Two new isomeric tricycloalternarenes from the marine alga-epiphytic fungus Alternaria alternata k23-3

1 | INTRODUCTION

Tricycloalternarenes (TCAs) and their possible precursors, bicycloalternarenes, represent a large class of fungal-derived meroterpenes, which are regarded as the products through hybrid mevalonate and shikimate pathways.[1–2] Totally, more than 70 members have been isolated and identified so far, with TCAs accounting for over 70%.[2–18] Most of the TCAs feature a ring system that is constructed by the fusion of a cyclohex-2-enonyl group and a cyclopentenyl/cyclopenyl group via a methylene group and an oxygen atom, and they have been obtained from some species of the genera Alternaria,[2–10] Aspergillus,[11] Guignardia,[12–15] Pycnoporus,[16] Septoria,[17] and Ulocladium.[18] In our ongoing investigation towards the chemical diversity and biological activity of secondary metabolites from marine algicolous fungi,[19–21] a marine red alga-epiphytic strain (k23) of Alternaria alternata was examined. As a result, two new 15-hydroxytricycloalternarenes (1 and 2) along with a known one, TCA 11a (3),[18] were isolated and identified (Figure 1). Details of the isolation, structure elucidation, and bioactivity of these compounds are described in this paper.

2 | RESULTS AND DISCUSSION

Compound 1 was obtained as a colorless oil. A molecular formula of C23H32O5 was determined on the basis of HREIMS (m/z 388.2256 [M]+, calcd for C23H32O5, 388.2250), requiring 8° of unsaturation. The UV spectrum exhibited a band at 263 nm due to the constant conjugation system of enone and oxygen, and the IR absorptions at 3,410 and 1,736 cm−1 suggested the presence of hydroxy and carbonyl groups. In EI mass spectrum, the fragment ion peaks at m/z 346 and 328 were proposed to be yielded by an acetoxy group. The 1H NMR spectrum (Table 1) showed three singlets and one doublet corresponding to four methyls, one multiplet assignable to a methine, a batch of triplets of one doublet doublet attributable to an oxygenated methine, one broad singlet ascribable to an oxygenated methylene, and one broad singlet and one triplet relatable to two olefinic protons. The 13C NMR spectrum (Table 1) displayed 23 resonances, classified into four methyls, seven methylenes, five methines, and seven nonprotonated carbons by DEPT and HSQC experiments. A detailed comparison of the MS and NMR data with those of ACTG-toxin E revealed their similarity, except for the presence of an acetyl group in 1. The HMBC correlation from H-1 to C-1 placed the acetoxy group at C-1, which was supported by the deshielded 13C NMR signal of C-1. The 1H-1H COSY and HMBC correlations as shown in Figure 2 further confirmed the planar structure of 1. The geometry of double bond at C-2 was assigned to be E by the NOE correlations between H-1 and H-3 and between Me-2′ and H-4, and Rings A and B were deduced to be cis-fused by the NOE correlation between Me-10′ and H-11 (Figure 3). Additionally, H-9b and Me-10′ were located on the same face based on their NOE correlation. H-15 exhibited a multiplet when processed with the spectrometer default settings (Figure 4). A further process with Gaussian multiplication plus zero filling and deconvolution with Lorentzian–Gaussian functions gave a subtle splitting pattern of ddt, and the two large coupling constants (J = 8.3, 5.0 Hz) were comparable to those (J = 7.1, 5.0 Hz) reported for TCA 11a.[8] Moreover, in view of the identical electronic circular dichroism (ECD) spectra between 1 (Figure 5) and TCA 11a,[8] the absolute configuration at C-15 was established to be S. However, the absolute configurations at C-6, C-10, and C-11 remained unable to be resolved due to the lack of valuable NOE correlations with H-15 and failure in crystallization. Compound 1 was trivially named (2E)-TCA 12a.

Compound 2 was also isolated as a colorless oil and assigned a molecular formula of C23H32O5, the same as for 1, by interpretation of HREIMS (m/z 388.2253 [M]+, calcd for C23H32O5, 388.2250). The UV, IR, MS, and 1H and 13C NMR data (Table 1) of 2 closely resembled those of 1, and the 1H-1H COSY and HMBC correlations (Figure 2) further supported their high similarity. A detailed comparison of NMR data (Table 1) revealed that 2 differed from 1 mainly at the side chain terminus.
The $^1$H NMR signals of H-1 and H-2’ of 2 split into a doublet and a quartet and shifted 0.09 and 0.12 ppm, respectively, towards high frequency relative to those of 1. The $^{13}$C NMR signal moved 7.0 ppm towards low frequency for C-1 and 7.4 ppm towards high frequency for C-2’. These variations suggested a geometric difference of the double bond at C-2, and its Z configuration was established by the NOE correlations between H-1 and H-4 and between H-2’ and H-3 (Figure 3). Moreover, Me-10’, H-9b, and H-11 were indicated to be syn by the NOE correlations of H-1’-H-9b and H-11, and the absolute configuration at C-15 was deduced to be S by the identical ECD spectrum (Figure 5) with 1 and TCA 11a.[8] Compound 2 was trivially named (2Z)-TCA 12a.

Compounds 1 and 2 represent a pair of E and Z isomers with the double bond being attached by an acetoxymethylene group, and their differences of chemical shifts reflect the effect of geometric isomerism and may contribute to the identification of some analogues in the future. In order to evaluate the ecological function of 1–3, they were assayed for inhibition of three marine phytoplankton (Chattonella marina, Heterosigma akashiwo, and Prorocentrum donghaiense) and one marine zooplankton (Artemia salina).[21,22] The results (Table 2) showed that 1–3 appeared weak to moderate to inhibit or kill the marine plankton tested, but it was interesting that 2 was more active to suppress the growth of all the three phytoplankton and less toxic to the zooplankton A. salina than 1.

3 | EXPERIMENTAL

3.1 | General experimental procedures

Optical rotation was measured on a JASCO P-1020 polarimeter (JASCO, Tokyo, Japan). The UV and ECD spectra were recorded on a Chirascan CD spectrometer (Applied Photophysics Ltd, Surrey, UK). IR spectrum was obtained on a JASCO FT/IR-4100 Fourier Transform Infrared spectrometer (JASCO, Tokyo, Japan). Mass spectrum was determined on an Autospec Premier P776 mass spectrometer (Waters Corp., Milford, MA, USA). HPLC separation was operated on an Agilent HPLC system (1260 infinity quaternary pump, 1260 infinity diode-array detector) using an Eclipse SB-C18 (5 μm, 9.4 × 250 mm) column (Agilent Technologies Inc., Santa Clara, CA, USA). Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Qingdao, China), RP-18 reversed-phase silica gel (AAG12S50, YMC Co. Ltd, Kyoto, Japan), and Sephadex LH-20 (GE, Uppsala, Sweden). Thin-layer chromatography (TLC) was carried out with precoated silica gel plates (GF-254, Qingdao Haiyang Chemical Co., Qingdao, China). The solvents were of analytical grade except for the spectral-grade MeOH for HPLC.

3.2 | NMR spectra

The 1D and 2D NMR spectra were recorded on a Bruker Avance III 500 NMR spectrometer (Bruker Corp., Billerica, MA, USA) equipped with 5 mm probe at 298 K. Chemical shifts (δ) in parts per million are referenced to tetramethylsilane (TMS) at 0.00 ppm for $^1$H and $^{13}$C. Coupling constants (J) are given in Hertz. The pulse conditions were as follows: for $^1$H, spectrometer frequency (SF) = 500.13 MHz, spectral width (SWH) = 10330.58 Hz, pulse 90° width (P1) = 11.00 μs, fourier transform size (SI) = 65536, line broadening (LB) = 0.30 Hz, acquisition time (AQ) = 3.17 s, relaxation delay (D1) = 1.00 s, and number of dummy scans (DS) = 0; for $^{13}$C, SF = 125.76 MHz, SWH = 29761.90 Hz, δ = 12.68 μs, SI = 32768; LB = 1.00 Hz, AQ = 1.10 s, D1 = 2.0 s, and DS = 4; for DEPT 101, SF = 125.76 MHz, δ = 29761.90 Hz, SI = 32768, LB = 1.00 Hz, AQ = 1.63 s, D1 = 2.0 s, and DS = 4; for DEPT 90, SF = 125.76 MHz, δ = 29761.90 Hz, SI = 32768, LB = 1.00 Hz, AQ = 1.63 s, D1 = 2.0 s, and DS = 4; for DEPT 135, SF = 125.76 MHz, SWH = 20161.29 Hz, SI = 32768, LB = 1.00 Hz, AQ = 1.63 s, D1 = 2.0 s, and DS = 4; for DEPT 151, SF = 125.76 MHz, SWH = 20161.29 Hz, SI = 32768, LB = 1.00 Hz, AQ = 1.63 s, D1 = 2.0 s, and DS = 4; for HSQC, SF = 500.13 (1H), δ = 125.76 Hz (13C), LB = 1.00 Hz, AQ = 1.63 s, D1 = 2.0 s, and DS = 4; for HMBC, SF = 500.13 Hz (1H), δ = 125.76 Hz (13C), LB = 1.00 Hz, AQ = 0.41, D1 = 1.5 s, and DS = 16; for NOESY, SF = 500.13 Hz, LB = 1.00 Hz, AQ = 0.41, D1 = 1.5 s, and DS = 16; and mixing time (D8) = 1.00 s.

3.3 | Fungal material and fermentation

The epiphytic fungus A. alternata k23-3 was isolated from the marine red alga Gelidiella acerosa that was collected
from Kongtong Island, Shandong Province, China, in July 2015. The strain was identified by morphological observation and analysis of the internal transcribed spacer (ITS) regions of its rDNA, whose sequence data have been deposited at GenBank (accession no. M374781). The fungal strain was grown on potato dextrose agar plates at 28 °C for several days, which was then cultured statically at room temperature for 30 days in 100 × 1 L Erlenmeyer flasks. Each flask contained 300 ml of the modified potato dextrose broth medium, which was prepared by adding 20 g glucose, 5 g peptone, and 5 g yeast extract powder into 1 L potato (200 g) broth.

| No. | 1δH | δC | 2δH | δC |
|-----|-----|----|-----|----|
| 1   | 4.43 (br s) | 70.3 (CH2) | 4.52 (br d, 2.1) | 63.3 (CH2) |
| 2   | 130.2 (C) |  | 130.0 (C) |  |
| 3   | 5.38 (t, 7.1)a | 129.7 (CH) | 5.31 (t, 6.9)b | 130.7 (CH) |
| 4a  | 1.92 (overlapped) | 25.9 (CH2) | 1.98 (overlapped) | 25.8 (CH2) |
| 4b  |  |  | 1.90 (overlapped) |  |
| 5a  | 1.50 (overlapped) | 34.5 (CH2) | 1.47 (overlapped) | 35.0 (CH2) |
| 5b  | 1.32 (ddt, 13.4, 9.9, 6.4)b |  | 1.32 (ddt, 13.3, 9.8, 6.4)b |  |
| 6   | 1.97 (overlapped) | 32.6 (CH) | 1.97 (overlapped) | 32.4 (CH) |
| 7   |  | 150.2 (C) |  | 150.1 (C) |
| 8   | 5.32 (br s) | 120.1 (CH) | 5.31 (br s) | 120.2 (CH) |
| 9a  | 2.61 (overlapped) | 45.1 (CH2) | 2.61 (overlapped) | 45.0 (CH2) |
| 9b  | 2.46 (dq, 16.2, 1.8)c |  | 2.46 (dq, 16.2, 1.8)c |  |
| 10  |  | 88.9 (C) |  | 88.9 (C) |
| 11  | 2.77 (m) | 46.8 (CH) | 2.77 (m) | 46.8 (CH) |
| 12a | 2.60 (overlapped) | 15.5 (CH2) | 2.60 (overlapped) | 15.5 (CH2) |
| 12b | 2.23 (overlapped) |  | 2.23 (overlapped) |  |
| 13  |  | 108.0 (C) |  | 107.9 (C) |
| 14  |  | 169.9 (C) |  | 170.1 (C) |
| 15  | 4.33 (ddt, 8.3, 5.0, 1.6)d | 66.6 (CH) | 4.35 (ddt, 8.3, 5.0, 1.6)d | 66.6 (CH) |
| 16a | 2.22 (overlapped) | 29.1 (CH2) | 2.22 (overlapped) | 29.1 (CH2) |
| 16b | 1.93 (overlapped) |  | 1.92 (overlapped) |  |
| 17a | 2.58 (overlapped) | 33.7 (CH2) | 2.57 (overlapped) | 33.8 (CH2) |
| 17b | 2.26 (overlapped) |  | 2.27 (overlapped) |  |
| 18  |  | 196.8 (C) |  | 196.8 (C) |
| 1′  |  | 171.1 (C) |  | 171.3 (C) |
| 2′  | 1.60 (br s) | 14.1 (CH3) | 1.72 (q, 1.3)g | 21.5 (CH3) |
| 6′  | 0.95 (d, 6.9)h | 20.3 (CH3) | 0.94 (d, 6.9)h | 20.3 (CH3) |
| 10′ | 1.49 (s) | 23.8 (CH3) | 1.49 (s) | 23.8 (CH3) |
| 1″  | 2.07 (s) | 21.2 (CH3) | 2.06 (s) | 21.1 (CH3) |

*aCoupling with H2-4.
*bCoupling with H-5a, H-6, and H2-4, respectively.
*cCoupling with H-9a, H-8, H-6, and H-11, respectively.
*dCoupling with H-16b, H-16a, and H2-12, respectively.
*eCoupling with H-6.
*fCoupling with H-3.
*gCoupling with H2-1 and H-3.
3.4 | Extraction and isolation

The cultured mycelia were separated from broth by filtration, which was then dried and extracted with a mixture of CH₂Cl₂ and MeOH (1:1, v/v) to the greatest extent. The solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc and H₂O to yield an EtOAc-soluble extract (33.8 g). On the other hand, the fermentation liquor was directly extracted with EtOAc and then concentrated to give an extract (9.0 g). These two parts were combined on the basis of their similar TLC profiles and then subjected to silica gel CC with step-gradient solvent systems consisting of petroleum ether (PE)/EtOAc (50:1 to 1:1) and CH₂Cl₂/MeOH (20:1 to 1:1) to afford 10 fractions (Fr. 1–10). Fr. 6 eluted with PE/EtOAc (1:1) and was further purified by RP-18 CC (MeOH/H₂O, 7:3), preparative TLC (PE/EtOAc, 1:1), and semi-preparative HPLC (MeOH/H₂O, 3:2 to 4:1) to produce 1 (1.7 mg) and 2 (1.3 mg). Fr. 7 eluted with CH₂Cl₂/MeOH (20:1) and was further purified by CC on RP-18 (MeOH/H₂O, 3:2) and Sephadex LH-20 (MeOH) to afford 3 (2.2 mg).

\((2E)\)-TCA 12a ((E)-6-((3aR,5S,9aS)-5-hydroxy-3a-methyl-8-oxo-3,3a,5,6,7,8,9,9a-octahydrocyclopenta\[b\] chromen-1-yl)-2-methylhept-2-enyl acetate, (1): colorless oil; \([\alpha]_{22}D + 69 (c 0.14, \text{MeOH}); \) UV (MeOH) \(\lambda_{\text{max}}\) (log ε) 263 (3.97) nm; ECD (0.25 g/L, MeOH) \(\lambda_{\text{max}}\) (Δε) 205 (−1.58), 244 (2.27), 310 (1.11) nm; IR (KBr) \(v_{\text{max}}\) 3,410, 2,931, 2,866, 1,736, 1,616, 1,385, 1,238, 1,084, 953, 829 cm\(^{-1}\); \(^1\)H and \(^{13}\)C NMR data (Table 1); EIMS \(m/z\) (%) 388 [M]\(^+\) (63), 346 (17), 328 (51), 247 (29), 219 (24), 187 (100), 145 (67), 108 (90), 91 (78); HREIMS \(m/z\) 388.2256 [M]\(^+\), calcld for C\(_{23}\)H\(_{32}\)O\(_5\), 388.2250.

\((2Z)\)-TCA 12a ((Z)-6-((3aR,5S,9aS)-5-hydroxy-3a-methyl-8-oxo-3,3a,5,6,7,8,9,9a-octahydrocyclopenta\[b\] chromen-1-yl)-2-methylhept-2-enyl acetate, (2): colorless oil; \([\alpha]_{21}D + 60 (c 0.09, \text{MeOH}); \) UV (MeOH) \(\lambda_{\text{max}}\)
TABLE 2  Inhibitory or toxic effects on four marine plankton of 1–3 at 100 μg/ml

|                          | Chattonella marina (%) | Heterosigma akashiwo (%) | Prorocentrum donghaiense (%) | Artemia salina (%) |
|--------------------------|------------------------|--------------------------|-----------------------------|--------------------|
| 1                        | 29.8 ± 1.1             | -18.6 ± 0.4              | 3.60 ± 4.0                  | 48.6 ± 1.3         |
| 2                        | 79.6 ± 0.8             | 23.8 ± 1.0               | 37.2 ± 3.3                  | 34.0 ± 1.7         |
| 3                        | 51.6 ± 7.7             | 44.8 ± 1.7               | 38.0 ± 3.9                  | 23.5 ± 4.2         |

(log ε) 263 (3.88) nm; ECD (0.29 g/L, MeOH) λ<sub>max</sub> (Δε) 206 (−0.90), 244 (2.75), 310 (0.72) nm; IR (KBr) ν<sub>max</sub> 3,433, 2,931, 2,858, 1,732, 1,628, 1,385, 1,238, 1,022 cm<sup>−1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data (Table 1); EIMS m/z (%) 388 [M]+ (44), 346 (10), 328 (31), 248 (18), 219 (15), 187 (100), 145 (44), 107 (87), 91 (59); HREIMS m/z 388.2253 [M]+, calcd for C<sub>23</sub>H<sub>32</sub>O<sub>5</sub>, 388.2250.

3.5  | Bioassay

The growth inhibition against three marine phytoplankton (C. marina, H. akashiwo, and P. donghaiense) and one marine zooplankton (A. salina) was assayed as described previously, and potassium dichromate (K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>) with 100% inhibition of the four plankton tested at 100 μg/ml was taken as a positive control.

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ORCID

Nai-Yun Ji  http://orcid.org/0000-0002-6526-4731

Zhen-Zhen Shi<sup>1,2</sup>
Xiu-Li Yin<sup>1</sup>
Sheng-Tao Fang<sup>1</sup>
Feng-Ping Miao<sup>1</sup>
Nai-Yun Ji<sup>1</sup><sup>†</sup>

<sup>1</sup>Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, China

<sup>2</sup>University of Chinese Academy of Sciences, Beijing 100049, China

†Contribute equally to this work.

Correspondence

Nai-Yun Ji, Yantai Institute of Coastal Zone Research, Chinese Academy of Sciences, Yantai 264003, China.
Email: nyji@yic.ac.cn

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