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Dedicated to the memory of Professor Roland K. Robins

The NH,NH-dihydrocycloadduct **1** (6-chloro-9,9-dimethyl-7,8-dihydro-9*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine) obtained by the cycloaddition of 2-diazopropane to 6-chlorotetrazolo[1,5-*b*]pyridazine, is transformed with protected or unprotected carbohydrates **2**, **5**, **7**, **9**, **11**, **13** and **15** in the presence of methyl acrylate (**3**) into the corresponding C-nucleosides **4**, **6**, **8**, **10**, **12**, **14** and **16**. In this one-pot synthesis two new chiral centers are formed stereoselectively, dependent on the chirality at C-atom next to aldehyde group in the carbohydrate.

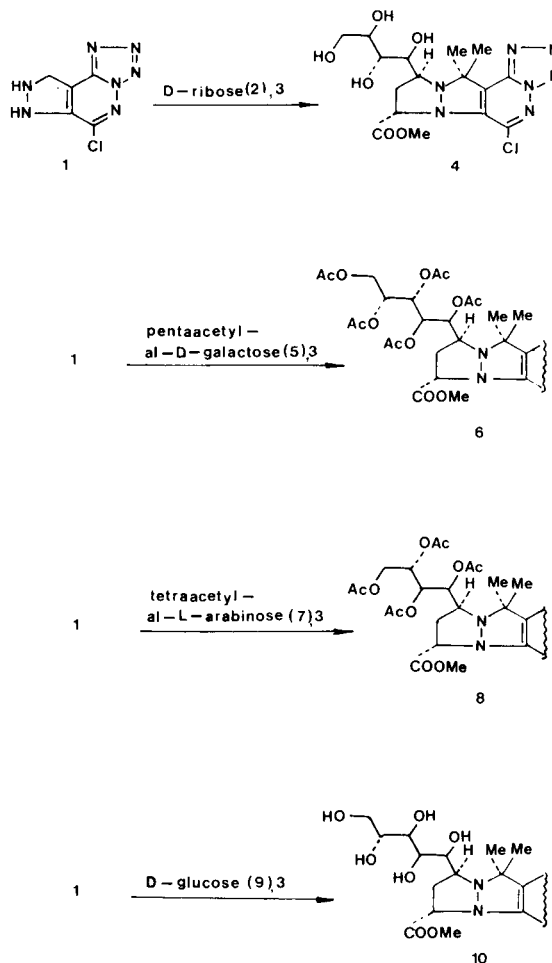
J. Heterocyclic Chem., **30**, 1209 (1993).

While studying the 1,3-dipolar cycloaddition reactions of diazoalkanes to heteroaromatic systems, especially to pyridazines and fused pyridazines, we observed that primary CH,CH-dihydrocycloadducts easily rearrange into NH,NH-dihydro cycloadducts. They form with aldehydes stable azomethine imines, which react as 1,3-dipoles with unsaturated compounds, such as olefins, acetylenes and arynes, forming new pyrazole ring fused to other heterocyclic system [1].

Since many naturally occurring C-nucleosides, such as Formycin A, Formycin B, Pyrazomycin and other antibiotics, contain a pyrazole structural element [2-7], we have applied recently the 1,3-dipolar cycloaddition of azomethine imines to the stereoselective synthesis of C-nucleosides [8]. In this connection, the stable chiral azomethine imines have been prepared as model compounds from 6-chloro-7,8-dihydropyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**1**) and protected and unprotected aldehyde sugars. They have been subsequently treated with methyl acrylate as the dipolarophile. During these studies we have observed also that with D-ribose the reaction can be carried out as a one-pot synthesis to give the corresponding C-nucleoside as a pure (>95% ee) stereoisomer.

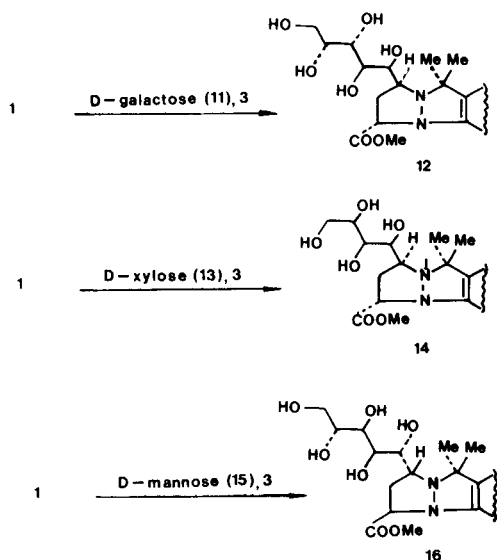
In this communication, we report on a one-pot synthesis of C-nucleosides by 1,3-dipolar cycloaddition of methyl acrylate to chiral azomethine imines, prepared from **1**, *in situ*, in the following manner. A mixture of the compound **1**, protected or unprotected aldehyde sugars **2**, **5**, **7**, **9**, **11**, **13**, and **15** and methyl acrylate (**3**) was heated in methanol in the presence of a catalytic amount of trifluoroacetic acid under reflux to give the C-nucleosides **4**, **6**, **10**, **12**, **14**, and **16**, respectively, as pure (>95% ee) stereoisomers (Scheme 1).

In these reactions new chiral centers at C₈ and C₁₀ are formed. The relative configurations at C₈ and C₁₀ and at



C₁₀ and C_{1'} were determined on the basis of ¹H nmr characteristics and the magnitude of the coupling constants according to the procedure described earlier [8]. Since the absolute configuration at C_{1'} is given by the carbohydrate, the absolute configurations for all three centers is therefore established. The C-nucleosides derived from 2'*R*-car-

Scheme 1



bohydrates, *i.e.*, the carbohydrates with *R*-configuration at the *C*-atom next to the aldehyde group, have the absolute configuration (1'*S*,8*S*,10*S*) while the *C*-nucleosides derived from 2'*S*-carbohydrates have the absolute configuration (1'*R*,8*R*,10*R*) (Scheme 2). It means, that absolute configuration at *C*₂ of the carbohydrate side chain attached at *C*₁₀ in the *C*-nucleoside, determines the absolute configuration at *C*₈ and *C*₁₀. The dipolarophile therefore reacts with azomethine imines from less hindered side.

This one-pot synthesis is advantageous in comparison to a two-step procedure described earlier [8], since the intermediary azomethine imines, especially those prepared from unprotected carbohydrates, are not needed to be isolated and purified.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ¹H nmr spectra were obtained on a Varian XL-VXR 300 or a Jeol JNM FX 90Q FT spectrometers with TMS as internal standard,

Scheme 2

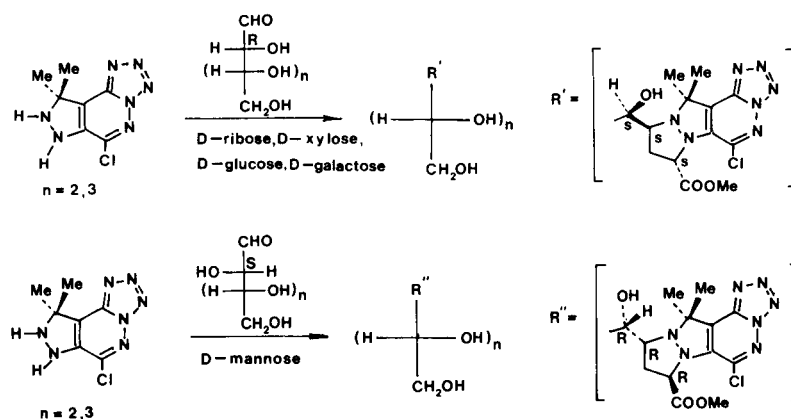


Table 1
Physical Data of Acyclic *C*-Nucleosides

Compound	Yield (%)	Mp (°C) (solvent for recrystallization)	[α] _D	Configuration	δ (ppm)			NMR Data			Solvent
					Me ₁₂	Me ₁₂ , H ₈	H ₈	COOMe	J _{H₈H₉} (Hz)	J _{H₈H₉'} (Hz)	
4	41	167-169 [a] (methanol)	+742±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.63	1.85	4.93	3.70	7.6	0	DMSO-d ₆
6	44	215-217 [a] (di- <i>n</i> -Butyl ether)	+332±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.71	1.93	4.68	3.72	7.8	2.0	CDCl ₃
8	32	156-157 [a] (benzene)	+304±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.77	1.89	4.60	3.68	7.0	3.0	CDCl ₃
10	44	176-178 (nitromethane)	+592±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.60	1.85	4.87	3.70	6.8	0	DMSO-d ₆
12	38	175-176 (ethyl acetate)	+643±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.58	1.85	4.91	3.70	6.8	0	DMSO-d ₆
14	51	177-179 (propionitrile)	+595±5°	1' <i>S</i> ,8 <i>S</i> ,10 <i>S</i>	1.60	1.85	4.91	3.70	6.8	0	DMSO-d ₆
16	34	188-190 (propionitrile)	-548±5°	1' <i>R</i> ,8 <i>R</i> ,10 <i>R</i>	1.62	1.85	4.93	3.71	8.1	0	DMSO-d ₆

[a] The compound is identical with the compound described previously (Ref 8).

microanalyses for C, H, and N on a Perkin-Elmer Analyser 2400, and optical rotation was measured on a Perkin-Elmer spectropolarimeter 241MC.

The following compounds were prepared according to the procedures described in literature: 6-chloro-9,9-dimethyl-7,8-dihydro-9*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**1**) [9], tetraacetyl-*α*-*L*-arabinose (**7**) [10], and pentaacetyl-*α*-*D*-galactose (**5**) [11].

Preparation of C-Nucleosides.

General Procedure.

To a mixture of **1** (0.002 mole), aldehyde sugar **2**, **5**, **7**, **9**, **11**, **13** or **15** (0.0027 mole) in methanol (4 ml) trifluoroacetic acid (0.02 ml) and methyl acrylate (**3**, 0.003 mole) were added and the mixture was heated under reflux for one hour. The precipitate was, after cooling in the refrigerator for several hours, collected by filtration and recrystallized from an appropriate solvent. In this manner the compounds **4**, **6**, **8**, **10**, **12**, **14**, and **16** were prepared (Table 1).

¹H NMR Spectral and Analytical Data.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(*D*-arabitol-1'-yl)-10*H*,12*H*-pyrazolo[1',2':1,2]pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**10**).

This compound had ¹H nmr (DMSO-*d*₆, 24°): δ ppm = 1.60 (s, 12-CH₃, 3H), 1.85 (s, 12-CH₃, 3H), 2.63-3.94 (m, 5'-H₂, CH, 9-H₂, 10-H, 4H), 3.70 (s, COOCH₃, 3H), 4.14-5.03 (m, 8-H, 5 x OH, 6H), 4.87 (d, 8-H, 1H), J_{8,9} = 6.8 Hz.

Anal. Calcd. for C₁₇H₂₄ClN₇O₇: C, 43.09; H, 5.11; N, 20.69. Found: C, 43.31; H, 5.22; N, 20.65.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(*D*-lyxitol-1'-yl)-10*H*,12*H*-pyrazolo[1',2':1,2]pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**12**).

This compound had ¹H nmr (DMSO-*d*₆, 23°): δ ppm = 1.58 (s, 12-CH₃, 3H), 1.85 (s, 12-CH₃, 3H), 2.74-3.98 (m, 5'-H₂, CH, 9-H₂, 10-H, 4H), 3.70 (s, COOCH₃, 3H), 4.03-4.92 (m, 8-H, OH, 6H), 4.91 (d, 8-H, 1H).

Anal. Calcd. for C₁₇H₂₄ClN₇O₇: C, 43.09; H, 5.11; N, 20.69. Found: C, 43.27; H, 5.26; N, 20.88.

(1'*S*,8*S*,10*S*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(*D*-threitol-1'-yl)-10*H*,12*H*-pyrazolo[1',2':1,2]pyrazolo[1',2':1,2]pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**14**).

This compound had ¹H nmr (DMSO-*d*₆, 23°, 90 MHz): δ ppm = 1.60 (s, 12-CH₃, 3H), 1.85 (s, 12-CH₃, 3H), 2.72-3.29 (m, 9-H₂, 2H), 3.29-3.83 (m, 10H, 1'-H, 2'-H, 3'-H, 4'-H, 5H), 3.70 (s, COOCH₃, 3H), 4.26-4.65 (m, 3 x OH, 3H), 4.68-4.97 (m, 8-H, OH, 2H), 4.91 (d, 8-H, 1H).

Anal. Calcd. for C₁₆H₂₂ClN₇O₆: C, 43.30; H, 5.00; N, 22.09. Found: C, 43.27; H, 5.11; N, 22.14.

(1'*R*,8*R*,10*R*)-8,9-Dihydro-6-chloro-12,12-dimethyl-8-methoxycarbonyl-10-(*D*-arabitol-1'-yl)-10*H*,12*H*-pyrazolo[1',2':1,2]pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**16**).

This compound had ¹H nmr (DMSO-*d*₆, 24°, 90 MHz): δ ppm = 1.62 (s, 12-CH₃, 3H), 1.85 (s, 12-CH₃, 3H), 2.66-4.74 (m, 5 x OH, 5'-H₂, CH, 9-H₂, 10H, 8H), 3.71 (s, COOCH₃, 3H), 4.93 (d, 8-H, 1H).

Anal. Calcd. for C₁₇H₂₄ClN₇O₇: C, 43.09; H, 5.11; N, 20.69. Found: C, 43.09; H, 5.30; N, 20.87.

Acknowledgement.

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