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1,3-Dipolar Cycloaddition of 4-Methoxybenzonitriloxide to α,β-Unsaturated Esters of α-*D*-*xylo*-Pentadialdo-1,4-Furanose Series

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Abstract

Regio- and diastereoselectivity of 1,3-dipolar cycloaddition of 4-methoxybenzonitriloxide to α,β-unsaturated esters of α-*D*-*xylo*-pentadialdo-1,4-furanose depending on the geometry of the double bond and the method of generation of nitriloxide is studied.

Key words: 1,3-dipolar cycloaddition, nitriloxides, α,β-unsaturated esters, regioselectivity, asymmetric induction, diastereoselectivity

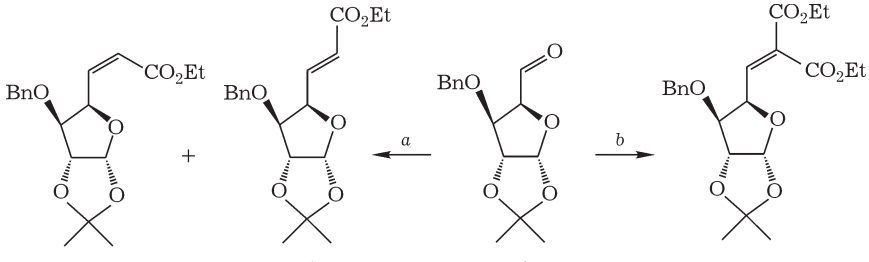
INTRODUCTION

1,3-Dipolar cycloaddition of nitriloxides to alkenes is a simple and convenient way to synthesize 4,5-dihydroisoxazoles [1-3] which are synthetic precursors of a large number of biologically active substances [4, 5], including glycosylated 1,3-amino alcohols possessing high antituberculosis activity against *M. Tuberculosis* H37Rv and *M. Tuberculosis* H37Ra strains [6].

RESULTS AND DISCUSSION

In order to develop an efficient method to synthesize optically active 1,3-amino alcohols, which are structural analogs of known antituberculosis agents [7], we tested region- and diastereoselectivity of two versions of the nitriloxide approach to obtaining the corresponding 4,5-dihydroisoxasols from α,β-unsaturated esters of α-*D*-*xylo*-pentadialdo-1,4-furanose series under the conditions of modelling the geometry of the double bond and the degree of its substitution.

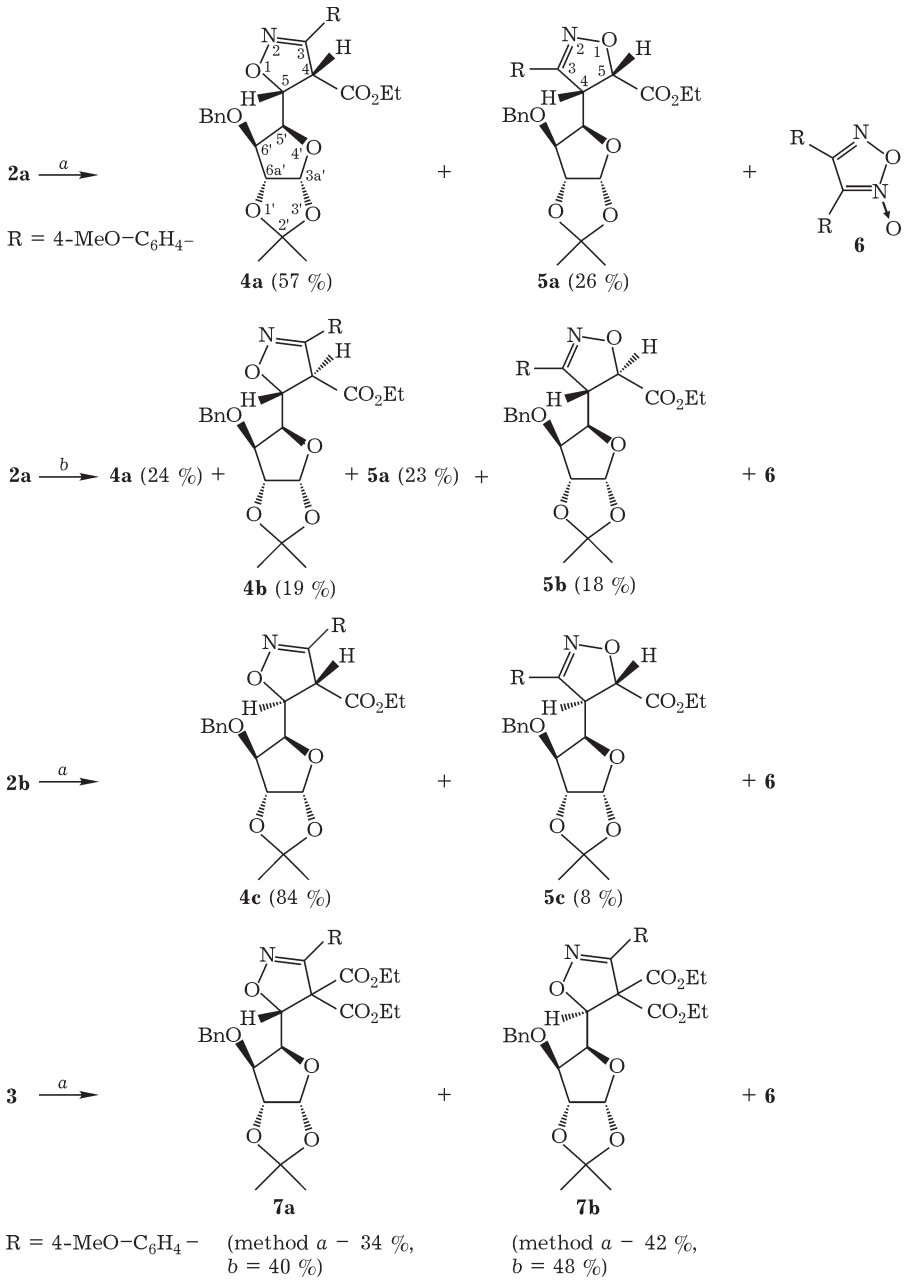
Initial Z-ester **2a** and E-ester **2b** were obtained through the reaction of 3-O-benzyl-1,2-O-isopropylidene-α-*D*-*xylo*-pentadialdo-1,4-furanose **1** [8] with carbethoxymethylidenetriphenylphosphorane and separated by means of column chromatography on SiO_2. The synthesis of malonate **3** was carried out under the



2a (67 %) **2b** (13 %) **1** **3** (89 %)

Reagents and conditions: *a*. $Ph_3PCHCOOEt$, THF; *b*. $CH(CO_2Et)_2$, Py, $TiCl_4$, THF.

Scheme 1.



Reagents and conditions: *a*. MeO−C_6H_4−CHNOH, chloramine B, TEA, EtOH; *b*. MeO−C_6H_4−CHNOH, aqueous solution 0.8 M NaOCl, ultrasonic dispersing, CH_2Cl_2, 5 °C.

Scheme 2.

conditions of Knoevenagel reaction in the modification proposed by Lehnert [9] (Scheme 1).

It was established previously [10] that the method of nitriloxide generation can have a substantial effect on the total yield of reaction products, so 4-methoxybenzonitriloxide was generated *in situ* from a mixture of *syn*- and *anti*-anisaldehyde oxime using two methods: the action of chloramine B in ethanol (method *a*) [11] and the aqueous solution of 0.8 M NaOCl in CH_2Cl_2 at 5 °C under the ultrasonic treatment of the reaction mixture (method *b*) [12]. The results of 1,3-dipolar cycloaddition of 4-methoxybenzonitriloxide to esters **2a, b** and **3** are shown in Scheme 2.

Comparison between the methods of nitriloxide generation showed that for Z-ester **2a** the regioselectivity of 1,3-dipolar cycloaddition is

not high: in the case of method *a* the ratio of regioisomers **4a** : **5a** is 3 : 2, while in the case of method *b* it is 1 : 1. Under the conditions of the first method, the formation of products **4a** and **5a** occurs diastereospecifically, while in the case of method *b* the formation of diastereomeric pairs of each regioisomer takes place. This fact is most likely due to epimerization of asymmetric centres C^4 (for **4a**) and C^5 (for **5a**) due to enolization of carbethoxy group under the reaction conditions (pH 11).

The interaction of 4-methoxybenzonitriloxide with E-ester **2b** was carried out only according to method *a* to avoid the indicated side effects. The change of the geometry of the double bond caused a sharp increase of regioselectivity: the ratio between 4,5-dihydroisoxazols **4c** : **5c** was 11 : 1. Diastereospecific formation of compounds **4c** and **5c** (similarly to the case of Z-ester **2a**) should be stressed.

The consequence of the introduction of an additional carbethoxy group into conjugated ester (malonate **3**) is that 1,3-dipolar cycloaddition becomes regiospecific with low diastereoselectivity: the ratio of products **7a** : **7b** in each case (methods *a* and *b*) is 12 : 1.

To confirm the structure of compounds **4a–c**, **5a–c**, **7a**,**b** and configurations of new asymmetric centres C^4 and C^5, we used ^1H and ^{13}C NMR and quantum chemical calculations.

Spectroscopic criteria for establishing stereo- and regio-isomerism of dihydroisoxazol ring in diastereomeric products of *syn*- and *anti*-addition were chemical shifts, spin-spin interaction constants $^3J_{HH}$, $^{1-3}J_{CH}$, as well as the qualitative estimation of nuclear Overhauser effect (NOE) values for the whole series of derivatives.

With the help of theoretical calculations, we determined the geometric parameters of diastereomeric dihydroisoxazols **4a–c** and **5a–c**. Optimization of the geometric parameters of compounds under investigation was carried out using the methods taking into account electron correlations: in approximation RB3LYP/6-311G(*d*, *p*). Comparison of experimental and theoretical (method CSGT in MPW1PW91/6-311+G(*2d*, *p*)) values of δ_H and δ_C provides evidence that they coincide almost completely: the correlation coefficient is 0.994–0.998. Generalization of the results of theoretical calculations points to the fact that conformational state of dihydroisoxazol cycle approaches the plane (Fig. 1), which agrees with literature data [13].

So, the range of vicinal spin-spin constants between protons H^4 and H^5 is characteristic and can serve as the criterion of *cis*/*trans* position of H^4 and H^5.

Orientation of protons in position 5 (for **4a–c**, **7a**,**b**) and position 4 (for **5a–c**) was determined by comparing the corresponding spin-spin interaction constants (SSIC) $J_{5-5'}$ and $J_{4-5'}$ with literature data [14]. On the basis of calculation data about the spatial structure of 4,5-dihydroisoxazol cycle and SSIC $J_{5-5'}$ and $J_{4-5'}$ equal to 9.8 Hz, dihydroisoxazols **4a** and **5a** were related to the products of *syn*-addition (the conformational state with dihedral angles between the vicinal protons H^4 and H^5 close to zero), while dihydroisoxazols **4b**,**c** and **5b**,**c** were related to the products of *anti*-addition (SSIC 4.8–6.9 Hz).

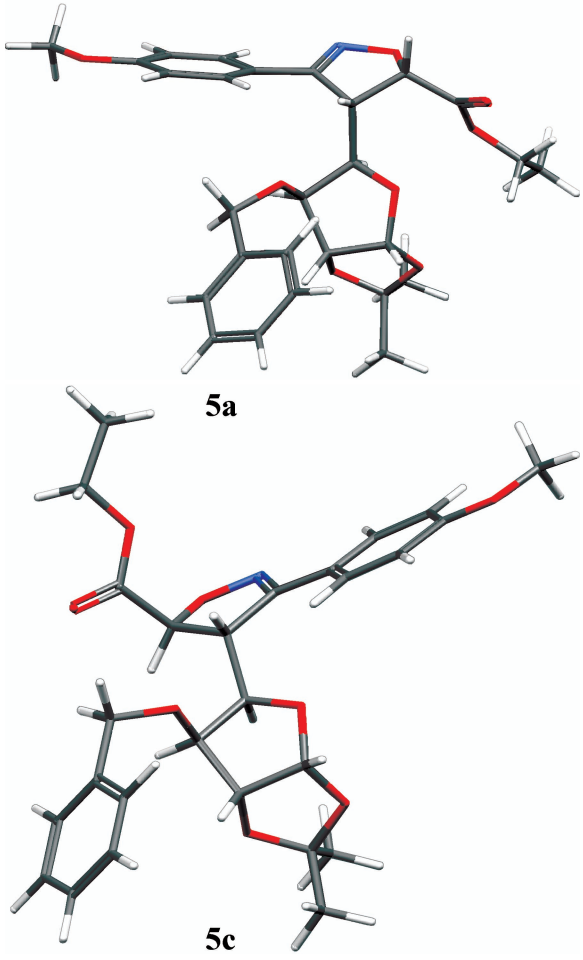


Fig. 1. Spatial structure of compounds **5a** and **5c** according to quantum chemical calculations in the approximation RB3LYP/6-311G(*d*, *p*).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with Bruker AM-300 with working frequencies 300.13 and 75.47 MHz, respectively, with TMS as internal standard. The angles of optical rotation were measured on a Perkin -Elmer 341 polarimeter ($\lambda = 589$ nm) at 20 °C in chloroform. Ultrasonic treatment of the reaction mixture was carried out with the ultrasonic dispersant UZDN-2T (44 kHz, 400 W) with submersible transmitter equipped with a conical head. Identity and purity of the synthesized compounds were tested by means of TLC on Sorbfil PTSKh-AF-V plates, column chromatography was carried out using silica gel (50–100 mesh) (Sorbpolimer Co.). Aldehyde **I** was obtained according to the procedure described in [15], a mixture of *syn*- and *anti*-oxime of anisaldehyde according to the data reported in [16]. Physicochemical constants of 3,4-bis(4-methoxyphenyl)furoxane **6** corresponded to literature data [17].

Ethyl ester of Z-(*3a′R,5′R,6′S,6a′R*)-3-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-2-propenic acid (2a) and ethyl ester of E-(*3a′R,5′R,6′S,6a′R*-3-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-2-propenic acid (2b). To the solution of 2.30 g (8.30 mmol) of aldehyde **1** in 20 mL of THF, we added 2.90 g (8.30 mmol) of (carbethoxymethylene)triphenylphosphorane and mixed at 20 °C. After the reaction was complete (controlled by means of TLC), the reaction mixture was concentrated, the residue was separated using chromatography on SiO_2 (hexane/ethylacetate = 20 : 1). Thus we isolated 1.94 g of Z-isomer **2a** and 0.38 g of E-isomer **2b** with the total yield of 80 %.

Compound **2a**: found, %: C 65.66, H 6.87. $C_{19}H_{24}O_6$. Calculated, %: C 65.50, H 6.94. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.23 t (3H, CH_3, ^3J = 7.1), 1.3 s (3H, CH_3), 1.5 s (3H, CH_3), 4.08 q (2H, CH_2, ^3J = 7.1), 4.27 dd (1H, C$^{6'}$H, ^3J = 2.7, ^3J = 3.2), 4.43 d (1H, CH_2, ^2J = 12.0), 4.58 d (1H, CH_2, ^2J = 12.0), 4.62 dd (1H, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.5), 5.61 dd (1H, C$^{5'}$H, ^3J = 6.7, ^3J = 3.2), 5.9 d (1H, C^{2}H, ^3J = 11.7), 6.0 d (1H, C$^{3a'}$H, ^3J = 3.5), 6.38 dd (1H, C^{3}H, ^3J = 6.7, ^3J = 11.7), 7.18–7.38 m (5H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.04 (CH_3), 26.26 (CH_3), 26.74 (CH_3), 60.20 (CH_2), 71.35 (CH_2), 78.02 (C$^{5'}$H), 82.93 (C$^{6'}$H), 83.60 (C$^{6a'}$H), 105.01 (C$^{3a'}$H), 111.57 (C$^{2'}$), 121.00 (C^{2}H), 127.60 (2CH, Ar), 127.70 (CH, Ar), 128.22 (2CH, Ar), 137.35 (C, Ar), 145.13 (C^{3}H), 165.31 ($\underline{C}^1OOC_2H_5$).

Compound **2b**: found, %: C 65.71, H 6.99. $C_{19}H_{24}O_6$. Calculated, %: C 65.50, H 6.94.

^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.30 t (3H, CH_3, ^3J = 7.3), 1.33 s (3H, CH_3), 1.50 s (3H, CH_3), 3.96 dd (1H$_e$, C$^{6'}$H, ^3J = 2.7, ^3J = 3.2), 4.22 q (2H, CH_2, ^3J = 7.3), 4.50 d (1H, CH_2, ^2J = 12.0), 4.63 d (1H, CH_2, ^2J = 12.0), 4.65 dd (1H$_a$, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.1), 4.80 dd (1H, C$^{5'}$H, ^3J = 5.0, ^3J = 3.2), 6.0 d (1H$_e$, C$^{3a'}$H, ^3J = 3.1), 6.16 d (1H, C^{2}H, ^3J = 15.7), 6.97 dd (1H, C^{3}H, ^3J = 5.0, ^3J = 15.7), 7.2–7.4 m (5H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.21 (CH_3), 26.21 (CH_3), 26.81 (CH_3), 60.44 (CH_2), 72.25 (CH_2), 79.49 (C$^{5'}$H), 82.82 (C$^{6'}$H), 82.95 (C$^{6a'}$H), 105.03 (C$^{3a'}$H), 111.93 (C$^{2'}$), 123.32 (C^{2}H), 127.79 (2CH, Ar), 128.05 (CH, Ar), 128.52 (2CH, Ar), 137.12 (C, Ar), 141.41 (C^{3}H), 166.01 ($\underline{C}^1OOC_2H_5$).

Diethyl ester of (*3a′R,5′R,6′S,6a′R*)-2{[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]methylene}malonic acid (3). To 100 mL of THF in the atmosphere of argon at a temperature of −5 °C and under vigorous agitation, we added 4.43 mL of $TiCl_4$ in 10 mL of CCl_4. Avoiding temperature rise above 0 °C, the solution of 5.56 g (0.02 mol) of aldehyde **1** and 3.05 mL (0.02 mol) of malonic ester in 45 mL of THF were added and mixed for 15 min. Then the solution of 6.49 mL of pyridine in 20 mL of THF was added. The reaction mixture was agitated for 48 h at 20 °C, then it was diluted with 50 mL of H_2O and extracted with Et_2O (3 × 50 mL). The organic layers were brought together, washed with the saturated solution of NaCl (3 × 50 mL), and dried with $MgSO_4$. Then the mixture was concentrated; the residue was separated by chromatography on SiO_2 (hexane/ethyl acetate = 5 : 1); the product was 7.48 g of compound **3** with the yield of 89 %.

Compound **3**: found, %: C 62.70, H 6.93. $C_{19}H_{28}O_9$. Calculated, %: C 62.85, H 6.71. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.25 t (6H, $2CH_3$, ^3J = 7.0), 1.30 s (3H, CH_3), 1.40 s (3H, CH_3), 4.20 q (4H, $2CH_2$, ^3J = 7.0), 4.25 dd (1H, C$^{6'}$H, ^3J = 2.7, ^3J = 3.3), 4.45 d (1H, CH_2, ^2J = 11.9), 4.58 d (1H, CH_2, ^2J = 11.9), 4.6 dd

(1H, $C^{6a'}H$, ^3J = 2.7, ^3J = 3.4), 5.05 dd (1H, $C^{5'}H$, ^3J = 7.0, ^3J = 3.3), 5.95 d (1H, $C^{3a'}H$, ^3J = 3.4), 7.05 d (1H, C^1H, ^3J = 7.0), 7.18–7.33 m (5H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.82 ($2CH_3$), 26.02 (CH_3), 26.51 (CH_3), 61.25 ($2CH_2$), 72.18 (CH_2), 77.56 ($C^{5'}H$), 82.70 ($C^{6'}H$), 84.12 ($C^{6a'}H$), 105.23 ($C^{3a'}H$), 111.69 ($C^{2'}$), 127.72 (2CH, Ar), 127.69 (CH, Ar), 128.19 (2CH, Ar), 128.92 (C^2, Ar), 136.95 (C), 144.94 (C^1H), 163.13 ($\underline{C}^3OOC_2H_5$), 163.91 ($\underline{C}^{1a}OOC_2H_5$).

*Interaction of esters **2a,b** and **3** with 4-methoxybenzonitriloxide*

Method *a*. To the solution of 0.08 g (0.53 mmol) of a mixture of *syn*- and *anti*-oxime of anisaldehyde, 0.18 g (0.53 mmol) of ester **2a** and 0.14 g (0.64 mmol) of chloramine B in 6 mL of EtOH under mixing, we added 0.5 mL of TEA. After the reaction was complete (monitored with TLC), the reaction mixture was concentrated and separated by chromatography on SiO_2 (hexane/ethyl acetate = 20 : 1). The resulting products were 0.15 g of isoxazol **4a** and 0.07 g of isoxazol **5a** with the yields 57 and 26 %, respectively, and 0.04 g of furoxane **6**.

Method *b*. A solution of 0.17 g (0.50 mmol) of ester **2a** in 10 mL of CH_2Cl_2 was poured into a reactor with submersible ultrasonic probe. Then 2.2 mL of the 0.8 M NaOCl aqueous solution was added at once. The reaction mixture was treated with ultrasound; a solution of 0.23 g (1.50 mmol) of a mixture of *syn*- and *anti*-oxime of anisaldehyde in 15 mL of CH_2Cl_2 was slowly added drop by drop; reaction temperature was maintained at about 5 °C. After the reaction was over (monitored with the help of TLC), the aqueous layer was separated, extracted with methylene chloride (5 × 10 mL). The organic layers were brought together and dried with $MgSO_4$, then concentrated and separated by means of chromatography on SiO_2 (hexane/ethyl acetate = 20 : 1). Thus we isolated 0.06 g of isoxazol **4a**, 0.05 g **4b**, 0.06 g **5a** and 0.04 g **5b** with the yields 24, 19, 23 and 18 %, respectively, and 0.20 g of furoxane **6**.

Ethyl ester of (*4S,5R,3a′R,5′S,6′S,6a′R*)-5-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-4-isoxazolcarboxylic acid **(4a)**. $[\alpha]_D^{20}$ −56.25°. Found, %: C 65.24, H 6.56, N 2.70. $C_{27}H_{31}NO_8$. Calculated, %: C 65.18, H 6.28, N 2.82. ^1H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.23 t (3H, CH_3, ^3J = 7.0), 1.30 s (3H, CH_3), 1.45 s (3H, CH_3), 3.80 s (3H, OCH_3), 4.17 dd (1H, $C^{6'}H$, ^3J = 2.8, ^3J = 3.2), 4.25 q (2H, CH_2, ^3J = 7.0), 4.57 dd (1H, $C^{5'}H$, ^3J = 9.8, ^3J = 3.2), 4.58 dd (1H, $C^{6a'}H$, ^3J = 2.8, ^3J = 3.5), 4.59 d (1H, C^4H, ^3J = 9.8), 4.68 d (1H, CH_2, ^2J = 11.6), 4.76 d (1H, CH_2, ^2J = 11.6), 5.18 t (1H, C^5H, ^3J = 9.8), 5.90 d (1H, $C^{3a'}H$, ^3J = 3.5), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.90 (CH_3), 26.45 (CH_3), 26.77 (CH_3), 55.26 (OCH_3), 56.21 (C^4H), 61.00 (CH_2), 72.76 (CH_2), 77.43 ($C^{5'}H$), 79.39 ($C^{6'}H$), 81.79 ($C^{6a'}H$), 82.71 (C^5H), 105.30 ($C^{3a'}H$), 112.12 ($C^{2'}$), 114.22 (2CH, Ar), 120.86 (C, Ar), 127.69 (2CH, Ar), 127.89 (CH, Ar), 128.23 (2CH, Ar), 128.41 (2CH, Ar), 137.48 (C, Ar), 155.04 (C^3=N), 161.23 (C, Ar), 167.93 ($\underline{C}OOC_2H_5$).

Ethyl ester of (*4R,5R,3a′R,5′S,6′S,6a′R*)-5-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-4-isoxazolcarboxylic acid (4b). $[\alpha]_D^{20}$ +159.1°. Found, %: C 65.34, H 6.41, N 2.97. $C_{27}H_{31}NO_8$. Calculated, %: C 65.18, H 6.28, N 2.82. ^1H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.01 t (3H, CH_3, ^3J = 7.0), 1.27 s (3H, CH_3), 1.39 s (3H, CH_3), 3.80 s (3H, OCH_3), 3.90 dd (H, $C^{6'}H$, ^3J = 3.2, ^3J = 2.7), 4.05 d (1H, C^4H, ^3J = 4.9), 4.14 q (2H, CH_2, ^3J = 7.0), 4.22 d (1H, CH_2, ^2J = 11.6), 4.27 d (1H, CH_2, ^2J = 11.6), 4.43 dd (1H, $C^{5'}H$, ^3J = 9.0, ^3J = 3.2), 4.51 dd (1H, $C^{6a'}H$, ^3J = 2.7, ^3J = 3.5), 4.68 dd (1H, C^5H, ^3J = 9.0, ^3J = 4.9), 5.84 d (1H, $C^{3a'}H$, ^3J = 3.5), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.69 (CH_3), 26.52 (CH_3), 26.80 (CH_3), 55.55 (OCH_3), 63.69 (C^4H), 60.92 (CH_2), 72.58 (CH_2), 77.20 ($2C^{5',6'}H$), 81.44 ($C^{6a'}H$), 83.28 (C^5H), 105.03 ($C^{3a'}H$), 111.57 ($C^{2'}$), 114.06 (2CH, Ar), 126.91 (C, Ar), 127.37 (2CH, Ar), 127.66 (CH, Ar), 128.38 (2CH, Ar), 129.48 (2CH, Ar), 137.02 (C, Ar), 157.03 (C^3=N), 161.77 (C, Ar), 167.15 ($\underline{C}OOC_2H_5$).

Ethyl ester of (*4S,5S,3a′R,5′S,6′S,6a′R*)-5-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxazol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-4-isoxazolcarboxylic acid (4c). $[\alpha]_D^{20}$ −79.2°. Found, %: C 65.44, H 6.99, N 2.81. $C_{27}H_{31}NO_8$. Calculated, %: C 65.18, H 6.28, N 2.82. ^1H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.15 t (3H, CH_3, ^3J = 7.0), 1.26 s (3H, CH_3), 1.31 s (3H, CH_3), 3.83 s (3H, OCH_3), 4.17 dd

(H, C$^{6'}$H, ^3J = 3.2, ^3J = 2.7), 4.12 q (2H, CH_2, ^3J = 7.0), 4.35 dd (1H, C$^{5'}$H, ^3J = 7.2, ^3J = 3.2), 4.62 dd (1H, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.7), 4.64 d (1H, CH_2, ^2J = 11.6), 4.67 d (1H, C^{4}H, ^3J = 5.3), 4.70 d (1H, CH_2, ^2J = 11.6), 5.35 dd (1H, C^{5}H, ^3J = 7.2, ^3J = 5.3), 5.96 d (1H, C$^{3a'}$H, ^3J = 3.7), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.93 (CH_3), 26.21 (CH_3), 26.83 (CH_3), 55.32 (OCH_3), 56.40 (C^{4}H), 61.80 (CH_2), 72.52 (CH_2), 79.74 (C$^{5'}$H), 81.50 (C$^{6'}$H), 82.23 (C$^{6a'}$H), 82.63 (C^{5}H), 105.35 (C$^{3a'}$H), 112.06 (C$^{2'}$), 114.20 (2CH, Ar), 120.87 (C, Ar), 127.97 (2CH, Ar), 128.56 (CH, Ar), 128.56 (2CH, Ar), 128.93 (2CH, Ar), 137.21 (C, Ar), 154.03 (C^3=N), 161.26 (C, Ar), 169.30 (C$\underline{O}$OC_2H_5).

Ethyl ester of (*4S,5S,3a′R,5′R,6′S,6a′R*)-4-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolcarboxylic acid (5a). $[\alpha]_D^{20}$ −34.2°. Found, %: C 65.34, H 6.51, N 2.97. $C_{27}H_{31}NO_8$. Calculated, %: C 65.18, H 6.28, N 2.82. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.20 t (3H, CH_3, ^3J = 7.0), 1.30 s (3H, CH_3), 1.45 s (3H, CH_3), 3.83 s (3H, OCH_3), 4.06 dd (H, C$^{6'}$H, ^3J = 3.2, ^3J = 2.7), 4.12 q (2H, CH_2, ^3J = 7.0), 4.22 d (1H, C^{5}H, ^3J = 9.8), 4.26 dd (1H, C$^{5'}$H, ^3J = 9.6, ^3J = 3.2), 4.58 d (1H, CH_2, ^2J = 11.6), 4.67 dd (1H, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.6), 4.73 d (1H, CH_2, ^2J = 11.6), 4.93 dd (1H, C^{4}H, ^3J = 9.8, ^3J = 9.6), 6.04 d (1H, C$^{3a'}$H, ^3J = 3.6), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 14.00 (CH_3), 26.42 (CH_3), 26.91 (CH_3), 55.01 (OCH_3), 55.28 (C^{4}H), 61.89 (CH_2), 72.17 (CH_2), 79.36 (C$^{5'}$H), 82.05 (C$^{6'}$H), 82.69 (C$^{6a'}$H), 83.27 (C^{5}H), 105.45 (C$^{3a'}$H), 112.00 (C$^{2'}$), 114.17 (2CH, Ar), 120.96 (C, Ar), 127.74 (2CH, Ar), 128.09 (CH, Ar), 128.27 (2CH, Ar), 128.58 (2CH, Ar), 137.19 (C, Ar), 155.72 (C^3=N), 161.27 (C, Ar), 168.12 (C$\underline{O}$OC_2H_5).

Ethyl ester of (*4S,5R,3a′R,5′R6′S,6a′R*)-4-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-*d*][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolcarboxylic acid (5b). $[\alpha]_D^{20}$ −169.5°. Found, %: C 65.23, H 6.11, N 2.59. $C_{27}H_{31}NO_8$. Calculated, %: C 65.23, H 6.11, N 2.59. $C_{27}H_{31}NO_8$. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.90 t (3H, CH_3, ^3J = 7.0), 1.30 s (3H, CH_3), 1.45 s (3H, CH_3), 3.84 s (3H, OCH_3), 3.88 dd (H, C$^{6'}$H, ^3J = 3.2, ^3J = 2.7), 4.12 q (2H, CH_2, ^3J = 7.0), 4.43 dd (1H, C$^{5'}$H, ^3J = 8.0, ^3J = 3.2), 4.48 d (1H, CH_2, ^2J = 11.6), 4.50 dd (1H, C^{4}H, ^3J = 8.0, ^3J = 4.8), 4.54 d (1H, C^{5}H, ^3J = 4.8), 4.55 dd (1H, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.5), 4.65 d (1H, CH_2, ^2J = 11.6), 5.90 d (1H, C$^{3a'}$H, ^3J = 3.5), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.67 (CH_3), 26.32 (CH_3), 26.74 (CH_3), 55.25 (OCH_3), 60.98 (CH_2), 62.49 (C^{4}H), 71.99 (CH_2), 78.74 (C$^{5'}$H), 80.80 (C$^{6'}$H), 81.53 (C$^{6a'}$H), 82.46 (C^{5}H), 105.40 (C$^{3a'}$H), 111.94 (C$^{2'}$), 114.08 (2CH, Ar), 126.90 (C, Ar), 127.68 (2CH, Ar), 127.97 (CH, Ar), 128.28 (2CH, Ar), 129.59 (2CH, Ar), 136.79 (C, Ar), 157.24 (C^3=N), 161.79 (C, Ar), 167.16 (C$\underline{O}$OC_2H_5).

Ethyl ester of (*4R,5S,3a′R,5′R,6′S,6a′R*)-4-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-d][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolcarboxylic acid (5c). $[\alpha]_D^{20}$ −116.7°. Found, %: C 65.23, H 6.34, N 2.98. $C_{27}H_{31}NO_8$. Calculated, %: C 65.18, H 6.28, N 2.82. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.05 t (3H, CH_3, ^3J = 7.0), 1.28 s (3H, CH_3), 1.33 s (3H, CH_3), 3.83 s (3H, OCH_3), 3.95 dd (H, C$^{6'}$H, ^3J = 3.2, ^3J = 2.7), 4.13 q (2H, CH_2, ^3J = 7.0), 4.37 d (1H, CH_2, ^2J = 11.8), 4.43 dd (1H, C$^{5'}$H, ^3J = 6.9, ^3J = 3.2), 4.45 d (1H, CH_2, ^2J = 11.8), 4.65 d (1H, C^{5}H, ^3J = 6.9), 4.66 dd (1H, C$^{6a'}$H, ^3J = 3.7, ^3J = 2.7), 5.31 t (1H, C^{4}H, ^3J = 6.9), 6.04 d (1H, C$^{3a'}$H, ^3J = 3.7), 6.90–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.69 (CH_3), 26.09 (CH_3), 26.60 (CH_3), 50.40 (C^{4}H), 56.58 (OCH_3), 61.56 (CH_2), 71.68 (CH_2), 77.23 (C$^{5'}$H), 80.42 (C$^{6'}$H), 81.49 (C$^{6a'}$H), 83.85 (C^{5}H), 105.57 (C$^{3a'}$H), 112.21 (C$^{2'}$), 114.03 (2CH, Ar), 120.39 (C, Ar), 127.84 (2CH, Ar), 128.40 (CH, Ar), 128.79 (2CH, Ar), 128.90 (2CH, Ar), 136.83 (C, Ar), 156.05 (C^3=N), 160.97 (C, Ar), 169.74 (C$\underline{O}$OC_2H_5).

Diethyl ester of (*5R,3a′R,5′S,6′S,6a′R*)-5-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-d][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,4(5H)-isoxazoldicarboxylic acid (7a). $[\alpha]_D^{20}$ −63.0°. Found, %: C 63.44, H 6.21, N 2.52. $C_{30}H_{35}NO_{10}$. Calculated, %: C 63.26, H 6.19, N 2.46. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 1.15 t (3H, CH_3, ^3J = 7.0), 1.20 t (3H, CH_3, ^3J = 7.0), 1.30 s (3H, CH_3), 1.40 s (3H, CH_3), 3.80 s (3H, OCH_3), 4.15 q (2H, CH_2, ^3J = 7.0), 4.17 dd (1H, C$^{6'}$H, ^3J = 2.7, ^3J = 3.4), 4.32 dd (1H, C$^{5'}$H, ^3J = 10.1, ^3J = 3.4), 4.36 q (2H, CH_2, ^3J = 7.0), 4.40 dd (1H, C$^{6a'}$H, ^3J = 2.7, ^3J = 3.5), 4.74 d (1H, CH_2, ^2J = 11.6), 4.82 d (1H, CH_2, ^2J = 11.6), 5.86 d (1H, C^{5}H, ^3J = 10.1), 5.93 d (1H, C$^{3a'}$H,

^3J = 3.5), 6.80–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.48 (CH_3), 13.68 (CH_3), 26.25 (CH_3), 26.68 (CH_3), 62.79 (CH_2), 62.90 (CH_2), 72.23 (C^4), 72.70 (CH_2), 76.19 ($C^{5'}H$), 82.03 ($C^{6'}H$), 82.26 ($C^{6a'}H$), 84.30 (C^5H), 105.51 ($C^{3a'}H$), 111.84 ($C^{2'}$), 113.43 (2CH, Ar), 120.65 (C, Ar), 127.67 (2CH, Ar), 128.36 (CH, Ar), 128.71 (2CH, Ar), 129.66 (2CH, Ar), 137.52 (C, Ar), 154.18 (C^3=N), 160.83 (C, Ar), 166.14 ($\underline{C}OOC_2H_5$), 165.39 ($\underline{C}OOC_2H_5$).

Diethyl ester of (*5S,3a′R,5′S,6′S,6a′R*)-5-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofura[2,3-d][1′,3′]dioxol-5′-yl]-3-(4-methoxyphenyl)-4,4(5H)-isoxazoldicarboxylic acid (7b). $[\alpha]_D^{20}$ +71.2°. Found, %: C 63.34, H 6.23, N 2.50. $C_{30}H_{35}NO_{10}$. Calculated, %: C 63.26, H 6.19, N 2.46. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, *J*, Hz): 0.80 t (3H, CH_3, ^3J = 7.0), 1.20 t (3H, CH_3, ^3J = 7.0), 1.30 s (3H, CH_3), 1.50 s (3H, CH_3), 3.80 s (3H, OCH_3), 3.55 dd (1H, $C^{5'}H$, ^3J = 7.1, ^3J = 3.4), 3.86 dd (1H, $C^{6'}H$, ^3J = 2.7, ^3J = 3.4), 4.28 q (4H, $2CH_2$, ^3J = 7.0), 4.54 d (1H, CH_2, ^2J = 11.8), 4.69 dd (1H, $C^{6a'}H$, ^3J = 2.7, ^3J = 3.6), 4.70 d (1H, CH_2, ^2J = 11.8), 5.48 d (1H, C^5H, ^3J = 7.1), 6.03 d (1H, $C^{3a'}H$, ^3J = 3.6), 6.80–8.10 m (9H, Ar). ^{13}C NMR ($CDCl_3$, δ, ppm): 13.37 (CH_3), 13.77 (CH_3), 26.60 (CH_3), 27.10 (CH_3), 62.56 (CH_2), 62.67 (CH_2), 70.44 (C^4), 71.34 (CH_2), 78.82 ($C^{5'}H$), 82.69 ($C^{6'}H$), 83.10 ($C^{6a'}H$), 87.60 (C^5H), 105.28 ($C^{3a'}H$), 112.30 ($C^{2'}$), 113.60 (2CH, Ar), 120.76 (C, Ar), 127.09 (2CH, Ar), 127.66 (CH, Ar), 128.30 (2CH, Ar), 129.10 (2CH, Ar), 137.45 (C, Ar), 155.07 (C^3=N), 160.88 (C, Ar), 165.50 ($\underline{C}OOC_2H_5$), 166.16 ($\underline{C}OOC_2H_5$).

CONCLUSION

New glycosylated 4,5-dihydroisoxazols of the series of α-*D*-xylopentadialdo-1,4-furanose were synthesized. These compounds are synthetic precursors of the corresponding 1,3-aminoalcohols which are the representatives of the structural group of highly active anti-tuberculosis agents. For each of diastereomeric 4,5-dihydroisoxazols isolated in the individual form, a number of physicochemical characteristics were determined, the stereochemistry of new asymmetrical centres was established. It was shown that regioselectivity of 1,3-dipolar cycloaddition of 4-methoxybenzonitriloxide (chloramine B, TEA) to conjugated esters of carbohydrate series increases when passing from Z- to E-ester. In the case of double-substituted double bond, the process becomes regiospecific. The contribution from reaction conditions (generation of nitriloxide by the action of NaOCl, USI) into the stereochemical result of cycloaddition was marked; the result is represented by the effect of epimerization of the asymmetric centre connected with the carbethoxy group due to its enolization in alkaline medium.

REFERENCES

1 Grigg R., Heaney F., Surendracumar S., *Tetrahedron*, 47 (1991) 4477.
2 Lakanatha Rai K. M. , *Top. Heterocycl. Chem.*, 13 (2008) 1.
3 Litvinovskaya R. P., Khripach V. A., *Usp. Khim.*, 70, 5 (2001) 464.
4 Akhrem A. A., Lakhvich F. A., Khripach V. A., *Khim. Geterotsikl. Soyed.*, 9 (1981) 1155.
5 Lakhvich F. A., Koroleva E. V., Akhrem A. A., *Khim. Geterotsikl. Soyed.*, 4 (1989) 435.
6 Rogoza L. N., Salahutdinov N. F., Tolstikov G. A., *Mini-reviews in Org. Chem.*, 6, 2 (2009) 135.
7 Katiyar D., Tiwari V. K., Verna S. S., Sinha S., Gaikwad A., Srivastava A., Srivastava B. S., Tripathi R. P., *Eur. J. Med. Chem.*, 40 (2005) 351.
8 Kocienski P., Yeates C., *J. Chem. Soc., Chem. Commun.*, (1984) 901.
9 Lehnert W., *Tetrahedron Lett.*, 11 (1970) 4723.
10 Ermolaeva N. A., Tsypysheva I. P., Dorogaya E. S., Gaylyunas I. A., Spirikhin L. V., Baikova I. P., Yunusov M. S., *Bash. Khim. Zh.*, 16, 2 (2009) 104.
11 Hasner A., Lokanatha R. K.M., *Synth. Commun.*, (1989) 57.
12 Bougrin K., Lamiri M., Soufiaoni M., *Tetrahedron Lett.*, 39 (1998) 4455.
13 Bruno G., Rotondo A., Grassi G., Foti F., Risitano F., Nicolo F., *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 60 (2004) 496.
14 Mancera M., Roffe I., Galbis J. A., *Tetrahedron*, 51, 22 (1995) 6349.
15 Zhdanov Yu. A., Dorofeenko G. N., Praktikum po Khimii Uglevodov, Vysshaya Shkola, Moscow, 1975.
16 Vogel A. I., Practical Organic Chemistry, Longman, London, 1956.
17 Khmelnitskiy L. I., Novikov S. S., Godovikova T. I., Khimiya Furoksanov: Stroyeniye i Sintez, Nauka, Moscow, 1996.