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The crystal structure of benzyl 3 β -acetylglycyrrhetate, C₃₉H₅₄O₅

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Table 1: Data collection and handling.

Crystal:	Colourless block
Size:	0.24 × 0.22 × 0.15 mm
Wavelength:	Cu K α radiation (1.54184 Å)
μ :	0.59 mm ⁻¹
Diffractometer, scan mode:	Xcalibur, ω
$\theta_{\max}$, completeness:	66.9°, 99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	17341, 5669, 0.024
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 5431
$N(\text{param})_{\text{refined}}$:	406
Programs:	CrysAlis ^{PRO} [1], Olex2 [2], SHELX [3]

Abstract

C₃₉H₅₄O₅, monoclinic, $P2_1$ (no. 4), $a = 6.98138(17)$ Å, $b = 37.9050(6)$ Å, $c = 7.28644(16)$ Å, $\beta = 117.789(3)^\circ$, $V = 1705.82(8)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0326$, $wR_{\text{ref}}(F^2) = 0.0872$, $T = 293(2)$ K.

CCDC no.: 2008558

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.

Source of material

Benzyl 3 β -acetylglycyrrhetate (systematic name: benzyl (2S, 4aS,6aS,6bR,10S,12aS,12bR,14bS)-10-acetyl-10-hydroxy-2,4a, 6a,6b,9,9,12a-heptamethyl-13-oxo-1,2,3,4,4a,5,6,6a,6b,7,8,8a, 9,10,11,12,12a,12b,13,14b-icosahydricene-2-carboxylate) is

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.4864(3)	0.32041(4)	0.0024(3)	0.0604(4)
C1	0.2614(4)	0.41188(6)	−0.1744(3)	0.0487(5)
H1A	0.1412	0.4197	−0.3034	0.058*
H1B	0.3915	0.4233	−0.1610	0.058*
O2	−0.0263(3)	0.47398(5)	−0.3207(2)	0.0633(5)
C2	0.2866(5)	0.37197(6)	−0.1838(4)	0.0529(6)
H2A	0.1541	0.3604	−0.2045	0.063*
H2B	0.3118	0.3662	−0.3005	0.063*
O3	−0.0299(4)	0.63530(5)	−0.3056(3)	0.0720(6)
C3	0.4726(4)	0.35879(6)	0.0134(4)	0.0492(5)
H3	0.6069	0.3692	0.0262	0.059*
O4	0.0348(3)	0.68426(4)	−0.1158(3)	0.0582(4)
C4	0.4547(4)	0.36724(6)	0.2106(3)	0.0474(5)
O5	0.7215(5)	0.32346(7)	−0.1239(5)	0.1022(9)
C5	0.4095(3)	0.40766(5)	0.2092(3)	0.0383(4)
H5	0.5403	0.4191	0.2198	0.046*
C6	0.3948(4)	0.41981(6)	0.4019(3)	0.0445(5)
H6A	0.5052	0.4080	0.5235	0.053*
H6B	0.2544	0.4135	0.3891	0.053*
C7	0.4260(4)	0.45969(6)	0.4281(3)	0.0421(5)
H7A	0.5723	0.4654	0.4554	0.050*
H7B	0.4103	0.4669	0.5482	0.050*
C8	0.2661(3)	0.48086(5)	0.2389(3)	0.0346(4)
C9	0.2469(3)	0.46436(5)	0.0336(3)	0.0336(4)
H9	0.3872	0.4692	0.0389	0.040*
C10	0.2211(3)	0.42328(5)	0.0082(3)	0.0376(4)
C11	0.0863(3)	0.48616(6)	−0.1490(3)	0.0418(5)
C12	0.0749(3)	0.52417(5)	−0.1149(3)	0.0420(5)

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Table 2 (continued)

Atom	x	y	z	U_{iso}^*/U_{eq}
H12	−0.0188	0.5377	−0.2277	0.050*
C13	0.1891(3)	0.54082(5)	0.0660(3)	0.0349(4)
C14	0.3514(3)	0.52010(5)	0.2539(3)	0.0341(4)
C15	0.3927(4)	0.53731(6)	0.4626(3)	0.0431(5)
H15A	0.2805	0.5296	0.4967	0.052*
H15B	0.5302	0.5289	0.5711	0.052*
C16	0.3965(4)	0.57757(6)	0.4610(3)	0.0452(5)
H16A	0.5211	0.5854	0.4465	0.054*
H16B	0.4128	0.5863	0.5927	0.054*
C17	0.1905(3)	0.59345(6)	0.2846(3)	0.0431(5)
C18	0.1675(3)	0.58071(5)	0.0744(3)	0.0374(4)
H18	0.0199	0.5866	−0.0301	0.045*
C19	0.3209(4)	0.59952(5)	0.0085(3)	0.0418(5)
H19A	0.4685	0.5923	0.1005	0.050*
H19B	0.2868	0.5920	−0.1307	0.050*
C20	0.3072(4)	0.63997(6)	0.0122(3)	0.0458(5)
C21	0.3532(4)	0.65112(6)	0.2308(4)	0.0513(5)
H21A	0.5000	0.6445	0.3287	0.062*
H21B	0.3419	0.6766	0.2356	0.062*
C22	0.1964(4)	0.63406(6)	0.2937(4)	0.0510(5)
H22A	0.0521	0.6429	0.2038	0.061*
H22B	0.2343	0.6413	0.4342	0.061*
C23	0.2849(6)	0.34408(7)	0.2282(5)	0.0649(7)
H23A	0.2539	0.3533	0.3342	0.097*
H23B	0.3392	0.3204	0.2634	0.097*
H23C	0.1548	0.3439	0.0979	0.097*
C24	0.6769(5)	0.35927(8)	0.3962(4)	0.0735(8)
H24A	0.7814	0.3760	0.3990	0.110*
H24B	0.7214	0.3359	0.3827	0.110*
H24C	0.6663	0.3610	0.5226	0.110*
C25	−0.0062(4)	0.41106(7)	−0.0349(4)	0.0526(5)
H25A	−0.0351	0.3882	−0.0993	0.079*
H25B	−0.1120	0.4276	−0.1257	0.079*
H25C	−0.0132	0.4097	0.0933	0.079*
C26	0.0439(4)	0.48055(6)	0.2371(4)	0.0481(5)
H26A	0.0504	0.4952	0.3474	0.072*
H26B	0.0082	0.4568	0.2561	0.072*
H26C	−0.0649	0.4895	0.1065	0.072*
C27	0.5704(3)	0.52206(6)	0.2482(3)	0.0401(4)
H27A	0.5471	0.5175	0.1097	0.060*
H27B	0.6680	0.5048	0.3410	0.060*
H27C	0.6317	0.5452	0.2903	0.060*
C28	−0.0076(4)	0.58161(7)	0.3055(5)	0.0602(6)
H28A	−0.1356	0.5919	0.1962	0.090*
H28B	0.0070	0.5891	0.4373	0.090*
H28C	−0.0189	0.5564	0.2960	0.090*
C29	0.0850(4)	0.65196(6)	−0.1532(3)	0.0485(5)
C30	0.4721(5)	0.65655(7)	−0.0464(5)	0.0639(7)
H30A	0.4459	0.6481	−0.1803	0.096*
H30B	0.6160	0.6501	0.0550	0.096*
H30C	0.4576	0.6818	−0.0504	0.096*
C31	−0.1643(5)	0.70011(7)	−0.2759(4)	0.0608(6)
H31A	−0.2353	0.7134	−0.2110	0.073*
H31B	−0.2623	0.6817	−0.3600	0.073*
C32	−0.1131(4)	0.72410(6)	−0.4108(4)	0.0535(6)
C33	−0.0552(6)	0.71064(8)	−0.5519(5)	0.0735(8)

Table 2 (continued)

Atom	x	y	z	U_{iso}^*/U_{eq}
H33	−0.0543	0.6864	−0.5700	0.088*
C34	0.0021(7)	0.73309(11)	−0.6676(6)	0.0915(11)
H34	0.0446	0.7239	−0.7613	0.110*
C35	−0.0038(6)	0.76938(10)	−0.6440(6)	0.0884(10)
H35	0.0379	0.7845	−0.7194	0.106*
C36	−0.0701(6)	0.78244(8)	−0.5118(6)	0.0791(9)
H36	−0.0803	0.8067	−0.5000	0.095*
C37	−0.1226(5)	0.76019(7)	−0.3943(5)	0.0648(7)
H37	−0.1656	0.7696	−0.3015	0.078*
C38	0.6153(4)	0.30643(7)	−0.0668(4)	0.0609(7)
C39	0.6069(6)	0.26696(8)	−0.0651(6)	0.0833(10)
H39A	0.6054	0.2592	0.0596	0.125*
H39B	0.7318	0.2575	−0.0703	0.125*
H39C	0.4781	0.2589	−0.1834	0.125*

synthesized by two-step reaction in turn. Glycyrrhetic acid was reacted with benzyl bromide and K₂CO₃ in DMF at room temperature for 1 h. The solution was dissolved in ice water and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na₂SO₄. After filtration, the ethyl acetate was evaporated in vacuo to yield a transparent oil. Then the acetic anhydride and 4-dimethylaminopyridine was added to a stirred solution of the products in pyridine at room temperature. The resulting solution was stirred at r.t. for 2 h and then poured into ice water, resulting in the title compound as the white powder. Suitable crystals of the title compound were obtained by recrystallization in dichloromethane and methanol.

Experimental details

Hydrogen atoms were situated in idealized positions with the carrier atom-H distances = 0.93 Å for alkene and aryl, 0.96 Å for methyl, 0.97 Å for methylene and 0.98 Å for methine.

The U values of the hydrogen atoms of methyl groups were set to 1.5 U_{eq} and the U values of all other hydrogen atoms were set to 1.2 U_{eq} (C). The absolute configuration was derived from the synthesis.

Comment

18 β -Glycyrrhetic acid (GA) is the main metabolite of glycyrrhizin. The pentacyclic system of GA is composed of condensed six-membered rings and a five-membered ring. At present, the structural modification of this compound mainly focuses on the hydroxyl group at C-3, the carboxyl group at C-20, and the ketone functional group at C-11 [4]. It has been shown to have numerous pharmacological effects, such as

anti-inflammatory [5, 6], anticancer [7, 8], antibacterial [9], antiviral [10]. The structural modification of glycyrrhetic acid may be valuable in obtaining new chemical derivatives for pharmacological screening and structure-activity relationship studies.

The single-crystal which was measured is obtained by crystallization in dichloromethane and methanol solution. As shown in figure, for the title compound, all the rings adopt chair conformations, except the enone ring, which is flattened to a half-chair. The sole *cis* ring juncture, between the benzyl ester-bearing ring and its neighbor, confers little skeletal flexibility because two of the remaining ring junctures are *trans* and the third involves an alkene. Three carbon-oxygen double bond exist in the compound, the C—O bond distance (C3—O1) is 1.463(3) Å, the C—O bond distance (C38—O1) is 1.330(3) Å; the C—O double bond distance (C11—O2) is 1.216(3) Å; the C—O double bond distance (C29—O3) is 1.202(3) Å; the C—O bond distance (C29—O4) is 1.336(3) Å, the C—O bond distance (C31—O4) is 1.463(3) Å; the C—O double bond distance (C38—O5) is 1.194(4) Å. The O3—C29—O4, O5—C38—O1 angles are 123.0(2)°, 123.8(3)°, respectively. The bond lengths and angles are all in the expected ranges.

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References

1. Agilent Technologies: CrysAlis^{PRO}. Agilent Technologies, Santa Clara, CA, USA (2013).
2. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J., Howard, J. A. K.; Puschmann, H.: OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **42** (2009) 339–341.
3. Sheldrick, G. M.: A short history of SHELX. *Acta Crystallogr. A* **64** (2008) 112–122.
4. Langer, D.; Czarczynska-Goslinska, B.; Goslinski, T.: Glycyrrhetic acid and its derivatives in infectious diseases. *Curr. Issues Pharm. Med. Sci.* **29** (2016) 118–123.
5. Kim, S. H.; Hong, J. H.; Lee, J. E.; Lee, Y. C.: 18 β -Glycyrrhetic acid, the major bioactive component of *Glycyrrhizae Radix*, attenuates airway inflammation by modulating Th2 cytokines, GATA-3, STAT6, and Foxp3 transcription factors in an asthmatic mouse model. *Environ. Toxicol. Phar.* **52** (2017) 99–113.
6. Jeon, Y. D.; Kang, S. H.; Bang, K. S.; Chang, Y. N.; Lee, J. H.; Jin, J. S.: Glycyrrhetic acid ameliorates dextran sulfate sodium-induced ulcerative colitis in vivo. *Molecules* **21** (2016) 523.
7. Wang, X. X.; Zhang, Y. Q.; Xiao, J.; Zhang, K.; Li, Q. X.; Chen, H. W.; Liu, F.: 18 beta-Glycyrrhetic acid ameliorates the cognitive functions and decreases the recurrence rate of pituitary adenomas patients. *EXCLI J.* **17** (2018) 753–761.
8. Csuk, R.; Schwarz, S.; Siewert, B.; Kluge, R.; Ströhl D.: Synthesis and antitumor activity of ring A modified glycyrrhetic acid derivatives. *Eur. J. Med. Chem.* **46** (2011) 5356–5369.
9. Kannan, S.; Sathasivam, G.; Marudhamuthu, M.: Decrease of growth, biofilm and secreted virulence in opportunistic nosocomial *Pseudomonas aeruginosa* ATCC 25619 by glycyrrhetic acid. *Microb. Pathog.* **126** (2019) 332–342.
10. Hardy, M. E.; Hendricks, J. M.; Paulson, J. M.; Faunce, N. R.: 18 β -Glycyrrhetic acid inhibits rotavirus replication in culture. *Virology J.* **9** (2012) 96.