Abstract: Six new diphenyl ethers (1–6) along with eleven known analogs were isolated from the ethyl acetate extract of a marine-derived Aspergillus sydowii guided by LC-UV-MS. Their structures were unambiguously characterized by HRESIMS, NMR, as well as chemical derivatization. Compounds 1 and 2 are rare diphenyl ether glycosides containing D-ribose. The absolute configuration of the sugar moieties in compounds 1–3 was determined by a LC-MS method. All the compounds were evaluated for their cytotoxicities against eight cancer cell lines, including 4T1, U937, PC3, HL-60, HT-29, A549, NCI-H460, and K562, and compounds 1, 5, 6, and 8–11 were found to exhibit selective cytotoxicity against different cancer cell lines.

Keywords: Aspergillus sydowii; fungal natural product; diphenyl ethers; structure elucidation; cytotoxicity

1. Introduction

Marine microorganisms have become an important source of pharmacologically active metabolites [1–5]. In particular, marine-derived fungi have been identified as promising producers of chemically and biologically diverse natural products [6]. The genus Aspergillus, with over 200 species, has attracted considerable attention as a rich source of bioactive compounds including polyketides, peptides, terpenoids [7–9] and others. Diphenyl ethers are a group of polyketides with simple structures that are widely distributed in various species of Aspergillus [10–13] and have been reported to show significant diverse bioactivities, such as antiviral [14], antimicrobial [14,15], β-glucuronidase enzyme inhibitory [16], radical-scavenging [17], cytotoxicity [10,14,18–24], anti-Aβ 42 aggregation [24], regulating actin function [25] and phytocidal activities [26]. The cytotoxicity of diphenyl ethers against a variety of cancer cell lines has been widely reported. For example, diorcinol, cordyol C, and 3,7-dihydroxy-1,9-dimethylphenaldehyde showed cytotoxicity against HeLa and DU145 cell lines with IC50 values of 1.20–7.12 µM [22]. Sinopestalotiollide D showed cytotoxicity against HeLa, HCT 116 and A549 cell lines with IC50 values of 1.19, 2.66 and 2.14 µM, respectively [19]. In order to further discover novel cytotoxic diphenyl ethers from natural sources, a marine-derived fungus...
Aspergillus sydowii strain FNA026 was investigated. As a result, seventeen diphenyl ethers 1–17 (Figure 1), including six new ones (1–6) were obtained from the ethyl acetate extract of A. sydowii guided by LC-UV-MS. Among them, compounds 1–3 were identified as diphenyl ether glycosides which are rare in marine secondary metabolites. Herein, we report the isolation, structure elucidation and cytotoxicities of the isolated compounds.

![Structures of compounds 1–17 and 6a.](image)

Figure 1. Structures of compounds 1–17 and 6a.

2. Results and Discussion

Compound 1 was obtained as colorless oil. Its IR spectrum suggested the presence of hydroxy (3320 cm\(^{-1}\)) and aromatic (1596, 1512, and 1464 cm\(^{-1}\)) groups. The molecular formula of 1 was established as C\(_{19}\)H\(_{22}\)O\(_{8}\) on the basis of HRESIMS, which gave a sodium adduct ion at \(m/z\) 401.1206 [M + Na\(^+\)]. The \(^1\)H NMR spectrum (in DMSO-\(d_6\)) of 1 exhibited signals for two methyl groups at \(\delta_H\) 2.15 (3H, s), 2.18 (3H, s), five aromatic protons at \(\delta_H\) 6.02 (1H, brs), 6.12 (1H, brs), 6.21 (1H, brs), 6.46 (1H, brs) and 6.81 (1H, brs), as well as two phenolic hydroxy groups at \(\delta_H\) 8.41 (1H, s) and 9.26 (1H, s). Analysis of its \(^{13}\)C NMR and HSQC spectra (see Supplementary Information Figures S4 and S6) indicated the presence of five sp\(^2\) methines at \(\delta_C\) 100.3, 107.5, 115.9, 112.9, and 115.9, seven sp\(^2\) quaternary carbons at \(\delta_C\) 127.3, 137.3, 139.5, 142.0, 145.7, 158.2, and 159.1 and two methyl carbons at \(\delta_C\) 20.6 and 21.2. Careful analysis of the \(^1\)H NMR and \(^{13}\)C NMR data (Tables 1 and 2) of 1 indicated that it was a diphenyl ether derivative with one tetra-substituted phenyl and one trisubstituted phenyl groups, as well as an additional pentose residue. The aglycone of 1 was identified as cordyol C [14] by comparison of the 1D NMR data of 1 with those of cordyol C and was supported by the key HMBC correlations from H-3 (\(\delta_H\) 2.18) to C-4 (\(\delta_C\) 112.9), C-5 (\(\delta_C\) 127.3), and C-6 (\(\delta_C\) 115.9), and from 2-OH (\(\delta_H\) 8.41) to C-1 (\(\delta_C\) 142.0), C-2 (\(\delta_C\) 137.3) and C-3 (\(\delta_C\) 145.7), from 3'-OH (\(\delta_H\) 9.26) to C-2' (\(\delta_C\) 100.3), C-3' (\(\delta_C\) 158.2), and C-4' (\(\delta_C\) 110.6), as well as from H-37' (\(\delta_H\) 2.15) to C-4' (\(\delta_C\) 109.6), C-5' (\(\delta_C\) 139.5), and C-6' (\(\delta_C\) 107.5). The pentose residue in 1 showed signals at \(\delta_C\) 101.3, 107.3, 73.2, 94.6, 86.6 and 61.6 in its \(^{13}\)C NMR spectrum and an anomic proton \(\delta_H\) 5.50 (1H, d, \(J = 4.6\) Hz) in its \(^1\)H NMR spectrum, which suggested the presence of an \(\alpha\)-ribofuranosyl moiety [27]. The key HMBC correlation from H-1'' (\(\delta_H\) 5.50) to C-3 (\(\delta_C\) 145.7) (Figure 2) established the connection between the ribose and the diphenyl...
ether moiety. The α-ribose was determined to have a D-configuration by comparison in LC-MS of the retention time of the thiocarbamoyl-thiazolidine derivative prepared after hydrolysis of 1 with those obtained from D-ribose and L-ribose standards (see Supplementary Information Figure S54). Thus, compound 1 was characterized as cordyol C-3-O-α-D-ribofuranoside.

Table 1. The 1H NMR spectroscopic data for compounds 1–6 and 6a (600 MHz).

| NO. | δH (J in Hz)                                      |
|-----|---------------------------------------------------|
| 2   | 6.20 t (2.2) 6.57 t (2.4) 6.24 d (2.3) 6.21 brs 6.13 t (2.4) 6.30 d (2.2) |
| 4   | 6.81 brs 6.27 brs 6.75 brs 6.35 d (2.3) 6.30 m 6.28 brs 6.48 brs |
| 6   | 6.46 brs 6.37 brs 6.53 brs 6.39 m 6.20 brs 6.43 brs |
| 7   | 2.18 s 2.27 s 2.26 s 2.47 s 2.53 q (7.5) 2.19 s 2.26 s |
| 8   | 1.18 t (7.5) 3.73 s |
| 9   | 4.40 q (7.5) |
| 10  | 1.40 t (7.5) |
| 2′  | 6.02 brs 6.57 t (2.8) 6.28 d (2.3) 6.28 d (2.7) 6.21 brs 6.33 d (2.8) 6.52 d (2.8) |
| 4′  | 6.21 brs 6.45 brs 6.28 brs |
| 6′  | 6.12 brs 6.72 brs 6.37 d (2.3) 6.56 d (2.7) 6.36 brs 6.26 d (2.8) 6.37 d (2.8) |
| 7′  | 2.15 s 2.22 s 2.21 s 2.35 s 2.22 s 2.17 s 2.20 s |
| 8′  | 3.78 s |
| 9′  | 3.78 s |
| 1″  | 5.50 d (4.6) 5.57 d (4.5) 5.35 d (3.6) |
| 2″  | 4.07 ddd (10.7, 6.8, 4.1) 4.15 dd (6.5, 4.5) 3.33 m |
| 3″  | 3.93 ddd (11.7, 5.9, 2.7) 4.06 dd (6.5, 3.2) 3.58 t (9.2) |
| 4″  | 3.98 q (4.0) 4.12 dd (6.9, 3.5) 3.17 t (9.2) |
| 5″  | 3.46 brt (5.1) 3.63 dd (12.1, 3.9) 3.69 dd (11.7, 3.4) 3.42 m |
| 6″  | 3.47 ddd (11.7, 5.2) 3.55 dd (11.8, 1.8) |
| 2′-OH | 8.41 s |
| 3″-OH | 9.26 s 10.26 s |
| 2″-OH | 5.14 d (6.0) |
| 3″-OH | 5.16 brs |
| 5″-OH | 4.81 t (5.6) |

*Recorded in DMSO-d6; †Recorded in CD3OD.

Compound 2 was isolated as colorless oil. Its molecular formula was determined to be C19H22O7, having one oxygen less than that of 1, on the basis of HRESIMS data. The detailed analysis of the 1H NMR and 13C NMR data (Tables 1 and 2) of 2 indicated that it had a diphenyl ether moiety with two trisubstituted benzene rings, and an additional pentose residue. The two trisubstituted rings were assigned by the HMBC correlations (Figure 2) from H3-7 (δH 2.27) to C-4 (δC 111.8), C-5 (δC 141.6), C-6 (δC 112.1) and from H-2 (δH 6.20) to C-1 (δC 159.6), C-4 (δC 111.8), C-6 (δC 112.1); from H3-7′ (δH 2.22) to C-4′ (δC 114.2), C-5′ (δC 141.7), C-6′ (δC 131.5) and H-2′ (δH 6.57) to C-1′ (δC 159.7), C-4′ (δC 114.2), C-6′ (δC 113.5). The anomeric proton signal at δH 5.57 (1H, d, J = 4.5 Hz) in its 1H NMR spectrum, and carbon signals at δC 102.3, 73.4, 71.2, 87.5 and 63.2 in its 13C NMR spectrum suggested the pentose residue in 2 was an α-ribofuranosyl. The sugar moiety in 2 was identified as D-ribose by using the same method as described for 1 (see Supplementary Information Figure S55). The key HMBC correlation
from H-1” (δH 5.57) to C-3 (δC 159.5) (Figure 2) established the connection between the ribose and the diphenyl ether moiety. As a result, compound 2 was determined as dioxorin-3-O-α-D-ribofuranoside.

Table 2. 13C NMR spectroscopic data for compounds 1–6 and 6a (150 MHz).

| NO. | 1a | 2b | 3a | 4b | 5b | 6b | 6a b |
|-----|----|----|----|----|----|----|------|
| 1   | 142.0 (C) | 159.6 (C) | 156.1 (C) | 163.2 (C) | 159.5 (C) | 161.2 (C) | 160.2 (C) |
| 2   | 137.3 (C) | 106.3 (CH) | 105.5 (CH) | 103.9 (CH) | 104.5 (CH) | 102.8 (CH) | 102.6 (CH) |
| 3   | 145.7 (C) | 159.5 (C) | 158.3 (CH) | 164.9 (C) | 159.7 (C) | 159.4 (C) | 162.3 (C) |
| 4   | 112.9 (CH) | 111.8 (CH) | 113.5 (CH) | 113.5 (CH) | 111.7 (CH) | 111.0 (CH) | 110.3 (CH) |
| 5   | 127.3 (C) | 141.6 (C) | 140.5 (C) | 144.1 (C) | 148.2 (C) | 141.4 (C) | 141.7 (C) |
| 6   | 115.9 (CH) | 112.1 (CH) | 113.6 (CH) | 109.7 (CH) | 110.8 (CH) | 110.4 (CH) | 112.2 (CH) |
| 7   | 20.6 (CH3) | 21.6 (CH3) | 21.1 (CH3) | 23.9 (CH3) | 29.8 (CH2) | 21.6 (CH3) | 21.7 (CH3) |
| 8   | 172.4 (C) | 172.4 (C) | 159.3 (CH3) | 55.7 (CH3) | 55.7 (CH3) | 62.5 (CH2) | 14.5 (CH3) |
| 9   | 158.3 (C) | 159.7 (C) | 159.8 (C) | 160.8 (C) | 159.6 (C) | 150.1 (C) | 154.3 (C) |
| 10  | 100.3 (CH) | 104.3 (CH) | 102.6 (CH) | 106.4 (CH) | 104.2 (CH) | 106.1 (CH) | 103.4 (CH) |
| 1’  | 159.1 (C) | 159.7 (C) | 159.8 (C) | 160.8 (C) | 159.6 (C) | 150.1 (C) | 154.3 (C) |
| 2’  | 106.4 (CH) | 104.2 (CH) | 102.6 (CH) | 106.4 (CH) | 104.2 (CH) | 106.1 (CH) | 103.4 (CH) |
| 3’  | 158.2 (C) | 159.4 (C) | 159.6 (C) | 155.8 (C) | 159.7 (C) | 146.8 (C) | 154.8 (C) |
| 4’  | 109.6 (CH) | 114.2 (CH) | 114.9 (CH) | 120.1 (CH) | 111.9 (CH) | 140.8 (C) | 144.5 (C) |
| 5’  | 139.5 (C) | 141.7 (C) | 139.1 (C) | 140.6 (C) | 141.6 (C) | 126.7 (C) | 133.5 (C) |
| 6’  | 107.5 (CH) | 113.5 (CH) | 110.7 (CH) | 114.9 (CH) | 110.6 (CH) | 113.6 (CH) | 113.7 (CH) |
| 7’  | 21.2 (CH3) | 21.5 (CH3) | 20.1 (CH3) | 20.2 (CH3) | 21.5 (CH3) | 16.2 (CH3) | 16.0 (CH3) |
| 8’  | 168.5 (C) | 168.5 (C) | 170.7 (C) | 56.3 (CH3) | 56.3 (CH3) | 51.9 (CH3) | 60.6 (CH3) |
| 9’  | 101.3 (CH) | 102.3 (CH) | 97.9 (CH) | 71.5 (CH) | 71.5 (CH) | 71.5 (CH) | 71.5 (CH) |
| 10’ | 72.3 (CH) | 73.4 (CH) | 71.5 (CH) | 71.5 (CH) | 71.5 (CH) | 71.5 (CH) | 71.5 (CH) |
| 3”  | 69.4 (CH) | 71.2 (CH) | 73.0 (CH) | 73.0 (CH) | 73.0 (CH) | 73.0 (CH) | 73.0 (CH) |
| 4”  | 86.7 (CH) | 87.5 (CH) | 69.8 (CH) | 69.8 (CH) | 69.8 (CH) | 69.8 (CH) | 69.8 (CH) |
| 5”  | 61.6 (CH2) | 63.2 (CH2) | 73.8 (CH) | 73.8 (CH) | 73.8 (CH) | 73.8 (CH) | 73.8 (CH) |
| 6”  | 60.6 (CH2) | 60.6 (CH2) | 60.6 (CH2) | 60.6 (CH2) | 60.6 (CH2) | 60.6 (CH2) | 60.6 (CH2) |

*a Recorded in DMSO-d6; b Recorded in CD3OD.

Figure 2. Key 1H–1H COSY (blue lines) and key HMBC (arrows) correlations of 1–5 and 6a.

The molecular formula C22H26O10 of compound 3 was deduced from positive HRESIMS which gave a sodium adduct ion at m/z 473.1403 [M + Na]+. Its 13C NMR spectrum (Table 2) displayed 22 carbon resonances, including 6 signals for a hexose residue at δC 97.9, 71.5, 73.0, 69.8, 73.8 and 60.6, suggesting 3 to be a glucoside [28]. The 1H and 13C NMR spectra for 3 (Tables 1 and 2) indicated the aglycone in 3 as 4-methoxybenzyl dioxorin [8], which was supported by key HMBC correlations from H-3’ (δH 2.26) to C-4’ (δC 113.5), C-5’ (δC 147.5), C-6’ (δC 113.6) and from H-2 (δH 6.57) to C-4 (δC 114.9), C-5’ (δC 139.1), C-6’ (δC 110.7), from H-2’ (δH 6.28) to C-4’ (δC 114.9), C-6’ (δC 110.7), and from 3’-OH (δH 10.26) to C-2’ (δC 102.6), C-3’ (δC 157.6), C-4’ (δC 114.9), as well as from H-3’-9’ (δH 3.78) to C-8’ (δC 168.5). The anomeric signal at
δ_H 5.35 (1H, d, J = 3.6 Hz)/δ_C 97.9 (C-1") and the one-bond coupling constant of 172.9 Hz between C-1" and H-1" (see Supplementary Information Figure S23) supported an α-configuration of the O-glucoside [29]. The absolute configuration of glucose moiety in 3 was determined as D-glucose based on LC-ESI-MS analysis (see Supplementary Information Figure S56). The key HMBC correlation from H-1" (δ_H 5.35) to C-3 (δ_C 158.3) (Figure 2) established the connection between the glucose and diphenyl ether moiety. Thus, the structure of compound 3 was determined to be 4-methoxycarbonyl diroprinol-3-O-α-D-glucoside.

Compound 4 was obtained as colorless oil. Its molecular formula was determined to be C_{18}H_{23}O_{7} by HRESIMS, having a fragment of C_{3}H_{4}O_{2} more than that of 4-carboxydioprinol (16). The 1H and 13C NMR spectra for 4 (Tables 1 and 2) and 16 showed very similar signals, with the exception that H-6 at δ_H 6.17 for 16 was replaced by another substitution in 4. Analysis of the 1H NMR and 13C NMR (Tables 1 and 2) and 1H-1H COSY correlation data (Figure 2) of 4 indicated the presence of an ester carbonyl (C-8) at δ_C 172.4 and an oxygenated ethyl group (C-9/C-10) at δ_C 62.5 and δ_C 14.5. The presence of an ethyl ester unit was confirmed by the HMBC correlation from H_{2}-9 (δ_H 4.40) to C-8 (δ_C 172.4) (Figure 2). Thus, the structure of 4 was elucidated as 2-(ethoxy carbonyl)-4'-carboxydioprinol.

The HRESIMS of 5 displayed a protonated ion [M + H]^+ at m/z 245.1183, corresponding to the molecular formula of C_{13}H_{16}O_{4}, one more carbon and two more hydrogens than that of diroprinol (8). The 1H and 13C NMR spectra for 5 (Tables 1 and 2) and 8 showed very similar signals, with the exception that a methyl at C-7 (δ_C 21.5) in 8 was substituted by an ethyl group in 5, which was confirmed by HMBC correlations from the ethyl protons at H_{2}-7 (δ_H 2.53) to C-4 (δ_C 111.7), C-5 (δ_C 148.2), and C-6 (δ_C 110.8). The full structure of 5 was further confirmed by COSY and HMBC experiments (Figure 2). As a result, 5 was elucidated as 7-ethyl dioprinol.

The molecular formula C_{14}H_{18}O_{4} of 6 was determined by negative HRESIMS at m/z 245.0808 [M − H]^−, one more oxygen than those of 8. The 1H and 13C NMR spectra for 6 (Tables 1 and 2) showed very similar signals to those of 8, with the exception that the tertiary carbon signal at δ_C 111.8 for 8 was replaced by a quaternary carbon signal at δ_C 140.8 for 6. These data indicated that the hydrogen at C-6 (δ_C 111.8) in 8 was substituted by a hydroxy group in 6. The two hydroxy groups in the B ring did not display any correlation in the HMBC spectrum, and therefore, the position of the ether linkage between the two benzene rings could not be determined by 2D NMR data at this stage. Therefore, full methylation of 6 was completed with CH$_3$I/K$_2$CO$_3$, which afforded its derivative 6a. HMBC correlations of 6a from H$_3$-8 (δ_H 3.73) to C-3 (δ_C 3.78) to C-3' (δ_C 154.8) and from H$_3$-8' (δ_H 3.75) to C-4 (δ_C 144.5) (Figure 2) demonstrated that the three free hydroxy groups of 6 were attached to C-3, C-3' and C-4', respectively. Therefore, 6a was unambiguously determined as 3-hydroxydioprinol.

The eleven known compounds (7-17) were identified as 4-methoxycarbonyl dioprinol (7) [10], diroprinol (8) [11], glyceryl diroprinic acid (9) [12], cordyol C (10) [14], aspergilol E (11) [13], 4-hydroxy-2-(3'-hydroxy-4-methoxycarbonyl-5'-methylphenoxy)-6-methylbenzoic acid (12) [16], gibellulin B (13) [11], dioprinol F (14) [30], 3,7-dihydroxy-1,9-dimethyl dibenzofuran (15) [31], 4-carboxydioprinol (16) [32] and aspermutarubol (17) [33] by comparison of their spectroscopic data to those reported in the literature.

The cytotoxicity of all the isolated compounds was tested against a series of cancer cell lines, including 4T1 (Mouse Breast Cancer cell line), U937 (Human Histiocytic Lymphoma cell line), PC3 (Human Prostate Cancer cell line), HL-60 (Human Leukemia cell line), HT-29 (Human Colorectal Adenocarcinoma cell line), A549 (Human Lung Adenocarcinoma cell line), NCI-H460 (Human Large Cell Lung Cancer cell line) and K562 (Human Myelogenous Leukemia cell line), with doxorubicin (DOX) as positive control (Table 3). None of the compounds showed cytotoxicity against the five solid cancer cell lines (4T1, PC3, HT-29 and NCI-H460). Compounds 1, 5, 8 and 9 showed moderate cytotoxicity against A549. These results suggested that glycosylation of the 3-hydroxy group seems to negatively contribute to its cytotoxicity against A549 cell line (2 vs. 8), while substitution at the same
3-OH position by a glycerol group positively compensate for cytotoxicity (16 vs. 9). In addition, compounds 1, 6, 9–11 showed selective cytotoxicity against different nonsolid cancer cell lines (U937, HL-60, and K562). Interestingly, only compounds 6, 10 and 11, which possess two adjacent hydroxy groups in one of the benzene rings and no substitution at C-2 position in the other ring exhibited varied inhibitory cytotoxicity on K562 cells. Moreover, by comparison of the structures of 9 and 3–4, 7, 11–12 and 16 having a carboxyl group, it was found that when the carboxyl group in the benzene ring is adjacent to a free hydroxy group, the cytotoxicity against HL-60 cells is lost. In summary, we found that when the ortho position of the carboxyl group in the diphenyl ethers is a free phenolic hydroxy group, it will lose all cytotoxicity against cancer cells, and the adjacent phenolic hydroxy groups confer selective cytotoxicity against several cell lines.

Table 3. Cytotoxicity (IC_{50} in µM) for compounds 1, 5–6, 8–11.

| Compounds | A549  | U937  | HL-60 | K562 |
|-----------|-------|-------|-------|------|
| 1         | 8.97 ± 0.48 | 4.64 ± 0.35 | /     | /    |
| 5         | 16.13 ± 1.24 | /     | /     | /    |
| 6         | /     | 11.98 ± 0.73 | 18.89 ± 1.14 | /    |
| 8         | 15.51 ± 1.59 | /     | /     | /    |
| 9         | 3.36 ± 0.68 | 21.22 ± 1.25 | /     | /    |
| 10        | /     | 16.52 ± 0.99 | 20.88 ± 1.60 | /    |
| 11        | /     | 13.33 ± 0.87 | 23.03 ± 1.34 | /    |
| DOX       | 0.19 ± 0.04 | <0.125 | <0.125 | 0.49 ± 0.08 |

"/" no cytotoxicity was detected. Inactive compounds were not shown here.

3. Materials and Methods

3.1. General Experimental Procedures

Optical rotations were measured with a JASCO P-2000 automatic digital polarimeter (JASCO, Easton, MD, USA). IR spectra were taken on a Nicolet 5700 FT-IR spectrometer (Thermo Electron Corporation, Madison, WI, USA). The NMR spectra in CD_{3}OD and DMSO-d_{6} with TMS as internal reference were obtained on a Bruker AVANCE III HD 600 MHz spectrometer equipped with a 5 mm cryogenic CPDCH probe (Bruker, Fällanden, Switzerland). HRESIMS were recorded on an Agilent Technologies 6520 Accurate Mass Q-TOF LC/MS spectrometer (Agilent Technologies, Santa Clara, CA, USA). Column chromatography (CC) was carried out on Sephadex LH-20 (GE Healthcare, Sweden), silica gel (300–400 mesh, Qingdao Marine Chemical Inc., Qingdao, China) and MCI gel CHP 20P/P120 (Middle Chromatogram Isolated Gel, Mitsubishi Chemical Corporation, Tokyo, Japan). TLC was performed on GF254 plates (Qingdao Chemical Factory, Qingdao, China). Medium pressure liquid chromatography (MPLC) was carried out on a TELEDYNE ISCO CombiFlash Rf+ [Universal Technology, Hong Kong, China]. HPLC was conducted using a SSI instrument with a Series 1500 photo diode array detector and COSMOSIL C_{18} column (5 µm, 4.6 × 250 mm). Standards of D/L-ribose and D/L-glucose were purchased from Sigma (St. Louis, MO, USA), and Derivatization reagents L-cysteine and o-tolyl isothiocyanate were purchased from J&K Scientific Ltd. (Beijing, China).

3.2. Fungal Material

The fungal strain FNA026 was isolated from marine water collected in the sea of China, Xiamen. The voucher specimen is deposited in our laboratory at −80 °C. The partial 18S rRNA sequence was compared to sequences in available databases using the Basic Local Alignment Search Tool and strain FNA026 determined to be an Aspergillus sydowii (Supplementary Information Figure S57).
3.3. Fermentation

The fungal strain FNA026 was grown on potato dextrose agar at 28 °C for 5 days. Five pieces (0.5 × 0.5 cm²) of mycelial agar plugs were inoculated into 500 mL Erlenmeyer flasks containing 500 mL of potato dextrose broth, which were then incubated on a rotary shaker at 250 rpm and 28 °C for 3 days. Then the seed liquid was spread in 500 mL Roux flasks (30 flasks) containing rice (100 g per flask) and artificial seawater (120 mL per flask). The flasks were incubated at 28 °C for 4 weeks.

3.4. Extraction and Isolation

The extraction and isolation procedures were guided by LC-MS screening with UV absorption characteristics (207 nm and 270 nm) and molecular weight (m/z 230–280 and m/z 380–480) as search criteria. The fermented rice inoculated with FNA026 (3 kg) was extracted three times with ethyl acetate (500 mL) at room temperature under sonication to give a crude extract (28.86 g), which was then dissolved in MeOH, and extracted three times using petroleum ether to afford MeOH-soluble (22.24 g) and petroleum ether-soluble (5.65 g) fractions. The MeOH-soluble fraction was subjected to MCI gel (Middle Chromatogram Isolated Gel) with a stepped gradient of MeOH–H₂O (20:80, 50:50, 90:10, 100:0 v/v) to give 4 fractions (A–D). Fraction C (2.79 g) was separated on a silica gel column eluting with a dichloromethane-methanol gradient (1:0–0:1, v/v) to give 12 fractions (C1–C12). Fraction C4 (0.83 g) was subjected to MPLC eluting with a gradient of increasing MeCN (20–50%) in H₂O to give 8 fractions (C4A–C4H), where pure compound 8 (328.6 mg) was obtained from fraction C4D. Fraction C4A (15.6 mg) was further purified by HPLC (1.0 mL/min; 46% MeCN in H₂O) to give compound 9 (tᵣ 15.6 min, 3.5 mg). Fraction C4E (5.3 mg) was further purified by HPLC (1.0 mL/min; 64% MeOH in H₂O) to give compound 5 (tᵣ 13.2 min, 1.2 mg). Fraction C4H (22.8 mg) was further purified by HPLC (1.0 mL/min; 69% MeOH in H₂O) to give compound 10 (tᵣ 22.2 min, 3.5 mg). Fraction C5 (390.4 mg) was subjected to MPLC eluting with a gradient of MeCN (30–60%) in H₂O to yield into 6 fractions (C5A–C5F). Fraction C5A (38.3 mg) was further purified by HPLC (1.0 mL/min; 59% MeOH in H₂O) to give compound 11 (tᵣ 17.3 min, 5.2 mg). Fraction C6 (58.8 mg) was chromatographed over Sephadex LH-20 and eluted with MeOH to yield fractions C6A–C6G. Pure compound 11 (3.7 mg) was obtained directly from fraction C6C. Fraction C7 (88.3 mg) was subjected to HPLC (1.0 mL/min; 32% MeCN in H₂O, 0.1%TFA) to yield into 4 fractions (C7A–C7D). Pure compound 14 (3.8 mg) was obtained directly from fraction C7B. Fraction C7D (10.9 mg) was further purified by HPLC (1.0 mL/min; 68% MeOH in H₂O) to give compound 12 (tᵣ 26.3 min, 3.1 mg). Fraction C9 (22.1 mg) was purified by HPLC (1.0 mL/min; 43% MeCN in H₂O, 0.1% TFA) to give compound 15 (tᵣ 12.1 min, 2.2 mg). Fraction C10 (476.4 mg) was subjected to MPLC eluting with a gradient of acetonitrile (30–53%) in H₂O to give 7 fractions (C10A–C10G), and two pure compounds 2 (5.2 mg) and 16 (4.2 mg) were obtained directly from fraction C10C and fraction C10E, respectively. Fraction C10F (165.4 mg) was applied to a Sephadex LH-20 column chromatography eluted with MeOH to give 17 fractions (C10F1–C10F17). Fraction C10F7 (8.2 mg) was further purified by HPLC (1.0 mL/min; 42% MeCN in H₂O, 0.1%TFA) to give compound 4 (tᵣ 14.2 min, 1.7 mg). Fraction C10F10 (25.8 mg) was further purified by HPLC (1.0 mL/min; 44% MeCN in H₂O) to give compound 6 (tᵣ 13.4 min, 1.6 mg). Fraction C11 (42.5 mg) was purified by HPLC (1.0 mL/min; 33% MeCN in H₂O, 0.1%TFA) to give compound 12 (tᵣ 18.5 min, 6.4 mg). Fraction C12 (495.6 mg) was subjected to the Sephadex LH-20 column chromatography eluted with MeOH to give 8 fractions (C12A–C12H). Fraction C12G (28.6 mg) was purified by HPLC (1.0 mL/min; 34% MeCN in H₂O, 0.1% TFA) to give compound 1 (tᵣ 24 min, 1.3 mg). Fraction C12H (18.6 mg) was further purified by HPLC (1.0 mL/min; 36% MeCN in H₂O, 0.1% TFA) to give compound 3 (tᵣ 20 min, 2.2 mg). Fraction D (1.33 g) was subjected to column chromatography on silica gel and eluted with dichloromethane–methanol gradient (1:0–0:1, v/v), which gave 8 fractions (D1–D8). Fraction D5 (325.2 mg) was further by MPLC eluting with a gradient of increasing MeCN (50–100%) in H₂O to give 5 fractions (D5A–D5E), and pure compound 7 (185.6 mg) was obtained directly from fraction D5C.
3.4.1. Cordyol C-3-O-α-D-ribofuranoside (1)

Colorless oil; [α]D25 +8.0 (c 0.20, MeOH), UV(MeOH) λmax (log ε): 204.8 (4.02) nm, 279.4 (3.25) nm; IR νmax: 3320.1, 1677.7, 1596.2, 1512.1, 1464.3, 1322.1, 1210.8, 1140.0, 1046.8, 997.6, 836.2 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 401.1206 [M + Na]+ (calcd. for C19H22O₇Na, 401.1207).

3.4.2. Diorcinol-3-O-α-D-ribofuranoside (2)

Colorless oil; [α]D25 −18.6 (c 0.40, MeOH), UV(MeOH) λmax (log ε): 207.2 (4.05) nm, 273.4 (3.25) nm; IR νmax: 3344.2, 2931.4, 1600.7, 1464.7, 1325.1, 1154.9, 1039.8, 839.2 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 385.1261 [M + Na]+ (calcd. for C20H26O10Na, 385.1258).

3.4.3. 4-Methoxycarbonyl Diorcinol-3-O-α-D-glucoside (3)

Colorless oil; [α]D25 +9.6 (c 0.20, MeOH), UV(MeOH) λmax (log ε): 214.2 (4.03) nm, 261.5 (3.64) nm, 298.4 (3.28) nm; IR νmax: 3334.5, 1651.3, 1579.3, 1454.2, 1324.9, 1268.4, 1161.2, 1023.9, 847.5 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 473.1403 [M + Na]+ (calcd. for C22H24O13Na, 473.1418).

3.4.4. 2-(Ethoxycarbonyl)-4′-carboxydiorcinal (4)

Colorless oil; UV(MeOH) λmax (log ε): 216.6 (4.04) nm, 259.2 (3.59) nm, 299.6 (3.26) nm; IR νmax: 3251.1, 1654.4, 1613.0, 1460.1, 1317.8, 1260.4, 1167.0, 845.9, 802.3 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 369.0954 [M + Na]+ (calcd. for C18H18O12Na, 369.0945).

3.4.5. 7-Ethylidiorcinol (5)

Colorless oil; UV(MeOH) λmax (log ε): 207.2 (4.03) nm, 280.5 (3.27) nm; IR νmax: 3343.5, 1598.3, 1459.8, 1329.8, 1155.3, 995.4, 841.3 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 245.1172 [M + H]+ (calcd. for C13H17O3, 245.1172).

3.4.6. 3-Hydroxydiorcinol (6)

Colorless oil; UV(MeOH) λmax (log ε): 221.3 (4.03) nm, 280.5 (3.71) nm; IR νmax: 3286.7, 1598.2, 1491.4, 1324.2, 1154.0, 1024.7, 976.7, 836.8 cm⁻¹; 1H and 13C NMR spectroscopic data see Tables 1 and 2; HRESIMS m/z 245.0819 [M – H]− (calcd. for C14H13O4, 245.0819).

3.5. Determination of the Absolute Configuration of Sugar Moieties in 1–3

To determine the absolute configurations of sugar moieties in 1–3, a modified method based on LC-ESI-MS analysis was performed, where the retention time of sugar samples obtained after hydrolysis of the parent compounds were compared with those from standard sugars (D/L) [34]. In detail, compounds 1, 2 and 3 (approximately 0.05 mg, each) were hydrolyzed with 2 mol/L HCl (400 µL) in a 2 mL glass vial at 80 °C for 4 h. The reaction mixture was then diluted with H2O (400 µL) and extracted with CHCl3 (400 µL) three times. The aqueous layer containing monosaccharides was concentrated in vacuo and extracted with CHCl3 (400 µL) to yield a dried sugar mixture. The resulting sugar mixture (not weighed out) and standard sugar samples (D/L-ribose and D/L-glucose, 0.1 mg for each) respectively, were heated with L-cysteine methyl ester (0.1 mg) in pyridine (400 µL) in a 2 mL glass vial at 60 °C for 60 min, then o-tolyl isothiocyanate (200 µL) was added to the reaction mixture and kept at 60 °C for additional 60 min. Then, the reaction mixture was directly analyzed by LC-ESI-MS (COSMOSIL 5 µm, 4.6 × 250 mm, C18 column). Analysis was performed at 30 °C with a flow rate of 1.0 mL/min, and the elution was carried out using a gradient of MeCN (0–30 min, 10–50%, linear gradient) in H2O. Source parameters in the positive ion mode were set as follows: Capillary entrance voltage = –4500 V, end plate offset = –500 V, nebulizer pressure (N2) = 11.6 psi, dry gas (N2) = 6.0 L/min, dry gas temperature = 220 °C. High-purity nitrogen (N2) were used as the nebulizing gas. Ion Peaks were
extracted at m/z 447 for ribose and at m/z 471 for glucose identified by comparison of retention time with those of standards. The retention time of D-ribose and D-glucose derivatives were 22.3 and 21.0 min, respectively.

3.6. Cytotoxicity Assay

Cancer cell lines, including 4T1, U937, PC3, HL-60, HT-29, A549, NCI-H460, and K562, were purchased from ATCC. All the cells were maintained in RPMI1640 supplemented with 10% FBS, 100 units/mL Penicillin G and 100 µg/mL streptomycin. All the cancer cells were incubated at 37 °C in humidified air containing 5% CO2. MTT assay was used to determine the cell viability. Cells were seeded in 96-well plates at 1.5–3.0 × 10^4/mL (100 µL/well). After 24 h incubation, 5 different concentrations (final concentrations were 1.6, 3.1, 6.3, 12.5 and 25.0 µM) of tested compounds were added into the wells in triplicate. Five concentrations of doxorubicin were tested, including 2.0, 1.0, 0.5, 0.25, and 0.125 µM. Cells were incubated for 96 h before MTT was added into the cells at a final concentration of 500 µg/mL, and the plates were incubated for an additional 4 h. The resultant formazan crystals were dissolved in 200 µL of DMSO, then a microplate reader (Synergy HT, Bio-Tek) was used to measure the absorbance of the plates at 570 nm for testing the cell viability of serial concentrations of compounds and the IC_{50} were estimated.

4. Conclusions

A total of 17 diphenyl ethers, including 6 new compounds, were isolated from a marine-derived Aspergillus sydowii. Compounds 1 and 2 are rare diphenyl ether glycosides containing a D-ribofuranose moiety. Although natural diphenyl ethers have been extensively investigated, their structures still exhibit variability due to the presence of hydroxy groups, and the diversity and location of sugar moieties. Furthermore, a modified method based on LC-MS analysis was used to determine the absolute configuration of sugar moieties. Comparing to conventional method based on LC-UV, which normally requires 0.5–3 mg of sample [34–37], our method has higher sensitivity due to the use of ESIMS detection, and as low as 0.05 mg of sample was enough to determine the absolute configuration of the sugar units using this procedure. Moreover, all the compounds were evaluated for their cytotoxicity against eight cancer cell lines, and compounds 1, 5, 6, and 8–11 were found to exhibit highly selective cytotoxicities against different cancer cell lines.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-3397/16/11/451/s1, Figures S1–S53: HRESIMS, 1D and 2D NMR, IR, and UV spectra of 1–19 and 6a, Figures S54–S56: LC-ESI-MS analysis of sugar derivatives of 1–3, Figure S57: the internal transcribed spacers (ITS) sequence of strain FNA026.

Author Contributions: Y.-N.W., Y.D. and Y.-H.M. conducted most of the isolation, acquirement of NMR spectra, structural determination and the bioactivity evaluation of compounds; Y.W., B.-Y.L., J.B., D.-J.Y. and L.Z. assisted the data analyzes. D.-Q.F. isolated the fungal species, Y.-H.P. and Y.-C.H. designed the experiments and wrote the manuscript. All authors reviewed the manuscript.

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