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Enantioselective synthesis of hydroxy-substituted α-methyl-α-amino acids using Al and Mn derivatives of cyclo-(*L*-Ala-*L*-Ala) bis-lactim ethers

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Aluminum and manganese derivatives of lithiated bis-lactim ethers of cyclo-(*L*-Ala-*L*-Ala) were used for the enantioselective synthesis of β-hydroxy and polyhydroxy α-amino acids of the 2-methylserine series. A new variant of the synthesis of these acids via 3-acyl-2,5-dialkoxy-3,6-dimethyl-3,6-dihydropyrazines is proposed.

Key words: optically active α-amino acids, bis-lactim ethers of 2,5-diketopiperazines, Al and Mn derivatives; metalated nitrogen heterocycles, acyldemetalation.

The bis-lactim ether method provides an important route to amino acid derivatives. It involves the reaction of a carbon electrophile with a lithiated 2,5-dialkoxy-3,6-dihydropyrazines derived from proteinogenic amino acids followed by acid hydrolysis of the imine bonds in the heterocycles obtained.[1,2]

Some aldol-type reactions of lithiated bis-lactim ethers and their Ti derivatives were studied previously. Thus, *threo*-β-hydroxy amino acids were prepared from cyclo-(*L*-Val-Gly) with high diastereoselectivity.[3,4]

We attempted to elaborate an alternative route to precursors of 2-methylserine derivatives based on the acylation of bis-lactim ethers of cyclo-(*L*-Ala-*L*-Ala) with acyl halides followed by enantioselective reduction of the carbonyl group in the 3-acylated piperazines. It is known that reactions of acyl chlorides with lithiated bis-lactim ethers of 2,5-diketopiperazines, including cyclo-(*L*-Ala-*L*-Ala), are accompanied by side processes, have a limited number of acceptable substrates, and cannot serve as a preparative procedure for the synthesis of ketones.[5] Here we shall demonstrate the advantages of Al and Mn derivatives of bis-lactim ethers.

This investigation is a continuation of the synthetic studies of the acyldemetalation of various aluminated nitrogen heterocycles.[6,7]

Results and Discussion

The (3*S*,6*S*)-di-ethyl bis-lactim ether of cyclo-(*L*-Ala-*L*-Ala) (**1**) (ca. 93% optical purity) was prepared from *L*-alanine.[8,9] Compound **1** was lithiated with

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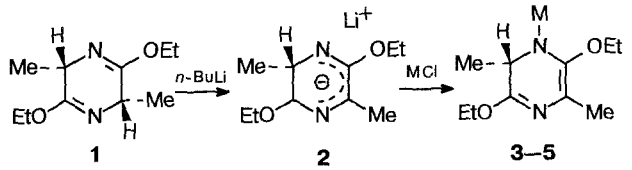
n-BuLi in THF at −50°C. Al, Mn, and Zn derivatives **3**—**5** were obtained *in situ* by adding equimolar amounts of Et_2AlCl, Li_2MnCl_4, or $ZnCl_2$ to Li salt **2** at −78°C (Scheme 1).

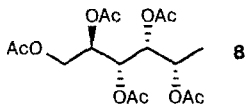
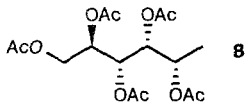
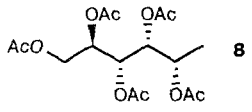
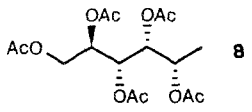
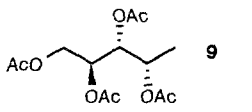
Scheme 1



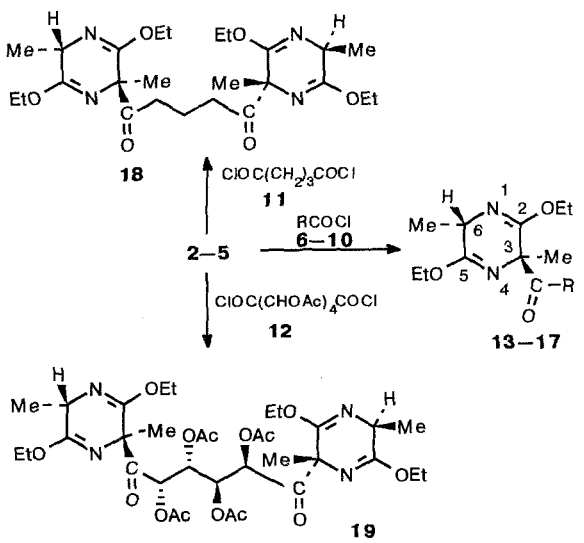
M = Li (**2**), Et_2Al (**3**), $MnCl \cdot 2LiCl$ (**4**), ZnCl (**5**)

Compounds **2**—**5** were acylated by acyl chlorides containing organometallic-sensitive functions, viz., chloroacetyl, 2,5-diacetoxybenzoyl, and peracetylated *D*-gluconyl and *L*-arabinohyl chloride. The possibility of the synthesis of diketones was studied with glutaryl and galactaryl dichloride (**11** and **12**, respectively) and Al and Mn derivatives **3** and **4** (Scheme 2). The diastereomeric purity of the reaction products was estimated with the aid of HPLC and on the basis of ^1H and ^{13}C NMR spectra. Table 1 lists the comparative efficiency of different metal derivatives, preparative yields, and diastereomeric ratios of the ketones.

Table 1. Yields of ketones **13**—**17** obtained in the reaction of acyl chlorides with metalated of bis-lactim ethers **2**—**5**

Ketone	Reagent	R in RCOCl	Yield (%)	de (%) (3*S*:3*R*)
13	**2**	CH_2Cl (**6**)	0	
13	**4**	CH_2Cl (**6**)	74	80
14	**2**	$C_6H_3(OAc)_2$ (**7**)	0	
14	**4**	$C_6H_3(OAc)_2$ (**7**)	78	≥95
15	**2**	 **8**	23	
15	**3**	 **8**	43	≥95
15	**4**	 **8**	78	≥95
15	**5**	 **8**	53	≥95
16	**4**	 **9**	88	≥95
17	**4**	Ph (**10**)	88	≥95

Scheme 2



R = CH_2Cl (**6**, **13**), $C_6H_3(OAc)_2$ (**7**, **14**), $CH_2OAc(CHOAc)_4$ (**8**, **15**), $CH_2OAc(CHOAc)_3$ (**9**, **16**), Ph (**10**, **17**)

The reaction of the Li derivative **2** with acyl chlorides **6** and **7** did not afford the desired ketones. Pentaacetyl-*D*-gluconyl chloride **8** reacted with **2** to give a mixture of products with a low content of **15**. With the Al (**3**) or Mn (**4**) derivatives, ketones **13** and **14** were obtained in high yields. A considerable increase in yield was achieved in the other cases (Table 1).

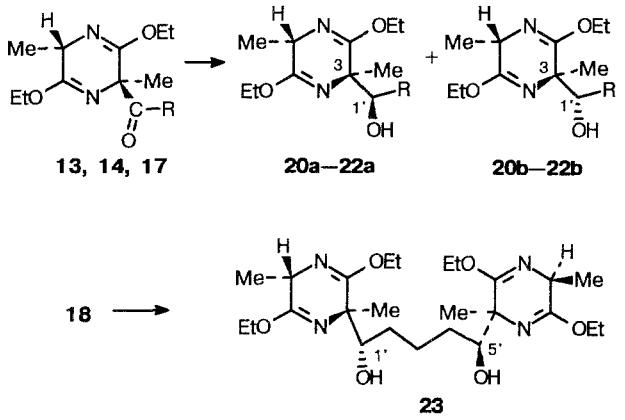
Glutaryl and galactaryl dichloride react with **4**, affording **18** and **19** in 64% and 70% yields, respectively. HPLC and ^1H and ^{13}C NMR spectroscopy of the products demonstrate that the reactions studied gave virtually one diastereomer. The case of **6** is an exception (3*S* : 3*R* = 90 : 10).

As was shown earlier, the carbanions of bis-lactim ethers have planar structures; electrophilic reagents attack them in the *trans* position to C(6).[1] The reaction of the lithiated ether of cyclo-(*L*-Val-*L*-Ala) with benzoyl chloride also gave the *trans* isomer with a high degree of asymmetric induction at the C(3) center (de ≥ 95 %).[5] Therefore, we propose that ketones **13**—**19** have a 3*S*,6*S* configuration.

To achieve chemo- and stereoselective reduction of the C=O group in 3-acylpiperazines, we investigated the following reducing agents: $NaBH_4$, *i*-Bu_2AlH,

(s-Bu_3)BHK (K-Selectride), and diisobutylaluminum-2,6-di-*tert*-butyl-4-methylphenoxide (Scheme 3, Table 2).

Scheme 3



13, 20 : R = CH_2Cl **17, 22** : R = Ph
14, 21 : R = $C_6H_3(OAc)_2$

A diastereomeric mixture of alcohols was obtained in all the cases when $NaBH_4$ or i-Bu_2AlH was employed. The reaction of **14** with $NaBH_4$ or i-Bu_2AlH was accomanied by reduction of the protective acetate groups. K-Selectride was inert towards **14** and **17**. We achieved high chemo- and stereoselectivity using diisobutylaluminum-2,6-di-*tert*-butyl-4-methylphenoxide. This reagent can be prepared from i-Bu_2AlH and Ionol in a toluene solution. Previously it was used for the enantioselective reduction of carbonyl functions in prostaglandins.[10] As was shown by HPLC and NMR spectroscopy of the reaction mixtures, alcohols **20—23** were obtained as the only isomers.

Attempts to carry out the analogous reduction of **15** and **16** were unsuccessful; their reactions with $NaBH_4$ gave a complex mixtures of products. The desired precursors of polychiral polyhydroxylated amino acids **24** and **25** were obtained from the corresponding aldehydes **26** and **27** with excellent stereoselectivity in 71 % and 58 % yields, respectively. Only one isomer (of the four possible) was obtained in each case.

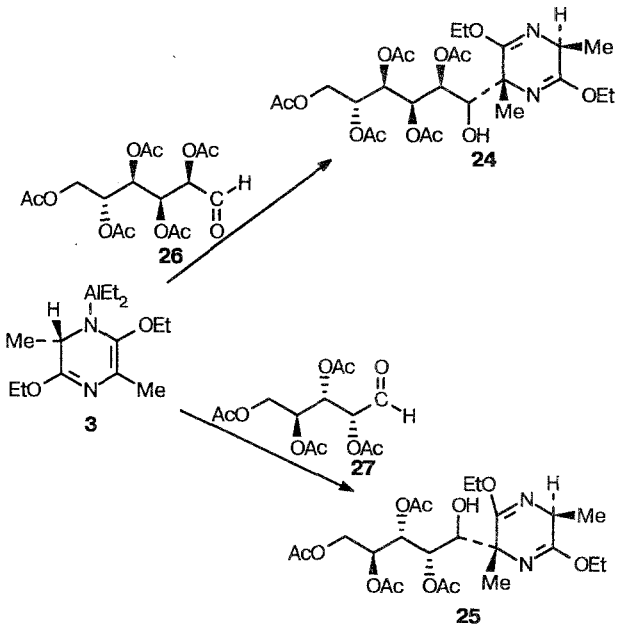
Alcohols **20—23** obtained from the ketones **13**, **14**, **17**, and **18**, respectively, have (3*R*,6*S*)-*trans* configurations (see above). The determination of the relative configurations of the substituents at C(3) and C(1') in **20—23** was performed as follows: alcohol **20a**, which was formed upon the reduction of ketone **13** by $NaBH_4$, and its stereoisomer **20b** (see above) were hydrolyzed with 0.5 *N* HCl at ambient temperature, and isomeric

Table 2. Hydride reduction of ketones **13**, **14**, **17**, and **18**

Ketone	Reducing agent	Total yield (%)	Ratio of diastereomers (*syn* : *anti*)
13	$NaBH_4$	58	1 : 1
13	*	82	>95% *syn*
14	$NaBH_4$	0	
14	i-Bu_2AlH	0	
14	**	0	
14	*	39	>95% *syn*
17	$NaBH_4$	46	1 : 1
17	i-Bu_2AlH	52	1 : 1
17	*	63	95% *syn*
17	**	0	
18	i-Bu_2AlH	36	1 : 1
18	*	39	>95% *syn*

*Diisobutylaluminum-2,6-di-*tert*-butyl-4-methylphenoxide.
** (s-Bu_3)KBH (K-Selec).

Scheme 4



ethyl esters of amino acids **28** and **29** were obtained in 52 % and 25 % yields, respectively, after purification by column chromatography on SiO_2. Diastereomers **28** and **29** were transformed into 2-oxazolidinones **30** and **31**, respectively, by the reaction with carbonyldiimidazole.

The ^{13}C NMR signal for the methyl group at C(4) in **30** (18.9 ppm) is shifted upfield in comparison to the corresponding signal in **31** (25.9 ppm) as a result of the "steric compression effect" arising from the spatial proximity of the *cis*-arranged methyl and chloromethyl groups.

Table 3. ^{13}C NMR spectra of 3-acyl derivatives of 2,5-diethoxy-3,6-dihydropyrazines (**13—19**), alcohols (**20—25**), ethyl butanoates (**28**, **29**), and 2-oxazolidinones (**30**, **31**)) ($CDCl_3$, TMS)

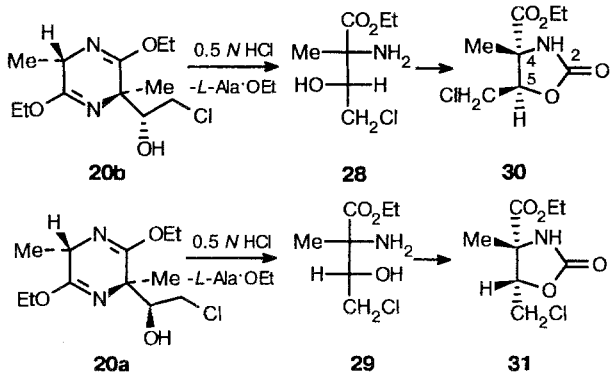
Compound	Chemical shift, δ
13	13.2 q, 12.9 q (OEt), 20.2 q (19.7 q) (CH_3), 22.9 q (22.1 q) (CH_3), 44.5 t (CH_2Cl), 51.32 d (50.7 d) (C-6), 60.6 t (OEt), 65.3 s (66.0 s) (C-3), 160.1 s (159.5 s) (C-2), 165.0 s (165.6 s) (C-5), 195.4 s (196.0 s) (C=O)
14	14.0 q, 14.1 q (OEt), 20.9 q, 21.1 q (OAc), 21.3 q (CH_3), 52.1 d (C-6), 61.3 t—61.5 t (OEt), 67.4 s (C-3), 121.5 d, 124.2 d, 124.55 d, 131.45 d, 145.9 d, 147.22 s (C arom.), 161.8 s (C-2), 165.6 s (C-5), 168.6 s, 169.2 s (C=O), 194.88 s (C=O)
15	14.0 q, 14.2 q (OEt), 20.2 q—20.8 q (OAc), 21.3 q (CH_3), 25.0 q (CH_3), 52.1 d (C-6), 61.5 t, 61.8 t (OEt), 65.6 s (C-3), 67.92 d, 68.5 d, 69.4 d, 70.92 d (CH-OAc), 161.4 s (C-2), 166.4 s (C-5), 168.7 s, 169.4 s, 169.7 s, 169.8 s, 170.5 s (C=O), 199.19 s (C=O)
16	14.0 q, 14.2 q (OEt), 20.3 q—20.8 q (OAc), 21.3 q (CH_3), 24.9 q (CH_3), 52.1 d (C-6), 61.8 t (CH_2-OEt), 61.5 t, 61.6 t (OEt), 66.3 s (C-3), 68.3 d—68.5 d (CH-OAc), 160.9 s (C-2), 166.5 s (C-5), 169.2 c—170.5 s (C=O), 198.75 s (C=O)
17	13.8 q, 14.1 q (OEt), 21.2 q (CH_3), 25.6 q (CH_3), 52.5 d (C-6), 61.4 t (OEt), 61.5 t, 65.8 s (C-3), 128.0 d, 128.5 d, 132.0 d, 136.4 s (C arom.), 163.9 s (C-2), 165.3 s (C-5), 194.8 s (C=O)
18	14.0 q, 14.3 q (OEt), 18.7 t (CH_2), 21.5 q (CH_3), 23.2 q (CH_3), 35.7 t (CH_2), 52.3 d (C-6), 61.3 t (CH_2,OEt), 66.8 s (C-3), 162.3 s (C-5), 165.7 s (C-2), 204.3 s (C=O)
19	14.0 q, 14.3 q (OEt), 20.1 q—20.4 q (OAc), 21.3 q (CH_3), 25.0 q (CH_3), 51.7 d (51.2 d) (C-6), 61.1 t, 61.4 t (CH_2, OEt), 67.7 d—67.9 d (CH-OAc), 70.3 s (70.8 s) (C-3), 158.8 s (160.0 s) (C-2), 165.5 s (166.4 s) (C-5), 170 s (C=O), 198.8 s, 199.0 s (C=O)
20a	14.1 q, 14.2 q (OEt), 21.5 q (CH_3), 26.1 q (CH_3), 47.2 t (CH_2Cl), 52.4 d (C-6), 60.4 s (C-3), 61.1 t (CH_2, OEt), 75.3 d (CHOH), 163.2 s (C-5), 165.3 s (C-2)
20b	14.2 q (OEt), 21.6 q (CH_3), 25.3 q (CH_3), 46.8 t (CH_2Cl), 51.9 d (C-6), 60.9 t, 61.2 t (CH_2, OEt), 77.1 d (CHOH), 163.3 s, 165.3 s (C-2, C-5)
21b	13.8 q, 14.1 q (OEt), 20.8 q (OAc), 26.3 q (CH_3), 52.0 d (C-6), 61.4 t, 61.5 t (CH_2, OEt), 63.0 s (C-3), 79.1 d (CHOH), 118.3 s, 122.6 d, 122.7 d, 124.1 d, 142.7 s, 153.2 s (C arom.), 162.1 s (C-5), 167.9 s (C-2), 169.3 s, 169.8 s (C=O)
22b	14.3 q, 14.4 q (OEt), 21.5 q (CH_3), 25.6 q (CH_3), 51.7 d (C-6), 60.7 t, 61.1 t (CH_2, OEt), 62.1 s (C-3), 79.1 d (CHOH), 127.5 d, 127.4 d, 128.0 d, 140.4 s (C arom.), 163.6 s (C-2), 164.9 s (C-5)
23b	14.3 q (OEt), 21.8 q (CH_3), 23.1 t (CH_2), 25.1 q (CH_3), 31.3 t (CH_2), 51.9 d (C-6), 60.7 t, 60.9 t (CH_2, OEt), 61.5 s (C-3), 77.1 d (CHOH), 164.6 s (C-2), 164.5 s (C-5)
24	14.2 q, 14.3 q (OEt), 20.4 q—20.8 q (OAc), 21.6 q (CH_3), 27.5 q (CH_3), 51.7 d (C-6), 57.9 s (C-3), 60.5 t, 61.2 t (CH_2, OEt), 68.1 t, 61.8 d, 68.2 d, 70.3 d, 71.1 d (CHOAc), 76.1 d (CHOH), 163.8 s (C-5), 164.6 s (C-2), 169.3 s, 169.6 s, 169.9 s, 170.6 s (C=O)
25	14.2 q, 14.4 q (OEt), 20.5 q—20.8 q (OAc), 21.5 q (CH_3), 27.3 q (CH_3), 51.9 d (C-6), 58.6 s (C-3), 60.8 t, 61.2 t (CH_2, OEt), 61.8 t, 68.9 d, 69.2 d, 71.6 d (CHOAc), 77.8 d (CHOH), 163.5 s (C-5), 164.9 s (C-2), 169.5 s—170.5 s (C=O)
28	13.9 q (OEt), 22.0 q (CH_3), 46.1 t (CH_2Cl), 60.8 s (C-NH_2), 61.4 t (CH_2, OEt), 75.4 d (CHOH), 175.6 s (COOEt)
29	14.1 q (OEt), 23.7 q (CH_3), 46.5 t (CH_2Cl), 60.6 s (C-NH_2), 61.6 t (CH_2, OEt), 75.9 d (CHOH), 175.2 s (COOEt)
30	13.9 q (OEt), 18.9 q (CH_3), 41.4 t (CH_2Cl), 62.7 s (C-NH_2), 63.1 s (C-4), 79.5 d (C-5), 156.8 s (C=O), 171.7 s (C=O)
31	14.0 q (OEt), 25.9 q (CH_3), 42.3 t (CH_2Cl), 62.8 s (C-NH_2), 63.2 s (C-4), 83.4 d (C-5), 157.0 s (C=O), 170.4 s (C=O)

Intramolecular NOE measurements proved their *cis* configuration in **31**: if the C(4) methyl was irradiated, the intensity of H(5) signal increased by *ca.* 10 %, whereas no effect was observed for **30**. Therefore, ethyl ester **29** and its precursor **20a** are *erythro* isomers, and **28** and **29** are *threo* isomers.

The *threo*-(*syn*) configuration of **22b** was established by means of ^1H NMR spectroscopy; the spectra of **22a** and **22b** were compared with those of the stereoisomeric *erythro*- and *threo*-2,6-dimethoxy derivatives of 3-[hydroxy(phenyl)methyl]-3,6-dimethoxy-3,6-dihydropyrazine.[2] The *syn* configurations of **21b** and **23b** were assigned by analogy.

Therefore, a novel procedure for the enantioselective synthesis of β-hydroxy and polyhydroxylated α-amino acids (of the 2-methylserine series) starting from the Mn and Al salts of cyclo-(*L*-Ala-*L*-Ala) bis-lactim ethers *via* 3-acyl-3,6-dihydropyrazines has been developed. The advantage of this new method, which is an alternative to aldol condensation, is confirmed by the following results. Lithiated bis-lactim ether **2** reacts with benzaldehyde to give a mixture of four diastereomeric alcohols; the content of the identified isomers **22a** (2*R*,3*R*,1′*R*) and **22b** (6*S*,3*R*,1′*R*) was 27 % and 30 %, respectively (HPLC) (cf. Ref.[2]). Diastereoselectivity cannot be achieved by varying the metal, which is an

Scheme 5



effective approach in aldol-type reaction.[3,4] Thus, the ratio of isomers did not change significantly when Al derivative **3** was used. With the tris(diethylamido)titanium derivative, high optical induction at the C(3) center could be achieved, but the selectivity at C(1') was low, the yields of stereoisomeric alcohols **22a** and **22b** being 30 % and 62 %, respectively.

Experimental

^1H and ^{13}C NMR spectra (δ, *J*, Hz) were recorded on a Bruker AM-300 (300 and 75 MHz, respectively) spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. The ^{13}C NMR spectral data are listed in Table 3. Specific rotations were measured for $CHCl_3$ solutions on an automatic Perkin Elmer 241 polarimeter. HPLC analyses were carried out on a DuPont 8800 liquid chromatograph equipped with a refractometric detector and Zorbax-Sil columns (25× 0.46 cm and 25×2.12 cm).

The diketopiperazine cyclo-(*L*-Ala-*L*-Ala) was prepared from *L*-alanine methyl ester.[8] Its optical purity was *ca.* 90—93 % after crystallization from water. **(3*S*,6*S*)-3,6-Dihydro-2,5-diethoxy-3,6-dimethylpyrazine 1** was obtained by the reaction of cyclo-(*L*-Ala-*L*-Ala) with triethyloxonium tetrafluoroborate in CH_2Cl_2.[9] Peracetylated aldonyl chlorides, peracetates of *aldehydo-D*-glucose and *aldehydo-L*-arabinose were prepared as reported in Ref.11.

Solutions of *n*-BuLi (1.3 *N*) in hexane, Li_2MnCl_4 in THF (0.6 *N*), and Et_2AlCl in hexane (2*N*) were used. Lithiated bis-lactim ether **2** was obtained as reported in Ref.2.Acid hydrolysis of isomeric alcohols **20a** and **20b** and separation of the products were performed in accordance with Ref.4 $Ti[(C_2H_5)_2N]_3Cl$ was prepared according to Refs.12,13. Titanium derivative of lithiated bis-lactim ether **2** was prepared as described.[3,4]

Acylation of metalated bis-lactim ethers of cyclo-(*L*-Ala-*L*-Ala). General procedure. A solution of *n*-BuLi in hexane (1.2 mL, 1.56 mmol) was added dropwise to a stirred solution of bis-lactim ether **1** (0.29 g, 1.5 mmol) in 6 mL of THF at −70°C under Ar. Then the temperature was raised to −45°C, the mixture was held for 15 min, and a solution of the acyl chloride (1.5 mmol) in THF was added at −70°C. The reaction mixture was heated slowly up to 20°C in 20 h. When **3** or **4** were used, a solution of Et_2AlCl in hexane (0.75 mL) or Li_2MnCl_4 in THF (2.5 mL), respectively, was added before the addition of a solution of **2**, and the reaction mixture was held at −70°C for 1 h. After the reaction was completed, the reaction mixture was treated with a phosphate buffer ($NaH_2PO_4 \cdot 2H_2O$ (28.1 g) and Na_2HPO_4 (106 g) in 50 mL of H_2O), the solvent was removed *in vacuo* at ambient temperature, the residue was extracted with ether, and the extract was dried with $MgSO_4$. After evaporation of the solvent the products were purified by flash chromatography on SiO_2 (eluent, hexane—ethyl acetate) and analyzed by HPLC and NMR spectroscopy.

(3*S*,6*S*)-3-Chloroacetyl-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazine (13). n_D^{20} 1.4770, $[\alpha]_D^{20}$ −45°. ^1H NMR, δ: 1.18 (m, 6 H, Me); 1.32 (d, 3 H, Me); 1.42 (s, 3 H, Me); 4.05 (m, 6 H, CH_2, CH); 4.25 (dd, 1 H, CH_2Cl). Found (%): C, 52.30; H, 6.98; N, 10.03; Cl, 12.20. $C_{12}H_{19}ClN_2O_3$. Calculated (%): C, 52.27; H, 7.25; N, 10.16; Cl, 12.89.

(3*S*,6*S*)-3-(2,5-Diacetoxybenzoyl)-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazine (14). $[\alpha]_D^{20}$ −59°. ^1H NMR, δ: 1.18 (t, 3 H, Me); 1.20 (t, 3 H, Me); 1.40 (d, 3 H, Me); 1.58 (s, 3 H, Me); 2.28 and 2.29 (both s, 6 H, OAc); 4.0—4.2 (m, 5 H, CH_2, CH); 7.12 (m), 7.38 (d, 3 H, arom. fragment).

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3,6-dimethyl-3-(2,3,4,5,6-penta-O-acetyl-D-gluconyl)pyrazine (15). Mp 105—107°C, $[\alpha]_D^{20}$ −15°. ^1H NMR, δ: 1.25 (t, 3 H, Me); 1.30 (t, 3 H, Me); 1.40 (d, 3 H, Me); 1.45 (s, 3 H, Me); 2.0—2.15 (m, 15 H, Me); 4.0—4.2 (m, 5 H, CH_2, OH); 4.1—4.25 (m, 2 H, H(6'); 5.10 (m, H(5')); 5.50 (dd, H(4')); 5.72 (m, 2 H, H(3'),H(2')). Found (%): C, 52.89; H, 6.11; N, 4.39. $C_{26}H_{38}N_2O_{13}$. Calculated (%): C, 53.24; H, 6.48; N, 4.78.

(3*S*,6*S*)-2,5-Diethoxy-3,6-dihydro-3,6-dimethyl-3-(2,3,4,5-tetra-O-acetyl-*L*-arabinonyl)pyrazine (16). Mp 78—80°C, $[\alpha]_D^{20}$ −31°. ^1H NMR, δ: 1.23 (t, 3 H, Me); 1.33 (t, 3 H, Me); 1.40 (d, 3 H, Me); 1.45 (c, 3 H, Me); 2.1 (m, 12 H, Me); 4.15 (m, 5 H, CH_2, CH); 4.25 (m, 2 H, H(5')); 5.10 (m, H(4')); 5.70 (d, H(2')); 5.90 (dd, H-3'). Found (%): N, 5.25. $C_{23}H_{34}N_2O_{11}$. Calculated (%): N, 5.45.

1,5-[Bis-(3*S*,6*S*)-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazin-3-yl]-1,5-pentanedione (18). Mp 37—39°C, $[\alpha]_D^{20}$ −45°. ^1H NMR, δ: 1.22 (t, 6 H, Me); 1.28 (t, 6 H, Me), 1.39 (d, 6 H, Me); 1.42 (s, 6 H, Me); 1.80 (m, 2 H, CH_2); 2.20 (m, 2 H, CH_2); 2.50 (m, 2 H, CH_2); 4.08 (m, 10 H, CH_2, CH). Found (%): C, 60.60; H, 8.10; N, 11.29. $C_{25}H_{40}N_4O_6$. Calculated (%): C, 60.98; H, 8.13; N, 11.38.

1,6-[Bis-(3*S*,6*S*)-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazin-3-yl]-2,3,4,5-tetraacetoxy-*D-galacto*-1,6-hexanedione (19). Mp 179—181°C, $[\alpha]_D^{20}$ +40°. ^1H NMR, δ: 1.20 m; 1.40 (m, 24 H, Me); 2.0 (m, 12 H, Me); 3.95—4.45 (m, 10 H, CH_2, CH); 5.26 (d, 1 H, CH); 5.48 (d, 1 H, CH); 5.83 (dd, 1 H, CH). Found (%): N, 7.35. $C_{34}H_{50}N_4O_{14}$. Calculated (%): N, 7.59.

Hydride reduction of carbonyl group in 13, 14, 17, and 18. General procedures

1. Reduction of the ketones by $NaBH_4$. To a stirred solution of the ketone (0.7 mmol) in 4 mL of ethanol $NaBH_4$ (0.35 mmol) was added at 5°C, the mixture was stirred at 20°C for 2—3 h, then 0.25 *N*, HCl was added dropwise to pH 6.6, ethanol was removed *in vacuo*, the residue was extracted with ether, and the extract was dried with $MgSO_4$. After evapora-

tion of the solvent, the mixture of *syn* and *anti* alcohols was separated by chromatography on SiO_2 (the eluent was hexane—ethyl acetate).

2. Reduction of the ketones by *i*-Bu_2AlH. To a stirred solution of the ketone (0.7 mmol) in 5 mL of CH_2Cl_2 (i-Bu)$_2$AlH (1.4 mmol) was added dropwise at −78°C, the mixture was stirred for 3 h, and then slowly heated up to −10°C. The excess of the reducing agent was decomposed with a phosphate buffer, the mixture was extracted with ether, and the extract was dried over $MgSO_4$.

3. Reduction of the ketones by diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide. To prepare the reagent a solution of (i-Bu)$_2$AlH (4.9 mmol) in 3 mL of CH_2Cl_2 was added dropwise to a solution of 2,6-di-*tert*-butyl-4-methylphenol (ionol) (2.16 g, 9 mmol) in 27 mL of CH_2Cl_2 at 4°C and stirred for 1 h. Then a solution of the ketone (2.45 mmol) in 3 mL of CH_2Cl_2 was added to the reagent thus prepared at −78°C. The mixture was stirred at −78°C for 3 h and then at −40°C for 2 h. The mixture was treated with a phosphate buffer, and the precipitate was filtered out and washed with ether. The filtrate was extracted with ether several times, and the combined extracts were dried with $MgSO_4$. After evaporation of the solvent, the reaction products were purified by chromatography on SiO_2. Ionol was eluted with hexane—ethyl acetate (10:1) and the target alcohols were eluted with hexane—ethyl acetate (4:1 or 1:1).

4. Reduction of the ketones by K-Selectride (s-Bu_3)KBH. To a solution of the ketone (0.36 mmol) in 15 mL of THF was added a solution of K-Selectride (1 *N*, 0.72 mL) in THF at −78°C, and the mixture was stirred at −78°C for 3 h and at −35°C for 2 h. In some experiments the temperature was increased up to 20°C. The mixture was treated with a phosphate buffer, extracted with ether, and the extract was dried with $MgSO_4$.

(3*R*, 6*S*, 1'*R*)-3-(2-Chloro-1-hydroxyethyl)-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazine (20a). $[\alpha]_D^{20}$ +16°. ^{1}H NMR, δ: 1.21 (t, 6 H, Me); 1.28 (d, 3 H, Me); 1.37 (s, 3 H, Me); 3.15 (dd, 1 H, CH_2Cl); 3.35 (dd, 1 H, CH_2Cl); 3.87 (m, 1 H, CHOH); 4.03 (m, 5 H, CH_2, CH).

(3*R*, 6*S*, 1'*S*)-3-(2-Chloro-1-hydroxyethyl)-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazine (20b). $[\alpha]_D^{20}$ −48°. ^{1}H NMR, δ: 1.25 (t, 3 H, Me); 1.30 (t, 3 H, Me); 1.33 (d, 3 H, Me); 1.35 (s, 3 H, Me); 3.60 (dd, 1 H, CH_2Cl); 3.81 (dd, 1 H, CH_2Cl); 3.95 (dd, 1 H, CHOH); 4.10 (m, 5 H, CH_2, CH).

(3*R*,6*S*,1'*S*)-3-[2,5-Diacetoxyphenyl(hydroxy)methyl]-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazine (21b). $[\alpha]_D^{20}$ −65°. ^{1}H NMR, δ: 1.35 (m, 9 H, Me); 1.45 (s, 3 H, Me); 2.15 and 2.25 (both s, 6 H, OAc); 3.90 (q, 1 H, H-6); 4.1—4.3 (m, 4 H, CH_2); 6.15 (s, 1 H, CHOH); 6.75—6.90 (m, 3H, arom. fragment). Found (%): C, 59.80; H, 6.63; N, 6.39. $C_{21}H_{28}N_2O_7$. Calculated (%): C, 60.00; H, 6.67; N, 6.67.

(3*R*,6*S*,1'*R*)-2,5-Diethoxy-3,6-dihydro-3-(α-hydroxybenzyl)-3,6-dimethylpyrazine (22a). $[\alpha]_D^{20}$ −91°. ^{1}H NMR, δ: 1.23 (d, 3 H, Me); 1.33 (t, 3 H, Me); 1.60 (s, 6 H, Me); 3.40 (q, 1 H, H-6); 3.75 (dq, 1 H, CH_2); 4.03 (dq, 1 H, CH_2); 4.18 (dq, 1 H, CH_2); 4.25 (dq, 1 H, CH_2); 4.82 (s, 1 H, CHOH); 7.1—7.2 (m, 5 H, arom. fragment). Found (%): C, 67.22; H, 7.86; N, 9.17. $C_{17}H_{22}N_2O_3$. Calculated (%): C, 67.11; H, 7.89; N, 9.21.

(3*R*,6*S*,1'*S*)-2,5-diethoxy-3,6-dihydro-3-(α-hydroxybenzyl)-3,6-dimethylpyrazine (22b). $[\alpha]_D^{20}$ −39°. ^{1}H NMR, δ: 1.21 (m, 12 H, Me); 3.65 (q, 1 H, H-6); 4.05 (m, 4 H, CH_2); 4.72 (s, 1 H, CHOH); 7.20 (m, 5 H, Ph).

(1*S*,5*S*)-Bis-[3*R*,6*S*-2,5-diethoxy-3,6-dihydro-3,6-dimethylpyrazin-3-yl]-1,5-pentanediol (23b). Mp 90—92°C, $[\alpha]_D^{20}$ −51°. ^{1}H NMR, δ: 1.25 (t, 12 H, Me); 1.33 (s, 6 H, Me); 1.35 (d, 6 H, Me); 1.4—1.7 (m, 6 H, CH_2); 3.6 (m, 2 H, CHOH); 4.10 (m, 10 H, CH_2, CH).

Reactions of aluminum azoenolate 3 with 2,3,4,5,6-penta-O-acetyl-*aldehydo*-*D*-glucose (26) and 2,3,4,5-tetra-O-acetyl-*aldehydo*-*L*-arabinose (27). To a stirred solution of **3** prepared from **1** (0.198 g, 1 mmol) in 4 mL of THF was added a solution of aldehyde **26** or **27** (1 mmol) in 2 mL of THF dropwise at −78°C. The mixture was held at −78°C for 3h, treated with a phosphate buffer, and extracted with ether. The extract was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography (SiO_2, hexane—ethyl acetate (2:1) as the eluent).

(3*R*, 6*S*, 1'*R* or 1'*S*)-3-(2,3,4,5,6-pentaacetoxy-*D*-*gluco*-hexyl)-2,5-diethoxy-3,6-dihydro-3,6-dimethyl-1-hydroxypyrazine (24). Mp 89—91°C. $[\alpha]_D^{20}$ −21°. ^{1}H NMR, δ: 1.20 (t, 3 H, Me); 1.22 (t, 3 H, Me); 1.26 (d, 3 H, Me); 1.40 (s, 3 H, Me); 1.8, 2.0, 2.05, 2.1, 2.15 (all s, 15 H, OAc); 3.65 (dd, 1 H, H-6'); 3.85 (dd, 1 H, H-6'); 4.20 and 4.25 (m, 5 H, CH_2, CHOH); 5.10 (m, 1 H, H(2')); 5.25 (d, 1 H, H5'); 5.50 (dd, 1 H, H-3'); 5.63 (dd, 1 H, H-4'). Found (%): N, 4.63. $C_{26}H_{40}N_2O_{13}$. Calculated (%): N, 4.76.

(3*R*, 6*S*, 1'*R* or 1'*S*)-3-(2,3,4,5-tetraacetoxy-*L*-*arabino*-pentyl)-2,5-diethoxy-3,6-dihydro-3,6-dimethyl-1-hydroxypyrazine (25). Viscous oil, $[\alpha]_D^{20}$ −63°. ^{1}H NMR, δ: 1.25 (m, 9 H, Me); 1.40 (s, 3 H, Me); 1.9 (s); 2.0 (m, 12 H, OAc); 3.33 (dd, 1 H, H-6'); 3.70 (dd, 1 H, H-6'); 3.80 (q, 1 H, H-6); 4.10 (m, 5 H, CH_2, CHOH); 5.04 (m, 1 H, H-2'); 5.25 (d, 1 H, H-4'); 5.41 (dd, 1 H, H-3'). Found (%): C, 53.73; H, 7.08; N, 5.15. $C_{23}H_{36}N_2O_{11}$. Calculated (%): C, 53.49; H, 6.98; N, 5.43.

Acid hydrolysis of diastereomeric alcohols 20a and 20b. A solution of HCl (11.2 mL, 0.5 *N*, 5.6 mmol) was added to a solution of alcohol **20b** (0.78 g, 2.8 mmol) in 3 mL of ether at 20°C, and the mixture was stirred for 3 days. The aqueous layer was extracted with ether, the organic extracts were discarded, and the aqueous layer was evaporated *in vacuo*. The residue was dissolved in MeOH and conc. NH_4OH was added to pH 10. Then methanol was removed *in vacuo*, and the residue was chromatographed on SiO_2 (the eluent was Et_2O—CH_3CN—NH_4OH (10:1:0.1)) to afford 0.29 g (52 %) of ethyl (2*R*,3*R*)-2-amino-4-chloro-3-hydroxy-2-methylbutanoate (**28**). $[\alpha]_D^{20}$ −17°. ^{1}H NMR, δ: 1.2 (m, 6 H, Me); 2.68 (m, 3 H, OH, NH_2); 3.6 and 3.7 (both m, 2 H, CH_2Cl); 4.0 (m, 1 H, CHOH); 4.15 (q, 2 H, CH_2).

Ethyl (2*R*,3*S*)-2-amino-4-chloro-3-hydroxy-2-methylbutanoate (**29**) was obtained analogously from alcohol **20a** in a 25 % yield. $[\alpha]_D^{20}$ +8°. ^{1}H NMR, δ: 1.2 (t, 3 H, Me); 1.35 (s, 2 H, Me); 3.0—3.2 (m, 3 H, OH, NH_2); 3.4—3.6 (m, 2 H, CH_2Cl); 3.82 (dd, 1 H, CHOH); 4.18 (q, 2 H, CH_2).

Synthesis of 2-oxazolidinones 30 and 31. To a stirred solution of amino acid ethyl ester **28** or **29** (1.1 mmol) in 6 mL of THF was added a solution of N,N'-carbonyldiimidazole (0.26 g, 1.6 mmol) in 10 mL of THF at 20°C under Ar. The mixture was left to stand for 36 h, then THF was removed *in vacuo*, and the residue was dissolved in 10 mL of CH_2Cl_2 and extracted with water (3×5 mL). The organic layer was dried with $MgSO_4$ and evaporated *in vacuo*, and the residue was held *in vacuo* for 1 h (*ca.* 2 Torr) at *ca.* 50°C. Compound **30** was obtained in a 63 % yield. HPLC analysis and NMR spectroscopy were performed without further purification. Oxazolinone **31** was purified by HPLC (Zorbax-Sil, hexane—ethyl acetate—CH_3CN, 210:90:5) and obtained in a 28 % yield.

(4*R*,5*R*)-5-Chloromethyl-4-ethoxycarbonyl-4-methyl-2-oxazolidinone (30). $[\alpha]_D^{20}$ −20°. ^{1}H NMR, δ: 1.25 (t, 3 H, Me); 1.5 (c, 3 H, Me); 3.66 (dd, 1 H, CH_2Cl); 3.73 (dd, 1 H,

CH_2Cl); 4.20 (q, 2H, CH_2); 4.87 (dd, 1 H, H5); 6.50 (1 H, NH).

(4*R*,5*S*)-5-Chloromethyl-4-ethoxycarbonyl-4-methyl-2-oxazolidinone (31). $[\alpha]_D^{20}$ +40°. ^1H NMR, δ: 1.32 (t, 3 H, Me); 1.68 (s, 3 H, Me); 3.80 (d, 2 H, CH_2Cl); 4.25 (q, 2 H, CH_2); 4.60 (t, 1 H, H5); 6.87 (1 H, NH). MS (70 eV), *m/z* (I_{rel}, %): 221 $[M]^{+\cdot}$(24), 172 $[M-CH_2Cl]^+$(12), 148 $[M-CO_2Et]^+$(100), 104 $[M-117]^+$(88).

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New type of interaction of 5-iodopyrimidine nucleosides with alkynes

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The interaction of 1-(β-*D*-xylofuranosyl)-5-iodo(bromo)uracil derivatives with terminal alkynes in the presence of catalytic amounts of 10% Pd/C and CuI affords the corresponding derivatives of 3-(β-*D*-xylofuranosyl)-6-*R*-furo[2,3-*d*]pyrimidin-2-ones in high yields.

Key words: 1-(β-*D*-xylofuranosyl)-5-iodo(bromo)uracils, alkynes; Pd/C catalysis, 3-(β-*D*-xylofuranosyl)-6-*R*-furo[2,3-*d*]pyrimidin-2-ones.

5-Substituted pyrimidine nucleosides possess high biological activity.[1,2] 5-Alkynyl derivatives are among the promising compounds of this series; their synthesis is usually carried out by $PdCl_2(PPh_3)_2$-catalyzed coupling of 5-iodonucleosides with terminal alkynes in the presence of CuI.[3—15] Recently, it was shown that the coupling of bromoarenes with alkynes also proceeds over a heterogeneous Pd/C catalyst in the presence of CuI and PPh_3.[17] Having used this catalyst in the reaction of 5-nucleosides with alkynes,[16] we have found that with acetonitrile as a solvent the addition of PPh_3 is not necessary. It must be noted, however, that heterocyclization proceeds in the course of the reaction with the resultant formation of furo[2,3-*d*]pyrimidine nucleosides. Thus, the reactions of nucleosides **1—4** with phenylacetylene (**5**) under the action of Pd/C and CuI in acetonitrile in the presence of triethylamine afford 3-(2-O-acetyl-3,5-di-O-benzoyl-β-*D*-xylofuranosyl)- and 3-(3,5-di-O-benzoyl-β-*D*-xylofuranosyl)-6-phenylfuro[2,3-*d*]pyrimidine-2-ones (**6,7**). Unlike iodides, which give products in a high yield, 5-bromides **3** and **4** react slowly and in a low yield.

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