Synthesis of new stereoisomeric nitrate esters derived from isosorbide-mononitrates

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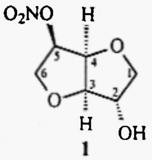
Abstract: - A synthesis of diastereomeric *(7R)* 7-*endo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (4b) and *(7S)* 7-*exo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (7b) is described using D-glucitol as a starting compound. Bicyclic δ-lactones **4** and **7** are obtained in the reaction of 1,4-3,6-dianhydro-2-keto-D-glucitol-5-acylates **3** and 1,4-3,6-dianhydro-5-keto-D-glucitol-2-acylates **6** with *m*-chloroperbenzoic acid. Hydrolysis of lactones **4b** and **7b** and subsequent esterification afforded the corresponding stereoisomeric *(3R,4R)* methyl (2-acetoxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetate **10** and *(3R,4S)* isomer **12**, respectively.

Isosorbide-5-mononitrate (1,4-3,6-dianhydro-D-glucitol-5-mononitrate) **1** possesses a noticeable vasodilating activity and, since the early eighties, has continuous pharmaceutical application as an antianginal agent.[1-3] These properties and applications of isosorbide-5-mononitrate increased a research related to the structural modifications of the parent compound.[3,4] Number of attempts were made in order to improve the pharmaceutical activities of compounds derived from **1**, because conversion of the free hydroxyl group into a different functional groups could therefore cause a changes in their biological activities.[3]



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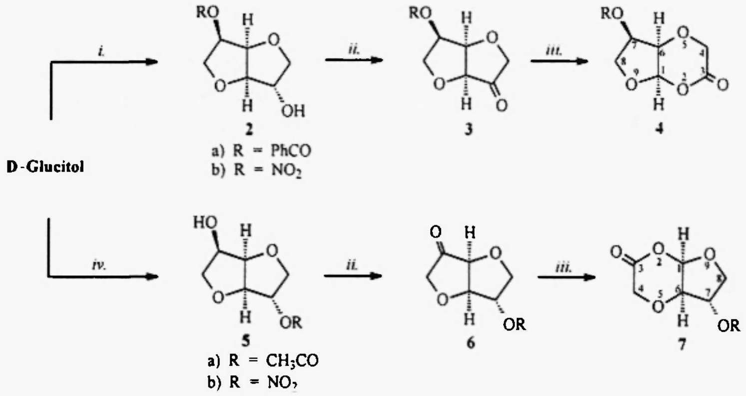
Our approach to modify isosorbide-5- (or -2-) moonitrate structures, possessing two *cis*-fused tetrahydrofuran rings, is directed to change of the tetrahydrofuran ring having a free hydroxyl group, with retention of stereochemistry and functionality of the tetrahydrofuran ring bearing a nitrate group, responsible for pharmaceutical activities. For these purposes we prepared several *(5R)* isosorbide-5-acylate **2** and *(2S)* isosorbide-2-acylates **5** by selective and controlled esterifications of isosorbide.[7,8] Since the keto group offers a diverse possibilities for further transformations we found a convenient procedure for oxidative conversion of the free hydroxyl group of isomeric monoacylates **2** and **5** to the corresponding 2-keto-isosorbide-5-acylates (1,4-3,6-dianhydro-2-keto-D-glucitol-5-benzoates **3a** and nitrate **3b**), as well as 5-keto-isosorbide-2-acylates (1,4-3,6-dianhydro-5-keto-D-glucitol-2-acetate **6a** and nitrate **6b**), respectively.

Results

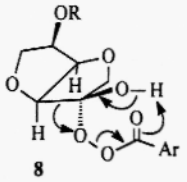
Conversion of monoacylates **2** and **5** to the corresponding keto-isosorbide-acylates were carried out by pyridinium-dichromate (PDC) in the presence of acetic anhydride and in methylene chloride solution (Scheme 1.).[9] Under these conditions stereochemistry of esters group, as well as *cis*-fused tetrahydrofuran ring in keto-esters **3** and **6** were preserved as in starting hydroxy esters **2** and **5**. It was found that oxidation of the isosorbide-5-acylates **2**, with *exo*-2-hydroxyl group proceeds slightly faster (reaction time 1.5 h for **2a**) than the oxidation of isosorbide-2-acylates with *endo*-5-hydroxyl group (reaction time 3 h for **5a**). We suppose that this difference in reactivity is because of steric hindrance of *endo*-5-hydroxyl group as well as because of pseudo-axial orientation of carbinol hydrogen atom to be abstracted, in the intermediary chromate ester derived from 2-*exo*-hydroxyl group. Keto esters **3** and **6** are obtained 60-80% yields (Scheme 1.). Similar yields of keto-esters **3a** and **3b** were obtained by oxidation of isosorbide-5-monoacylates by pyridinium chlorochromate. However, oxidation of isosorbide-5-benzoate **2a** and -nitrate **2b** by Dess-Martin periodinane also afforded the corresponding 2-keto-isosorbide-5-acylates (**3a** and **3b**) in slightly lower yields (40-49%).



Scheme 1 *i. Refs. 7, 12; ii. PDC, Ac_2O, CH_2Cl_2, 50°C, 4 h; iii. mCPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 15 min; iv. Refs. 8, 12.*

2-Keto-isosorbide-5-acylates **3** were treated with *m*-chloroperbrenzoic acid (mCPBA) in methylene chloride solution at 0°C in the presence of sodium hydrogen carbonate and Baeyer-Villiger rearrangement occurs.[10] Thus two δ-lactones (7-*endo*-benzoyloxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane **4a** and 7-*endo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]-nonane **4b**)[11] were obtained in good yields (70% and 81%, respectively) (Scheme 1.).

Baeyer-Villiger rearrangement of 2-keto-isosorbide-5-acylates **3** involves the intermediate **8**, in which the peracid has approached the keto group from the stereochemically less hindered convex face of the bicyclic structure. As expected, migration of the more substituted α-carbon atom occurs with retention of configuration, because the adjacent oxygen increases the relative migratory aptitude of the neighbouring carbon atom.



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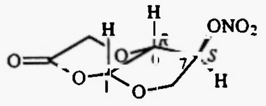
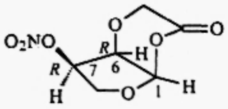
Under the same experimental conditions 5-keto-isosorbide-2-acylates **6a** and **6b** were also converted by mCPBA to the corresponding δ-lactones **7** (7-*exo*-acetoxy-3-oxo-2,5,9-trioxabicylo[4.3.0]nonane **7a** and 7-*exo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]-nonane **7b**) in 61% and 56% yields, respectively (Scheme 1.).

Keto-isosorbide-monoacylates **3** and **6** possessing *cis*-fused THF rings with fixed stereochemistry, were converted to the corresponding δ-lactones **4** and **7** with formal retention of stereochemistry of the THF ring bearing an acyloxy groups, while δ-lactone ring rather exists in boat-like conformation and bicyclic compounds have a more flexible stereochemistry (**4b** and **7b**).[13]



7b

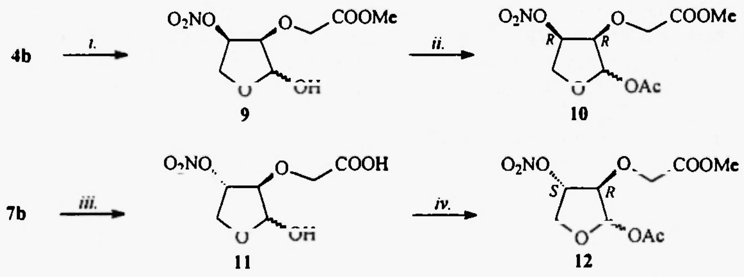


4b

Thus, using 1,4-3,6-dianhydro-D-glucitol as an easily available starting compound, two diastereomeric δ-lactones: (6*R*, 7*R*) 7-*endo*—nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane **4b** and (6*R*, 7*S*) 7-*exo*-nitrooxy-oxo-2,5,9-trioxabicyclo[4.3.0]nonane were prepared. The difference is only in the stereochemistry on the carbon atom at 7 position of bicyclic compounds. The distereomer **4b** corresponds to the (5*R*) isosorbide-5-mononitrate **1**, while isomeric δ-lactone **7b** corresponds to the (2*S*) isosorbide-2-mononitrate.

The stereochemical difference between two diastereomeric nitrate esters **4b** and **7b** may have influence on their vasodilating activities. Stereochemistry-vasodilating activities relationship of compounds **4b** and **7b** are under investigation and have to be compared with stereochemical influence on the difference in the activities of the (5*R*) isosorbide-5-mononitrate (1,4-3,6-dianhydro-D-glucitol-5-mononitrate) **1** and stereoisomeric (2*S*) 1,4-3,6-dianhydro-D-glucitol-2-mononitrate

Hydrolysis of δ-lactone **4b** under dry experimental conditions (methanolic potassium carbonate) and subsequent esterification afforded the corresponding (3*R*,4*R*) methyl (2-acetoxy-4-nitrooxy-tetrahydrofuran-3-yloxy)-acetate **10** [7], while δ-lactone **7b** under wet conditions afforded the (3*R*, 4*S*) (2-hydroxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetic acid **11** which was methylated and acetylated to give stereoisomeric (3*R*, 4*S*) methyl (2-acetoxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetate (**12**).



Scheme 2. *i.* K_2CO_3, *MeOH, r.t., 10 min.;* *ii.* Ac_2O, $Pb(OAc)_2$, CH_2Cl_2; *iii.* K_2CO_3,*THF, MeOH,* H_2O, *r.t., 10 min.;* *iv. a)* CH_2N_2, Et_2O; *b)* Ac_2O, *Pyr.*

Described sequence of reaction offers a suitable synthetic method for the preparation of two useful chiral 3*R*,4*R*- and 3*R*,4*S*-disubstituted tetrahydrofuran derivatives **10** and **12**, from easily available 1,4-3,6-dianhydro-D-glucitol as a staring compound.

Preliminary investigation of pharmacological activity of two stereoisomeric nitrate esters (7*R*) 7-*endo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (**4b**) and (7*S*) 7-*exo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (**7b**) on the heart rate and coronary blood flow of the isolated rat heart was carried out and compared with the activity of isosorbide-5-mononitrate (**1**). We also wanted to find out the influence of stereochemistry on the pharmacological activity.

It was found that both of the stereoisomers **4b** and **7b** show some decreasing of the contractivity as well as the heart rate and coronary blood flow, regarding to the isosorbide-5-mononitrate (**1**). However, (7*R*) 7-*endo*-isomer **4b**, possessing same stereochemistry of the tetrahydrofuran ring bearing a nitrate ester group as isosorbide-5-mononitrate has, is more active than (7*S*) 7-*exo*-stereoisomer **7b** which has a stereochemistry of the tetrahydrofuran ring resembling to isosorbide-2-

mononitrate. Further investigations of the pharmacological activities of nitrate esters **4b** and **7b** as well as compounds **10** and **12** are in progress.

Experimental

General details

Melting points were determined in open capillaries on a Electrothermal aparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 141 MC polarimetere. The IR spectra were recorded on a Perkin-Elmer 457 grating spectrometer, solid samples were examined as KBr discs and liquids as films on sodium chloride plates. ^{1}H-NMR spectra were recorded in $CDCl_3$ solutions (unless otherwise stated), using Varian Gemini 200 MHz spectrometer. Chemical shifts (δ) are expressed in ppm using TMS as internal standard. ^{13}C-NMR spectra were measured at 50 MHz on the same instrument. Mass spectra were performed on Finningan ITDS 700 instrument.

Thin layer chromatography (TLC) analysis were performed on Silica gel-60 F_{254} plates and compounds were visualized using ultraviolet light or by iodine vapors. Preparative chromatography were carried out on silica-gel 63-100 μm using eluents specified. Dry-flash chromatography was carried out on silica gel 60.

Oxidation of 1,4-3,6-dianhydro-D-glucitol monoesters

1,4-3,6-Dianhydro-D-glucitol-2-keto-5-nitrate (3b)

To a well stirred suspension of pyridinium dichromate (0.489 g. 1.3 mmol) in methylene chloride (4 ml) acetic anhydride (0.63 g, 6.2 mmol) was added and stirred for 15 min. at room temperature. A solution of isosorbide-5-mononitrate (**2b**) (0.5 g, 2 mmol) in methylene chloride (3 ml) was added into the oxidizing mixture. After exothermic reaction ceases stirring of the resulting mixture was continued for 2 h. The course of the reaction was monitored by TLC ($CHCl_3$/acetone 9 : 1). Methylene chloride was evaporated from the reaction mixture and the dry residue was dissolved in ethyl acetate (2 x 50 ml). The resulting suspension was filtered through a pad of celite (washed twice by ethyl acetate). Solvent was evaporated and the resulting oily residue was purified by dry-flash chromatography on silica gel (petroleum ether/ethyl acetate 7 : 3 and 6 : 4) as eluent. Keto-nitrate **3b** was obtained (0.38 g, 76%) as colorless oil (oxime derivative has mp 110°C). Anal. calc. for $C_6H_8N_2O_6$: C, 35.29; H, 3.92; N, 13.72%. Found: C, 35.00; H, 4.04; N 13.51%. IR (film) υ_{max} 3385, 2931, 2883, 1774, 1641, 1347, 1283, 1090 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.48 (dt. J_1 5.2, J_2 5.4, J_3 5.8, 1H C^5-H), 5.23 (dd, J_1 5.4, J_2 6.4, 1H C^4-H), 4.43 (d, J 6.4, 1H C^3-H), 4.23 (dd, J_1 10.8, J_2 5.8, 1H C^6-H), 4.18 (d, J 7.0, 2H C^1-H), 4.02 (dd, J_1 10.8, J_2 5.2, 1H C^6-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 69.17, 71.03, 78.17, 79.69, 80.82, 209.42.

Oxidation of isosorbide5-mononitrate (**2b**) (0.399 g, 209 mmol) in methylene chloride (6 ml) was carried out with Dess-Martin periodinane (1.06 g, 2.5 mmol) dissolved in methylene chloride (9 ml) in the presence of trifluoroacetic acid (0.1 ml). After standard work up procedure for Dess-Martin oxidation keto-nitrate **3b** was obtained (0.195 g, 49%) in addition to unreacted starting alcohol (0.09 g, 23%).

1,4-3,6-Dianhydro-D-glucitol-2-keto-5-benzoate (3a)

By use of a procedure similar to that described for the preparation of **3b** isosorbid-5-benzoate (2a) (0.5 g, 2 mmol) was converted into keto-benzoate **3a** as colorless oil (0.38 g, 76%), oxime derivative has mp 128°C. Anal. calc. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32%. Found: C, 59.01; H, 5.06, N, 5.60%. IR (film) υ_{max} : 3443, 2958, 2891, 1772, 1775, 1317, 1273, 1178, 1120, 1080, 972, 938, 914 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.08 (m, 2H, Ph), 7.64-7.27 (m, 3H, Ph), 5.53 (dd, J_1 5.5, J_2 5.7, 1H, C^5-H), 5.23 (dd, J_1 5.8, J_2 6.3, 1H C^4-H), 4.45 (d, J 6.3, 1H C^3-H), 4.29 (dd, J_1 5.7, J_2 9.8, 1H C^6-H), 4.12 (d, J 4.3, 2H, C^1H_2), 4.08 (dd, J_1 5.7, J_2 9.8, 1H C^6-H. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 70.92, 71.14, 74.11, 78.02, 79.82, 128.25, 129.67, 133.50, 165.20, 210.67. MS: 248 (M^+) 163, 126, 85.

Oxidation of isosorbide-5-benzoate (2a) by PCC

A solution of isosorbide-5-benzoate (2a) (0.5 g, 2 mmol) in dry benzene (25 ml) was heated to boil and pyridinium chlorochromate (PCC) (0.862 g, 2 mmol) was added to the stirring solution. The mixture was stirred for 2.5 h and reaction was monitored by TLC (benzene/ethyl acetate 8 : 2 eluent). Hot benzene solution was filtered through celite and dark-green residue was washed several times with hot benzene. Evaporation of benzene gave a pale-green sticky oil which was purified by dry flash chromatography (benzene/ethyl acetate 8 : 2) to give keto-ester **3a** as a colorless viscous oil (0.32 g, 64%) which has identical spectral evidences as same compound obtained in oxidation of **2a** with PDC.

1,4-3,6-Dianhydro-5-keto-D-glucitol-2-acetate (6a)

Oxidation of isosorbide-2-monoacetate (**5a**) (0.752 g, 4 mmol) by PDC (1.203 g, 3.2 mmol) in the presence of acetic anhydride (1.55 ml) in methylene chloride (12 ml) was carried out following the described procedure for the preparation of **3a** and **3b**. 1,4-3,6-Dianhydro-5-keto-D-glucitol-2-acetate (**6a**) was obtained (0.49 g, 64%) as a colorless oil, 2,4-dinitrophenylhydrizone has mp 165°C. Anal. calc. for $C_{14}H_{14}N_4O_8$ (hydrazone): C, 45.90; H, 3.83; N, 15.30%. Found: C, 45.52; H, 3.90; N, 15.12%. IR (film) υ_{max} : 3441, 2970, 2883, 1771, 1746, 1436, 1377, 1168, 1078, 989, 925 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.35 (dd, J_1 1.6, J_2 1.0, 1H C^2-H, 4.82 (d, J 4.4 1H, C^4-H), 4.34 (d, J 4.4, 1H, C^3-H, 4.07 (Abq, J 17.6, 2H C^6H_2), 4.10-4.00 (m, 2H, C^1H_2), 2.11 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.76, 70.01, 72.83, 78.18, 78.68, 84.79, 169.91, 209.56.

1,4-3,6-Dianhydro-5-keto-D-glucitol-2-nitrate (6b)

By use of a procedure similar to that described for the oxidations with PDC isosorbide-2-mononitrate (**5b**) (0.57 g, 2.98 mmol) was converted by PDC (0.752 g 2 mmol) and acetic anhydride (0.92 ml) in methylene chloride (13 ml) into 1,4-3,6-dianhydro-5-keto-D-glucitol-2-nitrate (**6b**, pale yellow oil), oxime derivative has mp 121°C. Anal. calc. for $C_6H_8N_2O_6$ (oxime): C, 35.29; H, 3.92; N, 13.73%. Found: C, 35.44. H, 4.20. N, 13.74%. IR (film) υ_{max} : 3380, 2950, 2889, 1772, 1649, 1350, 1280, 959, 847, 765 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 5.54 (dd. J_1 2.5. J_2 4.4, 1H, C2-H), 4.94 (dd, J_1 4.4, J_2 4.6, 1H C^3-H0. 4.45 (d. J 4.6. 1H. C^4-H). 4.21 (d. J 2.5. 2H. C^1H_2). 4.10 (ABq J 17.5. 2H. C^6H_2). ^{13}C NMR (50 MHz. $CDCl_3$) δ : 68.21, 70.22, 78.02, 79.82. 80.92. 209.20.

Baeyer-Villiger rearrangement of 1,4-3,6-dianhydro-keto-D-glucitol esters

(7*R*) 7-*endo*-Nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (4b)

To a solution of 1,4-3,6-dianhydro-2-keto-D-glucitol-5-nitrate (**3b**) (0.462 g, 2.5 mmol) in methylene chloride (4 ml) $NaHCO_3$ (0.01 g) was added. To the cooled and stirred mixture (0°C) 85% *m*-chloroperbenzoic acid (mCPBA) (0.635 g, 3.8 mmol) was added (in several protions) and stirred for 15 min. The course of reaction was monitored by TLC. The mixture was poured into methylene chloride (30 ml) and filtered. The organic solution was washed with 10% aqueous solution of Na_2SO_3 (2 x 5 ml) and water and dried (anh. Na_2SO_4). Solvent was evaporated and crude δ-lactone **4b** was obtained as a sticky crystals, which was purified by dry flash chromatography on silica gel (benzene/ethyl acetate 9 : 1 as eluent) and white crystalline 7-*endo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (**4b**) was obtained (0.41 g, 81%), mp 84°C (from chloroform/carbon tetrachloride mixture) $[\alpha]_D^{21}$ = +74.22° (c 1, AcOEt). Anal. calc. for $C_6H_7NO_7$: C, 35.13; H, 3.41; N, 6.83%. Found: C, 35.20; H, 3.17; N, 6.93%. IR (KBr) υ_{max} : 2953, 2890, 1760, 1640, 1496, 1285, 1088, 1009, 890, 855, 751 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ : 5.87 (d, J 4.4 1H). 5.52 (td. J_1 5.6. J_2 5.8, J_3 7.0, 1H), 4.62 (dd, J_1 4.4, J_2 5.6, 1H), 4.35 (dd, J_1 10.4, J_2 7.0, 1H), 4.27 (ABq J 16.4 2H). 4.16 (dd. J_1 10.4. J_2 5.8 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ : 62.82, 67.42, 70.90, 77.46, 99.25, 165.68.

(7*R*) 7-*endo*-Benzoyloxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (4a)

By use of a previous procedure (described for the preparation of δ-lactone **4b**) 1,4-3,6-dianhydro-2-keto-D-glucitol-5-benzoate (**3a**) (0.35 g, 1.41 mmol) in methylene chloride (2 ml) was treated with mCPBA (85%, 0.39 g, 2.26 mmol) in the presence of $NaHCO_3$ (0.8 g). A crude products was purified by dry flash chromatography (benzene/ethyl acetate 8 : 2) and crystalline (7*R*) 7-*endo*-benzoyloxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (4a) (0.26 g, 70%) was obtained, mp 144°C, $[\alpha]_D^{20}$ = -47.22° (c = 1, AcOEt). Anal. calc. for $C_{13}H_{12}O_6$: C, 59.09; H. 4.58%. Found: C, 59.05; H, 4.64%. IR (KBr) υ_{max} 2953, 2892, 1772, 1718 1278. 1179, 1139, 1122, 1006, 983, 957 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 8.05-7.51 (m. 5H, Ph), 5.82 (d, J 4.2, 1H), 5.56 (dd. J_1 6.2, J_2 6.0 1H), 4.59 (dd, J_1 6.0, J_2 4.2, 1H), 4.43 (dd, J_1 9.8, J_2 6.2, 1H), 4.37 (ABq, J 16.8 2H), 4.31 (dd, J_1 9.8, J_2 6.2, 1H). ^{13}C (50 MHz, $CDCl_3$) δ: 62.79, 70.41, 70.74, 71.10, 99,52, 128.24, 129.65, 133.65, 165.50, 166.19.

(7*S*) 7-*exo*-Acetoxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (7a)

By use of a procedure similar to that described for the preparation of δ-lactone **4b** 1,4-3,6-dianhydro-5-keto-D-glucitol-2-acetate (**6a**) (0.47 g, 2.53 mmol) was converted to δ-lactone 7a by mCPBA (85%, 0.71 g, 4.1 mmol) in the presence of $NaHCO_3$ (1.3 g) in methylene chloride (4 ml) solution. Pure (7*S*) 7-*exo*-acetoxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (**7a**) (0.37 g, 73%) was isolated as a viscous oil which solidify by standing with mp 65°C, $[\alpha]_D^{20}$ = -64.32° (c = 1, AcOEt). MS, *m/z*: 203 (M^+), 145 $(M-58)^+$. IR (film) υ_{max}: 2953, 1725, 1434, 1374, 1239, 1137, 1087, 1010, 988, 940 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 5.89 (d, J 3.8, 1H), 5.25 (d, J 3.8, 1H), 4.41 (d, J 3.8 1H), 4.35 (d, ! 10.7 1H), 4.22 (Abq, J 16.9, 2H), 4.01 (d, J 10.7, 1H), 2.12 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.29, 62.84, 71.32, 76.14, 76.38, 100.50, 165.85, 169.67.

(7*S*) 7-*exo*-Nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (7b)

By use of a procedure described for the preparation of δ-lactone (**4b**) 1,4-3,6-dianhydro-5-keto-D-glucitol-2-nitrate (**6b**) (0.36 g, 1.9 mmol) was oxidized by mCPBA (85%, 0.50 g, 2.9 mmol) in the presence of $NaHCO_3$ (0.67 g) in methylene chloride (5 ml) solution. The crude δ-lactone (**7b**) was purified by dry flash chromatography (benzene/ethyl acetate 9 : 1) and cristalline (7*S*) 7-*exo*-nitrooxy-3-oxo-2,5,9-trioxabicyclo[4.3.0]nonane (**7b**) (0.24 g, 62%) was obtained, mp 115°C, $[\alpha]_D^{22}$ = -31.49° (c = 1, AcOEt). Anal. calc. for $C_6H_7NO_7$: C, 35.13; H, 3.41; N, 6.83%. Found: C, 35.26; H, 3.59; N, 6.93%. IR (KBr) υ_{max} : 2948, 1758, 1648, 1340, 1278, 1082, 958, 840 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 5.91 (d, J 4.1, 1H), 5.45 (d, J 4.2, 1H), 4.49 (d, J 4.0, 1H), 4.43 (dd, J_1 4.2, J_2 11.6, 1H), 4.23 (Abq, J 16.6, 2H), 4.14 (d, J 11.6, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 62.91, 69.46, 76.31, 84.26, 99,94, 165.47.

Hydrolysis of δ-lactones 4b and 7b

(3*R*,4*R*) Methyl (2-acetoxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetaete (10)

A mixture of δ-lactone **4b** (0.12 g, 058 mmol) and potassium carbonate (0.09 g, 0.65 mmol) in dry methanol (2.5 ml) was stirred at r.t. for 10 min. The reaction mixture was cooled to 0°C and treated with saturated aqueous solution of NH_4Cl and several drops of 1N HCl to adjust pH to 6.5. The mixture was then extracted by ethyl acetate (3 x 25 ml) and organic solution was washed with brine and dried (anh. $MgSO_4$). Solvent was evaporated and the residue was purified by chromatography on silica gel column (benzene/ethyl acetate 8 : 2) and methyl (2-hydroxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetate (**9**) (mixture of two isomers) was obtained (0.1 g, 73%) as a colorless oil. IR (film) υ_{max} : 3419, 1753, 1641, 1440, 1352, 1284, 1135, 1090, 1063, 1031, 928, 860 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 5.60 (m, 2H), 4.37 (dd, J_1 6.0, J_2 10.8, 1H), 4.30 (m, 3H), 4.04 (dd, J_1 4.0, J_2 10.8, 1H), 3.77 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ: 52.31, 67.21, 68.68, 83.46, 100.65, 177.22.

Compound **9** (0.20 g, 0.43 mmol), from the previous experiment was dissolved in methylene chloride (2 ml) and acetylated by acetic anhydride (0.55 ml, 0.56 mmol) in the presence of anh. lead diacetate (2 mg). The mixture was stirred at r.t. for 1 h and poured into methylene chloride (35 ml). The mixture was washed by aqueous solution of NaHCO$_3$ (to neutral reaction), with water and dried (anh. Na$_2$SO$_4$). Solvent was evaporated to give the crude product which was purified by dry flash chromatography (benzene/ethyl acetate 9 : 1). *(3R, 4R)* Methyl (2-acetoxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetate (**10**) was obtained (0.09 g, 73%) as a colorless oil. IR (film) υ_{max} : 2959, 1750 (b), 1647, 1432, 1375, 1285, 1229, 1130, 1018, 950 cm^{-1}. Anal. calc. for $C_9H_{13}NO_9$: C, 38.71; H, 4.66: N, 5.01%. Found: C, 38.55; H, 4.73; N, 5.14%. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 6.20 (d, J 1.6, 1H), 5.59 (td, J_1 2, J_2 3.8, J_3 6.0, 1H), 4.41 (dd, J_1 1.6, J_2 2.0, 1H), 4.36 (dd, J_1 6.1, J_2 10.8, 1H), 4.21 (s, 2H), 4.15 (dd, J_1 3.8), J_2 10.8, 1H), 3.78 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ : 21.03, 52.15, 67.50, 69.87, 84.58, 85.60, 99.69, 169.80.

(3*R*,4*S*) Methyl (2-acetoxy-4-nitrooxytetrahydrifuran-3-yloxy)-acetate (12)

To a solution of δ-lactone **7b** (0.12 g, 0.59 mmol) in THF (2 ml) and methanol (1.5 ml) a solution of potassium carbonate (0.12 g, 0.87 mmol) in water (0.6 ml) was added. The mixture was stirred at r.t. and reaction was completed for 10 min. (monitored by TLC). The reaction mixture was cooled (0°C) and acidified by 1N HCl to pH 6.5, then extracted by THF (2 x 10 ml) and dried (anh., MgSO$_4$). Solvent was evaporated and residual viscous oil dissolved in THF (2.5 ml) and to the cooled solution ethereal solution of diazomethane (~40 mg) was added and the resulting solution stirred at ice bath for 20 min. THF was removed by evaporation and the residual oil (0.12 g) was dissolved in pyridine (3 ml) acetylated by acetic anhydride (0.055 ml). The resulting mixture was stirred at r.t. for 2 h (monitored by TLC). The reaction mixture was dissolved in ethyl acetate (30 ml), washed by saturated solution of NaHCO$_3$ (2 x 5 ml) and dried (anh. MgSO$_4$) Solvent was evaporated and 0.13 g of oily residue was obtained and purified by dry flash chromatography (benzene/ethyl acetate 8 : 2), to give *(3R, 4S)* methyl (2-acetoxy-4-nitrooxytetrahydrofuran-3-yloxy)-acetate (**12**) (0.11 g, 67%) as a colorless oil (mixture of two isomers). Anal. calc. for $C_9H_{13}NO_9$: C, 38.71; H, 4.66; N, 5.01%. Found: C, 38.60; H, 4.82; N, 5.21% IR (film) υ_{max} : 2959, 1756 (b), 1646, 1439, 1376, 1284, 1229, 1135, 1018, 949, 856 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$) δ: 6.40, (d, J 4.6, 0.25H), 6.23 (d, J 2.0, 0.75H), 5.49 (dd, J_1 6.2, J_2 3.6, 1H), 4.56 (dd, J_1 6.2, J_2 11.0, 1H) 4.31 (d, J 2.0 0.75H), 4.24 (d, J 4.6, 0.25H), 4.21 (s, 2H), 4.11 (dd, J_1 3.6, J_2 11.0, 1H), 3.79 (s, 2.25H), 3.76 (s, 0.75H), 2.15 (s, 0.75H), 2.10 (s, 2.25H). ^{13}C NMR (50 MHz, CDCl$_3$) δ: 20.99, 52.15, 67.49, 68.64, 69.86, 84.50, 85.59, 99.69, 169.80. MS : 280 (M+1).

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13 High coupling constants for geminal hydrogens on C_4 in all of δ-lactones **4** and **7** (ABq J = 16.4 - 16.9 Hz) indicates that C=O group is in bisected orientation with geminal hydrogens on adjacent carbon, which is possible when δ-lactone ring is in flexible boat conformation.

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