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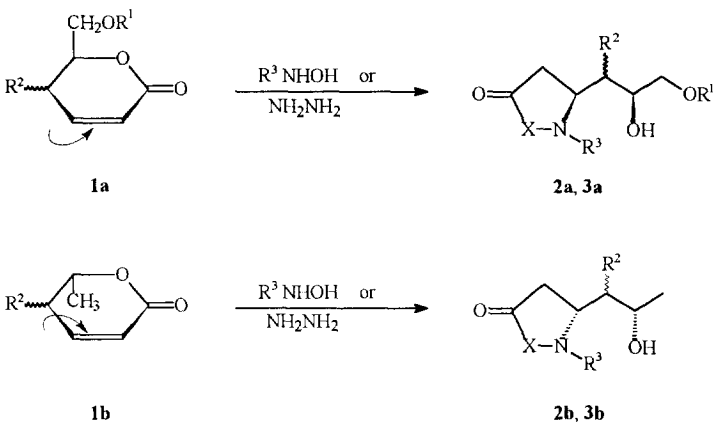
Synthesis, Structure and Chiroptical Properties of Isoxazolidin-5-ones#

Jadwiga Frelek*, Irma Panfil, Przemyslaw Gluzinski and Marek Chmielewski

Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44, 01-224 Warsaw, Poland

Abstract: Several isoxazolidin-5-ones were synthesized in an addition - rearrangement reaction from corresponding sugar lactones and hydroxylamines. The sign of the Cotton effect at ca. 220 nm can be correlated to the absolute configuration of the stereogenic center at C3 and can be predicted by Weigang's sector rule. X-ray diffraction study performed for **11** and **12** confirms the configuration at C3 to be 3*S* and 3*R*, respectively.

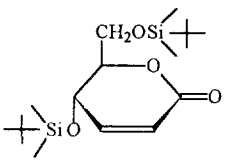
Recently we have reported the conjugate addition-rearrangement of hydroxylamines[1,2] and hydrazines[3,4] to sugar δ-lactones **1**, which led to the formation of isoxazolidin-5-ones **2** and pyrazolidin-3-ones **3**, respectively. It is known that stereoelectronic effects[5] promote an axial approach of the entering nucleophile, and that such additions proceed with excellent stereoselectivity to afford, in most cases, only one product (Scheme 1)



Scheme 1: R^1 = # H, Ac, Bn, Silyl ; R^2 = H, OAc, OBn, OSilyl ; R^3 = H, Bn, C_6H_{11} ; X = O, NH

In the case of hydroxylamine addition, we did not found any alternative stereoisomers[1,2,6]. Hence, for conformationally stable α,β-unsaturated sugar δ-lactones, the configuration of the C3 carbon atom of the isoxazoli-din-5-one ring depends upon configuration of the C5 carbon atom of the sugar lactone. Knowing the stereochemical pathway of the conjugate addition - rearrangement and the configuration of the starting lactone, assignment of the absolute configuration of isoxazolidin-5-one formed is straightforward. Direct proof of the configuration using NMR data is, however, uncertain or impossible. Such proof could be provided by circular dichroism (CD) spectra. The present paper reports on CD measurements of 3-substituted isoxazolidin-5-ones and presents the usefulness of this technique in assignment of their configuration.

This paper is dedicated to Professor Hans-Georg Kuball on the occasion of his 65th birthday.



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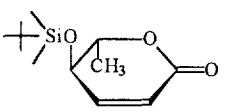


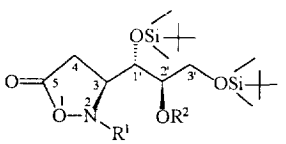
5

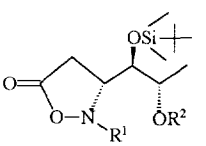
RNHOH

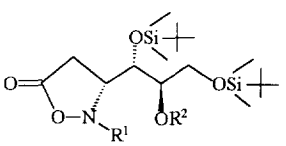
6 R = H
7 R = Me
8 R = *t*-Bu

Scheme 2

For the present study we selected D-*erythro* **4** and L-*erythro* **5** lactones and three hydroxylamines **6**, **7** and **8** (Scheme 2) . In the case of D-*erythro* lactone **4** addition - rearrangement reaction using **6** and **7** provided isoxazolidinones **9** and **10** as single products, whereas the respective reaction using **8** afforded two stereoisomers **11** and **12** in proportion 95:5, respectively (Scheme 3). Addition - rearrangement to L-*erythro* lactone **5** of hydroxylamines **6**, **7** and **8** produced in each case only one diastereomer **13**, **14** and **15**, respectively.







$R^1 = R^2 = H$	**9**	**13**	
R^1 = Me, R^2 = H	**10**	**14**	
R^1 = *t*-Bu, R^2 = H	**11**	**15**	**12**
R^1 = Me, R^2 = Ac	**16**	**19**	
R^1 = *t*-Bu, R^2 = Ac	**17**	**20**	**18**

Scheme 3

Acetylation of the hydroxyl group in **10** - **12**, **14** and **15** afforded the respective acetates **16** - **20**. Structures **11** and **12** were solved by X-ray crystal structure analysis (see Experimental), thus providing structural details of alternative stereoisomers that could be obtained as products of the addition - rearrangement reaction.

The need for a rapid and universal method for the determination of the absolute configuration of isoxazolidin-5-ones is obvious because of their frequent use as substrates for the synthesis of β-lactams[2] and deoxyaminosugars[6]. Until now, to the best of our knowledge, the chiroptical properties of isoxazolidin-5-ones have not been reported in the literature. In order to achieve a stereochemical assignment, we have undertaken a circular dichroic study of isoxazolidin-5-ones synthesized for this purpose. The chiroptical data for compounds **9** - **20** are collected in Table 1. As shown in the table, the compounds investigated fall under two different patterns of sign sequence. In the first one (Figure 1, right) the negative long wavelength CD band observed for compounds **9** - **11** and **16** - **17** is followed by the positive short wavelength CD band. In the second group, represented by compounds **12** - **15** and **18** - **20**, the opposite relation of sign pattern is observed, i.e. the

positive long wavelength CD band is followed by the negative short wavelength one (Figure 1, left). Regarding gross structure, all compounds of the first group differ from the respective compounds of the second group by the substitution of the terminal carbon atom, whereas the configuration of stereogenic centers of both groups remain in an enantiomeric relationship. According to the stereochemical pathway of the addition-rearrangements, isoxazolidin-5-ones **9** - **11** and **16** - **17** are 3*S* isomers, while isoxazolidin-5-ones **12** - **15** and **18** -**20** are 3*R* isomers. Comparison of the CD data presented in Table 1 and in Figure 1 indicates that respective pairs of isoxazolidin-5-ones show CD spectra with inverted signs of their CE's. Hence, one can conclude that stereochemistry at this carbon atom is responsible for the sign pattern of the CD curve and that the difference in substitution of the terminal carbon atom (t-butyldimethylsililoxy versus hydrogen atom) should not influence the CD curve.

Table 1. CD data of the isoxazolidin-5-ones **9** through **20** { $\Delta\varepsilon$ (λ_{max}/nm) :

Comp.	Acetonitryle		Isooctane		Methanol	
9	−3.50 (221.8)	+4.1 (191)			−6.73 (221.0)	+7.8 (193)
10	−7.13 (223.8)	+5.5 (192)	−8.53 (222.2)	+6.0 (193)	−14.31 (222.5)	+10.5 (194)
11	−12.24 (228.4)	+11.0 (198)	−17.69 (228.2)	+14.6 (198)	−16.89 (228.9)	+16.3 (201)
12	+17.68 (229.4)	−15.0 (200)	+13.21 (228.0)	−9.2 (200)	+15.44 (228.8)	−11.2 (201)
13	+5.41 (222.6)	−5.7 (193)			+5.09 (221.6)	−5.1 (193)
14	+7.13 (223.4)	−5.0 (194)	+7.24 (222.2)	−5.3 (193)	+7.38 (222.9)	−5.0 (194)
15	+9.62 (229.6)	−8.5 (199)	+9.10 (228.0)	−6.9 (199)	+9.61 (228.2)	−8.6 (199)
16	−9.01 (223.4)	+7.1 (195)	−6.99 (222.4)	+4.0 (195)		
17	−9.94 (229.0)	+9.0 (200)	−8.05 (228.6)	+6.6 (200)	−13.96 (228.9)	+13.0 (201)
18	+13.40 (229.2)	−11.7 (199)	+9.15 (228.0)	−7.2 (198)		
19	+6.68 (223.3)	−5.3 (194)	+7.07 (221.8)	−4.5 (193)	+7.51 (223.1)	−5.9 (192)
20	+14.12 (229.4)	−13.0 (200)	+11.92 (228.4)	−9.5 (200)	+14.35 (228.1)	−12.7 (200)

In addition, inspection of CD data for compounds **9** - **20** shows, that the position and the magnitude of Cotton effects are only slightly dependent on solvent polarity. Furthermore compounds **11**, **12**, **15**, **17**, **18** and **20**, all bearing the t-butyl substituent at the nitrogen atom, demonstrate a bathochromic shift of around 7 nm in comparison to compounds **9** and **13** with hydrogen attached to the nitrogen atom. This shift appears for both, long and short wavelength CE's and is independent of the solvent used and configuration at C3. No such shift, however, is observed for compounds with a nitrogen atom bearing a methyl group as in the case of compounds **10**, **14**, **16** and **19**. Moreover, the magnitude of particular CE's increases with the size of substituent at nitrogen atom along the following order: H, Me, ^{t}Bu. The acetylation of hydroxyl group at C6 does not significantly influence the position or the magnitude of the CD bands.

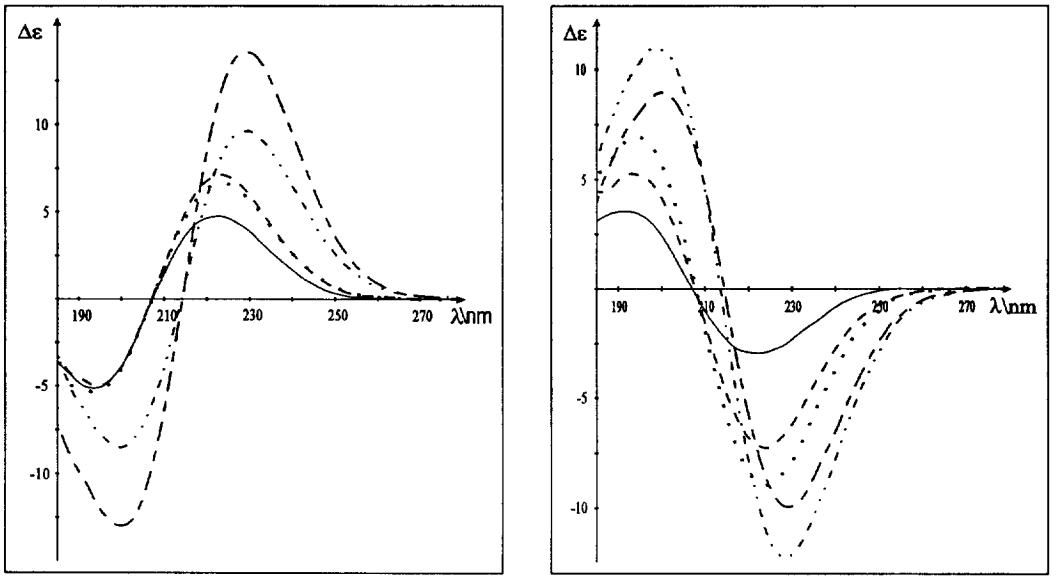


Figure 1: CD spectra of compounds **13** (———), **14** (- - - - -), **15** (- ·- · - ·- -) **19** (· · · · ·) and **20** (— — —) {left} and **9** (———), **10** (- - - - -), **11** (- ·- · - ·- -) **16** (· · · · ·) and **17** (— — —) {right} in acetonitrile.

In view of the similarity of the isoxazolidin-5-one ring to the γ-lactone system, we decided to examine the applicability of a lactone sector rule to conformational analysis of investigated compounds. The preference for co-planarity of the five atoms of the lactone group, C-CO-O-C, implies that the stable conformations of the γ-lactone ring are restricted to an enantiomeric pair of envelope conformers, in which the fifth ring atom, Cβ, is either above or below the lactone plane.[8] According to Beecham[9] the conformation of the ring in lactones plays a dominant rule and is the sign-determining factor. Due to his rule the sign of the nπ* Cotton effect in γ-lactones depends upon the location of Cβ relative to the planar lactone system. Another approach is based on several sector rules in which the Weigang's sector rule is the most general one and explains optical activity of lactones and lactams.[10]

For isoxazolidinones, which are structurally related to γ-lactones, the envelope form ought to be considered. Bulky substituent at C3 influences conformation of the isoxazolidin-5-one ring. Due to steric effects, conformation of the five-membered ring with a bulky substituent in quasi-equatorial position would be preferred. The MMX calculations[11] carried out for compounds **9** and **13,** which represent both configurational isomers at C3, confirm this assumption. The MMX calculations show that the five-membered ring in the low-energy conformers of isoxazolidin-5-ones **9** and **13** occurs in both cases as an envelope conformer. In the case of **9**, the C2 carbon atom, nitrogen atom and the O=C–O group lie in the same plane, whereas the C3 carbon atom lies above this plane, as shown in Figure 2d. In the case of compound **13**, however, the C3 carbon atom lies below the plane formed by the O=C–O group, C2 and nitrogen atoms (Figure 2b).

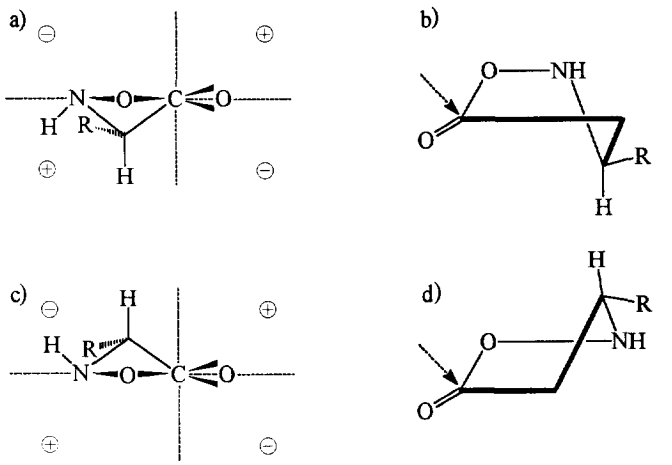


Figure 2: Conformations and sector projections of **9** (bottom) and **13** (upon). The arrows show direction of projections.

Direct extension of the Weigang's[10] sector rule to the above mentioned conformers of compounds **9** (3*S* isomer) and **13** (3*R* isomer) predicts that **9** would exhibit a negative CE around 220 nm and **13** a positive one in the same range. Those predictions are found to be in agreement with experimental data (see Table 1). In the case of compound **9**, the C3 carbon atom is placed in a negative sector, while C3 carbon atom of compound **13** is positioned in a positive one (Figure 2a,c). All 3*S* isomers investigated also show a negative sign of CE in this region, whereas all 3*R* isomers show a positive one. Thus the sign of the Cotton effect at *ca.* 220 nm may be correlated directly to the absolute configuration of the stereogenic center at C3. The strong magnitude of the long wavelength CD band, near Gaussian shape of bands and an absence of a solvent effect additionally hint to an existence of **9 - 20** in almost pure conformational states in a solution.

In both the CD and UV spectra of γ-lactons Cotton effects and absorption bands in the region between 220 and 215 nm are clearly defined as belonging to the nπ* transition. In the case of isoxazolidin-5-ones **9 - 20**, however, a weak absorption band occurring in this range is overlapped by a strong short wavelength band with a maximum of around 190 nm making the nπ* band undetectable in the UV spectrum. The presence of an auxochromic NX group next to oxocarbonyl fragment causes additionally hypsochromic shift of the short wavelength absorption band and thus the maximum of this band lies out of the measurement range for **9 - 20,** i.e. below 190 nm. The 220 nm CD band cannot be assigned to the pure nπ* transition because the characteristic for this transition hypsochromic shift caused by polar solvents is absent. As an example, Figure 3 clearly shows the absence of a solvent effect for compound **12**. The short wavelength band may belong to the ππ* transition, but assignment to the nσ* transtition cannot be excluded. The protonation of a NX group in isoxazolidin-5-ones **9 - 20**, in order to exclude the contributions from nσ* transtition (involving nitrogen lone pair), could not be performed due to instability of the isoxazolidinone ring under acidic conditions.

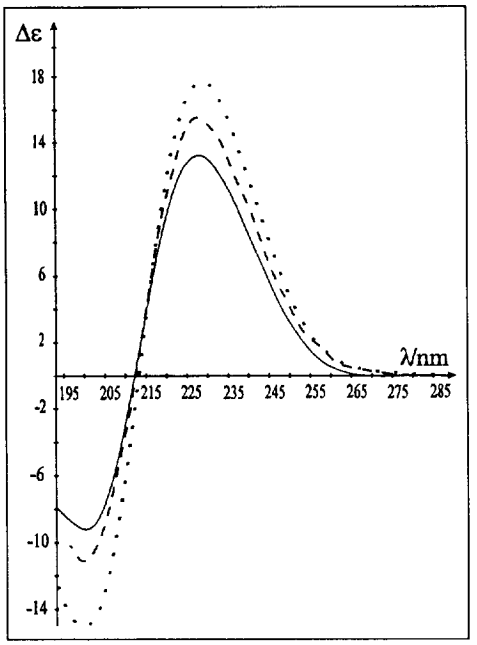


Figure 3. CD spectra of **12** in isooctane (———), acetonitryle (· · · · ·) and methanol (- - - - -).

X-ray diffraction analysis of the isoxazolidinones **11** and **12** confirms the configuration at C3 to be 3*S* and 3*R*, respectively. A perspective view of the molecules is shown in Figure 4 and selected structural parameters are listed in Table 3. The x-ray data also show that the five-membered ring occurs in both cases as an envelope conformer. In the case of compound **11** the oxocarbonyl group, the nitrogen atom and C4 atom form the plane with C3 carbon atom lying above this plane. Thereby the molecular conformation in the crystalline state of **11** agrees with the MMX calculation as a similar low-energy conformer has been proposed for compound **9** belonging to the same 3*S* configurational group. In the case of **12**, however, the x-ray data demonstrate the presence of a second envelope conformation with the C4 atom deviated from the ring plane which is formed by the oxocarbonyl group, the nitrogen atom and C3 carbon atom. The x-ray data also indicate a sterically preferred trans arrangement of bulky substituents at C3 and nitrogen atoms in **11** and **12** (Figure 4). In compound **12** an intramolecular hydrogen bond between the hydroxyl group at C2′ and the nitrogen lone pair is found in the crystalline state. The same configuration in the side chain and the opposite configuration at C3, in **11** compared to **12**, make formation of hydrogen bond in **11** impossible, as is clearly seen in Figure 4. It is noteworthy, that among all investigated compounds **9** - **20**, compound **12** is the only one which has the suitable spatial disposition to give an internal hydrogen bond. Presumably the presence of this intramolecular hydrogen bond together with a puckering of molecules in the solid state causes a change in the expected conformation of the isoxazolidin-5-one fragment of **12** which should be in enantiomeric relationship to that found for **11**.

The magnitude of particular Cotton effects for **12** in isooctane does not become greater then in methanol or acetonitrile (see Figure 3), although it could be expected due to stabilization of the conformer by intramolecular hydrogen bond in nonpolar solvent. The influence of internal hydrogen bridge in **12** has additionally been checked by comparison of the CD-spectrum with this of its O-acetoxy derivative **18**. The acetylation of the alcohol results only in small decreasing of magnitudes of the Cotton effects but the shapes of the CD curves remain unalterable. On the basis of the above results one can conclude that such an internal hydrogen bridging plays no important role in solutions studied.

In addition, the x-ray data may prove the suitability of the chosen lactone model for chiroptical considerations of isoxazolidinones. Comparison of bond lengths of isoxazolidinone ring in **11** and **12** with the

respective bond lengths of the γ-lactone model system **21**[12] (Figure 5, for clarity the numbering of atoms as for isoxazolidinones), confirms this assumption.

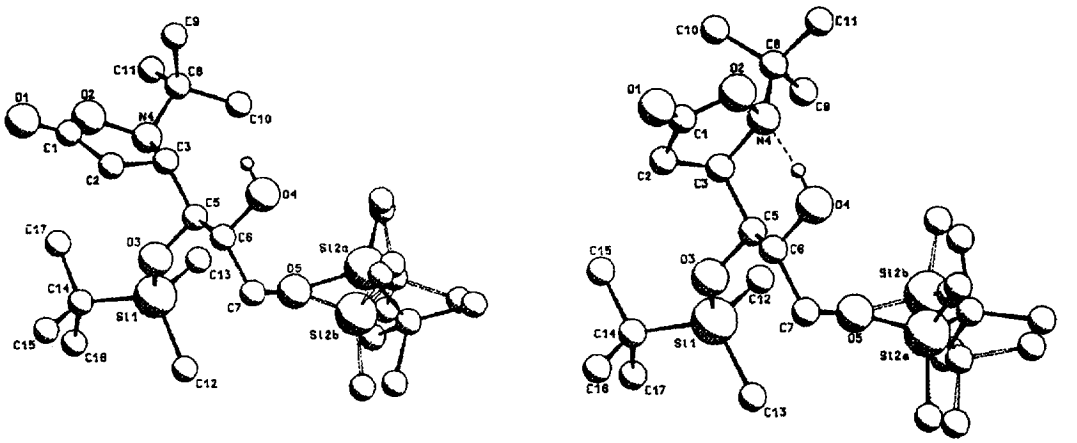


Figure 4. Parallel projections of **11** (left) and **12** (right) at approximately the same orientation to give the optimal view. (Numbering of atoms as used in the crystallographic analysis).

As given in Table 2, the bond lengths in an isoxazolidin-5-ones system are similar to those of the γ-lactone model compound **21**. The greatest difference in the lengths of bonds is found for N–C3 bond in **11** and **12** and C2–C3 in **21.** The nitrogen atom in both compounds **11** and **12** is pyramidal (the sum of the valence angles: O1–N–C3, O1–N–C^t and C3–N–C^t for **11** and **12** is equal to 325.3° and 330.0°, respectively). Moreover, the N–C3 distance in the compounds under consideration amounts to 1.483 Å for **11** and 1.496 Å for **12**, and approximates to the standard length of the N(sp3) –C(sp3) in amines[13] which is equal to 1.47 Å.

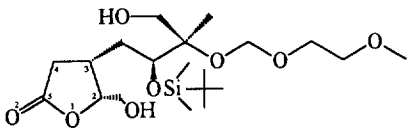


Figure 5. Model compound **21**.

Table 2. Some bond length of **11**, **12** and **21** and differences in bond lengths |**21-11**| and |**21-12**| in Å.

Bond	**11**	|**21 - 11**|	**12**	|**21 - 12**|	**21**
C5 – O2	1.193 (11)	0.008	1.185 (7)	0.016	1.201
C5 – O1	1.352 (10)	0.004	1.360 (7)	0.004	1.356
N(C)2 – O1	1.475 (7)	0.013	1.458 (5)	0.004	1.462
C4 – C5	1.449 (12)	0.052	1.485 (8)	0.01 6	1.501
C3 – C4	1.533 (9)	0.015	1.515 (6)	0.033	1.548
N(C)2 – C3	1.483 (8)	0.058	1.496 (6)	0.045	1.541

In conclusion, circular dichroism makes possible an unequivocal and fast determination of the absolute configuration of isoxazolidin-5-ones. Moreover, it is demonstrated that the Weigang's sector rule may be successfully applied in prediction of the long wavelength CE sign for isoxazolidinones. The contribution to the CD of nitrogen atom from isoxazolidinone moiety cannot be explained on the basis of the present data. Further studies on this subject involving the generality and the scope of the chiroptical method in assignment of absolute configuration of monosubstituted heterocycles are under investigation in our institute, presently.

Experimental

^{1}H NMR spectra were recorded with Bruker AM 500 and Varian Gemini 200 spectrometers. IR spectra were obtained on a FT-IR-1600 Perkin - Elmer spectrophotometer. CD spectra were recorded on a dichrograph AVIV 62D. Optical rotation were measured with a JASCO Dip - 360 digital polarimeter. Column chromatography was performed on Merck silica gel 230 - 400 mesh.

X-Ray data collection and structure determination.

Table 3. Crystal data, data collection and refinement parameters.

	Compound **11**	Compound **12**
General Formula:	$C_{22}H_{47}NO_5Si_2$	
Molecular Weight:	461.74	
Crystal system:	orthorombic	monoclinic
Cell constants: a (Å)	8.292 (3)	8.2536 (7)
b (Å)	10.902 (1)	10.728 (2)
c (Å)	32.821 (9)	16.373 (3)
β (°)	———	96.26 (3)
Cell volume (Å)	2967 (1)	1441 (4)
Molecular multiplicity:	Z = 4	Z = 2
Calculated density (g cm^{-3})	1.03	1.06
Space group:	$P22_12_1$[a]	$P2_1$ (no.4)
Number of electrons *F* (000)	1016	508
Linear absorption coeff. μ (cm^{-1})	14.9	15.4
Radiation (graphite monochromated)	Cu Kα	
Wavelength	(1.54178 Å)	
Diffractometer	MACH3 (Enraf-Nonius)	
Scan mode:	ω/2θ	
Scan range ($2\theta_{max}$) (°)	0 - 10	-10 - 10
h, k, l range *h*	0 - 13	0 - 13
k	0 - 40	-20 - 0
l		
Number of reflexion:		
Total measured:	3475	3222
Unique (with I > $2a_I$)	1868	2318
Method of refinement:	full-matrix least-squares (program SHELXL)	
Number of ref. params.	336	335
Reliability R (for all obs. reflens.)	0.0671	0.0567[b]
GooF	1.014	1.053

[a] Alternate setting of no. 18. [b] For opposite enantiomorph.

Well shaped colorless crystals of isomers **11** and **12** were chosen for X-ray diffractometric measurements. Isomer **11** (size 0.31×0.21×0.63 mm) was obtained from heptane solution. Isomer **12** (size 0.28×0.17×0.55 mm) was obtained from heptane solution. Table 3 gives the measurement conditions as well as main refinement results for both isomers.

The stability of the crystals was checked on three control reflections at 100 reflection intervals. No remarkable decay was observed. Lorentz and polarization but no absorption corrections were applied to all reflections.

The space groups for both cases were assigned from systematical absences of reflections. The structures were solved (program SHELXS-86[14]) by direct methods, revealing on E-maps positions of all non-hydrogen atoms except one chain-ending $SiMe_2{}^tBu$ group, where several weak peaks suggested the presence of some positional disorder. The same refinement procedure was applied to both cases.

The several-step refinement (program SHELXL-93[15]) of positional and initially isotropic and then anisotropic thermal parameters allowed to find on difference E-maps the positions of disordered $SiMe_2{}^tBu$ groups, whose population parameters were refined in further steps. Hydrogen atoms were generated geometrically by the program as "riding" on their adjacent atoms, except the hydroxyl hydrogen which was found in both cases from difference E-map.

Final population ratio was 51.5:48.5 for isomer **11** and 67.9:32.1 for isomer **12**. The final residual electron densities on difference E-maps was below 0.3 e A-3.

Synthetic procedures.

Lactones **4** and **5** were obtained from ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside and ethyl 2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranoside, respectively, by standard sequences which consisted in silylation followed by anomeric oxidation [7].

4,6-di-O-tbutyldimethylsilyl-2,3-dideoxy-D-erythro-hex-2-enoaldono-1,5-lactone **(4)**: mp 82 - 84°C; $[\alpha]_D$ +48.0 (*c* 1, CH_2Cl_2) ; IR (CCl_4): 1745 cm^{-1}; ^1H NMR ($CDCl_3$): 0.90, 0.91 (2s, 18 H, 2 *t*-Bu), 3.84 (dd, 1H, *J* 2.8, 11.8, Hz, H-6), 3.90 (dd, 1H, *J* 2.7, 11.8 Hz, H-6'); 4.19 (dt, 1H, *J* 2.7, 2.8, 9.0 Hz, H-5); 4.71 (dt, 1H, *J* 1.9, 2.1, 9.0 Hz, H-4); 5.92 (dd, 1H, *J* 1.9, 9.9 Hz, H-2); 6.72 (dd, 1H, *J* 2.1, 9.9 Hz, H-3). Anal. Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.06; H, 9.67. Found: C, 57.8; H, 9.8.

4-O-tbutyldimethylsilyl-2,3,6-trideoxy-L-erythro-hex-2-enoaldono-1,5-lactone **(5)**: mp 40 - 41°C, $[\alpha]_D$ -64.4 (*c* 1, CH_2Cl_2); IR (film): 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 0.92 (s, 9H, *t*-Bu), 1.43 (d, 1H, *J* 6.0 Hz, CH_3), 4.22 (dt, 1H, *J* 1.7, 1.9, 9.4 Hz, H-4), 4.30 (dq, 1H, *J* 6.0, 9.4 Hz, H-5), 5.93 (dd, 1H, *J* 1.9, 9.9 Hz, H-2), 6.71 (dd, 1H *J* 1.7, 9.9 Hz, H-3). Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.50; H, 9.09. Found: C, 59.4; H, 9.0.

Addition of hydroxylamines 6 - 8 to lactones 4 and 5. General procedure. To a solution of lactone (10 mmol) in anhydrous methanol (2 mL) was added hydroxylamine (freshly prepared from respective hydrochloride by the

sodium methoxide titration in methanol solution; 1.5 mmol). The mixture was stirred at room temperture for 3 h (in the case of **6** completion of reaction required 10 min only). Subsequently methanol was evaporated, water (10 mL) was added and the mixture was extracted with t-buthyl methyl ether. The extract was dried and evaporated. The residue was purified an silica gel column using hexane - ethyl acetate as an eluent to afford isoxazolidin-5-ones **9**, **10**, **13** - **15** in about 80% yield (in the case of addition of **8** to **4**, a mixture **11** and **12** was separated using hexane - ethyl acetate : as an eluent to give alternative diastereomers in proportion of about 20 : 1, respectively in overall yield 80%.

Acetylation of **10**, **12**, **14** and **15** was performed using standard acetic anhydride - pyridine procedure to afford **16** - **20** respectively.

(3S,1'S,2'R) 3-(1',3'-di-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-isoxazolidin-5-one **(9)**: syrup, $[\alpha]_D$ +1.5 (*c* 1, CH_2Cl_2); IR : (CCl_4) 1796 cm^{-1}; ^1H NMR ($CDCl_3$): 0.91 (s, 18 H, *t*-Bu), 2.69 (dd, 1H, *J* 7.9, 17.3 Hz, H-4a), 2.93 (dd, 1H, *J* 8.5, 17.3 Hz, H-4b), 3.5 - 3.8 (m, 3H, H-2', 3'a, 3'b), 3.86 (dd, 1H *J* 2.7, 6.1 Hz, H-1'), 4.20 (bq, 1H, H-3). MS (LSIMS) m/z: $(M + H)^+$ 406. Anal. Calcd for $C_{18}H_{39}NO_5Si_2$: C, 53.33; H, 9.62; N, 3.45. Found: C, 53.2; H, 9.5; N, 3.3.

(3S,1'S,2'R) 3-(1',3'-di-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-2-methyl-isoxazolidin-5-one **(10)**: mp 60 - 62°C; $[\alpha]_D$+78.8 (*c* 0.5, CH_2Cl_2); IR ($CHCl_3$): 1764 cm^{-1}; ^1H NMR ($CDCl_3$): 0.89, 0.91 (2s, 18H, 2 *t*-Bu), 2.68 (dd, 1H, *J* 8.1, 17.3, H-4a), 2.88 (s, 3H, NCH_3), 3.12 (dd, 1H, *J* 10.3, 17.3 Hz, H-4b), 3.46 (m, 1H, H-2'), 3.58 (ddd, 1H, *J* 1.4, 8.1, 10.3 Hz, H-3), 3.60 (dd, 1H, *J* 6.3, 9.8 Hz, H-3'a), 3.70 (dd, 1H, *J* 1.4, 7.6 Hz, H-1'), 3.76 (dd, 1H, *J* 4.2, 9.8 Hz, H-3'b). MS (EI) m/z: M+ 419. Anal. Calcd for $C_{19}H_{41}NO_5Si_2$: C, 54.41; H, 9.78; N, 3.34. Found: C, 54.6; H, 10.1; N, 3.1.

(3S,1'S,2'R) 2-^{t}butyl-3-(1',3'-di-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-isoxazolidin-5-one **(11)**: mp 81 - 83°C; $[\alpha]_D$ -73.9 (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1763 cm^{-1}; ^1H NMR ($CDCl_3$): 0.88, 0.90 (2s, 18H, 2 Si *t*-Bu), 1.15 (s, 9H, *t*-Bu), 2.75 (dd, 1H, *J* 10.6, 18.1 Hz H-4a), 2.94 (dd, 1H, *J* 4.7, 18.1 Hz, H-4b), 3.41 (bm, 1H, H-2'), 3.55 (dd, 1H, *J* 6.7, 9.7 Hz, H-3'a), 3.65 (dd, 1H, *J* 1.5, 9.7 Hz, H-1'), 3.79 (dd, 1H, *J* 3.7, 9.7 Hz, H-3'b), 4.06 (ddd, 1H, *J* 1.5, 4.7, 10.6 Hz, H-3). MS (LSIMS) m/z: $(M+H)^+$ 462. Anal. Calcd for $C_{22}H_{47}NO_5Si_2$: C, 57.26; H, 10.19; N, 3.03. Found: C, 57.2; H, 10.3; N, 3.0.

(3R,1'S,2'R) 2-^{t}butyl-3-(1',3'-di-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-isoxazolidin-5-one **(12)**: mp 83 - 85°C; $[\alpha]_D$ +43.0 (*c* 0.2, CH_2Cl_2); IR ($CHCl_3$): 1760 cm^{-1}; ^1H NMR ($CDCl_3$): 0.89, 0.92 (2s, 18H, 2Si *t*-Bu), 1.14 (s, 9H, *t*-Bu), 2.67 (dd, 1H, *J* 10.5, 18.2 Hz, H-4a), 2.93 (dd, 1H, *J* 4.6, 18.2 Hz, H-4b), 3.50 (ddd, 1H, *J* 2.8, 3.8, 6.7 Hz, H-2'), 3.61 (dd, 1H, *J* 3.8, 11.6 Hz, H-3'a), 3.70 (bd, 1H, H-3'b), 3.82 (dd, 1H, *J* 2.2, 6.7 Hz, H-1'), 3.95 (ddd, 1H, *J* 2.2, 4.6, 10.5 Hz, H-3). MS (EI/HR) m/z: M^+ calcd for $C_{22}H_{47}NO_5Si_2$: 461.22928. Found: 461.29925.

(3R,1'R,2'S) 3-(1'-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-isoxazolidin-5-one **(13)**: mp 146 - 148°C, $[\alpha]_D$ +3.0 (*c* 1, CH_2Cl_2); IR (film): 1782 cm^{-1}; ^1H NMR ($CDCl_3$): 0.93 (s, 9H, *t*-Bu), 1.20 (d, 3H, *J* 6.0 Hz, CH_3), 2.68 (dd, 1H, *J* 7.7, 17.5 Hz, H-4a), 2.95 (dd, 1H, *J* 9.2, 17.5, H-4b), 3.75 (dd, 1H, *J* 2.6, 4.0, H-1'), 3.89 (dq, 1H, *J* 4.0, 6.5 Hz, H-2'), 4.06 (m, 1H, H-3) . MS (EI) m/z: $(M + H)^+$ 276. Anal. Calcd for $C_{12}H_{25}NO_5Si$: C, 52.36; H, 9.09; N, 5.09. Found: C, 52.1; H, 9.2; N, 5.1.

(3R,1'R,2'S) 3-(1'-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-2-methyl-isoxazolidin-5-one **(14)**: mp 68 - 70°C; $[\alpha]_D$ -10.9 (*c* 0.5, CH_2Cl_2); IR ($CHCl_3$): 1773 cm^{-1}; ^1H NMR ($CDCl_3$): 0.91 (s, 9H, *t*-Bu), 1.20 (d, 1H, *J* 6.5 Hz, CH_3), 2.71 (dd, 1H, *J* 7.9, 17.5 Hz, H-4a), 2.87 (s, 3H, NCH_3), 3.12 (dd, 1H, *J* 10.0, 17.5, H-4b), 3.38 (ddd, 1H, *J* 1.8, 7.3, 10.0 Hz, H-3), 3.59 (dd, 1H, *J* 1.8, 4.8, H-1'), 3.78 (dq, 1H, *J* 4.8, 6.5 Hz, H-2'). MS (EI) m/z: M^+ 289. Anal. Calcd for $C_{13}H_{27}NO_4Si$: C, 53.97; H, 9.34; N, 4.84. Found: C, 53.9; H, 9.4; N, 4.9.

(3R,1'R,2'S) 2-^{t}butyl-3-(1'-^{t}butyldimethylsiloxy-2'-hydroxy)propyl-isoxazolidin-5-one **(15)**: syrup; $[\alpha]_D$ +36.0 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 1764 cm^{-1}; ^1H NMR ($CDCl_3$): 0.90 (s, 9H, Si *t*-Bu), 1.15 (s, 9H. *t*-Bu), 1.22 (d, 3H, *J* 6.4 Hz, CH_3), 2.75 (dd, 1H, *J* 10.4, 18.2, H-4a), 2.99 (dd, 1H, *J* 4.1, 18.2 Hz, H-4b), 3.55 (dd, 1H, *J* 2.2, 5.7 Hz, H-1'), 3.73 (quint. 1H, *J* 5.7, 6.4 Hz, H-2'), 3.86 (ddd, 1H, *J* 2.2, 4.1, 10.4 Hz, H-3). MS (EI/HR) m/z: M^+ calcd for $C_{16}H_{33}NO_4Si$: 331.21788. Found: 331.21787.

(3S,1'S,2'R) 3-(2'-acetoxy-1',3'-di-^{t}butyldimethylsiloxy)propyl-2-methyl-isoxazolidin-5-one **(16)**: syrup; $[\alpha]_D$ -95.0 (*c* 0.5, CH_2Cl_2); IR ($CHCl_3$): 1782, 1742 cm^{-1}; ^1H NMR ($CDCl_3$): 0.89 (s, 18H, 2 *t*-Bu), 2.07 (s, 3H, Ac), 2.68 (dd, 1H, *J* 7.6, 17.2 Hz, H-4a), 2.86 (s, 3H, NCH_3), 3.16 (dd, 1H, *J* 10.2, 17.2 Hz, H-4b), 3.35 (ddd, 1H, *J* 1.7, 7.6 10.2 Hz, H-3), 3.67 (dd, 1H, *J* 9.5, 11.1 Hz, H-3'a), 3.76 (dd, 1H, J 4.9, 11.1 Hz, H-3'b), 4.03 (dd, 1H, 1.7, 4.9 Hz, H-1'), 4.86 (q, 1H, *J* 4.9, 4.9, 5.5 Hz, H-2'). MS (EI) m/z: M^+ 461. Anal. Calcd for $C_{21}H_{43}NO_6Si_2$: C, 54.66; H, 9.32; N, 3.03. Found: C, 54.7; H, 9.5; N, 3.0.

(3S,1'S,2'R) 3-(2'-acetoxy-1',3'-di-^{t}butyldimethylsiloxy)propyl-2-^{t}butyl-isoxazolidin-5-one **(17)**: mp 50 - 52°C; $[\alpha]_D$ -68.4 (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1763, 1742 cm^{-1}; ^1H NMR ($CDCl_3$): 0.88 (s, 18H, 2Si *t*-Bu), 1.14 (s, 9H, *t*-Bu), 2.07 (s, 3H, Ac), 2.71 (dd, 1H, J 10.7, 18.3 Hz, H-4a), 3.06 (dd, 1H, J 4.6, 18.3 Hz, H-4b), 3.73 (d, 2H, H-3'a, 3'b), 3.84 (ddd, 1H, J 1.7, 4.6, 10.7 Hz, H-3), 3.99 (dd, 1H, J 1.7, 5.1 Hz, H-1'), 4.83 (q, 1H, H-2'). MS (EI) m/z: M^+ 503. Anal. Calcd for $C_{29}H_{49}NO_6Si_2$: C, 57.25; H, 9.74; N, 2.78. Found: C, 57.4; H, 10.0; N, 2.6.

(3R,1'S,2'R) 3-(2'-acetoxy-1',3'-di-^{t}butyldimethylsiloxy)propyl-2-^{t}butyl-isoxazolidin-5-one **(18)**: syrup; $[\alpha]_D$ +9.7 (*c* 0.1, CH_2Cl_2); IR ($CHCl_3$): 1763, 1742 cm^{-1}; ^1H NMR ($CDCl_3$): 0.89, 0.90 (2s, 18H, 2Si *t*-Bu), 1.14 (s, 9H, *t*-Bu), 2.06 (s, 3H, Ac), 2.77 (dd, 1H, J 3.2, 18.2 Hz, H-4a), 2.83 (dd, 1H, J 9.2, 18.2 Hz, H-4b), 3.72 (dd, 1H, J 6.3, 10.5 Hz, H-3'a), 3.81 (ddd, 1H, J 3.2, 7.4, 9.2 Hz, H-3), 3.86 (dd, 1H, J 1.7, 7.4 Hz, H-1'), 4.05 (dd, 1H, J 6.1, 10.5 Hz, H-3'b), 4.93 (dt, 1H, J 1.7, 6.1, 6.3 Hz, H-2'). MS (EI/HR) m/z: M^+ calcd for $C_{24}H_{49}NO_6Si_2$: 503.30984. Found: 503.30920.

(3R,1'R,2'S) 3-(2'-acetoxy-1'-'butyldimethylsiloxy)propyl-2-methyl-isoxazolidin-5-one **(19)**: mp 62 - 65°C; $[\alpha]_D$ +6.4 (*c* 0.25, CH_2Cl_2); IR ($CHCl_3$): 1776, 1762 cm^{-1}; ^1H NMR ($CDCl_3$): 0.91 (s, 9H, *t*-Bu), 1.21 (d, 3H, *J* 6.5 Hz, CH_3), 2.05 (s, 3H, Ac), 2.69 (dd, 1H, *J* 7.7, 17.3 Hz, H-4a), 2.87 (s, 3H, NCH_3), 3.13 (dd, 1H, *J* 9.7, 17.3 Hz, H-4b), 3.22 (ddd, 1H *J* 2.1, 7.7, 9.7 Hz, H-3), 3.76 (dd, 1H, *J* 2.1, 3.9 Hz, H-1'), 4.91(dq, 1H, *J*3.9, 6.5 Hz. H-2'). MS (EI) m/z: M^+ 331. Anal. Calcd for $C_{15}H_{29}NO_5Si$: C, 54.38; H, 8.76; N, 4.42. Found: C, 54.3; H, 8.9; N, 4.2.

(3R,1'R,2'S) 3-(2'-acetoxy-1'-'butyldimethylsiloxy)propyl-2-'butyl-isoxazolidin-5-one **(20)**: mp 67 - 69°C; $[\alpha]_D$ +73.2 (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1764, 1741 cm^{-1}; ^1H NMR ($CDCl_3$): 0.89 (s, 9H, Si *t*-Bu), 1.14 (s, 9H. *t*-Bu), 1.21 (d, 3H, *J* 6.5 Hz, CH_3), 2.05 (s, 3H, Ac), 2.73 (dd, 1H, *J* 10.3, 18.2, H-4a), 3.00 (dd, 1H, *J* 4.1, 18.2 Hz, H-4b), 3.64 (ddd, 1H, *J* 2.6, 4.1, 10.3 Hz, H-3), 3.93 (dd, 1H, J 2.6, 4.4 Hz, H-1'), 4.89 (dq, 1H, J 4.4, 6.5 Hz, H-2'). MS (EI) m/z: M^+ 373. Anal. Calcd for $C_{18}H_{35}NO_5Si$: C, 57.90; H, 9.38; N, 3.75. Found: C, 58.2; H, 9.7; N, 3.4.

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