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Chemistry and Structure of Diterpene Compounds of the Kaurane Series: IV.[1] Acylation of Reduction Products of the Isosteviol Keto Group

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Abstract — Acetylation with acetic anhydride of (4α,8β,13β)-16-hydroxy-13-methyl-17-norkaurane-18-carboxylic acid and its methyl ester, obtained by reduction of isosteviol and (4α,8β,13β)-18-methoxycarbonyl-13-methyl-16-oxo-17-norkaurane, respectively, gives rise to (4α,8β,13β)-16-acetoxy-13-methyl-17-norkaurane-18-carboxylic acid and (4α,8β,13β)-16-acetoxy-18-methoxycarbonyl-13-methyl-17-norkaurane. The molecular and crystal structures of the compounds were established by X-ray diffraction.

Earlier we studied reduction with sodium borohydride with the tetracyclic kauranoid isosteviol (**I**) isolated from *Stevia rebaudiana Bertoni* and obtained an individual reduction product of the keto group at C^{16}, namely, (4α,8β,13β)-16-hydroxy-13-methyl-17-norkaurane-18-carboxylic acid (II) [2]. It was found that the reaction occurs with a high degree of regio- and stereocontrol as a result from the attack of the borohydride anion from the least sterically hindered side of the isosteviol keto group, leading to a product with *gauche* orientation of the hydroxy group at C^{16} and the methyl group at C^{13}. The structure of hydroxyacid **II** was established by X-ray diffraction [2].

In the present communication we report the results of reduction of isosteviol methyl ester (**III**), acylation of the resulting hydroxy derivative **IV**, as well as acylation of hydroxyacid **II**. Methyl ester **III** was obtained by the reduction of isosteviol (**I**) with diazomethane by the scheme described in [3]. The reduction of methyl ester **III** with sodium borohydride in the same conditions as of isosteviol (**I**) results in a highly selective formation of (4α,8β,13β)-16-hydroxy-18-methoxycarbonyl-13-methyl-17-norkaurane (**IV**). From the reaction mixture which, according to TLC data, contained a single component of the kaurane structure we isolated compound **IV**. The IR spectrum of the latter lacked the ketone C=O absorption band of the starting ketone **III** at 1740 cm^{-1} and contained a broad band of stretching vibrations of associated OH group at 3540 cm^{-1}.

To detect the possible admixtures of stereoisomeric reduction products of isosteviol (**I**) and its methyl ester (**III**), we performed acylation of crude hydroxy derivatives **II** and **IV** with acetic anhydride. It is known that alcohol acetates as less polar products are better separated by TLC than the corresponding alcohols. This approach was earlier used to reveal as acetate a small admixture of the isomeric product in the starting alcohol [4]. The compositions of the mixtures resulting from acylation of compounds **II** and **IV** with acetic anhydride were studied by TLC. Both with hydroxyacid **II** and with hydroxyester **IV**, the acetylation smoothly occurs in excess acetic anhydride, involving the hydroxy group at C^{16} and yielding acetates **V** and **VI**, respectively. Thin-layer chromatography revealed no isomeric admixtures. The structure of compounds **V** and **VI** was proved by ^1H NMR and IR spectroscopy. The ^1H NMR spectra of acetates **V** and **VI** show, along with a complex set of signals of the tetracyclic kaurane skeleton, singlets at δ 2.00 and 2.13 ppm, respectively, due to CH_3COO protons. The IR spectra of these compounds contain the CH_3COO bands at 1723 (**V**) and 1740 (**VI**) cm^{-1}.

Thus, isosteviol (**I**) and its methyl ester (**III**) were reduced with sodium borohydride to obtain stereoisomerically pure hydroxy derivatives **II** and **IV**, whose reaction with acetic anhydride gave acetates **V** and **VI**.

[1] For communication III, see [1].

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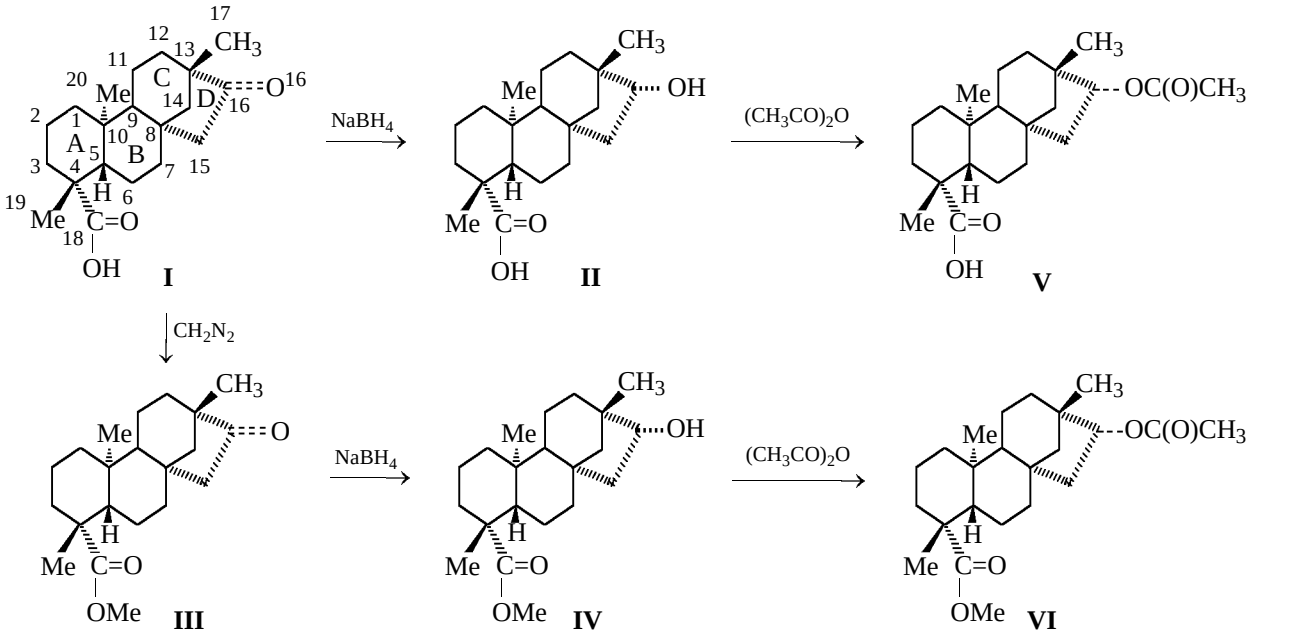

By analogy with the previously established steric structure of compound **II** [1], we can propose that compound **IV,** too, has the 13-CH_3 group *gauche* with respect to 16-OH, which should result from the fact that the hydrogenating agent approaches from the least sterically hindered side of the keto group at C^{16}.

For conclusive structural assessment of compounds **III**–**VI** ww used X-ray diffraction analysis. The resulting structures are depicted in Figs. 1–4. The crystal cell of **VI** contains two symmetrically independent molecules. The structures of the tetracyclic parts of molecules **III**–**VI** are in general similar to each other and to the structure of isosteviol (**I**) and its reduction product **II**, described in [2, 5]. The chiral atoms in the molecules have, according to X-ray diffraction data, the following absolute configurations: (*R*)-C^4, (*S*)-C^5, (*R*)-C^8, (*S*)-C^9, (*S*)-C^{10}, and (*S*)-C^{13}. Kauranes **IV**–**VI** have one more chiral atom, (*R*)-C^{16}.

The functional groups (carboxyl, ester, acetate) have published parameters [6]. The characteristic torsion angles are listed in Table 1. The torsion angles in compounds **IV**–**VI** are rather close to each other. At the same time, the ester group in isosteviol methyl ester (**III**), by contrast to what is observed in the other molecules, is turned about the C^4–C^{18} bond so that the methoxy group at C^{18} and the $C^{20}H_3$ group are in the *anti* position with respect to the tetracyclic carcass (Table 1, Figs. 1–4). Moreover, the conformation of the $C^{17}C^{13}C^{16}O^{16}$ fragment in this compound is close to *syn-periplanar*. The magnitude of the corresponding torsion angle [–36(1)°] is consistent with that we determined in isosteviol (**I**) [30.5(4)°] [5]. The distance between C^{17} and O^{16} in methyl ester **III** is smaller than the sum of the van der Walls radii of these atoms. This follows from a comparison of certain nonbonded distances (Å) in compound **III** [the sum of the van der Waals radii (ΣR) of carbon atoms is 3.44 Å; the ΣR for carbon and oxygen atoms is 3.12 Å].

$C^{15}\cdots C^{11}$	2.93	$C^{16}\cdots C^{14}$	2.30
$C^{16}\cdots C^{9}$	3.17	$C^{16}\cdots C^{17}$	2.53
$C^{16}\cdots C^{11}$	2.81	$C^{17}\cdots O^{16}$	2.91
$C^{16}\cdots C^{12}$	2.45		

Hydroxyester **IV** obtained with a high degree of stereoselectivity by reduction of methyl ester **III** with

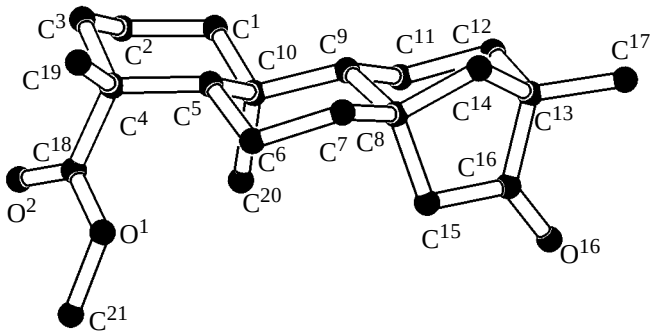

Fig. 1. Molecular geometry of (4α,8β,13β)-18-methoxycarbonyl-13-methyl-16-oxo-17-norkaurane (**III**) in crystal (hydrogen atoms are omitted).

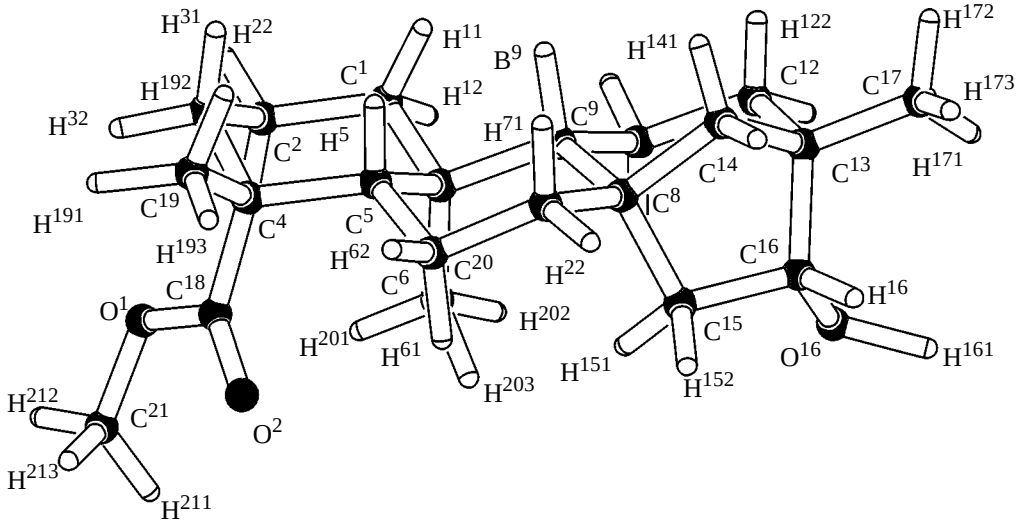

Fig. 2. Molecular geometry of (4α,8β,13β)-16-hydroxy-18-methoxycarbonyl-13-methyl-17-norkaurane (**IV**) in crystal.

sodium borohydride has *sc* orientation of the hydroxy group at C^{16} and the methyl group at C^{13} (Fig. 2). Such orientation is consistent with the mechanism of this reaction we proposed in [2], according to which the nucleophilic attack of complex metal hydrides occurs from the least sterically hindered side of the starting ketone. Actually, the access to the reaction center C^{16} from under the $C^8C^{15}C^{16}C^{13}$ plane of five-membered ring D is hindered by only two short intramolecular interatomic contacts $C^{16}\cdots C^{17}$ and $C^{16}\cdots C^{14}$, whereas the access to C^{16} from the other side of five-membered ring D is hindered by a minimum three short intramolecular interatomic contacts $C^{16}\cdots C^{11}$, $C^{16}\cdots C^{12}$, and $C^{16}\cdots C^{9}$.

EXPERIMENTAL

X-ray diffraction analysis of compounds III–VI (Table 2) was performed on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (λCuK_α radiation, λ 1.54184 Å, graphite monochromator, ω/2θ scanning, $4.2 \le \theta \le 74.3°$, scan angle $\omega = 1.2 + 0.35\tan\theta$, varied scan rate, 1–16.4 deg/min in θ). No intensity decay of control reflections was observed during

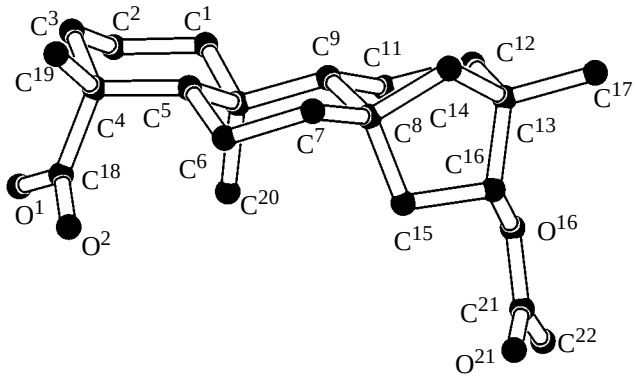

Fig. 3. Molecular geometry of (4α,8β,13β)-16-acetoxy-13-methyl-17-norkaurane-18-carboxylic acid (**V**) in crystal (hydrogen atoms are omitted).

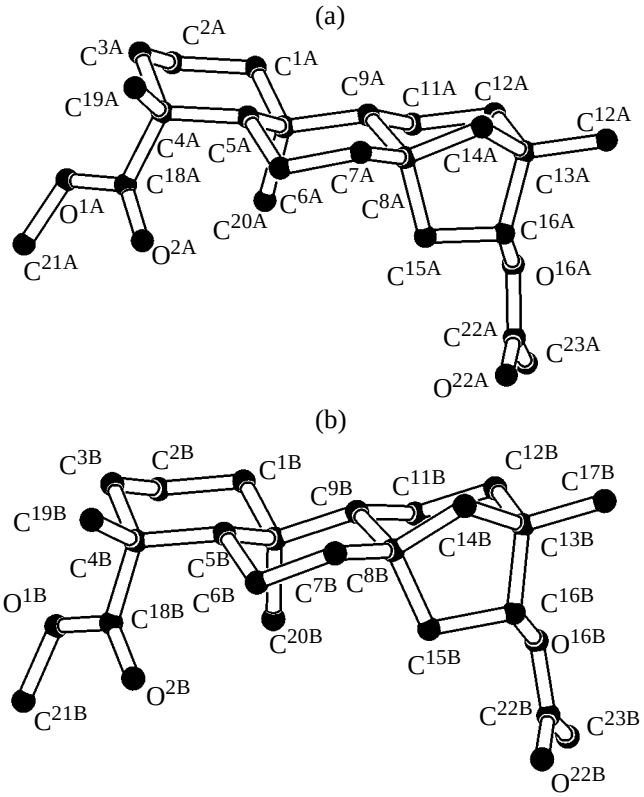

Fig. 4. Geometry of the independent molecules (a) **Va** and (b) **Vb** of (4α,8β,13β)-16-acetoxy-13-methyl-18-methoxycarbonyl-17-norkaurane in crystal (hydrogen atoms are omitted).

Table 1. Principal torsion angles (τ, deg) characterizing conformations of functional groups in compounds **III**–**VI**

Angle	**III**	**IV**	**V**	**VIa**	**VIb**
$C^{19}C^{4}C^{18}O^{1}$	–68.2(7)	108.3(6)	120.1(6)	99.4(2)	99.1(2)
$C^{19}C^{4}C^{18}O^{2}$	102.8(9)	–65.0(8)	–58.3(8)	–74.9(3)	–76.9(3)
$C^{5}C^{4}C^{18}O^{1}$	56.9(8)	–131.0(6)	–120.6(6)	–140.7(2)	–141.5(2)
$C^{4}C^{18}O^{1}C^{21}$	178.7(6)	–176.2(6)	–	–171.8(2)	–173.7(2)
$C^{4}C^{18}O^{1}H^{1}$	–	–	–147.2(5)	–	–
$C^{17}C^{13}C^{16}O^{16}$	–36(1)	–79.9(7)	–82.6(7)	–82.7(2)	–83.9(2)
$C^{13}C^{16}O^{16}H^{161}$	–	94.0(6)	–	–	–
$C^{16}O^{16}C^{21}O^{21}$	–	–	0.8(9)	–	–
$C^{16}O^{16}C^{22}O^{22}$	–	–	–	1.6(3)	–1.0(3)

Table 2. Crystal data for compounds **III**–**VI** and recording conditions[a]

Parameter	**III**	**IV**	**V**	**VI**
Unit cell parameters[b], Å				
a	8.887(6)	7.543(2)	7.5358(8)	12.491(5)
b	7.473(2)	14.923(3)	14.345(6)	8.576(5)
c	27.04(2)	16.750(4)	18.969(8)	39.92(2)
Volume, Å^3	1796(2)	1885.3(7)	2051(1)	4276(2)
Molecular weight	344.50	320.48	361.51	375.53
d_{calc}, g/cm^3	1.27	1.13	1.17	1.17
Absorption coefficient, cm^{-1}	6.13	0.69	5.94	5.86
F(000)	752	704	788	1640
Range of *h*, *k*, *l*	$0 \le h \le 11$, $0 \le k \le 9$, $-33 \le l \le 33$	$-9 \le h \le 0$, $-18 \le k \le 0$, $-20 \le l \le 0$	$0 \le h \le 9$, $0 \le k \le 17$, $-23 \le l \le 0$	$-13 \le h \le 0$, $-9 \le k \le 0$, $-43 \le l \le 39$
Reflections collected	4041	2219	2422	6944
Reflections with $I > 3\sigma(I)$	1628	970	1319	6275
Final divergence factors				
R	0.066	0.049	0.053	0.042
R_W	0.067	0.054	0.054	0.055
GOF	1.668	1.600	1.215	1.972
Reflections in final refinment cycles	1092	877	1150	5971

[a] The crystals of compounds **III**–**VI** are colorless, of prismatic shape, of rhombic syngony, space group $R2_12_12_1$, in structures **III**–**V** *Z* 4, in structure **VI** *Z* 8 (two independent molecules). [b] Values in parentheses are standard deviations.

measurements; no corrections for absorption were introduced; all computations were performed on Alpha Station-200 using the MolEN program package [7]; direct decoding, program SIR [8]; full-matrix least-squares refinment; minimization on $\Sigma w(|Fo| - |Fc|)^2$; no correction for extinction was applied; $4F_0^2/[\sigma(I)^2 + (0.04F_0^2)]^2$ weight scheme. Hydrogen atoms were revealed from difference electron density series after anisotropic refinment of non-hydrogen atoms, and their contributions in structure amplitudes were included in further refinment cycles with fixed positional and isotropic thermal parameters. Attempted establishment of the absolute crystal structures and, consequently, of the absolute molecular configurations of **III**–**VI** by the Hamilton method failed. The absolute molecular configurations of **III**–**VI** were set by the absolute molecular configuration of **I**, established in [1]. Analysis of intermolecular contacts, including hydrogen bonds in crystals, was performed using the PLATON program [9]. The crystal data,

recording conditions, and refinment results are given in Table 2. The atomic coordinates and geometric parameters of the structures are deposited in the Cambridge Structural Database and are also available from the authors.

The IR spectra were measured on a UR-20 spectrophotometer in the range 400–3600 cm^{-1} in Vaseline oil. The ^1H NMR spectra were obtained on Varian T-60 and Bruker MSL-400 instruments.

(4α,8β,13β)-18-Methoxycarbonyl-13-methyl-16-oxo-17-norkaurane (**III**) was obtained by treatment of isosteviol (**I**) with diazomethane (cf. [3]).

(4α,8β,13β)-16-Hydroxy-18-methoxycarbonyl-13-methyl-17-norkaurane (IV). To a solution of 0.77 g of compound **III** in 70 ml of methanol, heated to 50°C, we added 2.0 g of $NaBH_4$. The reaction mixture was left to stand at room temperature for 2 days, after which it was poured into water acidified with HCl, and the reaction product was extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with water, dried with $MgSO_4$, and the ether was removed to obtain 0.62 g (80%) of compound **IV**, mp 173–174°C (from methanol) (163–166°C [3]), $[\alpha]_D^{20}$ –74.9° (*c* 1.59, EtOH). IR spectrum, ν, cm^{-1}: 1714 (C=O), 3540(OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.63, 0.80, 1.11 s (9H, 10-CH_3, 13-CH_3, 4-CH_3); 3.59 s (3H, $COOCH_3$).

(4α,8β,13β)-16-Acetoxy-13-methyl-17-norkaurane-18-carboxylic acid (V). To a solution of 0.3 g of compound **II** in 25 ml of pyridine we added 15 ml of acetic anhydride. The reaction mixture was left to stand at room temperature for 2 days, poured into water acidified with HCl, and the reaction product was extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with water, dried with $MgSO_4$, and the ether was removed to obtain 0.28 g (82%) of compound **V**, mp 213–215°S (from methanol), $[\alpha]_D^{20}$ –79° (*c* 2.06, MeOH). IR spectrum, ν, cm^{-1}: 1705 (HOC=O), 1723 (CH_3C=O), 3260 (COOH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.78, 0.91, 1.11 s (9H, 10-CH_3, 13-CH_3, 4-CH_3); 0.85–2.12 m (kaurane carcass); 2.00 s (CH_3C=O).

(4α,8β,13β)-16-Acetoxy-18-methoxycarbonyl-13-methyl-17-norkaurane (VI) was obtained in a similar way from 0.1 g of compound **IV** in 10 ml of pyridine and 2.5 ml of acetic anhydride. Yield 0.08 g (73%), mp 97–99°C. IR spectrum, ν, cm^{-1}: 1730, 1740 (CH_3OC=O, CH_3C=O). ^1H NMR spectrum (CCl_4), δ, ppm: 0.87, 1.10, 1.32 s (9H, 10-CH_3, 13-CH_3, 4-CH_3); 0.85–2.12 m (kaurane carcass); 2.13 s (CH_3C=O); 3.70 s (3H, $COOCH_3$).

Crude alcohols **IV** and **V** obtained by reduction with sodium borohydride of compounds **I** and **III** were acetylated by the same procedures. The reaction mixtures were analyzed by TLC on Silufol UV-254 plates, eluents petroleum ether–ethyl acetate (1 : 1) and petroleum ether–diethyl ether (1 : 1).

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