11*R*)-Longipin-2-ene-1,7,9-trione (2). To 500 mg of **1** dissolved in acetone (20 mL) and cooled with an ice−water bath was added dropwise Jones reagent[17] (CrO_3/H_2SO_4). The reaction was monitored by color changes and formation of a blue precipitate. When the orange color persisted, the reagent addition was stopped and the mixture was stirred for 15 min. A slight excess of methanol was added, the reaction mixture was filtered, and solvent was removed by rotary evaporation to dryness to give a residue (ca. 410 mg), which showed a clear spot by TLC. The compound was recrystallized using ethanol, affording colorless crystals (yield 83%): mp 128−130 °C (ethanol); IR (KBr) ν_{max} 2971, 2874, 1718, 1691, 1618, 837, 751 cm^{-1}; ^{1}H and ^{13}C NMR data ($CDCl_3$), Table 1; HREIMS *m*/*z* 246.1278 [M]$^+$ (calcd for $C_{15}H_{18}O_3$, 246.1256).

(4*R*,5*S*,9*S*)-1,11-*seco*-Oxomorelian-2,10-dien-9,1-olide (3). Triketone **2** (100 mg) and *p*-toluenesulfonic acid monohydrate (80 mg) were dissolved in benzene (15 mL) and refluxed for 1 h in a Dean−Stark trap, resulting in a mixture of products as detected by TLC. The reaction mixture was allowed to reach room temperature and was neutralized with 10 mL of 5% aqueous $NaHCO_3$. The mixture was washed with dichloromethane (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel plates, eluted with dichloromethane, to obtain a white powder (yield 18%): mp 125−136 °C (dichloromethane); IR (KBr) ν_{max} 2973, 2872, 1711, 1678, 1639, 1622, 1107, 888, 854, 756 cm^{-1}; ^{1}H and ^{13}C NMR data ($CDCl_3$), Table 1; HREIMS *m*/*z* 246.1262 [M]$^+$ (calcd for $C_{15}H_{18}O_3$, 246.1256).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00041.

IR, HREIMS, 1D and 2D NMR data for compounds **1**−**3**, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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