Meroterpenoids and Isocoumarinoids from a Myrothecium Fungus Associated with Apocynum venetum

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Received: 31 August 2018; Accepted: 27 September 2018; Published: 1 October 2018

Abstract: Four new meroterpenoids 1–4 and four new isocoumarinoids 5–8, along with five known isocoumarinoids (9–13), were isolated from the fungus Myrothecium sp. OUCMDZ-2784 associated with the salt-resistant medicinal plant, Apocynum venetum (Apocynaceae). Their structures were elucidated by means of spectroscopic analysis, X-ray crystallography, ECD spectra and quantum chemical calculations. Compounds 1–5, 7, 9 and 10 showed weak α-glucosidase inhibition with the IC₅₀ values of 0.50, 0.66, 0.058, 0.20, 0.32, 0.036, 0.026 and 0.37 mM, respectively.

Keywords: endophytic fungus; Myrothecium sp.; meroterpenoids; isocoumarinoids; α-glucosidase inhibitors; salt-resistant plant; Apocynum venetum

1. Introduction

Since the discovery of penicillin, fungi have been an important source of lead compounds for drug development, which have provided a lot of attractive natural products (NPs) with different biological activities [1–3]. With the increase of study on the terrestrial fungal NPs, more and more known compounds were isolated repeatedly. Therefore, many researchers turned their attention to the fungi isolated from specific habitats, such as the marine-derived fungi [4–7] and the fungi associated with the plants or animals [8–11].

As part of our ongoing studies to search for bioactive NPs from fungi derived from special niche [12–16], we screened the fungus Myrothecium sp. OUCMDZ-2784 which is associated with the salt-resistant plant A. venetum (Apocynaceae) growing in the Yellow River Delta, a traditional Chinese medicine used for treatment of hypertension [17] and heart failure [18]. Myrothecium sp. has been reported to produce trichothecenes [19], sesquiterpenes [20,21], diterpenes [22] and cyclopeptides [23] with cytotoxic and antibacterial activities. The ethyl acetate (EtOAc) extract of the fermentation of Myrothecium sp. OUCMDZ-2784 showed 75% inhibition of α-glucosidase at 286 µg/mL. Chemical study resulted in the isolation and identification of four new meroterpenoids, myrothecins A–D (1–4) and four new...
isocoumarinoids, myrothalactones A–D (5–8), together with five known isocoumarinoids that were identified as tubakialactone B (9) [24], acremoneone G (10) [25], 6,8-dihydroxy-3-methylisocoumarin (11) [26], 3,4-dimethyl-6,8-dihydroxyisocoumarin (12) [27] and sesecandelin B (13) [28], respectively by comparing $^1$H and $^{13}$C NMR spectra (Figure S57, Table S1) as well as ESI-MS spectra (Figure S59) with those reported.

2. Results and Discussion

Myrothecisin A (1) was isolated as a pale yellow oil. Its molecular formula was assigned as C$_{25}$H$_{34}$O$_{7}$ by the HRESIMS peak at m/z 469.2188 [M + Na]$^+$ (Figure S58A), indicating nine degrees of unsaturation. The $^{13}$C NMR (Figure S6) spectrum of 1 showed 25 signals that were classified by DEPT (Figure S7) and HSQC (Figure S8) as an aldehyde carbonyl carbon ($\delta_{C}$ 193.8), one acyl carbonyl carbon ($\delta_{C}$ 170.3), five sp$^2$ non-protonated carbons ($\delta_{C}$ 167.3, 159.8, 149.5, 112.3, 111.2) and three sp$^3$ non-protonated carbons ($\delta_{C}$ 98.8, 42.8, 39.2), one sp$^2$ methine ($\delta_{C}$ 101.5) and four sp$^3$ methines ($\delta_{C}$ 78.2, 71.4, 45.6, 36.0), five sp$^3$ methylenes ($\delta_{C}$ 60.5, 35.1, 30.6, 30.4, 20.7) and five methyl carbons ($\delta_{C}$ 28.7, 21.3, 17.0, 16.6, 15.2) (Table 1). The $^1$H (Figure S5) and HSQC NMR showed the singlet signals at $\delta_{H}$ 10.06 and 6.56 for an aldehyde proton and an aromatic proton, respectively. The key HMBC (Figure S10) correlations from H-7′ ($\delta_{H}$ 10.06) to C-2′/C-3′/C-4′, 2′-OH ($\delta_{H}$ 12.16) to C-1′/C-2′/C-3′, H-5′ ($\delta_{H}$ 6.56) to C-1′/C-4′/C-6′/C-8′, H-8′ ($\delta_{H}$ 4.74) to C-3′/C-4′/C-5′ and 8′-OH ($\delta_{H}$ 5.44) to C-4′/C-8′ suggested a penta-substituted benzene ring (Figure 2). The COSY (homonuclear correlation spectroscopy) correlations from H-1 through H-2 to H-3 and H-5 through H-6, H-7 and H-8 to H-12 (Figure 1 and Figure S9), along with the key HMBC correlations from H-2 to C-4/C-10/C-16, H-3 to C-5/C-13/C-14, 3-OH to C-2/C-3/C-4, H-1 to C-2/C-3/C-10/C-15, H-15 to C-1/C-5/C-9/C-10, H-5 to C-3/C-4/C-6/C-13, H-6 to C-5, H-7 to C-8, H-13 to C-3/C-5/C-14, H-14 to C-3/C-5/C-13, H-12 to C-7/C-8/C-9 and H-17 to C-16 revealed a sesquiterpene fragment (Figure 2). The connection of the above-mentioned two fragments were confirmed by the key HMBC correlations from H-11 to C-8/C-9/C-10/C-1′/C-2′/C-6′ (Figure 2) [29]. The relative configuration of 1 was determined by the NOESY correlations from H-8 to H-11 and H-15, H-3 to H-5 and H-13, H-2 to H-14 and H-15 and H-11 to H-15 (Figure 3 and Figure S11). The absolute configuration of 1 was determined by calculation of electronic circular dichroism (ECD) using time-dependent density functional theory (TDDFT) (Figure S1) [30,31] and the measured ECD spectrum of 1 matched well with the calculated ECD spectrum for (2R,3R,5S,8R,9R,10S)-1 (Figure 4).

![Figure 1. Structures 1–13 isolated from Myrothecium sp. OUCMDZ-2784.](image-url)

The molecular formula of 2 was also determined as C$_{25}$H$_{34}$O$_{7}$ by the HRESIMS peak at m/z 469.2200 [M + Na]$^+$ (Figure S58B), implying that 2 is an isomer of 1. Comparison of its $^1$H and $^{13}$C NMR spectra (Figures S12–S16) with those of 1 revealed that the acetyloxy group in 2 was on C-3. This was confirmed by the HMBC (Figure S17) correlation from H-3 ($\delta_{H}$ 4.29) to C-16 ($\delta_{C}$ 170.3) (Figure 2). The similar NOESY correlations (Figure 3 and Figure S18) suggested that 2 has the same relative configuration as 1. The similarity of ECD curves between 2 and 1 (Figure 5) indicated the same absolute configurations of its stereogenic carbons. Therefore 2 was named myrothecisin B.
Table 1. $^1$H (600 MHz) and $^{13}$C (150 MHz) NMR data for 1–4 in DMSO-d$_6$.

| No. | 1 | 2 | 3 | 4 |
|-----|---|---|---|---|
| | $\delta$ (C, Type) | $\delta$H, Mult. (J in Hz) | $\delta$ (C, Type) | $\delta$H, Mult. (J in Hz) | $\delta$ (C, Type) | $\delta$H, Mult. (J in Hz) | $\delta$ (C, Type) | $\delta$H, Mult. (J in Hz) |
| 1  | 35.1, CH$_2$ | 1.16, m; 1.55$^a$ | 38.4, CH$_2$ | 1.17, m; 1.57$^a$ | 114.7, CH | 4.94, brs | 116.3, CH | 4.88, s |
| 2  | 71.4, CH | 4.83, ddd (11.5, 10.1, 4.1) | 64.4, CH | 3.65, m | 28.0, CH$_2$ | 1.89, m; 1.23, m | 31.6, CH$_2$ | 1.72, m |
| 3  | 78.2, CH | 2.96, dd (10.1, 4.8) | 83.3, CH | 4.29, d (9.9) | 75.6, CH | 4.62, dd (8.6, 6.5) | 71.5, CH | 3.30$^a$ |
| 4  | 39.2, C | | | 39.0, C | | 35.6, C | | 36.9, C |
| 5  | 45.6, CH | 1.56$^a$ | 45.5, CH | 1.63$^a$ | 43.1, CH | 2.54, m | 43.7, CH | 2.45, m |
| 6  | 20.7, CH$_2$ | 1.54$^a$; 1.47, m | 20.4, CH$_2$ | 1.56$^a$; 1.48, m | 26.7, CH$_2$ | 1.79, m | 26.7, CH$_2$ | 1.77, m |
| 7  | 30.6, CH$_2$ | 1.55$^a$; 1.35, m | 30.5, CH$_2$ | 1.57$^a$; 1.38, m | 30.2, CH$_2$ | 1.54, m | 30.3, CH$_2$ | 1.52, m |
| 8  | 36.0, CH | 1.83, m | 35.6, CH | 1.85, m | 43.3, CH | 1.30, m | 42.9, CH | 1.29, m |
| 9  | 98.8, C | | | 98.8, C | | 43.7, C | | 43.7, C |
| 10 | 42.8, C | | | 42.5, C | | 143.9, C | | 143.0, C |
| 11 | 30.4, CH$_2$ | 3.03, d (16.1); 2.79, d (16.0) | 30.2, CH$_2$ | 3.11, d (16.5); 2.81, d (16.5) | 23.5, CH$_2$ | 2.68, d (12.9); 2.53, d (12.9) | 23.3, CH$_2$ | 2.63, d (12.7); 2.50, d (12.7) |
| 12 | 15.2, CH$_3$ | 0.64, d (6.3) | 15.1, CH$_3$ | 0.68, d (6.3) | 17.1, CH$_3$ | 1.03, d (6.6) | 17.2, CH$_3$ | 1.02, d (6.7) |
| 13 | 28.7, CH$_3$ | 0.97, s | 28.4, CH$_3$ | 0.79, s | 25.0, CH$_3$ | 0.88, s | 25.2, CH$_3$ | 0.95, s |
| 14 | 17.0, CH$_3$ | 0.78, s | 17.5, CH$_3$ | 0.81, s | 17.1, CH$_3$ | 0.73, s | 14.8, CH$_3$ | 0.59, s |
| 15 | 16.8, CH$_3$ | 1.04, s | 16.6, CH$_3$ | 1.03, s | 23.0, CH$_3$ | 0.96, s | 22.9, CH$_3$ | 0.91, s |
| 16 | 170.3, C | | | 170.3, C | | 169.8, C | | 169.8, C |
| 17 | 21.3, CH$_3$ | 1.91, s | 21.0, CH$_3$ | 2.02, s | 21.0, CH$_3$ | 1.98, s | 21.0, CH$_3$ | 1.98, s |
| 1′ | 111.2, C | | | 111.2, C | | 111.4, C | | 111.3, C |
| 2′ | 159.8, C | | | 159.8, C | | 164.5, C | | 164.8, C |
| 3′ | 112.3, C | | | 112.2, C | | 110.2, C | | 110.2, C |
| 4′ | 149.5, C | | | 149.4, C | | 145.4, C | | 145.4, C |
| 5′ | 101.5, CH | 6.56, s | 101.6, CH | 6.61, s | 107.5, CH | 6.51, s | 107.3, CH | 6.50, s |
| 6′ | 167.3, C | | | 167.3, C | | 164.6, C | | 164.6, C |
| 7′ | 193.8, CH | 10.06, s | 193.8, CH | 10.07, s | 193.3, CH | 9.96, s | 193.4, CH | 9.96, s |
| 8′ | 60.5, CH$_2$ | 4.74, s | 60.4, CH$_2$ | 4.74, s | 59.9, CH$_2$ | 4.70, s | 59.8, CH$_2$ | 4.70, s |
| 2/3-OH | 4.94, d (4.7) | 4.62, d (4.9) | 4.94, d (4.7) | 4.62, d (4.9) | | | | |
| 2′-OH | 12.16, s | 12.24, s | 12.16, s | 12.24, s | 12.84, s | 12.78, s | | 10.55, brs |
| 6′-OH | 5.44, s | 5.39, s | 5.35, s | 5.36, s | | | | |

$^a$ Overlapped.
Compound 3 was also obtained as a pale-yellow oil. Its molecular formula was determined as $\text{C}_{25}\text{H}_{34}\text{O}_{6}$ according to the HRESIMS peak at $m/z$ 453.2238 [$\text{M} + \text{Na}^+$] (Figure S58C). The $^{13}$C NMR (Figure S20) spectrum of 3 showed one aldehyde carbonyl carbon ($\delta_C$ 193.3), one acyl carbonyl carbon ($\delta_C$ 169.8), six sp$^2$ non-protonated carbons ($\delta_C$ 164.6, 164.5, 145.4, 143.9, 111.4, 110.2) and two sp$^3$ non-protonated carbons ($\delta_C$ 43.7, 35.6), two sp$^2$ methines ($\delta_C$ 114.7, 107.5) and three sp$^3$ methines ($\delta_C$ 75.6, 43.3, 43.1), five sp$^3$ methylenes ($\delta_C$ 59.9, 30.2, 28.0, 26.7, 23.5) and five methyl carbons ($\delta_C$ 25.0, 23.0, 21.0, 17.1, 17.1) (Table 1). Analysis of its 1D and 2D NMR (Figures S19–S24) data revealed the presence of a substituted benzene ring and a sesquiterpene unit, indicating 3 was an analogue of 1 and 2. Comparison of the $^1$H and $^{13}$C NMR spectra with those of 1 and 2 suggested a same pentasubstituted benzene ring. The structure of the sesquiterpene unit was slightly modified and was determined by the COSY (Figure S23) correlations from H-1 through H-2 to H-3 and H-5 through H-6, H-7 and H-8 to H-12 and the key HMBC (Figure S24) correlations from H-3 to C-2/C-4/C-10/C-13/C-14, H-17 to C-16, H-1 to C-3/C-9, H-15 to C-10, H-8 to C-9, H-5 to C-9/C-13, H-12 to C-7 and H-2 to C-4/C-10 (Figure 2). The HMBC correlations from H$_2$-11 ($\delta_H$ 2.68/2.53) to C-8/C-10/C-15/C-2$/C'$-6$/C'$ (Figure 2) confirmed the connection between the sesquiterpene fragment and the benzene ring. The relative configuration of 3 was determined by the NOESY (Figure S25) correlations from H-13 to H-3 and H-5, H-8 to H-15, as well as H-5 to H-11 (Figure 3). The absolute configuration was determined as (3$R$,5$R$,8$R$,9$R$) by comparison of the calculated and experimental ECD spectra (Figure 4 and Figure S22). Therefore 3 was named myrothecisin C.

The molecular formula of 4 was assigned as $\text{C}_{23}\text{H}_{32}\text{O}_{5}$ by the HRESIMS peak at $m/z$ 411.2139 [$\text{M} + \text{Na}^+$] (Figure S58D), which was $\text{C}_{23}\text{H}_{32}\text{O}_{5}$ less than that of 3. The similarity of the UV and NMR data between 3 and 4 (Table 1) suggested that 4 possesses the same skeleton as 3. Careful comparison of their $^1$H and $^{13}$C NMR spectra (Figures S26–S31) showed that the acetyloxy group ($\delta_C$ 21.0/$\delta_H$ 1.98 and $\delta_C$ 169.8) in 3 was replaced by a hydroxy group ($\delta_H$ 4.13) in 4 (Table 1). The NOESY data (Figure 3 and Figure S32) suggested that 4 has the same relative configuration as 3. The ECD Cotton effects of 4 were nearly identical to those of 3 (Figure 5), indicating the same absolute configurations of the corresponding stereogenic carbons. Thus, 4 was named myrothecisin D.

![Figure 2. Key homonuclear correlation spectroscopy (COSY) and key HMBC correlations for 1-8.](image-url)
Compound 5 was obtained as a colorless crystal with the molecular formula C_{12}H_{12}O_{6} from the HRESIMS peak at m/z 251.0563 [M – H]⁻ (Figure S58E). The 1H NMR spectrum showed two meta-coupled aromatic protons at δ_{H} 6.78 (d, J = 2.2 Hz) and δ_{H} 6.63 (d, J = 2.2 Hz) (Table 2, Figure S33), indicating the presence of a tetra-substituted benzene ring. The 13C (Figure S34) NMR spectrum showed 12 carbon signals that were classified by DEPT (Figure S35) and HSQC (Figure S36) spectra as six sp² non-protonated carbons (δC 166.4, 165.4, 163.4, 137.6, 118.6, 99.9), three sp² methines (δC 143.1, 100.5, 100.4) and one sp³ methine (δC 68.8), one sp³ methylene (δC 64.8) and one methoxy group (δC 56.0) (Table 2). The key HMBC correlations (Figure 2 and Figure S38) from CH3O-6 to C-6, HO-11 to C-4/C-12, H-11 to C-3/C-10, H-3 to C-1/C-10, H-5 to C-4/C-7/C-9 and H-7 to C-9 along with the continuous COSY correlations of HO-11 (δ_{H} 5.50)/H-11 (δ_{H} 4.66)/H-12 (δ_{H} 3.51, 3.62)/HO-12 (δ_{H} 4.81) (Figure S37) revealed that 5 possesses a 4,6,8-trisubstituted isocoumarin skeleton with a hydroxy, a methoxy and a 1,2-dihydroxy ethyl at C-8, C-6 and C-4, respectively. The structure of 5 was obtained as a colorless crystal with the molecular formula C_{12}H_{10}O_{7} based on the HRESIMS peak at m/z 251.0563 [M − H]⁻ (Figure S58F). The UV and 13C NMR data of 6 (Table 2) were similar to those of 5, indicating that they have the same isocoumarin scaffold. Comparison of their 1H and 13C data (Figures S39–S43) indicated that the hydroxymethyl group (δC/H 64.8/3.62&3.51, δ_{H} 4.81) in 5 was replaced by the carboxyl group (δC 173.4). This change was verified by the key HMBC (Figure S44) correlations from H-11 to C-3/C-10/C-12. The absolute configuration of C-11 of 6 was determined as 11R− by comparison of the calculated and experimental ECD spectra (Figure 4 and Figure S4). Therefore, 6 was named myrothelactone A.

Compound 6 was obtained as a white powder. Its molecular formula was determined as C_{12}H_{10}O_{7} based on the HRESIMS peak at m/z 265.0355 [M − H]⁻ (Figure S58F). The UV and 13C NMR data of 6 (Table 2) were similar to those of 5, indicating that they have the same isocoumarin scaffold. Comparison of their 1H and 13C data (Figures S39–S43) indicated that the hydroxymethyl group (δC/H 64.8/3.62&3.51, δ_{H} 4.81) in 5 was replaced by the carboxyl group (δC 173.4). This change was verified by the key HMBC (Figure S44) correlations from H-11 to C-3/C-10/C-12. The absolute configuration of C-11 of 6 was determined as 11R− by comparison of the calculated and experimental ECD spectra (Figure 4 and Figure S4). Therefore, 6 was name myrothelactone B.
Table 2. $^1$H and $^{13}$C NMR data for 5–8 in DMSO-$d_6$.  

| No. | $\delta^a_{C, \text{Type}}$ | $\delta^a_{H, \text{mult. (J in Hz)}}$ | $\delta^b_{C, \text{Type}}$ | $\delta^b_{H, \text{mult. (J in Hz)}}$ | $\delta^b_{C, \text{Type}}$ | $\delta^b_{H, \text{mult. (J in Hz)}}$ | $\delta^b_{C, \text{Type}}$ | $\delta^b_{H, \text{mult. (J in Hz)}}$ |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| 1   | 165.4, C        | 144.4, CH       | 7.45, s         | 102.3, CH       | 7.46, s         | 101.6, CH       | 6.84, s         | 153.1, CH       | 8.47, s         |
| 2   | 118.6, C        | 117.7, C        | 6.78, d (2.2)   | 166.4, C        | 166.8, C        | 101.2, CH       | 6.68, s         | 99.8, CH        | 6.48, s         |
| 3   | 100.5, CH       | 101.6, CH       | 6.63, s         | 101.2, CH       | 6.68, s         | 101.6, CH       | 6.84, s         | 154.4, CH       | 8.47, s         |
| 4   | 68.8, C         | 136.8, C        | 6.63 (d, 2.2)   | 101.6, CH       | 6.84, s         | 101.6, CH       | 6.84, s         | 154.4, CH       | 8.47, s         |
| 5   | 56.0, CH        | 56.0, CH        | 3.88, s         | 56.0, CH        | 3.87, s         | 55.8, CH        | 3.80, s         | 154.4, CH       | 8.47, s         |
| 6   | 11.37, s        | 11.22, s        | 11.03, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        |
| 7   | 11.37, s        | 11.22, s        | 11.03, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        | 11.21, s        |

$^a$ Data were measured at 600 MHz ($^1$H) and 150 MHz ($^{13}$C). $^b$ Data were measured at 500 MHz ($^1$H) and 125 MHz ($^{13}$C).
Figure 4. Measured and calculated ECD spectra for 1, 3, 5 and 6.

Figure 5. ECD spectra for 1−4.

Figure 6. ORTEP diagram of 5.
Compound 7 was obtained as a white powder. Its molecular formula was determined as C_{12}H_{10}O_{6} according to its HRESIMS peak at m/z 249.0408 [M − H]− (Figure S58G), which was only two hydrogen atoms less than that of 5. The difference observed in the NMR spectra of 7 and 5 was that the signals for hydroxymethine (δC 68.8/4.66) in 5 were replaced by the signal of a carbonyl group (δC 198.3) in 7 (Table 2, Figures S45–S49). The HMBC (Figure S50) correlations from H-3 (δH 8.47) and H-12 (δH 4.57) to C-11 further confirmed the structure of 7 which was name myrothelactone C (Figure 2).

The molecular formula of compound 8 was determined as C_{12}H_{10}O_{6} on the basis of its HRESIMS peak at m/z 249.0407 [M − H]− (Figure S58H), which is an isomer of 7. Analysis of its 1H and 13C NMR spectra showed that 8 also had the same isocoumarin scaffold, whose difference is the replacement of carbonyl (δC 198.3), hydroxymethyl (δC 65.9, δH 4.57/5.28) and sp² methine (δC 153.1, δH 8.47) signals in 7 by two sp² non-protonated carbons (δC 173.9, 151.0) and methyl (δC 17.9, δH 2.29) signals in 8 (Table 2, Figures S51–S55). The HMBC correlations from H-12 (δH 2.29) to C-3 (δC 151.0) and C-4 (δC 118.7) suggested the methyl substitution at C-3 (Figure 2 and Figure S56). The chemical shift of the carboxyl signal (δC 173.9) together with 2D NMR data indicated the carboxyl substitution at C-4.

The structure of myrothelactone D (8) was therefore determined (Figure 2).

The α-glucosidase inhibitory activity of 1–13 was preliminarily investigated. Compounds 1–5, 7, 9 and 10 exhibited inhibitory activity against the human-sourced α-glucosidase recombinant expressed in Saccharomyces cerevisiae [31–33] with IC_{50} values of 0.50, 0.66, 0.058, 0.20, 0.32, 0.036 and 0.37 mM, while the IC_{50} value of positive control acarbose was 0.47 mM. Due to the low activity, the deeper investigation of the mechanism and type of enzymatic inhibition as well as the binding mode were not done.

3. Experimental Section

3.1. General Experimental Procedures

Optical rotations were measured using a JASCO P-1020 digital polarimeter (JASCO Corporation, Tokyo, Japan). UV spectra were obtained on a Beckman DU 640 spectrophotometer (Beckman Coulter, Inc., Brea, CA, USA). CD data were performed using a JASCO J-815 spectropolarimeter (JASCO Corporation, Brea, CA, USA). IR spectra were obtained on a Nicolet Nexus 470 spectrophotometer (Thermo Nicolet Corporation, Madison, WI, USA) as KBr discs. NMR spectra were recorded on a Varian System 500 spectrometer (Varian, Palo Alto, CA, USA) or a Bruker Avance 600 spectrometer (Bruker, Fallanden, Switzerland) using residual solvent signals for referencing and chemical shifts were recorded as δ values. HRESIMS spectra were measured using the Q-TOF ULTIMA GLOBAL GAA076 LC mass spectrometer (Waters Asia, Ltd., Singapore). Semi-preparative HPLC was performed using an ODS column (YMC-pack ODS-A, 10 mm × 250 mm, 5 µm, 4.0 mL/min, Kyoto, Japan). TLC and column chromatography (CC) were performed on plates pre-coated with silica gel GF 254 (10–40 µm, Qingdao Marine Chemical Factory, Qingdao, China) and Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden), respectively. Vacuum-liquid chromatography (VLC) utilized silica gel H (Qingdao Marine Chemical Factory).

3.2. Collection and Phylogenetic Analysis

The fungus OUCMDZ-2784 was isolated from Apocynum venetum (Apocynaceae) collected from the estuary of Yellow River, Dongying, China. The leaves of the plant were washed with tap water and sterile distilled water in sequence. Then, it was cut into small pieces, which were then put into a centrifuge tubes filled with different concentrations of sucrose solution. These tubes were centrifuged at 1200 rpm for 20 min. Four zones were separated by improved discontinuous sucrose gradient centrifugation. The interface between the third and the fourth bands was deposited on a PDA (200 g potato, 20 g glucose, 20 g agar per liter of sea water) plate containing chloramphenicol (100 µg/mL) as a bacterial inhibitor and was then cultured at 28 °C for 3 days. A single colony was transferred to PDA agar media and was identified as Myrothecium sp. according to its morphological characteristics and 18S rRNA gene sequences (GenBank accession No. KF977010).
3.3. Cultivation and Extraction

Fungus OUCMDZ-2784 was prepared on PDA agar medium. Spores were incubated at 28 °C for 48 h on a rotary shaker with shaking at 120 rpm in a 500 mL cylindrical flask containing 150 mL liquid medium (20 g maltose, 20 g mannitol, 10 g glucose, 3 g yeast extract, 10 g monosodium glutamate per liter of sea water). The cultures were transferred to 350 × 1000 mL Erlenmeyer flasks and each containing 300 mL liquid fermentation media (1 g peptone, 10 g soluble starch per liter of sea water, pH 7.0). The flasks were incubated at room temperature under static conditions for 30 days. The cultures were extracted three times by EtOAc and the combined EtOAc extracts were dried in vacuo to yield 20.1 g of extract.

3.4. Purification

The extract (20.1 g) was fractionated by VLC, eluting with a step gradient of CH₂Cl₂-petroleum ether (50–100%) and MeOH-CH₂Cl₂ (0–50%) and five fractions (Fr.1–Fr.5) were collected. Fraction 2 (3.2 g) was subjected to Sephadex LH-20 chromatography eluting with CH₂Cl₂/MeOH (1:1) to afford three subfractions (Fr.2.1–Fr.2.3). Fr.2.1 (1.0 g) was further purified by HPLC on an ODS column (80% MeOH/H₂O) to give compounds 1 (25.2 mg, tᵣ 6.3 min) and 3 (30.1 mg, tᵣ 10.2 min). Fr.2.2 (50.2 mg) was purified by HPLC on an ODS column (60% MeOH/H₂O) to yield compounds 11 (3.5 mg, tᵣ 10.4 min) and 8 (3.3 mg, tᵣ 15.2 min). Fr.2.3 (46.3 mg) was purified by HPLC on an ODS column (60% MeOH/H₂O) to yield compounds 12 (5.1 mg, tᵣ 12.6 min) and 13 (12.0 mg, tᵣ 16.4 min). Fraction 3 (3.8 mg) was separated into three subfractions (Fr.3.1–Fr.3.3) by Sephadex LH-20 eluting with MeOH-CH₂Cl₂ (1:1). Fr.3.1 (0.5 g) was purified by semi preparative HPLC on an ODS column (85% MeOH/H₂O) to yield compound 2 (36.2 mg, tᵣ 10.2 min). Fr.3.2 (1.1 g) was separated by silica gel VLC column eluting with CH₂Cl₂-petroleum ether (2:1) to yield compounds 10 (100.3 mg) and 5 (200.8 mg). Fr.3.3 (0.5 g) was further purified by Sephadex LH-20 eluting with MeOH to yield compound 9 (15.3 mg). Fraction 4 (1.8 g) was separated into three subfractions (Fr.4.1–Fr.4.3) by Sephadex LH-20 eluting with MeOH. Fr.4.1 (0.6 g) was further purified by semi preparative HPLC on an ODS column (85% MeOH/H₂O) to yield compound 4 (34.3 mg, tᵣ 12.2 min). Fr.4.2 (0.2 g) was further purified by semi preparative HPLC on an ODS column (50% MeOH/H₂O) to yield compound 7 (6.0 mg, tᵣ 12.7 min). Fr.4.3 (0.3 g) was purified by HPLC on an ODS column (40% MeOH/H₂O) to yield compound 6 (5.8 mg, tᵣ 10.6 min).

Myrothecin A (1): pale yellow oil; [α]₂⁰ D + 9.0 (c 0.1, CHCl₃); UV (MeOH) λ_max (log ε) 212 (4.13), 237 (3.60), 305 (3.93) nm; ECD (0.002 M, MeOH) λ_max (Δε) 207 (+1.69), 244 (−0.51), 304 (+1.06) nm; IR (KBr) ν_max 3443, 2926, 1719, 1635, 1372, 1267 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS m/z 469.2188 [M + Na]⁺ (calcd for C₂₅H₃₄O₇Na, 469.2197).

Myrothecin B (2): pale yellow oil; [α]₂⁰ D + 70.1 (c 0.1, CHCl₃); UV (MeOH) λ_max (log ε) 211 (4.10), 238 (3.62), 305 (3.88) nm; ECD (0.002 M, MeOH) λ_max (Δε) 207 (+1.62), 249 (−0.09), 305 (+0.49) nm; IR (KBr) ν_max 3424, 2940, 1733, 1638, 1460, 1371, 1263 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS m/z 469.2200 [M + Na]⁺ (calcd for C₂₅H₃₄O₇Na, 469.2197).

Myrothecin C (3): pale yellow oil; [α]₂⁰ D + 63.5 (c 0.1, CHCl₃); UV (MeOH) λ_max (log ε) 212 (4.09), 239 (3.65), 307 (3.81) nm; ECD (0.002 M, MeOH) λ_max (Δε) 219 (+2.29), 293 (−0.49), 327 (+0.22) nm; IR (KBr) ν_max 3480, 2936, 1732, 1612, 1373, 1254 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS m/z 453.2238 [M + Na]⁺ (calcd for C₂₅H₃₄O₆Na, 453.2248).

Myrothecin D (4): pale yellow oil; [α]₂⁰ D + 20.0 (c 0.1, CHCl₃); UV (MeOH) λ_max (log ε) 203 (4.16), 224 (3.56), 300 (3.86) nm; ECD (0.002 M, MeOH) λ_max (Δε) 220 (+1.57), 242 (+0.92), 295 (−0.27) nm; IR (KBr) ν_max 2928, 1718, 1621, 1370, 1264, 1027 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; HRESIMS m/z 411.2139 [M + Na]⁺ (calcd for C₂₅H₂₅O₅Na, 411.2142).

Myrothelactone A (5): colorless crystal; melting point (mp) 174–175 °C; [α]₂⁰ D − 36.0 (c 0.1, MeOH); UV (MeOH) λ_max (log e) 246 (3.82), 328 (3.19) nm; ECD (0.004 M, MeOH) λ_max (Δε) 206.5 (−0.22), 241
(+0.24), 259 (−0.27) nm; IR (KBr) ν max 3747, 3630, 3159, 2959, 1668, 1558, 1398, 1237 cm−1; 1H and 13C NMR data, see Table 2; HRESIMS m/z 251.0563 [M − H]− (calcd for C12H13O6, 251.0561).

**Myrothelactone B (6):** white powder; mp 169–171 °C; [α] D 20 − 30.0 (c 0.1, MeOH); UV (MeOH) λ max (log ε) 245 (3.81), 328 (3.17) nm; ECD (0.004 M, MeOH) λ max (Δε) 206.5 (−0.78), 241 (+0.24), 259 (−0.13) nm; IR (KBr) ν max 3749, 3673, 3445, 3197, 1716, 1682, 1539, 1457, 1399 cm−1; 1H and 13C NMR data, see Table 2; HRESIMS m/z 265.0355 [M − H]− (calcd for C12H9O7, 265.0354).

**Myrothelactone C (7):** white powder; mp 160–161 °C; UV (MeOH) λ max (log ε) 228 (3.91), 263 (3.43), 325 (3.16) nm; IR (KBr) ν max 3750, 3675, 3615, 1736, 1651, 1558, 1540, 1399 cm−1; 1H and 13C NMR data, see Table 2; HRESIMS m/z 249.0408 [M − H]− (calcd for C12H8O6, 249.0405).

**Myrothelactone D (8):** white powder; mp 219–221 °C; UV (MeOH) λ max (log ε) 231 (3.92), 263 (3.45), 325 (3.16) nm; IR (KBr) ν max 3749, 3673, 3445, 3197, 1716, 1682, 1539, 1457, 1399 cm−1; 1H and 13C NMR data, see Table 2; HRESIMS m/z 249.0407 [M − H]− (calcd for C12H9O6, 249.0405).

### 3.5. X-ray Structure Determination of Compound 5

Compound 5 was obtained as a colorless needles crystal with molecular formula C12H12O6. Orthorhombic, space group P212121, a = 4.9041(2) Å, b = 13.8470(5) Å, c = 15.7443(6) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 1069.15(7) Å3, Z = 4, D calc = 1.567 Mg/m3, μ = 1.089 mm−1, F(000) = 528, crystal size 0.30 mm × 0.18 mm × 0.15 mm, θ = 293(2) K. A total of 1478 unique reflections (2θ < 50°) were collected on a CCD area detector diffractometer with graphite monochromated Cu Kα radiation (λ = 1.54178 Å). The structure was solved by direct methods (SHELXS-97) and expanded using Fourier techniques (SHELXL-97). The final cycle of full-matrix least squares refinement was based on 1478 unique reflections (2θ < 50°) and 165 variable parameters and converged with unweighted and weighted agreement factors of R1 = 0.0326, wR2 = 0.0885 and R = 0.0880 for I > 2σ(I) data. Absolute structure parameter: −0.2(2). The deposited number of compound 5 in the Cambridge Crystallographic Data Centre is 980155.

### 3.6. α-Glucosidase Inhibitory Assays

The human-sourced α-glucosidase was recombinant expressed in the yeast *Saccharomyces cerevisiae* and the inhibitory effects of compounds 1–13 were tested using p-nitrophenyl-α-D-glucopyranoside (pNPG) as substrate [31–33]. The sample was dissolved in sodium phosphate buffer (PBS, pH 6.8) at three concentrations. 10 µL of the sample solution, 20 µL of 2.5 mM pNPG solution (in phosphate buffer) and 20 µL of PBS were mixed in a 96-well microplate and incubated at 37 °C for 5 min. A volume of 10 µL of α-glucosidase diluted to 0.2 U/mL by 0.01 M PBS was then added to each well. After incubating at 37 °C for 15 min, the absorbance at 405 nm was recorded by a Spectra max 190 micro plate reader (Molecular Devices Inc., San Jose, CA, USA). The blank was prepared by adding phosphate buffer instead of the α-glucosidase and the positive control was acarbose. Blank readings (no enzyme) were subtracted from each well and results were compared to the control. The inhibition (%) was calculated as [1 − (OD drug/OD blank)] × 100%. The IC50 value was calculated as the compound concentration that is required for 50% inhibition and the IC50 value of acarbose was 0.47 mM.

### 4. Conclusions

This study revealed eight new fungal NPs, meroterpenoids 1–4 and isoucomarinoids 5–8, from the culture of the salt-tolerant plant-associated fungus *Myrothecium* sp. OUCMDZ-2784. The new compounds 1–5 and 7 exhibited α-glucosidase inhibitory activity. Combined with bioactive NPs from mangrove-derived fungi [34–38], the results indicated that fungi living in the salt-tolerant plants are an important biological resources for new and bioactive NPs.
Supplementary Materials: The following are available online at http://www.mdpi.com/1660-3397/16/10/363/s1, Figures S1–S4: DFT-optimized structures for low-energy conformers of compounds 1, 3, 5 and 6, Figures S5–S11: NMR spectra of compound 1 in DMSO-d6, Figures S12–S18: NMR spectra of compound 2 in DMSO-d6, Figures S19–S25: NMR spectra of compound 3 in DMSO-d6, Figures S26–S32: NMR spectra of compound 4 in DMSO-d6, Figures S33–S38: NMR spectra of compound 5 in DMSO-d6, Figures S39–S44: NMR spectra of compound 6 in DMSO-d6, Figures S45–S50: NMR spectra of compound 7 in DMSO-d6, Figures S51–S56: NMR spectra of compound 8 in DMSO-d6, Figure S57: 1H- and 13C-NMR spectra of compounds 9–13 in DMSO-d6, Figure S58: HRESI-MS spectra of compounds 1–8, Figure S59: ESI-MS spectra of compounds 9–13, Table S1: 1H and 13C NMR data for compounds 9–13 in DMSO-d6.

Author Contributions: Y.X. performed the most experiments; C.W. prepared the draft of the manuscript; H.L. tested the α-glucosidase inhibitory activity; G.Z. performed the ECD calculations; P.F. checked the data; L.W. revised the manuscript; W.Z. designed and supervised the research and revised the final version.

Funding: This research was funded by the NSFC (Nos. 81561148012, U1501221, 81741150, U1606403), the 100 Leading Talents of Guizhou Province (fund for W. Zhu), the science and technology project of Guizhou (Grant No. QKHT Z-2014-4007) and the academician workstation of Guizhou (Grant No. QKHY YSZ-2015-4009).

Conflicts of Interest: The authors declare no conflict of interest.

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