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THIAZOLE C-NUCLEOSIDES IV. AN ENTRY TO PENT-1′-ENOPYRANOSYLTHIAZOLE DERIVATIVES[1,2]

Lajos Kovács,*[a] Pál Herczegh,*[b] Gyula Batta,[b] and István Farkas[a]

[a] Department of Organic Chemistry, L. Kossuth University, 4010 Debrecen, P.O.B. 20, and

[b] Research Group for Antibiotics, Hungarian Academy of Sciences, 4010 Debrecen, P.O.B. 70, Hungary

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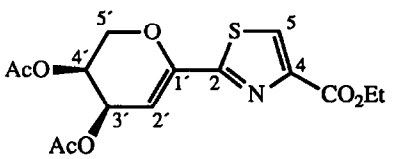
Key Words : C-nucleosides, unsaturated tiazofurin analogues, conformational study

Abstract : Starting from ethyl 2-(3′,4′-di-O-acetyl-2′-deoxy-L-erythro- or -D-threo-pent-1′-enopyranosyl)thiazole-4-carboxylate (1, 2) the synthesis of variously functionalized pent-1′-enopyranosylthiazoles (4-11, 15-20) was carried out with different O-, C-, S-, N-, and H-nucleophiles in the presence of Lewis acids. The regio- and stereoselective reactions proceeded with the Lewis acid-mediated formation of a carbocation (I) and the stereochemistry of the incoming nucleophile was determined by the neighbouring 4′-acetoxy group. However, with trimethylsilyl cyanide a 2′,3′-unsaturated 1′-C-cyano derivative (26) was formed. The configuration and conformation of prepared unsaturated compounds was thoroughly studied and the presence of a conformational equilibrium $^4H_5 \leftrightarrow {}^5H_4$ was deduced.

During the course of the synthesis of new analogues of 2-β-D-ribofuranosylthiazole-4-carboxamide (tiazofurin), a potent antitumor and antiviral agent, we observed the formation of pent-1′-enopyranosylthiazoles (**1-3**).[1]



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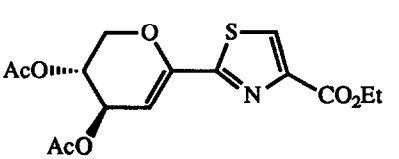

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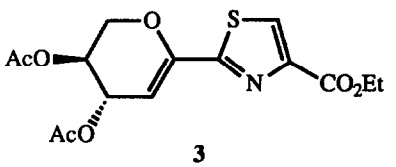
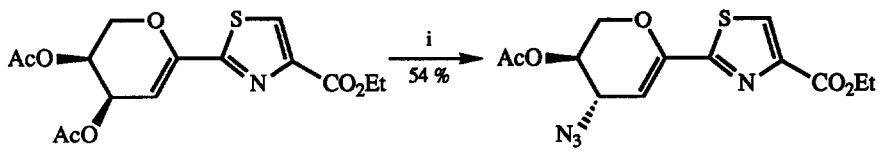


3

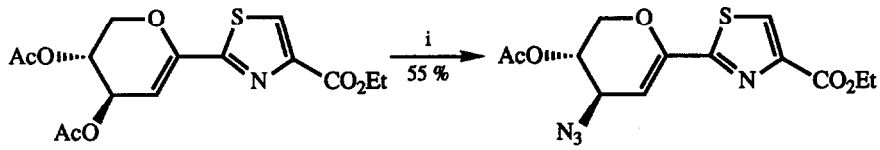
It is of particular interest that thiazole (**3**) was obtained in an epimerization reaction from (**1**) in acetic anhydride with boron trifluoride etherate.[1] The reaction is believed to proceed *via* an allylic-like carbocation generated with abstraction of 3′-acetoxy group by BF_3Et_2O and the stereochemistry of the arriving acetate ion is governed, mainly, by the adjacent 4′-acetoxy group.[1]

These observations prompted us to investigate whether *(a)* nucleophiles different from acetate could be introduced in position 3′, and, *(b)* what is the stereoselectivity of the reaction.

To this end we have allowed (**1**) and (**2**), respectively, to react with trimethylsilyl azide/boron trifluoride etherate in dichloromethane. These clean reactions afforded azides (**4**) and (**5**), respectively. In the reaction mixtures we could not detect diastereomers (t.l.c., ^{1}H n.m.r.), or, if they formed at all, their quantity was negligible. The enantiomeric relationship of (**4**) and (**5**) was proved by comparing their optical rotation, c.d., and ^{1}H n.m.r. spectra. Possible allylic rearrangement to C-1′-substituted pent-2′-enopyranosyl derivatives could be unequivocally excluded on the basis of u.v., ^{1}H, and ^{13}C n.m.r. evidences (see Tables).

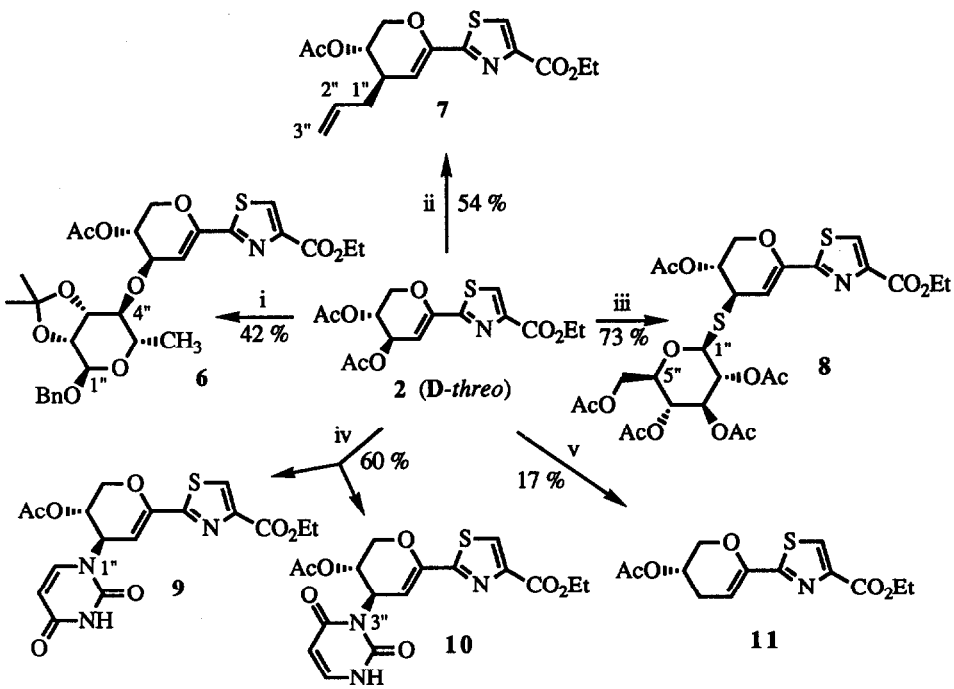


1 (L-*erythro*) **4** (L-*threo*) : $[\alpha]_D$ + 200.6



2 (D-*threo*) **5** (D-*threo*) : $[\alpha]_D$ - 200.4

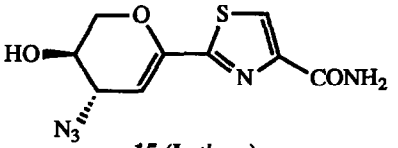
i : Me_3SiN_3, $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 30 min



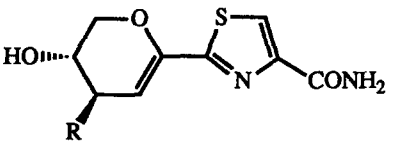
i : benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**12**),[3] $ClCH_2CH_2Cl$, $SnCl_4$; ii : allyltrimethylsilane, CH_2Cl_2, $BF_3.Et_2O$; iii : 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**13**),[4] CH_2Cl_2, $BF_3.Et_2O$; iv : 2,4-bis(trimethylsilyl)uracil (**14**),[6], $ClCH_2CH_2Cl$, $SnCl_4$; v : triethylsilane, CH_2Cl_2, $BF_3.Et_2O$,

Further experiments were carried out with (**2**), which is obtainable in crystalline state in contrast to syrupy (**1**). Using different *O*-, *C*-, *S*-, *N*-, and *H*-nucleophiles and Lewis acids we were able to synthesize pent-1´-enopyranosylthiazole derivatives (**6-11**) in moderate to good yields except for compound (**11**). Benzyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside (**12**) was prepared according to Lipták *et al.*[3] and 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose (**13**) was obtained in a known procedure.[4] The preparation of uracil derivatives (**9**, **10**) was realized following the procedure by Niedballa and Vorbrüggen[5] using 2,4-bis(trimethylsilyl)uracil (**14**).[6] The synthesis of (**11**) was devised from works by Grinkiewicz[7] and Mischnick-Lübbecke *et al.*[8] The observed low yield in the preparation of compound (**11**) was attributed to the poor nucleophilicity of triethylsilane, and therefore the initially formed allylic-like carbocation, probably, underwent decomposition reactions.

Treatment of the appropriate compounds with saturated NH_3/MeOH gave amides (**15-20**).



15 (L-*threo*)

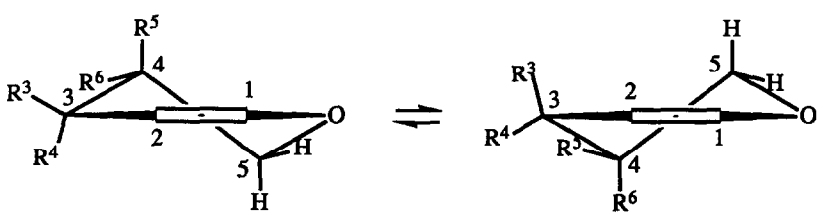


(D-*threo*)

	R
16	N_3
17	β-D-glucopyranosylthio
18	uracil-1-yl
19	uracil-3-yl
20	H

The structures of thiazoles (**4-11**) were proved by u.v., ^1H, ^{13}C n.m.r, and m.s. methods. The observed u.v. absorptions in the range 272-292 nm are in good agreement with the presence of a thiazole nucleus conjugated with a double bond.[1,9] The substitution pattern of uracil moiety in (**9**) and (**10**) was deduced from the u.v. spectra of their deprotected derivatives (**18**) and (**19**), respectively. Compound (**19**) in alkaline medium exhibited a significant bathochromic ($\Delta\lambda$ = 19 nm) and hyperchromic ($\Delta\varepsilon$ = 6 800) shift compared to the spectrum taken in neutral solution, which is characteristic of N^3-substituted uracil derivatives.[10-12] In the u.v. spectrum of compound (**18**) no significant changes could be observed upon basification. An additional proof for N^3-substitution in (**10**) was provided by the ^1H n.m.r. spectrum, *viz.*, the $^3J_{1'',2''}$ = 6.0 Hz coupling is observable only in compound (**10**) [see Table 1; the relevant coupling constants were not determinable from the spectra of compounds (**18**) and (**19**)]. The emergence of N^3-substituted uracils from reactions performed under conditions analogous to ours has already been reported.[13]

The configuration and conformation of pent-1´-enopyranosylthiazoles are in a close relationship. Their carbohydrate moiety contains the flexible 3,4-dihydro-2*H*-pyran unit. The substituted dihydropyrans could be described by two relatively stable but energetically non-equivalent half-chair conformations ($^4H_5$ and $^5H_4$, respectively).



$^4H_5$ $^5H_4$

Table 1. Selected ^{1}H n.m.r. Spectral Parameters of Thiazoles (1-11), (15-20), and (26)[a]

Chemical Shifts (δ in ppm, from Internal Tetramethylsilane)

Compd	H-5	H-2′	H-3′	H-4′	H-5′e[b]	H-5′a	Others
1[c,d]	7.85	6.18	5.65	5.23	3.84	4.03	
2[d,e]	7.63	6.49	5.31	4.92	4.06	3.75	
5[d,e]	7.72	6.16	3.61	4.70	3.94	3.71	
6[d]	7.65	6.70	5.46	---- 4.06 - 4.31----			5.17 (1"); 4.06-4.31 (2", 3"); 3.63-3.84 (4", 5")
7[f]	7.79	6.20	2.25	4.82	3.94	3.76	1.91 (1"); 5.49-5.70 (2"); 4.90; 4.97 (3")
8[d]	7.70	6.33	-----5.38----		3.71	3.87-4.58	4.67 (1"); 5.21-5.56 (2", 3"); 3.87-4.58 (4", 6"); 3.50 (5")
9[g]	8.44	6.07	5.24 -- 5.33		4.26 -- 4.52		5.58 (5"); 7.78 (6"); 10.40 (NH)
h	8.48	6.04	5.23	5.30	4.37	4.43	5.70 (5"); 7.74 (6");
10[h]	8.41	6.00	5.77 -- 5.88		4.57-4.64	4-17-4.28	5.63 (5"); 7.49 (6"); 10.09 (NH)
11[d]	7.74	6.08	1.87-2.18	4.84	3.93	3.64	
16[i,e]	8.32	6.03	4.03-4.24	3.83	4.03 -- 4.24		5.75 (OH); 7.67; 7.85 ($CONH_2$)
17[j]	8.12	5.95	----------3.33 - 3.99 (10 H); 4.78 (1H)----------				
18[i]	8.30	5.87	--------4.05 - 4.21 ---------				5.57 (OH); 5.05; 5.68 ($CONH_2$); 7.60; 7.70 (5", 6"); 11.25 (NH)
19[i]	8.20	5.84	5.50	4.58	4.33	3.92	5.50 (OH); 7.57; 7.74 ($CONH_2$); 5.59 (5"); 7.44 (6"); 11.15 (NH)
20[i]	8.19	5.94	2.08	3.97	3.82	4.10	5.15 (OH); 7.60; 7.73 ($CONH_2$)
26[d,k]	7.51	6.18	5.66	4.53	---- 3.81 ---		

Coupling Constants (J, in Hz)

Compd	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'e}$	$J_{4',5'a}$	$J_{5'e,5'a}$	$J_{3',5'e}$	$J_{2',4'}$	Others
1[d]	4.5	4.5	3.0	7.6	11.5	1.4	-	
2[d]	5.0	2.4	3.0	1.9	12.0	1.5	1.5	
5[d]	5.2	2.3	3.6	1.7	12.5	1.7	1.5	0.7 ($J_{3',5'a}$)
6[d]	5.3	-	-	-	-	1.6	-	
7[f]	4.5	-	4.5	2.1	~11	1.5	1.1	0.5 ($J_{3',5'a}$)
9[g]	4.0	-	-	-	-	-	1.4	8.0 ($J_{5",6"}$)
h	4.3	-	5.0	-	-	1.5	1.0	8.0 ($J_{5",6"}$); 2.5 ($J_{3",5"}$)
10[h]	~3	-	-	-	-	-	≤1	7.9 ($J_{5",6"}$); 6.0 ($J_{1",6"}$); 2.0 ($J_{1",5"}$)
11[d]	4.2	-	4.5	-	11.5	1.8	-	
18[i]	4.2	-	-	-	-	-	-	
20[i]	4.2	-	-	-	-	~1.5	≤0.5	
26[d,k]	10.0	5.5	-	-	-	0.9	-	

a Numbering of the heterocyclic and sugar rings is as shown for compd (**1**). Substituents attached to position 3′ are numbered as depicted at the appropriate substances (**6-10**). Deprotected derivatives (**15-20**) were numbered analogously. Data for compounds (**1, 2**) were taken, for comparison, from Ref. 1. *b*. The signal in which the long-range coupling $^4J_{3',5'e}$ was detectable in most of the cases was attributed to proton H-5′e. *c*. Assignment was made by a series of homonuclear decouplings. *d*. Benzene-d_6. *e*. In the case of enantiomeric pairs **2/3**, **4/5**, and **15/16** data were shown only for **D-*threo*** compounds. *f*. Assignment was confirmed by comparison with literature data,[29] and by COSY measurements.[30,31] *g* Methanol-d_4. *h*. Acetone-d_6. *i*. DMSO-d_6. *j*. D_2O. *k*. Assignment was performed by HETCORR[25] measurements.

Table 2. ^{13}C n.m.r. Chemical Shifts for Compounds (5-11), (15-20), and (26) [δ, ppm]

Compd	C-2	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′
5[b]	162.44	148.69*	128.07	149.03*	94.05	53.53	67.65	64.69
Others 14.24 ($CH_2\underline{C}H_3$); 20.18 ($\underline{C}H_3CO$); 61.12 ($\underline{C}H_2CH_3$); 161.09 (4-$\underline{C}O$); 169.11 (4′-$\underline{C}O$)								
6[b]	163.47	148.47*	128.01§	148.60*	96.78	65.40	68.19	64.88
Others 14.24 ($CH_2\underline{C}H_3$); 17.66 (C-6"); 20.36 ($\underline{C}H_3CO$); 26.32; 28.20 [$C(\underline{C}H_3)_2$]; 61.00 ($\underline{C}H_2CH_3$); 68.89; (C-5"); 69.18 ($Ph\underline{C}H_2$); 76.67; 78.08; 81.42 (C-2", 3", 4"); 98.04 (C-1"); 109.63 ($\underline{C}Me_2$); 127.52; 127.82; 128.04; 128.49; 128.61; 137.92 ($\underline{C}_6H_5$)§; 161.22 (4-$\underline{C}O$)							
7[b,c]	163.86	148.52	127.10	149.56	102.89	36.38	69.08	65.35
Others 14.28 ($CH_2\underline{C}H_3$); 20.51 ($\underline{C}H_3CO$); 38.80 (C-1"); 60.98 ($\underline{C}H_2CH_3$); 117.47 (C-2"); 134.89 (C-3"); 161.32 (4-$\underline{C}O$); 169.65 ($CH_3\underline{C}O$)								
8[b]	163.15	147.85*	127.66	148.55*	97.06	42.09	68.50	64.43
Others 14.25 ($CH_2\underline{C}H_3$); 20.14; 20.16; 20.27; 20.36; 20.46 (5*$\underline{C}H_3CO$); 61.04 ($\underline{C}H_2CH_3$); 61.74 (C-6"); 70.23; 70.66 (C-2", 4"); 74.40 (C-3"); 76.41 (C-5"); 86.23 (C-1"); 161.15 (4-$\underline{C}O$); 169.06 ; 169.11; 169.79; 169.55; 170.05 (5*$CH_3\underline{C}O$)								
9[d]	164.07	150.26*	129.92	151.44*	97.10	54.00	68.72	66.77
Others 14.56 ($CH_2\underline{C}H_3$); 20.67 ($\underline{C}H_3CO$); 62.59 ($\underline{C}H_2CH_3$); 102.97 (C-5"); 143.84 (C-6"); 152.70 (C-2"); 162.48 (4-$\underline{C}O$); 166.04 (C-4"); 171.29 (4′-$\underline{C}O$)								
10[e]	163.79	147.72*	128.62	148.59*	101.26	50.06	67.24	68.32
Others 14.52 ($CH_2\underline{C}H_3$); 20.70 ($\underline{C}H_3CO$); 61.62 ($\underline{C}H_2CH_3$); 102.32 (C-5"); 141.04 (C-6"); 152.16 (C-2"); 161.63 (4-$\underline{C}O$); 164.24 (C-4"); 170.43 (4′-$\underline{C}O$)								
11[b]	164.00	146.15*	126.86	146.15*	99.04	26.10	65.25	67.28
Others 14.27 ($CH_2\underline{C}H_3$); 20.51 ($\underline{C}H_3CO$); 61.01 ($\underline{C}H_2CH_3$); 161.38 (4-$\underline{C}O$); 169.75 ($CH_3\underline{C}O$)								
16[e]	161.65*	162.07*	124.91	147.72	95.82	57.25	65.41	67.93
Others 150.95 ($\underline{C}ONH_2$)								
17[f]	165.40	164.02	126.39	146.70	100.03	42.91	68.00*	67.28§
Others 61.34§ (C-6"); 69.87; 72.79; 77.67; 80.34 (C-2", 3", 4", 5")*; 86.58 (C-1"); 148.81 ($\underline{C}ONH_2$)								

(Table 2., continued)

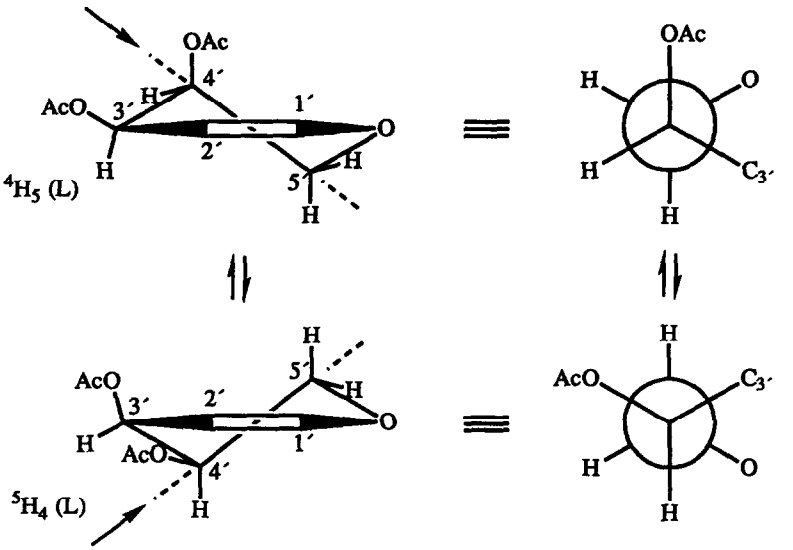
Compd	C-2	C-4	C-5	C-1′	C-2′	C-3′	C-4′	C-5′
18[e]	161.61*	162.04*	124.62	148.67§	101.37	54.76	64.24	68.52
Others	96.98 (C-5"); 142.78 (C-6"); 150.80§ (C-2"); 152.11§ ($\underline{C}ONH_2$); 163.31* (C-4")							
19[e]	162.00*	163.49*	123.67	145.73§	101.70	52.08	61.26	70.34
Others	100.00 (C-5"); 140.56 (C-6"); 150.67§ ($\underline{C}ONH_2$); 151.30§ (C-2"); 162.00 (C-4")							
20[e]	161.69*	162.49*	122.84	144.54	99.01	28.60	60.81	69.69
Others	150.12 ($\underline{C}ONH_2$)							
26[b,g]	165.48	148.13	129.43	72.11	129.61§	126.01§	62.04	66.48
Others	14.23 ($CH_2\underline{C}H_3$); 20.32 ($\underline{C}H_3CO$); 61.30 ($\underline{C}H_2CH_3$); 115.63 ($\underline{C}N$); 160.60 (4-$\underline{C}O$); 169.66 ($CH_3\underline{C}O$)							

a. For numbering policy see Table 1, caption a. Assignment was made by spin echo experiments and by comparing the pertinent data with those for compounds **1** - **3**, verified by selective INEPT measurement.[1] In the case of enantiomeric pairs **4/5** and **15/16** data were shown only for compound. *b*. Benzene-d_6. *c*. Assignment was confirmed by comparison with literature data.[29] *d*. Methanol-d_4. *e* DMSO-d_6. *f*. D_2O. *g*. Assigment was performed by HETCORR[25] measurements. *, § denote interchangeable assignments.

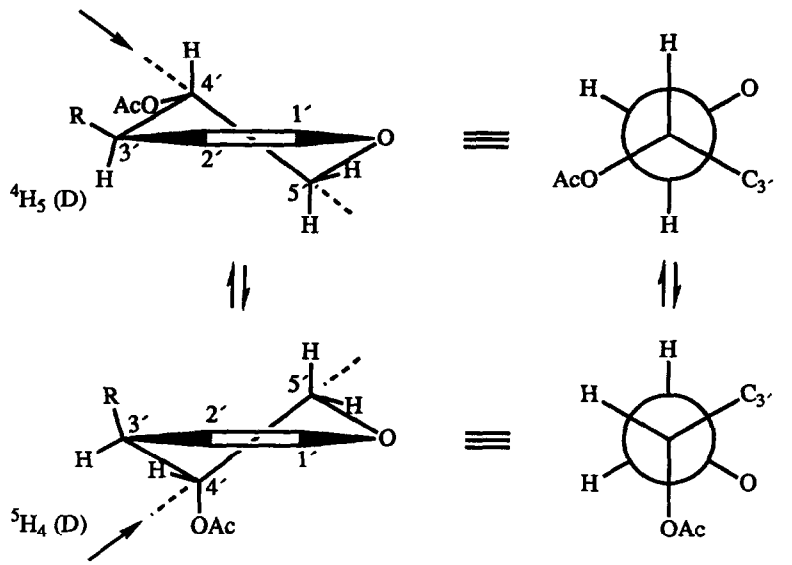
The same structural unit is to be found in glycals the conformational equilibrium of which has been thoroughly studied by the analysis of ^1H n.m.r. coupling constants.[14-16] Chalmers and Hall[14] explained the transition value of observed coupling constants by distortion (flattening) of the corresponding half-chair conformations but Rico and Santoro[15] demonstrated that for this was enough to suppose the interconversion equilibrium of $^4H_5$ and $^5H_4$ conformers. *E. g.* 3,4-di-*O*-acetyl-**D**-arabinal (**21**) resides preponderantly in $^4H_5$(D), 3,4-di-*O*-acetyl-**D**-xylal (**22**) mostly in $^5H_4$(D) conformation [in the case of enantiomers $^4H_5$(D) is energetically equivalent to $^5H_4$(L), and $^5H_4$(D) to $^4H_5$(L) conformer]. In a similar fashion, especially from the analysis of coupling constants $^3J_{4,5}$, Rico and Santoro,[15] and Zamojski *et al.*[16] found the prevalence of $^4H_5$(D) conformer in 3,4,6-tri-*O*-acetyl-**D**-glucal (**23**). Molecular mechanics calculations by Korytnyk and Dodson-Simmons corroborated the experimental findings (^1H n.m.r. and X-ray analysis) concerning the preferred conformations in the case of (**23**) and its deprotected derivative, **D**-glucal (**24**).[17,18]

Considering the coupling constants of compounds (**1**) and (**2**) (Table 1.) the presence of an analogous conformational equilibrium could be deduced. The $^3J_{4',5'}$ coupling constants of compound (**1**) [**L**-*erythro* configuration; 3.0 and 7.6 Hz] allows us to conclude the antiperiplanar (*trans*) and synclinal (*gauche*) arrangement of protons H-4′and H-5′, respectively, thus, the prevalence of $^5H_4$(L) conformer. It was corroborated by the long-range coupling $^4J_{3',5'e}$ (1.4 Hz), too, which is expected if the coupled protons are in a near coplanar W-shaped arrangement. Similarly, the absence of coupling $^4J_{2',4'}$ is characteristic of this conformation (the pertinent protons are in a near perpendicular position).

In compound (**2**) [**D**-*threo* configuration] the coupling constants $^3J_{4',5'a}$ and $^3J_{4',5'e}$ are comparable (3.0 and 1.9 Hz, respectively) and beyond $^4J_{3',5'e}$ is observable the coupling $^4J_{2',4'}$ (1.5 Hz; w-shaped arrangement), too, conclusively, the preponderance of $^5H_4$(D) conformer. The coupling constants of compounds (**5**) and (**7**) are very similar to those of (**2**), therefore **D**-*threo* configuration *and* an equilibrium shifted towards the $^5H_4$(D) conformer could be proved.



1 (L-*erythro*)



2 : R = OAc; **5** : R = N_3; **7** : R = $CH_2CH{=}CH_2$ (D-*threo*)

(Thiazole nucleus in position 1′ has been omitted for clarity)

Using the coupling constant $^3J_{4,5}$ applied in the conformational equilibrium estimation of glycals we have calculated the population of conformers for compounds (**1**), (**2**), (**5**), and (**7**) [the enantiomers (**3**), and (**4**) were omitted since they are energetically equivalent to compounds (**2**) and (**5**), respectively]. The data obtained from equations (1) and (2) are presented in Table 3 together with literature data for compounds (**21**) and (**22**).[15] $X(^5H_4)$ refers to the mole fraction of conformer $^5H_4$. In the calculations we tacitly assumed that the effect of 3′-substituent was of second order and thence negligible.

$$X(^5H_4) = \frac{J^{obs}_{4'a,5'a} - J_{4'e,5'e}}{J_{4'a,5'a} - J_{4'e,5'e}} \quad (1)$$

$$X(^5H_4) = \frac{J_{4'a,5'e} - J^{obs}_{4'e,5'a}}{J_{4'a,5'e} - J_{4'e,5'a}} \quad (2)$$

In compounds of D-*threo* series (**2**, **5**, **7**, **22**) the population of $^5H_4$(D) is high while in compounds of *erythro* series (**1**, **21**) the participation of $^4H_5$(L) (**1**) or the equivalent $^5H_4$(D) (**21**) conformer in the equilibrium is significant.

Table 3. Conformational Equilibrium of Some Glycals and Their Derivatives at 25 °C (%)

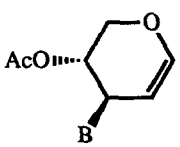
Compd	Solvent	Configuration	100 * X($^5H_4$)	100 * X($^4H_5$)
1[a]	C_6D_6	L-*erythro*	58 ± 3	42 ± 3
2[b]	C_6D_6	D-*threo*	89 ± 3	11 ± 3
5[b]	C_6D_6	D-*threo*	96 ± 4	4 ± 4
7[b]	C_6D_6	D-*threo*	82 ± 3	18 ± 3
21[c]	acetone-d_6	D-*erythro*	25 ± 2	75 ± 2
22[c]	acetone-d_6	D-*threo*	88 ± 3	12 ± 3

a. Calculated from eq (1) using the extreme values $^3J_{4'a,5'a}$ = 11.63 Hz; $^3J_{4'e,5'e}$ = (2.0 ± 0.3) Hz.[15]

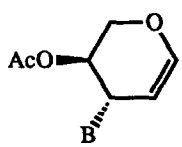
b. Calculated from eq (2) using the extreme values $^3J_{4'a,5'e}$ = (4.24 ± 0.09) Hz; $^3J_{4'e,5'a}$ = (1.6 ± 0.1) Hz.[15]

c. Ref. 15, t = 26 °C

Unfortunately, the coupling constants $^3J_{4',5'}$, which are the most conveniently applicable for the determination of configuration and conformational equilibrium, could not be extracted from the first-order analysis of the ^{1}H n.m.r. spectra of compounds (**6**, **8-10**). Even the couplings $^4J_{3',5'e}$ and $^2J_{2',4'}$, alluding to D-*erythro* configuration and the prevalence of $^5H_4$(D) conformation, were not determinable in all of the cases (see Table 1). In the rections leading to the formation of azides (**4**) and (**5**) we demonstrated that the stereochemical outcome was determined by the configuration of 4′-acetoxy group and it was independent from that of 3′-acetoxy group. It is improbable that nucleophiles applied in the preparation of compounds (**6**, **8-10**) would result in different stereochemical issue, therefore we believe that these substances with tentative stereochemistry all have D-*threo* configuration. This assumption is supported by the fact that in the reaction of acetylated glycals and different heterocycles the compounds formed among other products had always 3, 4 relative *trans* (D- or L-*threo*) configuration (**25a**) or (**25b**).[19-21]



25a



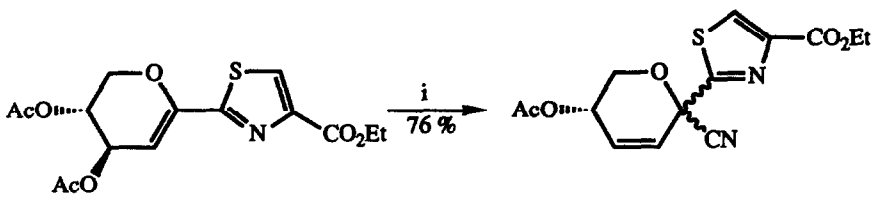
25b

B = heterocycle

However, further experimental proofs have been sought after to corroborate our conjecture.

When compound (**2**) was allowed to react with trimethylsilyl cyanide in the presence of $BF_3.Et_2O$ a pent-2′-enopyranosylthiazole derivative (**26**) was formed.

Compound (**26**) in contrast to pent-1′-enopyranoylthiazoles, exhibited an u.v. absorption at 237 nm (ε = 9 000) demonstrating the presence of an isolated thiazole ring.[1,9] In the ^{1}H n.m.r. spectrum of this substance most of the coupling constants were delusively similar to those of pent-1′-enopyranosylthiazoles, however, the

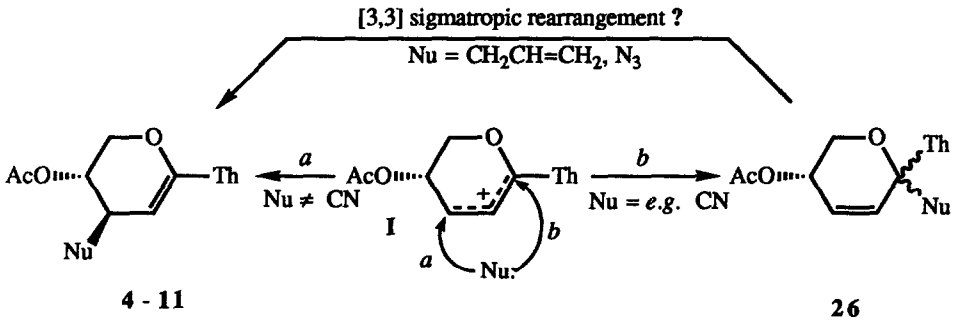


2 **26**

i : Me_3SiCN, $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 30 min

coupling $^3J_{2',3'}$ revealed the presence of *(Z)*-olefinic protons. The observed value (10.0 Hz) is a typical one for the pertinent protons of 2,3-dideoxyhex-2-enopyranosides,[22-24] while for our pent-1′-enopyranosides $^3J_{2',3'} \leq$ 5.0 Hz.To support the structure a HETCORR[25] experiment was carried out which fully confirmed the supposed structure. The quaternary C-1′ atom gave a low-intensity signal (δ 72.11 ppm) and sp^2 carbons C-2′and C-3′ resonated at 126.01 and 129.61 ppm, respectively. (*Cf.* the range 42-65 ppm for the sp^3 C-3′ of pent-1′-enopyranosides in Table 2.) Although in the i.r. spectrum there was no absorption[26] in the range of 2200-2300 cm^{-1}, the presence of nitrile group was verified through its carbon-13 resonance at 115.63 ppm. Alternative structures, such as isonitriles or a 3′,4′-*O*-(1-cyanoethylidene) derivative could be unequivocally excluded comparing the i.r. and ^{13}C n.m.r. data with literature relevances.[26,27] The available data, of course, have not been sufficient to establish the correct stereochemistry at the anomeric center of compound (**26**).

Acetylated hexopyranosyl glycals reacted with trimethylsilyl cyanide under Lewis acid catalysis to give 2,3-unsaturated glycosyl cyanides.[23,24] The formation of 3-*C*-cyano-hex-1-enopyranosyl derivatives was not detected even at elevated temperatures and prolongated reaction times, thus, there was not thermodynamic equilibration.[23] The tendency of nucleophiles to react at C-1 or C-3 of the supposed intermediate allylic-like carbocation has been explained by using Pearson's principle of hard and soft acids and bases, according to which the anomeric center of glycals is a relatively "hard" site for the binding of nucleophiles.[24] *C*-nucleophiles, typical soft bases, might be expected to react at C-3 (or the equivalent C-3′ of pent-1′-enopyranoylthiazoles, as it was indeed found in compound **7**).[24] The different reaction course of trimethylsilyl cyanide with acetylated glycals[23,24] or with compound (**2**) may be explained in kinetic terms.[24] If the rate of the reaction at C-1 (or the equivalent C-1′) is sufficiently greater than at C-3 (or C-3′), exclusive formation of glyc-2-enopyranosyl cyanides can be expected, since in these cases there is no possibility of thermodynamic equilibration.[24] According to the above mentioned the formation of compounds (**4-11**), and (**26**) is rationalized by the initial formation of carbocation I which reacts to give either C-3′- or C-1′-substituted products (paths *a* and *b*, respectively).



(Th stands for 4-ethoxycarbonylthiazol-2-yl nucleus)

However, in the case of compounds (**4**), (**5**), and (**7**) eventual [3,3] sigmatropic rearrangement[28] could not be excluded, *i.e.* fast reaction at C-1′ of I followed by a slower rearrangement to C-3′-substituted products. The driving force of this transformation, if any, is the higher thermodynamic stability of pent-1′-enopyranosylthiazoles over the non-conjugated pent-2′-enopyranosylthiazole system.

The biological evaluation of new pent-1′-enopyranosylthiazoles will be described elsewhere.

Experimental Section

General experimental details were as previously described.[1]

The ^1H and ^{13}C n.m.r. data for the obtained new compounds are to be found in Tables 1-2. For the preparation of substances (**4-11**) the following general procedures were used (the reactions were carried out on a 1-3 mmol scale):

Procedure A. The corresponding enose dissolved in abs. dichloromethane (10 mL/mmol) was allowed to react with 1.1 eq. of the appropriate nucleophile in the presence of 1.1 eq. of boron trifluoride etherate at 0 °C for 0.5 to 1 h. The reaction mixture was diluted with chloroform, washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), evaporated, and chromatographed in the appropriate eluent.

Procedure B. The corresponding enose dissolved in abs. 1,2-dichloroethane (10-15 mL/mmol) was allowed to react with 1.0-1.2 eq. of the appropriate nucleophile in the presence of 1.0-1.5 eq. of tin(IV) chloride at 0 °C. As t.l.c. indicated the completion of the reaction (1-24 h), the reaction mixture was poured into a vigorously stirred saturated $NaHCO_3$ solution. After total neutralization the suspension was filtered through fuller's earth pad and extracted with chloroform. The residue obtained after drying and evaporation was subjected to chromatographic purification in the appropriate eluent.

Ethyl 2-(4′-*O*-Acetyl-3′-azido-2′,3′-dideoxy-L-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxylate (4). Obtained from enose (**1**)[1] and trimethylsilyl azide (Proc. A) in 54.0 % yield as an oil after chromatography (B1). Further purification was carried out on a preparative layer (B3). $[\alpha]_D$ + 200.6 (c 0.51; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 283 (16 400). I.r.: 2095 cm^{-1}. C.d. (λ, nm; Δε; in acetonitrile): 343(-0.04); 291 (5.64); 264 (2.70); 235 (-10.39); 200 (14.93); 194 (15.21). M.s. (I, %): 339 (18, M+H); 296 (6, cation I); 278 (16); 236 (100, I-AcOH); 208 (19); 178 (24); 112 (12); 43 (69, Ac^+).

Anal. Calcd. for $C_{13}H_{14}N_4O_5S$; C 46.15, H 4.17, N 16.56, S 9.48; found C 46.34, H 4.01, N 16.30, S 9.27.

Ethyl 2-(4′-*O*-Acetyl-3′-azido-2′,3′-dideoxy-D-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxylate (5). Obtained from enose (**2**)[1] and trimethylsilyl azide (Proc. A) in 55.0 % yield as an oil. $[\alpha]_D$ - 200.4 (c 1.11; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 283 (16 400) The i.r. and m.s. data were identical with those of its enantiomer (**4**). C.d. (λ, nm; Δε; in acetonitrile): 337 (0.06); 290 (-7.10); 264 (-3.37); 236 (12.56); 203 (-17.43); 194 (-18.54); 189 (-17.39).

Anal. Calcd. for $C_{13}H_{14}N_4O_5S$; C 46.15, H 4.17, N 16.56, S 9.48; found C 46.20, H 4.11, N 16.70, S 9.55.

Ethyl 2-[4′-*O*-Acetyl-3′-*O*-(benzyl-2",3"-*O*-isopropylidene-α-L-rhamnopyranosid-4"-yl)-2′-deoxy-D-threo-pent-1′-enopyranosyl]thiazole-4-carboxylate (6). Obtained from enose (**2**) and rhamnose derivative (**12**)[3] using Proc. B. After chromatography (B1) the product was recrystallized from methanol (42.4 %), m.p. 152-153 °C. $[\alpha]_D$ - 57.5 (c 1.03; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 283 (14 000). M.s. (I, %): 589 (4, M^+); 498 (4, M-C_7H_7); 296 (11, I); 236 (90, I-AcOH); 43 (52, Ac^+).

Anal. Calcd. for $C_{29}H_{35}NO_{10}S$; C 59.07, H 5.98, N 2.38, S 5.44; found C 59.27, H 5.75, N 2.39, S 5.39.

Ethyl 2-(4′-*O*-Acetyl-3′-allyl-2′,3′-*O*-dideoxy-D-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxylate (7). Prepared from enose (**2**) and allyltrimethylsilane (Proc. A) in 53.5 % yield as an oil. $[\alpha]_D$ - 23.7 (c 1.02; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 285 (12 300).

Anal. Calcd. for $C_{16}H_{19}NO_5S$; C 56.96, H 5.68, N 4.15, S 9.50; found C 56.80, H 5.78, N 4.03, S 9.37.

Ethyl 2′-[4′-*O*-Acetyl-2′-deoxy-3′-*S*-(2",3",4",6"-tetra-*O*-acetyl-β-D-glucopyranosyl)-3′-thio-D-*threo*-pent-1′-enopyranosyl]thiazole-4-carboxylate (8). Prepared from enose (**2**) and glucose derivative (**13**)[4] (Proc. A) in 73.1 % yield, m.p. 81-92 °C. Further purification was performed on a preparative layer (B5). $[\alpha]_D$ - 36.0 (c 0.35; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 289 (13 800). M.s. (I, %): 659 (1, M^+); 599 (3, M-AcOH); 331 (13; 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylium ion); 296 (15, I); 236 (100, I-AcOH); 208 (10); 169 (49, 331-2*AcOH-CH_2=C=O); 109 (38, 169-AcOH); 43 (100, Ac^+).

Anal. Calcd. for $C_{27}H_{33}NO_{14}S_2$; C 49.16, H 5.04, N 2.12, S 9.72; found C 49.01, H 5.18, N 1.98, S 9.60.

Ethyl 2-[4′-O-Acetyl-2′,3′-dideoxy-3′-(uracil-1"-yl)-D-*threo*-pent-1′-enopyranosyl]-thiazole-4-carboxylate (9) and Ethyl 2-[4′-O-Acetyl-2′,3′-dideoxy-3′-(uracil-3"-yl)-D-*threo*-pent-1′-enopyranosyl]thiazole-4-carboxylate (10). Prepared from enose **2** and 2,4-bis(trimethyl-

silyl)uracil (**14**),[6] using Proc. B. Chromatographic separation (A1) gave first compound (**9**) (33.1 %), second mixture of (**9**) and (**10**) (12.3 %), and finally pure (**10**) (14.4 %), overall yield 59.8 %. Compound (**9**) was recrystallized from ethyl acetate, m.p. 138-139 °C. $[\alpha]_D$ - 25.1 (c 0.61; DMSO). U.v. (λ_{max}, nm; ε; EtOH) : 279 (20 200). M.s. (I, %): 407 (1, M^+); 347 (43, M-AcOH); 296 (3, I); 273 (12); 236 (39, I-AcOH); 208 (22); 163 (100); 122 (14); 43 (87, Ac^+).

Anal. Calcd. for $C_{17}H_{17}N_3O_7S.CH_3COOC_2H_5$ (the presence of crystal solvent was demonstrated by ^1H n.m.r.); C 50.90, H 5.09, N 8.48, S 6.47; found C 50.77, H 4.83, N 8.27, S 6.28.

Compound (**10**) : m.p. 108-110 °C. $[\alpha]_D$ - 44.3 (c 0.28; DMSO). U.v. (λ_{max}, nm; ε; EtOH) : 275 (15 200). M.s.: practically identical with that of compound (**9**).

Anal. Calcd. for $C_{17}H_{17}N_3O_7S$; C 50.12, H 4.21, N 10.31, S 7.87; found C 50.28, H 4.10, N 10.10, S 7.60.

Ethyl 2-(4′-O-Acetyl-2′,3′-dideoxy-D-*glycero*-pent-1′-enopyranosyl)thiazole-4-carboxylate (11). Obtained from enose (**2**) and triethylsilane (Proc. A), in 16.8 % yield after chromatography (B1) as an oil (the crude product contained numerous impurities beside the title compound). $[\alpha]_D$ -185.1 (c 1.08; $CHCl_3$).

Anal. Calcd. for $C_{13}H_{15}NO_5S$; C 52.51, H 5.09, N 4.71, S 10.78; found C 52.38, H 5.17, N 4.83, S 10.56.

Amides (15-20). The corresponding ester was dissolved in saturated NH_3/MeOH. When t.l.c. indicated the completion of the reaction the solution was evaporated and the product was purified by column chromatography and/or recrystallization. The reactions were run on a 0.2-2.0 mmol scale.

2′-(3′-Azido-2′,3′-dideoxy-L-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxamide (15). Obtained in 60.0 % yield after recrystallization from abs. ethanol, m.p. 196-196.5 °C. $[\alpha]_D$ + 230.4 (c 0.65; DMSO). U.v. (λ, nm; ε; H_2O) : 288 (7 200), 226 (6 800).

Anal. Calcd. for $C_9H_9N_5O_3S$; C 40.44, H 3.39, N 26.20, S 12.00; found C 40.20, H 3.38, N 26.17, S 12.07.

2′-(3′-Azido-2′,3′-dideoxy-D-*threo*-pent-1′-enopyranosyl)thiazole-4-carboxamide (16). Obtained as its enantiomer (**15**) in 60.0 % yield, m.p. 195-198 °C. $[\alpha]_D$ - 215.0 (c 1.04; DMSO). U.v. (λ, nm; ε; H_2O) : 288 (7 200), 226 (6 800).

Anal. Calcd. for $C_9H_9N_5O_3S$; C 40.44, H 3.39, N 26.20, S 12.00; found C 40.65, H 3.63, N 26.16, S 12.14.

2-[2′-Deoxy-3′-*S*-(β-D-glucopyranosyl)-3′-thio-D-*threo*-pent-1′-enopyranosyl]thiazole-4-carboxamide (17). Obtained after chromatographic purification (A3) and recrystallization from abs. ethanol in 62.0 % yield, m.p. 221-223 °C. $[\alpha]_D$ - 129.5 (c 0.47; DMSO). U.v. (λ, nm; ε; H_2O) : 292 (15 000), 221 (7 000).

Anal. Calcd. for $C_{15}H_{20}N_2O_8S_2$; C 42.85, H 4.79, N 6.66, S 15.25; found C 42.37, H 4.83, N 6.68, S 15.30.

2-[2′,3′-Dideoxy-3′-(uracil-1″-yl)-D-*threo*-pent-1′-enopyranosyl]thiazole-4-carboxamide (18). The crude product precipitated from the reaction mixture (94.7 %, m.p. 264-274 °C) was recrystallized from 50 % acetic acid, m.p. 272-278 °C. $[\alpha]_D$ - 30.0 (c 0.40; DMSO). U.v. (λ, nm; ε; DMSO) : 287 (16 200); in a mixture of [DMSO : 0.1 M NaOH = 3 : 7]: 283 (16 200).

Anal. Calcd. for $C_{13}H_{12}N_4O_5S$; C 46.42, H 3.60, N 16.66, S 9.53; found C 46.30, H 3.48, N 16.42, S 9.70.

2-[2′,3′-Dideoxy-3′-(uracil-3″-yl)-D-*threo*-pent-1′-enopyranosyl]-thiazole-4-carboxamide (19). The crude product was recrystallized from water, m.p. 286-289 °C. $[\alpha]_D$ - 97.1 (c 1.02; DMSO). U.v. (λ, nm; ε; H_2O) : 272 (13 400), 219 (8 200); in 0.1 M NaOH : 291 (20 200), 227 (10 200).

Anal. Calcd. for $C_{13}H_{12}N_4O_5S$; C 46.42, H 3.60, N 16.66, S 9.53; found C 46.37, H 3.72, N 16.51, S 9.68.

2-(2′,3′-Dideoxy-D-*glycero*-pent-1′-enopyranosyl)thiazole-4-carboxamide (20). Obtained in 67 % yield after recrystallization from abs ethanol, m.p. 170-172 °C. $[\alpha]_D$ + 20.7 (c 0.44; MeOH). U.v. (λ, nm; ε; EtOH) : 286 (8 600), 233 (4 400).

Anal. Calcd. for $C_9H_{10}N_2O_3S$; C 47.78, H 4.46, N 12.38, S 14.17; found C 47.59, H 4.31, N 12.10, S 14.38.

(1′-*RS*)-Ethyl 2-(4′-*O*-Acetyl-1′-*C*-cyano-2′,3′-dideoxy-D-*glycero*-pent-2′-enopyranosyl)thiazole-4-carboxylate (26). Prepared from enose (**2**) and trimethylsilyl cyanide (Proc. A) in 76 % yield as an oil after preparative layer chromatography (D1). An analytical sample was obtained after preparative layer

chromatography (D2). $[\alpha]_D$ + 22.3 (c 1.02; $CHCl_3$). U.v. (λ_{max}, nm; ε; EtOH) : 237 (9 000). M.s. (I, %) : 322 (8, M+); 293 (4); 251 (48); 233 (68); 205 (44); 160 (12); 102 (20); 43 (100, Ac^+).

Anal. Calcd. for $C_{14}H_{14}N_2O_5S$; C 52.16, H 4.38, N 8.69, S 9.95; found C 52.31, H 4.47, N 8.50, S 9.70.

References and Notes

1. For Part III, see *Tetrahedron*, preceding paper.
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