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Uvarialuridols A-C, three new polyoxygenated cyclohexenes from the twig and leaf extracts of *Uvaria lurida*

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ABSTRACT

The first phytochemical investigation of *Uvaria lurida* resulted in the isolation and identification of three new polyoxygenated cyclohexenes, (+)-(1*R*,2*S*,3*R*,6*S*)-uvarialuridols A-C (**1–3**), together with 10 known compounds (**4–13**). All new structures were elucidated by spectroscopic methods and HRESIMS. The absolute configurations of compounds **1** and **5** were confirmed by X-ray diffraction analysis using Cu Kα radiation. The absolute configurations of compounds **2–4** were identified from comparisons of their specific rotations and ECD spectra with those of known compounds. Compound **11** showed α-glucosidase inhibitory activity with an IC_{50} value of 30 μM which was better than the standard control, acarbose (74 μM) whereas, compound **10** exhibited nitric oxide (NO) production inhibitory activity with an IC_{50} value of 37 μM.

1. Introduction

The *Uvaria* genus belongs to the Annonaceae family and is widely distributed throughout tropical countries especially in South and Southeast Asia, Australia, and Papua New Guinea [1–3]. Its fruits are aggregates which are colored deep orange, yellow or a rich red and, for some species, are edible [4]. Many species of *Uvaria* have been used as traditional medicines. For example, the decoction of the roots of *U. cherrevensis* has been used for the treatment of urinary disorders, and the blood system and as a kidney tonic [5–8] whereas, the roots of *U. chamae* have been used as an antidiabetic and to treat infections [9] The wood and roots of *U. rufa* have been used to treat fever [10] The root and leaves of *U. narum* have been used to treat fevers, jaundice, rheumatic affections, and skin diseases [2,11–13]. Previous phytochemical investigations of the *Uvaria* genus resulted in the identification of cyclohexenes, [5,6,8,14–17] and flavonoids [6,10,14–16] as major phytochemical components with some minor compounds also isolated, including a naphthalene derivative [5], alkaloids [15], chalcones [6,9,16], benzoate esters [13,16], and a β-triketone derivative [18]. These isolated compounds displayed a wide range of biological activities, including antimalarial [5,9,16], cytotoxic [7,8,15,17], antifungal [13], α-glucosidase inhibitory [14], antitubercular [17], antitrypanosomal and antileishmanial activities [18]. *Uvaria lurida* (synonym: *Uvaria concava* Teijsm. & Binn.) [1] is a large woody scandent shrub which is distributed in the East of Thailand. To the best of our knowledge no phytochemical investigations or biological evaluations of this plant, as well as traditional medicine uses, have been reported. We report herein the first isolation and structure elucidation of three new polyoxygenated cyclohexenes (**1–3**) together with 10 known compounds (**4–13**) from the twig and leaf extracts of *U. lurida*, which were collected from Mae Fah Luang University, Chiang Rai Province, Thailand. Some isolated compounds were tested for their α-glucosidase inhibitory and nitric oxide (NO) production inhibitory activities.

2. Experimental

2.1. General experimental procedures

The general information on instruments and chromatographic materials were the same as in previous reports [19–23] (General Experimental Procedures, Supplementary material).

2.2. Plant material

The twigs and leaves of *U. lurida* were collected in June 2017 at Health Park, Mae Fah Luang University, Chiang Rai Province, Thailand.

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The voucher specimen (MFU-NPR0164) was deposited at the Natural Products Research Laboratory of Mae Fah Luang University.

2.3. Extraction and isolation

The twigs of *U. lurida* (564.4 g) were chopped, air-dried and extracted with EtOAc (10*L*) at room temperature and concentrated under reduced pressure to provide the EtOAc extract (36 g). The EtOAc extract was separated by quick column chromatography (QCC) over silica gel (100% hexanes to 100% EtOAc) to give eight fractions (Fr·U1- Fr·U8). Fr·U3 (86.8 mg) was fractionated by RP C_{18} HPLC (2:8 MeOH: H_2O) to provide five fractions (Fr.U3A- Fr.U3E). Compound **10** (4.1 mg, t_R = 53.9 min) was obtained from Fr.U3C (27.3 mg) by RP C_{18} HPLC (1.2:0.8 CH_3CN in H_2O, 2.0 mL/min) while compound **11** (4.1 mg) was isolated from Fr·U6 (3.65 g) by Sephadex LH-20 (100% MeOH) followed by PTLC (1:9 EtOAc: CH_2Cl_2).

Chopped and air-dried of *U. lurida* leaves (405.1 g) were extracted with EtOAc (10 L) at room temperature and concentrated under reduced pressure to yield the EtOAc extract (90 g). The EtOAc extract was subjected to quick column chromatography (QCC) over silica gel (100% hexanes to 100% EtOAc) to give 10 fractions (Fr.L1-Fr.L10). Fr.L2 (2 g) was separated by CC (2:8 EtOAc: hexanes) to give compound **12** (15.1 mg). Fr.L4 (589.7 mg) was further separated by Sephadex LH-20 (100% MeOH) to provide six fractions (Fr.L4A- Fr.L4F). Fr.L4D (241.5 mg) was further purified by CC (3:7 CH_2Cl_2: hexanes) to give a mixture of compounds **1** and **4** (100.7 mg). Further purification of these two compounds by RP C_{18} HPLC (1.2:0.8 CH_3CN in H_2O, 2.0 mL/min) gave compounds **1** (67.5 mg, t_R = 19.1 min) and **4** (30.5 mg, t_R = 21.8 min). Fr.L9 (1.7 mg) was purified by RP C_{18} HPLC (9:1 MeOH: H_2O) to give 16 fractions (HPLC L9A- HPLC L9P). Compounds **7** (1.8 mg) and **8** (2.1 mg) were isolated by CC (100% CH_2Cl_2) from Fr.L9M (732.6 g). Fr.L9K (80.6 mg) was separated by RP C_{18} HPLC (8:2 MeOH: H_2O) to give compound **13** (4.6 mg) and Fr.L9K1 (70.6 mg). Fr.L9K1 (70.6 mg) was further separated by CC (1:9 EtOAc: CH_2Cl_2) yielding compounds **2** (2.5 mg) and **3** (3.5 mg). Fr.L7 (380.4 mg) was separated by Sephadex LH-20 (100% MeOH) to give seven (Fr.L7A-Fr.L7G). Fr.L7D (94.5 mg) was further purified by RP C_{18} HPLC (9:1 MeOH: H_2O) to give six fractions (Fr.L7D1-Fr.L7D6). Fr.L7D2 (25.2 mg) was further separated by CC (1:9 EtOAc: CH_2Cl_2) to give compound **9** (15.7 mg). Compounds **5** (20.5 mg) and **6** (3.5 mg) were obtained from Fr.L7D3 (58.7 mg) by CC (2:8 EtOAc: CH_2Cl_2).

(+)-(1*R*,2*S*,3*R*,6*S*)-*Uvarialuridol A* ***(1):*** Colorless crystals; $[\alpha]_D^{23}$ + 33 (*c* 1, $CHCl_3$), mp 130–133 °C,UV (MeOH) λ_{max} (log ε) 275 (0.55), 231 (1.73), and 201 (1.75) nm, IR (neat) ν_{max} 3380, 1729, 1728, 1366, 1231, 717 cm^{-1}; ECD (5.31 × 10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$) 220 (+3.39), 244 (−3.05) nm. ^1H and ^{13}C NMR, see Table 1; HRESITOFMS *m/z* 401.1214 $[M + Na]^+$ (calcd for $C_{19}H_{22}O_8Na$, 401.1212).

(+)-(1*R*,2*S*,3*R*,6*S*)-*Uvarialuridol B* ***(2):*** Colorless viscous oil; $[\alpha]_D^{23}$ + 26 (*c* 1, MeOH), UV (MeOH) λ_{max} (log ε) 276 (0.46), 233 (1.59), and 201 (1.73) nm, IR (neat) ν_{max} 3481, 2932, 1718, 1269, 1249, 1097, and 711 cm^{-1}; ECD (6.85 × 10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$) 203 (+4.36), 236 (+4.76), 277 (−3.22) nm. ^1H and ^{13}C NMR, see Table 1; HRESITOFMS *m/z* 463.1370 $[M + Na]^+$ (calcd for $C_{24}H_{24}O_8Na$, 463.1369).

(+)-(1*R*,2*S*,3*R*,6*S*)-*Uvarialuridol C* ***(3):*** Colorless viscous oil; $[\alpha]_D^{23}$ + 38 (*c* 1, $CHCl_3$), UV (MeOH) λ_{max} (log ε) 274 (0.57), 231 (1.63), and 203 (1.62) nm, IR (neat) ν_{max} 3428, 2933, 1724, 1723, 1282, 1270, 1097, and 711 cm^{-1}; ECD (7.59 × 10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$) 209 (+3.32), 227 (+4.63), 252 (−4.48) nm. ^1H and ^{13}C NMR, see Table 1; HRESITOFMS *m/z* 359.1110 $[M + Na]^+$ (calcd for $C_{17}H_{20}O_7Na$, 359.1107).

2.4. Single crystal X-ray diffraction analysis of compounds *1* and *5*

Single colorless irregular-shaped crystals of **1** (0.20 × 0.18 × 0.09 mm^3) and **5** (0.35 × 0.23 × 0.16 mm^3) were mounted on a mylar loop in oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at a steady T = 90(2) K during data collection. The structure was solved with the XT [24,25] structure solution program using the Intrinsic Phasing solution method and by using Olex2 [26] as the graphical interface. The model was refined with version 2018/3 of XL [24,25] using Least Squares minimization.

X-ray crystallographic data for (+)-(1R,2S,3R,6S)-uvarialuridol A: $C_{19}H_{22}O_8$, M_r = 378.36, tetragonal, $P4_1$ (No. 76), a = 9.8944(2) Å, b = 9.8944(2) Å, c = 37.2068(8) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 3642.51(17) $Å^3$, T = 90(2) K, Z = 8, Z' = 2, μ(CuKα) = 0.912, 6417 reflections measured, 6358 unique (R_{int} = 0.064) which were used in all calculations. The final wR_2 was 0.0668 (all data) and R_1 was 0.0271 ($I > 2(I)$). The Flack parameter was refined to −0.03(9). The crystallographic data of (+)-**1** have been deposited in the Cambridge Crystallographic Data Centre as CCDC 1941051 and data can be obtained free of charge from the via http://www.ccdc.cam.ac.uk/data_request/cif.

X-ray crystallographic data for (-)-(1S,2S,3R)-zeylenone: $C_{21}H_{18}O_7$, M_r = 382.35, orthorhombic, $P2_12_12_1$ (No. 19), a = 7.3739(2) Å, b = 12.5767(3) Å, c = 19.8326(5) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 1839.26(8) $Å^3$, T = 90(2) K, Z = 4, Z' = 1, μ(CuKα) = 0.876, 16,730 reflections measured, 3366 unique (R_{int} = 0.0349) which were used in all calculations. The final wR_2 was 0.0669 (all data) and R_1 was 0.0260 ($I > 2(I)$). The Flack parameter was refined to −0.01(7). The crystallographic data of (-)-**5** have been deposited in the Cambridge Crystallographic Data Centre as CCDC 1941052 and data can be obtained free of charge from the via http://www.ccdc.cam.ac.uk/data_request/cif.

Table 1
^1H (600 MHz) and ^{13}C (150 MHz) NMR data of compounds **1–3** in $CDCl_3$.

Position	1		2		3	
	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)	δ_C	δ_H (mult., *J* in Hz)	δ_C
1		73.9		74.8		58.8
2	5.52, d (6.6)	71.5	5.62, d (6.5)	72.0	5.62, d (8.5)	71.8
3	4.15, d (6.6)	76.5	4.16, d (6.5)	76.9	4.12, d (8.5)	77.8
4	6.04, dd (10.3, 2.5)	130.2	6.06, dd (10.2, 2.3)	130.8	6.05, m	134.8
5	5.88, ddd (10.3, 3.9, 2.5)	124.9	5.96, ddd (10.2, 3.9, 2.3)	125.4	6.05, m	123.2
6	5.49, d (3.9)	70.8	5.71, d (3.9)	71.7	3.57, m	54.7
7	4.64, d (11.8); 4.47, d (11.8)	65.9	4.74, d (11.8); 4.49, d (11.8)	66.6	4.61, d (12.1) 4.43, d (12.1)	62.2
OH-1	3.04, s		3.04, s		–	
COMe-2	2.22, s	20.9	2.21, s	21.4	2.21, s	20.9
COMe-2		170.5		170.9		170.2
COMe-6	2.13, s	20.9				
CO-6		170.0		165.8		
CO-7		166.7		167.4		165.9
1′		129.3		130.1		129.4
2′/6′	8.07, m	129.7	7.99, m	129.5	8.07, m	129.8
3′/5′	7.50, m	133.4	7.43, m	128.9	7.49, m	128.5
4′	7.63, m	128.5	7.57, m	133.7	7.6, m	133.9
1″				130.2		
2″/6″			8.05, m	129.7		
3″/5″			7.43, m	128.8		
4″			7.57, m	133.9		
OMe-3	3.45, s	56.7	3.43, s	57.4	3.41, s	57.0

2.5. α-glucosidase inhibitory assay

A colorimetric α-glucosidase assay was performed using previously described method [14,23]. Acarbose was used as a positive control with an IC_{50} value at 73.74 μM.

2.6. Nitric oxide production inhibitory assay and cell viability

The procedure for the nitric oxide (NO) production inhibitory assay used the Griess reagent reaction, which is slightly modified from previous studies [27]. In brief, RAW 264.7 cells were added in 96-well plate with 1 × 105 cells/well and incubated overnight at 37 °C and 5% CO_2. After that, cells were treated with various concentrations of sample or vehicle (DMSO) for 2 h, followed by LPS 10 μg/mL. Then 18 h incubation, NO production in the culture medium was determined using the Griess reagent for 10 min and the absorbance was measured at 550 nm. Cell viability studies were carried out by the MTT assay, as previously described [27]. Indomethacin was used as a positive control with an IC_{50} value of 150 μM.

3. Results and discussion

The EtOAc extracts of the twigs and leaves of *U. lurida* were individually separated using various chromatographic techniques to provide three new polyoxygenated cyclohexenes (**1–3**) together with the ten known compounds; (+)-(1*R*,2*S*,3*R*,6*S*)-curcuminol F (**4**) [28], (−)-(1*S*,2*S*,3*R*)-zeylenone (**5**) [29], pinocembrin (**6**) [30], auriculatin (**7**) [31], auriculasin (**8**) [32], scandenone (**9**) [33], uvamalol F (**10**) [34], (2*E*)-3-(3,4-dihydroxyphenyl)-*N*-[2-(4-methoxyphenyl)ethyl]-2-propenamide (**11**) [35], goniopedalin (**12**) [36,37], and anabellamide (**13**) [38] identified by comparison of their spectroscopic and physical data with published values.

The structure of compound **1** was a polyoxygenated cyclohexene, which was confirmed by X-ray diffraction data analysis (Fig. 4, CCDC 1941051). Its molecular formula, $C_{19}H_{22}O_8$, was supported from the HRESITOFMS data ($[M + Na]^+$ *m/z* 401.1214, calcd 401.1212). The NMR spectroscopic data of **1** (Table 1), which were in agreement with the X-ray structure, displayed resonances for two olefinic protons [δ_H 6.04 (dd, *J* = 10.3, 2.5 Hz, H-4)/δ_C 130.2 and 5.88 (ddd, *J* = 10.3, 3.9, 2.5 Hz, H-5)/δ_C 124.9], three oxymethine protons [δ_H 5.52 (d, *J* = 6.6 Hz, H-2)/δ_C 71.5, 4.15 (d, *J* = 6.6 Hz, H-3)/δ_C 76.5 and 5.49 (d, *J* = 3.9 Hz, H-6)/δ_C 70.8], methyl protons of two acetate groups [δ_H 2.22 (s, CO<u>Me</u>-2)/δ_C 20.9 and 2.13 (s, CO<u>Me</u>-6)/δ_C 20.9], methoxy protons [δ_H 3.45 (s, OMe-3)/δ_C 56.7], monosubstituted aromatic protons [δ_H 8.07 (m, H-2'/H-6')/δ_C 129.7, 7.50 (m, H-3'/H-5')/δ_C 133.4, and 7.63 (m, H-4')/δ_C 128.5], one set of diastereomeric methylene protons [δ_H 4.64 (d, *J* = 11.8 Hz, H-1') and 4.47 (d, *J* = 11.8 Hz, H-1')/δ_C 65.9] and one hydroxy proton [δ_H 3.04 (s, OH-1)]. The NOSEY cross peaks (Supporting Information) of H-2 (δ_H 5.52) with OMe-3 (δ_H 3.43) and OH-1 (δ_H 3.04) with H-2 (δ_H 5.52) and H-6 (δ_H 5.49) indicated all of these protons were *syn*-orientation. The HMBC correlations displayed in Fig. 2 confirmed the locations of all substituents in the core skeleton. The (1*R*,2*S*,3*R*,6*S*) absolute configuration was established from the single-crystal X-ray diffraction analysis with Cu Kα radiation (Fig. 4) which had the Flack parameter of −0.03(9). This compound displayed a positive Cotton effect at 220 nm and a negative Cotton effect at 245 nm (Fig. 3) and its specific rotation was $[\alpha]_D^{23}$ + 33 (*c* 1, $CHCl_3$). Therefore, compound **1** was assigned as (+)-(1*R*,2*S*,3*R*,6*S*)-uvarialuridol A.

The molecular formula of compound **2**, $C_{24}H_{24}O_8$, was deduced from its HRESITOFMS data, which showed an $[M + Na]^+$ ion at *m/z* 463.1370 (calcd for $C_{24}H_{24}O_8Na$, 463.1369). The ^1H and ^{13}C NMR spectroscopic data of **2** (Table 1) were similar to those of **1** except that the resonances for the acetoxy group (δ_H 2.13/δ_C 20.9) at C-6 of **1** were replaced by resonances for a benzoyl unit [δ_H 8.05 (m, H-2″/H-6″)/δ_C 129.7, 7.43 (m, H-3″/H-5″)/δ_C 128.8, and 7.57 (m, H-4″)/δ_C 133.9]. This was further supported by the HMBC correlations shown in Fig. 1. The vicinal coupling constant between H-2 (δ_H 5.62) and H-3 (δ_H 4.16) of 6.5 Hz suggested H-2 and H-3 were in a 1,2-diaxial relationship [5]. The NOSEY cross peaks (Supplementary material) of OMe-3 (δ_H 3.43) with H-2 (δ_H 5.62) and OH-1 (δ_H 3.04) with H-2 (δ_H 5.62) and H-6 (δ_H 5.71) indicated the *syn*-orientation of H-2 with OMe-3, OH-1, and H-6. The ECD spectrum of **2** (Fig. 3) was similar to that of (+)-**1** and its specific rotation was also of the same sign {$[\alpha]_D^{23}$ + 26 (*c* 1, MeOH) for (+)-**2** and $[\alpha]_D^{23}$ + 33 (*c* 1, $CHCl_3$) for (+)-**1**} indicating that the absolute configuration of (+)-**2** was the same as that of (+)-**1**. Therefore, compound **2** was identified as (+)-(1*R*,2*S*,3*R*,6*S*)-uvarialuridol B.

Compound **3** ($[\alpha]_D^{23}$ + 38, *c* 1, $CHCl_3$) was isolated as a colorless viscous oil. Its molecular formula, $C_{17}H_{20}O_7$, was established on the basis of HRESITOFMS data which showed ion $[M + Na]^+$ ion at *m/z* 359.1110 (calcd for 359.1107, $C_{17}H_{20}O_7Na$). The ^1H and ^{13}C NMR spectroscopic data of **3** (Table 1) were closely related to those of **2** except for the lack of resonances for the benzoyl unit at C-6 of **2**. This C-6 substituent was replaced by a hydroxy group in **3** which was indicated by the relative shielding of the oxymethine proton H-6 at δ_H 3.57 (m). Its specific rotation, ECD spectrum (Fig. 3), and NOSEY cross peaks (Supporting Information) were similar to those of **1** and **2**, suggesting that they had the same absolute configuration. Thus, compound **3** was assigned as (+)-(1*R*,2*S*,3*R*,6*S*)-uvarialuridol C.

Compound **4**, curcuminol F, was first reported in 2009 from *Curcuma wenyujin* (Zingiberaceae) by Ma and co-workers [39] and its relative configuration, (1*S*,2*R*,3*S*,6*S*), was determined from NOESY experiments. This compound had a specific rotation of −62.3° (*c* 0.1, MeOH). In 2015, Hongthong and co-workers [28] also isolated the enantiomeric compound from *Dasymaschalon sootepense* (Annonaceae), with a specific rotation $[\alpha]_D^{25}$ + 35.6, *c* 0.1, MeOH, *ent*-curcuminol F [28]. In this study, we isolated compound **4** which displayed NMR spectroscopic data similar to those compounds isolated from *C. wenyujin* and *D. sootepense*. Herein, the absolute configuration of compound **4** was established by the comparison of its ECD spectrum {λ_{max} (Δε) 207 (+3.24), 245 (−2.87) nm} to that of **1** {λ_{max} (Δε) 220 (+3.39), 244 (−3.05) nm)} (Fig. 3). Therefore, compound **4** was identified as (+)-(1*R*,2*S*,3*R*,6*S*)-curcuminol F ($[\alpha]_D^{23}$ + 43, *c* 1, MeOH), corresponding to the same compound isolated by Hongthong [19].

Compound **5**, zeylenone (lit. $[\alpha]_D^{28}$ -126.5, *c* 0.747, $CHCl_3$) [29], was first isolated from *U. grandiflora* in 1997 by Liao and co-workers [29] but its absolute configuration was not identified. In this study, the (1*S*,2*S*,3*R*) absolute configuration of zeylenone was established from X-ray crystallographic data analysis (Fig. 5, CCDC 1941052) and the Flack parameter was refined to −0.01(7) as well as its ECD spectrum which displayed a strong negative Cotton effect at 250 nm (Fig. 3). Therefore, compound **5** was identified as (-)-(1*S*,2*S*,3*R*)-zeylenone ($[\alpha]_D^{22}$ - 33.7, *c* 1, $CHCl_3$).

It should be note that polyoxygenated cyclohexenes are well known as major compounds in the *Uvaria* genus [5,6,8,14–17,29,40]. The core cyclohexene structure contains one double bond and four chiral oxygenated carbons. The stereochemistry of these stereogenic carbons, as well as their substituent groups, is quite unique which is dependant on the enzymatic process in each plant species [5,6,8,14–17,29,40]. In this study, all cyclohexenes (**1–5**) contain a double bond at C-4/C-5 and the carbons containing the oxygenated substituent groups have the same stereochemistry: C-1 and C-2 are the same face of the molecules (β-orientation), whereas C-3 (α-orientation) is opposite to those of C-1 and C-2. Also, cyclohexenes **1–4** have the same stereochemistry at C-6 (α-orientation) whereas the OH-6 group of compound **5** was oxidized to a ketone group.

The biosynthetic pathway of polyoxygenated cyclohexenes from the *Uvaria* genus is known which comes from the shikimic acid pathway [5,8,40]. A putative biosynthetic pathway for **1–5** is shown in Scheme 1. Based on the results of our study, the key intermediate A is proposed as a precursor [8]. Epoxidation of the $\Delta^{1(6)}$ double bond followed by enzymatic acylation reactions, acetylation at C-2 or benzoylation at C-3, would give the intermediates C or D, respectively. Epoxide ring opening (hydroxylation) of intermediate D leads to intermediate diol E, which could be further oxidation at OH-6 to give compound **5**. Compound **4** could be obtained from intermediates C and F via epoxide ring opening (hydroxylation) and acetylation at C-3, respectively. On the

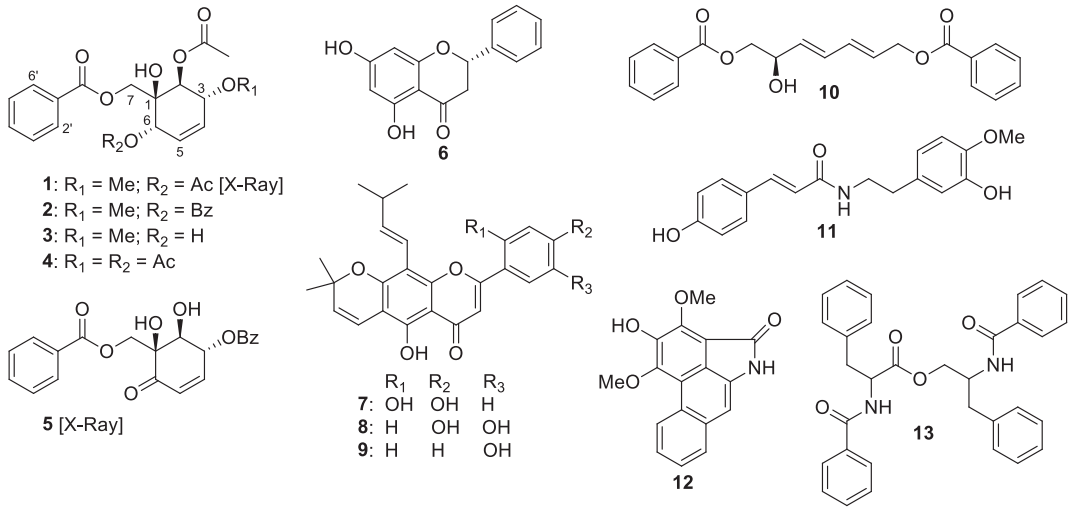


Fig. 1. Isolated compounds from twig and leaves extracts of *U. lurida*.

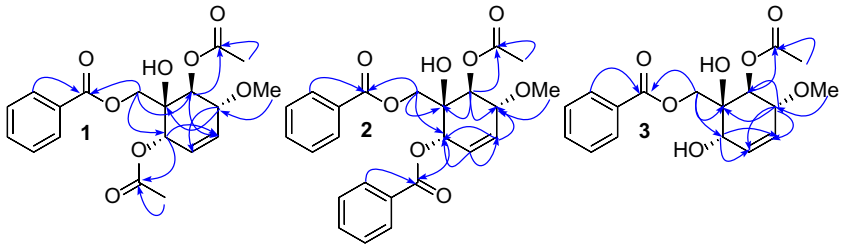


Fig. 2. Key HMBC correlations for compounds **1–3.**

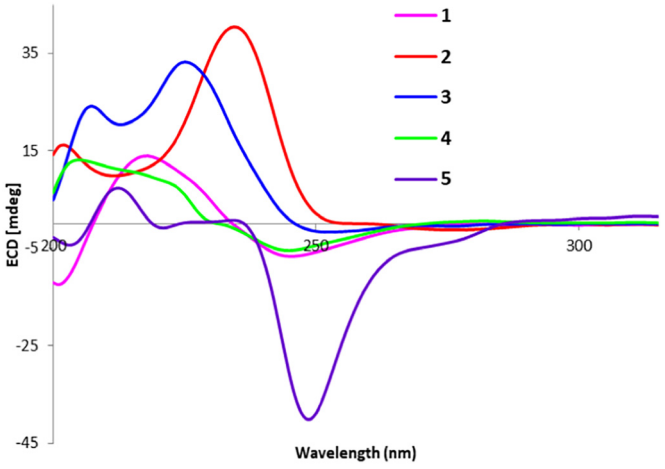


Fig. 3. ECD spectra (MeOH) of compounds **1–5**.

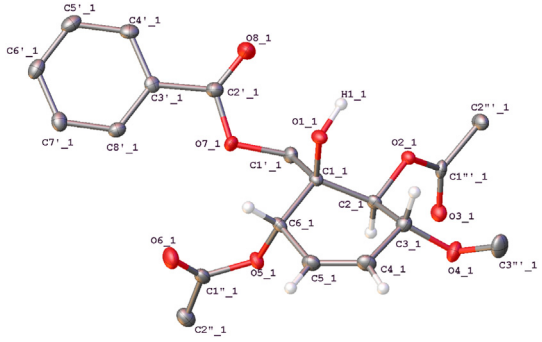


Fig. 4. ORTEP diagram for (+)-(1*R*,2*S*,3*R*,6*S*)-uvarialuridol A (**1**).

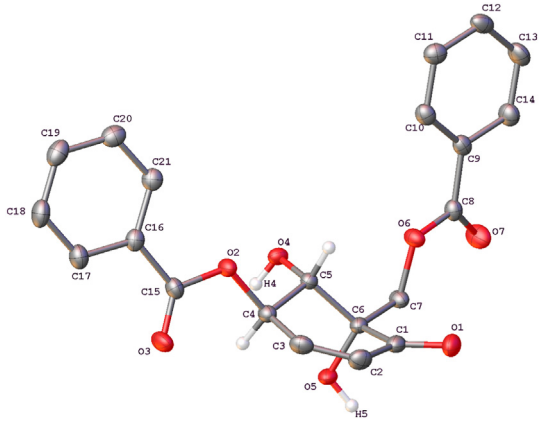
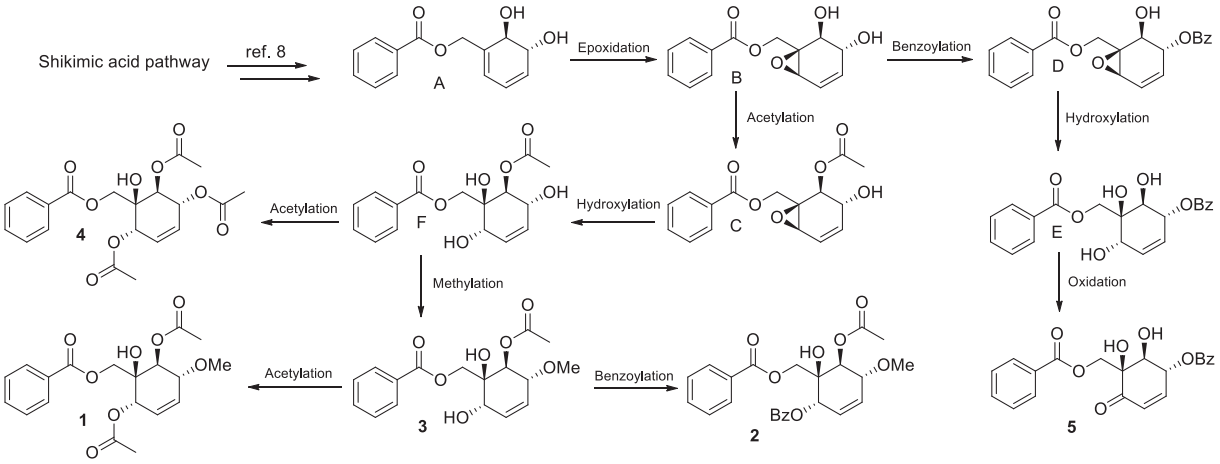


Fig. 5. ORTEP diagram for (−)-(1*S*,2*S*,3*R*)-zeylenone (**5**).

other hand, selective methylation of intermediate F at C-3 could give **3**, which upon acetylation or benzoylation at C-5 would give **1** or **2**, respectively.

Compounds **1**, **4–6**, **10**, and **11** were evaluated for their *α*-glucosidase inhibitory and NO production inhibitory activities. Compound **11** showed *α*-glucosidase inhibitory activity with an IC_{50} value of 30 μM which was better than that of the standard control (IC_{50} value of acarbose = 74 μM), whereas all remaining compounds were inactive at the concentration of 200 μg/mL. In addition, compound **10** showed NO production inhibitory activity with an IC_{50} value of 37 μM, while amide **11** showed weak NO production inhibitory with an IC_{50} value of 182 μM. The standard control for NO production inhibitory is indomethacin with an IC_{50} value of 150 μM.



Scheme 1. Putative biosynthetic pathway of compounds **1–5**.

Declaration of Competing Interest

The authors declare no competing financial interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2019.104340.

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