Oxygenated Cyclohexene Derivatives from the Stem and Root Barks of Uvaria pandensis

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ABSTRACT: Five new cyclohexene derivatives, dipandensin A and B (1 and 2) and pandensenos A–C (3–5), and 16 known secondary metabolites (6–21) were isolated from the methanol-soluble extracts of the stem and root barks of Uvaria pandensis. The structures were characterized by NMR spectroscopic and mass spectrometric analyses, and that of 6-methoxyzeylenol (6) was further confirmed by single-crystal X-ray crystallography, which also established its absolute configuration. The isolated metabolites were evaluated for antibacterial activity against the Gram-positive bacteria Bacillus subtilis and Staphylococcus epidermidis and the Gram-negative bacteria Enterococcus raffinosus, Escherichia coli, Paraburkholderia caledonica, Pectobacterium carotovorum, and Pseudomonas putida, as well as for cytotoxicity against the MCF-7 human breast cancer cell line. A mixture of uvaretin (20) and isouvaretin (21) exhibited significant antibacterial activity against B. subtilis (EC_{\text{50}} 8.7 \mu M) and S. epidermidis (IC_{\text{50}} 7.9 \mu M), (8α,9β-Dihydroxy)-3-farnesylindole (12) showed strong inhibitory activity (EC_{\text{50}} 9.8 \mu M) against B. subtilis, comparable to the clinical reference ampicillin (EC_{\text{50}} 17.9 \mu M). None of the compounds showed relevant cytotoxicity against the MCF-7 human breast cancer cell line.

RESULTS AND DISCUSSION

The separate CH_{3}OH extracts of the root and stem barks of U. pandensis were subjected to a repeated silica gel chromatographic separation. Further purification on Sephadex LH-20 and by HPLC and recrystallization yielded 21 compounds, of which five (1–5) were new. The structures of the isolated secondary metabolites were elucidated based on their NMR, IR, and UV spectroscopic and mass spectrometric data. The 16 known compounds, 6-methoxyzeylenol (6),5 zeylenol (7),5 cleistenediol C (8),5 cleistenediol F (9),5 cherrevenol I

Supporting Information

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(10), 3-methoxybenzylbenzoate (11), (8α,9β-dihydroxy-3-farnesylindole (12), (6,7′-dihydro-8′α,9′β-dihydroxy-3-farnesylindole (13), zeylenyl-2,6-diacetate (14), benzoic acid 2,3-diacetoxy-1,6-dihydroxycyclohex-4-enyl ester (15), lupeol (16), betulin (17), a mixture of stigmasterol (18) and β-sitosterol (19), and a mixture of uvaricin (20) and isouvaretin (21) were identified by comparison of their spectroscopic data (Supporting Information) to those previously reported in the literature.

Compound 1, [α]D 34 −33 (c 0.2, CH3OH), was isolated from the CH3OH extract of the stem bark of U. pandensis as a white solid. The HRESIMS showed a [M + NHe]+ peak at m/z 622.2442 (calcd 622.2652 for C34H40NO10), which in combination with the NMR data (Table 1) indicated 17 double-bond equivalents (DBEs). Additionally, the HRMS showed a base peak at m/z 545.1937 (calcd for [M + H - HOAc]+ 545.2175), indicative of the presence of an acetate group. The UV spectrum exhibited absorption maxima at 208, 229, and 274 nm, typical for a conjugated π-system. The IR spectrum of compound 1 consisted of absorption bands for hydroxy (3520 cm−1), ester carbonyl (1740 cm−1), and double-bond (1635 cm−1) stretches. The 1H and 13C NMR spectroscopic data (Table 1, Figures S1–S2, Supporting Information) of compound 1 showed signals evocative of dimeric polyoxygenated cyclohexene derivatives resembling those previously reported. Thus, the 1H and 13C NMR spectra showed signals at δH 7.97 (H-2′/6′)/130.3, 7.50 (H-3′/5′)/129.5, 7.62 (H-4′)/134.1, 131.0 (C-1), 166.7 (C-7′) and 8.04 (H-2′′/6′′)/130.4, 7.50 (H-3′′/5′′)/129.5, 7.62 (H-4′′)/134.2, 131.2 (C-1′′), 166.8 (C-7′′), corresponding to two benzoxolyl units. In addition, the resonances were observed corresponding to two olefinic groups [δH 7.97/4.77/6.62/6.75, 4.48 (2H, ABq, H-7′)] and two acetoxy groups [δH 1.99 (CH3COO-6)/21.1 and 171.3; 1.96 (CH3COO+4)/21.1 and 170.4], and two methoxy groups [δH 3.37 (OCH3-5)/57.9 and 3.32 (OCH3-7)/57.2]. The COSY and TOCSY spectra (Figures S3 and S6, Supporting Information) showed correlations between H-2 (δH 6.02) and H-3 (δH 3.04), H-2 and H-6 (allylic coupling), H-3 and H-4 (δH 3.09), H-4 and H-5 (δH 3.48), H-3 and H-6 long-range-coupling, H-5 and H-6 (δH 5.41), H-1″ (δH 6.28) and H-2″ (δH 5.75), H-1″ and H-6″ (δH 3.15), H-4″ (δH 5.09) and H-5″, and H-5″ (δH 3.10) and H-6″. These correlations indicated two distinct spin systems corresponding to two cyclohexenyl moieties. The linkage of these units and their substitution patterns were established from HMBC analyses (Table 1, Figure S5, Supporting Information). Thus, the HMBC correlations of δH 4.62/4.77 (H-7a/7b) to C-7 (δC 166.7), C-1 (135.2), C-2 (129.5), and C-6 (δC 70.5) and those of δH 4.48 (H-7″) to C-7″ (δC 166.8), C-2″ (δC 133.0), C-3″ (δC 47.6), and C-4″ (δC 76.5) indicated the two sets of benzoyloxyethyl units to be attached at C-1 and C-3″, respectively. The regiochemistry of the two methoxy and two acetate groups was indicated by the HMBC cross-peaks of CH3-O-5 (δH 3.37), H-6 (δH 5.41), H-4″ (δH 5.09), and CH3-O-5″ (δH 3.32) to C-5 (δC 81.4), OAc-6 (δC 171.3), OAc-4″ (δC 170.4), and C-5″ (δC 87.1), respectively. The HMBC correlations of H-6″ (δH 3.15) to C-3 (δC 40.2), C-4 (δC 31.1), and C-5 (δC 81.4) as well as those of H-4 (δH 3.09) to C-1″ (δC 132.6) and C-6″ (δC 34.1), and of H-5 (δH 3.09) to C-6″ (δC 34.2) suggested the linkage of the two sets of cyclohexenyl moieties. The NMR and MS data supported by retro-biogenetic analysis led to the conclusion that 1 is a dimer of 6-acetoxy-5-methoxy-1,3-dienyl)methylbenzoate moieties and hence the product of the Diels–Alder endo-addition (Figure 1). The fact that 1 was isolated as an optically active compound suggests that it is formed in an enzymatic Diels–Alder reaction, as the nonenzymatic alternative would be expected to provide a racemic product.

The relative configuration of 1 was established based on scalar coupling constants (Table 1) and NOESY correlations (Figure 1 and Figure S7, Supporting Information). Thus, JH-6/H-4 (6.5 Hz) and JH-6/H-5 (9.1 Hz) indicated the cis axial–equatorial and the trans diaxial orientation for the corresponding protons, establishing the relative configurations at C-4, C-5, and C-6. Moreover, H-6 exhibited a NOE with H-1″, which exhibited also a weak NOE correlation with H-5″. The NOE correlation of CH3-O-5″ to H-4″ was used to establish the relative configurations at C-4″, C-5″, and C-6″. The JH-6/H-4 (9.0 Hz) indicated a cisoid ring junction for the protons at C-3 and C-4. Such a large J value for the bridgehead protons suggested that their dihedral angle is inclined toward an eclipsed orientation. Based on the above spectroscopic data...
Table 1. NMR Spectroscopic Data (500 MHz, CD$_3$CN) for Dipandensin A (1)

| position | δ$_1$ type | δ$_1$ (J in Hz) | HMBC |
|----------|------------|-----------------|------|
| 1        | 135.2, C   |                 |      |
| 2        | 129.5, CH | 6.02 dd (2.9, 2.4) | C-1, C-3, C-4, C-6, C-7, C-3' |
| 3        | 40.2, CH  | 3.04 ddd (9.0, 2.9, 2.4) | C-1, C-2, C-4, C-5, C-6, 2", C"-3', C"-4', C"-6' |
| 4        | 311.1, CH | 3.09 dd (9.0, 1.5) | C-2, C-3, C-5, C-6, C-1', C-3', C-5', C-6' |
| 5        | 814.1, CH | 3.48 dd (9.1, 1.5) | C-1, C-3, C-4, C-6, C-1', OCH$_3$-5 |
| CH$_3$O-5 | 57.9, CH$_3$ | 3.37 s | C-5 |
| 6        | 70.5, CH  | 5.41 dd (9.1, 2.4, 2.4) | C-1, C-2, C-4, C-5, COO-6 |

OAc-6: 171.3, OC=O 1.99 COO-6 653.3, CH$_2$ 4.77 d (12.4) C-1, C-2, C-6, C-7' 4.62 d (12.4) C-1, C-2, C-6, C-7' 131.0, C 2/6' 130.3, CH 7.97 dd (8.3, 1.5) C-1', C-3'/5', C-4', C-7' 3/5' 129.5, CH 7.50 dd (8.3, 7.5) C-1', C-2'/6', C-4' 4' 134.1, CH 7.62 dd (7.5, 1.5) C-2'/6', C-3'/5' 7' 166.7, OC=O 6.28 dd (8.2, 6.8) C-4, C-2', C-3', C-5', C-6 2' 133.0, CH 5.75 d (8.2) C-3', C-4', C-6', C-7' 3' 47.6, C 76.5, CO 5.09 d (2.9) C-2', C-3', C-5', C-6', C-7', COO-4' OAc-4': 170.4, OC=O 21.1, CH$_3$ 1.96 COO-4' 87.1, CO 3.10 dd (2.9, 2.9) C-1', C-3', C-4', OCH$_3$-5', C-6 5' CH$_3$O-5 57.2, CH$_3$ 3.32 s C-5' 34.1, CH 3.15 dd (6.8, 2.9) C-3, C-4, C-5, C-1', C-2', C-4', C-5', 7' 62.3, CH$_2$ 4.48 AB$_x$ (120) C-3, C-3', C-2', C-3', C-4', C-7' 1' 131.2, C 2/6' 130.4, CH 8.04 dd (8.4, 1.5) C-1', C-3'/5', C-4', C-7 3'/5' 129.5, CH 7.50 dd (8.4, 7.5) C-1', C-2'/6', C-4' 4' 134.2, CH 7.62 tt (7.7, 1.5) C-2'/6', C-3'/5' 7' 1668.8, OC=O

The new compound 1 (dipandensin A) was characterized as benzoic acid 6α,4β-diacetoxy-3α-methylbenzoate-5β,5'S'-dimethoxytricyclo[6.2.2.0$^{3,6}$]dodeca-2,2'-dien-1-ylmethyl ester. Compound 2, [α]$_D^{24}$ = −40 (c 0.2, CH$_3$OH), was isolated from the stem bark CH$_3$OH extract as a white solid. Its HRESIMS (Figure S16, Supporting Information) spectrum exhibited a molecular ion [M + H]+ at m/z 621.2297 (calcd 621.2336), corresponding to the molecular formula C$_{34}$H$_{36}$O$_{11}$ with 17 DBEs, similar to 1. The established molecular formula was supported by the NMR data (Table 2). The UV spectrum showed absorption maxima at 205 and 230 nm, revealing a conjugated π-system. The IR spectrum, again similar to that of 1, showed absorption bands for hydroxy (3508 cm$^{-1}$), ester carbonyl (1730 cm$^{-1}$), and C=C bond (1630 cm$^{-1}$) stretches. The NMR spectroscopic data (Table 2 and Figures S9–S15, Supporting Information) closely resembled those of dipandensin A (1), with the only difference being saturation at C-1 and C-2. Thus, 2 exhibited a signal at δ$_1$ 3.43 (δ$_1$ 61.7) assignable to C-2, compared with δ$_1$ 6.02 (δ$_1$ 129.5) for the same position in 1. In addition, the $^{13}$C NMR data (Table 2, Figure S10, Supporting Information) of 2 consisted of a peak at δ$_1$ 60.8 for a tertiary oxygenated carbon, assignable to C-1, instead of δ$_1$ 135.2 observed for C-1 in 1. The carbon resonances at C-1 (60.8) and C-2 (61.7) were in agreement with a 1,2-epoxide derivative of 1. For a 1,2-diol, the carbons would have been expected to resonate at ~70 ppm. The oxymethine proton at δ$_1$ 3.43 (H-2) showed HMBC cross-peaks to C-1 (δ$_1$ 60.8), C-3 (δ$_1$ 38.6), C-4 (δ$_1$ 32.8), C-6 (δ$_1$ 70.3), C-7 (δ$_1$ 63.8), and C-3' (δ$_1$ 47.1), supporting its proposed positioning. The relative configurations at C-1 and C-2 were established based on the NOEs of H-2 (δ$_1$ 3.43) with H-3 (δ$_1$ 2.88), H-4 (δ$_1$ 2.91), H-7 (δ$_1$ 4.01), and H-7" (δ$_1$ 6.46) (Figure 2 and Figure S9, Supporting Information), indicating these protons to be cofacial. No scalar coupling was measurable between H-2 and H-3, consistent with their dihedral angle being close to 90°. The J$_{H3/4}$ (9.1 Hz) suggested their dihedral angle to be inclined toward an eclipsed cis orientation for these protons, whereas the J$_{H5/6}$ (9.9 Hz) indicated their transoid orientation, similar to that in 1. In compound 1, an allylic coupling of H-2 with H-6 was observed. This coupling was absent for H-2 and H-6 of the saturated cyclohexenyl ring of compound 2. The relative configurations of the other parts of 2 were similar to those of 1 as established by analysis of the NOEs (Figure 2 and Figure S9, Supporting Information) and of scalar couplings (Table 2). The HMBC analysis established the linkage of the subunits of 2 with all key cross-peaks being similar to 1 (Tables 1 and 2). Based on the spectroscopic data obtained, this new compound, dipandensin B (2), was characterized as benzoic acid 4β/6β-diacetoxy-1β,2β-epoxy-3α-methylbenzoate-5β,5'S'-dimethoxytricyclo[6.2.2.0$^{3,6}$]dodeca-1'-en-1-ylmethyl ester. Dimeric polyoxygenated cyclohexene derivatives, such as 1 and 2, are rare natural products with restricted occurrence in only a few plant species. They have been reported previously from Uvaria cherrevesia and Kaempferia rotundula (Zingiberaceae). Compound 3, [α]$_D^{24}$ = −173 (c 0.2, CH$_3$OH), was isolated from the CH$_3$OH extract of the stem bark of U. pandens as a colorless oil. The HRESIMS (Figure S24, Supporting Information) indicated a molecular ion [M + H]+ peak at m/z 281.1025 (calcd 281.1025), which along with the NMR data (Table 3) established the molecular formula C$_{14}$H$_{16}$O$_6$ suggesting 7 DBEs. The IR spectrum showed absorptions at 3330 cm$^{-1}$ for hydroxy, 2970 and 2944 cm$^{-1}$ for aliphatic C–H, 1737 cm$^{-1}$ for ester carbonyl, and 1601 cm$^{-1}$ for C=C stretches. The UV spectrum displayed absorptions at 206 and 229 nm, corresponding to conjugated π-system. Unlike compounds 1 and 2, the NMR data of compound 3 (Table 3, Figures S17–S23 Supporting Information) exhibited signals for only one cyclohexenyl core with benzoyloxy and oxymethylene substituents. The NMR data of 3 consisted of signals corresponding to a tetra-oxygenated cyclohexene skeleton (δ$_{13}$C 5.72 (H-1)/132.8, 5.71 (H-2)/128.2, 4.02 (H-3)/71.2, 3.65 (H-5)/74.4, 4.18 (H-6)/71.7, C-4 (76.4)), a benzoyloxy unit (δ$_{13}$C 8.02 (H-2'/6'/5')/130.5, 7.60 (H-4')/132.8, 7.48 (H-3'/5')/129.6, C-1 (134.2), C-7' (169.4)), and an oxymethylene unit (δ$_{13}$C 3.82 (H-1'/6'/5')). Contrary to 1 and 2 and to most polyoxygenated cyclohexenyl derivatives, 3–19,21–35,43–45 compound 3 lacked an HMBC cross-
the CH3OH extract of the stem bark of *U. pandensis* as a white solid. The HRESIMS (Figure S32, Supporting Information) exhibited a molecular ion [M + H]+ peak at m/z 323.1191 (calcd 323.1131), corresponding to the molecular formula C17H22O3, which indicated eight DBEs, corresponding to a benzene ring, a cyclohexene ring, and two carbonyl groups (NMR data, Table 4). The UV spectrum showed an absorption maximum at 230 nm, indicating a conjugated π-system. The IR spectrum exhibited absorption bands for hydroxy (3318 cm⁻¹), aliphatic C–H (2943 and 2832 cm⁻¹), C=O (1678 cm⁻¹), and C–O (1274 cm⁻¹) stretches. The 1H NMR spectrum (Table 4 and Figure S25, Supporting Information) displayed signals typical of a polyoxygenated cyclohexene derivative. Thus, the 1H NMR spectrum consisted of signals corresponding to protons of a benzyloxy moiety (δH 8.00 (H-2′/6′), 7.50 (H-3′/5′), 7.63 (H-4′)), an olefinic moiety [δH 5.90 (H-1), 5.76 (H-2)], three oxymethines [δH 5.41 (H-3), 4.18 (H-6), 3.76 (H-5)] and an acetoxy moiety (δH 1.87, CH3-1′). The corresponding carbon signals were assigned based on HSQC experiments (Table 4, Figure S28, Supporting Information). The COSY and TOCSY correlations (Figures S27 and S30, Supporting Information) for signals at δH 3.76 (H-5), 4.18 (H-6), 5.90 (H-1), 5.76 (H-2), and 5.41 (H-3) indicated a continuous spin system, confirming the presence of a cyclohexene core skeleton. The H-2 proton further exhibited allylic coupling with H-6, which in turn coupled with OH-6. Contrary to the previously described polyoxygenated cyclohexene derivatives, the oxymethylene unit (δH 4.31, δC 67.2) and the acetoxy protons (δH 1.87) showed mutual HMBC cross-peaks (Figure S29, Supporting Information) to the C-1″ (δC 171.5) carbonyl carbon, which supported the presence of an acetoxy methane unit. The HMBC cross-peaks of H-3 (δH 5.41) to C-1 (δC 135.8), C-4 (δC 74.2), C-5 (δC 75.3), C-1′ (δC 67.2), and C-7″ (δC 165.9), together with those of H-1″ (δH 4.31) to C-3 (δC 71.5), C-4 (δC 74.2), C-5 (δC 75.3), and C-1″ (δC 171.5), corroborated the placement of the benzoyloxy and acetoxy methane units at C-3 and C-4, respectively. The relative configurations of H-5 and H-6 were established as being trans (JH5-H6 = 7.6 Hz) in solution. Moreover, the NOE correlations (Figure 4 and Figure S31, Supporting Information) of H-6 (δH 4.18) to OH-4 (δH 3.42) and OH-5 (δH 3.34) and that of H-5 (δH 3.76) to H-1″ (δH 4.31) facilitated assignment of the relative configuration of compound 4 at C-3, C-4, C-5, and C-6. Coincidently, the key NOEs of compounds 4 and 6 were similar (Figures 4, S31 and S47, Supporting Information). A single-crystal X-ray structure of compound 6 was obtained (Figure S5), which further supported the configurational assignments of both 4 and 6. Based on the above-mentioned spectroscopic and X-ray crystallographic evidence, this new compound, pandenselenol B (4), was characterized as benzoic acid 3β,5β,α,α-trihydroxy-4α-hydroxymethylcyclohex-1-enyl ester.

Compound 5, [α]D20 +81 (c 0.2, CH3OH), was isolated from the CH3OH extract of the root bark of *U. pandensis* as a white solid. It was assigned the molecular formula C17H22O3 based on HRESIMS ([M + H]+ m/z 275.1674, calculated 275.1647; Figure S40, Supporting Information) and NMR data (Table 5) analyses. Its UV spectrum exhibited absorption maxima at 206, 228, and 273 nm corresponding to a conjugated π-system. The IR spectrum exhibited absorption bands for hydroxy (3439 cm⁻¹), C–H (2968 and 2926 cm⁻¹), C=O (1718 cm⁻¹), C=C (1601 cm⁻¹), and C–O (1271 cm⁻¹) stretches. Its NMR spectroscopic data (Table 5, Figures S33 and S34, Supporting Information) were to a large extent comparable to those of the polyoxygenated cyclohexene derivatives described above. The 1H and 13C NMR spectroscopic data consisted of signals corresponding to...
Table 2. NMR Spectroscopic Data (500 MHz, CD3CN) for Dipandensin B (2)

| position | $\delta_C$ type | $\delta_H$ (J in Hz) | HMBC |
|----------|-----------------|----------------------|------|
| 1        | 608.8, C        | 3.43 br, s           | C-1, C-3, C-4, C-6, C-7, C-3’ |
| 2        | 617.7, CH       | 3.86 d (9.1)         | C-1, C-2, C-4, C-5, C-2”, C-3’, C-5’ |
| 3        | 386.8, CH       | 2.88 d (9.1)         | C-2, C-3, C-3’, C-5’ |
| 4        | 328.2, CH       | 2.91 dd (9.1, 5.7)   | C-2, C-3, C-3’, C-5’ |
| 5        | 77.8, CH        | 3.62 d (5.9, 5.7)    | C-2, C-3, C-5’ |
| CH3O-5   | 58.1, CH4       | 3.28 s               | C-1, C-2, C-4, C-5, C-7 |
| 6        | 70.3, CH        | 5.29 d (9.9)         | C-1, C-2, C-4, C-5, C-7, COO-6 |
| OAc-6    | 171.1, OC==O    | 2.07 s               | COO-6 |
| 7        | 63.8, CH2       | 4.42 d (11.7)        | C-1, C-2, C-6, C-7 |

Table 3. NMR Spectroscopic Data (500 MHz, CD3OD) for Pandenselenol A (3)

| position | $\delta_C$ type | $\delta_H$ (J in Hz) | HMBC |
|----------|-----------------|----------------------|------|
| 1        | 132.8, CH       | 5.72 dd (10.2, 1.3)  | C-2, C-3, C-5, C-6 |
| 2        | 128.2, CH       | 5.71 dd (10.2, 4.1)  | C-1, C-3, C-4, C-6 |
| 3        | 71.2, CH        | 4.02 d (4.1)         | C-1, C-2, C-4, C-5, C-1’ |
| 4        | 76.4, CH        | 3.65 d (7.7)         | C-1, C-3, C-4, C-6, C-1’ |
| 5        | 74.3, CH        | 3.65 d (7.7, 1.3)    | C-1, C-2, C-4, C-5 |
| 6        | 71.7, CH        | 4.18 dd (7.7, 1.3)   | C-1, C-2, C-4, C-5 |
| 7        | 66.2, CH2       | 3.82 ABq (11.5)      | C-3, C-4, C-5 |
| 2’       | 169.4, C==O     | 8.02 dd (7.8, 2.1)   | C-1’, C-3’/5’, C-4’ |
| 3’/5’    | 132.9, CH       | 7.48 dd (7.8, 7.7)   | C-1’, C-2’/6’, C-4’ |
| 4’       | 132.8, CH       | 7.60 tt (7.7, 2.1)   | C-2’/6’, C-3’/5’ |

Figure 2. Key NOEs for compound 2, indicated as red arrows.

Figure 3. Key NOEs for compound 3, shown as red arrows.

Information) showed signals for an olefinic proton at $\delta_{H/C} 5.84$ (H-2)/125.9, methylene protons at $\delta_{H/C} 2.00$ (H-3) /26.4, two sets of diastereotopic protons at $\delta_{H/C} 2.18 (H-4a/H-4b)/26.8$ and $\delta_{H/C} 1.98 (H-5a/H-5b)/23.6$, a methine proton at $\delta_{H/C} 1.58 (H-6)/24.0$, and two methyl group protons at $\delta_{H/C} 1.20 (H-3’)/27.1$ and 1.21 (H-4’)/27.6. The COSY and TOCSY (Figures S35 and S38, Supporting Information) coupling patterns of these signals suggested the presence of a cyclohexene core structure. Thus, COSY correlations were observed for H-2 and H-3, H-4b (W-coupling), and H-1’ (allylic coupling). The H-3 proton further coupled to H-4a/b, which in turn coupled to H-5a/b, while H-6 coupled to H-5a/b and to H-4b (W-coupling).

The cyclohexene core structure was confirmed by the 1J HMBC cross-peaks of H-2 (H-2) (H-3, H-4a, H-4b, C-1, C-2, C-3, C-5, C-6) and H-6 (H-6) to C-2 (H-1, H-2, C-5, C-6). The cyclohexene core structure was confirmed by the 1J HMBC cross-peaks of H-2 (H-2) (H-3, H-4a, H-4b, C-1, C-2, C-3, C-5, C-6) and H-6 (H-6) to C-2 (H-1, H-2, C-5, C-6) (Table S5 and Figure S37, Supporting Information). In contrast to compounds 1–4, structure 5 lacks oxygenation within the cyclohexene skeleton. Instead, its 1H NMR spectrum exhibited...
signals at δH 1.21 (3H, s, H-4′) and 1.20 (3H, s, H-3′), which were assigned to two methyl groups substituted at the carbonyl carbon C-2′ (δC 72.7). This indicated the presence of an oxygenated isopropyl unit, which is different from the cyclohexene derivatives so far reported in the literature.⁵⁻⁸ and was corroborated by the HMBC cross-peaks of H-6 (δH 1.58) to C-2′ (δC 72.7) and those of the methyl groups (δH 1.21 and 1.20) to C-6 (δC 45.0) and C-2′ (δC 72.7). The position of the benzyloxyxymethylene unit was established at C-1 (δC 130.5), based on the cross-peaks of the oxymethylene protons H-1′ (δH 4.72) to C-6 (δC 45.0), C-1 (δC 130.5), and C-2 (δC 125.9). This was supported further by the HMBC cross-peaks of H-2 (δH 5.84) and H-6 (δH 1.58) to C-1′ (δC 68.9). The HMBC correlations of the oxymethylene protons (δH 4.72) and those of H-2′/6′ (δH 8.05) to C-7′ (δC 166.6) were consistent with the attachment of the methylene unit to the benzoyl unit. Based on the above spectroscopic evidence, the new compound pandensenol C (5) was characterized as benzoic acid 1-(2′-hydroxy-2′-methyl)ethylcyclohex-1-enyl methyl ester.

As similar secondary metabolites were reported to exhibit antibacterial and cytotoxic activities,¹²,³¹,₃² the isolated compounds were evaluated for their activity against the Gram-positive bacteria Bacillus subtilis and Staphylococcus epidermidis and the Gram-negative bacteria Enterococcus raffinosus, Escherichia coli, Paraburkholderia caledonica, Pectobacterium carotovorum, and Pseudomonas putida as well as for cytotoxicity against MCF-7 human breast cancer cells. The mixture of uvaretin and isouvaretin (20 and 21) obtained exhibited activity against B. subtilis (EC₅₀ 8.7 μM) and S. epidermidis (IC₅₀ 7.9 μM), but showed only moderate activity against E. coli (EC₅₀ 1130.8 μM) and P. carotovorum (EC₅₀ 20)

### Table 4. NMR Spectroscopic Data (600 MHz, CD₃CN) for Pandensenol B (4)

| Position | δC, type | δH | (J in Hz) | HMBC |
|----------|----------|----|-----------|------|
| 1        | 135.8, CH| 5.90 | dd (10.0, 2.1) | C-2, C-3, C-5, C-6 |
| 2        | 123.3, CH| 5.76 | ddd (10.0, 4.4, 2.2) | C-1, C-3, C-4, C-6 |
| 3        | 71.5, CH  | 5.41 | d (4.4) | C-1, C-2, C-4, C-5, C-7' |
| 4        | 75.3, C   |    |    | C-1, C-2, C-4, C-5, C-7' |
| 5        | 74.2, CH  | 3.76 | dd (7.6, 5.7) | C-1, C-3, C-4, C-5, C-6, C-7' |
| 6        | 70.7, CH  | 4.18 | dddd (7.6, 6.4, 2.2, 2.1) | C-1, C-2, C-4, C-5 |
| 1′       | 67.2, CH₂ | 4.31 | ABq (11.7) | C-3, C-4, C-5, C-1 |
| 1''      | 130.8, C |    |    | C-1, C-2, C-4, C-5, C-7' |
| 2''/6''  | 130.3, CH | 8.00 | dd (8.4, 1.4) | C-1′, C-3′/5′, C-4′ |
| 3''/5''  | 129.6, CH | 7.50 | dd (8.4, 7.6) | C-1′, C-2′/6′, C-4′ |
| 4''      | 134.3, CH | 7.63 | tt (7.6, 1.4) | C-2′/6′, C-3′/5′ |
| 5''      | 165.9, OC=O | 4.18 | dddd (7.6, 6.4, 2.2, 2.1) | C-1′, C-2′/6′, C-4′ |
| 5 OAc′   | 171.5, OC=O | 2.20 | d (5.7) | C-1′, C-3′/5′, C-4′ |
| OH-4     | 20.8, CH₃ | 1.87 | s | COO-1' |
| OH-5     |        | 3.42 | s | C-3′, C-4′, C-5′, C-1′ |
| OH-6     |        | 3.34 | d (5.7) | C-4′, C-5′, C-6 |

### Table 5. NMR Spectroscopic Data (500 MHz, CDCl₃) for Pandensenol C (5)

| Position | δC, type | δH | (J in Hz) | HMBC |
|----------|----------|----|-----------|------|
| 1        | 130.5, C |    |    | C-1, C-3, C-4, C-6, C-1′ |
| 2        | 125.9, CH | 5.84 | m | C-1, C-3, C-4, C-6, C-1′ |
| 3        | 26.4, CH₂ | 2.20 | m | C-1, C-2, C-4, C-5 |
| 4        | 26.8, CH₂ | 1.90 | m | C-3, C-5, C-6 |
| 5        | 23.6, CH₂ | 1.98 | ddd (12.5, 5.3, 2.3) | C-1, C-3, C-4, C-6, C-2′ |
| 6        | 450.0, CH | 1.58 | dddd (13.9, 11.5, 4.9, 2.5) | C-1, C-3, C-4, C-5, C-2′ |
| 7        | 80.8, CH₂ | 4.72 | m | C-1′, C-2′, C-4′, C-7'' |
| 1''      | 72.7, C –O | 2.18 | m | C-1′, C-2′, C-4′, C-7'' |
| 3''      | 27.1, CH₂ | 1.20 | s | C-2′, C-4′ |
| 4''      | 27.6, CH₂ | 1.21 | s | C-2′, C-3′ |
| 5''      | 133.1, C |    |    | C-1′, C-2′, C-4′, C-7'' |
| 6''/5''  | 129.7, CH | 8.05 | dd (8.2, 1.4) | C-3′/5′, C-4′, C-7'' |
| 3''/5''  | 128.5, CH | 7.44 | dd (8.2, 7.4) | C-2′/6′, C-4′, C-7'' |
| 4''      | 133.0, CH | 7.56 | tt (7.4, 1.4) | C-2′/6′, C-3′/5′ |
| 7''      | 166.6, C=O |    |    | C-1′, C-2′, C-4′, C-7'' |

Figure 4. Key NOEs of compounds 4 and 6, indicated as red arrows.
263.1 μM). Compound 13 also showed modest activity against B. subtilis, EC<sub>50</sub> 1154.1 μM, whereas compound 12 gave strong inhibition with an EC<sub>50</sub> of 9.8 μM (Figure S148, Supporting Information) and was comparable to the known ampicillin antibiotic clinical reference value (EC<sub>50</sub> 17.9 μM, Figure S151, Supporting Information). All other compounds showed no or low activity against the tested bacterial strains (MIC > 725 μM) and no relevant cytotoxicity (EC<sub>50</sub> > 10 μM) (Figure S150, Supporting Information).

In conclusion, 21 natural products including the five new cyclolohexene derivatives 1–5 were isolated and characterized from separate CH<sub>3</sub>OH extracts of the stem and root barks of <i>U. pandensis</i>. This is the first report of all but compounds 12<sup>36</sup> and 13<sup>36</sup> from this plant. Poly-oxygenated cyclolohexenes and C-benzylated chalcones have restricted occurrence in plants. They are known to be produced by the members of the Uvariae tribe of the family Annonaceae. Hence, their occurrence in <i>U. pandensis</i> is of chemotaxonomic importance, confirming the placement of this plant in the Uvariae taxon. Some of the isolated compounds showed activity against Gram-positive bacteria, along with low to moderate cytotoxicity.

**EXPERIMENTAL SECTION**

**General Experimental Procedures.** Optical rotations were determined using a 341ILC OROT polarimeter (589 nm, 20 °C), whereas UV measurements were done using a 264 UV–vis spectrophotometer. A MIR 450FT-IR spectrometer was used to record the IR spectra. NMR spectra were acquired on either a Bruker Avance III HD 600/500 or 400 MHz spectrometer and were analyzed with the MestReNova (v 10.0.0) software. Structural assignments were based on 1H NMR, 13C NMR, COSY, TOCSY, NOESY, HSQC, and HMBC spectra. LC-MS (ESI) spectra were acquired with a PerkinElmer PE SCIEX API 150 EX instrument equipped with a Turbolon spray ion source and a Gemini 5 mm RP-C<sub>18</sub> 110 Å column, using a gradient of H<sub>2</sub>O–CH<sub>3</sub>CN (80:20 to 20:80) in the presence of 0.2% HCO<sub>2</sub>H and a separation time of 8 min. HRESIMS were obtained with a Q-TOF-LC/MS spectrometer with a lock mass ESI source (Stenhagen Analysis Lab AB, Gothenburg, Sweden), using a 2.1 × 30 mm 1.7 μm RP-C<sub>18</sub> column and an elution gradient of H<sub>2</sub>O–CH<sub>3</sub>CN (5:95 to 95:5, with 0.2% HCO<sub>2</sub>H). Analytical TLC was performed on aluminum plates precoated with silica gel 60 F254 (Merck). After development with an appropriate solvent system, the plates were evaluated under UV light (254 and 366 nm) and then sprayed with 4-anisaldehyde light (254 and 366 nm) and then sprayed with 4-anisaldehyde.

**Plant Material.** The root (230.0 g) and stem (983.7 g) barks of <i>U. pandensis</i> were collected separately from the Mkugwulo and Mtakayo clans’ sacred forest graveyards in Fukayosi Village, Bagamoyo District, in Pwani Region, at GPS location 6°24’51.918” S 38°40’19.308” E altitude 78.80 m. The taxonomic identification of the plant species was performed by Mr. F. M. Mbagi in the field and confirmed at the Herbarium, Botany Department of the University of Dar es Salaam, where a voucher specimen (EMM-3807) was deposited.

**Extraction and Isolation.** The stem and root barks of <i>U. pandensis</i> were air-dried for 2 weeks and then powdered to obtain 230.0 and 983.7 g samples, respectively. The ground materials were then soaked in CH<sub>3</sub>OH for 48 h twice for each of the plant parts. The filtrates were concentrated in vacuo on a rotary evaporator at 40 °C to obtain 45 g of root bark and 23.0 g of stem bark crude extracts.

Gravity column chromatography of the root bark crude extract (45 g) was performed by adsorbing the extract on silica gel followed by gradient elution with solvent systems ranging from 5% EtOAc–isoheaxane to 10% EtOAc–CH<sub>3</sub>OH. Altogether 215 fractions of ca. 250 mL each were collected, then combined to obtain 33 fractions based on TLC analysis. Prior to combining, fraction 165 obtained with 50% EtOAc–isoheaxane elution precipitated and was further purified using isoheaxane to give zeylenol (7, 9.2 mg). Fraction 79, obtained with 5% EtOAc–isoheaxane, precipitated from CH<sub>3</sub>OH to give 17.6 mg of a mixture of stigmasterol (18) and β-sitosterol (19). Fraction 20 (117–131) obtained with 50% EtOAc–isoheaxane was subjected to passage over a Sephadex column (1:1 CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub>) to afford 18 fractions, from which subsequent subfractions 1 (5–7), 3 (9–12), and 4 (15–16) gave cherrevenol 1 (10, 12.4 mg), pandensol C (5, 6.7 mg), and (8α,9β)-dihydroxy)-3-farnesylindole (12, 12.1 mg), respectively. Fraction 21 (132–133) obtained with 50% ethyl acetate–isoheaxane precipitated from EtOAc–isoheaxane and crystallized on standing in EtOAc to give 6-methoxyzeylenol (6, 18.5 mg). The soluble portion of fraction 21 (132–133) was subjected to preparative HPLC utilizing a H<sub>2</sub>O–CH<sub>3</sub>OH eluent system, affording 3-methoxybenzylbenzoate (11, 5.2 mg) and (6′-dihydro-8α,9β-dihydroxy)-3-farnesylindole (13, 8.7 mg), at 9.45 and 12.46 min retention times, respectively. Fraction 25 (155–167) obtained with 50% EtOAc–isoheaxane was subjected to Sephadex column separation utilizing CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub> (1:1) as eluent system to afford seven fractions (ca. 2 mL each). Subfraction 2 contained pandensol A (3, 9.2 mg), while the rest of the subfractions contained complex mixtures of inseparable compounds. Fraction 25 (142–145) was subjected to passage over a Sephadex column eluting with CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub> (1:1) to afford 12 subfractions of ca. 2 mL each. Subfractions 5–8 were then subjected to HPLC utilizing a H<sub>2</sub>O–CH<sub>3</sub>OH eluent system to afford cleistenediol C (5.5 mg, 8) and cleistenediol F (3.6 mg, 9) with retention times of 9.88 and 13.43 min, respectively.

The stem bark crude extract (23.0 g) was adsorbed on silica gel and subjected to gravity column chromatography employing gradient elution ranging from 5% EtOAc–isoheaxane to 10% CH<sub>3</sub>OH–EtOAc, to afford 356 fractions (ca. 200 mL each). Based on TLC analysis, the fractions were combined to obtain 69 fractions, of which fraction 44 (206–208), eluted with 30–50% EtOAc–isoheaxane, was purified further using reversed-phase HPLC, which afforded a mixture (10.3 mg) of uvarretin (20) and isouvaretin (21) at a retention time of 13.53 min. Fraction 54 (274–278), obtained with 50–70% EtOAc–isoheaxane, precipitated in CH<sub>3</sub>OH to give benzoic acid 2,3-diacetoxy-1,6-dihydroxycyclohex-4-enyl methyl ester (15, 6.4 mg). Fraction 59 (291–294) precipitated in EtOAc to furnish 11.5 mg of lupeol (16). Fraction 47 (246–253), obtained with 50–70% EtOAc–isoheaxane, was subjected to gel filtration using a Sephadex column (1:1 CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub>) to give 30 subfractions that on TLC analysis were combined to obtain a further nine subfractions. Subfraction 4 (19–20) was subjected to reversed-phase HPLC for further purification, from which at a retention time of 14.29 min 2-methylene-2,6-diaceitate (14, 5.2 mg) was collected. Combined fraction 66 (319–327), obtained with 50–70% EtOAc–isoheaxane, was subjected to Sephadex column (1:1 CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub>) purification and then reversed-phase HPLC utilizing CH<sub>3</sub>OH–H<sub>2</sub>O to give pandensol A (3, 3.6 mg) at a retention time of 11.30 min. Fraction 69 (351–356), obtained with 50–70% EtOAc–isoheaxane, was subjected to separation over a Sephadex column (1:1 CH<sub>3</sub>OH–CH<sub>2</sub>Cl<sub>2</sub>) whereby 35 subfractions of ca. 1 mL each were collected, which were then combined to obtain 13 subfractions upon TLC analysis. Subfraction 4 precipitated in CH<sub>3</sub>OH to give betulin (17, 3.4 mg). Subfraction 12 was subjected to reversed-phase HPLC, affording pandensol B (4, 4.2 mg), dipandensin A (1, 4.2 mg), and dipandensin B (2, 3.4 mg) at retention times of 9.48, 11.32, and 14.56 min, respectively. The remaining subfractions resulted into either reisolation of the compounds or inseparable mixtures.
Dipandensin A (1). White solid; [α]D ± 33 (c 0.2, CH3OH); UV (CH3OH) λmax (log ε) 273 (3.40), 230 (2.37), 205 (3.24) nm; IR νmax 3520, 2973, 2940, 2915, 2824, 2325, 2120, 1740, 1722, 1635, 1471, 1453, 1369, 1315, 1270, 1230, 1216 cm−1; 1H and 13C NMR data, see Table 1; HR-EI-MS m/z 622.2652 [M + NH4]⁺ (calcd for C34H37O11, 622.2442).

Dipandensin B (2). White solid; [α]D + 40 (c 0.2, CH3OH); UV (CH3OH) λmax (log ε) 274 (3.43), 230 (4.27), 205 (4.24) nm; IR νmax 3508, 2949, 2947, 2833, 2262, 1386, 1199, 1026, 833 cm−1; 1H and 13C NMR data, see Table 2; HR-EI-MS m/z 621.2297 [M + H]⁺ (calcd for C34H37O11, 621.2336).

Pandenseno A (3). Colorless oil; [α]D ± 173 (c 0.2, CH2Cl2); UV (CH3OH) λmax (log ε) 229 (2.33), 206 (3.44) nm; [α]D + 173 (c 0.2, CH2Cl2); IR νmax 3330, 2970, 2944, 1737, 1634, 1601, 1561, 1413, 1316, 1229, 1171, 1032 cm−1; 1H and 13C NMR data, see Table 3; HR-EI-MS m/z 281.0252 [M + H]⁺ (calcd for C16H19O7, 281.0125).

Pandenseno B (4). White solid; [α]D + 85 (c 0.3, CH3Cl); UV (CH3OH) λmax (log ε) 230 (2.48) nm; IR νmax 3318, 2943, 2832, 1678, 1451, 1402, 1274, 1112, 1023 cm−1; 1H and 13C NMR data, see Table 4; HR-EI-MS m/z 323.1191 [M + H]⁺ (calcd for C16H19O7, 323.1131).

Pandenseno C (5). White solid; [α]D + 82 (c 0.2, CH3OH); UV (CH3OH) λmax (log ε) 273 (2.04), 228 (3.01), 206 (3.37) nm; IR νmax 5439, 2906, 2926, 1718, 1601, 1584, 1451, 1367, 1314, 1271, 1176, 1106, 1112, 1026, 916, 809, 677, 711 cm−1; 1H and 13C NMR data, see Table 5; HR-EI-MS m/z 275.1674 [M + H]⁺ (calcd for C16H18O7, 275.1647).

X-ray Diffraction Analysis of 6-Methoxyxenyleinol (6). The solid state structure of 6 was determined from single crystals of 6, obtained by crystallization from EtOAc. Data were collected on a Bruker D8 APEX-II equipped with a CCD camera using Mo Kα radiation (λ = 0.71073 Å). Crystals were mounted on a fiber loop and fixed using Fomblin oil. Data reduction was performed with SAINT, and absorption corrections for the area detector were performed using SADABS. The structure was solved in the orthorhombic space group P2₁,2₁,2₁ by direct methods and refined by least-squares methods on F² using the SHELX and the OLEX2 software suits. The data were collected at 150(2) K. Nonhydrogen atoms were refined anisotropically. Hydrogen atoms were constrained in geometrical positions relative to their parent atoms. A Flack parameter of 0.2(8) precluded determination of the absolute structure based on anomalous dispersion.

Antibacterial Assays. The antibacterial activity of the isolated compounds was determined against two Gram-positive bacteria, Bacillus subtilis (NBRC/ATCC #114170) and Staphylococcus epidermidis (ATCC #35984) and five Gram-negative bacteria, Escherichia coli MG1655 (CGSC #6300), Paraburkholderia caledonica (NBRC/ATCC #100650), Pseudomonas putida (NBRC/ATCC #101488), Pantoea ananatis (NBRC/ATCC #13280), and Enterococcus raffinosus (NBRC/ATCC #100492). The bacteria were cultured as previously described by Mueller and Hinton, and Doyle. Initially, the compounds were dissolved at 10 mg/mL in 100% DMSO, then further diluted 30X in H2O and stored at −20 °C. For in vitro determination of antibacterial activity, a culture of bacterial cells was grown to OD 600nm = 0.5. The culture was diluted 10X with prewarmed medium, and the compounds to be tested were added to the culture medium for a final concentration of 30 µg/mL, each at 100 µL in a 96-well microtiter plate, then incubated at 37 °C without agitation for 18 h. To measure cell viability, the resazurin-based assay was used, as described previously. To each well was added 12 µL of 10X alamarBlue solution (resazurin solution, ThermoFisher), and the plate incubated at 37 °C for 1 h. Next, the fluorescence was measured using a POLARStar Omega microplate-reader from BMG Labtech with the excitation filter set to 544 nm and the emission filter at 590 nm. Cells exposed to an equivalent concentration of DMSO were used as a negative control. Bleed-through of fluorescence from resorufin between wells in the microtiter plate fluorescence reader was measured and found to be <1% between adjacent wells. To check for quenching of fluorescence by any of the investigated compounds, grown bacterial cultures were mixed after 1 h of incubation with resazurin and the compound of interest at the highest concentration to be assayed, and the measured fluorescence was compared with samples without compound added. All tests of compound activity were performed in three independent replicates. Those compounds where a reduction of fluorescence by at least 50% relative to the solvent control was observed in any of the bacterial species tested were followed up by additional tests for more accurate determination of the degree of antibacterial activity in terms of minimum inhibitory concentration (MIC). EC₅₀ values, from three independent replicate experiments, using 2-fold dilution intervals were also calculated.

Cytotoxicity Assay. The cytotoxicity levels of the isolated compounds were evaluated against human MCF-7 cells grown in Dulbecco’s modified Eagle medium supplemented with 10% fetal calf serum and kept in exponential growth as previously reported. Before the assay, cells were reseeded into 96-well microtiter plates at a density allowing continued exponential growth and allowed to settle for 24 h. The isolated compounds were added from a stock solution in DMSO, for a final concentration of 0.3% v/v of the solvent in the culture medium. After 24 h of incubation in the presence of the compound, cell viability was assayed using PrestoBlue Cell Viability Reagent (ThermoFisher) according to the manufacturer’s instructions. A Polar Star Omega plate reader (BMG LabTech) was used to measure resorufin fluorescence at 544 nm excitation/590 nm emissions. Survival was expressed as percentage of the solvent-only control. EC₅₀ values for each compound were calculated, from three independent replicate experiments, using 2-fold dilution intervals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.1c00811.

NMR, MS, ORD, UV, and IR data for the isolated compounds (PDF)

X-ray crystallographic data of compound 6 ( CIF)

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Notes

The authors declare no competing financial interest.

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