ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 1, pp. 129–137. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © B.T. Sharipov, O.Yu. Krasnoslobodtseva, L.V. Spirikhin, F.A. Valeev, 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 1, pp. 128–135.

Cleavage of the 1,6-Anhydro Bridge in the Levoglucosenone Adduct with Isoprene and Its Derivatives

B. T. Sharipov, O. Yu. Krasnoslobodtseva, L. V. Spirikhin, and F. A. Valeev

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences,
pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: sinvmet@anrb.ru

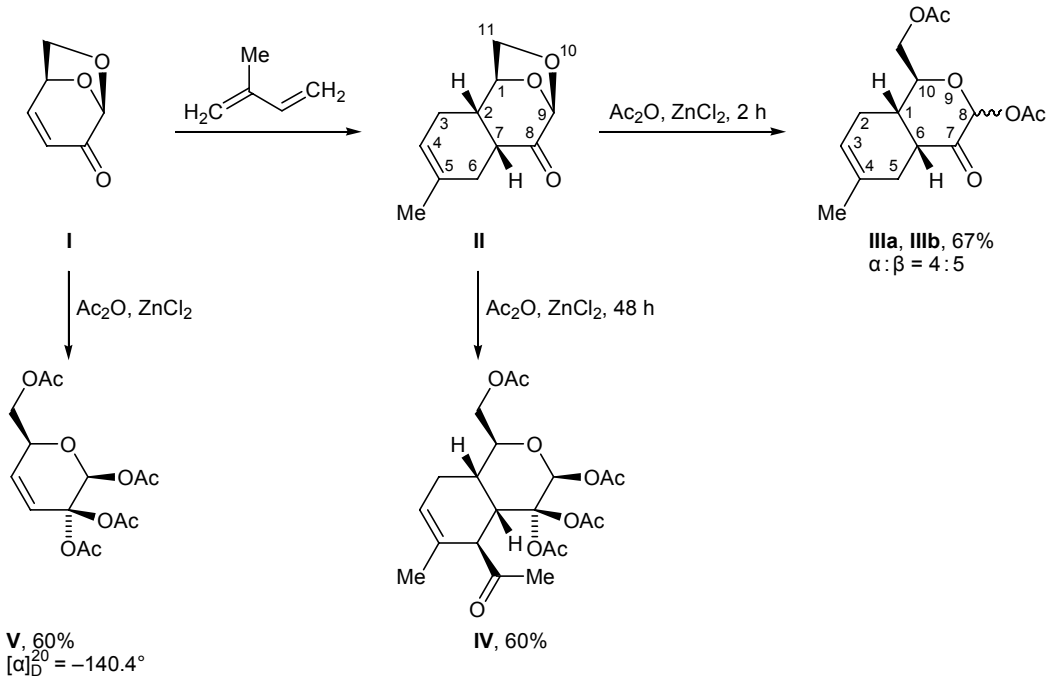
Received December 3, 2008

Abstract—Methods of opening of the 1,6-anhydro bridge in levoglucosenone ($ZnCl_2$–Ac_2O), its adducts with isoprene ($ZnCl_2$–Ac_2O, HCl–MeOH), and hydroxy derivatives (H_3PO_4–Ac_2O) were studied. Cleavage of the 1,6-anhydro bridge in anomeric acetoxy derivatives of levoglucosenone–isoprene adduct by the action of $BF_3 \cdot Et_2O$–Ac_2O was accompanied by acetylation at the allylic C^6 position.

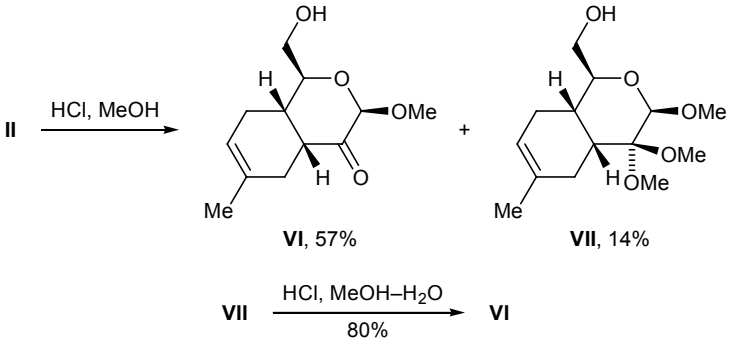
DOI: 10.1134/S1070428010010148

Levoglucosenone (**I**) as dienophile undergoes thermal Diels–Alder reaction with butadiene to give the corresponding adduct at the α-side with high stereoselectivity [1]. Analogous reactions of **I** with cyclopentadiene [2, 3], isoprene [4], and piperilene [5] lead to the formation of mixture of regioisomeric pairs of *endo* and *exo* diastereoisomers. An important problem related to further application of the above adducts in organic synthesis is cleavage of the 1,6-anhydro bridge. We believed that study on such transformation of levoglucosenone–isoprene adduct **II** as an example would give rise to procedures applicable to all other levoglucosenone adducts, which should extend the series of available chiral substrates. Known methods for opening of the 1,6-anhydro bridge involved the corresponding protected hydroxy derivatives rather

Scheme 1.



Scheme 2.



than the adducts themselves [6]. Development of procedures for direct cleavage of the 1,6-anhydro bridge should shorten the necessary transformation sequence. We made attempts to open the 1,6-anhydro bridge in adduct **II** with the use of the following systems: Ac_2O–$BF_3 \cdot Et_2O$, isopropenyl acetate–$BF_3 \cdot Et_2O$, Ac_2O–H_2SO_4, and Ac_2O–H_3PO_4; however, in all cases, the reaction was accompanied by strong tarring. Treatment of **II** with acetic anhydride in the presence of a softer Lewis acid ($ZnCl_2$, 2 h) gave a mixture of α- and β-anomeric products **IIIa** and **IIIb** (yield 67%) which were difficult to separate (Scheme 1).

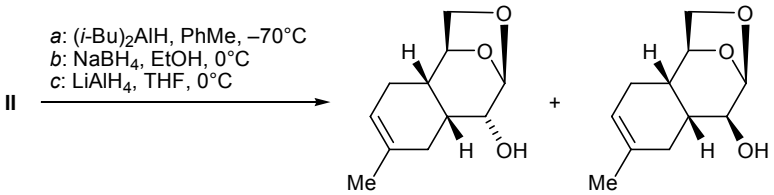
The ratio of anomers **IIIa** and **IIIb** was determined on the basis of the ^{1}H NMR data, and they were assigned to α- or β-series* using ^{13}C NMR spectroscopy. The C^8 and C^{10} atoms in the major anomer (**IIIa**) resonated in a stronger field (δ_C 90.10 and 72.61 ppm) than those of minor anomer **IIIb** (δ_C 90.23 and 74.03 ppm, respectively). The observed upfield shift indicated *syn* interaction between the substituents on C^8 and C^{10}, i.e., β-orientation of the acetoxy group. This conclusion is confirmed by the ^{1}H NMR data: the 8-H signal of major β-anomer **IIIa** appears in a weaker field (δ 6.09 ppm), in keeping with equatorial orientation of the 8-H proton; signal from the corresponding (more shielded) proton of α-anomer **IIIb** is located at δ 5.59 ppm.

Increase of the reaction time (48 h) leads to acetylation of compound **II** at the more accessible allylic position (C^6), and the oxo group is converted into acylal moiety (compound **IV**). It is known that opening of the 1,6-anhydro bridge in highly reactive levoglucosenone (**I**) involves difficulties. Nevertheless, treatment of compound **I** with $ZnCl_2$–Ac_2O resulted in stereoselective formation of acylal **V**.

Another procedure for cleavage of oxygen bridges in carbohydrates involves treatment with a solution of hydrogen chloride in methanol. The reaction of adduct **II** with a 15% solution of HCl in MeOH in 5 h gave 57% of methyl acetal **VI** and up to 14% of dimethyl ketal **VII** (Scheme 2). The latter underwent hydrolysis to compound **VI** on addition of water, so that the overall yield of **VI** reached 70%.

Opening of the 1,6-anhydro bridge was more effective in diastereoisomeric hydroxy derivatives **VIIIa** and **VIIIb**. The oxo group in adduct **II** was reduced using (i-Bu)$_2$AlH, $NaBH_4$, or $LiAlH_4$. In all cases, the corresponding α-hydroxy derivative **VIIIa** was formed

Scheme 3.



* Atom numbering in the NMR spectra corresponds to that shown in the respective scheme.

as the major product (Scheme 3). Spectral identification of epimers **VIIIa** and **VIIIb** was based initially on general relations holding in the spectra of epimeric alcohols derived from levoglucosenone [7]. The most informative signal is that belonging to the 1-H proton. It is located at δ 5.48 ppm ($J_{1,2}$ = 2.5 Hz) for the major *threo* isomer (2*S*-epimer) and at δ 5.52 ppm ($J_{1,2}$ = 1.6 Hz) for the *erythro* isomer (2*R*-epimer). The pyran ring in hydroxy derivatives **VIIIa** and **VIIIb** may adopt both *chair* and *boat* conformation, depending on the substituent on C^8. Correspondingly, couplings between 8-H and the neighboring protons change. In the ^{1}H NMR spectrum of the major epimer, the 9-H signal appears at δ 5.37 ppm ($J_{8,9}$ = 2.5 Hz), while the 8-H proton resonates at δ 3.44 ppm ($J_{8,9}$ = 2.5, $J_{8,7}$ = 3.1 Hz). In the spectrum of the minor epimer, the 9-H and 8-H signals are located at δ 5.35 (overlapped by the 4-H signal) and 3.35 ppm ($J_{8,9}$ = 1.4, $J_{8,7}$ = 10.0 Hz), respectively.

Thus, on the basis of only $J_{8,9}$ values we can presume that the major stereoisomer is characterized by *S* configuration at the C^8 atom, as in other alcohols derived from levoglucosenone [7]. On the other hand, the large coupling constant $J_{8,7}$ = 10.0 Hz for the minor isomer indicates axial orientations of 7-H and 8-H, which is also possible for the (8*S*)-epimer with *chair* conformation of the pyran ring. By contrast, small value of $J_{8,7}$ (3.1 Hz) for the major diastereoisomer suggests axial–equatorial interaction possible for the (8*R*)-epimer in both *chair* and *boat* conformations. Therefore, additional spectral studies are necessary to unambiguously assign stereochemical structure of the newly formed asymmetric center.

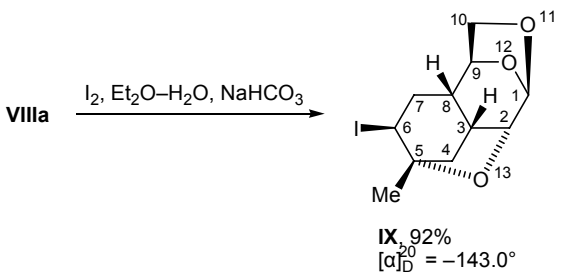
In order to elucidate this problem, both epimers were subjected to iodocyclization. The results showed that only the major (8*S*)-epimer (**VIIIa**) underwent intramolecular cyclization with closure of tetrahydrofuran ring (compound **IX**, Scheme 4) and that minor (8*R*)-epimer **VIIIb** failed to react. Taking into account the mechanism of this reaction proposed in [8], we presumed that closure of tetrahydrofuran ring occurs at the stage of formation of β-oriented iodonium cation via nucleophilic attack by the hydroxy group. This is possible only in the structure with α-oriented hydroxy group. After cleavage of the iodine-containing ring, the iodine atom appears β-configured. The ^{1}H NMR spectrum of compound **IX** is consistent with stereochemical aspects of the above transformation. The most informative ^{1}H NMR signals characterizing the structure of **IX** are those belonging to 6-H (δ 4.27 ppm, d.d, *J* = 10.3, 4.0 Hz), 7-H_{ax} (δ 2.22 ppm, d.d.d, $J_{7,8}$ = 2.2 Hz) and 7-H_{eq} (δ 2.67 ppm, d.d, ^2J = 10.8 Hz), and 8-H (δ 1.72 ppm, d.d, *J* = 2.2 Hz). The observed couplings may occur only in the structure with β-orientation of the iodine atom in the *gauche* conformation of **IX**.

The hydroxy group in **VIIIa** can be protected via transformation into *p*-toluenesulfonate, acetate, and trimethylsilyl or methyl ether moieties (Scheme 5). Although the methoxy group in **XIII** cannot be hydrolyzed directly, methyl protection can be removed by complete opening of the sugar fragment and α-ketol rearrangement.

Treatment of acetates **XI** and **XIV** with $BF_3 \cdot Et_2O$ in acetic anhydride results in more effective (as compared to adduct **II**) acetylation at the allylic C^6 position with simultaneous opening of the 1,6-anhydro bridge (Scheme 6). Analogous reactions with H_2SO_4–Ac_2O or $BF_3 \cdot Et_2O$–isopropenyl acetate give only mixtures of anomeric products **XV** and **XVII**, but the efficiency of cleavage of the 1,6-anhydro bridge is lower. The reactions of alcohols **VIIIa** and **VIIIb** with H_3PO_4–Ac_2O afforded anomeric acetates **XV** and **XVII** in high yields. Here, (8*R*)-epimer **VIIIb** reacted almost instantaneously, while the transformation of (8*S*)-epimer **VIIIa** required 1 h.

Thus, opening of the 1,6-anhydro bridge is possible both in adduct **II** with conservation of the oxo group and in its 8-hydroxy and 8-acetoxy derivatives.

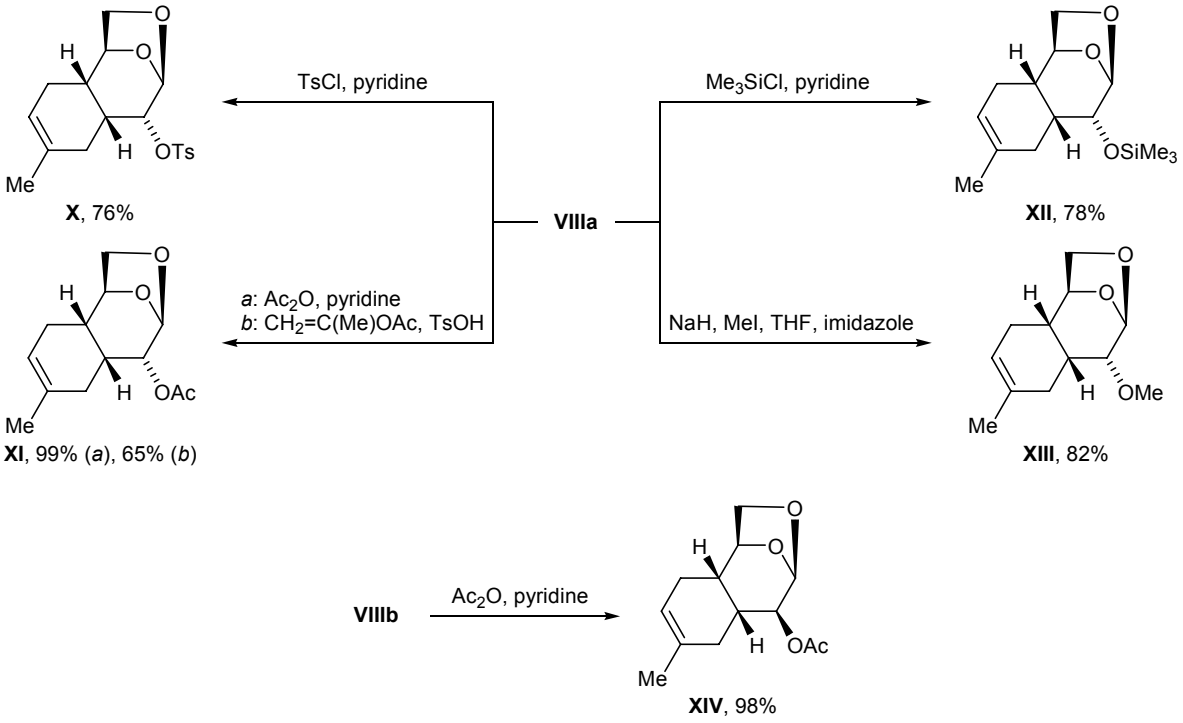
Scheme 4.



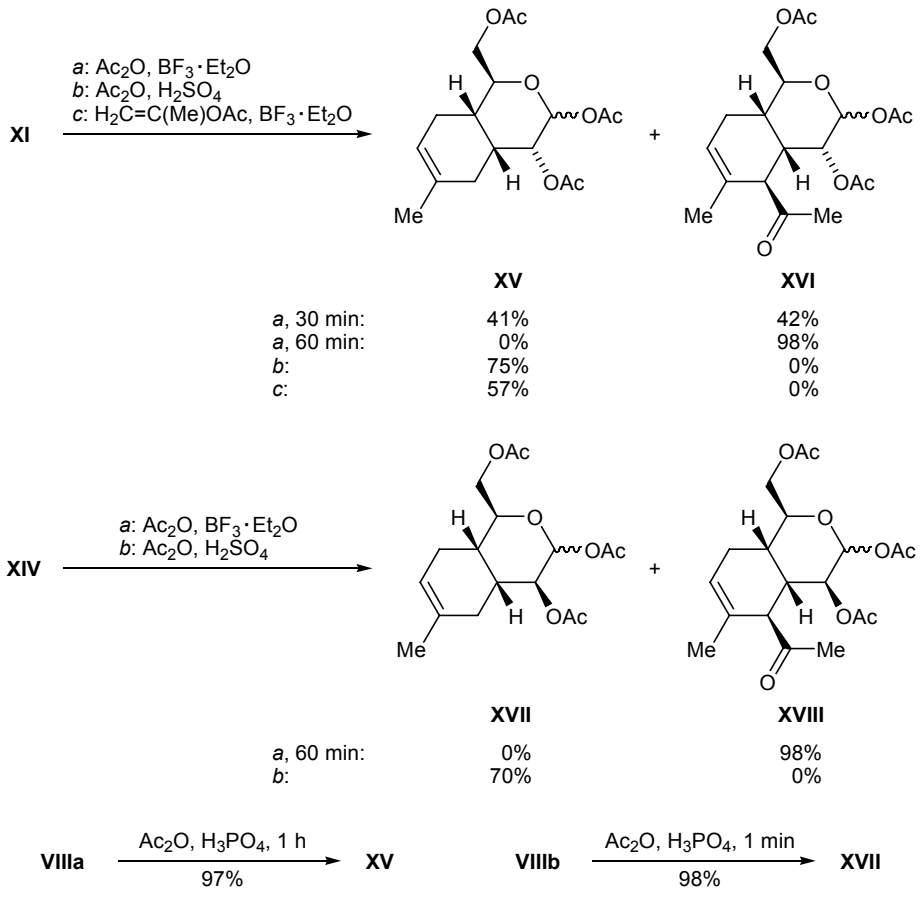
EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 (^{1}H) and 75.47 MHz (^{13}C) using $CDCl_3$ as solvent unless otherwise stated. The melting points were measured on a Kofler S 30A/G melting point apparatus (DDR). Analytical thin-layer chromatography was performed on Sorbfil PTSKh-AF-A plates (*Sorbpolimer* Ltd., Krasnodar, Russia). The elemental compositions were determined on an Evro-2000 CHNS(O) analyzer. The

Scheme 5.



Scheme 6.



mass spectra (atmospheric pressure chemical ionization) were obtained on a Shimadzu 2010EV GC–MS instrument. The optical rotations were measured on a Perkin–Elmer 341 polarimeter.

(1*S*,3*RS*,4a*R*,8a*S*)-1-Acetoxymethyl-6-methyl-4-oxo-3,4,4a,5,8,8a-hexahydro-1*H*-isochromen-3-yl acetate (IIIa/IIIb). A solution of 1.0 g (5.15 mmol) of compound **II** in 10 ml of acetic anhydride was cooled to 0°C, 0.70 g (5.15 mmol) of anhydrous zinc(II) chloride was added, and the mixture was stirred for 2 h at 0°C, poured onto ice, neutralized with a saturated solution of sodium hydrogen carbonate, and extracted with ethyl acetate (3×50 ml). The extract was dried over $MgSO_4$ and evaporated, and the residue was purified by chromatography. Yield 1.03 g (67%), **IIIa**:**IIIb** = 5:4, oily substance, R_f 0.3 (petroleum ether–ethyl acetate, 5:1). ^{1}H NMR spectrum,** δ, ppm: 1.60 s [1.60 s] (3H, 4-CH_3), 1.83–2.10 m [1.83–2.10 m] (3H, CH, CH_2), 1.95 s [2.05 s] (3H, CH_3), 2.08 s [2.12 s] (3H, CH_3), 2.48 m [2.48 m] (1H, CH_2), 2.60 m [2.60 m] (1H, CH_2), 3.08 m [3.08 m] (1H, CH), 4.03 d [4.05 d] (1H, 1-H, *J* = 7.1 Hz), 4.08 d [4.11 d] (1H, 1-H, *J* = 7.1 Hz), 4.22 m [4.40 m] (1H, 10-H), 5.35 m [5.35 m] (1H, 3-H), 6.09 s [5.59 s] (1H, 8-H). ^{13}C NMR spectrum, δ_C, ppm: 20.54 [20.88] (CO**C**H_3), 21.68 [22.52] (C^2), 23.27 [20.81] (4-CH_3), 32.64 [30.76] (C^5), 33.71 [31.43] (CO**C**H_3), 34.11 [35.75] (C^1), 41.01 [39.92] (C^6), 64.99 [64.84] (C^1), 72.61 [74.03] (C^{10}), 90.10 [90.23] (C^8), 118.59 [118.33] (C^3), 130.64 [131.02] (C^4), 168.76 [167.97] (**C**OCH_3), 170.53 [168.54] (**C**OCH_3), 204.49 [202.01] (C^7). Found, %: C 60.57; H 7.03. $C_{15}H_{20}O_6$. Calculated, %: C 60.80; N 6.80.

(1*S*,3*S*,4a*S*,5*R*,8a*S*)-1-Acetoxymethyl-5-acetyl-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromene-3,4,4-triyl triacetate (IV) was synthesized in a similar way from 1.0 g (5.15 mmol) of compound **II**; the reaction mixture was stirred for 48 h at room temperature. Yield 1.36 g (60%), oily substance, R_f 0.3 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.68 s (3H, 4-CH_3), 1.90–2.00 m (2H, CH_2), 2.0 s (3H, CH_3), 2.04 s (3H, CH_3), 2.07 s (3H, CH_3), 2.11 s (3H, CH_3), 2.20 s (3H, CH_3), 2.28 d.d (1H, 6-H, *J* = 6.8, 3.6 Hz), 2.64 d.d.d (1H, 1-H, *J* = 15.6, 11.0, 3.6 Hz), 3.09 d (1H, 5-H, *J* = 6.8 Hz), 3.88 d.d.d (1H, 10-H, *J* = 11.0, 4.7, 2.9 Hz), 4.22 d.d (1H, 1′-H, *J* = 5.2, 4.7 Hz), 4.24 d.d (1H, 1′-H, *J* = 5.2, 2.9 Hz), 5.55 d (1H, 3-H, *J* = 5.1 Hz), 6.69 d (1H, 8-H, *J* = 1.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.45 (CO**C**H_3), 20.62 (CO**C**H_3), 20.89 (CO**C**H_3), 21.36 (CO**C**H_3), 21.71 (C^2), 22.90 (4-CH_3), 28.20 ($C^{2''}$), 30.07 (C^1), 33.94 (C^6), 53.08 (C^5), 63.57 ($C^{1'}$), 68.65 (C^{10}), 88.38 (C^8), 99.65 (C^7), 121.94 (C^3), 135.40 (C^4), 167.49 (**C**OCH_3), 167.75 (**C**OCH_3), 167.75 (**C**OCH_3), 170.53 (**C**OCH_3), 208.05 ($C^{1''}$). Found, %: C 57.47; H 6.21. $C_{21}H_{28}O_{10}$. Calculated, %: C 57.27; H 6.41.

Acetyl 2,2,6-tri-*O*-acetyl-3,4-dideoxy-β-D-hex-3-enopyranoside (V) was synthesized in a similar way from 1.0 g (7.93 mmol) of levoglucosenone (**I**); the reaction mixture was stirred for 12 h at room temperature. Yield 1.57 g (60%), mp 112–113°C, R_f 0.3 (petroleum ether–ethyl acetate, 1:1), $[\alpha]_D^{20}$ = –140.4° (*c* = 0.95, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 2.10 s (3H, CH_3), 2.12 s (3H, CH_3), 2.18 s (3H, CH_3), 4.22 d (1H, 6-H, *J* = 7.7 Hz), 4.23 d.d (1H, 6-H, *J* = 7.7, 5.7 Hz), 4.38 d.d (1H, 5-H, *J* = 5.7, 2.4 Hz), 5.39 d.d (1H, 4-H, *J* = 6.2, 2.4 Hz), 6.08 d (1H, 3-H, *J* = 6.2 Hz), 6.38 s (1H, 1-H). Found, %: C 50.85; H 5.55. $C_{14}H_{18}O_9$. Calculated, %: C 50.91; H 5.49.

(1*S*,3*R*,4a*R*,8a*S*)-1-Hydroxymethyl-6-methyl-4a,5,8,8a-tetrahydro-1*H*-isochromen-4(3*H*)-one (VI) and [(1*S*,3*R*,4a*R*,8a*S*)-3,4,4-trimethoxy-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromen-1-yl]-methanol (VII). A solution of 10.0 g (51.54 mmol) of compound **II** in 30 ml of methanol was cooled to 0°C, 90 ml of a 20% solution of HCl in methanol was added, and the mixture was stirred for 5 h at room temperature. When the reaction was complete (TLC), the mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with ethyl acetate (3×50 ml), the extracts were combined, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography on silica gel to isolate 6.64 g (57%) of hydroxy ketone **VI** and 1.96 g (14%) of compound **VII**.

Compound **VI**. Oily substance. R_f 0.4 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.60 s (3H, CH_3), 1.86 m (2H, CH_2), 1.98–2.17 m (3H, CH, CH_2), 2.43 br.s (1H, OH), 2.68 d.d.d (1H, 6-H, *J* 12.1, 9.1, 6.6 Hz), 3.42 s (3H, OCH_3) 3.62 d.d (1H, 1′-H, *J* = 12.0, 5.6 Hz), 3.78 d.d (1H, 1′-H, *J* = 12.0, 2.4 Hz), 4.0 m (1H, 10-H), 4.58 s (1H, 8-H), 5.38 m (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 23.17 (C^2), 23.35 (CH_3), 32.33 (C^5), 40.50 (C^1), 43.37 (C^6), 55.17 (OCH_3), 62.15 ($C^{1'}$), 73.50 (C^{10}), 100.57 (C^8), 119.50 (C^3), 131.26 (C^4), 203.32 (C^7). Mass spectrum: *m*/*z* 227 $[M + H]^+$. Found, %: C 63.79; H 7.93. $C_{12}H_{18}O_4$. Calculated, %: C 63.70; H 8.02.

Compound **VII**. Oily substance, R_f 0.2 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum, δ, ppm:

** Hereinafter, the data for α-epimer are given in brackets.

1.55 s (3H, CH_3), 1.70–2.30 m (6H, CH, CH_2), 3.31 s (3H, OCH_3), 3.35 s (3H, OCH_3), 3.40 s (3H, 8-OCH_3), 3.43 m (1H, 10-H), 3.55 d.d (1H, 1′-H, J = 11.4, 5.5 Hz), 3.68 d.d (1H, 1′-H, J = 11.4, 1.4 Hz), 4.60 s (1H, 8-H), 5.31 m (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 23.25 (CH_3), 23.63 (C^2), 32.03 (C^5), 33.50 (C^1), 38.85 (C^6), 50.22 (OCH_3), 50.61 (OCH_3), 54.74 (8-OCH_3), 62.90 ($C^{1'}$), 73.59 (C^{10}), 97.25 (C^7), 97.93 (C^8), 120.11 (C^3), 130.75 (C^4). Mass spectrum: *m*/*z* 273 $[M + H]^+$. Found, %: C 61.57; H 8.73. $C_{14}H_{24}O_5$. Calculated, %: C 61.74; H 8.88.

(1*S*,2*S*,7*R*,8*R*,9*R*)-5-Methyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-en-8-ol (VIIIa) and (1*S*,2*S*,7*R*,8*S*,9*R*)-5-methyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-en-8-ol (VIIIb). *a*. A solution of 1.0 g (5.15 mmol) of compound **II** in 30 ml of THF was cooled to –78°C, 1.5 ml (6.2 mmol) of a 73% solution of $(i\text{-Bu})_2$AlH in toluene was slowly added under argon, and the mixture was stirred for 30 min at that temperature. The mixture was then diluted with 5 ml of ethyl acetate and allowed to warm up to 0°C, 20 ml of 10% hydrochloric acid was added, and the mixture was stirred until it became homogeneous and extracted with ethyl acetate (3×30 ml). The extracts were combined and dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was subjected to chromatography on silica gel to isolate 0.71 g (71%) of **VIIIa** and 0.10 g (10%) of **VIIIb**.

b. A solution of 1.0 g (5.15 mmol) of compound **II** in 20 ml of ethanol was cooled to 0°C, and 0.20 g (5.15 mmol) of sodium tetrahydridoborate was added in small portions under vigorous stirring. When the reaction was complete (TLC), the mixture was diluted with 5 ml of acetone and evaporated, and the residue was subjected to chromatography to isolate 0.57 g (57%) of **VIIIa** and 0.21 g (21%) of **VIIIb**.

c. A solution of 1.0 g (5.15 mmol) of compound **II** in 20 ml of THF was cooled to 0°C, and 0.20 g (5.15 mmol) of lithium tetrahydridoaluminate was added in small portions under vigorous stirring. When the reaction was complete (TLC), the mixture was diluted with 5 ml of acetone and evaporated, and the residue was subjected to chromatography to isolate 0.53 g (53%) of **VIIIa** and 0.21 g (17%) of **VIIIb**. The spectral parameters of compounds **VIIIa** and **VIIIb** were identical to those reported in [4].

(1*R*,2*R*,3*R*,5*S*,6*S*,8*S*,9*S*)-6-Iodo-5-methyl-11,12,13-trioxatetracyclo[7.2.1.1^{2,5}.0^{3,8}]tridecane (IX). Compound **VIIIa**, 0.50 g (2.55 mmol), was dissolved in a mixture of 15 ml of diethyl ether and 3 ml of water, the solution was cooled to 0°C, and 0.52 g (5.1 mmol) of $NaHCO_3$ and 1.30 g (5.1 mmol) of iodine were added. The mixture was allowed to warm up to room temperature, stirred for 1 h, diluted with a saturated solution of sodium chloride, and extracted with ethyl acetate (3×30 ml). The extracts were combined, washed with a solution of $Na_2S_2O_3$ and water, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography. Yield 0.75 g (92%), oily substance, R_f 0.45 (petroleum ether–ethyl acetate, 5:1), $[\alpha]_D^{20}$ = –143.0° (*c* = 1.58, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.28 s (3H, CH_3), 1.72 d.d (1H, 8-H, J = 2.6, 2.2 Hz), 1.92 d.d (1H, 3-H, J = 10.8, 2.0 Hz), 2.06 d.d (1H, 4-H, J = 14.1, 10.8 Hz), 2.22 d.d.d (1H, 7-H, J = 10.8, 10.3, 2.2 Hz), 2.52 d.d (1H, 4-H, J = 14.1, 2.0 Hz), 2.67 d.d (1H, 7-H, J = 10.8, 4.0 Hz), 3.70 d (1H, 2-H, J = 3.0 Hz), 3.72 d.d (1H, 10-H, J = 7.3, 4.7 Hz), 3.82 d (1H, 10-H, J = 7.3 Hz), 4.21 d.d (1H, 9-H, J = 4.7, 2.6 Hz), 4.27 d.d (1H, 6-H, J = 10.3, 4.0 Hz), 5.27 d (1H, 1-H, J = 3.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 25.55 (CH_3), 27.38 (C^6), 31.80 (C^7), 32.31 (C^8), 34.22 (C^3), 38.64 (C^4), 65.56 (C^{10}), 70.96 (C^5), 72.61 (C^2), 75.88 (C^9), 99.89 (C^1). Found, %: C 41.21; H 4.59. $C_{11}H_{15}IO_3$. Calculated, %: C 41.01; H 4.69.

(1*S*,2*S*,7*R*,8*R*,9*R*)-5-Methyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-en-8-yl *p*-toluenesulfonate (X). A solution of 0.50 g (2.55 mmol) of alcohol **VIIIa** in 10 ml of pyridine was cooled to 0°C, 0.58 g (3.06 mmol) of *p*-toluenesulfonyl chloride was added, and the mixture was stirred for 12 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate (3×50 ml). The extracts were combined, washed with 5% hydrochloric acid, a saturated solution of NaCl, and water, dried over $MgSO_4$, and concentrated. Yield 0.68 g (76%), mp 152–155°C, R_f 0.6 (petroleum ether–ethyl acetate, 2:1), $[\alpha]_D^{20}$ = –7.9° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum (CD_2Cl_2), δ, ppm: 1.50 d (1H, CH_2, J = 16.1 Hz), 1.60 s (3H, CH_3), 1.78 m (1H, CH_2, J = 16.1, 3.1 Hz), 2.20 m (1H, CH_2), 2.35 m (1H, CH), 2.45 m (2H, CH, CH_2), 2.45 s (3H, $C_6H_4C\mathbf{H}_3$), 3.78 d.d (1H, 11-H, J = 7.4, 5.1 Hz), 3.88 d (1H, 11-H, J = 7.4 Hz), 4.22 d (1H, 8-H, J = 2.2 Hz), 4.33 d (1H, 1-H, J = 5.1 Hz), 5.10 m (1H, 4-H), 5.32 d (1H, 9-H, J = 2.2 Hz), 7.32 m and 7.72 d (2H each, H_{arom}). ^{13}C NMR spectrum (CD_2Cl_2), δ_C, ppm: 21.63 ($C_6H_4\mathbf{C}H_3$), 23.71 (5-CH_3), 25.96 (C^7), 26.21 (C^3), 30.11 (C^6), 35.20 (C^2), 67.49 (C^{11}), 76.71 (C^1), 79.46 (C^8), 100.39 (C^9), 118.24 (C^4), 127.89 (C_{arom}), 129.91 (C_{arom}), 132.63 (C^5), 133.98 (C_{arom}), 145.28 (C_{arom}). Found, %: C 61.79; H 6.35. $C_{18}H_{22}O_5S$. Calculated, %: C 61.70; H 6.33.

(1*S*,2*S*,7*R*,8*R*,9*R*)-5-Methyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-en-8-yl acetate (XI). *a*. Acetic anhydride, 0.48 ml (5.1 mmol), was added to a solution of 0.50 g (2.55 mmol) of compound **VIIIa** in 10 ml of anhydrous pyridine, and the mixture was left overnight at 20°C. Methanol, 5 ml, was slowly added, the mixture was stirred for 30 min, 20 ml of 10% hydrochloric acid was added, and the mixture was extracted with ethyl acetate (3×20 ml). The extracts were combined, washed with 5% hydrochloric acid and a saturated solution of sodium chloride, and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, and the residue was subjected to chromatography on silica gel. Yield 0.60 g (99%). The product was identical to that described in [4].

b. A catalytic amount of *p*-toluenesulfonic acid was added to a solution of 0.50 g (2.55 mmol) of alcohol **VIIIa** in 5 ml of isopropenyl acetate, and the mixture was stirred for 1 h. Excess reagent was distilled off on a rotary evaporator, and the residue was purified by chromatography on silica gel. Yield 0.40 g (65%).

(1*S*,2*S*,7*R*,8*R*,9*R*)-5-Methyl-8-trimethylsiloxy-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-ene (XII). Chloro(trimethyl)silane, 0.98 ml (7.65 mmol), was added to a solution of 0.50 g (2.55 mmol) of alcohol **VIIIa** in 10 ml of anhydrous pyridine, and the mixture was left overnight at 20°C. The mixture was then slowly treated with 20 ml of 10% hydrochloric acid and extracted with ethyl acetate (3×20 ml). The extracts were combined, washed with a saturated solution of sodium chloride and water, and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, and the residue was purified by chromatography on silica gel. Yield 0.53 g (78%), oily substance, R_f 0.6 (petroleum ether–ethyl acetate, 10:1), $[\alpha]_D^{20}$ = +21.4° (*c* = 1.4, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.02 s (9H, $SiCH_3$), 1.62 s (3H, 5-CH_3), 1.60–1.90 m (3H, CH, CH_2), 2.12 m (1H, CH), 2.30 d (1H, CH, *J* = 2.8 Hz), 2.60 d (1H, CH_2, *J* = 11.8 Hz), 3.47 d.d (1H, 8-H, *J* = 2.8, 2.1 Hz), 3.82 d.d (1H, 11-H, *J* = 7.0, 4.9 Hz), 3.92 d (1H, 11-H, *J* = 7.0 Hz), 4.32 d (1H, 1-H, *J* = 4.9 Hz), 5.15 d (1H, 9-H, *J* = 2.1 Hz), 5.28 m (1H, 4-H). ^{13}C NMR spectrum, δ_C, ppm: 0.01 ($SiCH_3$), 23.57 (5-CH_3), 26.90 (C^3), 26.91 (C^7), 30.78 (C^6), 35.78 (C^2), 66.89 (C^{11}), 72.14 (C^8), 76.34 (C^1), 103.07 (C^9), 118.14 (C^4), 132.60 (C^5). Found, %: C 62.52; H 9.12. $C_{14}H_{24}O_3Si$. Calculated, %: C 62.64; H 9.01.

(1*S*,2*S*,7*R*,8*R*,9*R*)-8-Methoxy-5-methyl-10,12-dioxatricyclo[7.2.1.0^{2,7}]dodec-4-ene (XIII). Compound **VIIIa**, 0.55 g (2.55 mmol), and imidazole, 0.01 g, were added in succession under argon to a solution of 0.10 g (4.1 mmol) of sodium hydride in 10 ml of tetrahydrofuran. The mixture was stirred for 5 h at 50°C and cooled to room temperature, and 0.32 ml (5.1 mmol) of methyl iodide was added. When the reaction was complete (TLC), the mixture was carefully treated with water and extracted with ethyl acetate (3×15 ml). The extract was dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was subjected to chromatography on silica gel. Yield 0.44 g (82%), mp 66–68°C, R_f 0.4 (petroleum ether–ethyl acetate, 5:1). ^{1}H NMR spectrum (CCl_4–C_6D_6), δ, ppm: 1.48 m (1H, CH_2), 1.50 m (1H, CH), 1.55 s (3H, 5-CH_3), 1.72 br.d (1H, CH_2, *J* = 16.4 Hz), 2.07 m (1H, CH), 2.12 m (1H, CH_2), 2.48 d (1H, CH_2, *J* = 16.4 Hz), 2.73 br.s (1H, 8-H), 3.14 s (3H, OCH_3), 3.55 m (2H, 11-H), 3.98 d (1H, 1-H, *J* = 4.0 Hz), 5.15 m (1H, 4-H), 5.27 br.s (1H, 9-H). ^{13}C NMR spectrum, δ_C, ppm: 23.57 (5-CH_3), 26.22 (C^7), 26.31 (C^3), 30.23 (C^6), 35.66 (C^2), 58.73 (OCH_3), 66.69 (C^{11}), 76.07 (C^1), 80.87 (C^8), 99.76 (C^9), 118.13 (C^4), 132.33 (C^5). Found, %: C 68.32; H 8.86. $C_{12}H_{18}O_3$. Calculated, %: C 68.55; H 8.63.

(1*S*,2*S*,7*R*,8*S*,9*R*)-5-Methyl-10,12-dioxatricyclo-[7.2.1.0^{2,7}]dodec-4-en-8-yl acetate (XIV) was synthesized as described above for compound **XI** from 0.30 g (1.53 mmol) of alcohol **VIIIb**. Yield 0.36 g (98%); the product was identical to that described in [4].

(1*S*,3*RS*,4*R*,4a*R*,8a*S*)-1-Acetoxymethyl-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromene-3,4-diyl diacetate (XV) and (1*S*,3*RS*,4*R*,4aS,5*R*,8a*S*)-1-acetoxymethyl-5-acetyl-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromene-3,4-diyl diacetate (XVI). *a*. A solution of 0.30 g (1.26 mmol) of acetate **XI** in 5 ml of acetic anhydride was cooled to 0°C, 0.31 ml (2.52 mmol) of $BF_3 \cdot Et_2O$ was added dropwise under stirring, and the mixture was allowed to warm up to room temperature. After 30 min (or 1 h), the mixture was neutralized with a saturated solution of $NaHCO_3$ and extracted with methylene chloride (3×15 ml), the extracts were combined and washed with a saturated solution of sodium chloride, the solvent was distilled off on a rotary evaporator, and the residue was subjected to chromatography on silica gel to isolate 0.18 g (41%) of epimeric triacetates **XV** and 0.20 g (42%) of epimeric acetyl derivatives **XVI** (in 30 min) or only 0.42 g (98%) of **XVI** (in 1 h).

b. A solution of 0.30 g (1.26 mmol) of acetate **XI** in 10 ml of acetic anhydride was cooled to 0°C, a solution of 0.2 ml of H_2SO_4 in 1.5 ml of Ac_2O was added,

and the mixture was stirred for 20 min at 0°C. The mixture was poured into an ice–water mixture containing 45 g of $NaHCO_3$, stirred until gas no longer evolved, and extracted with ethyl acetate (3×50 ml). The extracts were combined, washed with a saturated solution of $NaHCO_3$, a saturated solution of NaCl, and water, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography to isolate 0.33 g (75%) of epimeric acetates **XV**.

c. A solution of 1.26 mmol of compound **XI** in 3.0 ml of methylene chloride–isopropenyl acetate (1:1) was cooled to 0°C, 0.2 ml (2.52 mmol) of $BF_3 \cdot Et_2O$ was slowly added, and the mixture was stirred until the reaction was complete. The mixture was then treated with 5 ml of water and extracted with methylene chloride (3×15 ml), the extracts were combined and dried over $MgSO_4$, the solvent was distilled off on a rotary evaporator, and the residue was subjected to chromatography. Yield of triacetate **XV** 0.25 g (57%).

d. A solution of 0.50 g (2.55 mmol) of compound **VIIIa** in 10 ml of acetic anhydride was cooled to 0°C, a mixture of 0.5 ml of H_3PO_4 and 0.5 ml of Ac_2O was added dropwise under stirring, and the mixture was stirred for 1 h at room temperature. The mixture was then poured into an ice–water mixture containing 40.0 g of $NaHCO_3$, stirred until gas no longer evolved, and extracted with ethyl acetate (3×100 ml). The extracts were combined, washed with a solution of $NaHCO_3$, a saturated solurtion of NaCl, and water, dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography to isolate 0.84 g (97%) of epimers **XV**.

Compound **XV**. Oily substance, R_f 0.55 (petroleum ether–ethyl acetate, 3:1), β:α = 2:1. ^{1}H NMR spectrum, δ, ppm: 1.63 s [1.63 s] (3H, CH_3), 1.80 m [1.80 m] (1H, CH_2), 2.0–2.22 m [2.0–2.22 m] (4H, CH, CH_2), 2.02 s (6H, CH_3), 2.08 s [2.09 s] (3H, CH_3), [2.10 s (3H, CH_3)], [2.12 s (3H, CH_3)], 2.52 m [2.36 m] (1H, CH_2), 3.89 m [4.04 m] (1H, CH), 4.20 m [4.20 m] (2H, 1′-H), 4.89 d.d (1H, 10-H, *J* = 7.6, 5.3 Hz) [5.12 d.d (1H, 10-H, *J* = 5.1, 4.7 Hz)], 5.36 m [5.40 m] (1H, 3-H), 6.0 d (1H, 8-H, *J* = 7.5 Hz) [6.24 d (1H, 8-H, *J* = 4.2 Hz)]. ^{13}C NMR spectrum, δ_C, ppm: 20.67 [20.58] (CO**C**H_3), 20.93 [21.08] (CO**C**H_3), 22.11 [22.11] (C^2), 23.33, [23.33] (4-CH_3), 30.37 [29.49] (C^5), 32.03 [32.03] (CO**C**H_3), 33.21 [33.21] (C^6), 33.61 [33.61] (C^1), 64.44 [64.12], ($C^{1'}$), [70.06 (C^{10})], 72.15 [67.73] (C^7), [72.39 (C^{10})], 90.28 [90.12] (C^8), 118.08 [119.28] (C^3), 131.27 [130.32] (C^4), 169.29 [169.09] (**C**OCH$_3$), 169.69 [169.29] (**C**OCH$_3$), 170.70 [169.80] (**C**OCH$_3$). Found, %: C 60.19; H 6.91. $C_{17}H_{24}O_7$. Calculated, %: C 59.99; H 7.11.

Compound **XVI**. Oily substance, R_f 0.26 (petroleum ether–ethyl acetate, 2:1), β:α = 1:1. ^{1}H NMR spectrum, δ, ppm: 1.64 s [1.61 s] (3H, CH_3), 1.93–2.07 m [1.93–2.07 m] (1H, CH), 1.99 s [2.00 s] (3H, CH_3), 2.02 s [2.05 s] (3H, CH_3), 2.06 s [2.09 s] (3H, CH_3), 2.19–2.24 m [2.19–2.24 m] (2H, CH_2), 2.19 s [2.20 s] (3H, $COCH_3$), 2.45 m [2.45 m] (1H, CH), 3.12 m [3.12 m] (1H, 5-H), 3.80 d.t [3.71 m] (1H, 10-H, *J* = 10.9, 3.4 Hz), 4.20 m [4.20 m] (2H, 1′-H), [4.94 d.d (1H, 7-H, *J* = 8.8, 5.9 Hz)], 5.07 d.d (1H, 7-H, *J* = 4.6, 3.8 Hz), [5.45 d (1H, 3-H, *J* = 3.7 Hz)], 5.50 d (1H, 3-H, *J* = 5.1 Hz), [5.78 d (1H, 8-H, *J* = 8.8 Hz)], 6.19 d (1H, 8-H, *J* = 3.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.36 [20.36] (CO**C**H_3), 20.45 [20.65] (CO**C**H_3), 20.84 [21.80] (4-CH_3), 21.71 [20.18] (C^2), 22.99 [22.90] ($C^{2''}$), 28.88 [28.70] (CO**C**H_3), 29.40 [31.20] (C^1), 35.0 [35.41] (C^6), 52.56 [52.09] (C^5), 63.47 [60.01] ($C^{1'}$), 68.62 [70.16] (C^{10}), 68.86 [74.39] (C^7), 89.56 [89.88] (C^8), 122.20 [121.83] (C^3), 135.33 [135.03] (C^4), 166.77 [166.11] (**C**OCH$_3$), 169.37 [169.0] (**C**OCH$_3$), 170.56 [169.11] (**C**OCH$_3$), 208.75 [208.23] ($C^{1''}$). Found, %: C 59.57; H 6.96. $C_{19}H_{26}O_8$. Calculated, %: C 59.68; H 6.85.

(1*S*,3*RS*,4*S*,4a*R*,8a*S*)-1-Acetoxymethyl-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromene-3,4-diyl diacetate (XVII) and (1*S*,3*RS*,4*S*,4a*S*,5*R*,8a*S*)-1-acetoxymethyl-5-acetyl-6-methyl-3,4,4a,5,8,8a-hexahydro-1*H*-isochromene-3,4-diyl diacetate (XVIII). The reactions were performed as described above for compounds **XV** and **XVI**.

a. $BF_3 \cdot Et_2O$–Ac_2O. From 0.30 g (1.26 mmol) of acetate **XIV** (reaction time 1 h) we obtained 0.42 g (98%) of acetyl derivative **XVIII**.

b. H_2SO_4–Ac_2O. From 0.30 g (1.26 mmol) of acetate **XIV** we obtained 0.30 g (70%) of triacetate **XVII**.

c. H_3PO_4–Ac_2O. From 0.30 g (1.53 mmol) of alcohol **VIIIb** we obtained 0.51 g (98%) of triacetate **XVII**.

Compound **XVII**. Oily substance, R_f 0.5 (petroleum ether–ethyl acetate, 3:1), β:α = 1:1. ^{1}H NMR spectrum, δ, ppm: 1.66 s [1.70 s] (3H, CH_3), 1.98 m [1.98 m] (1H, CH_2), 2.0–2.20 m [2.0–2.20 m] (3H, CH, CH_2), [2.10 s (3H, CH_3)], [2.12 s (3H, CH_3)], 2.13 s [2.06 s] (3H, CH_3), 2.14 s (6H, CH_3), 2.30 m, [2.30 m] (1H, CH_2), 2.42 m [2.42 m] (1H, CH_2), 3.88 m, [4.06 m] (1H, CH), 4.32 m [4.25 m] (2H, 1′-H), 4.74 d.d (1H, 10-H, *J* = 3.6, 2.7 Hz) [4.98 d.d

(1H, 10-H, J = 9.7, 3.1 Hz)], 5.37 m [5.30 m] (1H, 3-H), 6.0 d (1H, 8-H, J = 2.4 Hz), [6.22 d (1H, 8-H, J = 3.2 Hz)]. ^{13}C NMR spectrum, δ_C, ppm: 20.92 [20.74] (CO**C**H_3), 21.00 [21.08] (CO**C**H_3), 23.36 [23.36] (4-CH_3), 23.63 [24.34] (C^2), 27.86 [27.86] (CO**C**H_3), 30.07 [30.07] (C^6), 30.19, [30.38] (C^5), 32.75 [32.17] (C^1), 64.90 [64.21] ($C^{1'}$), 67.07 [69.47] (C^7), 70.07 [74.50] (C^{10}), 89.76 [91.91] (C^8), 118.76 [117.64] (C^3), 131.10 [131.94] (C^4), 168.62 [169.23] (**C**OCH_3), 169.83 [170.18] (**C**OCH_3), 170.81 [170.67] (**C**OCH_3). Found, %: C 59.77; H 7.33. $C_{17}H_{24}O_7$. Calculated, %: C 59.99; H 7.11.

Compound **XVIII** (major epimer). Oily subsance, R_f 0.25 (petroleum ether–ethyl acetate, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.62 s (3H, CH_3), 1.82 m (1H, CH_2), 2.04 s (3H, CH_3), 2.06 s (3H, CH_3), 2.08 s (3H, CH_3), 2.0–2.32 m (2H, CH), 2.19 s (3H, CH_3CO), 2.55 m (1H, CH_2), 3.17 d (1H, 5-H, J = 6.8 Hz), 3.80 d.t (1H, CH, J = 14.5, 3.8 Hz), 4.22 m (2H, 1′-H), 4.58 br.s (1H, 10-H), 5.50 d (1H, 3-H, J = 4.7 Hz), 6.0 s (1H, 8-H). ^{13}C NMR spectrum, δ_C, ppm: 20.26 (CO**C**H_3), 20.61 (CO**C**H_3), 20.61 (4-CH_3), 22.73 ($C^{2''}$), 24.55 (C^2), 28.91 (CO**C**H_3), 30.24 (C^1), 30.96 (C^6), 52.42 (C^5), 63.95 ($C^{1'}$), 69.0 (C^{10}), 69.67 (C^7), 90.81 (C^8), 122.55 (C^3), 134.65 (C^4), 168.01 (**C**OCH_3), 169.48 (**C**OCH_3), 170.59 (**C**OCH_3), 208.59 ($C^{1''}$). Found, %: C 60.57; H 7.03. $C_{15}H_{20}O_6$. Calculated, %: C 60.80; H 6.80.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 08-03-97033-r_povolzh'e_a, NSh-1725.2008.3).

REFERENCES

1. Isobe, M., Fukami, N., Nishikawa, T., and Goto, T., *Heterocycles*, 1987, vol. 25, p. 521.
2. Miftakhov, M.S., Valeev, F.A., and Gaisina, I.P., *Usp. Khim*., 1994, vol. 63, p. 922.
3. Bhaté, P. and Horton, D., *Carbohydr. Res*., 1983, vol. 122, p. 189.
4. Valeev, F.A., Gaisina, I.P., Sagitdinova, Kh.F., Shitikova, O.V., and Miftakhov, M.S., *Russ. J. Org. Chem*., 1996, vol. 32, p. 1319.
5. Valeev, F.A., Gaisina, I.P., and Miftakhov, M.S., *Izv. Ross. Akad. Nauk, Ser. Khim*., 1996, no. 10, p. 2584.
6. Valeev, F.A., Gaisina, I.N., and Gainullin, K.K., *Russ. J. Org. Chem*., 1997, vol. 33, p. 331.
7. Brimacombe, J.S., Hunedy, F., and Tucker, L.C.N., *Carbohydr. Res*., 1978, vol. 60, p. 11.
8. Cipolla, L., Lay, L., and Nicotra, F., *J. Org. Chem*., 1997, vol. 62, p. 6678.