Modified *ent*-Abietane Diterpenoids from the Leaves of *Suregada zanzibariensis*

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**ABSTRACT:** The leaf extract of *Suregada zanzibariensis* gave two new modified *ent*-abietane diterpenoids, zanzibariolides A (1) and B (2), and two known triterpenoids, simiarenol (3) and β-aminor (4). The structures of the isolated compounds were elucidated based on NMR and MS data analysis. Single-crystal X-ray diffraction was used to establish the absolute configurations of compounds 1 and 2. The crude leaf extract inhibited the infectivity of herpes simplex virus 2 (HSV-2, IC$_{50}$ 11.5 μg/mL) and showed toxicity on African green monkey kidney (GMK AH1) cells at CC$_{50}$ 52 μg/mL. The isolated compounds 1–3 showed no anti-HSV-2 activity and exhibited insignificant toxicity against GMK AH1 cells at ≥100 μM.

**RESULTS AND DISCUSSION**

Repeated column chromatographic separation of the leaf extract (CH$_3$OH–CH$_2$Cl$_2$ 7:3, v/v) of *S. zanzibariensis* yielded two new diterpenoids (1 and 2) along with the known triterpenoids simiarenol (3) and β-aminor (4). The structures of the isolated compounds were determined by NMR spectroscopic and mass spectrometric analyses supported by single-crystal X-ray diffraction analysis.

**Compound 1, [α]$_D^{24}$ +82.5 (c 0.03, CH$_2$Cl$_2$), was isolated as white crystals from a 1:1 mixture of CH$_3$Cl–isohexane. Its HRESIMS (Figure S8, Supporting Information) showed a molecular ion [M + H]$^+$ at m/z 329.1754 (calcd 329.1753)
consistent with the molecular formula, C_{34}H_{52}O_4, suggesting nine double-bond equivalents. The compound gave a UV absorption at \( \lambda_{\text{max}} \) 264 nm, supporting the occurrence of an \( \alpha,\beta \)-unsaturated carbonyl moiety, typical for diterpenoid lactones. Its strong IR absorption bands at 3460 and 1705 cm \(^{-1} \) indicated the presence of hydroxy and carbonyl groups, respectively. The \(^1\)H NMR spectrum (Table 1, Figure S1, Supporting Information) cross-peaks of H-20 (\( \delta_H 4.72 \)) and H-9 (\( \delta_H 3.52 \)) to C-1 (\( \delta_C 210.9 \)) as well as those of H-3 (\( \delta_H 3.10 \)) to C-4 (\( \delta_C 151.9 \)), C-5 (\( \delta_C 80.4 \)), and C-18 (\( \delta_C 114.2 \)) allowed the assignment of ring A. While the cross-peaks of H-19 (\( \delta_H 1.32 \)) to C-4 (\( \delta_C 151.9 \)) and H-18a/b (\( \delta_H 5.16/5.09 \)) to C-5 (\( \delta_C 80.4 \)) further supported the assignment of ring A, those of H-9 (\( \delta_H 3.52 \)) to C-5 (\( \delta_C 80.4 \)) and H-6a/b (\( \delta_H 1.97/1.93 \)) to C-4 (\( \delta_C 151.9 \)), C-8 (\( \delta_C 150.8 \)), and C-10 (\( \delta_C 58.0 \)) were used to deduce the linkage of ring A and B. Furthermore, the HMBC cross-peaks of the proton at \( \delta_H 4.72 \) (H-12) to C-16 (\( \delta_C 175.5 \)) and C-14 (\( \delta_C 115.5 \)) and those of \( \delta_H 1.83 \) (H-17) to C-16 (\( \delta_C 175.5 \)) and C-13 (\( \delta_C 156.0 \)) enabled the assignment of rings C and D. The COSY cross-peak of H-9 (\( \delta_H 3.52 \)) with H-11b (\( \delta_H 1.81 \)) and H-14 (\( \delta_H 6.35 \)) corroborated the proposed linkage of rings B and C. The H-14 signal (\( \delta_H 6.35 \)) appeared as a broad singlet and showed COSY cross-peaks to H-9 (\( \delta_H 3.52 \)), H-7a (\( \delta_H 2.70 \)), H-12 (\( \delta_H 4.72 \)), and H-17 (\( \delta_H 1.83 \)), linking rings B, C, and D. Further assignments were supported by the TOCSY spectrum of I (Figure S6, Supporting Information).

The relative configuration of I was deduced from coupling constants (Table 1) and NOESY correlations (Figure S7, Supporting Information). Thus, the NOEs observed between H-12 (\( \delta_H 4.72 \)) and H-20 (\( \delta_H 1.13 \)) suggested these protons to be syn oriented. A weak positive Cotton effect was observed for the \( \pi \rightarrow \pi^* \) transition at 299 nm, and a negative Cotton effect was observed at ca. 214 nm for the \(^1\)La electron transition was seen in the electronic circular dichroism (ECD) spectrum of I (Figure S17, Supporting Information). Single-crystal X-ray diffraction analysis using Cu K\( \alpha \) radiation was performed (Figure S18, Supporting Information), establishing unambiguously the absolute configuration of I as 3S,5S,9S,10S,12R (Figure 1b). Based on the spectroscopic data obtained, this new compound, zanzibarilactone A (I), was characterized as the \( \alpha \)-abietane (3S,5S,9S,10S,12R)-5-hydroxy-3,10,15-trimethyl-4,7,11-trimethylenemethylene-2,4,6,8,10,12-hexahydropyridine-2,6,8-trione (Ia). The compound was isolated as white crystals and assigned the molecular formula C_{34}H_{52}O_4 based on HR-ESIMS ([M + H]+ at \( m/z \) 435.1702, calc 345.1702, Figure S16, Supporting Information) and NMR (Table 1) analyses. This molecular formula indicated nine double-bond equivalents. Its UV absorption at \( \lambda_{\text{max}} \) 270 nm suggested the presence of an \( \alpha,\beta \)-unsaturated carbonyl moiety. Strong IR absorption bands were observed at 3456 and 1710 cm \(^{-1} \).
cm⁻¹ that were in line with the presence of hydroxy and carbonyl groups, respectively. The NMR spectroscopic data of 2 (Table 1, Figures S9–S15, Supporting Information) resembled those of compound 1, except for the differences associated with an epoxy moiety, which was established to be at C-8 and C-14 of ring C. This epoxy group was identified by the presence of signals at δ_C 60.4 (C-8) and δ_C 55.6 (C-14), replacing those at δ_C 150.8 and δ_C 115.5 observed for compound 1. Therefore, the ¹H NMR spectrum of 2 contained a signal at δ_H 3.73 (H-14), compatible with an oxymethine functionality, instead of the olefinic proton signal at δ_H 6.35 that was observed for 1.

Similar to 1, the ¹H NMR spectrum of 2 displayed signals typical for geminal protons of a terminal alkene at δ_H 5.22/5.19 (H-18a/18b) and for an oxymethine proton at δ_H 4.85 (H-12), two methine protons at δ_H 3.33 (H-9) and δ_H 3.08 (H-3), four pairs of diastereotopic protons at δ_H 2.96/2.26 (H-2a/2b), 2.09/1.91 (H-6a/6b), 2.49/1.40 (H-7a/7b), and 2.29/1.63 (H-11a/11b), and three methyl protons at δ_H 1.97 (H-17), 1.33 (H-19), and 1.26 (H-20). Its ¹³C NMR spectrum (Figure 2, Figure S10, Supporting Information) consisted of signals corresponding to 20 carbons, which is in agreement with a diterpenoid skeleton. Similar to the HMBC spectrum of compound 1, that of 2 (Figure 2, Figure S13 and Table S1, Supporting Information) showed cross-peaks from H-20 (δ_H 1.26), H-2a/b (δ_H 2.96/2.26), H-3 (δ_H 3.08), and H-9 (δ_H 3.33) to C-1 (δ_C 210.4), which together with the HMBC cross-peaks from H-3 to C-4 (δ_C 151.9), C-5 (δ_C 79.9), and C-18 (δ_C 114.5) aided in the assignment of ring A. In addition, the cross-peaks of H-12 (δ_H 4.85) to C-16 (δ_C 174.1) and of C-14 (δ_C 55.4) and H-17 (δ_H 1.97) to C-16 (δ_C 174.1) and C-13 (δ_C 155.2) confirmed the assignment of rings C and D. The HMBC cross-peak of H-9 to C-5 (δ_C 79.9), C-14 (δ_C 55.4), and C-12 (δ_C 76.0) along with the long-range J_H12-H17 coupling observed in the COSY spectrum (Figure S11, Supporting Information) supported the proposed linkage of rings B and C.

The relative configuration of 2 was determined based on NOE observations (Figure 2a, Figure S15, Supporting Information) and scalar couplings (Table 1). Thus, the strong NOE cross-peak between H-12 (δ_H 4.85) and H-20 (δ_H 1.26) suggested these protons to be syn-oriented, similar to 1. The ECD spectrum of 2 (Figure S17, Supporting Information) showed a positive Cotton effect for the π → π* transition at ca. 293 nm, a positive Cotton effect for the n → π* transition at ca. 256 nm, a negative Cotton effect at ca. 241 nm for the n → π*, and a weak positive Cotton effect at 210 nm for the ¹La electronic transition. This is different from that observed for 1 and for other previously reported ent-abietane diterpenoids. Single-crystal X-ray diffraction analysis using Cu Kα radiation (Figure 2b) established unambiguously the absolute configuration of 2 as 3S,5S,8S,9S,10S,12R,14R. Based on the above spectroscopic analyses, this new compound, zanzibariolide B (2), was characterized as the ent-abietane (3S,5S,8S,9S,10S,12R,14R)-5-hydroxy-8,14-epoxy-3,10,15-trimethyl-4-methylene-2,3,6,7,9,11,12,14-decahydrophenanthro[3,2-f]furan-1,16-dione.

The proposed biogenesis of 1 and 2 is shown in Scheme 1. The terminal double bond at C-4 is proposed to arise through an enzymatic 1,2-methyl shift, either of CH₂ at C-4 to C-3, followed by dehydrogenation. Such a methyl shift is a common phenomenon in terpene biosynthesis. However, modified ent-abietane diterpenoids have been reported from various plants, including also Suregada species. Modified ent-abietane diterpenoids with a terminal olefinic bond at C-4, as in compounds 1 and 2, are rare. The structures of the isolated known triterpenoids, simiarenoles (3), and α-amyrin (4) were confirmed by comparison of their spectroscopic data (Figures S18–S30, Supporting Information) to those reported in the literature. The relative configuration of 3 was confirmed by single-crystal X-ray diffraction analysis (Figure 3).

The anti-HSV-2 activity and the cytotoxicity of the leaf crude extract and of compounds 1–3 are shown in Figures 4 and 5, respectively. The crude extract exhibited anti-HSV-2
activity at nontoxic concentrations. Encouraged by these data, compounds 1–3, purified from this extract, were tested for their bioactivities. None exhibited anti-HSV-2 activity at a concentration up to 100 μM (Figure 5a). Compounds 1–3 were evaluated also for their ability to inhibit infection of A549 cells by the tick-borne encephalitis virus (TBEV) and infection of HeLa cells by the human rhinovirus type 2 (HRV-2) (page S23, Supporting Information). Under the concentration range tested (0.032–100 μM) compounds 1–3 exhibited no anti-TBEV nor HRV-2 activities. These compounds showed very little or no toxicity for GMK AH1 cells at ≥100 μM (Figure 5b). Nonetheless, the potential cytotoxic effect of the leaf crude extract at 100 μg/mL raises safety concerns as the concoction of leaves from the plant is used in folk medicine for various ailments.\cite{1,2} On the other hand, compound 3 has previously been reported to exhibit significant activity against α-glucosidase\cite{3} and to be toxic (IC_{50} 1.78 μM) against human acute monocytic leukemia cells (THP-1).\cite{3} Compound 4 was not tested for anti-HSV-2 activity, as it was isolated in low amount; however, it is known to exhibit significant anti-inflammatory activity by inhibition of PGE2 and IL-6 secretion.\cite{4}

### General Experimental Procedures

Optical rotations were determined using a 341 LC OROT polarimeter at 589 nm and 24.0 °C, whereas ECD spectra were acquired on a JASCO J-810, Rev.1.00, spectropolarimeter. UV spectra were obtained using CH\_\_OH as the solvent on a Shimadzu UV-1650PC UV/vis spectrophotometer. Infrared (IR) spectra were recorded on a PerkinElmer Spectrum FT-IR spectrometer using liquid samples. NMR spectra were acquired either on an Agilent 400MR 400 MHz spectrometer equipped with a OneNMRProbe or on a Bruker Avance Neo 600 MHz spectrometer equipped with a TCI cryogenic probe and were processed using MestraNova (v14.0.0). Chemical shifts were referenced to the residual carbon and proton signals of the deuterated solvents (CDCl\_3, δ\_C 77.16) as internal standard. Assignments were based on 1D (\_H and \_C) and 2D (COSY, HSQC, HMBC, TOCSY, and NOESY) NMR spectra. Mass spectra were acquired on a Waters Micromass ZQ, Multimode Ionization ESCI in ESI mode, connected to an Agilent 1100 series gradient pump system and a C18 Atlantis T3 column (3.0 × 50 mm, 5 μm), and using Milli-Q H\_2O–MeOH (5:95 to 95:5, with 1% HCO\_3H and a flow rate of 0.75 mL/min over 6 min). HRESIMS spectra were obtained with a Q-TOF-LC/MS spectrometer using a 2.1 × 30 mm 1.7 μM RPC\_18 and H\_2O–CH\_3CN gradient (5:95–95:5 in 0.2% formic acid, v/v) at Sternhagen Analyt Lab AB, Gothenburg, Sweden. Thin layer chromatography (TLC) was performed on silica gel 60 F\_254 (Merck, Darmstadt, Germany).

### EXPERIMENTAL SECTION
using precoated aluminum plates to monitor isolation processes. TLC plates were visualized under UV light (254 and 366 nm) and by spraying with an anisaldehyde reagent (prepared by mixing 5.3 mL of 4-anisaldehyde with 2.5 mL of concentrated sulfuric acid, 4 mL of glacial acetic acid, and 90 mL of methanol) followed by heating (80–100 °C). Column chromatography was run on silica gel 60 (230–400 mesh), whereas gel filtration on Sephadex LH-20 (GE Healthcare).

**Plant Material.** The leaves of *S. zanzibaricus* were collected in May 2017 from Umasaini bushland near Mping’ongo Bridge (6°25′20.814″ S; 38°42′13.722″ E at an elevation of 40 m altitude) in Fukayosi village, Bagamoyo District, Pwani Region in Tanzania. The plant was identified by Mr. F. M. Mbago, a senior taxonomist of the Herbarium, Botany Department, University of Dar es Salaam, and the specimens were deposited with voucher number FMM 3811 at the Herbarium, Botany Department, University of Dar es Salaam.

**Extraction and Isolation.** The air-dried leaves of *S. zanzibaricus* were ground to a fine powder to obtain a 1603 g sample, which was soaked three times in 3 L of CH₂OH−CH₂Cl₂ (7:3) at room temperature for 48 h, yielding a total of 74 g of crude extract after evaporation under reduced pressure at 40 °C. The crude extract (71 g) was adsorbed onto silica gel (1:1) and loaded on a silica gel 60 (400 mesh) column. Gravitational elution was performed with a gradient of increasing polarity using EtOAc (0−55 %) and CH₂Cl₂−isohexane (7:3) at room temperature in a humidified atmosphere comprising 5% CO₂ in N₂. Subsequently, 50 mg of zanzibariolide A (1), 236 mg as white needle-like crystals. Furthermore, the combined fractions 62−84 eluted with 60−80% were washed with isohexane and crystallized from CH₂Cl₂−isohexane (1:1) to afford zanzibariolide B (2, 1800 mg) as white needle-like crystals.

**Zanzibariolide A (1):** White crystals; [α]D²⁰ +82.5 (c 0.03, CH₂Cl₂); UV (CH₂Cl₂) λmax 264 nm; ECD (c 0.025, CH₂OH) λmax (Δε) 310 (11), 287 (−34.1), 214 (−186.0); IR νmax 3460, 1740 cm⁻¹; 1H and 13C NMR, see Table 1; HRESIMS m/z 329.1754 [M + H]+ (calc 329.1753 for [C9H14O3H]+)

**Zanzibariolide B (2):** White crystals; [α]D²⁰ +87.5 (c 0.03, CH₂Cl₂); UV (CH₂Cl₂) λmax 2700 (sh) nm; ECD (c 0.05, CH₂OH) λmax (Δε) 293 (18.7), 256 (31.0), 241 (−6.3); IR νmax 3456, 1752 cm⁻¹; 1H and 13C NMR, see Table 1; HRESIMS m/z 345.1702 [M + H]+ (calc 345.1702 for [C10H14O4H]+)

**X-ray Crystal Structure Analysis.** Single-crystal X-ray data for 1 and 2 were measured using a Rigaku SuperNova Dual-source Oxford diffractometer equipped with an Atlas detector using mirror-monochromatized Cu Kr radiation (λ = 1.5418 Å, 4°). The data collection and reduction were performed using the program CryAlisPro, and a numerical absorption correction based on Gaussian integration was applied. The data were solved by intrinsic phasing (ShelXT) and refined by full-matrix least-squares on F² using the Olex2 software, which utilizes the ShelXL module. Anisotropic displacement parameters were assigned to non-H atoms. All C−H hydrogen atoms were refined using riding models with a Uiso(H) of 1.2Uiso(C) for methyl groups and a Uiso(H) of 1.5Uiso(C) for all other C−H groups. Single-crystal X-ray diffraction measurements for compound 3 were performed using graphite-monochromatized Mo Kr radiation (λ = 0.71073) using a Bruker D8 APEX-II equipped with a CCD camera. Data reduction was performed with SAINT. Absorption corrections for the area detector were performed using SADABS. The structure was solved by direct methods and refined by full-matrix least-squares techniques against F² using all data (ShelXT, ShelXS). All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were constrained in geometric positions to their parent atoms using OLEX2. Diffuse contribution to diffraction in 3 was accounted for by using solvent modification. The X-ray structures of 1 (CCDC 2181946), 2 (CCDC 2181947), and 3 (CCDC 2118304) have been deposited at the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0)1223-336033 or email: deposit@ccdc.cam.ac.uk).

**Crystal data for 1:** C₉H₁₄O₃, M = 328.39, colorless block, orthorhombic, space group P2₁2₁2₁, a = 8.4509(1) Å, b = 10.5790(2) Å, c = 18.4968(2) Å, V = 1681.793(3) Å³, Z = 4, Dcalc = 1.297 g cm⁻³, F(000) = 704, μ = 0.72 mm¹⁻¹, T = 200.0(1) K, θmax = 76.4°, 3400 total reflections, 3328 with I > 2σ(I), Rexp = 0.020, 3400 data, 223 parameters, no restraints, GoF = 1.03, R₁ = 0.028, wR₂ = 0.075, 0.22 < Δρ < −0.14 e Å⁻³, Fcalc = 0.067 (6), CCDC 2181946.

**Crystal data for 2:** C₁₀H₁₄O₄, M = 344.39, colorless plate, monoclinic, space group P2₁, a = 6.2085(1) Å, b = 16.2459(3) Å, c = 8.6284(1) Å, β = 93.354(2)°, V = 832.54(2) Å³, Z = 2, Dcalc = 1.374 g cm⁻³, F(000) = 368, μ = 0.80 mm⁻¹, T = 200.0(1) K, θmax = 67.4°, 3374 total reflections, 3278 with I > 2σ(I), R₁ = 0.0227, 3374 data, 232 parameters, 1 restraint, GoF = 1.05, R₁ = 0.015, R₁[obs] = 0.0092 and wR₂ = 0.075, 0.19 < Δρ < −0.14 e Å⁻³, Fcalc = 0.04(7), CCDC 2181947.

**Crystal data for 3:** C₉H₂₀O₅ (M = 426.70 g mol⁻¹), trinodal, space group R3, a = 32.206(6) Å, c = 7.3631(14) Å, V = 7903.0(3) Å³, Z = 9, T = 180.15 K, μ(Mo Kα) = 0.047 mm⁻¹, Dcalc = 1.070 g cm⁻³, 30 808 reflections measured (4.008° ≤ 2θ ≤ 50.236°), 6228 unique (Rint = 0.0080, Rsigma = 0.0839) which were used in all calculations. The final R₁ = 0.0592 and wR₂ = 0.1334 (all data), CCDC 218304.

**Antiviral Assay.** African green monkey kidney epithelial cells were employed for screening of antiviral and cytotoxic activities of both crude extracts and pure compounds isolated thereof. The HSV-2 333 strain was used. An HSV-2 plaque reduction assay was used to determine the effects of the plant extract and compounds on HSV-2 infectivity in GMK AH1 cells. Briefly, the plant extract and all tested compounds were solubilized in DMSO, and the stocks (10 mg/mL) were stored at −20 °C. Prior to the assay, the test samples were subjected to serial 5-fold dilutions in Eagle’s minimum essential medium supplemented with 1% penicillin/streptomycin and 1% l-glutamine stocks (EMEM-M) to obtain a concentration range 1.6−100 μg/mL (extract) or 1.6−100 μM (compounds). The control sample comprised various concentrations of DMSO solvent. The GMK AH1 cells were seeded in 24-well plates, and confluent, 3-day-old monolayers (ca. 3.7 × 10⁴ cells/well) were used. The supernatant culture medium was removed, the cells were rinsed once with 200 μL of EMEM-M medium, and 400 μL of fresh EMEM-M was added. Then, the cells in duplicate wells received 50 μL of serial 5-fold dilutions of extract or compounds and after gentle shaking were left at 37 °C in a humidified atmosphere comprising 5% CO₂ (the CO₂ incubator). Subsequently, 50 μL of EMEM-M medium comprising 100 plaque forming units of HSV-2 333 strain was added to each well, and following gentle shaking, the cells were left in the CO₂ incubator for 90 min. Then, the supernatant medium was removed, and the cells were overlaid with 750 μL of a 1% solution of methyl cellulose in EMEM-M (supplemented with 2% fetal calf serum) that contained the same concentrations of the test extract or compounds. Following incubation of cells for 3 days in the CO₂ incubator, the overlay medium was removed and the cells were stained with 1% crystal violet solution to visualize the viral plaques.

**Cytotoxicity of the test extract or compounds for GMK AH1 cells** was assayed as described by Said et al. Briefly, 3-day-old monolayer cultures of GMK AH1 cells growing in 96-well cluster plates were used. The culture medium was removed, the cells were rinsed with 200 μL of EMEM-M medium, and 50 μL of fresh EMEM was added. Subsequently, 50 μL of EMEM-M comprising the test samples at 5-fold dilutions was added in duplicate wells. The final concentrations of...
the extract and compounds were 100, 20, 4, 0.8, 0.16, and 0 (DMSO control) μg/mL (extract) or μM (compounds). Following incubation of cells with the test samples for 3 days in the CO2 incubator, 15 μL of the CellTiter 96 AQeuos One Solution reagent (Promega, Madison, WI, USA) was added. After shaking, the cells were left in the CO2 incubator for a further 1 h, and absorbance at 490 nm was recorded.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.2c00147.

NMR and MS data for the isolated compounds (PDF)
X-ray crystallographic data for compound 1 (CIF)
X-ray crystallographic data for compound 2 (CIF)
X-ray crystallographic data for compound 3 (CIF)

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**Notes**
The authors declare no competing financial interest.
The original MS and NMR spectra for all compounds, along with the corresponding NMRspectData for the new compounds 1 and 2, are freely available on Zenodo as DOI 10.5281/zenodo.5920668.

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