Russian Journal of General Chemistry, Vol. 75, No. 4, 2005, pp. 583–589. Translated from Zhurnal Obshchei Khimii, Vol. 75, No. 4, 2005, pp. 622–628.

15-Halo-substituted Isosteviols

V. A. Mamedov, V. A. Al'fonsov, G. A. Bakaleinik, V. E. Kataev, G. I. Kovylyaeva, O. I. Militsina, I. Yu. Strobykina, D. V. Beskrovnyi, A. T. Gubaidullin, I. A. Litvinov, I. Kh. Rizvanov, and R. Z. Musin

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, Kazan, Tatarstan, Russia

Received December 10, 2003

Abstract — The isosteviol ditererpenoid regio- and stereoselectively reacts with sulfuryl chloride, bromide, and HBr in DMSO to form crystalline 15-halo derivatives of isosteviols. The absolute configuration and crystal structure of the products were established by X-ray diffraction analysis.

Our research (see, for example, [1–4]) on the chemistry and structure of the isosteviol terpenoid (**I**), obtained by hydrolysis of glycosides of *Stevia rebaudiana Bertoni*, is aimed at creating molecular receptors on its basis. Previously we showed that isosteviol forms with aromatic compounds crystalline inclusion complexes that possess a unique helix supramolecular crystal structure [1, 2]. By reaction of isosteviol chloride with diols of various structures we prepared a series of tweezers-like structures (isosteviol diesters) in which the tetracyclic hydrocarbon carcasses of two isosteviol fragments linked by oxyalkylene spacers are oriented in one side parallel to each other, with their polar groups pointing inward to form an intramolecular pseudo-cavity [3, 4].

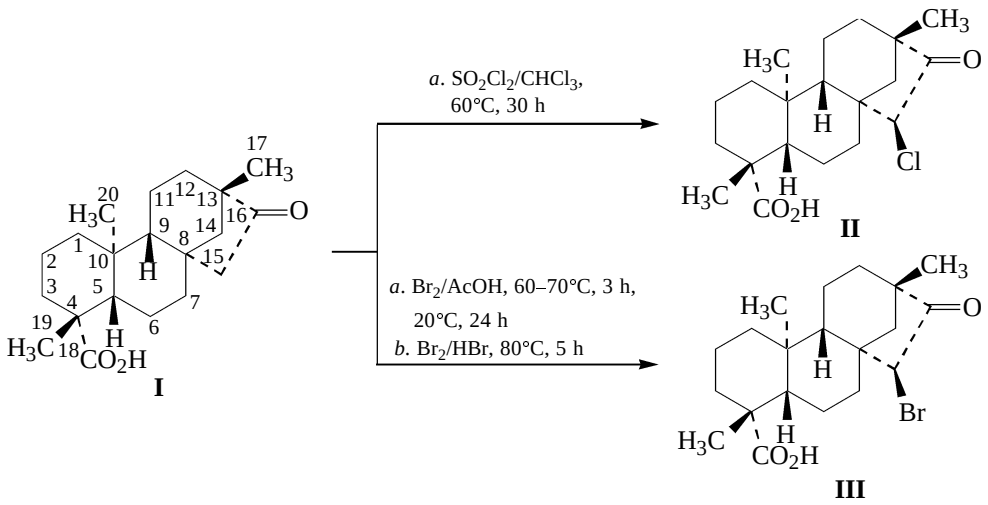
Design of molecular receptors makes provision not only for variation of the size and configuration of the accepting part of host molecules, but also for introduction in them active centers capable of effectively binding guest molecules [5]. The tweezers-like structures we obtained in [3, 4] contained isosteviol fragments bound by the C^4 atoms and having as binding centers ester and carbonyl groups and oxyalkylene oxygen atoms. It seemed reasonable to synthesize tweezers-like structures whose isosteviol carcasses would we cross-linked by the C^{15} and C^{16} atoms of the five-membered rings and having as binding centers the carboxy groups at C^4, which would stronger, compared to carbonyl, bind host molecules via formation of strong intermolecular bonds. First we had to prepare the starting compounds. The presence of a reactive $CH_2C(O)$ group in the five-membered ring of isosteviol make possible various approaches to functionalization of this part of the molecule, involving mobile hydrogen atoms of the α-methylene group.

In the present work we report on the synthesis of 15-halo derivatives of isosteviol, which are convenient starting materials for preparing tweezers-like structure with the isosteviol carcasses cross-linked by C^{15} and C^{16}.

Isosteviol was chlorinated using sulfuryl chloride, since, unlike other chlorinating agents (molecular chlorine inclusive), it is readily batched and is more selective toward systems with mobile α-hydrogen atoms [6]. The reaction was performed in chloroform under reflux for ~30 h. The yield of 15-chloroisosteviol (**II**) is high (96–98%).

Bromination of isosteviol was performed in two ways. The first involves heating with a slight excess of bromine in acetic acid medium for some hours and results in quantitative formation of 15-bromoisosteviol (**II**). By analogy with data in [7–9], we can suggest that this bromination occurs by an ionic mechanism through a slow enolization stage with the participation of acid. It should therewith borne in mind that this catalytic stage can involve not only the solvent (acetic acid), but also isosteviol itself, since, being an organic acid, it contains a free carboxy group. The subsequent fast stages involve bromination of the enolic form of isosteviol by an aldol reaction scheme. The second bromination procedure makes use of the HBr–DMSO system which is a known selective oxidizing [10] and oxidative bromination agent [11]; therewith, in both cases the reaction begins with bromination. We found that isosteviol in this reaction undergoes monobromination exclusively to form 15-bromoisosteviol in quantitative yield, i.e. the reaction stops on the first stage. Apparently, this result is explained by the lack in isosteviol of vicinal, with respect to the bromina-

1070-3632/05/7504-0583



tion center (C^{15}), substituents sensitive to bromination and oxidation and favoring further reaction stages.

The time of reactions *a* and *b* was determined from the mass spectra of samples taken from the reaction mixtures in the course of the reactions. The reaction completion was established by the disappearance of the peak of isosteviol at *m/z* 318. The mass spectra contained molecular ion peaks at *m/z* 352 (15-chloroisosteviol in the chlorination reaction) or *m/z* 397 (15-bromoisosteviol in the bromination reaction). Moreover, we obtained high-resolution electron impact mass spectra of compounds **II** and **III**. In the mass spectrum of 15-chloroisosteviol (**II**), the relative intensity of the molecular ion peaks is 46% ($M^{+\cdot}_{found}$ 352.1800. $C_{20}H_{29}ClO_3$. $M^{+\cdot}_{calc}$ 352.1805; *m* 5.10–4). In the high-mass region, the most abundant are *m/z* 334, 317, 316, 307, and 275 ion peaks. Their elemental composition suggests loss of H_2O, Cl, HCl, CO_2, and C_2H_2OCl, respectively. Most peaks in the medium- and low-mass regions relate to hydrocarbon ions which are presumably formed by degradation of the isosteviol fragment. The mass spectrum of 15-bromo–isosteviol (**III**) contains molecular ion peaks at *m/z* 396 and 398 ($C_{20}H_{29}BrO_3$) of equal intensity, which corresponds to the natural abundances of Br^{79} and Br^{81}.

The structure of compounds **II** and **III** was confirmed by physicochemical methods. In the IR spectra, the ν(ketone C=O) band of isosteviol (1735 cm^{-1}) shifts blue by 10 cm^{-1} in going to 15-chloroisosteviol and by 8 cm^{-1} in going to 15-bromoisosteviol (to 1745 and 1743 cm^{-1}, respectively), implying introduction of halogen α to the carbonyl group. Conclusive evidence for the conversion of isosteviol to 15-haloisosteviols is provided by the disappearance in the ^1H NMR spectra of the doubled doublet of the methylene protons at C^{15} and appearance of a doublet signal of the methine proton at C^{15} ($^4J_{HH}$ 2 Hz) at 4.22 ppm for 15-chloroisosteviol and 4.44 ppm for 15-bromoisosteviol. The lack of other signals in the region of 4.0–4.5 ppm suggests lack in the reaction mixture of other compounds containing CHBr fragments and, consequently, high regio- and stereoselectivity of the halogenation reactions. However, the evidence in hand was insufficient for rigorous configurational assessment of the carbon atom in the newly formed hydrocarbon fragment.

To find out the stereochemistry of the above conversions, we performed an X-ray diffraction study of single crystals of compounds **II** and **III**. The molecular structures of 15-chloro- and 15-bromoisosteviols, depicted in Figs. 1 and 2, provide unambiguous evidence to show that the C^{15} atom of the carbocyclic carcass has an *S* configuration, i.e. halogenation always occurs in a stereospecific fashion. We consider the halogenation reactions studied in the present work to have much in common, in the stereochemical aspect, with the reduction of the isosteviol hydroxy group, we studied previously [12]. Comparison of the stereochemical congestion of the *re* and *si* enantiofacial sides of the carbonyl group at C^{16} in reaction with $NsBH_4$ points to an almost complete shielding of the latter side, which predetermines formation of 16-hydroxyisosteviol with (*R*)-C^{16} [12]. Apparently, the same situation takes place in halogenation of isosteviol. The fact that the C^{15}=C^{16} bond in the enol form of isosteviol is impossible to attack from the *re* side result in the stereospecific formation od (*S*)–C^{15}.

15-Chloroisosteviol (**II**) was crystallized from methanol. Its molecules, like molecules of the parent isosteviol in crystal [13], are joined into dimers by intermolecular hydrogen bonds O^1–$H^{1\cdots 2'}$ of the

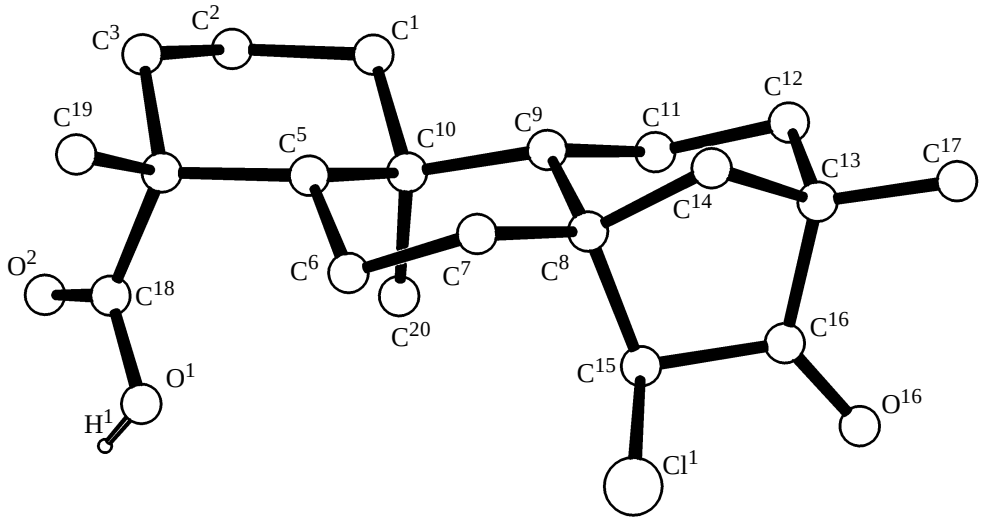


Fig. 1. Molecular geometry of 15-chloroisosteviol (**II**). Shown is only the carboxyl hydrogen atom, the solvatemethanol molecule is not shown.

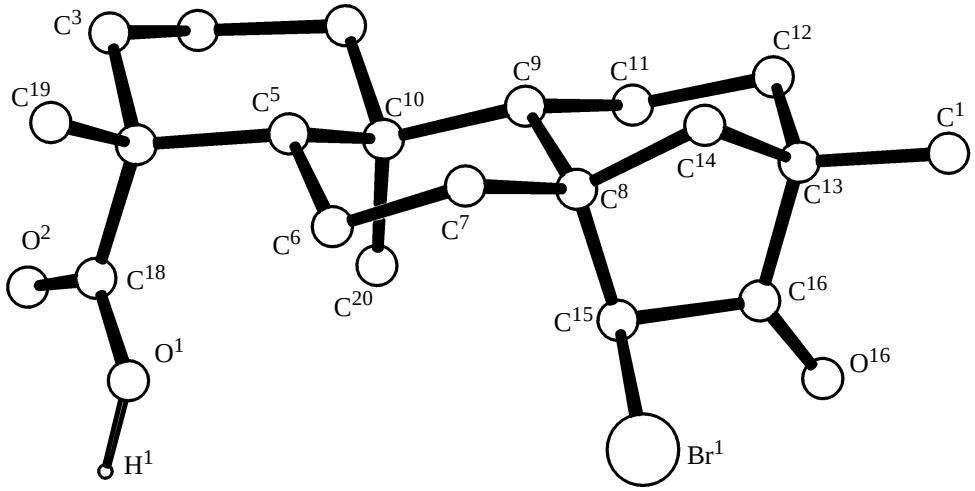


Fig. 2. Geometry of one of the independent molecules of 15-bromoisosteviol (**III**). Shown is only the carboxyl hydrogen atom.

classical "acid" type characteristic of carboxylic acids. These intermolecular hydrogen bonds have the following parameters: $d(O^1–H^1)$ 0.89, $d(H^1\cdots O^{2'})$ 1.74 Å, $\angle O^1H^1O^{2'}$ 167.7°, symmetry code (*1 – x, y, –z*). Between the H^{122} atoms at C^{12} and the chlorine atoms of 15-chloroisosteviol molecules belonging to neighboring dimers, there is a short contact with the following parameters: $d(H^{122}\cdots Cl^{1''})$ 2.73 Å, $\angle C^{12}H^{122}Cl^{1''}$ 150° (*–1/2 + x, 1/2 + y, z*). Note that this contact between two dimer molecules is realized in two mutually perpendicular directions. Thus, 15-chloroisosteviol molecules pack in crystal to form a bilayer structure (Fig. 3). Infinite layers of hydrogen-bonded dimers alternate along the 0*z* crystal axis with layers of disordered solvent (methanol) molecules.

On crystallization of 15-chloroisosteviol (**II**) from DMF form crystals of another type (**IV**), in which the independent part of the crystal comprises chloroketone and DMF molecules (Fig. 4). in intermolecular hydrogen bonds, the latter, by our data, acts both as hydrogen acceptor and hydrogen donor. The carboxyl hydrogen atom of 15-chloroisosteviol and the carbonyl oxygen atom of DMF form a short contact $O^1–H^1\cdots O^{30}$ with the following parameters: $d(O^1–H^1)$ 0.64, $d(H^1\cdots O^{30})$ 2.02 Å, $\angle O^1H^1O^{30}$ 158°, (*1 – x, –1/2 + y, 1 – z*). This contact form a hydrogen-bonded dimer. Moreover, a short contact $C^{31}–H^{312}\cdots O^2$ is realized between one of the methyl groups of DMF and the carboxyl oxygen atom of 15-chloroisosteviol. The geometric parameters of this contact are as follows: $d(C^{31}–H^{311})$ 1.03, $d(H^{312}\cdots O^2)$ 2.58 Å, $\angle C^{31}H^{312}O^2$ 147°, symmetry code (*–x, 1/2 + y, 1 – z*).

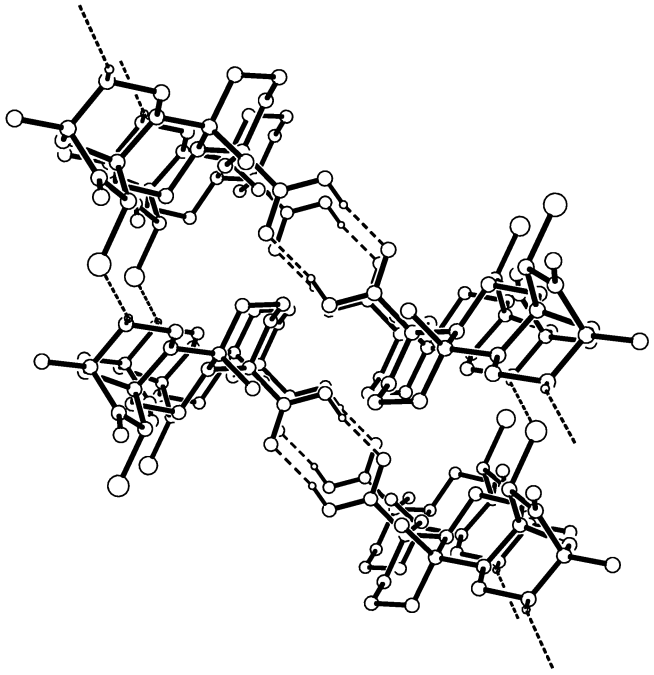


Fig. 3. System of hydrogen bonds and packing of 15-chloroisosteviol molecules in crystal. Shown are only the hydrogen atoms of the carboxy group and at C^{15}, the solvate methanol molecule is not shown. View along the 0*y* crystal axis.

The crystal of 15-bromoisosteviol (**III**) comprises two independent molecules, and the system of intermolecular hydrogen bonds in it differs from that characteristic of 15-chloroisosteviol (**II**) (Fig. 5). The hydrogen bonds in the crystal of 15-bromoisosteviol (**III**) have the following parameters: $d(O^{1A}–H^{1A})$ 1.008, $d(H^{1A}\cdots O^{2B'})$ 1.609 Å, $\angle O^{1A}H^{1A}O^{2B'}$ 169.9°, $d(O^{1B}–H^{1B})$ 0.985, $d(H^{1B}\cdots O^{2A'})$ 1.801 Å, $\angle O^{1B}H^{1B}O^{2A'}$ 156°. Moreover, there is a $C^{14B}–H^{141B}\cdots O^{1A}$ contact [$d(C^{14B}–H^{141B})$ 1.020, $d(H^{141B}\cdots O^{1A'})$ 2.585 Å, $C^{14B}H^{141B}O^{1A'}$ 144°], due to which zigzag molecular chains are formed, running along the 0*b* crystal axis. Therewith, the carboxy groups in the crystals of compounds **II** and **III** are differently oriented with respect to the rigid tetracyclic hydrocarbon skeleton. In going from 15-chloro- to 15-bromoisosteviol, the torsion angle of the tetracyclic hydrocarbon carcasses relative to each other changes by ~10–13°.

Thus, the halogenation of isosteviol occurs regio- and stereospecifically with quantitative formation of 15-haloisosteviols with (*S*)-C^{15}.

EXPERIMENTAL

The melting points were determined using a Boetius hot stage. The IR spectra were recorded on Specord IR-75 and UR-20 spectrophotometers at 400–3600 cm^{-1} for thin films or Nujol mulls. The ^1H NMR spectra were measured on a Bruker WM-250 instrument at 250.13 MHz. The chemical shifts were measured in δ relative to $CDCl_3$.

The mass spectra of the reaction mixtures and pure samples of 15-chloroisosteviol (**II**) were obtained on

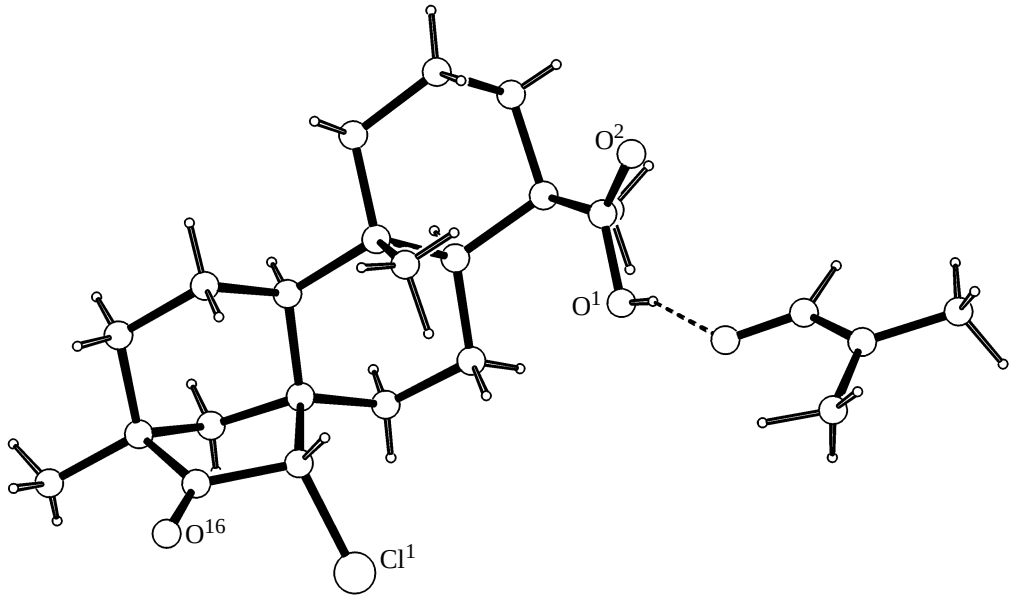


Fig. 4. Independent part of crystal **IV** of the complex of 15-chloroisosteviol with DMF and the system of intermolecular hydrogen bonds in it.

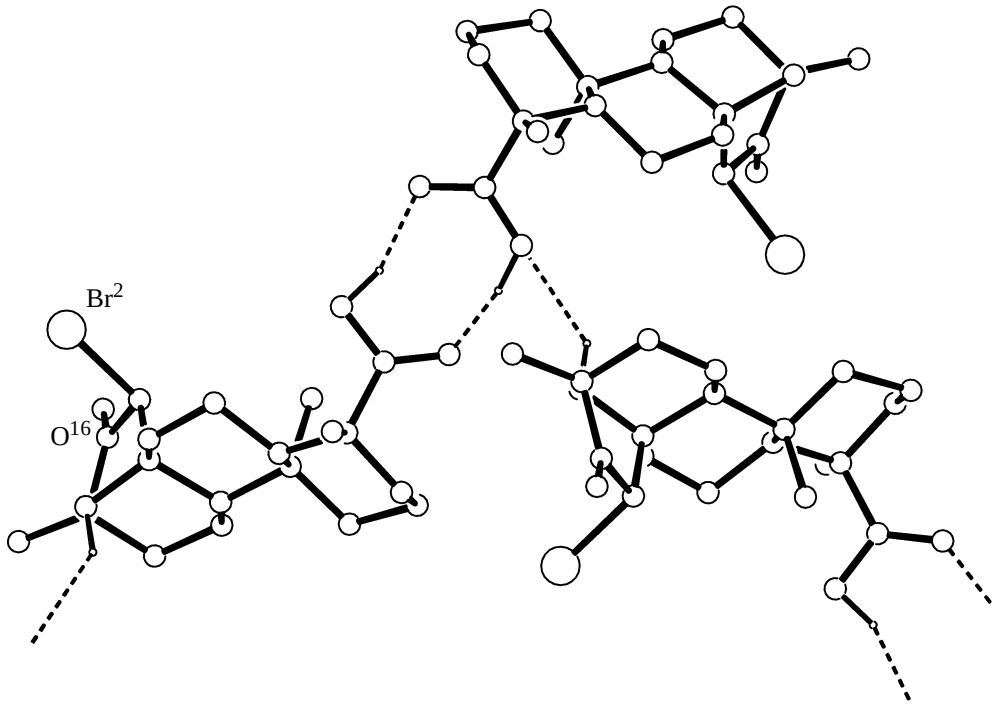


Fig. 5. System of intermolecular hydrogen bonds in the crystal of compound **III**. View along the 0*b* crystal axis.

an MX-1310 instrument (*R* 1500), ionizing energy 70 eV, collector current 30–60 μA, ion source oven temperature 80–200°C, an SVP-5 direct inlet probe.

The electron impact mass spectra of 15-bromoisosteviol (**III**) were obtained on Trace-MS Finnigan-MAT instrument, ionizing energy 70 eV, ion source temperature 200°C. The direct inlet probe was heated from 35 to 150°C at a rate of 35 deg/min. The mass spectral data were treated using the XCALIBUR program.

X-ray diffraction study of 15-haloisosteviols was performed on an Enraf–Nonius CAD-4 automated diffractometer at the Department for X-ray diffraction studies of Collective Spectral Analytical Center of the Russian Foundation for Basic Research. The unit cell parameters and reflection intensities were measured under CuK_α-radiation (λ 1.54184 Å, graphite monochromator, ω/2θ scanning, θ ≤ 74.02°) at 20°C. Crystal stability during measurements were controlled by three reference reflections measured every 2 h, and crystal orientation, by two reference reflections measures every 200 reflections. The structures were solved by the direct method using the SIR program [13].

Solvate of 15-chloroisosteviol with methanol (II). The crystals of the compound $C_{20}H_{29}O_3Cl \cdot 1/2CH_3OH$ are monoclinic, colorless, and prysmatic. Cell parameters: *a* 12.032(5), *b* 9.879(4), *c* 16.766(7) Å; β 93.52(4)°, *V* 1989(2) Å^3, d_{calc} 1.178 g cm^{-3}, *Z* 4, space group *C*2. Intensities of 2268 unique reflections, 2109 of which with $I > 3\sigma(I)$, were measured. No intensity decay of the three reference reflections was observed during measurements. No absorption corrections were applied (μCu 18.12 cm^{-1}). The structure was refined first isotropically and then anisotropically. Hydrogen atoms were located by difference synthesis and refined isotropically at the final refinement stage. To assess the absolute configuration, divergence factors were measured both for the direct and inverted structures. The divergence factors on 2073 unique reflections with $F^2 \geq 3$. were as follows: direct structure: *R* 0.043 and R_W 0.062; inverted structure: *R* 0.044 and R_W 0.062. According to Hamilton's test, the direct structure corresponds to absolute with a probability of 95%.

15-Bromoisosteviol (III). The crystals of the compound $C_{20}H_{29}O_3Br$ are rhombic, light yellow, prysmatic. Cell parameters: *a* 8.516(2), *b* 18.621(3), *c* 24.258(4) A; *V* 3847(1) Å^3, d_{calc} 1.372 g cm^{-3}, *Z* 8, space group $P2_12_12_1$ (independent molecules A and B). Intensities of 5261 reflections, 2308 of which with $I \geq 2\sigma$, were measured. No intensity decay of the three reference reflections was observed during measurements. No absorption corrections were applied (μCu 30.28 cm^{-1}). The structure was solved by the direct method and refined first isotropically and then anisotropically. Hydrogen atoms were located by difference

synthesis and included in structure amplitudes with fixed positional and isotropic temperature parameters. The final divergence factors were R 0.080 and R_W 0.061, on 2202 unique reflections. The absolute configuration of the molecule was set the same as those determined previously for isosteviol and its derivatives.

Solvate of 15-chloroisosteviol with dimethylformamide (IV). The crystals of the compound $C_{20}H_{29}\cdot O_3Cl\cdot C_2H_7NO$ are monoclinic, colorless, prysmatic. Cell parameters: *a* 6.931(4), *b* 7.327(8), *c* 22.706(5) Å; β 92.73(4)°, *V* 1152(2) Å^3, d_{calc} 1.197 g cm^{-3}, *Z* 2, space group $P2_1$. Intensities of 3694 of unique reflections, 2871 of which with $I > 3\sigma(I)$, were measured. No intensity decay of the three reference reflections was observed during measurements. No absorption corrections were applied (μCu 16.75 cm^{-1}). The structure was refined first isotropically and then anisotropically. Hydrogen atoms were located by difference synthesis and refined isotropically at the final refinement stage. The final divergence factors were R 0.043 and R_W 0.052, on 2613 unique reflections with $F^2 \geq 3\sigma$. The absolute configuration of the molecule was set the same as that determined previously for isosteviol.

Even though the three structures all contain heavy atoms, we failed to account for absorption. The main reason for this failure was the lack of sufficiently intense large-angle reflections ($\chi \geq 80°$), required to measure ψ curves.

All calculations were performed by the MolEN program [14] on an AlphaStation-200 computer. Intermolecular contacts were analyzed and structure drawings were obtained using the PLATON program [15]. The atomic coordinates of the structures are deposited in the Cambridge Structural Database and can be provided by the authors.

15-Chloroisosteviol (II). Sulfuryl chloride, 0.75 g, was added to a solution of 1.5 g of isosteviol (**I**) in 30 ml of chloroform. The resulting mixture was refluxed for 30 h, and the solvent and excess SO_2Cl_2 were then removed in a vacuum. Recrystallization of the crude reaction product from methanol gave 1.61 g (97%) of 15-chloroisosteviol (**II**), mp 224–225°C, $[\alpha]_D^{25}$ –61.3° (*c* 0.34, CH_3OH). IR spectrum, ν, cm^{-1}: 1690 (carboxyl C=O), 1745 (ketone C=O), 2400–3570 (carboxyl OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.77 s (3H, CH_3), 1.17 s (3H, CH_3), 1.21 s (3H, CH_3), 0.77–2.20 m (18H, isosteviol), 4.42 d (1H, CHCl, *J* 2.05 Hz). ^{13}C–{^{1}H} NMR spectrum ($CDCl_3$), δ_C, ppm: 13.50, 18.81, 19.80, 20.43, 20.78, 28.89, 36.09, 37.53, 37.90, 38.47, 39.47, 43.31, 43.67, 48.15, 49.83, 56.51, 57.19, 62.51, 184.15, 215.7. Found, %: C 68.64; H 7.82; Cl 10.15. $C_{20}H_{28}ClO_3$. Calculated, %: C 68.30; H 7.96; Cl 10.08.

15-Bromoisosteviol (III). *a*. Bromine, 0.80 g, was added to a stirred solution of 1.5 g of isosteviol (**I**) in 10 ml of glacial acetic acid. The reaction mixture was kept for 3 h at 60–70°C and 1 day at room temperature, after which it was poured into a Petri dish. As the solvent evaporated, pale yellow needle-like crystals of 15-bromoisosteviol (**III**), suitable for X-ray diffraction measurements, formed. Yield 1.87 g (100%), mp 246–248°C, $[\alpha]_D^{25}$ –12.3° (*c* 0.16, C_2H_5OH). IR spectrum, ν, cm^{-1}: 1695 (carboxyl C=O), 1743 (ketone C=O), 2400–3570 (carboxyl OH), 628 (CBr). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.77 s (3H, CH_3), 1.04 s (3H, CH_3), 1.21 s (3H, CH_3), 0.77–2.22 m (18H, isosteviol), 4.44 d (1H, CHCl, *J* 2.07 Hz). ^{13}C–{^{1}H} NMR spectrum ($CDCl_3$), δ_C, ppm: 14.13, 19.84, 20.77, 21.19, 21.77, 38.94, 38.69, 39.25, 30.50, 40.18, 43.90, [5] 44.13, 48.96, 50.63, 56.70, 57.62, 57.63, 179.01, 215.16. Mass spectrum $[M]^+$: *m/z* 396, 398. Found, %: [6] C 60.41; H 7.20; Br 20.29. $C_{20}H_{28}BrO_3$. Calculated, %: C 60.64; H 7.07; Br 20.17.

b. Isosteviol, 0.16 g, was added to a mixture of 0.45 g of 48% HBr and 4.5 ml of DMSO. The reaction mixture was kept for 5 h at 80°C, poured into water (10 ml), and the reaction product was extracted with chloroform (3.5 ml). The extract was washed with water and dried with MgSO4. The solvent was removed, and the solid residue (0.2 g, individual substance, according to TLC) was washed with petroleum ether and recrystallized from ethanol–ethyl acetate. Yield 0.16 g (80%), mp 249–252°C. The NMR, mass, and IR spectra, as well as the $[\alpha]_D^{25}$ value are identical to those for the sample obtained by procedure *a*.

ACKNOWLEDGMENTS

The work was financially supported by the Russian Foundation for Basic Research (project nos. 04-03-32 063, 04-03-32 133, 02-03-32 280).

REFERENCES

1. Alfonsov, V.A., Bakaleynik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Andreeva, O.V., and Korochkina, M.G., *Mendeleev Commun.*, 1999, no. 6, p. 227.
2. Al'fonsov, V.A., Andreeva, O.V., Bakaleinik, G.I., Beskrovnyi, D.V., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Korochkina, M.G.,

Litvinov, I.A., Strobykina, I.Yu., and Musin, R.Z., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 8, p. 1323.

3. Alfonsov, V.A., Bakaleynik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Andreeva, O.V., and Korochkina, M.G., *Mendeleev Commun.*, 2000, no. 5, p. 177.
4. Al'fonsov, V.A., Andreeva, O.V., Bakaleinik, G.I., Beskrovnyi, D.V., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Korochkina, M.G., Latypov, Sh.K., Litvinov, I.A., Musin, R.Z., and Strobykina, I.Yu., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 7, p. 1186.
5. Lehn, J.-M., *Supramolecular Chemistry: Concepts and Perspectives*, Weinheim: VCH, 1998.
6. Tabichi, I. and Kitaguchi, H., in *Pizey Synthetic Reagents*, New York: Wiley, 1981, vol. 4, p. 336.
7. Tapuchi, E. and Jencks, W.P., *J. Am. Chem. Soc.*, 1982, vol. 104, no. 21, p. 5758.
8. Pinkus, A.G. and Gopalan, R., *Tetrahedron*, 1986, vol. 42, no. 13, p. 3411.
9. Deno, N.C. and Fishbein, R., *J. Am. Chem. Soc.*, 1973, vol. 95, no. 22, p. 7445.
10. Floyd, M.B., Du, M.T., Fabio, P.F., and Johnson, B.D., *J. Org. Chem.*, 1985, vol. 50, no. 25, p. 5022.
11. Yusubov, M.S., Drygunova, L.A., and Tkachev, A.V., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2001, no. 8, p. 1350.
12. Al'fonsov, V.A., Bakaleinik, G.A., Gubaidullin, A.T., Kataev, V.E., Kovylyaeva, G.I., Konovalov, A.I., Litvinov, I.A., Strobykina, I.Yu., Strobykin, S.I., Andreeva, O.V., and Korochkina, M.G., *Zh. Obshch. Khim.*, 2000, vol. 70, no. 6, p. 1018.
13. Altomare, A., Cascarano, G., Giacovazzo, C., and Viterbo, D., *Acta Crystallogr., Sect. A*, 1991, vol. 47, no. 4, p. 744.
14. Straver, L.H. and Schierbeek, A.J., *MolEN. Structure Determination System*, Vol. 1, *Program Description*, Nonius, B.V., 1994.
15. Spek, A.L., *PLATON. A Miltipurpouse Crystallographic Tool*, Utrecht: Utrecht Univ. Press, 2000.