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SHORT REPORT

Cyclocarioside Z15, a new 3,4-*seco* dammarane triterpenoid glycoside from the leaves of *Cyclocarya paliurus* with α-glucosidase inhibitory activity

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Abstract: A new 3,4-*seco* dammarane triterpenoid glycoside, cyclocarioside Z15 (**1**), along with three known compounds cypaliuruside B (**2**), 2α,3α,23-trihydroxyurs-12,20(30)-dien-28-oic acid (**3**) and asiatic acid (**4**) were isolated from the leaves of *Cyclocarya paliurus*. The chemical structures were elucidated by 1D and 2D NMR, HR-ESI-MS, and acid hydrolysis. All compounds were measured for their α-glucosidase inhibitory activity, and only compound **1** exhibited weak activity with an IC_{50} value of 77.98 μM.

Keywords: *Cyclocarya paliurus*, 3,4-*seco* dammarane triterpenoid glycoside, α-glucosidase inhibitory activity

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1 Plant Source

The leaves of *Cyclocarya paliurus* were collected from Hefeng County, Enshi Prefecture, Hubei Province in 2021 and authenticated by Prof. Kang-Ping Xu (Xiangya School of Pharmaceutical Sciences, Central South University). The specimen (No. 20210905) is deposited in the Department of Natural Medicinal Chemistry, Central South University.

2 Previous Studies

Cyclocarya paliurus (Batal.) Iljinsk, a deciduous tree of the genus Cyclocarya in the family Juglandaceae, is a unique single-species genus plant in China. Traditional Chinese medicine classics have documented its efficacy in clearing heat, detoxifying, promoting fluid production, and relieving thirst. Modern pharmacological studies have further validated these uses, demonstrating a wide range of activities, including hypoglycemic, lipid-lowering, antihypertensive, antibacterial, antioxidant, anti-tumor, anti-aging, and hepatoprotective effects (He et al., 2024; Wang et al., 2022; Zhao et al., 2019). Chen et al. (2022) summarized a total of 210 active ingredients in the leaves of *C.paliurus*, illustrating that triterpenoids, flavonoids, polysaccharides and phenylpropanoids are primary components. Among them, triterpenoids accounted for 65.2%. However, Xi et al. (2025) noted that since 2015, the research on triterpenoids (18.4%) has been relatively limited compared to that on flavonoids (25.1%) and polysaccharides (44.3%), suggesting that triterpenoids warrant further investigation. In our previous study, several novel dammarane triterpenoid saponins with hypoglycemic and cytotoxic effects were isolated (Sun et al., 2021; Sun et al., 2020; Sun et al., 2022; Xu et al., 2025), ongoing phytochemical research generated a new compound named cyclocarioside Z15 (**1**) along with three known ones (**2**–**4**) (Figure 1). This study evaluated their α-glucosidase inhibitory activity, found that compound **1** exhibited weak activity with an IC_{50} value of 77.98 μM.

3 Present Study

The dried leaves of *C.paliurus* (5.0 kg) were refluxed three times with 70% ethanol, and the residue was obtained after removing the solvent by vacuum as the total extract. Then, the residuum was suspended in water and extracted with dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and n-butanol (*n*-BuOH), respectively. The CH_2Cl_2 extract

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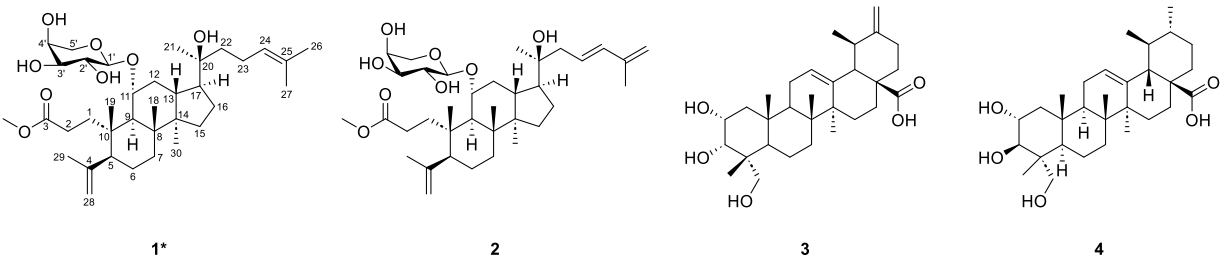

1* 2 3 4

Figure 1. Chemical structures of compounds **1**–**4**

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data of Compound **1** (Pyridine-d_5)

Position	δ_H, (*J* in Hz)	δ_C, type	Position	δ_H, (*J* in Hz)	δ_C, type
1	1.75, 2.98, m	38.0, CH_2	19	1.25, s	20.8, CH_3
2	2.43, 2.98, m	30.6, CH_2	20	–	75.0, C
3	–	176.4, C	21	1.48, s	27.3, CH_3
4	–	148.9, C	22	1.84, 1.89, m	41.3, CH_2
5	2.14, m	52.4, CH	23	2.34, 2.43, m	23.8, CH_2
6	1.35, 1.95, m	25.7, CH_2	24	5.36, t (7.0)	126.5, CH
7	1.13, 1.53, m	35.2, CH_2	25	–	131.3, C
8	–	51.4, C	26	1.71, s	26.3, CH_3
9	2.05, m	45.0, CH	27	1.68, s	18.2, CH_3
10	–	40.5, C	28	4.88, 4.95, br s	114.3, CH_2
11	4.44, td (10.7, 4.8)	75.8, CH	29	1.80, s	24.2, CH_3
12	1.65, 2.98, m	34.2, CH_2	30	1.01, s	17.1, CH_3
13	2.14, m	41.0, CH	1′	4.80, d (7.4)	101.6, CH
14	–	41.8, C	2′	4.37, t (8.1)	73.2, CH
15	1.13, 1.53, m	31.9, CH_2	3′	4.04, dd (9.3, 3.6)	74.4, CH
16	1.75, 1.89, m	26.1, CH_2	4′	4.20, br s	70.2, CH
17	2.05, m	50.6, CH	5′	3.62, d (12.6); 4.26, d (12.0)	67.9, CH_2
18	1.05, s	17.2, CH_3	3-COOMe	3.52, s	51.7, CH_3

(132.0 g) was chromatographed by using HP20 macroporous adsorption resin, eluting with a gradient mixture of H_2O-EtOH gradient system (from 1:0 to 0:1) to acquire Fr.A-E. Fr.C (64.0 g) was decolorized by polyamide column with H_2O-EtOH mixtures (from 1:0 to 0:1) to give Fr.C1-C7. Fr.C4 (9.6 g) was loaded to a chromatography column on silica gel eluted with gradients of CH_2Cl_2-MeOH (from 1:0 to 10:2) for further purification, which yielded twelve fractions numbered as Fr.C4a-i. Among them, Fr.C4c (2.7 g) was applied to silica gel column and eluted with CH_2Cl_2-MeOH (from 1:0 to 10:2) to gain Fr.C4c1-2. Fr.C4c2 (1.8 g) was subjected to preparative HPLC, eluted with MeOH-H_2O (15 mL/min, 80%–90%) to afford Fr.C4c2-1 to Fr.C4c2-2, and compounds **2** (18.7 mg), **3** (2.0 mg) were obtained from Fr.C4c2-1 (1.1 g) by semipreparative HPLC (eluted with 70%–90% MeOH-H_2O, 3 mL/min). In addition, Fr.C4c2-2 (0.3 g) was subjected to semipreparative HPLC to afford compound **1** (8.4 mg). Fr.C4e was subjected to silica gel column and semipreparative HPLC to obtain compound **4** (12.2 mg).

*Cyclocarioside Z15 (**1**)*. White amorphous powder; $[\alpha]_D^{25}$ +4.4 (*c* 0.12, MeOH); UV (ACN) λmax: 203 nM; negative HR-ESI-MS *m/z* calculated for $C_{37}H_{61}O_{10}$ [M + HCOOH – H]$^-$ 665.4270, found: 665.4278; ^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data see Table 1.

Biological Activity Assay: The compounds **1**–**4** were evaluated for their α-glucosidase inhibitory activity according to the manufacturer's kit instructions (Azmi et al., 2021; Chen et al., 2019). During the initial screening, a single concentration (100 μM) was set for each compound. For the IC_{50} determination, six concentration gradients (12.5, 25, 50, 100, 200, and 400 μM) were established. Acarbose was selected as the positive control.

Compound **1** was obtained as white amorphous powder with the molecular formula $C_{36}H_{60}O_8$, yielded a negative-ion peak [M + HCOOH – H]$^-$ at *m/z* 665.4278 (calcd. for $C_{37}H_{61}O_{10}^-$, 665.4270) in its HR-ESI-MS spectrum (Figure S1). The ^{1}H NMR spectrum (Figure S3 and Table 1) of **1** showed seven quaternary methyl singlets at δ_H 1.01 (s, 30-CH_3), 1.05 (s, 18-CH_3), 1.25 (s, 19-CH_3), 1.48 (s, 21-CH_3), 1.68 (s, 27-CH_3), 1.71 (s, 26-CH_3), 1.80 (s, 29-CH_3); a methoxy group at δ_H 3.52 (s, 3-OCH_3); a terminal double bond bearing olefinic protons at δ_H 4.88 (br s, H-28a), 4.95 (br s, H-28b); an olefinic methine proton at δ_H 5.36 (t, *J* = 7.0 Hz, H-24); and an anomeric proton of glycosyl at δ_H 4.80 (d, *J* = 7.4 Hz, H-1′). The ^{13}C NMR and DEPT spectra

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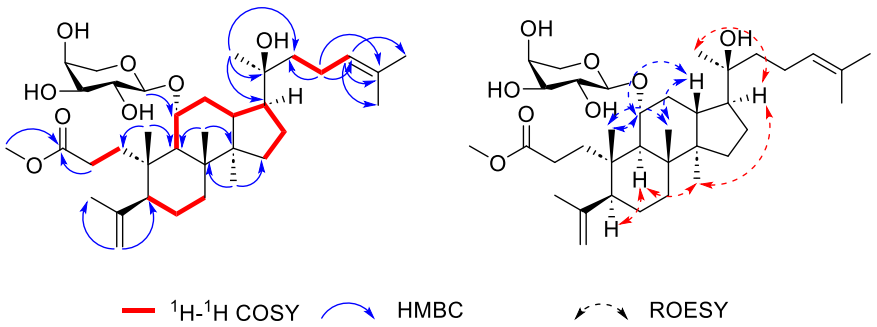

Figure 2. Key ^{1}H-^{1}H COSY, HMBC and ROESY correlations of compound **1**

(Figure S4, Figure S5 and Table 1) exhibited 36 carbon signals of **1**, of which 8 methyls, 11 methylenes, 10 methines, and 7 quaternary carbons. The molecular formula revealed that **1** possesses seven degrees of unsaturation, which are attributed to one ester group, two double bonds, one glycosyl ring, and three rings. These data demonstrated that **1** shared close structural similarity with cypaliuruside D (Zhou et al., 2021) (Figure S11, Table S1 and Table S2), suggesting **1** includes the basic 3,4 *seco*-dammarane triterpenoid skeleton, differing from cypaliuruside D principally in the signals of the side chain. The ^{1}H-^{1}H correlations spectroscopy (COSY) correlations (Figure 2 and Figure S9) of H-1/H-2, H-5/H-6/H-7, H-9/H-11/H-12/H-13/H-17 and H-22/H-23/H-24 confirmed the existence of the four fragments -CH_2CH_2-, -$CHCH_2$CH-, -$CHCHCH_2CHCH$- and -CH_2CH_2CH-. In its heteronuclear multiple bond correlation (HMBC) (Figure 2 and Figure S8), correlations from H-3-OCH_3 (δ_H 3.52, s) to C-3 (δ_C 176.4) suggested the existence of carbomethoxy at C-3. The cross peaks from H-28 (δ_H 4.88, 4.95, br s) to C-5 (δ_C 52.4) and C-29 (δ_C 24.2) indicated the terminal double bond (-C=CH_2-) was linked to C-4. The HMBC correlations from H-26-CH_3 and H-27-CH_3 to each other (δ_C 26.3 and δ_C 18.2, respectively), as well as to C-25 (δ_C 131.3) and C-24 (δ_C 126.5), illustrated the presence of a $\triangle^{24(25)}$ double bond. The HMBC correlations from H-21-CH_3 (δ_H 1.48, s) to C-17 (δ_C 50.6) confirmed that the side chain was linked to C-17. The HMBC correlations from the H-1′ (δ_H 4.80, d, J = 7.4 Hz, anomeric proton) to C-11 (δ_C 75.8) suggested that the arabinopyranose was linked to C-11. This had to be emphasized by the HMBC correlations of H-19-CH_3 (δ_H 1.23) with C-1 (δ_C 38.0), C-9 (δ_C 45.0) and C-10 (δ_C 40.5), together with the spin systems of H-9/H-11/H-12 in ^{1}H–^{1}H COSY spectrum.

Furthermore, a set of oxygenated carbon signals (δ_C 101.6, 73.2, 74.4, 70.2, 67.9) accompanied by the presence of fragment ion of m/z 173.0421 (calcd. for $C_5H_{10}NaO_5^+$, 173.0420) indicated that the pentose unit was L-arabinopyranosyl. Acid hydrolysis of **1** with 1 M HCl confirmed the sugar residue (Figure S12) (Liu et al., 2020; Xu et al., 2025). The coupling constant of $J_{H\text{-}1'/H\text{-}2'}$ = 7.4 Hz of the anomeric proton, along with the ROESY correlations (Figure 2 and Figure S10) of H1′/H3′ and H3′/H5′ established the L-arabinopyranose was α-oriented. The ROESY correlations between H-5/H-9/H-17/H-CH_3-21/H-CH_3-30 declared that they are α-oriented, and the relative configuration of H-11/H-13/H-CH_3-19/H-CH_3-18 were determined as β-oriented. Thus, the structure of **1** was expounded as shown, and named as cyclocarioside Z15.

Table 2. α-Glucosidase inhibitory activities of compounds **1**–**4**

Compounds	IC_{50} (μM)
1	77.98 ± 0.63
2	>100
3	>100
4	>100
Acarbose	0.056 ± 0.001

The known compounds (**2**–**4**) were characterized as cypaliuruside B (**2**) (Zhou et al., 2021), 2α,3α,23-trihydroxyurs-12,20(30)-dien-28-oic acid (**3**) (Sashida et al., 1992) and asiatic acid (**4**) (Bisoli et al., 2008) by comparing their NMR data (^{1}H and ^{13}C) with those reported in the literatures.

Compounds **1**–**4** were assayed for their α-glucosidase inhibitory activity with acarbose as the positive control. As shown in Table 2, only compound **1** exhibited weak activity with an IC_{50} value of 77.98 ± 0.63 μM. Comparison of the structures of **1** and **2** indicated that the sole structural difference is in the side chain, suggesting that the presence of a conjugated double bond in the side chain of 3,4-*seco* dammarane triterpenes might be responsible for the diminished activity.

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Author Contributions

Qian Yao: Methodology, Data analysis, Writing original manuscript; Xi-Fan Wei: Data analysis, Writing original manuscript; Lu Wang: Manuscript review & editing; Rui Gui: Manuscript review & editing; Yi-Heng Liu: Format review & correction; Dan-Dan Li: Format review & correction; Xiao-Ai He: Data analysis; Xia Yu: Methodology, Supervision. Kang-Ping Xu: Project design & promotion & supervision, Manuscript review & editing.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Ethics Approval

No human participants or live animals were involved in this study.

Conflicts of Interest

The authors declare no competing financial interest.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products.

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