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Chemistry and Structure of Diterpene Compounds of the Kaurane Series: VI.[1] Isosteviol Esters

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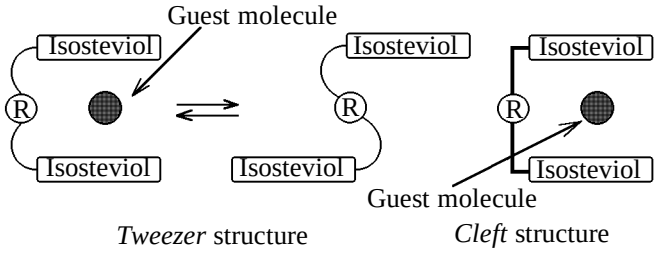
Abstract—Esterification with alcohols and diols of (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylic acid chloride prepared by treatment of the acid (isosteviol) with thionyl chloride yields the corresponding esters. The molecular and crystal structures of a series of esters were determined by single crystal X-ray diffraction. The diethylene glycol diester in the crystal has a *tweezer* structure with an intramolecular cavity. The supramolecular structure of some isosteviol derivatives in the crystal is characterized by alternation of lipophilic and hydrophilic regions.

We have initiated recently the studies of properties and molecular and supramolecular structures of derivatives of (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylic acid I (isosteviol), a diterpene of the kaurane series isolated pure from the hydrolysis products of sweet glycozides present in *Stevia rebaudiana Bertoni* plant [2]. Isosteviol with its rigid tetracyclic hydrocarbon skeleton and two polar reactive substituents (carboxy and carbonyl groups at the C^4 and C^{16} atoms, respectively), arranged on the one side of the tetracyclic core, seems to be an ideal starting compound for constructing complex molecular structures capable of noncovalent binding of small and medium-size molecules. The molecule (or molecular ensemble) serving as a basis for formation of a supramolecular structure is usually termed "host" or "receptor," and the molecule bound by it, "guest." The molecular recognition (and subsequent reception) can only be realized if the "host" and "guest" are complementary; the process is governed by specific (hydrogen and coordination bonds) and nonspecific (van der Waals, dispersion, electrostatic) attractive intermolecular interactions. An interest in molecular receptors is due to their high selectivity as sorbents, extractants, catalysts, matrices for separation of enantiomers, synthetic membranes, etc. [1–7]. Among numerous molecular receptors, the most attractive are the *tweezer* structures based on cholic acids [3, 4, 7] and *cleft* structures based on the so-called Kemp acid [5, 6, 8]. All these structures contain rigid hydrocarbon skeletons.

Similar *tweezer* and *cleft* structures can be obtained by reactions of isosteviol **I** with binucleophilic agents HX–R–XH (X = O, N, S; R is an aliphatic or aromatic fragment containing heteroatoms). If the chain R is conformationally labile, the resulting bisisosteviol derivatives will have the *tweezer* structure, and the mutual orientation of the rigid tetracyclic hydrocarbon moieties will be governed by the solvent effect. The isosteviol fragments will either hang over each other to form a cavity theoretically capable of binding "guest" molecules via the polar groups oriented inside, or turn apart from each other (as a result of competition of intracavity and outer-sphere specific and nonspecific interactions), releasing the "guest" molecule to the bulk of the solvent.



If the chain R is conformationally rigid, the so-called *cleft* structure will exist in media of any aggregation and polarity.

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

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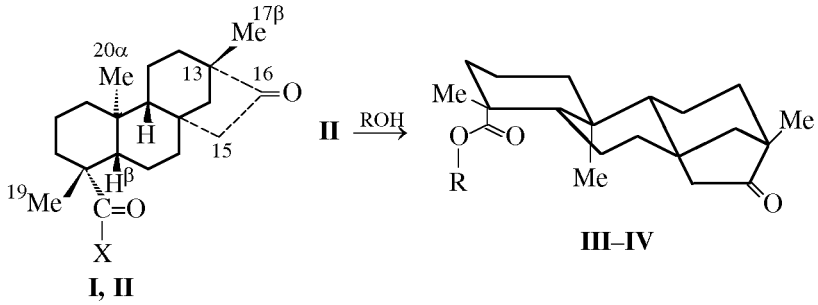
In this work we studied the products of reaction of isosteviol and its acid chloride **II** with mono- and bifunctional reagents and obtained the first representatives of the *tweezer* structures.

Chloride **II** was prepared previously by treatment of isosteviol with thionyl chloride [1, 9]. Refluxing of **II** in excess of appropriate alcohol, followed by purification of the reaction products by column chromatography, gave isosteviol esters **III**–**VI** in high yields (65–90%). All of them, except ester **V** isolated in the crystalline form, are viscous liquids. When the reactions were performed in the presence of triethylamine, the ester yields did not increase, but the product purification became more difficult because of problems with separation of the amine hydrochloride.

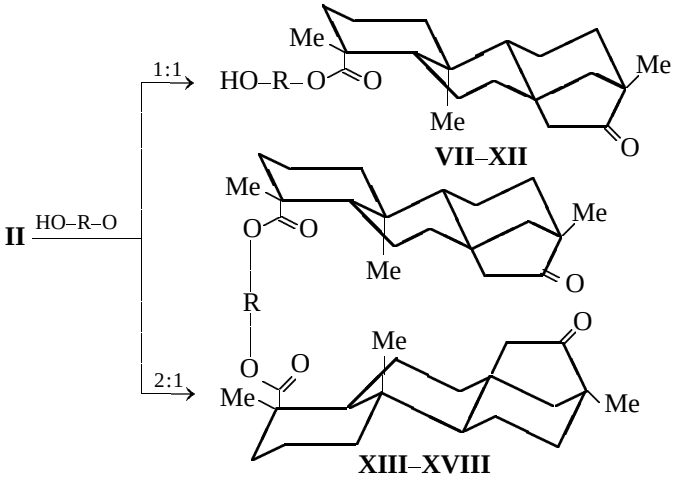


X = H (**I**), Cl (**II**); R = *n*-C_6H_{13} (**III**), *n*-$C_{10}H_{21}$ (**IV**), cyclohexyl (**V**), –H_2C–  (**VI**).

The structures of **III**–**VI** were proved by elemental analysis and by ^{1}H NMR and IR spectroscopy. The IR spectra of **III**–**VI** contain bands of the ester (~1160, 1180, 1720 cm^{-1}) and keto groups (~1740 cm^{-1}), whereas the OH absorption is absent (range above 3000 cm^{-1}).

Tetracyclic fragments of some steroids were successfully linked previously by reactions of diols with acid chlorides derived from appropriate natural acids [8]. We used a similar reaction for linking the kaurane cores of isosteviol. The degree of conversion and structure of the products depend on the reactant ratio.

Heating of equimolar amounts of **II** and a diol in CCl_4 in the presence of Et_3N gave monoesters **VII**–**XII** in 20–60% yields. According to TLC, the diesters are also always formed in these reactions in small amounts; the diesters can be isolated chromatographically. Only the monoesters of ethylene glycol (**VII**) and diethylene glycol (**XI**) were isolated in the crystalline form; the other monoesters are viscous liquids.



R = CH_2CH_2 (**VII, XIII**), $CH_2CH_2CH_2$ (**VIII, XIV**), $CH_2(CH_2)_2CH_2$ (**IX, XV**), $CH_2CH_2(CH_3)CH$ (**X, XVI**), $CH_2CH_2 \cdot OCH_2CH_2$ (**XI, XVII**), $CH_2(CH_2)_4CH_2$ (**XII, XVIII**).

The mass, ^{1}H NMR, and IR spectra confirm the structure of **VII**–**XII**. The IR spectra contain both the bands of the ester moiety and the OH stretching vibration bands at 3400–3600 cm^{-1}, as well as the C–O stretching bands at ~1060 cm^{-1} characteristic of primary alcohols. Compound **X** exhibits absorption at about 1100 cm^{-1} characteristic of secondary alcohols, which suggests predominant esterification of the primary hydroxy group. The ^{1}H NMR spectrum of this monoester contains no signal at about 5.0 ppm, which was assigned in the spectrum of **XVI** to the CH proton in the $CH_2(CH_3)C\mathit{H}OC(O)$ fragment (see below). This fact also confirmed occurrence of esterification at the primary hydroxyl of the diol. The methine protons in the $CH_2(CH_3)C\mathit{H}OH$ group give a complex multiplet together with the protons of the methylene group $CH_2OC(O)$ at 4.2 ppm.

The structure of **XI** was confirmed by single crystal X-ray diffraction. The molecular structure of **XI** is shown in Fig. 1. The $C^{22}O^{23}C^{24}C^{25}$ fragment of the oxypolymethylene chain in **XI** is virtually parallel to the tetracyclic core. The torsion angles (deg) in this conformation are as follows: $\varphi_1(C^{19}C^4C^{18}O^2)$ 111.58(0.40), $\varphi_2(C^{19}C^4C^{18}O^1)$ –65.26(0.35), $\varphi_3(C^4C^{18}O^1C^{21})$ –177.91(0.30), $\varphi_4(C^{18}O^1C^{21}C^{22})$ –168.32(0.33), $\varphi_5(O^1C^{21}C^{22}O^{23})$ –62.09(0.47), $\varphi_6(C^{21}C^{22}O^{23}C^{24})$ 141.76(0.42), $\varphi_7(C^{22}O^{23}C^{24}C^{25})$ –177.81(0.39), $\varphi_8(O^{23}C^{24}C^{25}O^{26})$ –87.24(0.54), and $\varphi_9(C^{24}C^{25}O^{26}H^{26})$ –60.24(0.55).

The hydroxyl hydrogen in the oxypolymethylene chain of one molecle of **XI** forms an intermolecular hydrogen bond O^{26}–$H^{26}\cdots O^{23'}$ [$d(H^{26}\cdots O^{23'})$ 2.28, $d(O^{26}$–$H^{26})$ 0.97, $d(O^{26}\cdots O^{23})$ 2.929(5) Å, $\angle(O^{26}$–$H^{26}\cdots O^{23'})$ 123°] with the ester oxygen atom in the oxypolymethylene chain of another molecule of **XI** [symmetry transformation (–1/2 + *x*, 1/2 – *y*, 1 – *z*)]. Also, there are nonclassical hydrogen bonds (short interatomic contacts) between the hydrogen atom of the methylene group in the ester moiety of **XI** and the keto oxygen atom of the same molecule, C^{22}–$H^{222}\cdots O^{16'}$ [$d(C^{22}$–$H^{222})$ 1.17, $d(H^{222}\cdots O^{16})$ 2.49, $d(C^{22}\cdots O^{16})$ 3.598(5) Å, $\angle(C^{22}$–$H^{222}\cdots O^{16})$ 157°], and between the hydrogen atom of the $C^{19}H_3$ methyl group and the carboxyl oxygen atom of another molecule, C^{19}–$H^{192}\cdots O^{2''}$ [$d(C^{19}$–$H^{192})$ 1.07, $d(H^{192}\cdots O^2)$ 2.53, $d(C^{19}\cdots O^2)$ 3.602(4) Å, $\angle(C^{19}$–$H^{192}\cdots O^2)$ 177°, symmetry transformation (–*x*, 1/2 + *y*, 1/2 – *z*)].

Refluxing of **II** with diols in a 2 : 1 ratio in CCl_4 in the presence of Et_3N gives, as a rule, the corresponding diesters **XIII**–**XVIII** in high yields (50–70%). According to TLC, a single reaction product is formed under these conditions, with its R_f being larger compared to **II**. Only with 1,3-butanediol a mixture of diester **XVI** with monoester **X** (33 and 17%, respectively) is formed. The TLC of the reaction mixture reveals two substances in this case: the diester whose R_f is larger than that of **II** and the monoester whose R_f is smaller than that of **II**. The above ratio (determined from the weights of the corresponding chromatographic fractions) is quite expected, because the secondary hydroxy group in 1,3-butanediol is acylated more difficultly than the primary hydroxy group. All the diesters obtained are crystalline substances. The IR spectra of **XIII**–**XVIII** contain characteristic ester absorption bands (1160, 1180, 1720 cm^{-1}), whereas the bands of hydroxy groups at 3400–3500 cm^{-1} are absent.

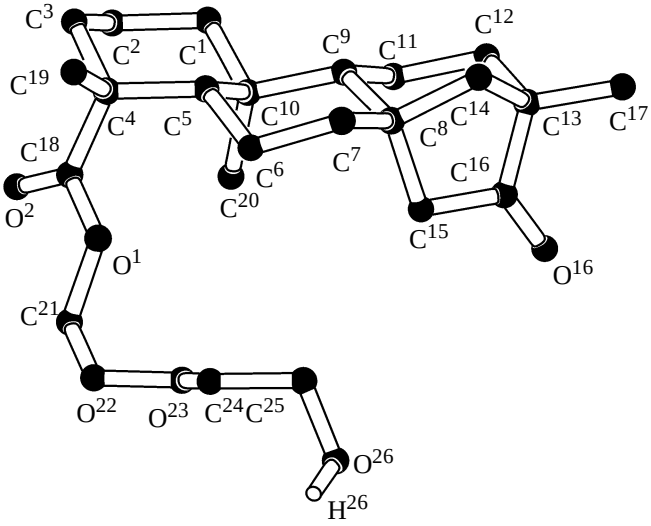


Fig. 1. Moleclar geometry of 2-(2-hydroxyethoxy)ethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate **XI**. Among hydrogen atoms, only the hydroxyl hydrogen in the ester moiety is shown.

The structure of diesters **XIII**, **XIV**, and **XVII** was proved by single crystal X-ray diffraction. The molecular structures of these compounds are shown in Figs. 2–4. The unit cell of **XIII** contains two symmetry-independent kinds of molecules, and the cells of isosteviol anhydride **XIX**, **XIV**, and **XVII**, only one kind of molecules. The structure of the tetracyclic core in **XIII**, **XIV**, and **XVII** is, on the whole, similar and close to that in the previously determined structures of **I** and its derivatives [1, 2, 10–12].

Comparison of Figs. 2–4 clearly shows how the length of the chain linking the tetracyclic cores of the bisisosteviol derivatives affects their mutual orientation. In anhydride **XIX** [1] in which the kaurane fragments are separated only by the anhydride moiety and

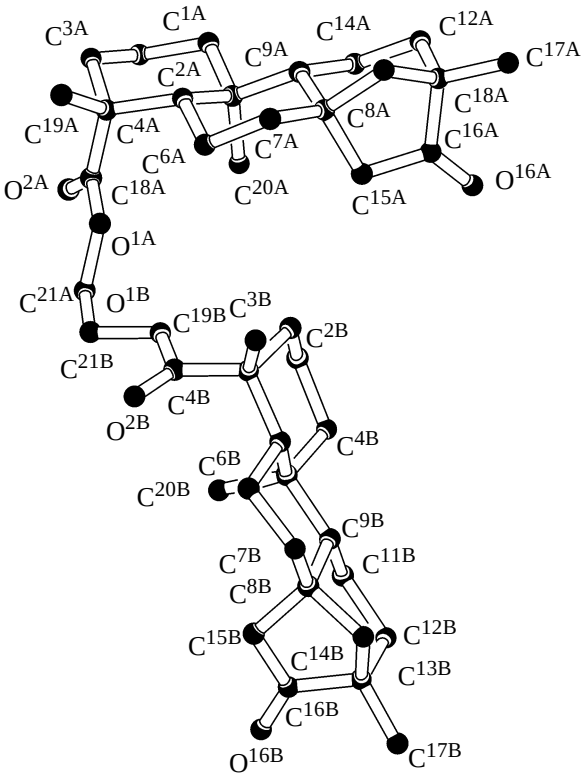


Fig. 2. Geometry of one of symmetry-independent molecules of ethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate], **XIIIa**. The hydrogen atoms are not shown.

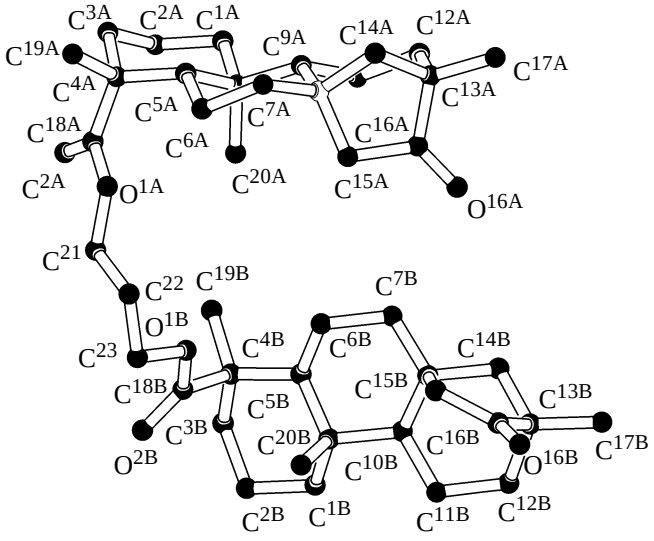


Fig. 3. Molecular geometry of trimethylene bis-[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] **XIV**. The hydrogen atoms are not shown.

in ethylene glycol diester **XIII**, these cores are virtually orthogonal, probably because of steric interactions of the kaurane fragments. Introduction of one more methylene unit into the bridging chain decreases the steric hindrance. In propanediol diester **XIV**, the isosteviol fragments are arranged approximately one over another, but in mutually orthogonal planes. Diethylene glycol diester **XVII** forms a *tweezer* structure with the tetracyclic cores "hanging" one over another in approximately parallel planes. Figure 4 shows that compound **XVII** in the crystal has an intramolecular cavity with the polar groups oriented inside. The size of this cavity is characterized by the following distances (Å) betwenn the nonbonded atoms: $O^{2A}\cdots O^{16B}$ 6.18, $O^{16A}\cdots O^{2B}$ 6.09, $O^{16A}\cdots O^{20B}$ 3.75, $O^{16A}\cdots O^{16B}$ 5.50, $O^{20A}\cdots O^{16B}$ 3.88, $O^{20A}\cdots O^{15B}$ 3.94, and $O^{15A}\cdots O^{20B}$ 3.80.

This fact suggests that diester **XVII** can exhibit molecular receptor properties toward medium-size organic molecules which can be accommodated and bound in the cavity. It should be noted that the intracavity binding is not the only way of reception of "guest" molecules; e.g., isosteviol **I** containing no intramolecular cavity forms an individual stable complex with aniline both in the crystalline state and in solution [13, 14].

The mutual orientation of the tetracyclic cores in bisisosteviol derivatives can be characterized by the

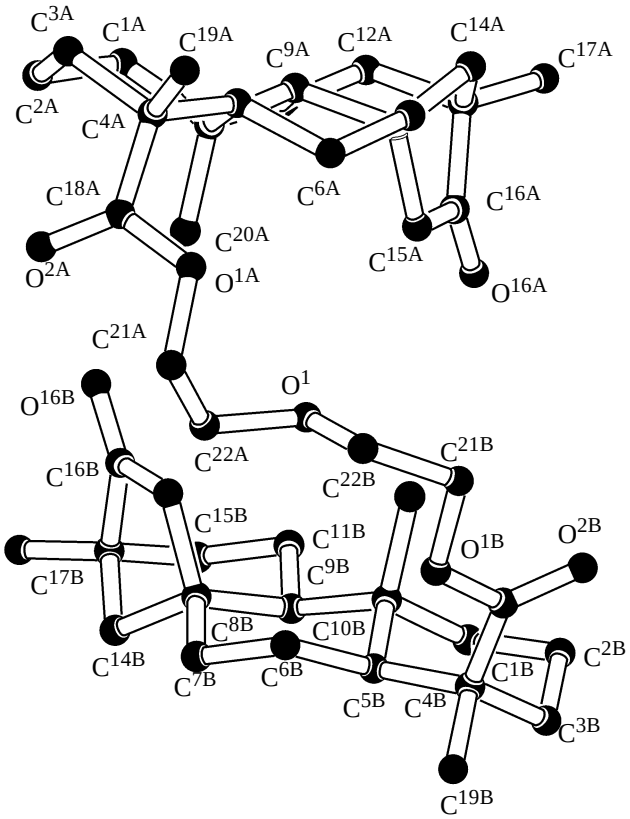


Fig. 4. Molecular geometry of oxydiethylene bis-[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] **XVII**. The hydrogen atoms are not shown.

Table 1. Torsion angles (deg) characterizing the conformations of the fragments linking the tetracyclic hydrocarbon cores in isosteviol anhydride **XIX**[a] and diesters **XIII, XIV**, and **XVII**[b]

Torsion angle	**XIX**	**XIIIa**	**XIIIb**	**XIV**	**XVII**
$\varphi_1(C^{19A}C^{4A}C^{18A}O^{2A})$	114.35(0.75)	113.45(0.81)	–67.86(0.80)	105.93(0.30)	118.20(0.65)
$\varphi_2(C^{19A}C^{4A}C^{18A}O^{1A})$	–71.87(0.65)	–59.82(0.70)	105.55(0.59)	–73.90(0.25)	–59.25(0.60)
$\varphi_3(C^{4A}C^{18A}O^{1A}C^{21A})$	–	177.98(0.53)	–173.56(0.50)	–170.99(0.20)	–179.29(0.50)
$\varphi_4(C^{4A}C^{18A}O^{1}C^{18B})$	156.75(0.60)	–	–	–	–
$\varphi_5(C^{18A}O^{1A}C^{21A}C^{22A})$	–	–	–	–	99.67(0.75)
$\varphi_6(C^{18A}O^{1A}C^{21A}C^{21B})$	–	–173.84(0.56)	171.65(0.54)	–	–
$\varphi_7(C^{18A}O^{1A}C^{21}C^{22})$	–	–	–	165.85(0.22)	–
$\varphi_8(O^{1A}C^{21A}C^{22A}O^{1})$	–	–	–	–	50.43(0.98)
$\varphi_9(O^{1A}C^{21A}C^{21B}O^{1B})$	–	–68.05(0.61)	–68.59(0.63)	–	–
$\varphi_{10}(O^{1A}C^{21}C^{22}C^{23})$	–	–	–	–160.54(0.26)	–
$\varphi_{11}(C^{21A}C^{22A}O^{1}C^{22B})$	–	–	–	–	69.90(0.83)
$\varphi_{12}(C^{21B}C^{22B}O^{1}C^{22A})$	–	–	–	–	156.50(0.53)
$\varphi_{13}(O^{1B}C^{23}C^{22}C^{21})$	–	–	–	71.73(0.33)	–
$\varphi_{14}(O^{1B}C^{21B}C^{21A}O^{1})$	–	–	–	–	–71.50(0.66)
$\varphi_{15}(C^{18B}O^{1B}C^{21B}C^{21A})$	–	179.86(0.49)	–165.81(0.51)	–	–
$\varphi_{16}(C^{18B}O^{1B}C^{23}C^{22})$	–	–	–	–150.58(0.25)	–
$\varphi_{17}(C^{18B}O^{1B}C^{21B}C^{22B})$	–	–	–	–	166.13(0.58)
$\varphi_{18}(C^{4B}C^{18B}O^{1B}C^{23})$	–	–	–	174.35(0.22)	–
$\varphi_{19}(C^{4B}C^{18B}O^{1}C^{18A})$	154.42(0.62)	–	–	–	–
$\varphi_{20}(C^{4B}C^{18B}O^{1B}C^{21B})$	–	177.14(0.48)	174.75(0.48)	–	–171.55(0.54)
$\varphi_{21}(C^{19B}C^{4B}C^{18B}O^{1B})$	–	120.98(0.52)	–67.89(0.64)	–65.88(0.28)	–65.46(0.64)
$\varphi_{22}(C^{19B}C^{4B}C^{18B}O^{1})$	73.04(0.75)	–	–	–	–
$\varphi_{23}(C^{19B}C^{4B}C^{18B}O^{2B})$	–90.14(0.88)	–60.28(0.77)	106.76(0.82)	109.75(0.32)	114.16(0.72)

[a] Data of [1]. [b] For **XIII**, data are given for both symmetry-independent molecules **XIIIa** and **XIIIb**.

torsion angles in the linking chain (Table 1). A certain regular trend in the structures of diesters **XIII**, **XIV**, and **XVII** can be seen. The angles φ_1 and φ_2 characterizing the orientation of the ester group C(O)O relative to the tetracyclic core are approximately equal in all the diesters except symmetry-independent molecule **XIIIb** in which, instead of φ_1 and φ_2, we should consider angles φ_{23} and φ_{21}, respectively. Angles φ_3 and φ_{20} characterizing the conformation of the $C^4 \cdot C^{18}O^1C$ chain, and angles φ_6, φ_7, φ_{15}, φ_{16}, and φ_{17} characterizing the conformation of the $C^{18}OCC$ chain are also approximately equal in all the esters. Thus, molecules of **XIII**, **XIV**, and **XVII** in the crystal are characterized by similar conformation of the $C^{19}C^4 \cdot C^{18}O^1CC$ fragment, and the differences in the mutual orientation of the tetracyclic cores are described by angles φ_4, φ_5, φ_8, φ_9, φ_{10}–φ_{14}, and φ_{18}–φ_{23}.

The mutual orientation of the tetracyclic cores can also be described by dihedral angles ψ between the arbitrarily chosen planes *X*0*Z* accommodating the C^1, C^2, C^4, and C^5 atoms; *X*0*Y* accommodating the C^9, C^{10}, C^{13}, and C^{17} atoms; and *Y*0*Z* accommodating the C^8, C^{10}, and C^{20} atoms (Fig. 5).

Indeed, angle ψ_1 between the *X*0*Z* plane passing through one tetracyclic fragment and *X*0*Z* plane passing through the other tetracyclic fragment of the same molecule characterizes the turn of the isosteviol fragments relative to each other around the 0*X* and 0*Z* axes. Dihedral angle ψ_2 between the *X*0*Y* plane passing through the C^9, C^{10}, C^{13}, and C^{17} atoms of one of the tetracyclic cores of the diester molecule and the similar plane passing through the same atoms of the other core of the same molecule describes the turn of the isosteviol fragments of the diester molecule relative to each other around the 0*X* and 0*Y* axes. Finally, angle ψ_3 characterizes the turn of the isosteviol cores relative to each other around the 0*Y* and 0*Z* axes. Thus, mutual orientation of the rigid tetracyclic cores and the extent to which the molecular structure approaches the optimal *tweezer* structure can be described by angles ψ_1–ψ_3; apparently, in the ideal *tweezer* structure all these angles should be zero.

The values of dihedral angles ψ_1–ψ_3 in **XIII**, **XIV**, **XVII**, and **XIX** (Table 2) show that none of the molecular structures has the ideal *tweezer* geometry.

Table 2. Dihedral angles (deg) between the planes *X*0*Z* (ψ_1), *X*0*Y* (ψ_2), and *Y*0*Z* (ψ_3) in two tetracyclic fragments in diesters **XIII, XIV**, and **XVII** and in anhydride **XIX**

Comp. no.	Ψ_1	Ψ_2	Ψ_3
XIII	74.61 ± 0.32	20.24 ± 1.84	104.08 ± 0.44
XIV	86.19 ± 0.10	87.10 ± 0.53	9.06 ± 0.76
XVII	1.82 ± 1.52	71.27 ± 0.44	107.01 ± 0.18
XIX	108.48 ± 0.31	5.88 ± 3.26	68.44 ± 0.52

the tetracyclic cores is made longer, namely, in going from anhydride **XIX** to diethylene glycol diester **XVII**, Ψ_1 decreases from 109° to 2°, i.e., the extent to which the molecular geometry approaches the *tweezer* structure grows, reaching a maximum in **XVII**. This can be seen from simple visual comparison of the molecular geometries in Figs. 2–4. We believe, in conformity with published data [13, 14], that realization of an "ideal" *tweezer* structure in the crystal is not a necessary condition for binding "guest" molecules by the isosteviol molecule. Probably, realization of the *tweezer* structure of **XVII** and specific structures of **XIII**, **XIV**, and **XIX** is due to the effects of crystal packing and intermolecular interactions.

According to single crystal X-ray diffraction data, in the crystal of **XIII** there is a short interatomic contact (nonclassical intermolecular hydrogen bond) between the methylene hydrogen atom at the C^{21A} atom and the carbonyl atom O^{2B} of the carboxy group of another, symmetry-independent molecule. The parameters of this C^{21A}–$H^{211A}\cdots O^{2B}$ contact are as follows: $d(C^{21A}$–$H^{211A})$ 0.95, $d(H^{211A}\cdots O^{2B})$ 2.56, $d(C^{21A}\cdots O^{2B})$ 3.078(8) Å; $\angle(C^{21A}$–$H^{211A}\cdots O^{2B})$ 115°. The whole set of forces acting in the crystal of **XIII** leads to formation of a supramolecular structure with alternating lipophilic regions between the external sides of the isosteviol cores of adjacent molecules (Fig. 6). The short contacts between the hydrogen atoms of the methylene groups of the tetracyclic hydrocarbon core and the oxygen atoms of the carboxy group arise also in the crystal of **XIV**. These contacts are characterized by the following parameters. C^{2B}–$H^{22B}\cdots O^{2B}$: d(C–H) 1.03(2), d(H···O) 2.34(2), d(C···O) 3.104(4) Å; $\angle(C^{2B}$–$H^{22B}\cdots O^{2B})$ 130(1)°. C^{6A}–$H^{61A}\cdots O^{1A}$: $d(C^{6A}$–$H^{61A})$ 1.02(2), d(H···O) 2.52(2), d(C···O) 2.895(3) Å, $\angle(C^{6A}$–$H^{61A}\cdots O^{1A})$ 101(1)°.

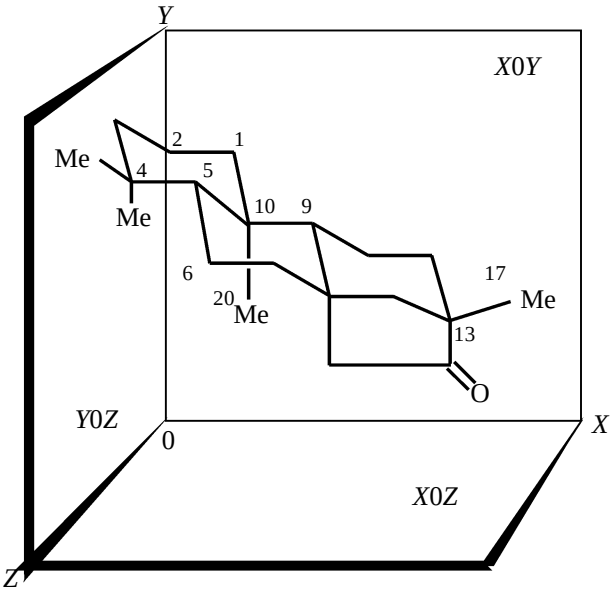


Fig. 5. Arrangement of the molecule in arbitrarily chosen coordinates 0*XYZ*.

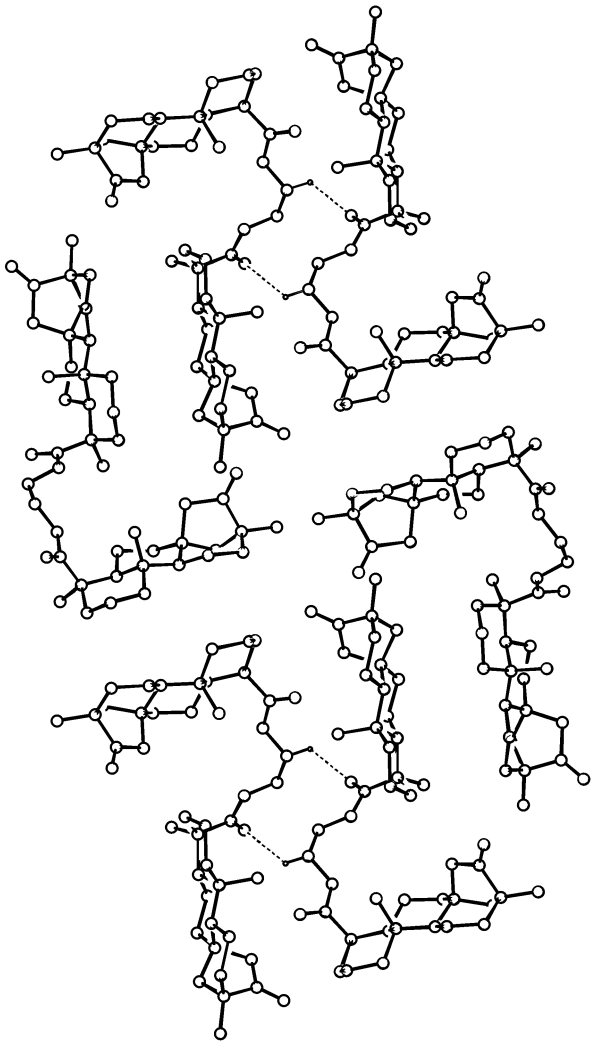


Fig. 6. Supramolecular structure of **XIII** in the crystal. The dotted loines denote short contacts between atoms not linked by valence bonds.

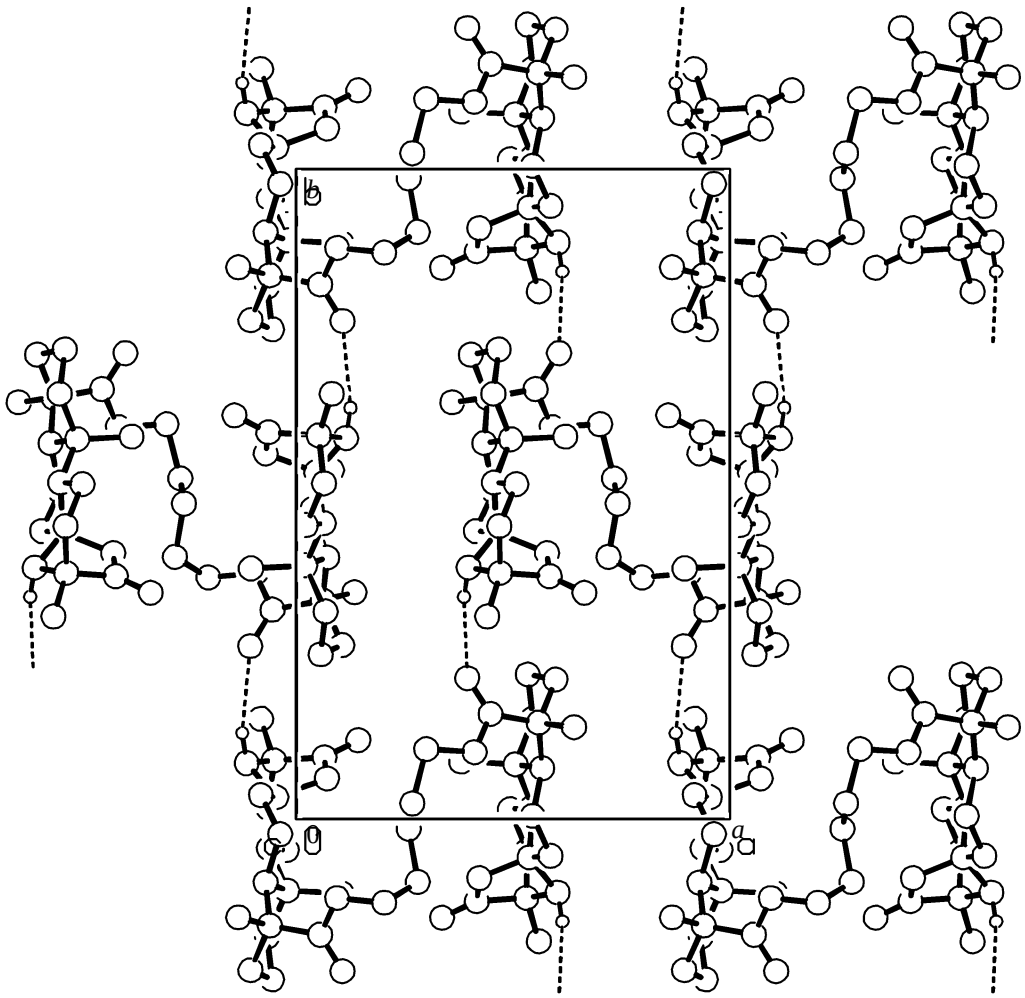


Fig. 7. Supramolecular structure of compound **XVII** in the crystal. View along the 0*z* axis. The short contacts are denoted by dashed lines.

The supramolecular structure formed in the crystal of **XIV** consists of stacks of molecules oriented at a definite angle along the twofold axis; the layers are formed along the same axis. In diester **XVII**, there are short contacts between the methylene protons of the kaurane fragment and oxygen atoms of the carboxy groups of the adjacent molecules related to the initial molecules by the symmetry operations (1 – *x*, –1/2 + *y*, 1/2 – *z*) (*) and (–*x*, 1/2 + *y*, 1/2 – *z*) (**). The parameters of these contacts are as follows. C^{14B}–$H^{142B}\cdots O^{2B*}$: 0.94(4), 2.54(4), 3.473(5) Å, ∠ 169(3)°; C^{14A}–$H^{142A}\cdots O^{2A}$: 0.98(3), 2.48(3), 3.406(5) Å, ∠157(2)°.

Each molecule has four such contacts. The mutual orientation realized in this case gives rise to infinite zigzag chains of molecules of **XVII**, running along the 0*b* crystallographic direction. The chains are combined in infinite layers arranged parallel to the 0*ab* plane. The supramolecular organization of *tweezer* structure of **XVII** can be represented as parallel packing of these layers (along the 0*c* direction), or as packing of stacks with antiparallel orientation of molecules along the 0*a* direction (Fig. 7). Inside these stacks, the lipophilic and hydrophilic regions alternate. The lipophllic region is the region of van der Waals contacts between the external hydrocarbon sides of the tetracyclic cores of adjacent molecules of **XVII**, and the hydrophilic region involves intramolecular cavities with the polar groups oriented inside. In Fig. 7, the alternation of the lipophilic and hydrophilic regions can be seen along both 0*a* and 0*b* directions. We have shown previously [10] that isosteviol reduction product **XX** in the crystal forms a molecular H complex with water molecules This complex has a similar layered "Big Mac" structure in which water molecules are arranged in the hydrophilic regions and are linked to the polar groups of **XX** and the lipophilic regions are formed by the external surfaces of the hydrocarbon tetracyclic cores. Thus, formation of layered or stack structures with alternating lipophilic and hydrophilic regions is one of characteristic features of the supra-

molecular structure of isosteviol derivatives in the crystal.

Apparently, realization in **XVII** of the above-described *tweezer* structure is due to intermolecular interactions and crystal packing effects. In solution, owing to the conformational lability of the chain linking the tetracyclic cores, the steric structure of the molecule can change, and the kaurane fragments can turn apart from each other. The conformations and receptor activities of diesters **XIII**–**XVIII** will be studied in the subsequent works.

EXPERIMENTAL

Single crystal X-ray diffraction study of **XI**, **XIII**, **XIV**, and **XVII** was performed with an Enraf-Nonius CAD-4 automated four-circle diffractometer (CuK_α radiation, λ 1.54184 Å, graphite monochromator, ω/2θ scanning in the range $4.2° \le \theta \le 78.4°$, scanning angle ω $1.2 + 0.35\tan\theta$, variable scanning rate, 1–16.4 deg min^{-1} for θ). The reference reflections (two for orientation check and three for intensity check) were measured after collecting every 200 reflections. Corrections of the reflection intensities and those absorption correction were not made, because the reference reflections showed no decrease in the intensity, and the linear absorption coefficients of the crystals were low. The structures were solved by the direct method using the SIR program [15] and refined by the full-matrix least-squares method; the function to be minimized was $\Sigma w(|Fo| - |Fc|)^2$; extinction was not taken into account; the weight scheme was $4F_0^2/[\sigma(I)^2 + (0.04 \times F_0^2)]^2$. All the calculations were performed with an Alpha Station 200 computer using MolEn program package [16]. The PLATON program [17] was used to analyze the intermolecular contacts in the crystals and to make figures of the molecules and crystal packing. The parameters of the crystals, experimental conditions, and results of structure refinement are listed in Table 3. The atomic coordinates and geometric parameters of the structures are filed at the Cambridge crystallographic data bank and are also available from the authors (I.A.L.).

The IR spectra were recorded on a UR-20 spectrophotometer in the range 400–3600 cm^{-1}. Crystallline samples were prepared as mulls in mineral oil, and liquid samples, as films between KBr plates. The mass spectra were taken with an MKh-1310 mass spectrometer at the ionizing electron energy of 70 eV; the ion source temperature was 120°C. An SVP-5 system for direct sample inlet was used; *R* 10 000. Accurate values of *m/z* were determined automatically using reference peaks of perfluorokerosene. The determination error did not exceed 1×10^{-5} amu. The ^{1}H NMR spectra were measured on Varian T-60 and Bruker MSL-400 spectrometers. Column chromatography was performed with Chemapol silica gel as sorbent and chloroform as eluent. Reaction mixtures were analyzed by TLC on Silufol UV-254 plates; eluent petroleum ether–ethyl acetate, 1 : 1.

Hexyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate III. To 0.2 g of isosteviol acid chloride **II** we added 3 ml of 1-hexanol. The mixture was heated for 8 h at a bath temperature of 125°C. Excess hexanol was removed at reduced pressure. The residue was purified by column chromatography. A light yellow viscous liquid was obtained, n_D^{20} 1.5060, which crystallized with time, mp 48–53°C. Yield 0.18 g (90%). $[\alpha]_D^{20}$ –68.5° (*c* 0.011, CCl_4). IR spectrum, ν, cm^{-1}: 1155, 1180 (COC), 1730, 1740 (C=O). ^{1}H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.03 m (2H), 2.52 d.d (1H, *J* 18.4, 3.4), 2.15 d (1H, *J* 13.2), 1.8 m (13H), 1.4 m (13H), 1.19 s (3H), 0.90 s (3H), 0.89 t (3H, *J* 6.5), 0.75 s (3H). Found, %: C 77.21; H 11.05. $C_{26}H_{42}O_3$. Calculated, %: C 77.56; H 10.51.

Decyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate IV. To 0.24 g of **II** we added 3 ml of 1-decanol. The mixture was heated for 5 h at a bath temperature of 130°C. Excess decanol was removed at reduced pressure. The remaining dark yellow liquid was purified by column chromatography; 0.35 g (86%) of a viscous liquid was obtained, n_D^{20} 1.5036. $[\alpha]_D^{20}$ –50.7° (*c* 0.014, CCl_4). IR spectrum, ν, cm^{-1}: 1155, 1185 (COC), 1720, 1740 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.96 m (2H), 2.58 d.d (1H, *J* 18.3, 3.1), 1.75 d (1H, *J* 18.3), 2.14 d (1H, *J* 13.1), 1.8 m (15H), 1.4 m (18H), 1.14 s (3H), 0.93 s (3H), 0.83 t (3H, *J* 6.0), 0.66 s (3H). Found, %: C 79.06; H 11.32. $C_{30}H_{50}O_3$. Calculated, %: C 78.55; H 10.98.

Cyclohexyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate V. To a solution of 0.13 g of **II** in 2 ml of absolute CCl_4, we added 0.039 ml of cyclohexanol and 0.05 ml of triethylamine. The mixture was heated for 30 h at a bath temperature of 85°C, washed with water, and dried over $CaCl_2$. The product was purified by column chromatography and recrystallized from hexane. Yield of **VI** 0.07 g (46%), mp 90–92°C. IR spectrum, ν, cm^{-1}: 1160, 1180 (COC), 1720, 1740 (C=O). ^{1}H NMR spectrum (CCl_4), δ, ppm (*J*, Hz): 5.66 m (1H), 4.33 m (1H), 3.66 m (1H), 2.7 d (1H, *J* 18.1), 2.4 d (1H, *J* 13.1), 1.8 m (10H), 1.4 m (16H), 1.2 s (3H), 0.9 s (3H), 0.7 s (3H). Found, %: C 77.68; H 10.57. $C_{26}H_{40}O_3$. Calculated, %: C 77.89; H 10.06.

Table 3. Parameters of crystals of **XI, XIII, XIV**, and **XVII** and conditions of the X-ray diffraction experiment[a]

Parameter	XI	XIII	XIV	XVII
Color, habit	Colorless, prismatic	Colorless, prismatic	Colorless, needle-shaped	Colorless, rhombic
Crystal system	Rhombic	Monoclinic	Monoclinic	Rhombic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P2_12_12_1$
Unit cell parameters, Å	*a* 7.453(2) *b* 10.810(4) *c* 28.028(15)	*a* 22.330(8) *b* 7.536(8) *c* 22.506(8)	*a* 13.024(7) *b* 10.507(8) *c* 13.918(6)	*a* 12.137(4) *b* 18.24(1) *c* 18.462(8)
Angle, deg	–	β 98.32(3)	β 97.54(5)	–
Unit cell volume, Å^3	2258(2)	3748(4)	1888(2)	4086(4)
Z	4	4	2	4
Molecular weight	406.54	662.92	676.99	706.97
d_{calc}, g cm^{-3}	1.196	1.174	1.191	1.149
Absorption coefficient, cm^{-1}	6.22	5.69	5.74	5.68
F(000)	888	1448	740	1544
Range of variation of *h, k, l*	$-9 \le h \le 0$, $-13 \le k \le 0$, $-35 \le l \le 0$	$-24 \le h \le 24$, $-8 \le k \le 8$, $-22 \le l \le 24$	$0 \le h \le 13$, $-16 \le k \le 16$, $-17 \le l \le 17$	$0 \le h \le 14$, $0 \le k \le 22$, $0 \le l \le 23$
Number of reflections measured	2680	6202	8141	4388
Number of observed reflections with $I > 3\sigma(I)$	1833	5784	6076	2631
Conditins of setting and refining hydrogen atoms	Revealed from differential series, not refined	Revealed from differential series, not refined	Revealed from differential series, refined isotropically	Revealed from differential series, not refined
Final divergence factors	*R* 0.041 R_W 0.047	*R* 0.048 R_W 0.049	*R* 0.048 R_W 0.055	*R* 0.064 R_W 0.086
Fitting parameter	1.440	1.260	1.615	2.884
Δ/σ	0.02	0.01	0.33	0.13
Number of reflections in final least-squares cycles	1603	4520	5418	2349
Number of refined parameters	410	864	697	460

[a] Figures in parentheses are standard deviations.

1-Cyclohexenylmethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate VI. To 0.27 g of **II** we added 1 ml of 1-cyclohexenylcarbinol. The mixture was heated for 1 h at a bath temperature of 80°C. Excess alcohol was distilled off at reduced pressure, and the residue was purified by column chromatography; 0.22 g (66.5%) of a viscous liquid was obtained, n_D^{20} 1.5220. IR spectrum, ν, cm^{-1}: 1150, 1180 (COC), 1720, 1740 (C=O). ^{1}H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.71 m (1H), 2.52 d.d (1H, *J* 18.4, 3.4), 2.13 d (1H, *J* 13.2), 1.8 m (10H), 1.4 m (16H), 1.19 s (3H), 0.90 s (3H), 0.75 s (3H). Found, %: C 78.54; H 10.01. $C_{27}H_{40}O_3$. Calculated, %: C 78.60; H 9.77.

Preparation of diol monoesters and diesters from (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylic acid chloride *(general procedure).* To a solution of 0.6–1 mmol of **II** in 3 ml of absolute CCl_4, we added 0.6–1 mmol (for monoesters) or 0.3–0.5 mmol (for diesters) of appropriate diol and 0.6–1 mmol of triethylamine. The mixture was heated for 10–30 h at a bath temperature of 85–90°C, after which it was washed with distilled water and dried over $CaCl_2$. The solvent was removed at reduced pressure. The product was purified by column chromatography.

2-Hydroxyethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate VII. Yield 47%, mp 123–125°C. $[\alpha]_D^{20}$ –66.3° (*c* 0.036, CCl_4). IR spectrum, ν, cm^{-1}: 1080 (C–O), 1150, 1160 (COC), 1720 sh, 1730 (C=O), 3420 (OH). ^{1}H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.06 d.d (2H, *J* 10.2, 6.5), 3.72 d.d (2H, *J* 5.1, 9.8), 2.52 d.d (1H, *J* 18.4, 3.4), 2.16 d (1H, *J* 13.2), 1.8 m (9H), 1.4 m (9H),

1.19 s (3H), 0.90 s (3H), 0.75 s (3H). Mass spectrum, $[M]^+$: m/z_{exp} 362, m/z_{calc} 362.2457. Found, %: C 72.45; H 9.53. $C_{22}H_{34}O_4$. Calculated, %: C 72.89; H 9.45.

3-Hydroxypropyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate VIII. Yield 18%, viscous liquid. $[\alpha]_D^{20}$ –37.6° (*c* 0.034, CCl_4). IR spectrum, ν, cm^{-1}: 1060 (C–O), 1150, 1180 (COC), 1720, 1740 (C=O), 3460 (OH). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.98 m (2H), 3.60 t (2H), 2.58 d.d (1H, *J* 18.3), 1.75 d (1H, *J* 18.3), 2.13 d (1H, *J* 13.1), 1.8 m (9H), 1.4 m (10H), 1.14 s (3H), 0.93 s (3H), 0.66 s (3H). Mass spectrum, $[M]^+$: m/z_{exp} 376, m/z_{calc} 376.2613. Found, %: C 73.28; H 9.71. $C_{23}H_{36}O_4$. Calculated, %: C 73.38; H 9.56.

4-Hydroxybutyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate IX. Yield 47%, viscous liquid. $[\alpha]_D^{20}$ –65.5° (*c* 0.02, CH_3CN). IR spectrum, ν, cm^{-1}: 1060 (C–O), 1155, 1180 (COC), 1720, 1735 (C=O), 3455 (OH). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.02 m (2H), 3.55 br.s (2H), 2.52 d.d (1H, *J* 18.3, 3.4), 2.14 d (1H), 1.76 d (1H, *J* 18.3), 1.8 m (10H), 1.4 m (11H), 1.18 s (3H), 0.90 s (3H), 0.73 s (3H). Mass spectrum, $[M]^+$: m/z_{exp} 390, m/z_{calc} 390.2770. Found, %: C 73.36; H 9.95. $C_{24}H_{38}O_4$. Calculated, %: C 73.79; H 9.73.

3-Hydroxybutyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate X. Yield 17%, viscous liquid. $[\alpha]_D^{20}$ –60.2° (*c* 0.011, CCl_4). IR spectrum, ν, cm^{-1}: 1100 (C–O), 1155, 1180 (COC), 1720, 1740 (C=O), ~3450 (OH). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.14 m (2H), 3.89 m (1H), 2.90 br.s (1H), 2.52 d.m (1H, *J* 18.2), 2.14 d (1H, *J* 13.2), 1.77 m (9H), 1.47 m (9H), 1.21 m (3H), 1.18 d (3H, *J* 7), 1.18 s (3H), 1.05 t.d (1H, *J* 13.4, 4.0), 0.96 t.d (1H, *J* 13.4, 4.3), 0.90 s (3H), 0.74 s (3H). Mass spectrum, $[M]^+$: m/z_{exp} 390, m/z_{calc} 390.2770. Found, %: C 73.77; H 10.06. $C_{24}H_{38}O_4$. Calculated, %: C 73.79; H 9.73.

2-(2-Hydroxyethoxy)ethyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate XI. Yield 23%, mp 72–75°C. $[\alpha]_D^{20}$ –48.0° (*c* 1.65, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1080 (C–O), 1160, 1180 (COC), 1720, 1740 (C=O), 3470 (OH). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.13 m (2H), 3.67 m (2H), 3.62 m (2H), 43.52 m (2H), 2.52 d.d (1H, *J* 18.4, 3.4), 2.13 d (1H, *J* 13.2), 1.8 m (9H), 1.4 m (9H), 1.19 s (3H), 0.90 s (3H), 0.75 s (3H). Found, %: C 70.73; H 9.76. $C_{24}H_{38}O_5$. Calculated, %: C 70.90; H 9.42.

6-Hydroxyhexyl (4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate XII. Yield 44%, viscous liquid. IR spectrum, ν, cm^{-1}: 1060 (C–O), 1160, 1180 (COC), 1725, 1740 (C=O), 3400 (OH). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.03 m (2H), 3.52 t (2H, *J* 5.4), 2.54 d.d (1H, *J* 18.3, 3.4), 2.14 d (1H, *J* 13.1), 1.8 m (12H), 1.4 m (14H), 1.18 s (3H), 0.90 s (3H), 0.74 s (3H). Mass spectrum, $[M]^+$: m/z_{exp} 418, m/z_{calc} 418.3083. Found, %: C 74.36; H 10.48. $C_{26}H_{42}O_4$. Calculated, %: C 74.58; H 10.04.

Ethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] XIII. Yield 53%, mp 183–185°C. $[\alpha]_D^{20}$ –103.0° (*c* 0.0082, CCl_4). IR spectrum, ν, cm^{-1}: 1150, 1180 (COC), 1720, 1740 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.29 m (4H), 2.52 d.d (2H, *J* 18.29, 3.6), 2.17 d (2H, *J* 13.2), 1.81 d (2H, *J* 18.3), 1.80 m (15H), 1.47 m (15H), 1.22 s (6H), 1.09 t.d (2H, *J* 13.4, 4.3), 0.98 t.d (2H, *J* 13.4, 4.5), 0.90 s (6H), 0.76 s (6H). Mass spectrum, $[M]^+$: m/z_{exp} 662, m/z_{calc} 662.4546. Found, %: C 76.54; H 9.73. $C_{42}H_{62}O_6$. Calculated, %: C 76.08; H 9.35.

Trimethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] XIV. Yield 57%, mp 153–155°C. $[\alpha]_D^{20}$ –82.1° (*c* 0.0056, CCl_4). IR spectrum, ν, cm^{-1}: 1160, 1180 (COC), 1725, 1740 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.16 m (4H), 2.04 m (2H), 2.53 d.d (2H, *J* 18.5, 3.8), 2.15 d (2H, *J* 13.8), 1.84 d (2H, *J* 18.5), 1.80 m (15H), 1.47 m (15H), 1.09 t.d (2H, *J* 13.4, 4.3), 0.98 t.d (2H, *J* 13.4, 4.5), 1.19 s (6H), 0.90 s (6H), 0.75 s (6H). Found, %: C 76.42; H 9.86. $C_{43}H_{65}O_6$. Calculated, %: C 76.29; H 9.52.

Tetramethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] XV. Yield 53%, mp 124–126°C. $[\alpha]_D^{20}$ –73.0° (*c* 0.0046, CCl_4). IR spectrum, ν, cm^{-1}: 1160, 1180 (COC), 1720, 1740 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.08 m (4H), 1.78 m (4H), 2.52 d.d (2H, *J* 18.3, 3.8), 2.15 d.m (2H, *J* 12.9), 1.80 m (15H), 1.47 m (15H), 1.19 s (6H), 1.07 t.d (2H, *J* 13.6, 4.3), 0.97 t.d (2H, *J* 13.4, 4.5), 0.90 s (6H), 0.75 s (6H). Found, %: C 75.77; H 9.76. $C_{44}H_{66}O_6$. Calculated, %: C 76.48; H 9.63.

1-Methyltrimethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] XVI. Yield 33%, mp 70–85°C. $[\alpha]_D^{20}$ –74.0° (*c* 0.0089, CCl_4). IR spectrum, ν, cm^{-1}: 1155, 1180 (COC), 1715, 1730 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 5.04 m (1H), 1.26 d (3H, *J* 6.5), 1.92 m (2H), 4.12 m (2H), 2.53 d (2H, *J* 18.1), 2.16 m (2H), 1.83 d (2H, *J* 18.3), 1.80 m (15H), 1.47 m (19H), 0.91 s (6H), 0.79 s (3H), 0.74 s (3H), 1.20 s (6H). Mass spectrum, $[M]^+$: m/z_{exp} 690, m/z_{calc} 690.4860. Found, %: C 75.89; H 9.83. $C_{44}H_{66}O_6$. Calculated, %: C 76.48; H 9.63.

Oxydiethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate] XVII. Yield 71%, mp 153–155°C. $[\alpha]_D^{20}$ –61.7° (*c* 0.0064, CCl_4). IR spectrum, ν, cm^{-1}: 1130, 1180 (COC), 1720, 1740 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.17 m (4H), 3.73 d.d (4H, *J* 4.9, 5.1), 2.54 d.d (2H, *J* 18.3, 3.4), 2.15 d (2H, *J* 13.1), 1.80 m (17H), 1.47 m (19H), 1.20 s (6H), 0.90 s (6H), 0.76 s (6H). Found, %: C 73.96; H 9.75. $C_{44}H_{66}O_7$. Calculated, %: C 74.25; H 9.41.

Hexamethylene bis[(4α,8β,13β)-13-methyl-16-oxo-17-norkaurane-18-carboxylate XVIII. Yield 52%, mp 130–137°C. $[\alpha]_D^{20}$ –66.1° (*c* 0.05, CCl_4). IR spectrum, ν, cm^{-1}: 1155, 1180 (COC), 1725 (C=O). ^1H NMR spectrum (CD_3COCD_3), δ, ppm (*J*, Hz): 4.04 m (4H), 2.53 d.d (2H, *J* 18.3, 3.7), 2.15 d (2H, *J* 13.1), 1.82 d (2H, *J* 18.3), 1.80 m (20H), 1.47 m (22H), 1.19 s (6H), 0.90 s (6H), 0.75 s (6H). Found, %: C 76.17; H 9.87. $C_{46}H_{70}O_6$. Calculated, %: C 76.84; H 9.81.

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