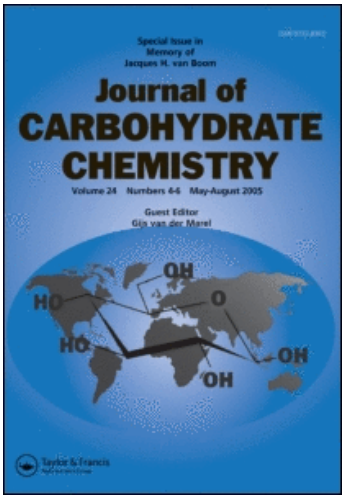

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From Tri-*O*-Acetyl-D-Glucal to (2*R*,3*R*,5*R*)-2,3-Diazido-5-Hydroxycyclohexanone Oxime

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From Tri-*O*-Acetyl-D-Glucal to (2*R*,3*R*,5*R*)-2,3-Diazido-5-Hydroxycyclohexanone Oxime

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CONTENTS

ABSTRACT

Methyl 3-azido-2,3-dideoxy-α/β-D-*arabino*- and -α/β-D-*ribo*-hexopyranosides were transformed into 6-iodo analogues *via* *p*-tolylsulfonyl compounds. Elimination of hydrogen iodide from 6-iodo glycosides provided methyl 4-*O*-acetyl-3-azido-2,3,

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6-trideoxy-α- and -β-D-*threo*-hex-5-eno-pyranosides or 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*threo*- and -β-D-*erythro*-hex-5-eno-pyranosides. Ferrier's carbocyclization of 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α- and -β-D-*threo*-hex-5-eno-pyranosides gave (2*S*,3*R*,5*R*)-2-acetoxy-3-azido-5-hydroxycyclohexanone, which was converted into oxime. The 2-OAc group in oxime was substituted by azide ion to yield (2*R*,3*R*,5*R*)-2,3-diazido-5-hydroxycyclohexanone oxime. The configuration and conformation of all products are widely discussed on the basis of the ^{1}H and ^{13}C NMR.

Key Words: Azide; Tosylation; Iodination; Hex-5-eno-pyranoside; Ferrier's carbocyclization; Oxime.

INTRODUCTION

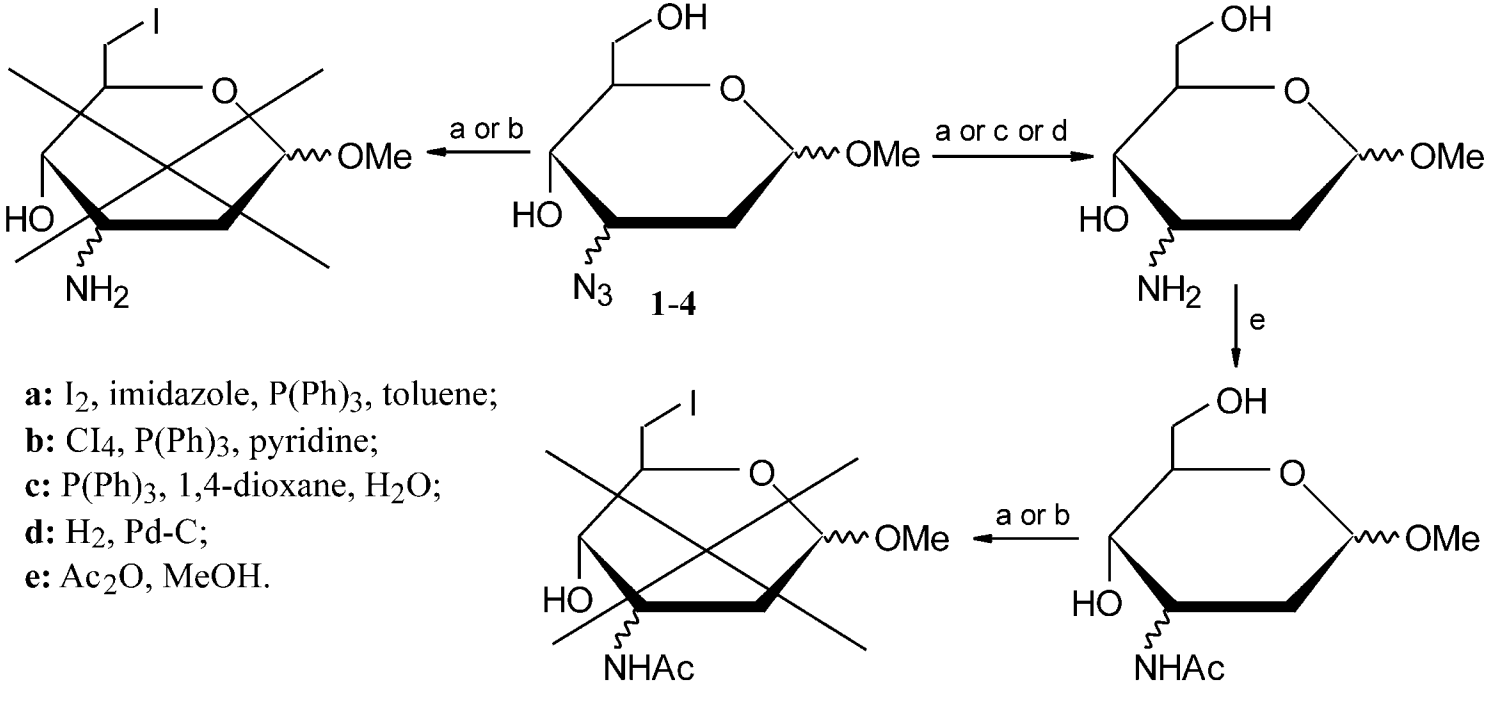
Ferrier's carbocyclization reaction is one of the most efficient methods for the preparation of chiral substituted cyclohexanones from aldohexoses.[1,2] Products of this reaction are used as precursors of different bio-active substances such as cyclitols and aminocyclitols[3–10] as well as natural compounds and their analogues containing a cyclitol unit.[11–20] Previously our interest was focused on the addition of hydrazoic acid to α,β-unsaturated aldehydes derived from acetylated glycals, a useful source of 3-azido-2,3-dideoxy sugars.[21–23] In this paper, we report the preparation of 2-acetoxy-3-azido-5-hydroxycylohexanone oxime from tri-*O*-acetyl-D-glucal *via* addition of hydrazoic acid followed by Ferrier's carbocyclization. Combination of this addition with Ferrier's carbocyclization could be a simple procedure of obtaining amino- and diaminocyclitols. Bearing in mind our previous experiences concerning 2-hydroxyimino glycosides,[24–26] we explored the ability of substitution of 2-OAc group by azide ion in this cyclohexanone oxime.

RESULTS AND DISCUSSION

Four stereoisomers of methyl 3-azido-2,3-dideoxyhexopyranosides (**1**–**4**, Schs. 1 and 2) were synthesized starting from tri-*O*-acetyl-D-glucal as previously reported.[22] In order to transform them into methyl 3-amino-6-iodo-2,3,6-trideoxyhexopyranosides, first Garegg's method [I_2, imidazole, $P(Ph)_3$] was employed.[27] We assumed that triphenylphosphine, used in iodination procedure, would also reduce 3-N_3 group. This idea was abandoned because the only product formed during reaction course was identified as methyl 3-amino-2,3-dideoxyhexopyranoside (Sch. 1). No iodination reaction occurred, no matter whether the reaction was carried out at room or at higher temperatures (70°C and 120°C). The same 3-amino-2,3-dideoxyhexopyranoside was obtained by direct reduction of 3-N_3 group when triphenylphosphine or catalytic hydrogenation was used. Because Garegg's method was applied successfully with other compounds,[3,16,17] we concluded that 3-N_3 group, present in our substrates, is responsible for the lack of the iodination reaction.

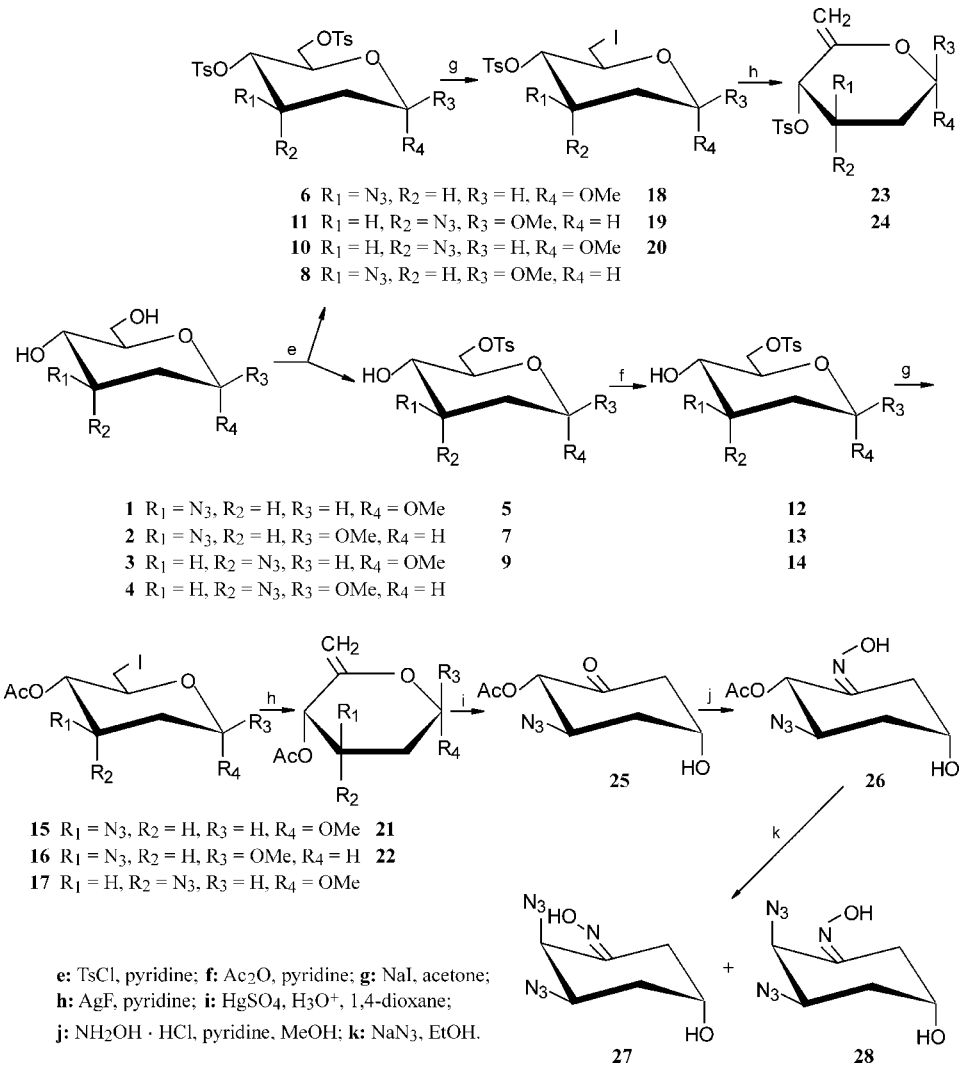
Similarly, iodination products were not detected while Anisuzzaman's method [CI_4, $P(Ph)_3$, pyridine] was applied to 3-azido glycosides (Sch. 1).[28]

Iodination of methyl 3-acetamido-2,3-dideoxyhexopyranosides, derived from 3-amino analogues (Sch. 1) with Garegg's or Anisuzzaman's strategy, was also unsuccessful.



a: I_2, imidazole, $P(Ph)_3$, toluene;
b: CI_4, $P(Ph)_3$, pyridine;
c: $P(Ph)_3$, 1,4-dioxane, H_2O;
d: H_2, Pd-C;
e: Ac_2O, MeOH.

Scheme 1.



Scheme 2.

These negative results prompted us to introduce iodide ion *via* tosylation reaction of the terminal hydroxyl group. Tosylation of **1**–**4** with *p*-tolylsulfonyl chloride in pyridine (Sch. 2) gave respective mixtures of methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl- (**5**, **7**, **9**) and -4,6-di-*O*-*p*-tolylsulfonylhexopyranosides (**6**, **8**, **10**, **11**). Contrary to our expectation, tosylation reaction was not regioselective, thus both the primary and secondary hydroxyl groups were substituted. In the case of **4** only ditolylsulfonyl derivative **11** was gained.

The presence of the tosyl groups in **5**–**11** is undoubtedly proved by IR, ^{1}H, and ^{13}C NMR data. Worthy of notice is a significant difference in the chemical shifts of H-4

protons in **5**–**11** when monotosyl (4-OH) and ditosyl (4-OTs) analogues are compared ($\Delta\delta$ 0.8–0.9), showing the deshielding influence of the *p*-tolylsulfonyl group (Table 1).

Acetylation of monotosyl glycosides **5**, **7**, and **9** led to **12**, **13**, and **14**, which were refluxed with sodium iodide in acetone to yield methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxyhexopyranosides (**15**, **16**, and **17**, respectively). The same iodination reaction of ditosyl glycosides (**6**, **10**, and **11**) was regioselective and gave only methyl 3-azido-6-iodo-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxyhexopyranosides (**18**, **19**, and **20**, respectively). The signals of the protons of *p*-tolylsulfonyl group were absent in the ^{1}H NMR spectra of **15**–**17** and corresponded to one tosyl group in **18**–**20**. Additionally, the H-6 protons signals of 6-iodo compounds (**15**–**20**) were shifted to a higher field by ~0.9 ppm as compared to H-6 protons of 6-OTs glycosides (**5**–**14**), indicating replacement of the *p*-tolylsulfonyl group. Noteworthy is the relatively small chemical shift of C-6 carbon in the ^{13}C NMR spectra of **15**–**20** (δ 4–6), which we found characteristic for 6-iodo sugars (Table 3).

The coupling constants of glycosides **5**–**20** confirm their structures (Table 2). Thus, the coupling constants $J_{2a,3} \sim 12$ Hz and $J_{3,4} \sim J_{4,5} = 9-10$ Hz are indicative for D-*arabino* (**5**–**8**, **12**, **13**, **15**, **16**, **18**) while $J_{2a,3} \sim J_{3,4} = 3-4$ Hz and $J_{4,5} = 9-10$ Hz for D-*ribo* configurations (**9**–**11**, **14**, **17**, **19**, **20**). All anomeric protons usually appear as doublets with coupling constant $J_{1,2a} = 3-4$ Hz (α anomers) or 8–9 Hz (β anomers). The $J_{1,2e}$ coupling constant is not recorded or is small (1–2 Hz) for 2-deoxyglycosides **5**–**20**, which is due to the anti-periplanar orientation of the ring oxygen atom to equatorially oriented H-2$_e$ proton.[29] Additional proof for configuration of the anomeric carbon comes from the chemical shifts of H-1 protons. The H-1 signals of α anomers (**5**, **6**, **9**, **10**, **12**, **14**, **15**, **17**, **18**, **20**) appear at higher δ values than those of the analogous protons of β anomers (**7**, **8**, **11**, **13**, **16**, **19**), owing to the respective equatorial and axial orientation of the H-1 proton (Table 1).

All the aforementioned findings are in accordance with the $^4C_1$ (D) conformation of compounds **5**–**20**.

6-Iodo glycosides (**15**–**20**) treated with silver fluoride in pyridine gave methyl 4-*O*-acetyl-3-azido- (**21**, **22**) and -3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-hex-5-eno-pyranosides (**23**, **24**), respectively. Lack of both, the H-5 proton signal and geminal coupling constant $J_{6,6'} = 10-14$ Hz, in the ^{1}H NMR spectra of **21**–**24** is an evidence for 5-eno structure of **21**–**24**. Next, the chemical shifts of the H-6 protons ($\delta \sim 4.7$) show deshielding influence of the double bond, which is also observed in the ^{13}C NMR spectra by the chemical shifts of the C-5 and C-6 carbons (~150 and ~100 ppm, respectively).

Introduction of an exocyclic double bond to the pyranose ring has a significant influence on the conformation of 5-enoglycosides (**21**–**24**, Sch. 3). Only these with α-D-*threo* configurations (**21** and **23**) keep the $^4C_1$ form, which is demonstrated by coupling constants $J_{2a,3} \sim 12$ Hz and $J_{3,4} \sim 10$ Hz. The $^4C_1$ conformation is optimal for **21** and **23** because both 3-N_3 and 4-OAc groups are equatorially oriented and an anomeric effect is omitted. The opposite configuration of the anomeric carbon is the sole difference when **21** (α-D-*threo*) and **22** (β-D-*threo*) are compared. This difference causes a deviation from $^4C_1$ form in the case of **22**, probably due to an unfavorable anomeric effect. The coupling constants $J_{2a,3} = J_{3,4} = 8.1$ Hz and $J_{1,2a} = 5.8$ Hz allow us to presume the conformational equilibrium between $^4C_1$ and $^1C_4$ forms in **22**. Both an anomeric effect and axially oriented 3-N_3 group are responsible for the change of the $^4C_1$ into $^1C_4$ form in **24**. The $^1C_4$ conformation of **24** is established on the basis of $J_{1,2a} = 3.5$ Hz and

Table 1. The chemical shifts in ^{1}H NMR spectra (ppm) for compounds **5**–**24** (400 MHz, $CDCl_3$).

	H-1	H-2_a	H-2_e	H-3	H-4	H-5	H-6	H-6′	4-OAc	4-OH	OCH_3	OTs
5	4.74	1.66	2.11	3.77	3.49	3.71	4.20	4.41	—	2.74	3.29	7.59 (2d)
	(d)	(td)	(dd)	(qd)	(d)	(m)	(dd)	(dd)		(bs)	(s)	2.46 (s)
6	4.73	1.67	2.13	3.78	4.29	3.92	4.10	4.42	—	—	3.30	7.58 (4d)
	(d)	(td)	(dd)	(qd)	(t)	(qd)	(dd)	(dd)			(s)	2.46 (s)
												2.47 (s)
7	4.40	1.56	2.18	3.46	3.31	3.43	4.37	4.27	—	2.87	3.43	7.57(2d)
	(d)	(m)	(m)	(m)	(t)	(m)	(dd)	(dd)		(bs)	(s)	2.46 (s)
8	4.39	1.61	2.22	3.48	4.23	3.66	4.05	4.43	—	—	3.43	7.59 (4d)
	(dd)	(td)	(dd)	(m)	(t)	(td)	(dd)	(dd)			(s)	2.46 (s)
9	4.68	1.98	2.14	4.09	3.72	3.97	4.35	4.23	—	2.58	3.32	7.58 (2d)
	(d)	(dt)	(dd)	(m)	(m)	(dd)	(dd)	(d)		(bs)	(s)	2.45 (s)
10	4.60	1.96	2.07	4.15	4.57	4.17	3.98	4.13	—	—	3.27	7.57(4d)
	(d)	(dt)	(dd)	(m)	(dd)	(m)	(dd)	(dd)			(s)	2.46 (s)
												2.48 (s)
11	4.53	1.70	2.01	4.19	4.48	3.95	3.87	4.07	—	—	3.31	7.57 (4d)
	(dd)	(td)	(dd)	(m)	(dd)	(m)	(dd)	(dd)			(s)	2.46 (s)
												2.48 (s)
12	4.75	1.68	2.12	3.86	4.75	3.92	4.04	4.09	2.09	—	3.32	7.57 (2d)
	(d)	(td)	(dd)	(qd)	(t)	(qd)	(dd)	(dd)	(s)		(s)	2.46 (s)
13	4.42	1.60	2.21	3.56	4.70	3.64	4.06	4.08	2.09	—	3.44	7.55 (2d)
	(dd)	(td)	(dq)	(qd)	(t)	(qd)	(dd)	(dd)	(s)		(s)	2.45 (s)

14	4.60 (d)	1.93 (td)	2.02 (dd)	4.13 (dt)	4.79 (dd)	4.20 (dq)	4.08 (dd)	4.17 (dd)	1.96 (s)	—	3.26 (s)	7.50 (2d) 2.38 (s)
15	4.84 (dd)	1.75 (td)	2.17 (dd)	3.88 (qd)	4.70 (t)	3.73 (td)	3.12 (dd)	3.29 (dd)	2.15 (s)	—	3.44 (s)	—
16	4.47 (dd)	1.67 (td)	2.25 (dq)	3.57 (qd)	4.68 (t)	3.43 (td)	3.14 (dd)	3.27 (dd)	2.15 (s)	—	3.56 (s)	—
17	4.76 (d)	2.08 (dt)	2.11 (dd)	4.19 (q)	4.75 (dd)	4.02 (qd)	3.23 (dd)	3.41 (dd)	2.16 (s)	—	3.47 (s)	—
18	4.82 (d)	1.74 (td)	2.18 (dd)	3.80 (dq)	4.26 (t)	3.75 (td)	3.22 (dd)	3.64 (dd)	—	—	3.42 (s)	7.62 (2d) 2.46 (s)
19	4.65 (dd)	1.79 (td)	2.06 (dd)	4.18 (q)	4.43 (t)	3.80 (td)	2.97 (dd)	3.33 (dd)	—	—	3.50 (s)	7.60 (2d) 2.48 (s)
20	4.70 (d)	2.00 (dt)	2.08 (dd)	4.11 (m)	4.44 (dd)	3.97 (td)	2.98 (dd)	3.36 (dd)	—	—	3.41 (s)	7.59 (2d) 2.45 (s)
21	4.88 (dd)	1.88 (qd)	2.23 (dq)	3.98 (dq)	5.28 (dt)	—	4.71 (t)	4.52 (t)	2.21 (s)	—	3.41 (s)	—
22	4.72 (dd)	1.88 (qd)	2.34 (dq)	3.70 (td)	5.32 (d)	—	4.76 (s)	4.55 (s)	2.17 (s)	—	3.51 (s)	—
23	4.83 (dd)	1.84 (qd)	2.22 (qd)	3.89 (qd)	4.81 (dt)	—	4.78 (s)	4.77 (s)	—	—	3.38 (s)	7.63 (2d) 2.46 (s)
24	4.94 (dd)	2.25 (td)	1.98 (dq)	3.88 (dt)	5.09 (d)	—	4.69 (s)	4.60 (s)	—	—	3.37 (s)	7.60 (2d) 2.44 (s)

Table 2. The ^{1}H-^{1}H coupling constants (Hz) for compounds **5**–**24** (400 MHz).

	Configuration	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
5	α-D-*arabino*	3.4	—	13.5	12.5	5.3	9.6	9.6	4.3	1.9	11.1
6	α-D-*arabino*	3.3	—	13.1	12.3	5.7	10.2	9.4	6.5	2.0	11.1
7	β-D-*arabino*	9.0	—	12.9	12.4	3.4	9.6	9.6	3.9	—	11.3
8	β-D-*arabino*	9.2	1.8	12.9	12.0	3.4	9.2	9.2	6.5	2.8	11.1
9	α-D-*ribo*	3.8	—	14.7	4.3	2.4	3.3	9.9	4.3	—	11.4
10	α-D-*ribo*	4.0	—	14.9	4.0	2.0	2.9	10.0	4.9	2.0	10.9
11	β-D-*ribo*	8.4	1.6	13.7	3.2	1.5	3.2	9.0	4.7	1.1	11.1
12	α-D-*arabino*	3.7	—	13.2	12.2	4.7	9.5	10.1	5.8	2.6	10.6
13	β-D-*arabino*	9.3	2.1	13.2	12.3	4.7	9.8	9.8	5.9	3.4	10.6
14	α-D-*ribo*	3.8	—	14.9	3.8	2.9	3.8	9.6	3.9	1.9	12.0
15	α-D-*arabino*	3.4	1.5	13.5	12.4	5.1	10.1	9.6	9.0	2.8	11.3
16	β-D-*arabino*	9.2	1.0	12.7	12.7	4.6	9.7	9.2	9.2	2.0	10.7
17	α-D-*ribo*	4.0	1.5	15.0	4.0	3.3	3.7	9.5	7.3	2.6	10.6
18	α-D-*arabino*	2.9	—	13.2	12.4	5.1	9.5	9.5	8.8	2.6	11.0
19	β-D-*ribo*	9.0	2.0	14.0	3.5	4.0	3.5	9.0	8.0	3.5	11.0
20	α-D-*ribo*	4.5	—	14.5	4.5	2.7	3.6	9.0	8.1	2.7	10.9
21	α-D-*threo*	3.3	1.5	13.6	12.1	4.8	9.9	—	—	—	1.5
22	β-D-*threo*	5.8	3.5	13.9	8.1	5.2	8.1	—	—	—	—
23	α-D-*threo*	3.3	1.8	13.6	11.7	4.8	10.2	—	—	—	—
24	β-D-*erythro*	3.5	1.0	13.0	13.0	4.5	3.0	—	—	—	—

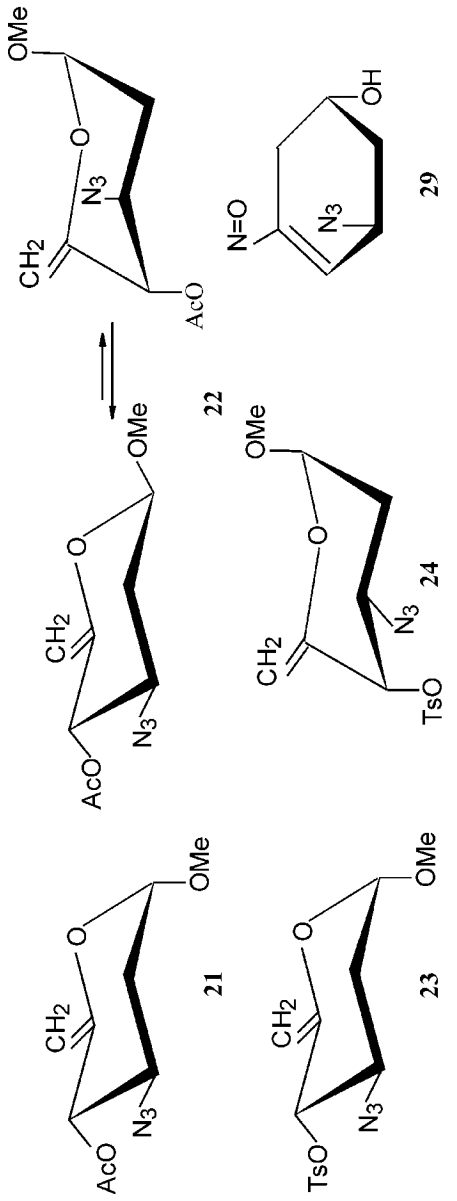
$J_{2a,3} = 13.0$ Hz coupling constants, which are characteristic for equatorial (H-1) and axial (H-2$_a$ and H-3) orientation of the respective protons. These findings are in accordance with the findings of the Sztaricskai group.[10]

As demonstrated, the conformation of the 5-eno glycosides (**21**–**24**) is flexible, and even a small change in their configuration has a significant influence on their conformation. This can be explained by an sp^2 hybridization of the C-5 carbon, which causes no significant differences between $^4C_1$ and $^1C_4$ forms. If the $-CH_2OR$ group is bonded to an sp^3 hybridized C-5 carbon atom, its equatorial orientation is strongly preferred and forces the $^4C_1$ (D) form.

The mercury salt mediated carbocyclic ring transformation reaction of **21** and **22** led to (2*S*,3*R*,5*R*)-2-acetoxy-3-azido-5-hydroxycyclohexanone (**25**). As expected,[10,30] carbocyclization was highly stereoselective and provided only cyclohexanone with 5-OH and 3-N_3 groups *trans*. The structure of **25** was established as follows. Instead of one, there are two methylene groups in the ^{1}H NMR spectrum of **25** with chemical shifts at 1.91 (H-4$_a$), 2.42 (H-4$_e$), 2.64 (H-6$_a$), and 2.68 (H-6$_e$) (Table 4). Presence of the 5-OH group is demonstrated by the signal at 3.75 ppm and by the IR spectra, where OH band (3467 cm^{-1}) is recorded. In the ^{13}C NMR spectra the C-1 carbon atom is the most dishielding (δ 199.08), indicating ketone carbonyl group (Table 6). The crucial question in the structure of **25** refers to the configuration of the newly generated asymmetric center (C-5). The coupling constants $J_{2,3} = 10.5$ and $J_{3,4a} = 12.5$ Hz point to the axial orientation of H-2, H-3, and H-4$_a$ protons and the $^2C_5$ conformation of **25**. The $^2C_5$ form, together with coupling constants $J_{4a,5} = 3.5$ Hz, $J_{4e,5} = 2.0$ Hz, and $J_{5,6a} = J_{5,6e} = 3.0$ Hz, indicate 5*R* configuration of C-5 carbon atom (Table 5).

Table 3. The chemical shifts in ^{13}C NMR spectra (ppm) for compounds **5**–**24** (400 MHz).

	C-1	C-2	C-3	C-4	C-5	C-6	CH_3 (Ac)	CH_3 (Ts)	OMe	$-C_6H_4-$ (Ts)	C=O (Ac)
5	97.82	34.77	60.07	69.99	69.92	68.99	—	21.89	55.07	145.24–128.11	—
6	97.03	35.58	58.25	77.23	68.07	68.63	—	22.03 22.01	55.28	145.44–128.08	—
7	100.80	35.80	62.12	74.41	70.05	68.76	—	21.92	56.87	145.29–128.25	—
8	100.17	36.24	60.15	76.97	72.77	68.58	—	21.99 21.94	56.99	145.74–128.16	—
9	96.87	32.46	58.22	66.59	66.54	69.67	—	21.89	55.69	145.18–128.12	—
10	96.90	33.15	56.67	74.25	63.35	68.27	—	21.96 21.87	55.84	146.06–128.18	—
11	98.45	35.11	57.89	74.34	68.04	69.72	—	21.98 21.86	56.70	146.22–128.11	—
12	97.48	34.95	57.72	70.60	68.06	68.08	20.90	21.93	55.25	145.15–128.26	169.74
13	100.53	35.92	59.75	72.62	70.62	68.62	21.01	21.96	56.98	145.17–128.13	169.87
14	97.20	32.78	55.89	68.73	63.70	68.29	20.79	21.97	55.80	144.99–128.07	169.92
15	97.72	35.27	57.67	74.47	70.01	4.46	21.05	—	55.50	—	170.10
16	100.57	36.29	59.78	74.12	74.65	4.11	21.22	—	57.19	—	169.82
17	97.40	33.20	56.20	73.53	64.90	6.40	21.00	—	56.00	—	169.80
18	97.37	35.95	58.16	81.46	69.55	5.35	—	22.05	55.67	145.39–128.04	—
19	98.87	35.91	58.55	78.59	71.33	4.60	—	22.00	57.02	146.11–128.30	—
20	97.18	33.51	56.79	78.53	64.83	5.21	—	21.88	56.11	145.84–128.06	—
21	98.80	35.20	55.60	71.90	151.60	96.30	21.10	—	57.80	—	169.70
22	100.45	33.25	56.65	70.72	151.37	97.59	21.28	—	57.68	—	169.42
23	99.10	35.66	58.46	78.47	150.93	98.66	—	22.12	55.63	145.30–128.08	—
24	99.13	29.65	54.20	77.05	149.63	103.39	—	22.00	55.73	144.98–128.01	—



Scheme 3.

Table 4. The chemical shifts in ^{1}H NMR spectra (ppm) for compounds **25**, **26** (400 MHz) and **27**, **28** (100 MHz).

	H-2	H-3	H-4$_a$	H-4$_e$	H-5	H-6$_a$	H-6$_e$	2-OAc	5-OH	NOH
25	5.18	4.22	1.91	2.42	4.50	2.64	2.68	2.24	3.75	—
$CDCl_3$	(d)	(qd)	(qd)	(dq)	(qw)	(dd)	(dd)	(s)	(bs)	
26	5.16	4.06	1.84	1.97	3.91	2.41	2.76	2.09	5.01	11.00
DMSO	(d)	(td)	(m)	(m)	(oct)	(dd)	(dd)	(s)	(d)	(s)
27	4.43	3.98	2.09	2.30	4.01	2.52	3.27	—	5.27	*
$CDCl_3$	(d)	(m)	(m)	(m)	(m)	(dd)	(dd)		(b)	
28	4.01	4.02	1.85	2.25	4.28	2.55	3.07	—	5.00	*
$CDCl_3$	(d)	(m)	(dq)	(dq)	(m)	(dd)	(dd)		(b)	

*Not determinated.

Reaction of ketone **25** with hydroxylamine yielded the oxime **26**. The transformation of carbonyl into hydroxyimino group is proved by the signal of N-OH proton in the ^{1}H NMR spectrum of **26** in DMSO solution (δ 11.00) and by the change in chemical shifts of the C-1 carbon atom in the ^{13}C NMR spectrum (Table 6). The signal of oxime carbon atom in **26** is shifted to the higher field (δ 150.15) in comparison to the carbonyl carbon atom in **25** (δ 199.08). The configuration of **26** remains the same as of **25**. However, a new stereogenic center resulting from an oxime group was created. Our investigations in NOESY experiment showed the interactions between N-OH and equatorially oriented H-6$_e$ protons and, consequently, the lack of the interactions between N-OH and H-2 protons. This means that oxime **26** has *E* configuration, which should be favorable because the equatorially oriented 2-OAc group in **26** is a steric hindrance for the *Z* orientation of hydroxyimine group.

It was reported that some groups neighboring to hydroxyimino function are easily eliminated to cause their replacement by nucleophiles including azide ion.[24–26] Thus, reaction of oxime **26** with sodium azide in ethanol provided (*Z*) and (*E*) (2*R*,3*R*,5*R*)-2,3-diazide-5-hydroxycyclohexanone oximes (**27** and **28**, respectively). Lack of the carbonyl group vibrations in the IR spectra of **27** and **28** (1760 cm^{-1} for **26**) indicates the substitution of 2-OAc group by azide ion. Additionally, the chemical shift of H-2 proton of starting oxime **26** is shifted to the lower fields when compared with H-2 proton signals of **27** and **28** ($\Delta\delta$ 0.73 and 1.15, respectively), which is due to the change of the 2-OAc into 2-N$_3$ group.[23] The $J_{5,6a} = 2.5$ and 3.5 Hz coupling constants

Table 5. The ^{1}H-^{1}H coupling constants (Hz) for compounds **25**, **26** (400 MHz) and **27**, **28** (100 MHz).

	$J_{2,3}$	$J_{3,4a}$	$J_{3,4e}$	$J_{4a,4e}$	$J_{4a,5}$	$J_{4e,5}$	$J_{5,6a}$	$J_{5,6e}$	$J_{5,OH}$	$J_{6a,6e}$
25	10.5	12.5	5.0	14.4	3.5	2.0	3.0	3.0	*	14.4
26	8.1	9.3	3.9	13.2	2.9	5.8	3.7	5.6	3.4	14.4
27	3.0	10.5	3.5	14.0	3.0	*	2.5	3.0	*	15.0
28	3.0	11.5	5.0	13.0	3.0	2.0	3.5	5.5	*	15.0

*Not determinated.

Table 6. The chemical shifts in ^{13}C NMR spectra (ppm) for compounds **25** and **26** (400 MHz).

	C-1	C-2	C-3	C-4	C-5	C-6	CH_3 (Ac)	C=O (Ac)
25	199.08	80.70	59.39	36.80	65.96	47.49	20.92	169.87
26	150.15	72.84	58.76	35.14	63.16	30.55	20.65	169.13

preclude the $^5C_2$ form for **27** and **28**; thus, relatively small $J_{2,3} = 3$ Hz coupling constant results from equatorial orientation of H-2 proton in **27** and **28**, which adopt $^2C_5$ form. This means that the configuration of C-2 carbon atom changed during reaction course and is *R* now. Discussed reaction occurs *via* elimination–addition mechanism, which probably involves a reactive intermediate **29** (Sch. 3)[24] and thus the change of C-2 as well as oxime configurations seems to be possible. The oxime and neighboring equatorial groups are nearly coplanar placed; therefore, the azide group prefers axial orientation in newly generated oximes **27** and **28**. This arrangement avoids unfavorable steric and electrostatic interactions. Bearing in mind previous conclusions concerning the effect of the hydroxyimino group on the position of ^1H NMR signals of adjacent protons[31,32] as well as the chemical shifts of H-2 for **27** (δ 4.43) and **28** (δ 4.01), it is established that oxime group has the *Z* orientation in **27** and *E* orientation in **28**.

EXPERIMENTAL

General methods. Melting points are uncorrected. Optical rotations were recorded at room temperature (20°C) using a Hilger-Watt polarimeter for solutions in $CHCl_3$. TLC was performed on the Merc Kieselgel 60 F-254 plates with: A, petroleum ether–AcOEt (1 : 2); B, petroleum ether–AcOEt (2 : 1); C, petroleum ether–AcOEt (4 : 1); D, CCl_4–acetone (3 : 1); E, n-heptane–AcOEt (1 : 2); F, n-heptane–AcOEt (1 : 1); G, $CHCl_3$–AcOEt (1 : 2); H, $CHCl_3$–AcOEt (2 : 1). Column chromatography was performed on MN Kieselgel 60 (<0.08 mm). The ^1H and ^{13}C NMR spectra ($CDCl_3$ or DMSO, internal Me_4Si) were recorded with a Varian Mercury 400 (400.49/100.70 MHz) or Varian XL-100 (100 MHz) instruments. IR spectra were recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. Elemental analyses were conducted with a Carlo Erba EA1108 elemental analyzer.

Methyl 3-azido-2,3-dideoxy-α-D-*arabino*- (1), -β-D-*arabino*- (2), -α-D-*ribo*- (3), and -β-D-*ribo*-hexopyranosides (4). Prepared according to procedure previously reported.[22]

General procedure for tosylation. To the solutions of **1**–**4** (0.2 g, 1 mmol) in CH_2Cl_2 (10 mL), dry pyridine (0.5 mL) and *p*-toluenesulfonyl chloride (0.95 g, 5 mM) were added. The mixtures were stirring at rt for 24–72 h, depending on the substrate. The end of the reactions was detected by TLC (solvent A). Then the mixtures were diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrates were concentrated and diluted with $CHCl_3$. The organic solutions were washed with satd $NaHCO_3$ solution, and with water and dried over Na_2SO_4. Concentration under reduced pressure led to the crude products, which were chromatographed (solvent B).

Methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl- (5) and -4,6-di-*O*-*p*-tolylsulfonyl-α-D-*arabino*-hexopyranosides (6). Tosylation of **1** yielded a mixture of two products, which were separated by column chromatography to give **5** and **6**, reported previously.[22]

Methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl- (7) and -4,6-di-*O*-*p*-tolylsulfonyl-β-D-*arabino*-hexopyranosides (8). Tosylation of **2** yielded a mixture of two products, which were separated by column chromatography to give first **7** (77%, syrup); $[\alpha]_D^{20} -3^\circ$ (*c* 0.8, $CHCl_3$); R_f 0.45 (solvent B); IR: ν 3511 (OH), 2103 (N_3), 1597 (C═C_{ar}), 1360, 1190, 1176 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C 47.05, H 5.35, N 11.76, S 8.97; Found: C 47.83, H 5.48, N 11.11, S 8.99.

Eluted second was **8** (2%); mp 119–121°C; $[\alpha]_D^{20} + 44^\circ$ (*c* 0.2, $CHCl_3$); R_f 0.52 (solvent B); IR: ν 2106 (N_3), 1597 (C═C_{ar}), 1362, 1190, 1176 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{21}H_{25}N_3O_8S_2$: C 49.30, H 4.93, N 8.21, S 12.54; Found: C 49.75, H 4.97, N 8.17, S 11.95.

Methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl- (9) and -4,6-di-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranosides (10). Tosylation of **3** yielded a mixture of two products, which were separated by column chromatography to give first **9** (53%, syrup); $[\alpha]_D^{20} + 177^\circ$ (*c* 0.3, $CHCl_3$); R_f 0.31 (solvent B); IR: ν 3496 (OH), 2105 (N_3), 1597 (C═C_{ar}), 1357, 1175 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_3O_6S$: C 47.05, H 5.35, N 11.76, S 8.97; Found: C 48.50, H 5.31, N 10.68, S 9.31.

Eluted second was **10** (18%, syrup); $[\alpha]_D^{20} + 125^\circ$ (*c* 1.2, $CHCl_3$); R_f 0.47 (solvent B); IR: ν 2107 (N_3), 1597 (C═C_{ar}), 1365, 1190, 1176 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{21}H_{25}N_3O_8S_2$: C 49.30, H 4.93, N 8.21, S 12.54; Found: C 50.77, H 5.34, N 7.90, S 11.50.

Methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-β-D-*ribo*-hexopyranoside (11). Tosylation of **4** yielded a crude product, which was chromatographed to give **11** (62%); mp 99–101°C; $[\alpha]_D^{20} + 26^o$ (*c* 0.6, $CHCl_3$); R_f 0.62 (solvent B); IR: ν 2104, (N_3), 1597 (C═C_{ar}), 1363, 1190, 1176 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{21}H_{25}N_3O_8S_2$: C 49.30, H 4.93, N 8.21, S 12.54; Found: C 49.46, H 4.92, N 7.88, S 12.32.

General procedure for acetylation. Compounds **5**, **7**, and **9** (0.357 g, 1 mmol) were acetylated with Ac_2O (2 mL) and pyridine (2 mL), respectively. During 0.5 h the reactions were over (TLC, solvent B). After dilution with CH_2Cl_2 (10 mL) the organic solutions were washed with satd $NaHCO_3$ solution and with water and dried over Na_2SO_4. Concentration under reduced pressure led to the crude products, which were chromatographed (solvent B).

Methyl 4-*O*-acetyl-3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-α-D-*arabino*-hexopyranoside (12). Acetylation of **5** led to **12**, reported previously.[22]

Methyl 4-*O*-acetyl-3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-β-D-*arabino*-hexopyranoside (13). Acetylation of **7** gave **13** (92%); mp 95–97°C; $[\alpha]_D^{20} + 15^\circ$ (*c* 0.6, $CHCl_3$); R_f 0.59 (solvent B); IR: ν 2102 (N_3), 1749 (C═O), 1597 (C═C_{ar}), 1364, 1189, 1176 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{16}H_{21}N_3O_7S$: C 48.11, H 5.30, N 10.52, S 8.03; Found: C 48.26, H 5.41, N 9.83, S 7.76.

Methyl 4-*O*-acetyl-3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-α-D-*ribo*-hexopyranoside (14). Acetylation of **9** yielded **14** (85%, syrup); $[\alpha]_D^{20}$ +131° (*c* 0.2, $CHCl_3$); R_f 0.56 (solvent B); IR: ν 2104 (N_3), 1742 (C═O), 1597 (C═C_{ar}), 1366, 1189, 1177 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{16}H_{21}N_3O_7S$: C 48.11, H 5.30, N 10.52, S 8.03; Found: C 48.69, H 5.25, N 10.01, S 7.58.

General procedure for substitution of 6-OTs group by iodide ion. The solutions of **6**, **10**, **11** (0.511 g, 1 mmol), and **12**–**14** (0.399 g, 1 mmol) in acetone (15 mL) containing NaI (0.75 g, 5 mmol) were refluxed, respectively. After 24 h the mixtures were cooled and diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrates were concentrated and acetone (15 mL) containing NaI (0.75 g, 5 mmol) was added again. The mixtures were refluxed the next 24 h. The end of reactions was verified by TLC (solvent C). Then the mixtures were cooled and diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrates were concentrated and diluted with $CHCl_3$. The organic solutions were washed with aq $Na_2S_2O_3$ and water, dried over Na_2SO_4, and concentrated to give the crude products, which were chromatographed (solvent C).

Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (15). Iodination of **12** gave **15**, reported previously.[22]

Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-β-D-*arabino*-hexopyranoside (16). Iodination of **13** yielded **16** (42%); mp 79–80°C; $[\alpha]_D^{20}$ +6° (*c* 0.4, $CHCl_3$); R_f 0.65 (solvent C); IR: ν 2101 (N_3), 1746 (C═O) cm^{-1}.

Anal. Calcd for $C_9H_{14}N_3O_4I$: C 30.44, H 3.97, N 11.83; Found: C 30.63, H 3.93, N 11.72.

Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (17). Iodination of **14** led to **17** (40%, syrup); $[\alpha]_D^{20}$ +103° (*c* 0.2, $CHCl_3$); R_f 0.58 (solvent C); IR: ν 2103 (N_3), 1739 (C═O) cm^{-1}.

Methyl 3-azido-6-iodo-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (18). Iodination of **6** gave **18**, reported previously.[22]

Methyl 3-azido-6-iodo-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-β-D-*ribo*-hexopyranoside (19). Reaction of **11** with NaI yielded **19** (36%); mp 78–80°C; $[\alpha]_D^{20}$ +7° (*c* 0.4, $CHCl_3$); R_f 0.58 (solvent C); IR: ν 2104 (N_3), 1597 (C═C_{ar}), 1371, 1190, 1177 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_3O_5SI$: C 35.99, H 3.88, N 8.99, S 6.86; Found: C 36.78, H 3.90, N 8.72, S 6.59.

Methyl 3-azido-6-iodo-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*ribo*-hexopyranoside (20). Reaction of **10** with NaI led to **20** (38%); mp 88–90°C; $[\alpha]_D^{20}$ +111° (*c* 1.3, $CHCl_3$); R_f 0.39 (solvent C); IR: ν 2106 (N_3), 1597 (C═C_{ar}), 1369, 1190, 1177 (O═S═O) cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_3O_5SI$: C 35.99, H 3.88, N 8.99, S 6.86; Found: C 37.07, H 3.92, N 8.76, S 6.86.

General procedure for elimination of hydrogen iodide. To the solutions of **15**, **16** (0.284 g, 0.4 mmol) and **18**, **19** (0.187 g, 0.4 mmol) in pyridine (2 mL), AgF (0.076 g, 0.6 mmol) was added, respectively. The mixtures were protected against the light and stirred. After 48 h TLC (solvent C) indicated the end of the reactions. Then the mixtures were diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrates were concentrated and diluted with $CHCl_3$. The organic solutions were washed with aq $Na_2S_2O_3$ and water, dried over Na_2SO_4, and concentrated. The crude products were chromatographed (solvent C).

Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-D-*threo*-hex-5-eno-pyranoside (21). Reaction of **15** with AgF in pyridine gave **21** (69%, syrup); $[\alpha]_D^{20}$ +112° (*c* 0.2, $CHCl_3$); R_f 0.72 (solvent C); IR: ν 2105 (N_3), 1746 (C═O), 1662 (C═C) cm^{-1}.

Anal. Calcd for $C_9H_{13}N_3O_4$: C 47.57, H 5.77, N 18.49; Found: C 47.96, H 5.97, N 18.06.

Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*threo*-hex-5-eno-pyranoside (22). Reaction of **16** with AgF in pyridine yielded **22** (72%, syrup); $[\alpha]_D^{20}$ −105° (*c* 0.3, $CHCl_3$); R_f 0.60 (solvent C); IR: ν 2104 (N_3), 1749 (C═O), 1663 (C═C) cm^{-1}.

Anal. Calcd for $C_9H_{13}N_3O_4$: C 47.57, H 5.77, N 18.49; Found: C 47.77, H 5.93, N 17.50.

Methyl 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*threo*-hex-5-eno-pyranoside (23). Reaction of **18** with AgF in pyridine led to **23** (63%, syrup); $[\alpha]_D^{20}$ +174° (*c* 0.2, $CHCl_3$); R_f 0.50 (solvent C); IR: ν 2107 (N_3), 1664 (C═C), 1599 (C═C_{ar}), 1371, 1190, 1177 (O═S═O) cm^{-1}.

Methyl 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-β-D-*erythro*-hex-5-eno-pyranoside (24). Reaction of **19** with AgF in pyridine gave **24** (68%, syrup); $[\alpha]_D^{20}$ +20° (*c* 0.2, $CHCl_3$); R_f 0.48 (solvent C); IR: ν 2105 (N_3), 1668 (C═C), 1597 (C═C_{ar}), 1365, 1190, 1177 (O═S═O) cm^{-1}.

(*2S*, *3R*, *5R*)-2-Acetoxy-3-azide-5-hydroxycyclohexanone (25). To a solution of **21** (0.12 g, 0.53 mmol) in 1,4-dioxane (3 mL), 5 mM H_2SO_4 (1.3 mL) and catalytic amount of $HgSO_4$ were added. The mixture was boiled under reflux. After 15 min TLC (solvent C) showed the end of the reaction. The cooled mixture was extracted with ethyl acetate (4 × 5 mL). The combined extracts were washed with aq $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated. The residue was chromatographed (solvent D) to give **25** (88%); mp 80–81°C; $[\alpha]_D^{20}$ −14° (*c* 1.0, $CHCl_3$); R_f 0.38 (solvent D); IR: ν 3467 (OH), 2109 (N_3), 1744 (ester C═O), 1736 (ketone C═O) cm^{-1}.

Anal. Calcd for $C_8H_{11}N_3O_4$: C 45.07, H 5.20, N 19.71; Found: C 45.12, H 5.42, N 19.27.

Analogous procedure applied to **22** led to **25** in 85% yield.

(*E*)-(*2S*, *3R*, *5R*)-2-acetoxy-3-azide-5-hydroxycyclohexanone oxime (26). To a solution of **25** (0.09 g, 0.42 mmol) in MeOH (1.3 mL), hydroxylamine hydrochloride (0.0293 g, 0.42 mmol) and pyridine (0.16 mL) were added. The mixture was stirred at rt. After 1 h TLC (solvent E) indicated the lack of the substrate. Then the mixture was diluted with $CHCl_3$, extracted with H_2O, dried (Na_2SO_4), and concentrated. Column chromatography (solvent F) of the residue yielded **26** (92%, syrup); $[\alpha]_D^{20}$ −64° (*c* 1.1, $CHCl_3$); R_f 0.52 (solvent E); IR: ν 3600 (OH), 2100 (N_3), 1760 (ester C═O), 1640 (C═N oxime), 1240 (ester C-O-C) cm^{-1}.

Anal. Calcd for $C_8H_{12}N_4O_4$: C 42.11, H 5.30, N 24.55; Found: C 43.63, H 5.17, N 25.73.

(*Z*) and (*E*) (*2R*, *3R*, *5R*)-2,3-diazide-5-hydroxycyclohexanone oximes (27, 28). To a solution of **26** (0.14 g, 0.61 mmol) in 96% ETOH (30 mL), NaN_3 (0.5 g, 7.7 mmol) was added. The mixture was refluxed at ~40°C. After 2 h TLC (solvent G) showed the end of the reaction. Then the mixture was diluted with Et_2O (30 mL). Precipitated salts were filtered off. The filtrate was concentrated and diluted with AcOEt. The organic solution was washed with water, dried (Na_2SO_4), and concentrated. The crude product was chromatographed (solvent H) to give first **27** (34%, syrup); $[\alpha]_D^{20}$ −47° (*c* 0.1, $CHCl_3$); R_f 0.50 (solvent H); IR: ν 3200 (OH), 2100 (N_3), 1650 (C═N oxime) cm^{-1}.

Anal. Calcd for $C_6H_9N_7O_2$: C 34.12, H 4.30, N 46.43; Found: C 35.21, H 4.43, N 46.32.

Eluted second was **28** (47%, syrup); $[\alpha]_D^{20}$ -25° (*c* 0.4, $CHCl_3$); R_f 0.48 (solvent H); IR: ν 3240 (OH), 2200 (N_3), 1660 (C═N oxime) cm^{-1}.

Anal. Calcd for $C_6H_9N_7O_2$: C 34.12, H 4.30, N 46.43; Found: C 36.61, H 4.62, N 46.94.

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