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ORIGINAL PAPER

X-ray Crystal Structure of Grandiflorenic Acid [(−)-kaura-9(11)-16-dien-19-oic Acid] Methyl Ester, a Compound Formerly Considered as an Oily Derivative

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Abstract Grandiflorenic acid [(−)-kaura-9(11)-16-dien-19-oic acid] methyl ester (**2**), $C_{21}H_{30}O_2$, was synthesized from grandiflorenic acid, isolated from the plant *Montanoa tomentosa*. Compound (2) was formerly described as an oily derivative. X-ray diffraction analysis of (2) demonstrated that it consists of four rings, three six-membered rings (I, II and III) and one five-membered ring (IV). I, II and III rings occur in chair, twist, and envelope conformations, respectively. Ring IV occurs in a conformation between envelope and half-chair. The crystal of grandiflorenic acid methyl ester is in monoclinic crystal system with space group $P2_1$, lattice constants: $a = 7.2170(10)$, $b = 11.4170(10)$, $c = 11.2850(10)$ Å, $\beta = 98.700(10)°$, $V = 919.1(2)$ Å^3 and $Z = 2$.

Keywords Diterpenes · Kauradienoic acid derivative · Structure and stereochemistry

Introduction

The synthesis and assessment of the spatial conformation of grandiflorenic acid methyl ester **2** is a relevant topic due to the important pharmacological effects reported for the parent grandiflorenic (or kauradienoic) acid **1** and related compounds [1].

We have previously carried out a comparative study of the solution and crystal structures of three major terpenic acids present in *Montanoa tomentosa* including the parent acid compound **1** used herein [2].

The synthesis of grandiflorenic acid and its methyl ester derivative **2** prepared with diazomethane has been reported [3], and the latter compound was described as an uncrystallizable oil although its spectroscopic data (IR, ^{1}H-NMR, MS) agree with the expected structure. Since other reports refer to the isolation of **1** and its derivatization into the methyl ester **2** [4, 5] a definitive proof of structure is necessary to meet the growing importance in assessing the molecular arrangements for this type of compounds [6]. In the present work, the esterification of grandiflorenic acid was accomplished with an ethereal solution of diazomethane produced by reaction of *N*-nitroso-methyl urea and aqueous KOH. The reaction gave a single product by TLC which proved adequate to obtain single crystals of **2**.

In this paper, we report the synthesis and crystal structure of grandiflorenic acid methyl ester **2** derived from *N*-nitroso-methyl urea/KOH/eter system with grandiflorenic acid **1**.

The need for a definitive proof of the crystal structure of **2** is due to the growing importance in assessing the molecular arrangements known for this type of compounds [6].

Experimental

Synthesis

The title compound **2** was synthesized by addition of an ethereal solution (20 mL) of *N*-nitroso-*N*-methyl urea (5 g)

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Table 1 Crystal data, collection parameters and refinements for compound **2**

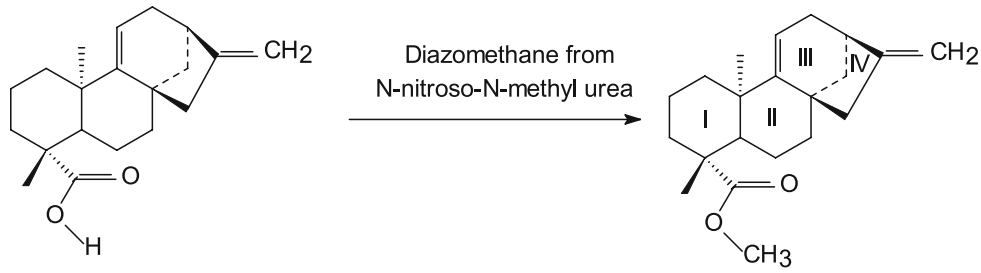
Compound	**2**
CCDC deposit no.	639253
Crystal size (mm)	0.50 × 0.28 × 0.26
Color/shape	Colorless/prism
Empirical formula	$C_{21}H_{30}O_2$
Formula weight	314.45
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	7.2170(10)
b, (Å)	11.4170(10)
c (Å)	11.2850(10)
β (°)	98.700(10)
Volume (Å)^3	919.1(2)
Z	2
Density (calculated) (g cm^{-3})	1.136
Absorption coefficient (mm^{-1})	0.547
$F_{(000)}$	344
θ range for data collection (°)	2.16–24.99
Index ranges	$-1 \le h \le 7$, $-1 \le k \le 12$, $-12 \le l \le 12$
Reflections collected/unique	1,856/1,457
Observed reflections ($I > 2\sigma(I)$)[a]	1,354($R_{int} = 0.0236$)
Data/restraints/parameters	1,354/0/209
Goodness-of-fit[a] on F^2	1.067
Final R indices [$(I) > 2\sigma(I)$][a]	$R_1 = 0.0378$, $wR_2 = 0.1062$
R indices (all data)[a]	$R_1 = 0.0410$, $wR_2 = 0.1097$
Largest diff. peak and hole (e A^{-3})	0.119 and −0.113

[a] $R_{int} = \frac{\sum |F_o^2 - (F_o^2)|}{\sum F_o^2}$, $R_1 = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$, $wR_2 = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}}$, $S = \sqrt{\frac{\sum w(F_o^2 - F_c^2)^2}{m-n}}$

to KOH (1.0N, 30 mL) solution. The formation of diazomethane was corroborated by a yellowish coloration ethereal phase. The organic phase was separated and 15 mL of grandiflorenic acid (50 mg) was slowly added to it. The reaction mixture was stirred on an ice bath during the addition. When diazomethane was completely added, the mixture was allowed to room temperature, and ether was removed by slow evaporation. White single crystals of compound **2** were obtained from MeOH by slow evaporation and mp 55–57 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm main signals: 5.23, 4.91, 4.79 (vinylic hydrogens), 1.18 and

Table 2 Bond distances (Å) and angles (°) for compound **2**

Bond lengths (Å)			
O1–C19	1.331(5)	O1–C21	1.447(5)
O2–C19	1.188(4)	C1–C2	1.519(5)
C1–C10	1.536(5)	C2–C3	1.492(7)
C3–C4	1.542(5)	C4–C19	1.528(5)
C4–C18	1.533(5)	C4–C5	1.565(4)
C5–C6	1.525(5)	C5–C10	1.547(4)
C6–C7	1.520(5)	C7–C8	1.518(5)
C8–C9	1.524(5)	C8–C15	1.540(4)
C8–C14	1.540(4)	C9–C11	1.330(5)
C9–C10	1.545(4)	C10–C20	1.539(4)
C11–C12	1.513(5)	C12–C13	1.519(7)
C13–C16	1.514(5)	C13–C14	1.517(5)
C15–C16	1.512(4)	C16–C17	1.314(5)
Bond angles (°)			
C19–O1–C21	116.5(4)	C2–C1–C10	114.0(3)
C3–C2–C1	110.2(3)	C2–C3–C4	114.9(3)
C19–C4–C18	107.3(3)	C19–C4–C3	107.5(3)
C18–C4–C3	109.1(3)	C19–C4–C5	115.3(2)
C18–C4–C5	109.3(3)	C3–C4–C5	108.2(3)
C6–C5–C10	113.9(3)	C6–C5–C4	113.0(3)
C10–C5–C4	116.2(2)	C7–C6–C5	114.7(3)
C6–C7–C8	113.7(3)	C7–C8–C9	111.5(3)
C7–C8–C15	114.5(3)	C9–C8–C15	108.4(2)
C7–C8–C14	112.1(3)	C9–C8–C14	108.9(3)
C15–C8–C14	100.9(2)	C11–C9–C8	118.7(3)
C11–C9–C10	122.8(3)	C8–C9–C10	118.5(2)
C1–C10–C20	109.7(3)	C1–C10–C9	109.3(3)
C20–C10–C9	108.9(3)	C1–C10–C5	108.0(3)
C20–C10–C5	112.8(3)	C9–C10–C5	108.1(2)
C9–C11–C12	123.2(4)	C13–C12–C11	112.7(3)
C16–C13–C12	110.6(3)	C16–C13–C14	102.7(3)
C12–C13–C14	107.6(3)	C13–C14–C8	101.5(3)
C16–C15–C8	104.8(3)	C17–C16–C13	126.2(3)
C17–C16–C15	126.2(3)	C13–C16–C15	107.6(3)
O2–C19–O1	121.2(4)	O2–C19–C4	126.3(3)
O1–C19–C4	112.4(3)		



Scheme 1 Synthesis of grandiflorenic acid [(−)-kaura-9(11)-16-dien-19-oic acid] methyl ester

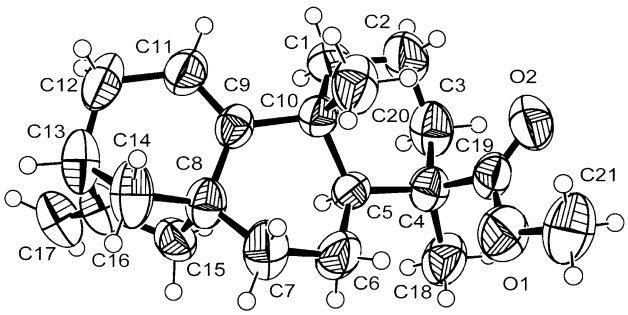


Fig. 1 Molecular structure of **2**, with displacement ellipsoids at the 50% probability level. Hydrogen atoms are drawn as *circles* with an arbitrary radius

0.931 (methyl groups); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 177.95, 158.55, 156.02, 114.86, 105.43, 51.24, 50.33, 46.64, 44.96, 44.88, 42.27, 41.26, 40.82, 38.65, 38.43, 37.92, 29.75, 28.17, 23.48, 20.24, 18.60, MS (EI, 70 eV) (*m/z*, %) 314 (M^+, 62), 299 (100), 255 (32), 239 (95). IR KBr (cm^{-1}): 2,936, 1,717, 1,462, 1,432, 1,208, 1,147.

Crystal Structure Determination

X-ray data were collected on a Nicolet P3/F Single crystal diffractometer with a graphite monochromator and Mo–Kα radiation ($\lambda = 0.71073$ Å) by the ω-scan method. The observed reflections were corrected for Lorentz and polarization effects, but not for X-rays absorption. The structure was solved using direct methods and refined [7] on F^2 by full-matrix least-squares with anisotropic displacements parameters for all non-hydrogen atoms. All hydrogen atoms were geometrically fixed and allowed to ride on the parent C atoms. The crystals data and pertinent details of the experimental conditions are summarized in Table 1. The software used to prepare material for publication was PARST97 [8]. The synthetic scheme for the synthesis of compound **2** is depicted in Scheme 1.

Results and Discussion

Table 2 gives the bond distances and bond angles of non-hydrogen atoms, respectively. In all essential details, the molecular geometry of (2) in terms of the bond lengths and angles are in good agreement with standard values. However, the C10–C5–C4 and C19–C4–C5 bond angles of 116.2(2) and 115.3(2)° have been increased to minimize the steric interactions between the methyl group at C10 and the O atoms of the methyl ester group at C4. Figure 1 represents the ORTEP [9] diagram of the molecule with thermal ellipsoids drawn at 50% probability. The molecule is comprised of a quadricyclic skeleton consisting of three six-membered rings (I, II and III) and one five-membered ring (IV). Rings I:II, and II:III are *cis*- and *trans*-fused at C5–C10 and C8–C9, respectively. Ring IV is fused at C8–C14–C13 to ring III. For the puckering-parameters values (Φ_2, θ_2 and Q) [10], rings I, II and III occur in chair ($^4C_1$), twist ($^3T_1$), and envelope (E_6) conformations, respectively. Ring IV occurs in a conformation between envelope and half-chair. Although the absolute configuration could not be determined from the diffraction data alone, it was

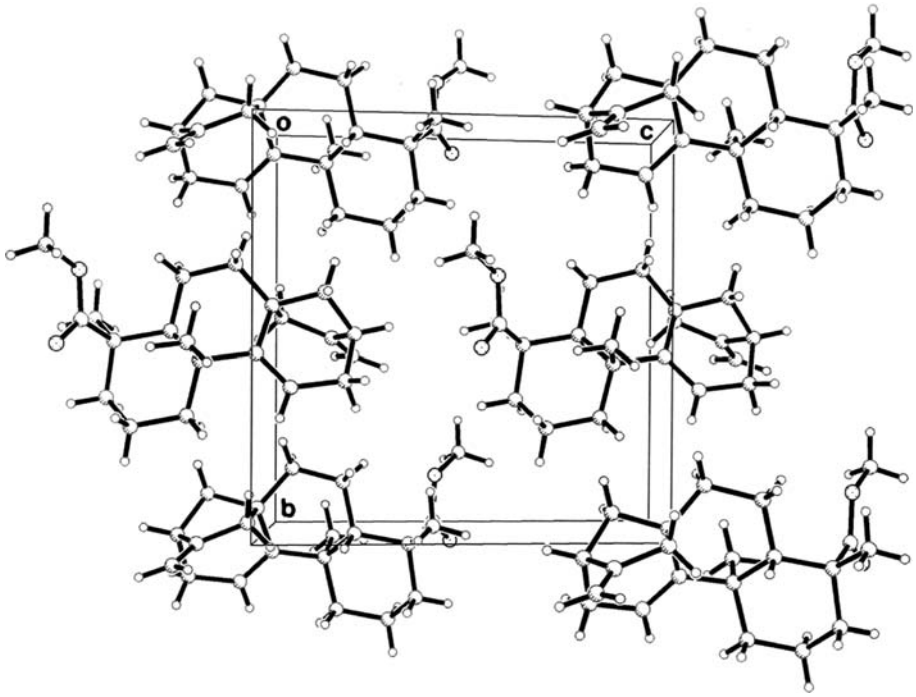


Fig. 2 The packing diagram for **2** projected along the *a*-axis

established by the configuration of compound **1**. The stereochemistry of the title compound is as follows: C5–βH is *trans* to C10–αCH_3; C5–βH is *trans* to C4–$\alpha COOCH_3$; C5–βH is *cis* to C4–βCH_3. Figure 2 shows the unit-cell packing arrangement for two along the *a*-axis. The molecules in the crystal are packed at normal van der Waals distances.

Supplementary Materials

CCDC-639253 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44-1223-336033.

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