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Note

Synthesis and conformational studies on methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-hex-5-enopyranosides of the L series

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Abstract—Methyl 3-azido-2,3-dideoxy-α-D-*xylo*-, -α-D-*lyxo*-, and -β-D-*xylo*-hexopyranosides were converted into 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy analogues via 6-*O*-*p*-tolylsulfonyl compounds. The elimination of hydrogen iodide from 6-iodo glycosides yielded methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-L-*erythro*-, -α-L-*threo*-, and -β-L-*threo*-hex-5-enopyranosides. The configuration and conformation of all products are evaluated in depth on the basis of ^{1}H and ^{13}C NMR data. Factors determining conformational energy in 4-*O*-protected-3-azido-2,3,6,-trideoxy-hex-5-enopyranosides are discussed.

Keywords: Tosylation; Iodination; Hex-5-enopyranosides; Enantiomers; Anomeric effect; Equatorial or axial orientation

6-Deoxy-hex-5-enopyranosides are compounds of great interest as they are used as substrates in carbocyclization reactions. The Ferrier rearrangement is the most common method for preparing chiral substituted cyclohexanones from aldohexoses.[1,2] This commonly used reaction has turned out to be the most appropriate for synthesizing different cyclitols and aminocyclitols,[3,4] aminocyclitol[5,6] and other antibiotics,[7] inositols[8,9] and its phosphates,[10–12] cyclophellitols,[13] pseudodisaccharides,[6] sesquiterpenes,[14,15] and carbaglucose-1-phosphate.[16] In 1997, Sinaÿ and co-workers[17] reported a triisobutylaluminum mediated rearrangement of 6-deoxy-hex-5-enopyranosides into cyclohexane derivatives. Triisobutylaluminum-mediated carbocyclization was successfully applied by van Boom and co-workers[18] Additionally, Sinaÿ and co-workers[19] outlined the titanium(IV) catalyzed rearrangement of 6-deoxy-hex-5-enopyranosides into cyclohexanones. On the other hand, hex-5-enopyranosides were successfully applied to the preparation of 2-[20] or 3-amino-2,3,6-trideoxy-hexopyranosides, carbohydrate constituents of anthracycline antibiotics and their analogues.[21–25] Recently, 6-deoxy-hex-5-enopyranosyl azides have been used as substrates in the synthesis of iminosugars.[26]

As a result of my interest in obtaining new chiral aminocyclitols from 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol, 4-*O*-acetyl-3-azido-2,3,6-trideoxy-hex-5-enopyranosides of the L series were synthesized and interesting conformational dependences were found, especially when compared with those of the D series. Conformational studies on the pyranose ring are important and have been meticulously investigated, because a detailed knowledge of the conformations of sugars is essential for understanding their physical, chemical, and biological properties.[27–31] The conformations of 6-deoxy-hex-5-enopyranosides undoubtedly play a significant role in the stereochemistry of the ring-closure reaction during carbocyclization.[32,33]

Methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-D-hexopyranosides (**1**–**3**, Scheme 1) were prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (tri-*O*-acetyl-D-galactal) as previously reported.[34]

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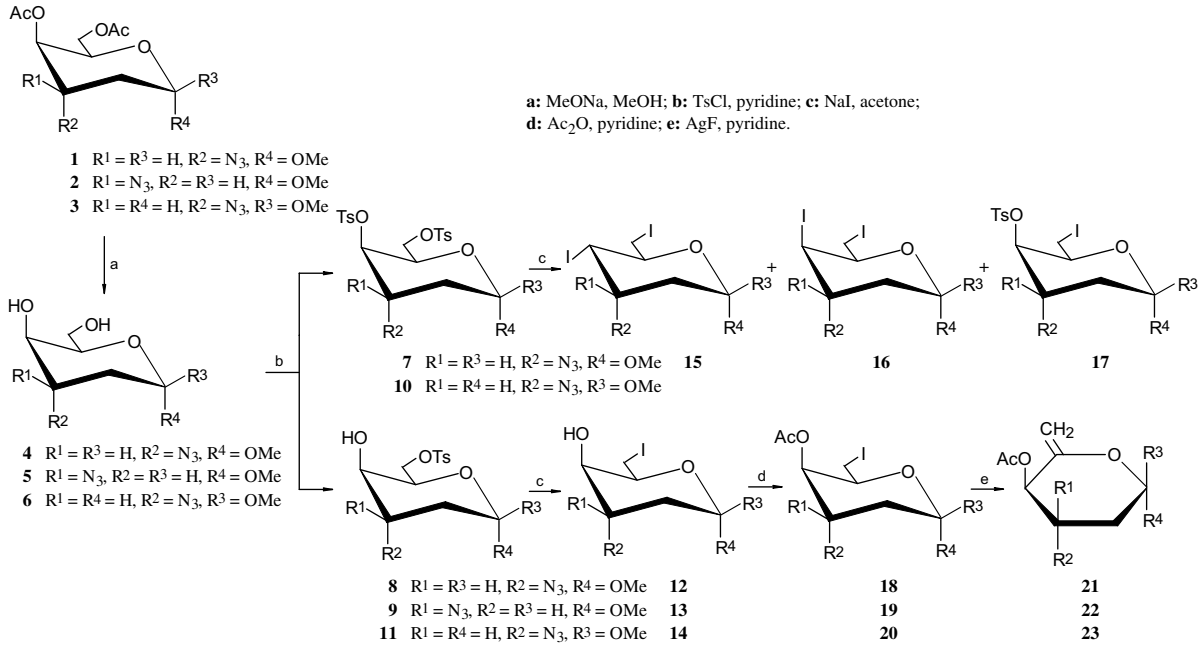

Scheme 1.

O-Deacetylation of **1**–**3** yielded methyl 3-azido-2,3-dideoxy-α-D-*xylo*- (**4**),[35] -α-D-*lyxo*- (**5**),[36] and -β-D-*xylo*-hexopyranosides (**6**), respectively. In order to transform compounds **4**–**6** into methyl 3-azido-2,3,6-trideoxy-hex-5-enopyranosides, an iodo substituent was introduced at C-6 and this step was followed by the elimination of hydrogen iodide. As reported earlier,[37] an application of both Garegg's[38] and Whistler–Anisuzzaman's[39] methods of direct iodination was not possible in the case of 3-azido-2,3-dideoxyhexopyranosides, probably because of the presence of the azide group. The classical strategy, involving the displacement of a *p*-tolylsulfonyl group with iodide, was therefore applied.

Tosylation of **4** with two equivalents of *p*-tolylsulfonyl chloride in pyridine gave a mixture of methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl- (**7**) and -6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranosides (**8**), which were separated by column chromatography as described previously.[35] The analogous tosylation of **5** was more regioselective and yielded solely methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexopyranoside (**9**). A mixture of methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-(**10**) and -6-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranosides (**11**), separated by column chromatography, was obtained when **6** was tosylated. The location of the tosyl groups in **7**–**11** was proven beyond doubt by IR, ^{1}H, and ^{13}C NMR data (Tables 1 and 3).

Iodination of monotosyl glycosides **8**, **9**, and **11** with sodium iodide in acetone led to **12**, **13**, and **14**, respectively. The same iodination reaction of ditosyl glycoside **7** provided a mixture of the 4,6-dideoxy-4,6-diiodo (**15** and **16**) and 6-deoxy-6-iodo-4-*O*-*p*-tolylsulfonyl compounds (**17**). The signals of the protons of the *p*-tolylsulfonyl group were absent from the ^{1}H NMR spectra of **12**–**16** confirmed the absence of tosyl group and the presence of such substituent in **17**. Additionally, comparison of the chemical shifts of 6-*O*-*p*-tolylsulfonyl glycosides (**7**–**9** and **11**) with their 6-iodo analogues (**17**, **12**–**14**) indicates the shielding influence of the iodine atom on the position of the H-6 proton signals in ^{1}H NMR spectra ($\Delta\delta \sim 0.8$–0.9). A more substantial shielding effect was observed in the ^{13}C NMR spectra of **13** and **14** for the C-6 carbon atoms bound to the iodo group. Such C-6 carbon atoms resonate at about 2–4 ppm: this we found characteristic of the other 6-iodo sugars, too.[37]

In order to enable the elimination of hydrogen iodide from 6-iodo glycosides, the unprotected 4-OH group in **12**–**14** was acetylated to yield **18**–**20**.

For our later conformational analysis, it is important to emphasize that the coupling constants of **4**–**19** (Table 2) confirm their configurations and the $^4C_1$ (D) conformation. Thus, the coupling constants $J_{2a,3} \sim 12.4$ Hz and the lack of observable coupling between the H-4 and H-5 protons indicate that **5**, **9**, **13**, and **19** have a D-*lyxo* configuration.[36] Similarly, the coupling constants $J_{2a,3} \sim 4$ Hz and $J_{4,5} \leqslant 1.6$ Hz are diagnostic for the D-*xylo* configuration in **4**, **6**–**8**, **10**–**12**, **14**, and **16**–**18**, likewise, $J_{2a,3} = 4$ Hz and $J_{4,5} = 10$ Hz for the D-*ribo* structure of **15**. All anomeric protons usually appear as doublets with coupling constant $J_{1,2a} \sim 4$ Hz (α anomers) or 8–9 Hz (β anomers). The $J_{1,2e}$ coupling constant in the case of α-anomers is obscured or small (1.2 Hz), which we found characteristic for 2-deoxyglycosides.[36] The $J_{1,2e}$ coupling constant of the β-anomers

Table 1. ^{1}H NMR chemical shifts ($CDCl_3$) for **4**–**19** and **21**–**23**

	H-1	H-2$_a$ [b]	H-2$_e$ [b]	H-3	H-4	H-5	H-6	H-6′	4-OAc	4-OH	6-OH	OCH_3	OTs
4[35]	4.81 (d)	2.28 (dt)	1.87 (dm)	3.81 (q)	3.72 (bd)	4.00 (td)	3.96 (dd)	3.91 (dd)	—	[c]	[c]	3.37 (s)	—
5[36]	4.93 (d)	2.18 (td)	1.93 (dd)	3.79 (ddd)	4.00 (bs)	3.76 (q)	3.97–3.85 (m)		—	2.84 (bs)	2.29 (b)	3.36 (s)	—
6	4.64 (dd)	2.04 (ddd)	1.86 (dt)	3.97 (m)	3.72 (dd)	3.79 (td)	3.90 (dd)	3.96 (dd)	—	[c]	[c]	3.52 (s)	—
7[35]	4.67 (d)	2.14 (dt)	1.86 (dm)	3.93 (q)	4.18 (d)	4.22 (ddd)	3.92 (dd)	3.73 (dd)	—	—	—	3.27 (s)	7.35 (d) 7.38 (d) 7.73 (d) 7.77 (d) 2.47 (s) 2.48 (s)
8[35]	4.72 (d)	2.17 (dt)	1.88 (dm)	3.81 (q)	3.55 (bs)	4.24 (td)	4.12 (dd)	4.19 (dd)	—	2.26 (b)	—	3.33 (s)	7.36 (d) 7.81 (d) 2.46 (s)
9	4.83 (d)	2.05 (td)	1.92 (dd)	3.81 (ddd)	3.86 (b)	3.97 (t)	4.13 (dd)	4.23 (dd)	—	2.10 (bs)	—	3.32 (s)	7.36 (d) 7.81 (d) 2.46 (s)
10	4.54 (dd)	1.93 (ddd)	1.86 (dt)	4.10 (m)	4.30 (dd)	4.06 (ddd)	3.99 (dd)	3.81 (dd)	—	—	—	3.41 (s)	7.36 (d) 7.74 (d) 7.76 (d) 2.46 (s) 2.48 (s)
11	4.56 (dd)	1.92 (ddd)	1.87 (dt)	3.94 (q)	3.58 (d)	4.02 (td)	4.13 (dd)	4.21 (dd)	—	[c]	—	3.44 (s)	7.36 (d) 7.80 (d) 2.46 (s)
12[a]	4.72 (dd)	2.20 (dt)	1.76 (dm)	3.78 (q)	3.55 (d)	4.05 (ddd)	3.27 (dd)	3.32 (dd)	—	[c]	—	3.43 (s)	—
13	4.88 (d)	2.05 (td)	1.89 (dd)	3.82 (ddd)	4.03 (b)	3.89 (t)	3.33 (d)			1.96 (d)	—	3.42 (s)	—
14	4.60 (dd)	1.92 (ddd)	1.85 (dt)	3.98 (q)	3.74 (dd)	3.94 (td)	3.31 (d)		—	2.30 (d)	—	3.55 (s)	—
15	4.90 (d)	2.25 (dt)	2.17 (ddd)	4.12 (q)	4.21 (dd)	3.83 (ddd)	3.53 (dd)	3.69 (dd)	—	—	—	3.48 (s)	—
16	4.76 (d)	2.55 (dt)	1.89 (bd)	4.21 (m)	4.37 (b)	3.41 (td)	3.25 (dd)	3.04 (dd)	—	—	—	3.43 (s)	—
17	4.75 (d)	2.16 (dt)	1.86 (dm)	3.97 (q)	4.34 (d)	4.20 (dd)	3.07 (dd)	2.87 (dd)	—	—	—	3.44 (s)	7.39 (d) 7.81 (d) 2.48 (s)
18	4.82 (d)	2.11 (dt)	1.89 (dm)	3.88 (q)	4.83 (d)	4.27 (td)	3.15 (d)		2.14 (s)	—	—	3.49 (s)	—
19	4.93 (d)	2.06 (td)	1.92 (dd)	3.82 (ddd)	5.35 (d)	3.99 (dd)	3.09 (t)	3.17 (dd)	2.17 (s)	—	—	3.45 (s)	—
21	4.71 (dd)	1.87 (ddd)	2.33 (ddd)	3.69 (td)	5.32 (d)	—	4.75 (t)	4.54 (t)	2.16 (s)	—	—	3.50 (s)	—
22	4.98 (bs)	2.30 (td)	2.03 (dd)	3.89 (dt)	5.54 (d)	—	4.74 (s)	4.77 (s)	2.14 (s)	—	—	3.41 (s)	—
23	4.88 (dd)	1.88 (ddd)	2.23 (ddd)	3.97 (ddd)	5.27 (dt)	—	4.71 (t)	4.51 (t)	2.21 (s)	—	—	3.41 (s)	—

[a] Solvent CD_3OD.

[b] Notations H-2$_a$ and H-2$_e$ refer to the axial and equatorial H-2 protons, respectively. In the case of **21** (conformational equilibrium), H-2 protons are neither axial nor equatorial, however they are still chemically and magnetically different.

[c] Not determined.

Table 2. ^{1}H–^{1}H coupling constants (Hz) for **4**–**19** and **21**–**23**

	Configuration	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,OH}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
4[35]	α-D-*xylo*	4.4	—	14.8	4.4	2.8	3.2	1.2	[b]	3.6	3.6	11.6
5[36]	α-D-*lyxo*	3.6	—	12.8	12.8	4.8	2.4	~0	[b]	9.2	5.2	[b]
6	β-D-*xylo*	9.2	2.0	14.0	3.6	3.2	3.6	1.6	[b]	4.4	4.4	12.0
7[35]	α-D-*xylo*	4.4	—	15.2	4.4	2.4	3.6	0.8	—	7.2	4.8	10.8
8[35]	α-D-*xylo*	4.4	—	15.2	4.4	2.8	3.6	1.2	[b]	6.8	5.6	10.4
9	α-D-*lyxo*	3.2	—	13.2	12.4	4.8	3.2	~0	[b]	6.0	5.6	10.4
10	β-D-*xylo*	8.8	2.4	14.4	3.6	2.8	3.6	0.8	—	6.8	5.2	10.0
11	β-D-*xylo*	8.4	3.6	14.4	4.0	3.2	3.6	1.2	[b]	6.8	6.0	10.4
12[a]	α-D-*xylo*	4.4	1.2	14.8	4.4	4.0	3.2	1.6	[b]	8.8	5.2	10.4
13	α-D-*lyxo*	3.2	—	12.8	12.4	4.8	2.4	~0	4.8	6.8		—
14	β-D-*xylo*	8.8	3.6	14.4	3.6	3.6	3.6	1.2	10.0	6.8		—
15	α-D-*ribo*	4.0	—	14.8	4.0	2.8	3.6	10.0	—	5.6	2.8	10.8
16	α-D-*xylo*	4.4	—	15.2	4.4	1.2	0.8	1.6	—	7.6	5.6	10.4
17	α-D-*xylo*	4.4	—	14.8	4.4	1.2	3.2	~0	—	8.8	4.8	10.4
18	α-D-*xylo*	4.4	—	15.2	4.4	3.2	3.2	1.2	—	7.6		—
19	α-D-*lyxo*	3.2	—	12.8	12.4	4.8	3.2	~0	—	9.2	4.4	10.8
21	β-L-*threo*	5.6	3.2	14.4	8.0	5.6	8.0	—	—	—	—	1.6
22	β-L-*erythro*	3.2	—	12.8	12.4	4.4	3.2	—	—	—	—	~0
23	α-L-*threo*	3.2	1.6	13.6	12.0	4.8	10.0	—	—	—	—	1.6

[a] Solvent CD_3OD.
[b] Not determined.

Table 3. Chemical shifts (ppm) of the carbon atoms in the ^{13}C NMR spectra ($CDCl_3$) of **4**–**11**, **13**, **14**, **17**–**19**, and **23**

	C-1	C-2	C-3	C-4	C-5	C-6	CH_3 (Ac)	CH_3 (Ts)	OCH_3	$-C_6H_4-$	C=O
4[35]	97.79	27.36	57.32	69.28	64.96		—	—	55.67	—	—
5[36]	98.32	28.97	56.66	68.91	69.34	64.11	—	—	55.18	—	—
6	99.75	30.80	59.95	68.24	72.57	63.85	—	—	56.86	—	—
7[35]	96.69	27.33	54.83	73.49	63.27	68.43	—	22.11	55.83	130.38	—
								22.02		129.97	
										128.02	
										127.95	
8[36]	97.25	27.52	57.26	66.43	64.31	69.02	—	22.01	55.79	130.03	—
										128.08	
9	98.04	29.01	56.37	66.41	67.96	68.93	—	21.88	55.29	130.14	—
										128.21	
10	98.76	30.93	57.93	72.49	70.03	67.80	—	21.97	56.79	130.42	
								21.91		130.15	—
										128.16	
										128.08	
11	99.41	30.90	59.74	65.84	71.20	68.43	—	21.89	56.76	130.18	—
										128.20	
13	98.83	28.85	57.08	67.96	70.84	3.41	—	—	55.58	—	—
14	99.97	30.58	60.24	67.09	74.22	2.60	—	—	56.98	—	—
17	97.46	27.17	55.36	74.93	66.22	2.09	—	21.94	56.17	130.45	—
										128.16	
18	97.62	27.83	54.89	68.90	66.10	2.57	21.02	—	56.15	—	170.21
19	98.34	29.67	54.66	69.03	70.33	2.31	20.93	—	55.71	—	170.56
23	98.91	35.15	57.82	71.88	151.82	96.28	21.00	—	55.49	—	169.78

in the range 2.0–3.6 Hz is typical of the equatorial and axial orientation of the coupled protons.

6-Iodo glycosides **18**–**20** treated with silver fluoride in pyridine gave methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-hex-5-enopyranosides (**21**–**23**). The lack of both the H-5 proton signal and geminal coupling constant $J_{6,6'} = 10$–12 Hz in the ^{1}H NMR spectra of **21**–**23** is evidence for the 5-eno structure of these compounds. In the case of **21**–**23**, the coupling constant $J_{6,6'} = 1.6$ Hz is recorded, which is typical of geminal protons on an sp^2 hybridized carbon atom. Next, the chemical shifts of the H-6 protons ($\delta \sim 4.5$–4.7) show the deshielding influence of the double bond, which is also indicated in the ^{13}C NMR spectra of **23** by the chemical shifts of the C-5 and C-6 carbons (~150 and ~96 ppm, respectively).

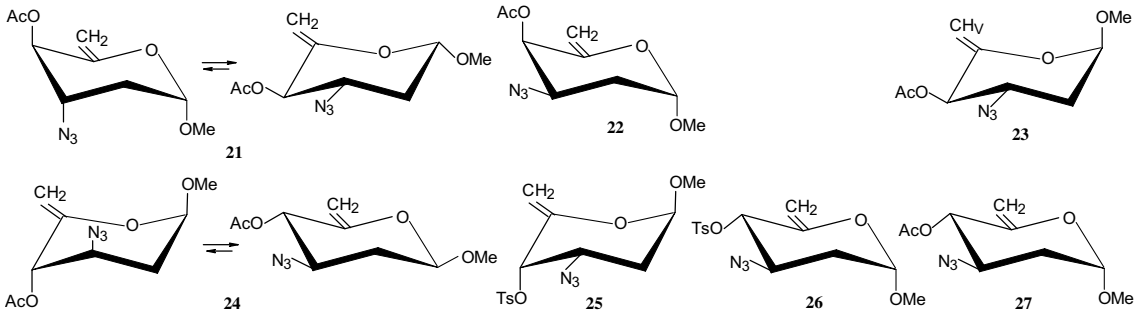

Figure 1. Compounds **24**–**27** were previously reported.[37]

As we reported earlier,[37] introducing an exocyclic double bond to the pyranose ring causes the conformation of the methyl 4-*O*-protected-3-azido-2,3,6-trideoxy-hex-5-enopyranosides to become more flexible and even a small change in its configuration has a significant influence on the conformation. Among the 5-eno compounds described here, only the one with the β-L-*erythro* configuration (**22**) adopts the $^4C_1$ conformation (Fig. 1): this is demonstrated by the coupling constants $J_{1,2a} = 3.2$, $J_{2a,3} = 12.4$, $J_{2e,3} = 4.4$ and $J_{3,4} = 3.2$ Hz. The $^4C_1$ conformation is optimal for **22** since the 3-N_3 group is equatorially oriented, and the anomeric effect is favorable because the diaxial interaction of 1-OMe and 3-N_3 groups is avoided. The opposite configuration of the C-3 carbon atom is the sole difference when **22** (β-L-*erythro*) and **21** (β-L-*threo*) are compared. This difference causes a deviation from $^4C_1$ form in the case of **21**, which is due to the unfavorable axial orientation of the azide group. The conclusion to be drawn from coupling constants $J_{1,2a} = 5.6$, $J_{2a,3} = 8.0$, $J_{2e,3} = 5.6$ and $J_{3,4} = 8.0$ Hz is that conformational equilibrium exists between the $^4C_1$ and $^1C_4$ forms in **21**. It is also possible that **21** adopts one of the skew-boat forms.

Both the favorable anomeric effect and the equatorially oriented 3-N_3 group in the $^1C_4$ conformation of **23** (α-L-*threo*) are responsible for the adoption of this chair. The $^1C_4$ conformation of **23** was established on the basis of the coupling constants $J_{1,2a} = 3.2$, $J_{2a,3} = 12.0$ and $J_{3,4} = 10.0$ Hz, which are characteristic of the equatorial orientation of the H-1 proton, and the axial orientation of the H-3 and H-4 protons.

Reported earlier,[37] our investigations of methyl 3-azido-2,3,6-trideoxy-hex-5-enopyranosides derived from tri-*O*-acetyl-D-glucal showed the same conformational flexibility of the sugar ring as described here. Among other compounds synthesized previously, we obtained methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-D-*threo*- (**24**) and -α-D-*threo*-hex-5-enopyranosides (**27**) as well as 3-azido-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-β-D-*erythro*- (**25**) and α-D-*threo*-hex-5-enopyranosides (**26**) (Fig. 1).[37] On comparing the 5-eno glycosides, synthesized then and now, and their conformations, we see that both **21** (β-L-*threo*) and **24** (β-D-*threo*) as well as **23** (α-L-*threo*) and **27** (α-D-*threo*) are pairs of enantiomers. Previously established conformations of **24**–**27**[37] are in agreement with the presently described conformations for **21**–**23**, which is the stereochemical proof for the correctness of our conformational analysis.

On the basis of earlier[37] and the present results, a few conclusions can be formulated. Firstly, the most important factor forcing methyl 3-azido-2,3-dideoxy-D-hexopyranosides (see all the precursors of 3-azido-2,3,6-trideoxy-hex-5-enopyranosides) to adopt the $^4C_1$ (D) form, is the equatorial orientation of the 5-CH_2OR group bound to an sp^3 hybridized C-5 carbon atom. None of the changes in the configuration of methyl 3-azido-2,3-dideoxy-D-hexopyranosides disturbs its $^4C_1$ (D) conformation, owing to the presence of an equatorially oriented 5-CH_2OR group. This means that the increase in stability resulting from the equatorial orientation of the 5-CH_2OR group is greater than the decrease in stability resulting from a combination of the axial orientation of the 4-OR and 3-N_3 groups and the unfavorable anomeric effect in the $^4C_1$ conformation of methyl 3-azido-2,3-dideoxy-β-D-*xylo*-hexopyranosides (**3**, **6**, **10**, **11**, and **14**). This most significant factor disappears when a double bond is formed on the C-5 carbon atom. Sp^2 hybridization of the C-5 carbon atom reduces the free energy differences between the $^4C_1$ and $^1C_4$ forms. The 5-eno compounds adopt the $^4C_1$ (**22**, **26**, **27**) or $^1C_4$ conformations (**23**, **25**) if other factors are advantageous, that is, if the 3-N_3 group is equatorially oriented and the anomeric effect is favorable (Table 4). If these two factors are not compatible (**21** and **24**) the conformation is not so evident.

The second important factor influencing the conformation, though not as strongly as the first one, is the anomeric effect. The opposite configuration of the anomeric carbon atom is the sole factor differentiating **24** from **27**, however **27** adopts a $^4C_1$ conformation while **24** exists in the $^4C_1/^1C_4$ conformational equilibrium. Such an equilibrium state means that the increase in stability resulting from the equatorial orientation of the 4-OAc and 3-N_3 groups in the $^4C_1$ form of **24** (or in the

Table 4. Increase (+) or decrease (−) in stability resulting from the different orientations of the 4-OR and 3-N_3 groups or from the anomeric effect in the chair conformations of **21**–**27**

Compound	Configuration	$^4C_1$ conformation			$^1C_4$ conformation		
		Orientation of		Anom. effect	Orientation of		Anom. effect
		4-OR	3-N_3		4-OR	3-N_3	
21	β-L-*threo*	−	−	+	+	+	−
22	β-L-*erythro*	−	+	+		Not adopted	
23	α-L-*threo*		Not adopted		+	+	+
24	β-D-*threo*	+	+	−	−	−	+
25	β-D-*erythro*		Not adopted		−	+	+
26	α-D-*threo*	+	+	+		Not adopted	
27	α-D-*threo*	+	+	+		Not adopted	

$^1C_4$ form of **21**) is comparable with the decrease in stability resulting from the removal from the anomeric effect, which takes place in this conformation. On the other hand, the anomeric effect has to be significantly diminished in the $^1C_4$ form of **24** (or in the $^4C_1$ form of **21**) because of unfavorable 1,3-diaxial interaction of 3-N_3 and 1-OMe groups.

Comparison of **22** and **27** shows that the axial orientation of 4-OAc group does not disturb the $^4C_1$ conformation of **22**. Next, the axial orientation of the 3-N_3 group, which forces the change in the conformations in **21** and **24** is accompanied by the axial orientation of the 4-OAc group. Unfortunately, we have no example in which the axial orientation of the 3-N_3 group can be compared with the axial orientation of the 4-OR group and the anomeric effect together (α-D-*erythro* configuration). Nevertheless, it is obvious that the axial orientation of the 3-N_3 group in **21** and **24** must be very unfavorable because of the 1,3-diaxial orientation of this group and an aglycone. On the other hand, it seems that the advantage originating from the equatorial orientation of the 4-OR group should be diminished because of the unfavorable coplanar arrangement of the methylene and equatorial 4-OR groups.[40] As a result, the equatorial orientation of the 4-OR group may have a smaller influence on the stability of the 5-eno glycosides.

To summarize the discussion on the conformation of methyl 3-azido-2,3,6-trideoxy-hex-5-enopyranosides and their precursors, three mathematical notations are proposed (Eqs. 1–3):

$$\Delta E_{\text{eq 5-CH}_2\text{OR}} > \Delta E_{\text{EA}} + \Delta E_{\text{eq 3-N}_3} + \Delta E_{\text{eq 4-OR}}, \quad (1)$$

$$\Delta E_{\text{EA}} \sim \Delta E_{\text{eq 3-N}_3} + \Delta E_{\text{eq 4-OR}}, \quad (2)$$

$$\Delta E_{\text{eq 3-N}_3} > \Delta E_{\text{eq 4-OR}}, \quad (3)$$

where ΔE is an energy gain (increase in stability) resulting from the equatorial orientation of the 5-CH_2OR or 3-N_3 or 4-OR groups or from an anomeric effect (EA).

1. Experimental

1.1. General methods

Melting points are uncorrected. Optical rotations were determined at room temperature with a Hilger–Watt polarimeter in 1 dm tubes at the D line of sodium for solns in $CHCl_3$. The IR spectra were recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. The ^1H and ^{13}C NMR spectra ($CDCl_3$, internal Me_4Si) were measured with a Varian Mercury 400 (400.49/100.70 MHz) instrument. TLC was performed on the E. Merck Kieselgel 60 F-254 plates using the following eluent systems (v/v): A, 4:1 petroleum ether–EtOAc; B, 1:4 petroleum ether–EtOAc; C, 2:1 toluene–EtOAc; D, 1:1 petroleum ether–$CHCl_3$; E, 3:1 toluene–EtOAc; F, 1:1 petroleum ether–EtOAc; G, 2:1 petroleum ether–EtOAc; H, 3:1 petroleum ether–EtOAc; I, 8:1 petroleum ether–EtOAc; J, 6:1 petroleum ether–EtOAc; K, 4:1 toluene–EtOAc. Column chromatography was performed on MN Kieselgel 60 (<0.08 mm).

1.2. Methyl 4,6-di-*O*-acetyl-3-azido-2,3-dideoxy-α-D-*xylo*- (1), -α-D-*lyxo*- (2), and -β-D-*xylo*-hexopyranosides (3)

These were synthesized as previously reported.[34]

1.3. Methyl 3-azido-2,3-dideoxy-α-D-*xylo*-hexopyranoside (4)

This was prepared from **1** as previously reported.[35]

1.4. Methyl 3-azido-2,3-dideoxy-α-D-*lyxo*-hexopyranoside (5)

This was synthesized from **2** as previously reported.[36]

1.5. Methyl 3-azido-2,3-dideoxy-β-D-*xylo*-hexopyranoside (6)

Deacetylation procedure reported earlier[36] and applied to **3** (1.564 g) led to **6** (1.067 g, 96%, syrup); $[\alpha]_D$ +13

(*c* 1.1, $CHCl_3$); R_f 0.38 (solvent B); IR: *v* 3405 (OH), 2102 (N_3) cm^{-1}.

1.6. General procedure for tosylation

To the soln of **4**, **5**, or **6** (0.2 g, 1 mM) in CH_2Cl_2 (10 mL), dry pyridine (0.5 mL) and *p*-toluenesulfonyl chloride (0.38 g, 2 mM) were added. The mixture was stirred at rt for 6–24 h, depending on the substrate. The end of the reaction was detected by TLC (solvent B). The mixture was then diluted with Et_2O (10 mL) and the precipitated salts were filtered off. The filtrate was concentrated and diluted with $CHCl_3$. The organic soln was washed with satd $NaHCO_3$ and water and dried over Na_2SO_4. Concentration under diminished pressure led to the crude products, which were chromatographed (solvent C).

1.6.1. Methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside (7) and methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-α-D-*xylo*-hexopyranoside (8). These were synthesized as previously reported.[35]

1.6.2. Methyl 3-azido-2,3-dideoxy-6-*O*-*p*-tolylsulfonyl-α-D-*lyxo*-hexopyranoside (9). Tosylation of **5** (0.843 g) yielded **9** (1.138 g, 77%, syrup); $[\alpha]_D^{20}$ +58 (*c* 0.9, $CHCl_3$); R_f 0.11 (solvent D); IR: *v* 3292 (OH), 2100 (N_3), 1597 (C=C_{ar}), 1357, 1189, 1175 (O=S=O) cm^{-1}.

1.6.3. Methyl 3-azido-2,3-dideoxy-4,6-di-*O*-*p*-tolylsulfonyl-(10) and -6-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranosides (11). Tosylation of **6** (1.023 g) led to a mixture of two product, which were separated by column chromatography to give first **10** (0.847 g, 33%, syrup); R_f 0.69 (solvent E); IR: *v* 2108 (N_3), 1597 (C=C_{ar}), 1190, 1176 (O=S=O) cm^{-1}.

Eluted second was **11** (0.682 g, 38%, syrup); $[\alpha]_D^{20}$ −6 (*c* 0.8, $CHCl_3$); R_f 0.53 (solvent E); IR: *v* 3447 (OH), 2103 (N_3), 1598 (C=C_{ar}), 1190, 1176 (O=S=O) cm^{-1}.

1.7. General procedure for substitution of 6-OTs group by iodide ion

The soln of **7**, **8**, **9**, or **11** (0.357 or 0.511 g, 1 mM) in acetone (12 mL) containing NaI (1.5 g, 10 mM) was refluxed. If the reaction was not completed within 24 h (TLC, solvent F) the mixture was cooled and diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrate was concentrated and acetone (10 mL) containing NaI (0.75 g, 5 mM) was added again. The reaction mixture was refluxed for 24–48 h. The end of reactions was verified by TLC (solvent F). The mixture was then cooled and diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrate was concentrated and diluted with $CHCl_3$. The organic soln was washed with aq $Na_2S_2O_3$ and water, dried over Na_2SO_4 and concentrated to give the crude product, which was chromatographed (solvent C).

1.7.1. Methyl 3-azido-6-iodo-2,3,6-trideoxy-α-D-*xylo*-hexopyranoside (12). Iodination of **8** (0.474 g) yielded **12** (0.357 g, 87%, syrup); R_f 0.47 (solvent G); IR: *v* 3439 (OH), 2106 (N_3) cm^{-1}.

1.7.2. Methyl 3-azido-6-iodo-2,3,6-trideoxy-α-D-*lyxo*-hexopyranoside (13). Iodination of **9** (1.095 g) gave **13** (0.807 g, 77%, syrup); $[\alpha]_D^{20}$ +90 (*c* 1, $CHCl_3$); R_f 0.45 (solvent A); IR: *v* 3459 (OH), 2102 (N_3).

1.7.3. Methyl 3-azido-6-iodo-2,3,6-trideoxy-β-D-*xylo*-hexopyranoside (14). Iodination of **11** (0.638 g) led to **14** (0.412 g, 75%, syrup); $[\alpha]_D^{20}$ +6 (*c* 0.7, $CHCl_3$); R_f 0.35 (solvent H); IR: *v* 3404 (OH), 2101 (N_3) cm^{-1}.

1.7.4. Methyl 3-azido-4,6-diiodo-2,3,4,6-tetradeoxy-α-D-ribo- (15) and -α-D-*xylo*-hexopyranosides (16), and methyl 3-azido-6-iodo-4-*O*-*p*-tolylsulfonyl-2,3,6-trideoxy-α-D-*xylo*-hexopyranoside (17). Iodination of **7** (0.530 g) followed by column chromatography (solvent I) gave first a mixture of **15** and **16** (0.105 g, 24%, syrup, **15**:**16** ~1:1.6, estimated by comparison of the area of H-1 peaks of the respective isomers in ^1H NMR spectra); R_f 0.73 and 0.56 (solvent J); IR: *v* 2107 (N_3).

Eluted second was **17** (0.159 g, 33%, mp 98–100 °C); $[\alpha]_D^{20}$ +107 (*c* 1, $CHCl_3$); R_f 0.17 (solvent J); IR: *v* 2111 (N_3) cm^{-1}, 1598 (C=C_{ar}), 1370, 1191, 1177 (O=S=O) cm^{-1}.

1.8. General procedure for acetylation

Compound **12**, **13**, or **14** (0.313 g, 1 mM) was acetylated with Ac_2O (3 mL) and pyridine (3 mL). The reaction was over within 1–2 h (TLC, solvent G). After dilution with CH_2Cl_2 (100 mL), the organic soln was washed with satd $NaHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated under diminished pressure.

1.8.1. Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-α-D-*xylo*- hexopyranoside (18). Acetylation of **12** (0.312 g) gave **18** (0.348 g, 98%, syrup); R_f 0.80 (solvent G).

1.8.2. Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-α-D-*lyxo*-hexopyranoside (19). Acetylation of **13** (0.763 g) led to **19** (0.834 g, 96%, syrup); R_f 0.81 (solvent G); IR: *v* 2102 (N_3), 1747 (C=O), 1215 (C–O) cm^{-1}.

1.8.3. Methyl 4-*O*-acetyl-3-azido-6-iodo-2,3,6-trideoxy-β-D-*xylo*-hexopyranoside (20). Acetylation of **14** (0.379 g) yielded **20** (0.419 g, 97%, syrup); R_f 0.83 (solvent G).

1.9. General procedure for elimination of hydrogen iodide

To the soln of **18**, **19**, or **20** (0.142 g, 0.4 mM) in pyridine (2 mL) AgF (0.076 g, 0.6 mM) was added. The reaction mixture was protected against the light and stirred at rt. After 3–4 days, TLC (solvent G) indicated the end of the reaction. The mixture was then diluted with Et_2O (10 mL). Precipitated salts were filtered off. The filtrate was concentrated and diluted with $CHCl_3$. The organic soln was washed with aq $Na_2S_2O_3$ and water, dried over Na_2SO_4, filtered, and concentrated. The crude product was chromatographed (solvent K).

1.9.1. Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-L-*threo*-hex-5-enopyranoside (21). The reaction of **18** (0.301 g) with AgF in pyridine yielded **21** (0.123 g, 64%, syrup); $[\alpha]_D^{20}$ +106 (*c* 1, $CHCl_3$); R_f 0.72 (solvent K); IR: *v* 2105 (N_3), 1749 (C=O), 1664 (C=C), 1226 (C–O) cm^{-1}; Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.93; H, 5.98; N, 18.05.

1.9.2. Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-β-L-erythro-hex-5-enopyranoside (22). The reaction of **19** (0.785 g) with AgF in pyridine gave **22** (0.356 g, 71%, syrup); $[\alpha]_D^{20}$ +13 (*c* 1, $CHCl_3$); R_f 0.75 (solvent K); IR: *v* 2102 (N_3), 1746 (C=O), 1662 (C=C), 1220 (C–O) cm^{-1}; Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.87; H, 6.02; N, 17.99.

1.9.3. Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-α-L-*threo*-hex-5-enopyranoside (23). The reaction of **20** (0.371 g) with AgF in pyridine led to **23** (0.185 g, 78%, syrup); $[\alpha]_D^{20}$ −111 (*c* 1, $CHCl_3$); R_f 0.74 (solvent K); IR: *v* 2104 (N_3), 1748 (C=O), 1663 (C=C), 1221 (C–O) cm^{-1}; Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.86; H, 5.95; N, 18.11.

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Supplementary data

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