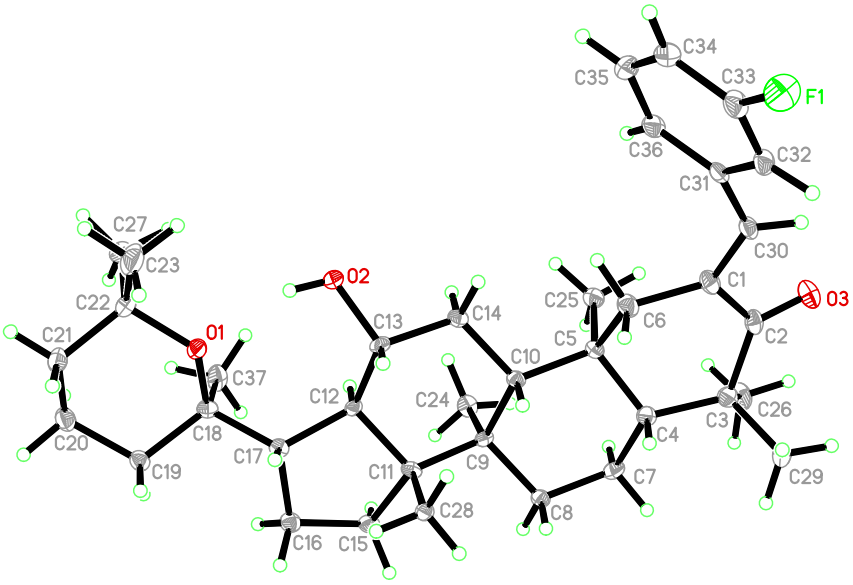
Kuo Cheng, Ya-Bin Song*, Qing-Guo Meng, Bao-Gang Wang, Yun Hou, Wen-Shui Wang and Sheng Jiang

Crystal structure of (5*R*,8*R*,9*R*,10*R*,12*R*,13*R*,14*R*,17*S*)-2-(*E*-3-fluorobenzylidene)-12-hydroxy-4,4,8,10,14-pentamethyl-17-((*R*)-2,6,6-trimethyltetrahydro-2*H*-pyran-2-yl) hexadecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one, $C_{37}H_{53}FO_3$



https://doi.org/10.1515/ncrs-2023-0470
Received October 30, 2023; accepted December 28, 2023; published online January 15, 2024

***Corresponding author: Ya-Bin Song**, State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, 100071 Beijing, P.R. China, E-mail: songyb@126.com
Kuo Cheng and Qing-Guo Meng, School of Pharmacy, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Yantai University, Yantai, P.R. China. https://orcid.org/0009-0008-7100-7871 (K. Cheng)
Bao-Gang Wang, State Key Laboratory of Pathogen and Biosecurity, Beijing Institute of Microbiology and Epidemiology, 100071 Beijing, P.R. China
Yun Hou, School of Pharmacy, Department of Histology and Embryology, Basic Medical College, Binzhou Medical University, Yantai, 264003, P.R. China. https://orcid.org/0000-0001-8440-8035
Wen-Shui Wang and Sheng Jiang, Shandong Shenxiangchuanqi Biotechnology Co., Ltd., Weihai, Shandong, 264400, China

Abstract
$C_{37}H_{53}FO_3$, orthorhombic, $P2_12_12_1$ (no. 19), a = 7.4716(8) Å, b = 15.0009(15) Å, c = 28.065(5) Å, V = 3145.5(7) Å^3, Z = 4, $R_{gt}(F)$ = 0.0643, $wR_{ref}(F^2)$ = 0.1464, T = 293 K.

CCDC no.: 2283345

The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

1 Source of material

Total saponins from ginseng stems and leaves were added to an ethanol solution of 18 % sulfuric acid and heated to reflux for 4 h. The reaction solution was cooled to room temperature, appropriate amount of sodium carbonate was added to neutralize sulfuric acid, the reaction solution was adjusted to

Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.15 × 0.13 × 0.12 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.08 mm^{-1}
Diffractometer, scan mode:	SuperNova,
θ_{max}, completeness:	25.5°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	10139, 5655, 0.057
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 4379
$N(param)_{refined}$:	379
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3]

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
C1	0.6411 (6)	0.0540 (3)	0.25259 (16)	0.0250 (10)
C2	0.5605 (6)	−0.0356 (3)	0.24405 (16)	0.0246 (10)
C3	0.3790 (6)	−0.0434 (3)	0.21838 (17)	0.0274 (11)
C4	0.3220 (5)	0.0443 (3)	0.19277 (16)	0.0222 (10)
H4	0.256298	0.078136	0.216962	0.027*
C5	0.4772 (5)	0.1065 (3)	0.17742 (16)	0.0197 (10)
C6	0.5760 (6)	0.1325 (3)	0.22391 (17)	0.0283 (11)
H6A	0.677847	0.169683	0.215817	0.034*
H6B	0.495993	0.167770	0.243537	0.034*
C7	0.1863 (6)	0.0282 (3)	0.15306 (17)	0.0267 (11)
H7A	0.244156	−0.003253	0.127091	0.032*
H7B	0.090440	−0.009221	0.165024	0.032*
C8	0.1078 (5)	0.1146 (2)	0.13440 (16)	0.0207 (10)
H8A	0.038396	0.142394	0.159554	0.025*
H8B	0.026801	0.101110	0.108379	0.025*
C9	0.2489 (5)	0.1810 (2)	0.11684 (15)	0.0166 (9)
C10	0.3940 (5)	0.1937 (3)	0.15613 (16)	0.0186 (9)
H10	0.330666	0.221638	0.182805	0.022*
C11	0.1636 (5)	0.2755 (3)	0.10745 (15)	0.0181 (9)
C12	0.3077 (5)	0.3404 (2)	0.08845 (15)	0.0166 (9)
H12	0.361478	0.312149	0.060422	0.020*
C13	0.4573 (5)	0.3530 (3)	0.12480 (16)	0.0221 (10)
H13	0.409607	0.384209	0.152726	0.027*
C14	0.5332 (6)	0.2627 (3)	0.14047 (16)	0.0222 (10)
H14A	0.601597	0.237894	0.114257	0.027*
H14B	0.615396	0.272611	0.166686	0.027*
C15	0.0239 (5)	0.2811 (3)	0.06694 (16)	0.0226 (10)
H15A	0.059275	0.244497	0.040070	0.027*
H15B	−0.092950	0.261901	0.077960	0.027*
C16	0.0214 (6)	0.3796 (3)	0.05330 (17)	0.0240 (10)
H16A	−0.078830	0.409407	0.068463	0.029*
H16B	0.009225	0.386020	0.019062	0.029*
C17	0.2014 (5)	0.4217 (2)	0.07037 (16)	0.0186 (9)
H17	0.174667	0.459274	0.098014	0.022*
C18	0.2874 (5)	0.4814 (3)	0.03234 (16)	0.0206 (10)
C19	0.1547 (6)	0.5498 (3)	0.01323 (17)	0.0231 (10)
H19A	0.071774	0.520280	−0.008175	0.028*
H19B	0.086120	0.573913	0.039603	0.028*
C20	0.2452 (6)	0.6262 (3)	−0.01321 (18)	0.0298 (11)
H20A	0.304118	0.603528	−0.041517	0.036*
H20B	0.155940	0.669366	−0.023118	0.036*
C21	0.3815 (6)	0.6711 (3)	0.01873 (18)	0.0309 (11)
H21A	0.319665	0.700109	0.044862	0.037*
H21B	0.443573	0.716795	0.000679	0.037*
C22	0.5180 (6)	0.6062 (3)	0.03884 (19)	0.0323 (12)
C23	0.6146 (8)	0.6442 (3)	0.0817 (2)	0.0564 (17)
H23A	0.529313	0.657967	0.106225	0.085*
H23B	0.676983	0.697505	0.072639	0.085*
H23C	0.698840	0.601177	0.093503	0.085*
C24	0.3296 (6)	0.1431 (3)	0.07029 (16)	0.0243 (10)
H24A	0.343066	0.079721	0.073180	0.036*
H24B	0.444465	0.169828	0.064707	0.036*
H24C	0.251319	0.156366	0.044107	0.036*
C25	0.6128 (6)	0.0601 (3)	0.14458 (17)	0.0281 (11)
H25A	0.693058	0.103594	0.131454	0.042*
H25B	0.550274	0.030527	0.119208	0.042*
H25C	0.679782	0.017046	0.162561	0.042*
C26	0.3873 (7)	−0.1254 (3)	0.18501 (19)	0.0366 (13)
H26A	0.465577	−0.112776	0.158722	0.055*
H26B	0.269586	−0.138391	0.173220	0.055*
H26C	0.432035	−0.175815	0.202369	0.055*
C27	0.6551 (6)	0.5790 (3)	0.0012 (2)	0.0503 (16)
H27A	0.720333	0.527817	0.012198	0.075*
H27B	0.736597	0.627377	−0.004220	0.075*
H27C	0.594464	0.564600	−0.027936	0.075*
C28	0.0703 (5)	0.3142 (3)	0.15232 (15)	0.0197 (10)
H28A	0.156058	0.319918	0.177599	0.030*
H28B	−0.024115	0.274842	0.162142	0.030*
H28C	0.021163	0.371697	0.144972	0.030*
C29	0.2456 (7)	−0.0632 (3)	0.2587 (2)	0.0415 (14)
H29A	0.271794	−0.120487	0.272305	0.062*
H29B	0.126071	−0.063334	0.246192	0.062*
H29C	0.255695	−0.018190	0.282894	0.062*
C30	0.7624 (6)	0.0587 (3)	0.28762 (16)	0.0243 (10)
H30	0.782540	0.006029	0.304246	0.029*
C31	0.8686 (6)	0.1364 (3)	0.30341 (16)	0.0223 (10)
C32	0.8743 (6)	0.1573 (3)	0.35243 (16)	0.0271 (10)
H32	0.809143	0.124435	0.374530	0.033*
C33	0.9780 (6)	0.2271 (3)	0.36631 (17)	0.0310 (11)
C34	1.0831 (6)	0.2757 (3)	0.33611 (18)	0.0309 (11)
H34	1.154299	0.321914	0.347458	0.037*
C35	1.0807 (6)	0.2543 (3)	0.28823 (18)	0.0345 (12)
H35	1.151275	0.285739	0.266717	0.041*
C36	0.9725 (6)	0.1858 (3)	0.27274 (17)	0.0277 (11)
H36	0.969566	0.172529	0.240384	0.033*
C37	0.3677 (6)	0.4253 (3)	−0.00826 (16)	0.0315 (11)
H37A	0.389003	0.462763	−0.035422	0.047*
H37B	0.285598	0.378782	−0.016783	0.047*
H37C	0.478640	0.399502	0.002094	0.047*
F1	0.9792 (4)	0.24862 (19)	0.41389 (10)	0.0484 (8)
O1	0.4259 (4)	0.52890 (18)	0.05861 (11)	0.0257 (7)
O2	0.6064 (4)	0.40139 (19)	0.10659 (12)	0.0311 (8)
H2	0.573599	0.451070	0.098096	0.047*
O3	0.6373 (4)	−0.10299 (18)	0.25643 (12)	0.0340 (8)

pH 7. The residue was extracted with ethyl acetate, washed with saturated brine, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure to obtain the crude product, and the crude product was recrystallized with ethyl acetate to obtain the pure product of 20(*R*)-panaxadiol. 20(*R*)-panaxadiol and PCC (pyridinium chlorochromate) were dissolved in 25 mL of dichloromethane, and the reaction mixture was stirred at room temperature for 4 h. The intermediate 20(*R*)-3-oxopanaxadiol was purified by silica gel column chromatography. Methanol (1.4 mL), 20(*R*)-3-oxopanaxadiol (100 mg, 0.22 mmol), and 2-fluorobenzaldehyde (0.023 mL, 0.22 mmol) were added to a round-bottomed flask, to which 0.72 mL (25 %) aqueous sodium hydroxide was added dropwise, and the flask was stirred for 4 h at room temperature. The reaction was monitored by thin layer chromatography (TLC, 254 nm). At the end of the reaction, appropriate amount of water was added, the reaction mixture was transferred to a partition funnel and extracted with ethyl acetate (twice), the organic phases were combined and washed with saturated sodium chloride solution, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure and the crude product was purified by silica gel column chromatography. Recrystallization with ethyl acetate solution gave crystals of the target compound.

2 Experimental details

The H atoms were placed in idealized positions and treated as riding on their parent atoms [3].

3 Comment

Ginseng saponins include protopanoxadiol-type saponin, panaxatriol-type saponin and oleanane-type saponin, sharing a tetrahydrofuran ring and a dammarane skeleton [4]. In recent years, our laboratory has carried out research on the synthesis and single crystal X-ray diffraction of protopanoxadiol derivatives [5–7] and protopanaxatriol derivatives [8, 9], and the title compound is a 20(*R*)-panaxadiol derivative. Ginsenosides are important saponins among ginsenosides and their structures can be modified [10].

The ORTEP diagram is presented in the Figure. The title compound contains one drug molecule in the asymmetric unit (cf. the figure). Bond lengths and angles are all in the expected ranges. The title compound has a dammarane type as the parent structure [11], with a benzene ring structure attached to C(1). An α,β-unsaturated ketone group is formed between the benzene ring and the parent nucleus through the Claisen–Schmidt reaction effect. The angle of twist of C(30) = C(1)–C(2) = O(3) is −22.608°. The bond length of C(2)–O(3) is 1.2137 Å. The bond length of C(33)–F(1) is 1.374(5) Å. There is a fluorine substitution on the benzene ring. The benzene ring is non-coplanar with the saturated cyclic ketone and the dihedral angle between them is 54.048°. This twisted configuration may increase the likelihood of interactions with bioactive molecules or the purposes of creating more potent biological activity [12, 13]. The bond length of C(18)–O(1) is 1.4564 Å. The bond length of C(22)–O(1) is 1.4585 Å. There is a pyran ring substitution at the C(17) position and the oxygen atom on the ring acts as a hydrogen bond acceptor to form an intramolecular hydrogen bond. The bond length of C(13)–O(2) is 1.4251 Å. The pyran ring is connected to the five-membered ring *via* C(17)–C(18), the bond length of C(17)–C(18) is 1.374 Å. It is assumed that the dihedral angles between the five-membered ring and the pyran ring and the six-membered ring where the hydroxyl group is located are small, 3.031 Å and 0.604 Å, respectively, probably due to hydrogen bonding. The compound has a total of 8 chiral carbons, which are: 5*R*,8*R*,9*R*, 10*R*,12*R*,13*R*,14*R*,17*S*.

Acknowledgments: This work was supported by Science and Technology Innovation Development Plan of Yantai (No. 2020XDRH105) and the National Natural Science Foundation of China (No. 81473104).

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Competing interests: The authors declare no conflicts of interest regarding this article.

Research funding: Science and Technology Innovation Development Plan of Yantai (No. 2020XDRH105) and the National Natural Science Foundation of China (No. 81473104).

References

1. Rigaku O. D. CrysAlis^{PRO}; Rigaku Oxford Diffraction Ltd: Yarnton, Oxfordshire, England, 2017.
2. Sheldrick G. M. A short history of *SHELX*. *Acta Crystallogr.* 2008, *A64*, 112–122.
3. Sheldrick G. M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Liu J., Xu Y. R., Yang J. J., Wang W. Z., Zhang J. Q., Zhang R. M., Meng Q. G. Discovery, semisynthesis, biological activities, and metabolism of ocotillol-type saponins. *J. Ginseng Res.* 2017, *41*, 373–378.
5. Liu J., Xu Y. R., An X. S., Hou G. G., Meng Q. G. Synthesis and crystal structures of a 3-acetylated (20*S*,24*S*)-ocotillol-type saponin and its C-24 epimer. *Acta Crystallogr.* 2017, *C73*, 464–469.

6. Zhang M., Meng Q. G., Hou G. G., Jiang S., Jin Y. S., Gao Y. Crystal structure of (8*R*,10*R*,14*R*,*Z*)-2-((3-fluoropyridin-4-yl) methylene)-12-hydroxy-4,4,8,10,14-pentamethyl-17-((*R*)-2,6,6-trimethyltetrahydro-2*H*-pyran-2-yl) hexadecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one, $C_{36}H_{52}FNO_3$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 1139–1142.
7. Luo Q., Meng Q. G., Hou G. G., Jiang S., Jin Y. S., Gao Y. Crystal structure of (8*R*,10*R*,14*R*,*Z*)-12-hydroxy-2-((6-methoxypyridin-2-yl) methylene)-4,4,8,10,14-pentamethyl-17-((*R*)-2,6,6-trimethyltetrahydro-2*H*-pyran-2-yl) hexadecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one-water (2/1), $C_{37}H_{56}NO_{4.5}$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 1223–1226.
8. Xu Y. R., Yang J. J., Liu J., Hou G. G., Meng Q. G. Synthesis and crystal structures of C24-epimeric 20(*R*)-ocotillol-type saponins. *Acta Crystallogr*. 2016, *C72*, 498–503.
9. Sun K. W., Wang X. H., Ma G. Q., Luo Q., Wang Y. H., Meng Q. G. The crystal structure of (5*R*,8*R*,9*R*,10*R*, 12*R*,13*R*,14*R*)-12-hydroxy-4,4,8,10,14-pentamethyl-17-((*R*)-2,6,6-trimethyltetrahydro-2*H*pyran-2-yl) tetradecahydro-3*H*-cyclopenta[*a*] phenanthrene-3,6(2*H*)-dione, $C_{30}H_{48}O_4$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 17–20.
10. Wang C. M., Liu J., Deng J. Q., Wang J. Z., Weng W. Z., Chu H. X., Meng Q. G. Advances in the chemistry, pharmacological diversity, and metabolism of 20(*R*)-ginseng saponins. *J. Ginseng Res.* 2020, *44*, 14–23.
11. Ma Y., Wang H. Y., Zhang X. F., Zhao F. L., Meng Q. G. Crystal structure of (3*S*,8*R*,10*R*,12*R*,14*R*)-12-hydroxy-4,4,8,10, 14-pentamethyl-17-((*R*)-2,6,6-trimethyltetrahydro-2*H*pyran-2-yl) hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ylacetate, $C_{32}H_{54}O_4$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 163–166.
12. Sun J. J., Zhang X. F., Meng Q. G., Li H. J., Wang C. H. Crystal structure and anti-inflammatory activity of (*E*)-7-fluoro-2-((5-methoxypyridin-3-yl) methylene)-3,4-dihydronaphthalen-1(2*H*)-one, $C_{17}H_{14}FNO_2$. *Z. Kristallogr. N. Cryst. Struct.* 2021, *236*, 1097–1099.
13. Zhang S. N., Zhao F. L., Meng Q. G. Crystal structure of (*E*)-7-hydroxy-2-((6-methoxypyridin-3-yl)methylene)-3,4-dihydronaphthalen-1(2*H*)-one, $C_{17}H_{15}NO_3$. *Z. Kristallogr. N. Cryst. Struct.* 2022, *237*, 1–3.