ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 1, pp. 117–127. © Pleiades Publishing, Ltd., 2014.
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Eleuthesides and Their Analogs: V.* Medium- and Large-Ring Lactones Based on Levoglucosenone

Yu. A. Khalilova, L. V. Spirikhin, Sh. M. Salikhov, 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 July 31, 2013

Abstract—Ozonolysis of the bridging double bond in bicyclic enol ethers obtained by the Michael reaction and subsequent intramolecular etherification afforded chiral decanolides fused to a tetrahydropyran ring. Three-step procedures were developed for the synthesis of chiral lactones with medium and large rings via oxidative cleavage with pyridinium chlorochromate of mixed bicyclic ketals which were prepared by treatment with methanolic HCl of Michael adducts derived from levoglucosenone and cyclopenta-, cyclohexa-, cyclohepta-, and cyclododecanone.

DOI: 10.1134/S1070428014010229

Taking into account anticancer activity of eleutheSides [2–4] and some medium- and large-ring lactones [5], an important aspect of studying structure–activity relations in this series of compounds is the synthesis of both eleutheside analogs possessing a lactone functionality in the B ring and lactones modified according to the eleutheside type.

We made an attempt to use levoglucosenone as a chiral source in the synthesis of medium-ring lactones with a view to obtain eleutheside oxa analogs possessing a ten-membered lactone ring. There are two synthetic strategies ensuring approach to medium-ring lactones. The first strategy involves closure of linear chain termini to a ring of appropriate size, and the second is based on oxidative cleavage of bridging C–C bond in bicyclic systems by the action of ozone [6, 7], 3-chloroperoxybenoic acid, CrO_3 [5, 8], $Pb(OAc)_4$ [9, 10], $HgO–I_2$ [11, 12], or $PhI(OAc)_2$ [13, 14].

It is known that levoglucosenone adduct with dimedone is capable of undergoing spontaneous cyclization with formation of mixed ketal **II** having a bridging double C=C bond [15]. We tried to synthesize the corresponding lactone starting from compound **II**. Hemiketal **II** was synthesized by ultrasonic irradiation of a solution of levoglucosenone (**I**) and dimedone in toluene in the presence of K_2CO_3 (Scheme 1). In the next steps, a difficult problem was to stabilize ketal **II** as dihydropyran derivative. The conversion of **II** into methanesulfonate **III** or *p*-toluenesulfonate **IV**, followed by reductive elimination of the corresponding group by the action of nickel borohydride (prepared *in situ*), afforded conjugated cyclohexenone **V**.

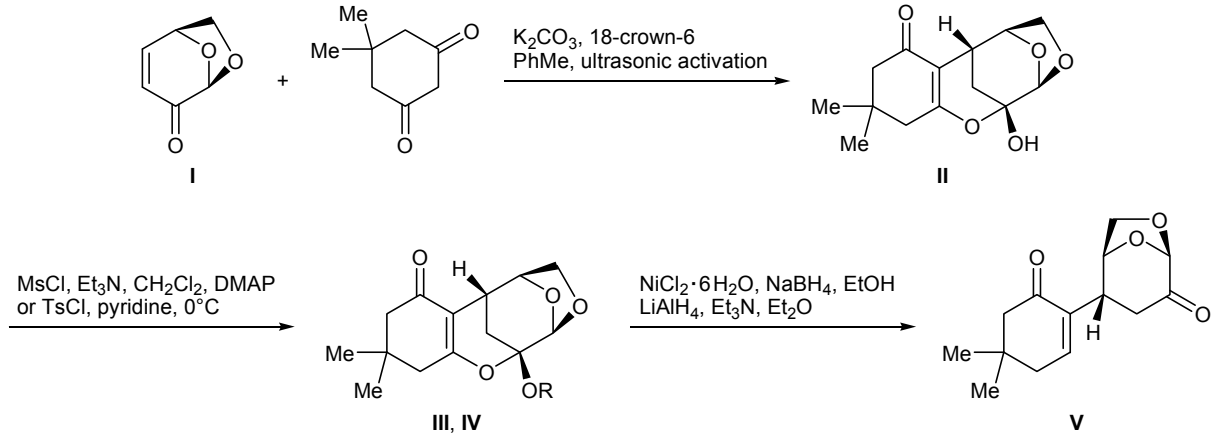
Following an alternative route, hemiketal **II** was treated with methanol in the presence of *p*-toluenesulfonic acid. Methoxy derivative **VI** was thus obtained with high efficiency and was subjected to ozonolysis in methylene chloride. As a result, a mixture of products which were difficult to separate was formed, presumably due to intermediacy of labile α-diketone. When the ozonolysis was carried out in methanol and the peroxide ozonolysis products were treated with sodium tetrahydridoborate, we isolated in good yield diastereoisomeric lactones **VIIa** and **VIIb** as products of intramolecular transesterification of intermediate lactone (Scheme 2). Treatment of **VI** with a solution of HCl in methanol produced trimethyl ketal **VIII** and stereoisomeric dimethyl ketals **IXa** and **IXb**.

Unlike compounds **VI** and **IXa**/**IXb**, trimethyl ketal **VIII** derived from primary alcohol is more stable. Ozonolysis of the double C=C bond in **VIII** and subsequent treatment of intermediate ozonide with $NaBH_4$ afforded stable substituted decanolide **Xa**/**Xb** as a mixture of two diastereoisomers (Scheme 3).

The structure of decanolides **Xa**/**Xb** follows from the structure of their precursors and is confirmed by

* For communication IV, see [1].

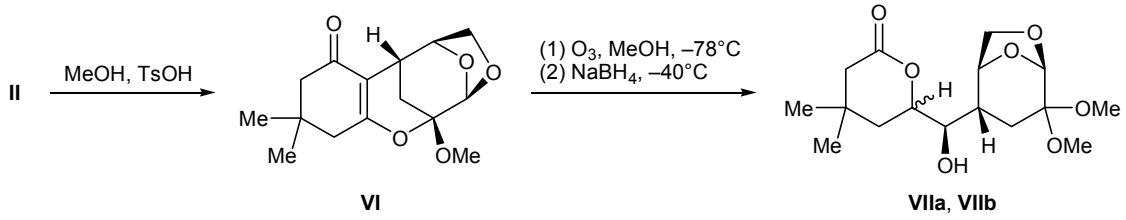
Scheme 1.



I **II** **III**, **IV** **V**

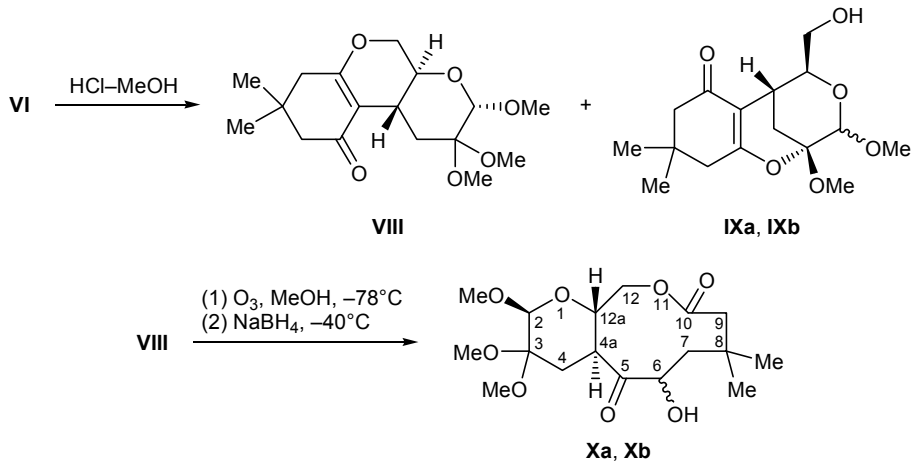
III, R = Ms; **IV**, R = Ts.

Scheme 2.



II **VI** **VIIa**, **VIIb**

Scheme 3.

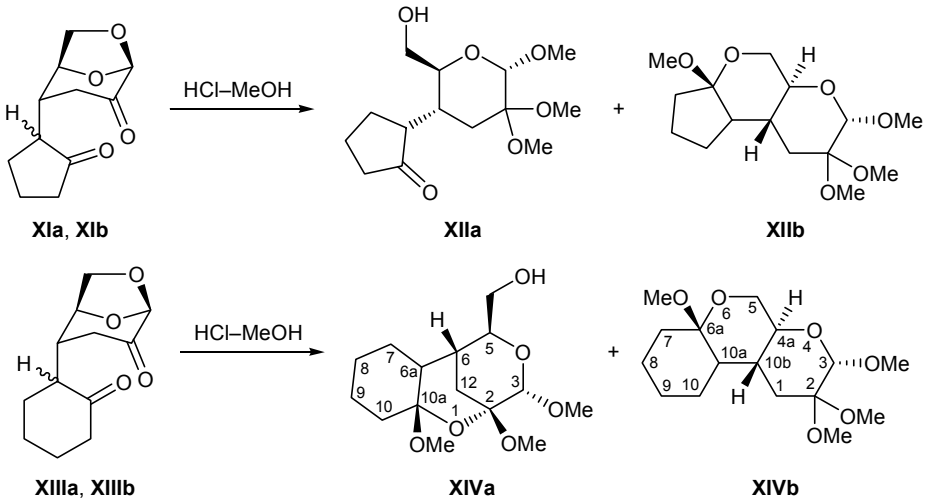


VI **VIII** **IXa**, **IXb** **VIII** **Xa**, **Xb**

the ^{1}H and ^{13}C NMR spectra. Three methoxy groups give singlets at δ 3.24, 3.38, and 3.40 ppm for **Xa** and at δ 3.20 and 3.40 ppm for **Xb**. Both stereoisomers displayed in the ^{13}C NMR spectrum coinciding signals from C^{12} and C^{6} at δ_C 62.70 and 69.37 ppm, respectively, ketal and acetal (δ_C 97.60 and 97.65 ppm, lactone carbonyl (C^{10}, δ_C 172.85 ppm), and ketone carbonyl carbon atoms (δ_C 211.35 ppm).

Methyl ketals **XIIa**, **XIIb**, **XIVa**, and **XIVb** were synthesized in a similar way from stereoisomeric Michael adducts **XIa**/**XIb** and **XIIIa**/**XIIIb** prepared previously [16] from levoglucosenone and cycloalkanones (Scheme 4). Individual compounds **XIIa**, **XIIb**, **XIVa**, and **XIVb** were isolated by column chromatography. In the ^{13}C NMR spectrum of trimethyl ketal **XIVa**, the C^{12} signal appeared at δ_C 38.14 ppm. Tetramethyl ketal **XIVb** whose formation also involved acetalization with the primary hydroxy group displayed in the ^{13}C NMR spectrum a signal at δ_C 28.38 ppm from C^{1} which corresponds to C^{12} in **XIVa**.

Scheme 4.



XIa, **XIb** **XIIa** **XIIb**

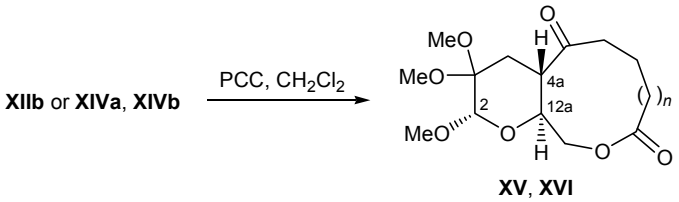
XIIIa, **XIIIb** **XIVa** **XIVb**

Oxidative cleavage of the C^{6a}–C^{10a} bridge in **XIVa** with Jones' reagent [9] was accompanied by considerable tarring of the reaction mixture, while only a small amount of compound **XVI** was formed. The use of a milder oxidant, pyridinium chlorochromate (PCC), ensured smooth formation of lactone **XVI** in 24 h. Under analogous conditions, tetramethyl ketal **XIVb** was also converted into lactone **XVI**. Therefore, there is no need of separating compounds **XIVa** and **XIVb**; oxidative cleavage of mixture **XIVa**/**XIVb** was equally efficient. Likewise, treatment of **XIIb** with PCC afforded nonanolide **XV** (Scheme 5).

Presumably, the formation of lactone **XVI** involves initial transformation of trimethyl ketal **XIVa** into hemiketal **A** (Scheme 6) whose oxidative fragmentation produces medium-ring lactone **XVI** [20].

The structure of the isolated medium-ring lactones was proved using various NMR techniques. As an example, structure determination of decanolide **XVI** is described below. The configuration of some chiral centers in molecules **XV** and **XVI** is set by the structure of the initial Michael adduct, and it does not change in the course of its transformations. The vicinal coupling constant $^3J_{12a,4a}$ = 10.0 Hz indicates *anti* orientation of the 4a-H proton. The C^2 atom was assigned *S* configuration on the basis of the observed nuclear Overhauser effect (NOE) between 2-H and 4a-H. The HMBC spectrum revealed coupling between 12-H and lactone carbonyl carbon atom (C^{10}) resonating at δ_C 172.58 ppm), and the position of the ketone carbonyl group follows from the presence of a cross peak between 4a-H and C^5. The ^{13}C NMR spectrum of

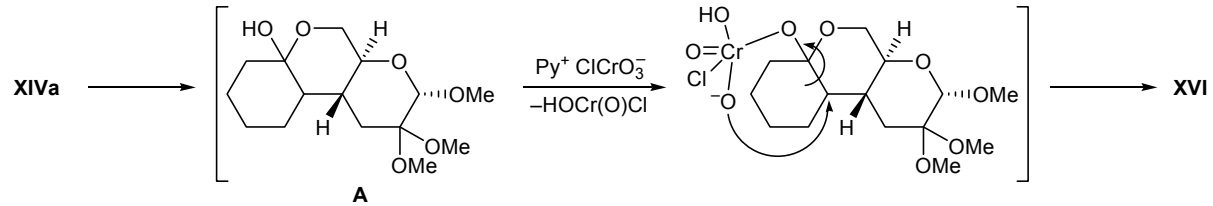
Scheme 5.



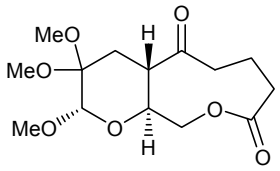
XIIb or **XIVa**, **XIVb** **XV**, **XVI**

XV, n = 1; **XVI**, n = 2.

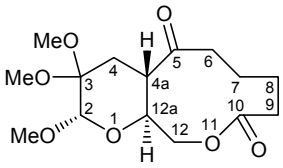
Scheme 6.



XIVa **A** **XVI**



XV



XVI

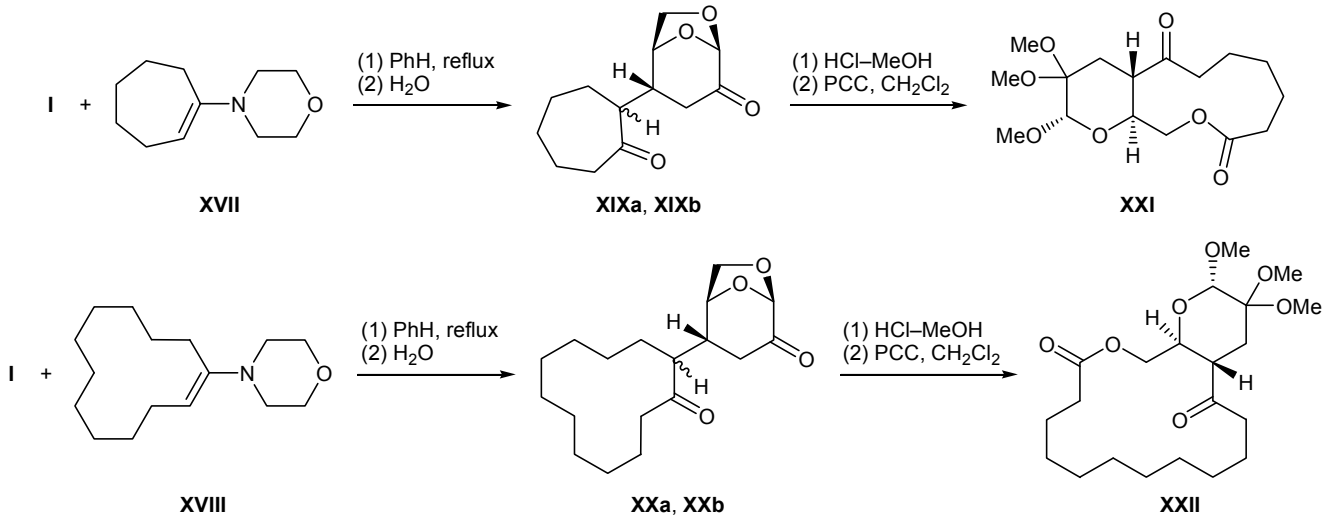
XVI contained signals from the acetal (δ_C 97.35 ppm) and ketal carbon atoms (δ_C 96.54 ppm) and the corresponding methoxy groups (δ_C 55.30, 48.24, 47.85 ppm). The lactone and ketone carbonyl signals appeared as δ_C 172.58 and 208.11 ppm, respectively. The two ketal methoxy groups gave singlets at δ 3.16 and 3.18 ppm in the ^{1}H NMR spectrum, and protons in the acetal methoxy group resonated as a singlet at δ 3.40 ppm. In addition, signals from the $C^{12}H_2$ methylene group were observed at δ 4.05 and 4.30 ppm (d.d, ^2J = 10.5 Hz), and the 12a-H signal was a double doublet of doublets at δ 4.15 ppm (J = 10.3, 10.0, 4.2 Hz).

Thus, the synthesis of nonanolide **XV** fused to a trimethoxy-substituted pyran ring and of decanolide **XVI** may be regarded as the first step toward oxa analogs of eleuthesides. The developed procedure for the synthesis of medium-ring lactones is promising from the viewpoint of preparation of macrolides. For this purpose we examined analogous transformations with cycloheptanone and cyclododecanone derivatives.

4-(Cyclohept-1-en-1-yl)morpholine (**XVII**) was synthesized according to the procedure described in [15–19] using toluene instead of benzene, and 4-(cyclododec-1-en-1-yl)morpholine (**XVIII**) was prepared according to [19]. Unlike dimedone adducts (Scheme 1), Michael adducts of levoglucosenone with cycloheptanone and cyclododecanone were obtained by heating compound **I** with cycloalkenylmorpholines **XVII** and **XVIII** in boiling benzene for 2 h, followed by hydrolysis. As a result, we isolated diastereoisomer mixtures **XIXa**/**XIXb** and **XXa**/**XXb** (Scheme 7). Treatment of the latter with a solution of HCl in MeOH and subsequent oxidation of intermediate methyl ketal mixtures with pyridinium chlorochromate smoothly afforded substituted undecanolide **XXI** and lactone **XXII** (Scheme 7). The hexadecanolide ring in **XXII** is the key structural fragment of a number of natural macrocycles [23].

Lactone **XIV** was subjected to modification with *N*-methylurocanic acid (**XXIV**). The reduction of **XIV** with $NaBH_4$ in EtOH was accompanied by cleavage of the lactone ring and esterification of the carboxy group to produce ethyl ester **XXIII**, and treatment of **XXIII** with *N*-methylurocanic acid (**XXIV**) [24] gave bis-ester **XXV** as a result of esterification with the primary hydroxy group in **XXIII** (Scheme 8). The structure of **XXV** was proved by ^{1}H and ^{13}C NMR spectroscopy. Nuclear Overhauser effect was observed between 1‴-H and 4-H, so that the $C^{1'''}$ carbon atom was assigned *R* configuration; the 1‴-H and 4-H signals were multiplets. The HMBC spectrum of **XXV** contained a cross peaks between 1′-H and ester carbonyl carbon atom (δ_C 167.71 ppm), the 1″-CH_3 and $C^{4''}$ signals were observed in the ^{13}C NMR spectrum at

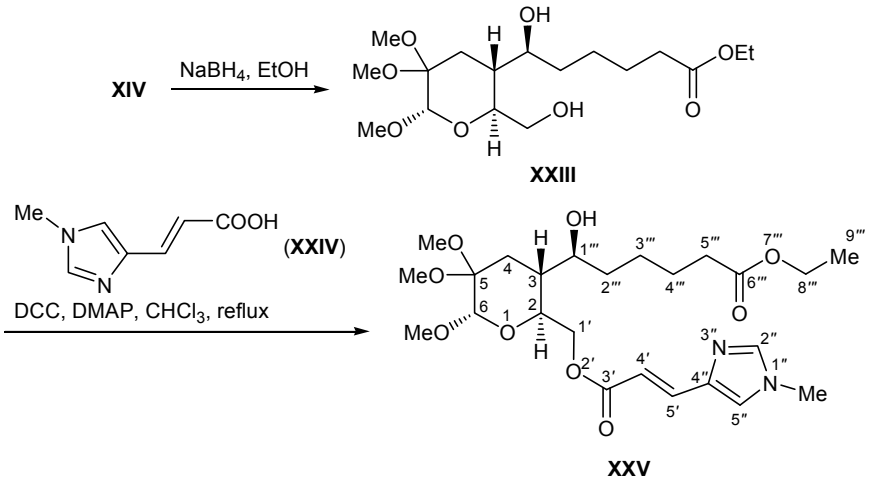
Scheme 7.



XVII **XIXa**, **XIXb** **XXI**

XVIII **XXa**, **XXb** **XXII**

Scheme 8.



δ_C 33.63 and 138.38 ppm, respectively, and the position of the C_2H_5O group followed from the presence of a cross peak between 8‴-H and $C^{6'''}$.

In summary, we have developed procedures for four-atom ring expansion of cycloalkanones into chiral medium- and large-ring lactones on the basis of levoglucosenone.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{15}N NMR spectra were recorded at 298 K on a Bruker Avance-III pulse spectrometer at 500.13, 125.47, and 50.58 MHz, respectively, using a 5-mm PABBO *Z*-gradient probe. The chemical shifts in the ^{13}C and ^1H NMR spectra were measured relative to tetramethylsilane as internal reference. Digital resolution was enhanced by zero-filling and multiplication of the Fourier image by the exponential function (lb 0.1 Hz for ^1H and 1 Hz for ^{13}C). The ^{13}C NMR spectra with power-gated decoupling were recorded with the use of composite WALTZ-16 sequence with the following parameters: spectral width 29.8 kHz, 64 K data points, pulse duration (30°) 3.2 μs, relaxation delay 2 s, number of scans 512–2048. The ^{13}C NMR spectra were edited on the basis of DEPT-90 and DEPT-135 experiments. The coupling constants J_{CH} were determined from the ^{13}C NMR spectra recorded with the use of gated decoupling sequence in order to conserve NOE: spectral width 29.8 kHz, 64 K data points, accumulation time 1.1 s, pulse duration (30°) 3.2 μs, relaxation delay 2 s, number of scans 4096.

The two-dimensional spectra were recorded using standard multipulse sequences. The gsCOSY spectrum was obtained with the following parameters: 4 K data points, 512 increments, spectral width 5.0 kHz; the data were processed using a sine bell-shaped function for the F_1 and F_2 projections (ssb 2). The gsHSQC spectra were recorded with a pulse delay optimized for a J_{CH} value of 145 Hz; 2 K data points, 256 increments. The gsHMBC spectra were measured with a small constant evolution delay of 71.4 ms for ^1H–^{13}C; 2 K data points, 256 increments. The NOESY spectra were acquired using 2 K data points, 256 increments, spectral width 5.0 kHz, mixing time 0.5 s. All NMR spectra were recorded from solutions in $CDCl_3$ unless otherwise stated.

The IR spectra were recorded from films or Nujol mulls on Shimadzu IR Prestige-21 and Bruker Tensor 27 instruments. The mass spectra were obtained on a Hewlett Packard HP 5973 mass-selective detector coupled with an HP 6890 gas chromatograph. Analytical TLC was performed using Sorbfil PTSKh-AF-A plates manufactured by *Sorbpolimer* closed corporation (Krasnodar, Russia). The melting points were measured on a Boetius PHMK 05 melting point apparatus. The elemental compositions were determined with a Euro 2000 CHNS(O) analyzer. The optical rotations were measured on a Perkin Elmer 341 polarimeter.

(2*R*,3*R*,6*S*,7*R*)-3,6-Epoxy-2-hydroxy-10,10-dimethyl-2,7-methano-2,3,5,6,7,9,10,11-octahydro-8*H*-1,4-benzodioxonin-8-one (II). Levoglucosenone (**I**), 2.0 g (16.0 mmol), was dissolved in 50.0 mL of toluene, 2.0 g (16.0 mmol) of 5,5-dimethylcyclohexane-1,3-dione, 13.8 g (100.0 mmol) of potassium carbonate, and 0.3 g (a catalytic amount, 5%) of dicyclohexano-18-crown-6 were added at room temperature,

and the mixture was subjected to ultrasonic irradiation for 6 h. When the reaction was complete (TLC), the mixture was concentrated, and the residue was purified by chromatography. Yield 2.5 g (60%), colorless crystals, mp 73°C, $[\alpha]_D^{20} = -123.2°$ (c = 1.0, $CHCl_3$), R_f 0.2 (petroleum ether–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 3138, 2924, 2852, 1581, 1112. ^1H NMR spectrum, δ, ppm: 1.04 s (3H, CH_3), 1.08 s (3H, CH_3), 1.64 d.d (1H, 12-H, J = 1.9, 12.9 Hz), 2.23 s and 2.26 s (1H each, 11-H), 2.33 s and 2.35 s (1H each, 9-H), 2.38 d.d (1H, 12-H, J = 3.2, 12.9 Hz), 3.08 m (1H, 7-H), 3.88 d.d (1H, 5-*exo*-H, J = 4.4, 7.2 Hz), 4.11 d (1H, 5-*endo*-H, J = 7.2 Hz), 4.36 br.s (1H, 6-H), 5.18 d (1H, 3-H, J = 1.9 Hz), 5.70 br.s (OH). ^{13}C NMR spectrum, δ_C, ppm: 28.09 (CH_3), 28.29 (CH_3), 28.73 (C^{12}), 31.07 (C^7), 31.07 (C^{10}), 41.87 (C^{11}), 49.84 (C^9), 68.71 (C^5), 76.10 (C^6), 99.76 (C^2), 103.57 (C^3), 112.70 (C^{7a}), 174.66 (C^{11a}), 196.79 (C^8). Mass spectrum: m/z 265 $[M + H]^+$. Found, %: C 63.16; H 6.78. $C_{14}H_{18}O_5$. Calculated, %: C 63.15; H 6.81. M 266.2897.

(2*R*,3*R*,6*S*,7*R*)-3,6-Epoxy-10,10-dimethyl-8-oxo-2,7-methano-2,3,5,6,7,9,10,11-octahydro-8*H*-1,4-benzodioxonin-2-yl methanesulfonate (III). Compound **II**, 1.00 g (3.76 mmol), was dissolved in 20.0 mL of methylene chloride, 0.65 g (5.64 mmol) of methanesulfonyl chloride, 1.14 g (11.28 mmol) of triethylamine, and a catalytic amount (5%) of DMAP were added at room temperature, and the mixture was stirred for 1 h (TLC). The mixture was treated with water and extracted with methylene chloride (3×20 mL), and the extract was dried over $CaCl_2$ and evaporated. Yield 0.70 g (60%), colorless crystals, mp 158°C, R_f 0.6 (EtOAc), $[\alpha]_D^{20} = -66.4°$ (c = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2947, 2852, 1649, 1622, 1359, 1078, 835. ^1H NMR spectrum, δ, ppm: 1.08 s (6H, CH_3), 2.21 d.d (1H, 12-H, J = 12.7, 1.9 Hz), 2.24 s (2H, 11-H), 2.40 s (2H, 9-H) 2.66 d.d (1H, 12-H, J = 3.5, 12.7 Hz), 3.15 m (1H, 7-H), 3.16 s (3H, SO_2CH_3), 3.91 d.d (1H, 5-*exo*-H, J = 7.6, 4.4 Hz), 4.17 d (1H, 5-*endo*-H, J = 7.6 Hz), 4.36 br.s (1H, 6-H), 5.36 d (1H, 3-H, J = 1.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 27.47 (C^{10}), 27.67 (CH_3), 28.54 (CH_3), 31.43 (C^7), 32.73 (C^{12}), 41.10 (C^{11}), 41.32 (SO_2CH_3), 49.97 (C^9), 68.92 (C^5), 76.30 (C^6), 102.20 (C^3), 105.54 (C^2), 113.64 (C^{7a}), 174.99 (C^{11a}), 195.40 (C^8). Mass spectrum: m/z 345 $[M + H]^+$. Found, %: C 52.33; H 5.78; S 9.28. $C_{15}H_{20}O_7S$. Calculated, %: C 52.31; H 5.85; S 9.31. M 344.3811.

(2*R*,3*R*,6*S*,7*R*)-3,6-Epoxy-10,10-dimethyl-8-oxo-2,7-methano-2,3,5,6,7,9,10,11-octahydro-8*H*-1,4-benzodioxonin-2-yl 4-methylbenzenesulfonate (IV). Compound **II**, 0.400 g (1.5 mmol), was dissolved in 10.0 mL of pyridine, 0.573 g (3.0 mmol) of *p*-toluenesulfonyl chloride was added under stirring at 0°C, and the mixture was stirred for two weeks (TLC). The mixture was then treated with 3% aqueous HCl and with water and extracted with ethyl acetate. The organic phase was separated and repeatedly washed with water to remove pyridine, the aqueous phase was extracted with ethyl acetate (3×10 mL), the extracts were combined with the organic phase, dried over $MgSO_4$, and evaporated, and the residue was purified by chromatography. Yield 0.500 g (83%), colorless oily substance, R_f 0.5 (EtOAc). IR spectrum, ν, cm^{-1}: 2935, 2870, 1732, 1614, 1196, 1169, 1105. ^1H NMR spectrum, δ, ppm: 1.02 s (3H, CH_3), 1.08 s (3H, CH_3), 2.05–2.40 m (4H, CH_2), 2.37 d (1H, 9-H, J = 15.8 Hz), 2.42 c (3H, $C_6H_4C\mathbf{H}_3$), 2.67 d (1H, 9-H, J = 15.8 Hz), 3.21 d (1H, 7-H, J = 8.8 Hz), 3.84 m (1H, 5-*exo*-H), 4.32 br.s (1H, 6-H), 4.35 m (1H, 5-*endo*-H), 5.01 s (1H, 3-H), 7.40–7.80 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.42 (CH_3), 27.57 (CH_3), 27.63 (CH_3), 33.92 (C^{12}), 35.42 (C^7), 42.89 (C^{11}), 51.27 (C^9), 67.87 (C^5), 76.57 (C^6), 101.04 (C^3), 101.99 (C^2), 113.35 (C^{7a}); 127.73, 130.09, 133.15, 144.52 (C_{arom}); 162.61 (C^{11a}), 196.70 (C^8). Mass spectrum: m/z 421 $[M + H]^+$. Found, %: C 60.00; H 5.78; S 7.63. $C_{21}H_{24}O_7S$. Calculated, %: C 59.99; H 5.75; S 7.63. M 420.47771.

(1*S*,2*R*,5*R*)-2-(4,4-Dimethyl-6-oxocyclohex-1-en-1-yl)-6,8-dioxabicyclo[3.2.1]octan-4-one (V). Sodium tetrahydridoborate, 0.36 g (9.6 mmol), was added under argon to a solution of 0.288 g (1.2 mmol) of $NiCl_2 \cdot 6H_2O$ in 3.0 mL of ethanol. A black–green solution was formed, and 0.2 g (0.48 mmol) of sulfonate **IV** or 0.48 mmol of **III** was added. When the reaction was complete (TLC), the mixture was filtered through a Schott filter. The filtrate was treated with water and extracted with methylene chloride (3×10 mL), the extract was dried over $MgSO_4$ and concentrated, and the residue was purified by chromatography. Yield 0.1 g (80%), colorless crystals, mp 122°C, R_f 0.4 (EtOAc), $[\alpha]_D^{20} = -190.8°$ (c = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3000, 1726, 1666, 1465, 1400, 1114, 914. ^1H NMR spectrum, δ, ppm: 0.85 m (1H, 3′-H), 1.02 s (3H, CH_3), 1.03 s (3H, CH_3), 2.23 d (1H, 3′-H, J = 16.7 Hz), 2.30 m (1H, 3′-H, J = 4.1 Hz), 2.32 br.s (2H, 3-H), 2.93 d.d (1H, 3-H, J = 16.7, 8.6 Hz), 3.49 d (1H, 2-H, J = 8.6 Hz), 4.00 d.d (1H, 7-*exo*-H, J = 7.7, 4.4 Hz), 4.12 d (1H, 7-*endo*-H, J = 7.7 Hz), 4.52 d (1H, 1-H, J = 4.4 Hz), 5.08 s (1H, 5-H), 6.68 t (1H, 2′-H, J = 4.1, 4.1 Hz). ^{13}C NMR spectrum, δ_C, ppm: 27.77 (CH_3), 28.37 (CH_3), 33.80 ($C^{3'}$), 35.47 ($C^{4'}$), 39.26 (C^2), 40.10

(C^3), 51.80 ($C^{5'}$), 68.14 (C^7), 75.35 (C^1), 100.69 (C^5), 137.76 ($C^{1'}$), 145.14 ($C^{2'}$), 196.67 (C^4), 200.86 ($C^{6'}$). Mass spectrum: *m*/*z* 251 $[M + H]^+$. Found, %: C 68.18; H 25.60. $C_{14}H_{18}O_4$. Calculated, %: C 67.18; H 25.57. *M* 250.2903.

(2*R*,3*R*,6*S*,7*R*)-3,6-Epoxy-2-methoxy-10,10-dimethyl-2,7-methano-2,3,5,6,7,9,10,11-octahydro-8*H*-1,4-benzodioxonin-8-one (VI). A catalytic amount of *p*-toluenesulfonic acid (5%) was added to a solution of 1.0 g (3.76 mmol) of compound **II** in 15.0 mL of methanol. When the reaction was complete (TLC), the mixture was treated with a solution of sodium carbonate to pH 7, the remaining methanol was distilled off, and the product was extracted into ethyl acetate (3×10 mL). The combined extracts were dried over $MgSO_4$ and concentrated, and the residue was purified by chromatography. Yield 1.0 g (95%), colorless crystals, mp 97°C, $[\alpha]_D^{20}$ = –69.3° (*c* = 0.35, $CHCl_3$), R_f 0.5 (EtOAc). IR spectrum, ν, cm^{-1}: 2900, 2800, 1641, 1612, 1463, 1390, 1118. ^1H NMR spectrum, δ, ppm: 1.05 s (3H, CH_3), 1.10 s (3H, CH_3), 1.77 br.d (1H, 12-H, *J* = 12.4 Hz), 2.02 br.d (1H, 12-H, *J* = 6.1, 12.4 Hz), 2.22 br.s (2H, 11-H), 2.23 br.s and 2.36 br.s (1H each, 9-H), 3.13 d.d (1H, 7-H, *J* = 3.0, 6.1 Hz), 3.36 s (3H, OCH_3), 3.86 d.d (1H, 5-*exo*-H, *J* = 4.6, 7.6 Hz), 4.07 d (1H, 5-*endo*-H, *J* = 7.6 Hz), 4.33 br.s (1H, 6-H), 5.12 d (1H, 3-H, *J* = 1.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 25.30 (C^{12}), 27.99 (CH_3), 28.50 (CH_3), 30.99 (C^7), 32.72 (C^{10}), 41.68 (C^{11}), 50.03 (C^9), 50.03 (OCH_3), 68.61 (C^5), 76.96 (C^6), 102.23 (C^2), 103.05 (C^3), 113.01 (C^{7a}), 173.70 (C^{11a}), 195.84 (C^8). Mass spectrum: *m*/*z* 279 $[M + H]^+$. Found, %: C 64.30; H 7.08. $C_{15}H_{20}O_5$. Calculated, %: C 64.27; H 7.19. *M* 280.3163.

(6*RS*)-6-{(1*R*)-[(1*S*,2*R*,5*R*)-4,4-Dimethoxy-6,8-dioxabicyclo[3.2.1]oct-2-yl](hydroxy)methyl}-4,4-dimethyltetrahydro-2*H*-pyran-2-one (VIIa/VIIb). An ozone–oxygen mixture was passed at –78°C through a solution of 0.437 g (1.7 mmol) of methoxy derivative **VI** in methanol. When the reaction was complete (TLC), the mixture was purged with argon, and 0.162 g (4.25 mmol) $NaBH_4$ was added in small portions at –40°C. When the reducing agent was consumed completely, the mixture was allowed to warm up to room temperature, the solvent was distilled off, and the residue was subjected to chromatography to isolate 0.366 g (68%) of a mixture of (6*R*) and (6*S*) isomers **VIIa** and **VIIb** at a ratio of 1:1. Colorless oily substance, R_f 0.46 (EtOH–EtOAc, 1:1), $[\alpha]_D^{20}$ = –164° (*c* = 0.5). IR spectrum, ν, cm^{-1}: 3500, 2958, 1718, 1373, 1246, 1112, 908, 600. ^1H NMR spectrum (hereinafter, differing signals of the other diastereoisomer are given in brackets), δ, ppm: 1.06 s (6H, CH_3), 1.09 s (6H, CH_3), 1.24 m (2H, CH_2), 2.12–1.50 m (4H, CH, CH_2), 2.21 d and 2.36 d (2H each, 3-H, *J* = 16.8 Hz), 3.21 s [3.24] (3H, OCH_3), 3.30 s [3.35] (3H, OCH_3), 4.02 m (2H, 6-H), 4.05 m (4H, 7″-H), 4.52 m (2H, 1′-H), 4.82 br.s (2H, 1″-H), 5.31 s (2H, 5″-H). ^{13}C NMR spectrum, δ_C, ppm: 24.75 (C^4), 27.68 (CH_3), 29.51 [30.93] ($C^{3''}$), 33.51 (CH_3), 37.33 (C^5), 37.68 [38.20] ($C^{2''}$), 44.73 [44.70] (C^3), 48.05 [47.94] (OCH_3), 48.82 [48.74] (OCH_3), 68.55 [68.44] ($C^{7''}$), 73.38 [73.14] ($C^{1''}$), 74.55 [74.33] (C^6), 77.70 [78.32] ($C^{1'}$), 96.73 [96.61] (OCH_3), 99.52 ($C^{5''}$), 171.38 [171.25] (C^2). Found, %: C 58.90; H 7.93. $C_{16}H_{26}O_7$. Calculated, %: C 58.17; H 7.93.

Cleavage of the 1,6-anhydro bridge in VI by the action of HCl in methanol. A solution of 0.529 g (1.9 mmol) of compound **VI** in 5.0 mL of methanol was cooled to 0°C, 20.0 mL of a 18% 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 to pH 6 with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate (3×20 mL). The combined extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator, and the residue was subjected to chromatography on silica gel. We thus isolated 0.256 g (44%) of ketal **VIII** and 0.091 g (16%) of diastereoisomer mixture **IXa**/**IXb**.

(3*S*,4a*S*,10b*R*)-2,2,3-Trimethoxy-2,3,4a,5,7,8,-9,10b-octahydropyrano[2,3-*c*]chromen-10(1*H*)-one (VIII). Colorless crystals, mp 149°C, $[\alpha]_D^{20}$ = +209.3° (*c* = 2.0, $CHCl_3$), R_f = 0.5 (petroleum ether–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 2955, 1608, 1385, 1062, 1005. ^1H NMR spectrum, δ, ppm: 0.98 s (3H, CH_3), 1.18 s (3H, CH_3), 1.22 d.d (1H, CH_2, *J* = 12.6, 12.9 Hz), 2.08–2.22 m (5H, CH_2), 2.55 d.d.d (1H, 10b-H, *J* = 1.6, 9.5, 9.6 Hz), 3.21 s and 3.28 s (3H each, 2-OCH_3), 3.44 s (3H, 3-OCH_3), 3.75 d.d (1H, 5-H, *J* = 5.8, 6.9 Hz), 3.79 d (1H, 5-H, *J* = 6.9 Hz), 4.21 d (1H, 4a-H, *J* = 9.6 Hz), 4.58 d (1H, 3-H, *J* = 1.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 26.86 (CH_3), 28.60 (CH_3), 29.14 (C^1), 32.65 (C^{10b}), 41.75 (C^7), 41.75 (C^8), 47.35 and 47.68 (2-OCH_3), 50.68 (C^9), 54.58 (3-OCH_3), 66.21 (C^{4a}), 67.89 (C^5), 97.53 (C^2), 99.46 (C^3), 109.52 (C^{10a}), 169.05 (C^{6a}). Mass spectrum: *m*/*z* 311 $[M - CH_3]^+$. Found, %: C 62.16; H 8.02. $C_{17}H_{26}O_6$. Calculated, %: C 62.56; H 8.03. *M* 326.3847.

(2*R*,3*RS*,5*S*,6*R*)-5-Hydroxymethyl-2,3-dimethoxy-9,9-dimethyl-2,6-methano-2,3,6,8,9,10-hexa-

hydro-1,4-benzodioxocin-7(5*H*)-one (IXa/IXb, a mixture of *R* and *S* isomers at a ratio of 3:1**).** Colorless oily substance, R_f 0.08 (petroleum ether–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 3000, 1618, 1458, 1375, 1076, 721. ^1H NMR spectrum (double number of protons is given for coinciding signals of diastereoisomers), δ, ppm: 0.98 s (6H, CH_3), 1.02 m (2H, CH_2), 1.18 s (6H, CH_3), 1.78–2.30 m (10H, CH, CH_2), 3.38 m (2H, CH_2), 3.51 s (6H, 3-OCH_3), 3.43 (6H, 2-OCH_3), 3.86–4.22 m (6H, CH, CH_2), 3.98 [4.08] s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 28.96 [28.12], (CH_3), 29.13 (CH_3), 30.07 (C^{12}), 32.16 [33.69] (C^6), 34.07 [34.13] (C^9), 37.75 [37.74] (C^{10}), 51.16 [51.12] (C^8), 54.97 [54.98] (2-OCH_3), 54.76 [54.14] (3-OCH_3), 60.39 [61.16] (C^{11}), 81.76 [81.38] (C^5), 95.91 [96.85] (C^2), 106.25 [107.52] (C^4), 116.90 [114.87] (C^{6a}), 117.26 [177.02] (C^{10a}), 194.67 [195.14] (C^7). Found, %: C 61.50; H 8.00. $C_{16}H_{24}O_6$. Calculated, %: C 61.52; H 7.74.

(2*S*,4a*R*,6*RS*,12a*S*)-6-Hydroxy-2,3,3-trimethoxy-8,8-dimethyldecahydropyrano[3,2-*c*]oxecine-5,10-dione (Xa/Xb) was synthesized as described above for **VIIa**/**VIIb** from 0.233 g (0.7 mmol) of **VIII**. Yield 0.051 g (25%), colorless oily substance, R_f 0.45 (petroleum ether–EtOAc, 1:1). IR spectrum, ν, cm^{-1}: 1736, 1151, 1057. ^1H NMR spectrum (double number of protons is given for coinciding signals of diastereoisomers), δ, ppm: 1.04 s (6H, CH_3), 1.12 s (6H, CH_3), 1.70–2.03 m (4H, CH_2), 2.32–2.82 m (6H, CH, CH_2), 2.68 d and 2.81 d (2H each, 9-H, J = 17.2 Hz), 3.18 m (4H, 12-H), 3.24 [3.20] s (3H, 3-OCH_3), 3.38 [3.40] s (6H, 2-OCH_3, 3-OCH_3, 3.68 [3.60] m (1H, 6-H), 3.72 m (2H, 12a-H), 4.50 [4.52] s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 28.36 (CH_3), 32.83 (C^4), 36.41 (CH_3), 38.63 (C^8), 44.14 (C^9), 47.83 (3-OCH_3), 47.07 (C^7), 48.23 (3-OCH_3), 51.32 (C^{4a}), 54.91 (2-OCH_3), 62.70 (C^{12}), 69.37 (C^6), 79.67 (C^{12a}), 97.60 (C^3), 97.65 (C^2), 172.85 (C^{10}), 211.35 (C^5). Mass spectrum: *m*/*z* 360 $[M + H]^+$. Found, %: C 56.60; H 7.76. $C_{17}H_{28}O_8$. Calculated, %: C 56.65; H 7.83. *M* 360.3994.

As described above for the synthesis of **VIII**, from 0.5 g (2.4 mmol) of **XIa**/**XIb** we obtained 0.149 g (22%) of **XIIa** and 0.294 g (41%) of **XIIb**.

Methyl (1′*R*,1*S*,2*S*,4*R*)-3,4-dideoxy-2-methoxy-2-*O*-methyl-4-(2-oxocyclopentyl)-*erythro*-hexopyranoside (XIIa). Colorless oily substance, $[\alpha]_D^{20}$ = +95° (*c* = 1.0, $CHCl_3$), R_f 0.14 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2976, 2866, 1381, 1122. ^1H NMR spectrum, δ, ppm: 1.43–2.38 m (10H, CH, CH_2), 3.45–3.80 m (3H, CH, CH_2), 3.19 s (3H, 2-OCH_3), 3.21 s (3H, 2-OCH_3), 3.40 s (3H, 1-OCH_3), 4.53 s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 20.53 ($C^{4'}$), 23.67 ($C^{5'}$), 25.99 (C^3), 32.26 (C^4), 38.38 ($C^{3'}$), 47.48 (2-OCH_3), 47.88 (2-OCH_3), 48.91 ($C^{1'}$), 54.74 (1-OCH_3), 62.80 ($C^{1''}$), 71.36 (C^5), 97.37 (C^2), 98.20 (C^1), 218.00 ($C^{2'}$). Found, %: C 58.30; H 8.40. $C_{14}H_{24}O_6$. Calculated, %: C 58.32; H 8.39.

(3a*S*,5a*S*,7*S*,9a*R*,9b*R*)-3a,7,8,8-Tetramethoxydecahydro-1*H*-cyclopenta[*b*]pyrano[3,2-*d*]pyrane (XIIb). Colorless oily substance, $[\alpha]_D^{20}$ = +119° (*c* = 1.0, $CHCl_3$), R_f 0.37 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2957, 2924, 1063, 407. ^1H NMR spectrum, δ, ppm: 1.55–2.03 m (10H, CH, CH_2), 3.22 s (3H, 3a-OCH_3), 3.23 s and 3.25 s (3H each, 8-OCH_3), 3.43 s (3H, 7-OCH_3), 3.50 d.d (1H, 5-H, J = 10.7, 5.0 Hz), 3.62 d.d (1H, 5-H, J = 5.6, 10.7 Hz), 3.78 d.d.d (1H, 5a-H, J = 4.7, 5.0, 5.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.22 (C^2), 23.38 (C^1), 29.41 (C^9), 33.02 (C^{9a}), 33.91 (C^3), 46.60 (3a-OCH_3), 47.47 and 47.78 (8-OCH_3), 50.01 (C^{9b}), 54.66 (7-OCH_3), 62.96 (C^5), 63.36 (C^{5a}), 97.68 (C^8), 98.75 (C^7), 107.80 (C^{3a}). Found, %: C 59.60; H 8.60. $C_{15}H_{26}O_6$. Calculated, %: C 59.58; H 8.67.

Following the procedure described above for the synthesis of **VIII**, from 0.4 g (1.8 mmol) of **XIIIa**/**XIIIb** we obtained 0.155 g (50%) of **XIVa** and 0.144 g (27%) of **XIVb**.

[(2*R*,3*S*,5*S*,6*R*,6a*R*,10a*R*)-2,3,10a-Trimethoxydecahydro-2,6-methano-1,4-benzodioxocin-5-yl]methanol (XIVa). Colorless crystals, mp 130°C, $[\alpha]_D^{20}$ = +86° (*c* = 1.0, $CHCl_3$), R_f 0.3 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 3425, 2920, 2852, 1450, 1056, 974. ^1H NMR spectrum, δ, ppm: 1.22 m (6H, CH_2), 1.50–1.8 m (6H, CH, CH_2), 3.22 s (3H, 10a-OCH_3), 3.25 s (3H, 2-OCH_3), 3.47 s (3H, 3-OCH_3), 3.54 d.d (1H, 11-H, J = 5.1, 10.4 Hz), 3.68 d.d (1H, 11-H, J = 5.2, 10.4 Hz), 3.92 m (1H, 5-H), 4.56 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 20.78 (C^7), 24.28 (C^9), 25.14 (C^8), 28.18 (C^{10}), 32.71 (C^6), 38.14 (C^{12}), 45.89 (C^{6a}), 47.30 (10a-OCH_3), 47.73 (2-OCH_3), 54.49 (3-OCH_3), 62.61 (C^{11}), 68.19 (C^5), 95.74 (C^2), 97.56 (C^{10a}), 98.06 (C^3). Found, %: C 59.61; H 8.48. $C_{15}H_{26}O_6$. Calculated, %: C 59.58; H 8.67.

(3*S*,4a*S*,6a*S*,10a*R*,10b*R*)-2,2,3,6a-Tetramethoxydodecahydropyrano[2,3-*c*]chromene (XIVb). Colorless crystals, mp 118°C, $[\alpha]_D^{20}$ = +117° (*c* = 1.0, $CHCl_3$), R_f 0.6 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2900, 1735, 1458, 1151, 1064, 1049, 979. ^1H NMR spectrum, δ, ppm: 1.17–1.40 m (8H, CH_2), 1.56–1.90 m (4H, CH, CH_2), 3.17 s (3H, 6a-OCH_3), 3.22 s and 3.25 s (3H each, 2-OCH_3), 3.46 s

(3H, 3-OCH_3), 3.60 m (2H, 5-H), 3.58 m (1H, 4a-H), 4.56 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 22.20 (C^8), 24.23 (C^{10}), 25.23 (C^9), 28.38 (C^1), 31.31 (C^7), 34.33 (C^{10b}), 46.88 (C^{10a}), 46.47 (6a-OCH_3), 47.47 and 47.91 (2-OCH_3), 54.66 (3-OCH_3), 62.48 (C^5), 68.20 (C^{4a}), 97.73 (C^2), 98.05 (C^{6a}), 98.31 (C^3). Found, %: C 60.74; H 8.90. $C_{16}H_{28}O_6$. Calculated, %: C 60.74; H 8.92.

(2*S*,4a*S*,11a*S*)-2,3,3-Trimethoxyhexahydro-2*H*-pyrano[2,3-*c*]oxonane-5,9(3*H*,6*H*)-dione (XV). Pyridinium chlorochromate, 0.215 g (1.0 mmol), was added in small portions under thorough stirring to a solution of 0.157 g (0.5 mmol) of compound **XIIb** in 5.0 mL of methylene chloride. After 48 h (TLC), the mixture was diluted with 5.0 mL of diethyl ether, the precipitate was filtered off through a layer of silica gel on a Schott filter, the filtrate was evaporated, and the residue was subjected to chromatography on silica gel. Yield 0.071 g (45%), colorless oily substance, $[\alpha]_D^{20}$ = +45° (*c* = 1.0, $CHCl_3$), R_f 0.18 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2976, 2864, 1383, 1122. ^1H NMR spectrum, δ, ppm: 1.90–2.00 m (3H, CH, CH_2), 2.55 d.d.d (1H, 6-H, *J* = 2.0, 10.3, 14.3 Hz), 2.90 d.d (1H, 6-H, *J* = 6.7, 10.3 Hz), 3.18 s and 3.22 s (3H each, 3-OCH_3), 3.43 s (3H, 2-OCH_3), 4.01 d.d (1H, 11-H, *J* = 9.3, 10.7 Hz), 4.29 d.d.d (1H, 11a-H, *J* = 6.3, 9.3, 9.6 Hz), 4.49 d.d (1H, 11-H, *J* = 6.3, 10.7 Hz), 4.52 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.99 (C^7), 28.09 (C^4), 33.32 (C^8), 41.19 (C^6), 47.81 and 48.17 (3-OCH_3), 55.24 (2-OCH_3), 50.89 (C^{4a}), 63.58 (C^{11}), 69.20 (C^{11a}), 96.27 (C^3), 97.23 (C^2), 171.62 (C^9), 210.52 (C^5). Mass spectrum: *m*/*z* 301 $[M + H]^+$. Found, %: C 55.62; H 7.34. $C_{14}H_{22}O_7$. Calculated, %: C 55.62; H 7.33. *M* 302.3203.

(2*S*,4a*S*,12a*S*)-2,3,3-Trimethoxydecahydropyrano[2,3-*c*]oxecine-5,10-dione (XVI) was synthesized in a similar way from 0.268 g (0.9 mmol) of **XIVa** or 0.9 mmol of **XIVb**. Yield 0.164 g (59%, from **XIVa**) or 0.117 g (42%, from **XIVb**), colorless crystals, mp 74°C, $[\alpha]_D^{20}$ = +56° (*c* = 1.0, $CHCl_3$), R_f 0.16 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2853, 1730, 1064, 968. ^1H NMR spectrum, δ, ppm: 1.50 m (1H, 8-H), 1.58 m and 1.75 m (1H each, 7-H), 1.87 m (1H, 4-H), 1.90 m (1H, 8-H), 1.95 m (1H, 4-H), 2.22 m (1H, 9-H), 2.32 m (1H, 6-H), 2.40 m (1H, 9-H), 2.48 m (1H, 6-H), 2.62 d.d.d (1H, 4a-H, *J* = 4.0, 10.0, 12.6 Hz), 3.16 s and 3.18 s (3H each, 3-OCH_3), 3.40 s (3H, 2-OCH_3), 4.05 d.d (1H, 12-H, *J* = 4.2, 10.5 Hz), 4.15 d.d.d (1H, 12a-H, *J* = 4.2, 10.0, 10.3 Hz), 4.30 d.d (1H, 12-H, *J* = 10.3, 10.5 Hz), 4.50 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 20.29 (C^7), 22.50 (C^8), 28.17 (C^4), 34.10 (C^9), 40.00 (C^6), 47.85 and 48.24 (3-OCH_3), 51.72 (C^{4a}), 55.30 (2-OCH_3), 64.81 (C^{12}), 67.70 (C^{12a}), 96.54 (C^3), 97.35 (C^2), 172.58 (C^{10}), 208.11 (C^5). Mass spectrum: *m*/*z* 316 $[M + H]^+$. Found, %: C 56.98; H 7.66. $C_{15}H_{24}O_7$. Calculated, %: C 56.95; H 7.65. *M* 316.3469.

1,6-Anhydro-3,4-dideoxy-4-[(1*RS*)-2-oxocyclohept-1-yl]-β-D-*erythro*-hex-2-ulose (XIXa/XIXb). 4-(Cyclohept-1-en-1-yl)morpholine (**XVII**), 0.348 g (1.9 mmol), was added to a solution of 0.200 g (1.6 mmol) of levoglucosenone (**I**) in 10.0 mL of benzene, and the mixture was heated for 2 h under reflux. When the reaction was complete (TLC), the mixture was treated with water and was heated for 1 h more under reflux. The mixture was cooled to room temperature and extracted with ethyl acetate (4×10 mL), and the combined extracts were dried over $MgSO_4$ and evaporated. Yield 0.184 g (48%, a mixture of *R* and *S* isomers at a ratio of 2:1), colorless oily substance, $[\alpha]_D^{20}$ = +0.2° (*c* = 1.0, $CHCl_3$), R_f 0.2 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2927, 1735, 1701, 1115, 429. ^1H NMR spectrum (double number of protons is given for coinciding signals), δ, ppm: 1.11 m (4H, CH_2), 1.58 m (6H, CH_2), 2.00 m (4H, CH_2), 2.21–2.40 m (8H, CH, CH_2), 2.38 m (2H, 4-H), 2.51 m and 2.67 m (2H each, 3′-H), 2.70 m (2H, 3-H), 2.85 m (2H, 1′-H), 3.87 m (2H, 6-*exo*-H), 3.95 m (2H, 6-*endo*-H), 4.52 d (1H, 5-H, *J* = 4.7 Hz) [4.68 d (1H, 5-H, *J* = 3.7 Hz)], 5.00 [5.02] s (1H). ^{13}C NMR spectrum, δ_C, ppm: 23.09 [23.32 ($C^{4'}$), 27.93 [27.85] ($C^{6'}$), 27.97 [28.41] ($C^{7'}$), 28.48 [29.31] ($C^{5'}$), 33.95 [36.08] (C^3), 41.26 [42.00] (C^4), 43.73 [44.04] ($C^{3'}$), 51.72 [51.85] ($C^{1'}$), 68.10 [68.17] (C^6), 73.73 [74.96] (C^5), 101.19 [101.15] (C^1), 200.12 [200.18] (C^2), 215.13 [214.40] ($C^{2'}$). Found, %: C 65.54; H 7.61. $C_{13}H_{18}O_4$. Calculated, %: C 65.53; H 7.61.

1,6-Anhydro-3,4-dideoxy-4-[(1*RS*)-2-oxocyclododecyl]-β-D-*erythro*-hex-2-ulose (XXa/XXb) was synthesized in a similar way from 0.500 g (8.0 mmol) of levoglucosenone (**I**). Yield 0.285 g (24%, a mixture of *R* and *S* isomers at a ratio of 2:1), colorless crystals, mp 83°C, $[\alpha]_D^{20}$ = –132° (*c* = 1.0, $CHCl_3$), R_f 0.48 (petroleum ether–EtOAc, 6:1). IR spectrum, ν, cm^{-1}: 2930, 1730, 1697, 1468, 1121, 914, 727, 430. ^1H NMR spectrum (double number of protons is given for coinciding signals), δ, ppm: 1.05–1.18 m (4H, CH_2), 1.20–1.40 m (26H, CH_2), 1.58–1.63 m (2H, CH_2), 1.74–1.82 m (2H, CH_2), 1.90 m (2H, CH_2), 2.07 m (2H, CH_2), 2.12–2.20 m (2H, CH_2), 2.30 d (2H, CH_2, *J* = 16.4 Hz), 2.60 m (2H, CH_2), 2.75 [2.90] m (1H, CH), 3.0 m (2H, CH), 3.94 d.d (1H, 6-*exo*-H, *J* = 5.4,

6.6 Hz), 4.01–4.09 m (1H, 6-*endo*-H) [4.01–4.09 m (2H, 6-H)], 4.41 d (1H, 5-H, J = 5.4 Hz) [4.67 d (1H, 5-H, J = 3.9 Hz)], 5.03 [5.05] s (1H, 1-H). ^{13}C NMR spectrum, δ_C, ppm: 19.93 ($C^{5'}$), 21.43 ($C^{6'}$), 21.78 ($C^{4'}$), 22.46 ($C^{10'}$), 23.05 ($C^{7'}$), 23.74 ($C^{9'}$), 25.80 ($C^{8'}$), 26.11 ($C^{11'}$), 26.29 ($C^{12'}$), 33.42 ($C^{3'}$), 33.42 (C^3), 39.41 [39.10] (C^4), 52.27 [50.88] ($C^{1'}$), 68.29 [67.87] (C^6), 75.46 [73.91] (C^5), 101.37 [109.98] (C^1), 200.67 [200.67] (C^2), 212.94 [211.98] ($C^{2'}$). Found, %: C 70.25; H 9.18. $C_{18}H_{28}O_4$. Calculated, %: C 70.10; H 9.15.

(2*S*,4a*S*,13a*S*)-2,3,3-Trimethoxyoctahydro-2*H*-pyrano[2,3-*c*]oxacycloundecine-5,11(3*H*,6*H*)-dione (XXI). A solution of 0.184 g (0.8 mmol) of diastereoisomer mixture **XIXa**/**XIXb** in 2.0 mL of methanol was cooled to 0°C, 10.0 mL of a 18% solution of HCl in methanol was added, and the mixture was stirred for 3 days at room temperature. When the reaction was complete (TLC), the mixture was neutralized to pH 7 with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate (3×8 mL), the extracts were combined, dried over $MgSO_4$, and concentrated on a rotary evaporator, the residue was dissolved in 5.0 mL of methylene chloride, and 0.215 g (1.0 mmol) of PCC was added in small portions under thorough stirring. After 48 h (TLC), the mixture was diluted with 5.0 mL of diethyl ether and filtered through a layer of silica gel on a Schott filter, the filtrate was evaporated, and the residue was subjected to chromatography on silica gel to isolate 0.071 g (28%) of compound **XXI** as colorless crystals with mp 54°C, $[\alpha]_D^{20}$ = +19° (c = 1.0, $CHCl_3$), R_f 0.27 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2930, 1740, 1050. ^{1}H NMR spectrum, δ, ppm: 1.14 m (1H, CH_2), 1.52 m (2H, CH_2), 1.72 m (2H, CH_2), 1.83 m (1H, CH_2), 2.00 m (2H, CH_2), 2.28 m (1H, CH_2), 2.44 m (1H, CH_2), 2.69 m (1H, CH_2), 3.07 d.d.d (1H, 4a-H, J = 3.2, 3.5, 10.0 Hz), 3.22 s and 3.32 s (3H each, 3-OCH_3), 3.51 s (3H, 2-OCH_3), 3.82 d.d (1H, 8-H, J = 5.7, 11.4 Hz), 4.28 d.d (1H, 8-H, J = 4.2, 11.4 Hz), 4.56 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.73 (C^9), 22.33 (C^8), 25.49 (C^7), 29.01 (C^4), 33.78 (C^{10}), 40.98 (C^6), 47.75 (C^{4a}), 47.76 and 48.22 (3-OCH_3), 55.08 (2-OCH_3), 65.09 (C^{13}), 67.16 (C^{13a}), 96.39 (C^3), 97.67 (C^2), 172.92 (C^{11}), 210.63 (C^5). Mass spectrum: m/z 330 $[M + H]^+$. Found, %: C 58.17; H 7.96. $C_{16}H_{26}O_7$. Calculated, %: C 58.17; H 7.93. M 330.3734.

(2*S*,4a*S*,18a*S*)-2,3,3-Trimethoxyhexadecahydropyrano[2,3-*c*]oxacyclohexadecine-5,16-dione (XXII) was synthesized in a similar way from 0.138 g (0.4 mmol) of diastereoisomer mixture **XXa**/**XXb**. Yield 0.055 g (30%), colorless oily substance, $[\alpha]_D^{20}$ = +27° (c = 1.0, $CHCl_3$), R_f 0.38 (petroleum ether–EtOAc, 3:1). IR spectrum, ν, cm^{-1}: 2990, 1750, 1030, 500. ^{1}H NMR spectrum, δ, ppm: 1.15–1.35 m (8H, CH_2), 1.41–1.82 m (4H, CH_2), 2.40 m (3H, CH_2), 3.0 m (1H, CH), 3.20–3.40 m (2H, CH_2), 4.11–4.20 m (3H, CH, CH_2), 3.22 s and 3.28 s (3H each, 3-OCH_3), 3.43 s (3H, 2-OCH_3), 4.57 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.66 (C^8), 24.01 (C^{14}), 25.21 (C^7), 25.71 (C^{10}), 25.80 (C^{11}), 26.11 (C^{13}), 26.68 (C^9), 29.09 (C^4), 40.87 (C^6), 46.32 (C^{4a}), 47.90 and 48.30 (3-OCH_3), 55.12 (2-OCH_3), 64.30 (C^{18}), 66.96 (C^{18a}), 96.41 (C^3), 97.60 (C^2), 173.63 (C^{16}), 210.56 (C^5). Mass spectrum: m/z 400 $[M + H]^+$. Found, %: C 62.99; H 9.11. $C_{21}H_{36}O_7$. Calculated, %: C 62.98; H 9.06. M 400.5063.

Ethyl (6*S*)-6-hydroxy-6-[(2*S*,3*R*,6*S*)-2-hydroxymethyl-5,5,6-trimethoxytetrahydro-2*H*-pyran-3-yl]-hexanoate (XXIII) and {(2*S*,3*R*,6*S*)-3-[(1*S*)-6-ethoxy-1-hydroxy-6-oxohexyl]-5,5,6-trimethoxytetrahydro-2*H*-pyran-2-yl}methyl (2*E*)-3-(1-methyl-1*H*-imidazol-4-yl)prop-2-enoate (XXV). Sodium tetrahydridoborate, 0.032 g (0.8 mmol), was added to a solution of 0.220 g (0.7 mmol) of lactone **XIV** in 5.0 mL of ethanol, the mixture was stirred until the reaction was complete (TLC), 1.0 mL of acetone was added, the mixture was concentrated on a rotary evaporator, and the residue was subjected to chromatography on silica gel to isolate 0.090 g (41%) of alcohol **XXIII** (major product). Compound **XXIII**, 0.090 g (0.3 mmol), was dissolved in 10.0 mL of chloroform, 0.137 g (0.9 mmol) of *N*-methylurocanic acid (**XXIV**), 0.247 g (1.2 mmol) of *N*,*N*′-dicyclohexylcarbodiimide, and 0.183 g (1.5 mmol) of 4-dimethylaminopyridine were added, and the mixture was heated under reflux until the reaction was complete (TLC). The mixture was then treated with a saturated solution of ammonium chloride and extracted with chloroform (3×5 mL), the combined extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator, and the residue was purified by chromatography on silica gel. Yield of **XXV** 0.077 g (60%).

Compound **XXIII**. Colorless oily substance, R_f 0.9 (petroleum ether–EtOAc, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3, J = 7.2 Hz), 1.30–1.60 m (6H, CH, CH_2), 1.79–2.00 m (3H, CH, CH_2), 2.30 m (2H, CH_2), 3.20 s (6H, 5-OCH_3), 3.40 s (3H, 6-OCH_3), 3.51 br.s (1H, 2-H), 3.53 br.s (1H, 1″-H), 3.70 d.d (1H, 1′-H, J = 11.5, 3.8 Hz), 3.75 d.d (1H, 1′-H, J = 11.5 Hz), 4.08 q (2H, 8‴-H, J = 7.1 Hz), 4.50 s (1H, 6-H). ^{13}C NMR spectrum, δ_C, ppm: 14.19 (CH_3), 24.61

($C^{4''}$), 25.24 ($C^{3''}$), 26.66 (C^4), 32.44 ($C^{5''}$), 34.11 ($C^{2''}$), 40.40 (C^3), 47.63 and 48.13 (5-OCH_3), 54.88 (6-OCH_3), 60.34 (CH_2O), 63.89 ($C^{1'}$), 70.66 ($C^{1''}$), 71.97 (C^3), 97.48 (C^5), 97.77 (C^6), 173.81 ($C^{6''}$).

Compound **XXV**. Colorless oily substance, $[\alpha]_D^{20}$ = +48.6° (c = 1.05, $CHCl_3$), R_f 0.9 (EtOAc). IR spectrum, ν, cm^{-1}: 1713, 1271, 1169, 1057. ^1H NMR spectrum, δ, ppm: 1.25 t (3H, CH_3, J = 7.2 Hz), 1.34–1.42 m (3H, 2‴-H, 2‴-H), 1.53 d.d (1H, 3-H, J = 13.2, 13.2 Hz), 1.55–1.68 m (3H, 3‴-H, 4‴-H), 1.96 m (1H, 3-H), 2.08 d.d (1H, 4-H, J = 13.2, 2.6 Hz), 2.30 m (2H, 5‴-H), 3.22 s and 3.23 s (3H each, 5-OCH_3), 3.44 s (3H, 6-OCH_3), 3.68 m (1H, 1‴-H), 3.71 s (3H, NCH_3), 3.81 d.d.d (1H, 2-H, J = 9.2, 6.4, 2.3 Hz), 4.12 q (2H, 8-H, J = 7.2 Hz), 4.23 d.d (1H, 7-H, J = 12.0, 6.4 Hz), 4.52 d.d (1H, 7-H, J = 12.0, 2.3 Hz), 4.59 s (1H, 6-H), 6.59 d (1H, 4′-H, J = 15.6 Hz), 7.10 s (1H, 5″-H), 7.48 s (1H, 7″-H), 7.57 d (1H, 5′-H, J = 15.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.24 ($C^{9'''}$), 24.71 ($C^{3'''}$), 25.51 ($C^{4'''}$), 26.49 (C^4), 32.23 ($C^{2'''}$), 33.63 (NCH_3), 34.19 ($C^{5'''}$), 40.62 (C^3), 47.77 and 48.13 (5-OCH_3), 54.90 (6-OCH_3), 60.29 ($C^{8'''}$), 65.28 ($C^{7'''}$), 69.26 (C^2), 70.90 ($C^{1'''}$), 97.34 (C^5), 97.49 (C^6), 115.52 ($C^{4'}$), 122.76 ($C^{5''}$), 136.58 ($C^{5'}$), 138.38 ($C^{4''}$), 139.25 ($C^{2''}$), 167.71 ($C^{3'}$), 173.74 ($C^{6'''}$). Mass spectrum: m/z 498 $[M + H]^+$. Found, %: C 57.79; H 7.70; N 5.62. $C_{24}H_{38}N_2O_9$. Calculated, %: C 57.82; H 7.68; N 5.62. M 498.5666.

This study was performed under financial support by the Russian Foundation for Basic Research (project nos. 11-03-97024-r_povolzh'e_a, 13-00-14056).

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