Two New Abietane Diterpenes From the Stems of Clerodendrum trichotomum Thunb

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Abstract

Two new abietane diterpenoids (4α, 5β, 10β)-12-(β-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl ester (1) and (3β, 5β, 10β)-3β-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranosyl)oxy-12-β-D-glucopyranosylxyabieta-8,11,13-triene-11,16-diol (2), along with 5 known terpene glycosides (3–7) were isolated from the n-butanol extract of the stems of Clerodendrum trichotomum Thunb. The structures of the new compounds were determined by analysis of spectroscopic data, chemical correlations, and electronic circular dichroism calculations. Besides, all compounds were evaluated for cytotoxic activities against cultured K562, MCF-7, A549, and HepG2 cell lines. None of them showed good antitumor activities.

Keywords

Clerodendrum trichotomum Thunb., abietane diterpenoids, terpene glycosides, n-butanol extract, structure identification

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Introduction

Clerodendrum trichotomum Thunb., genus Clerodendrum family Verbenaceae, also called “chou wu tong” in Chinese owing to its bad smell,1,2 has been used as a folk medicine for the treatment of rheumatic arthritis, hypertension, and migraine.3 The plant’s bad smell,1,2 has been used as a folk medicine for the treatment of rheumatic arthritis, hypertension, and migraine.3 The major constituents reported include phenylpropanoids, terpenoids, flavonoids, and steroids.4,5 In earlier work,6,7 the chemical constituents of the ethyl acetate fraction from the stems of Clerodendrum trichotomum have been studied systematically. However, relatively few papers have been devoted to the n-butanol extract so far.

Abietane diterpenoids are characteristic constituents of the genus Clerodendrum, which exhibit remarkable antitumor,8 anti-inflammatory,9 and insecticidal activities.10 This paper focused on the study of the chemical constituents from the n-butanol extract of Clerodendrum trichotomum stems, and 2 new abietane diterpenoids, (4α, 5β, 10β)-12-(β-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl ester (1) and (3β, 5β, 10β)-3β-[β-D-glucopyranosyl-(1→6)]-β-D-glucopyranosyl)oxy-12-β-D-glucopyranosylxyabieta-8,11,13-triene-11,16-diol (2), along with 5 known terpene glycosides (3–7) were isolated and characterized (Figure 1, 1–7). Compounds 1–7 were evaluated for cytotoxicity against several cancer cell lines, and all of them were inactive.

Results and Discussion

The n-butanol part of 85% ethanol extract from the stems of Clerodendrum trichotomum Thunb was subjected to repeated column chromatography (CC) to yield 7 compounds 1–7. Compounds 3–7 were identified as szemaoenoid A (3),11 leucasinoside (4),12 melittoside (5),13 8-epiloganic acid (6),14 and trijugaoside A (7)15 by comparison of their spectroscopic data with those previously reported in the literature. Compound 4 has been named as 12-O-β-D-glucopyranosyl-11, 16-dihydroxyabieta-8, 11, 13-triene,12 but it should be 11,16-dihydroxy-12-(β-D-glucopyranosyl)oxyabieta-8,11,13-triene-19-oic acid (an unfortunate typing/printing error deleted the main suffix). A few closely related abietane diterpene glycosides (Figure 1, 8–11) have been previously reported: 12-β-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid β-D-glucopyranosyl ester (8, unfortunately named as 12,19-di-
Figure 1. Structures of compounds 1 to 11.
O-D-glucopyranosyl-11-hydroxyabieta-8,11,13-triene-19-one \(^{16}\) or 19-O-\(\beta\)-D-carboxyglucopyranosyl-12-O-\(\beta\)-D-glucopyranosyl-11,16-dihydroxyabieta-8,11,13-triene \(^{15}\), 3,12-bis(\(\beta\)-D-glucopyranosyl)oxyabieta-8,11,13-triene-11,16-diol \(^{9}\). Correct name is 3-(\(\beta\)-D-glucopyranosyl)oxyabieta-8,12-(\(\beta\)-D-glucopyranosyl)oxyabieta-8,11,13-triene-11,16-diol, 12-(\(\beta\)-D-glucopyranosyl)oxyabieta-8,11,13-triene-3\(\beta\),11,16-triol \(\text{I} \), 12-O-\(\beta\)-D-glucopyranosyl-3,11,16-tri-hydroxyabieta-8,11,13-triene-19-oic acid \(\beta\)-D-glucopyranosyl ester\(^{16}\). The differences in the NMR spectra were a group of carbon signals at \(\delta_C\) 104.9, 78.0, 78.0, 75.3, 71.2, and 70.0, which were resonances of 1 additional sugar unit. This observation was verified by the HMBC correlations from \(\delta_H\) 4.30 (1H, \(d\), \(J = 7.8\) Hz, H-1\(^{10}\)) to \(\delta_C\) 70.0 (C-6\(^{8}\)).

The nuclear overhauser effect spectroscopy (NOESY) correlations (Supplemental Figure S10) of H-5/H-18, H-1a/H-5, and H-3a/H-5 suggested that these protons were co-facial, pointing out their \(\alpha\)-orientation, whereas the correlation of H-20/H-6b indicated that these protons were \(\beta\)-oriented (Figure 3). All \(^1\)H and \(^{13}\)C NMR data of compound \(\text{I} \) were assigned (Table 1). The absolute configuration of \(\text{I} \) was assigned as \(4S\), \(5S\), and \(10S\) by comparing the computational and experimental electronic circular dichroism (ECD) (Figure 4). Thus, compound \(\text{I} \) was established as \(4(S), 5(S), 10(S)\)-12-(\(\beta\)-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid \(\beta\)-D-glucopyranosyl-(1\(\rightarrow\)6)-\(\beta\)-D-glucopyranosyl ester.

Compound \(\text{I} \) was obtained as a yellow solid, which had the molecular formula C\(_{38}\)H\(_{58}\)O\(_{19}\) based on the negative high resolution electrospray ionization mass spectrometry (HR-ESI-MS) ion at \(m/z \) 817.3496 [M-H]\(^{-}\); calcd for 817.3486 (Supplemental Figure S1), indicating 10 degrees of unsaturation. The infrared (IR) spectrum of \(\text{I} \) showed the presence of 3 sugar units as a glycoside. Gas chromatography (GC) analysis (Supplemental Figure S4) showed the presence of 3 sugar units as a glycoside. The 1H-1H homonuclear chemical-shift correlated spectroscopy (COSY) spectrum (Supplemental Figure S9) of \(\text{I} \) showed that correlations of H-1a (\(\delta_H\) 1.08, m, 1H), H-2b (\(\delta_H\) 1.99, m, 1H), and H-3a (\(\delta_H\) 2.24, m, 1H) indicated the fragment C-1/C-2/C-3 in ring A, and correlations of H-5 (\(\delta_H\) 1.47, m, 1H), H-6b (\(\delta_H\) 1.85, m, 1H), and H-7 (\(\delta_H\) 2.70, m, 2H) corresponded to fragment C-5/C-6/C-7 in ring B. The key correlations are shown with blue bold lines in Figure 2. These characteristic signals implied that \(\text{I} \) was an abietane diterpenoid.

Further examination of the \(^1\)H detected heteronuclear multiple quantum coherence (HMQC) and \(^1\)H detected heteronuclear multiple bond correlation (HMBC) spectroscopic data (Supplemental Figures S7 and S8) of compound \(\text{I} \) indicated that it was structurally similar to \(\text{8} \) 12-(\(\beta\)-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid \(\beta\)-D-glucopyranosyl ester\(^{15}\).
In the $^1$H-NMR spectrum (Supplemental Figure S15), 1 doublet methyl and 3 singlet methyl proton resonances were displayed at $\delta_H$ 0.95 (3H, s, H-19), 1.12 (3H, s, H-18), 1.30 (3H, s, H-20), and 1.13 (3H, d, $J$ = 7.2 Hz, H-17). In addition, 3 doublet anomeric proton resonances at $\delta_H$ 4.36 (1H, d, $J$ = 7.6 Hz, H-1′), 4.46 (1H, d, $J$ = 8.4 Hz, H-1′′), and 4.44 (1H, d, $J$ = 7.6 Hz, H-1′′′) showed the presence of 3 sugar units as a glycoside. The GC analysis spectrum (Supplemental Figure S14) showed that the sugar derivative in the acid hydrolysate of 2 had the same retention time $t_R$ = 28.97 min as the derivative of D-glucose, which indicated that 2 had $\beta$-D-gluco-pyranosyl moieties. A singlet proton at $\delta_H$ 6.36 (1H, s, H-14) was the proton signal on a benzene ring, and the others were diterpene hydrogen and sugar proton signals. The $^{13}$C-NMR spectrum (Supplemental Figure S16) showed 38 carbon signals, including 6 aromatic carbon signals at $\delta_C$ 135.2 (C-8), 134.7 (C-9), 149.2 (C-11), 143.3 (C-12), 136.5 (C-13), and 118.3 (C-14); the anomeric carbon signals of 3 glucopyranose moieties were at $\delta_C$ 106.9 (C-1′), 104.9 (C-1′′), and 107.9 (C-1′′′), an obvious methylol resonance was at $\delta_C$ 69.2 (C-16), and the others were of diterpene and sugar moieties.

In addition, the $^1$H-$^1$H COSY spectrum (Supplemental Figure S19) of compound 2 showed that correlations of H-1a ($\delta_H$ 1.36, m, 1H), H-2b ($\delta_H$ 1.81, m, 1H), and H-3 ($\delta_H$ 3.25, m, 1H) indicated the fragment C-1/C-2/C-3 in ring A; correlations of H-5 ($\delta_H$ 1.21, d, $J$ = 12.0 Hz, 1H), H-6b ($\delta_H$ 1.57, m, 1H), and H-7 ($\delta_H$ 2.75, m, 2H), corresponded to fragment C-5/C-6/C-7 in ring B. These correlations are shown with blue bold lines in Figure 5. Based on the 1D NMR spectrum, compound 2 was an abietane diterpenoid. Examination of the HMOC and HMBC spectra (Supplemental Figures S17 and S18) of 2 indicated that it was structurally similar to [3-(β-D-glucopyranosyl)oxy-12-(β-D-glucopyranosyl)oxyabieta-8,11,13-triene-11,16-diol]. The differences in the NMR spectra were a group of carbon signals ($\delta_C$ 104.7, 77.7, 77.1, 75.2, 71.7, and 69.8) in 2. This observation was correlated by the HMBC correlations from $\delta_H$ 4.46 (1H, d, $J$ = 8.4 Hz, H-1′′) to $\delta_C$ 69.8 (C-6′). NOESY correlations (Supplemental Figure S20) of H-6a/H-18, H-3/H-1a, and H-3/H-5 revealed their co-facial relationship, and they were assigned arbitrarily as $\alpha$-oriented, whereas those of H-2b/H-20 and H-6b/H-19 implied these protons were $\beta$-oriented (Figure 6). All the $^1$H and $^{13}$C NMR data of compound 2 were assigned (Table 1). The absolute configuration of 2 was elucidated as 3S, 5S, 10S, and 15S by comparison of the calculated ECD data with the experimental data (Figure 7). Based on the above evidence, compound 2 was established as (3S, 5S, 10S, 15S)-3β-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]oxy-12-(β-D-glucopyranosyl)oxyabieta-8,11,13-triene-11,16-diol.

The antitumor activities of compounds 1–7 were evaluated against 4 cell lines, K562 human leukemia, MCF-7 human breast cancer, A549 human lung cancer, and HepG2 human hepatoma, using the MTT (methyl thiazolyl tetrazolium) assay. However, all the compounds were inactive (IC$_{50}$ > 50 µM).

Figure 4. Experimental and calculated electronic circular dichroism (ECD) spectra of compound 1 (in MeOH).
2D NMR spectra on a BRUKER 600 NEO NMR spectrometer (Bruker Co. Ltd) and JEOL ECS 400 NMR spectrometer (Jeol), and UV spectra on an UV-2700 spectrometer (Shimadzu Co. Ltd). Optical rotation values were measured on a Bellingham-Stanley ADP 440 + polarimeter (Bellingham-Stanley Co. Ltd), and IR spectra on a IR Tracer-100 spectrophotometer (Shimadzu Co. Ltd). A JASCO J-715 spectrometer (Jasco) was used to record the ECD. GC analysis was carried out on a Shimadzu-2010 Plus gas chromatograph (Shimadzu Co. Ltd), using a ZB-5 capillary column (30 m × 0.25 mm id. × 0.25 μm), an flame ionization detector at 280 °C, and a column initial temperature of 200 °C. CC was performed with a macroporous resin (D101, Tianjin Haiguang Chemical Co. Ltd), silica gel (200–300 mesh and 300–400 mesh, Qingdao Haiyang chemical Co. Ltd), Toyopearl HW-40C (Tocho corporation), Toyopearl HW-40F (Tocho corporation), and Sephadex LH-20 (Pharmacia Biotech). For thin-layer chromatography, silica gel GF 254 plates were used (Qingdao Haiyang Chemical Co. Ltd).

**Plant Material**

*C. trichotum* Thunb. was collected from Nanjing, Jiangsu Province, and identified by Yao Gan researcher, Jiangsu Institute of Botany Chinese Academy of Sciences. The voucher specimens are preserved in the Engineering Research Center for the Development and Application of Ethnic Medicine and Traditional Chinese Medicine (Ministry of Education), Guizhou Medical University.

**Extraction and Isolation**

The stems of *C. trichotum* (15 kg) were extracted with 85% ethanol under reflux, and the extract was partitioned with petroleum, ethyl acetate, and n-butanol, sequentially. Three parts were obtained: the petroleum part (50 g), the EtOAc part (70 g), and the n-butanol part (470 g). The n-butanol part was dissolved in water and separated through a D101 macroporous resin, following elution in proper order by water, ethanol–water (30%, 60%, 95%, v/v), and 50% ethanol under re-flux.

The 60% ethanol eluted fraction was separated into 8 fractions (Fr.1–8) by octade-cysyl silica gel ODS (MeOH/H₂O 10:90→100:0) CC. Fr.2 was fractionated by silica gel CC eluting with EtOAc–MeOH (30:1 to 5:1) to yield compound 5 (23 mg). Fr.5 was chromatographed on a Sephadex LH-20 column (MeOH–Water, 1:1) to obtain 5 sub-fractions (Fr.5.1–5.5). Fr.5.2 was further separated by ODS (MeOH/H₂O 10:90→70:30), silica gel (EtOAc–MeOH 30:1 to 5:1), Sephadex LH-20 (MeOH–Water, 1:1), and HW-40F CC (MeOH) to obtain compounds 1 (21 mg), 2 (25 mg), 3 (51 mg), and 7 (33 mg). Fr.7 was separated repeatedly by ODS (MeOH/H₂O 10:90→50:50) and HW-40F (MeOH) CC to obtain compound 4 (3 mg). Compound 6 (3 mg) was purified from the 30% ethanol eluted fraction by repeated ODS (MeOH/H₂O 10:90→50:50) and Sephadex LH-20 (MeOH–Water, 1:1) CC.

### Table 1. NMR Spectroscopic Data of Compound 1 [¹H (600 MHz) and ¹³C (150 MHz)] and 2 [¹H (400 MHz) and ¹³C (100 MHz)] in CD₃OD.

| Position | δ₁H (ppm, J in Hz) | δ₁C (ppm) | δ₁H (ppm, J in Hz) | δ₁C (ppm) |
|----------|--------------------|-----------|--------------------|-----------|
| 1        | Ha 1.08, m         | 37.4      | 1.36, m            | 36.2      |
|          | Hb 3.27, m         |           | 3.35, m            |           |
| 2        | Ha 1.44, m         | 21.0      | 2.00, m            | 28.2      |
|          | Hb 1.99, m         | 1.81, m   |                    |           |
| 3        | Ha 2.24, m         | 39.0      | 3.25, m            | 90.7      |
|          | Hb 1.09, m         | 45.6      |                    | 40.9      |
| 4        | 1.47, m            | 57.3      | 1.21, d (12.0)     | 54.6      |
| 5        | 2.14, m            | 22.5      | 1.81, m            | 20.1      |
| 6        | Ha 1.85, m         | 1.57, m   |                    |           |
|          | Hb 2.70, m         | 34.9      | 2.75, m            | 33.9      |
| 7        | 1.35                 |           | 1.32, s            |           |
| 8        | 1.11                 | 24.4      | 1.13, d (7.2)      | 18.5      |
| 9        | 1.30                 | 29.7      | 1.12, s            | 28.9      |
| 10       | 178.4                |           | 0.95, s            | 17.4      |
| 11       | 1.20                 | 18.2      | 1.30, s            | 20.0      |
| 12       | 4.36, d (7.8)       | 108.1     | 4.36, d (7.6)      | 106.9     |
| 13       | 3.49, m             | 75.6      | 3.45, m            | 75.8      |
| 14       | 3.30                 | 78.4      | 3.30, m            | 77.9      |
| 15       | 3.30                 | 71.6      | 3.30, m            | 71.7      |
| 16       | 3.78, d (2.4)       | 62.3      | 4.09, dd (12.0, 1.6) | 69.8 |
|          | Hb 3.74, d (4.8)    | 3.83, m   |                     |           |
| 17       | 5.41, d (7.8)       | 95.7      | 4.46, d (8.4)      | 104.9     |
| 18       | 3.42, m             | 74.3      | 3.21, m            | 75.2      |
| 19       | 3.39, m             | 78.3      | 3.31, m            | 77.1      |
| 20       | 4.39, m             | 71.2      | 3.30, m            | 71.7      |
| 21       | 4.39, m             | 78.2      |                     | 77.4      |
| 22       | 4.08, dd (12.0, 1.6) | 70.0     | 3.89, m            | 62.8      |
|          | Hb 3.72, d (4.8)    | 3.71, m   |                     |           |
| 23       | 4.30, d (7.8)       | 104.9     | 4.44, d (7.6)      | 107.9     |
| 24       | 3.18, m             | 75.3      | 3.49, m            | 75.7      |
| 25       | 3.45, m             | 78.0      | 3.44, m            | 71.4      |
| 26       | 3.45, m             | 78.0      |                     | 68.0      |
| 27       | 3.80, d (2.4)       | 62.4      | 3.88, m            | 63.1      |
|          | Hb 3.63, m          | 3.68, m   |                     |           |
Acid Hydrolysis and Sugar Identification

Compounds 1 and 2 (each 0.5 mg) were hydrolyzed with 2 mol/L HCl (2.0 mL) at 95 °C for 3 h, respectively. After cooling, the reaction mixture was partitioned between water and ethyl acetate, 3 times. The water extract was dried under reduced pressure in a rotary evaporator to obtain the test sample. Separately, the test sample, D-glucose and L-glucose (each 0.5 mg) were dissolved in pyridine (0.4 mL) and reacted with L-cysteine methyl ester hydrochloride (1.0 mg), followed by heating at 60 °C for 1 h. Then, N-trimethylsilylimidazole (0.15 mL) was added to the mixture and reacted at 60 °C for another 1 h. After that, the reaction solution was blown to dryness by nitrogen. The reaction residue was dissolved in water (1.0 mL), and extracted with n-hexane (0.5 mL) 3 times. The n-hexane extract was subjected to GC analysis using an HP-5 column. Acid hydrolysis derivatives of compounds 1 and 2 (t<sub>R</sub> = 28.97 min) were compared with D-glucose (t<sub>R</sub> = 28.97 min) and L-glucose (t<sub>R</sub> = 29.31 min) derivatives.

ECD Calculations

Conformational analysis of all the plausible stereoisomers of compounds 1 and 2 were performed by using a random search algorithm, the MMFF94s force field, and MMFF94 charge in Sybyl X 2.1 software. All the conformers obtained were screened based on the energy of optimized structures at the B3LYP/6-31+G(d) level in an energy window of 3 kcal/mol in Gaussian 16 software. The ECD data of all the
selected conformers were calculated with the TD/B3LYP/6-311 + G(2d, p) methods in the gas phase, respectively. The overall simulated CD curves were weighted by Boltzmann distributions of each conformer (with a half-bandwidth of 0.3 eV) and compared to the experimental ones in SpecDis 1.7 software.

Cytotoxicity Assay

Antiproliferative activities were evaluated as IC_{50} against the K562 human leukemia, MCF-7 human breast cancer, A549 human lung cancer, and HepG2 human hepatoma cell lines, using the methyl thiazolyl tetrazolium (MTT) assay. The cell lines were cultured in humidified incubators (37 °C and 5% CO₂). They were maintained in RPMI1640 medium (Sigma), supplemented with 10% fetal bovine serum (HyClone), 100 Unit/mL of penicillin G (Sigma), and 100 mg/mL of streptomycin (Sigma). The cells were seeded in a 96-well plate and cultured overnight, then treated with compounds 1–7 at 5 concentrations (0.15, 1.5, 5, 15, and 50 μM) for 24 h. Then, 20 μL of MTT solution (5 mg/mL) was added to each well. Following an additional 4 h incubation, 150 μL of dimethylsulfoxide (DMSO) solution was added to each well to dissolve the formazan crystals. Absorbance was determined at 490 nm by a Bio-Rad Model 680 multi-well scanning spectrophotometer (Bio-Rad). The concentrations required to inhibit growth by 50% (IC_{50} values) were calculated from survival curves.

Conclusions

Two new abietane diterpenoids, (4S, 5S, 10S)-12-(β-D-glucopyranosyl)oxy-11-hydroxyabieta-8,11,13-triene-19-oic acid β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl ester (1) and (3S, 5S, 10S, 15S)-3β-[β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl]oxy-12-(β-D-glucopyranosyl)oxyabieta-8,11,13-triene-11,16-diol (2), together with five known terpene glycosides, named szemaenoide A (3), leucasinoside (4), melittoside (5), 8-epiloganic acid (6), and trijugaoside A (7), were isolated from the n-butanol extract of C. trichotomum stems. The new structures were determined by extensive analysis of HR-ESI-MS, NMR spectra, chemical correlations, and ECD calculations. All these isolated compounds were evaluated for in vitro cytotoxicity against the K562, MCF-7, A549, and HepG2 tumor cell lines, but their IC_{50} values were all over 50 μM.

Declaration of Conflicting Interests

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