1,3-Dipolar Cycloaddition of 4-Methoxybenzonitriloxide to \(\alpha,\beta\)-Unsaturated Esters of \(\alpha\)-D-xylo-Pentadialdo-1,4-Furanose Series

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Abstract

Regio- and diastereoselectivity of 1,3-dipolar cycloaddition of 4-methoxybenzonitriloxide to \(\alpha,\beta\)-unsaturated esters of \(\alpha\)-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, \(\alpha,\beta\)-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 \(\alpha,\beta\)-unsaturated esters of \(\alpha\)-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-\(\alpha\)-D-xylo-pentadialdo-1,4-furanose 1 [8] with carboxymethylidenetriphenylphosphorane and separated by means of column chromatography on \(SiO_2\). The synthesis of malonate 3 was carried out under the

\[\begin{align*}
2a & \quad (67\%) \\
2b & \quad (13\%) \\
1 & \quad (89\%)
\end{align*}\]

Reagents and conditions: a. Ph$_3$PCHCOOEt, THF; b. CH(CO$_2$Et)$_2$, Py, TiCl$_4$, THF.

Scheme 1.
Reagents and conditions: a. MeO–C₆H₄–CHNOH, chloramine B, TEA, EtOH; b. MeO–C₆H₄–CHNOH, aqueous solution 0.8 M NaOCl, ultrasonic dispersing, Ñ˝ 2Ñl2, 5 °C.

Scheme 2.

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 CH₂Cl₂ 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 C4 (for 4a) and C5 (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 C4 and C5, we used 1H and 13C 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 \( J_{HH}, J_{CH}, J_{CC} \), 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 \( \delta_H \) and \( \delta_C \) 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 \( H^1 \) and \( H^5 \) is characteristic and can serve as the criterion of cis/trans position of \( H^1 \) 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 \( H^1 \) 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).
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. Identification and purity of the synthesized compounds were tested by means of TLC on Sorbfil PTSDKh-AF-V plates, column chromatography was carried out using silica gel (50–100 mesh) (Sorpolimer Co.). Aldehyde 1 was obtained according to the procedure described in [15], a mixture of $\text{syn}$- and $\text{anti}$-oxime of anisaldehyde according to the data reported in [16]. Physicochemical constants of 3,4-bis(4-hydroxyphenyl)furoxane 6 corresponded to literature data [17].

Ethyl ester of Z-(3a'R,5'R,6'S,6a'R)-3-[6'-
(benzyloxy)-2',2'-dimethyltetrahydrofurfuryl]-2-proponic acid (2a) and ethyl ester of E-(3a'R,5'R,6'S,6a'R)-3-[6'-
(benzoxy)-2',2'-dimethyltetrahydrofurfuryl]-2-proponic 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 SiO2 (hexane/ethyl acetate = 5 : 1); the product was 7.48 g of compound 3 with the 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$_3$, $\delta$, ppm, J, Hz): 1.23 t (3H, CH$_3$, $^3$J = 7.1), 1.3 s (3H, CH$_3$), 1.5 s (3H, CH$_3$), 4.08 q (2H, CH$_2$, $^3$J = 7.1), 4.27 dd (1H, C$^3$H, $^2$J = 2.7, $^3$J = 3.2), 4.43 d (1H, CH$_2$, $^2$J = 12.0), 4.58 dd (1H, CH$_2$, $^2$J = 12.0), 4.62 dd (1H, C$^6$H, $^2$J = 7.3, $^3$J = 3.5), 5.61 dd (1H, C$^3$H, $^2$J = 6.7, $^3$J = 3.2), 5.9 d (1H, C$^2$H, $^3$J = 11.7), 6.0 d (1H, C$^3$H, $^3$J = 6.7, $^2$J = 11.7), 7.18–7.38 m (5H, Ar). $^{13}$C NMR (CDCl$_3$, $\delta$, ppm): 14.04 (CH$_3$), 26.26 (CH$_3$), 26.74 (CH$_3$), 60.20 (CH$_2$), 71.35 (CH$_3$), 78.02 (C$^5$H), 82.93 (C$^6$H), 83.60 (C$^2$H), 105.01 (C$^3$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 (C$^2$OOC$^3$H$_2$).

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$_3$, $\delta$, ppm, J, Hz): 1.30 t (3H, CH$_3$, $^3$J = 7.3), 1.33 s (3H, CH$_3$), 1.50 s (3H, CH$_3$), 3.96 dd (1H, $^3$J = 3.5, $^2$J = 3.2), 4.22 q (2H, CH$_2$, $^3$J = 7.3), 4.50 d (1H, CH$_2$, $^2$J = 12.0), 4.63 d (1H, CH$_2$, $^2$J = 12.0), 4.65 dd (1H, C$^6$H, $^3$J = 27, $^3$J = 31), 4.80 dd (1H, C$^2$H, $^2$J = 3.5, 2$^2$J = 3.2), 6.0 d (1H, C$^3$H, $^3$J = 3.1), 6.16 d (1H, C$^2$H, $^2$J = 15.7), 6.97 dd (1H, C$^2$H, $^2$J = 5.0, $^2$J = 15.7), 7.2–7.4 m (5H, Ar). $^{13}$C NMR (CDCl$_3$, $\delta$, ppm): 14.21 (CH$_3$), 26.21 (CH$_3$), 26.81 (CH$_3$), 60.44 (CH$_2$), 72.25 (CH$_2$), 79.49 (C$^3$H), 82.82 (C$^2$H), 82.95 (C$^2$H), 105.03 (C$^3$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$^2$H), 166.01 (C$^2$OOC$^3$H$_2$).

Diethyl ester of (3a'R,5'R,6'S,6a'R)-2-[6'-
(benzyloxy)-2',2'-dimethyltetrahydrofurfuryl]-3-[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$_2$O and extracted with Et$_2$O (3 x 50 mL). The organic layers were brought together, washed with the saturated solution of NaCl (5 x 50 mL), and dried with MgSO$_4$. Then the mixture was concentrated; the residue was separated using 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. $C_{19}H_{24}O_9$. Calculated, %: C 62.85, H 6.71. $^1$H NMR spectrum (CDCl$_3$, $\delta$, ppm, J, Hz): 1.25 t (6H, 2CH$_3$, $^3$J = 7.0), 1.30 s (3H, CH$_3$), 1.40 s (3H, CH$_3$), 4.20 q (4H, 2CH$_2$, $^3$J = 7.0), 4.25 dd (1H, C$^5$H, $^2$J = 27, $^3$J = 3.3), 4.45 d (1H, CH$_2$, $^2$J = 11.9), 4.58 d (1H, CH$_2$, $^2$J = 11.9), 4.6 dd
Interaction of esters 2a, b and 3 with 4-methoxybenzotriazole oxide

**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 chlorine 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 SiO2 (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 CH2Cl2 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 CH2Cl2 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 MgSO4, then concentrated and separated by means of chromatography on SiO2 (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'-(benzoxiloxy)-2',2'-dimethyltetrahydrofurura[2,3-d][1',3']dioxazol-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.

\[ \text{C}_2\text{H}_5\text{NO}_5 \]

C17H15NO5. Calculated, %: C 65.18, H 6.28, N 2.82. 1H NMR spectrum (CDCl3, δ, ppm, J, Hz): 1.27 t (3H, CH3, 3J = 7.0), 1.30 s (3H, CH3), 1.45 s (3H, CH3), 3.80 s (3H, OCH3), 4.17 dd (1H, C6°, 3J = 7.0), 4.25 q (2H, CH2, 3J = 7.0), 4.90 dd (1H, C4H, 3J = 9.0, 3J = 3.2), 4.68 dd (1H, C6a°, 3J = 9.0, 3J = 3.5), 5.81 s (1H, C5H, 3J = 3.5), 6.90–8.10 m (9H, Ar). 13C NMR (CDCl3, δ, ppm): 13.90 (CH3), 26.45 (CH3), 26.77 (CH3), 55.26 (OCH3), 56.21 (C4H), 61.00 (CH3), 72.76 (CH3), 77.43 (C5H), 79.39 (C6H), 81.79 (C6a°H), 82.71 (C5°H), 105.30 (C3a°H), 114.22 (C2), 115.44 (C3), 117.39 (C, Ar), 124.01 (C, Ar), 125.79 (CH2, 3J = 11.6), 4.18 t (1H, C5H, 3J = 9.0), 5.90 d (1H, C3a°H, 3J = 3.5), 6.90–8.10 m (9H, Ar).

Ethyl ester of (4R,5R,3a'R,5'S,6'S,6a'R)-5-[6'-(benzoxiloxy)-2',2'-dimethyltetrahydrofurura[2,3-d][1',3']dioxazol-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. C17H13NO5. Calculated, %: C 65.18, H 6.28, N 2.82. 1H NMR spectrum (CDCl3, δ, ppm, J, Hz): 1.01 t (3H, CH3, 3J = 7.0), 1.27 s (3H, CH3), 1.39 s (3H, CH3), 3.80 s (3H, OCH3), 3.90 dd (H, C6°, 3J = 3.2, 3J = 2.7), 4.05 d (1H, C4H, 3J = 4.9), 4.14 q (2H, CH2, 3J = 7.0), 4.22 d (1H, CH3, 3J = 11.6), 4.27 d (1H, CH2, 3J = 11.6), 4.43 dd (1H, C5H, 3J = 9.0, 3J = 3.2), 4.51 dd (1H, C6a°H, 3J = 2.7, 3J = 3.5), 4.68 dd (1H, C5°H, 3J = 9.0, 3J = 4.9), 5.84 d (1H, C6H, 3J = 3.5), 6.90–8.10 m (9H, Ar). 13C NMR (CDCl3, δ, ppm): 13.69 (CH3), 26.52 (CH3), 26.80 (CH3), 55.55 (OCH3), 63.69 (C4H), 60.92 (CH2), 72.58 (CH2), 77.20 (C2°H), 81.44 (C6a°H), 83.28 (C5°H), 105.03 (C3a°H), 111.57 (C2), 114.06 (2CH, Ar), 126.91 (C, Ar), 127.37 (2CH, Ar), 127.66 (CH, Ar), 128.38 (2CH, Ar), 129.84 (2CH, Ar), 137.02 (C, Ar), 157.03 (C3°=N), 161.77 (C, Ar), 167.15 (COOC2H5).

Ethyl ester of (4S,5S,3a'R,5'S,6'S,6a'R)-5-[6'-(benzoxiloxy)-2',2'-dimethyltetrahydrofurura[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. C17H15NO5. Calculated, %: C 65.18, H 6.28, N 2.82. 1H NMR spectrum (CDCl3, δ, ppm, J, Hz): 1.15 t (3H, CH3, 3J = 7.0), 1.26 s (3H, CH3), 1.31 s (3H, CH3), 3.83 s (3H, OCH3), 4.17 dd (1H, C6°, 3J = 7.0).
Ethyl ester of (4S,5S,3a'R,5'R,6'S,6a'R)-4-[(6'- (benzoxyl)-2',2'-dimethyltetrahydrofuro[2,3-d]-1',3']dioxol-5'-yl]-3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolocarboxylic acid (5a).

\[ \alpha_{D}^{20} = -34.2^\circ \] Found, %: C 65.23, H 6.26, N 2.97. 

C$_{29}$H$_{30}$NO$_{10}$. 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$_6^\delta$H, $^3J = 3.2$, $^3J = 2.7$), 4.12 q (2H, CH$_2$, $^3J = 7.0$), 4.22 d (1H, C$_6^\delta$H, $^3J = 9.8$), 4.26 dd (1H, C$_6^\beta$H, $^3J = 9.6$, $^3J = 3.2$), 4.58 d (1H, CH$_2$, $^3J = 11.6$), 4.67 dd (1H, C$_6^\alpha$H, $^3J = 2.7$, $^3J = 3.6$), 4.73 dd (1H, CH$_2$, $^3J = 11.6$), 4.93 dd (1H, C$_6^\gamma$H, $^3J = 9.8$, $^3J = 9.6$), 6.04 d (1H, C$_6^\delta$H, $^3J = 3.8$), 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$_6^\gamma$H), 61.89 (CH$_3$), 72.17 (CH$_3$), 79.36 (C$_6^\beta$H), 82.05 (C$_6^\alpha$H), 82.69 (C$_6^\delta$H), 83.37 (C$_6^\gamma$H), 105.45 (C$_6^\delta$H), 112.00 (C$_6^\beta$H), 114.17 (2CH$_2$), 120.96 (C$_6^\gamma$H), 127.74 (2CH$_2$), 128.09 (CH$_2$), 128.27 (2CH$_2$), 128.58 (2CH$_2$), 137.19 (C, Ar), 155.72 (C$_5^\gamma$N), 161.27 (C, Ar), 168.12 (COOC$_3$H$_3$).

Ethyl ester of (4S,5R,3a'R,5'R,6'S,6a'R)-4-[(6'-(benzoxyl)-2',2'-dimethyltetrahydrofuran[2,3-d]-1',3']dioxol-5'-yl]-3-(4-methoxyphenyl)-4,5-dihydro-5-isoxazolocarboxylic acid (5b).

\[ \alpha_{D}^{20} = -169.5^\circ \] Found, %: C 65.23, H 6.11, N 2.59. 

C$_{29}$H$_{30}$NO$_{10}$. Calculated, %: C 65.23, H 6.11, N 2.59. C$_{29}$H$_{30}$NO$_{10}$. $^1$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$_6^\delta$H, $^3J = 3.2$, $^3J = 2.7$), 4.12 q (2H, CH$_2$, $^3J = 7.0$), 4.43 dd (1H, C$_6^\delta$H, $^3J = 8.0$, $^3J = 3.2$), 4.48 d (1H, CH$_2$, $^3J = 11.6$), 4.50 dd (1H, C$_6^\gamma$H, $^3J = 8.0$, $^3J = 4.8$), 4.54 d (1H, C$_6^\delta$H, $^3J = 4.8$), 4.55 dd (1H, C$_6^\alpha$H, $^3J = 2.7$, $^3J = 3.5$), 4.65 d (1H, CH$_2$, $^3J = 11.6$), 5.90 d (1H, C$_6^\delta$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$_2$), 55.25 (OCH$_3$), 60.98 (CH$_2$), 62.49 (C$_6^4$H), 71.99 (CH$_3$), 78.74 (C$_5^3$H), 80.80 (C$_6^4$H), 81.53 (C$_6^\alpha$H), 82.46 (C$_6^\gamma$H), 105.40 (C$_6^\delta$H), 111.94 (C$_5^3$), 114.08 (2CH$_2$), 126.90 (C, Ar), 127.68 (2CH$_2$), 127.97 (CH, Ar), 128.28 (2CH$_2$), 129.59 (2CH$_2$), 136.79 (C, Ar), 157.24 (C$_5^3$=N), 161.79 (C, Ar), 167.16 (COOC$_3$H$_3$).

Diethyl ester of (5R,3a'R,5'S,6'S,6a'R)-5-[(6'-(benzoxyl)-2',2'-dimethyltetrahydrofuran[2,3-d]-1',3']dioxol-5'-yl]-3-(4-methoxyphenyl)-4,5(5H)-isoxazolocarboxylic acid (7a).

\[ \alpha_{D}^{20} = -63.0^\circ \] Found, %: C 63.44, H 6.21, N 2.52. 

C$_{30}$H$_{35}$NO$_{10}$. Calculated, %: C 63.26, H 6.19, N 2.98. $^1$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$_6^\delta$H, $^3J = 2.7$, $^3J = 3.4$), 4.32 dd (1H, C$_6^\gamma$H, $^3J = 10.1$, $^3J = 3.4$), 4.36 q (2H, CH$_2$, $^3J = 7.0$), 4.40 dd (1H, C$_6^\delta$H, $^3J = 2.7$, $^3J = 3.5$), 4.74 d (1H, CH$_2$, $^3J = 11.6$), 4.82 d (1H, CH$_2$, $^3J = 11.6$), 5.86 d (1H, C$_6^\gamma$H, $^3J = 10.1$), 5.93 d (1H, C$_6^\delta$H, $^3J = 4.8$), 5.94 d (1H, C$_6^\delta$H, $^3J = 4.8$).
$^{3}J = 3.5$, 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$_1$), 72.70 (CH$_2$), 76.19 (C$_2$), 82.03 (C$_3$), 82.26 (C$_{6a}$), 84.30 (C$_4$), 105.51 (C$_{6a}$), 111.84 (C$_2$), 113.43 (2CH, Ar), 120.65 (C, Ar), 127.66 (CH, Ar), 128.30 (2CH, Ar), 129.10 (2CH, Ar), 137.52 (C, Ar), 154.18 (C$_{3a}$), 160.83 (C, Ar), 166.14 (COOC$_2$H$_3$), 165.59 (COOC$_2$H$_3$).

Diethyl ester of (5S,3a′R,5′S,6′S,6a′R)-5′-[6′-(benzyloxy)-2′,2′-dimethyltetrahydrofuran][2,3-d][1′,3′dioxol-5′-yl]-3-(4-methoxyphenyl)-4(5H)-isoxazolidicarboxylic acid (7b).

$^{[\alpha]^20}_{D} + 71.2$. Found, %: C 63.34, H 6.23, N 2.50.

C$_{35}$H$_{33}$NO$_{19}$. 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$_3$, $^{3}J = 7.0$), 1.20 t (3H, CH$_3$, $^{3}J = 7.0$), 1.30 s (3H, CH$_3$), 1.50 s (3H, CH$_3$), 3.80 s (3H, OCH$_3$), 3.55 dd (1H, C$_3$H, $^{3}J = 7.1$), $^{3}J = 3.4$), 3.86 dd (1H, C$_6$H, $^{2}J = 2.7$, $^{3}J = 3.4$), 4.28 q (4H, 2CH$_2$, $^{2}J = 7.0$), 4.54 d (1H, CH$_2$, $^{2}J = 11.8$), 4.69 dd (1H, C$_{6a}$H, $^{2}J = 2.7$, $^{3}J = 3.6$), 4.70 d (1H, CH$_2$, $^{3}J = 11.8$), 5.48 d (1H, C$_5$H, $^{3}J = 7.1$), 6.03 d (1H, C$_{6a}$H, $^{3}J = 3.6$), 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$_1$), 71.34 (CH$_2$), 78.82 (C$_3$), 82.69 (C$_5$), 83.10 (C$_{6a}$), 87.60 (C$_5$), 105.28 (C$_{6a}$), 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$_{3a}$), 160.88 (C, Ar), 165.50 (COOC$_2$H$_3$), 166.16 (COOC$_2$H$_3$).

CONCLUSION

New glycosylated 4,5-dihydroisoxazols of the series of α-D-xylo-pentodialdo-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 cycladdition 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 cycladdition 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