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Preliminary communication

Stereospecific synthesis of 1,2-*cis*-glycosides of 2-amino sugars

Nicolay K. Kochetkov, Evgeny M. Klimov, Nelly N. Malysheva and Alexey V. Demchenko

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow B-334 (Russian Federation)

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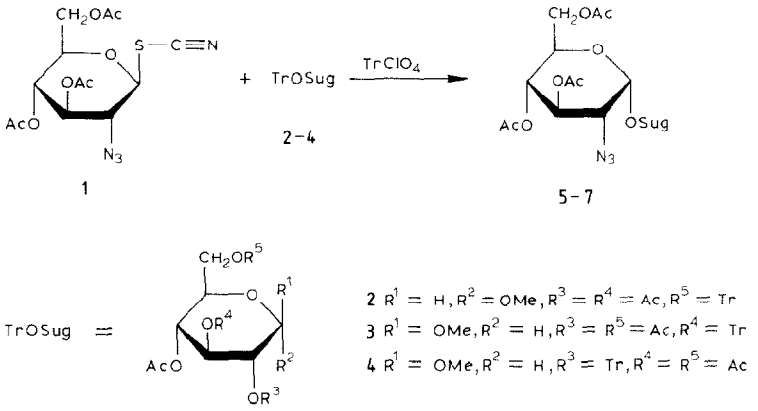
The highly stereoselective synthesis of a 1,2-*cis*-glycosidic linkage is difficult and a satisfactory solution remains a problem in the synthetic chemistry of carbohydrates. Recently, we proposed a new approach to specific 1,2-*cis*-glycosylation, by using 1,2-*trans*-glycosyl thiocyanates with a non-participating substituent at C-2 as the glycosylation reagent[1–3].

We report now the application of this approach to the stereospecific synthesis of 1,2-*cis*-glycosides of 2-amino sugars, which can also be regarded as a difficult problem [cf. ref. 4]. The corresponding 1,2-*trans*-2-azido-2-deoxyglycosyl thiocyanate was used as glycosyl donor with subsequent conversion of the azido into an amino group. The stereospecific synthesis of 1,2-*cis*-glycosaminides is demonstrated by the synthesis of derivatives of α-D-glucosaminyl-D-glucoses with different types of glycosidic linkages.

3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl thiocyanate (**1**) has been obtained by treatment of the known 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl bromide[5] (5.6 mmol) with KSCN (16.9 mmol, dried in vacuo at 110°C) in the presence of 18-crown-6 (1.7 mmol, dried in vacuo at 20°C) in acetone (6.5 h, TLC control, 20°C). After evaporation, addition of benzene, filtration through SiO_2, evaporation, and chromatography (SiO_2, benzene–ether gradient), **1**, mp 124.5–125.5°C (from ether–hexane), $[\alpha]_D^{29}$ −84.4° (*c* 1.15, $CHCl_3$), was isolated in 71% yield *; ν_{max} 2162 cm^{-1} (SCN), 2116 cm^{-1} (N_3); ^1H NMR data: δ 5.19 (dd, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.09 (dd, 1 H, $J_{4,5}$ 9.5 Hz, H-4), 4.55 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 4.16–4.30 (m, 2 H, $J_{5,6a}$ 5, $J_{5,6b}$ 2.5, $J_{6a,6b}$ 10 Hz, H-6a,6b), 3.86 (d, 1 H, $J_{2,3}$ 9.5 Hz,

* All crystalline compounds have the correct elemental analysis.



Scheme 1.

H-2), 3.77–3.84 (m, 1 H, H-5), 2.06, 2.13, and 2.16 (3 s, 9 H, OAc); ^{13}C NMR data: δ 169.43–170.52 (C=O), 107.30 (SCN), 83.28 (C-1), 77.23 (C-5), 74.13 (C-3), 67.62 (C-4), 63.74 (C-2), 61.54 (C-6), and 20.59 (OAc).

As glycosyl acceptors, the corresponding trityl ethers of acetylated methyl D-glucopyranosides, 6-*O*-trityl[6] (**2**), 3-*O*-trityl (**3**), and 2-*O*-trityl (**4**), have been explored. Compounds **3** and **4** were synthesised by tritylation of the corresponding hydroxy derivatives, as follows[7]. Methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside[8] (2.8 mmol) reacts with $TrClO_4$ (4.3 mmol) in dry CH_2Cl_2 containing collidine (5.7 mmol, 15 h, 20°C in the dark). After addition of $CHCl_3$, washing with water, evaporation, and chromatography (SiO_2, hexane–ether gradient), **3**, mp 174–175°C, $[\alpha]_D^{27}$ −12° (*c* 1.21, $CHCl_3$), was obtained in 94% yield and with the expected ^1H NMR spectrum. Similarly, methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside[9] (0.62 mmol) and $TrClO_4$ (0.94 mmol) gave **4** (98%), with the expected ^1H NMR spectrum, as a syrup, $[\alpha]_D^{27}$ +16.3° (*c* 1.46, $CHCl_3$).

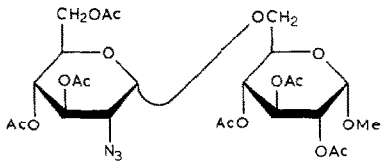
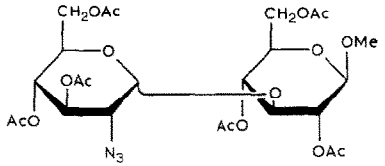
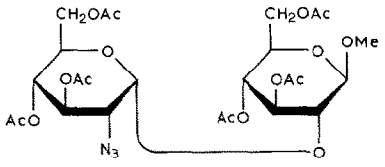
The glycosylation reaction was carried out as described earlier[2,3]. The trityl derivative (**2–4**, 1 mmol), glucosyl thiocyanate **1** (1.1–1.5 mmol), and $TrClO_4$ (0.1 mmol) in dry CH_2Cl_2 were kept at 20°C. After 10–12 h (TLC control), the reaction was quenched by a few drops of pyridine, the mixture was diluted with $CHCl_3$, washed with water, evaporated, and acetylated (Ac_2O–Py) *, and, after chromatography on SiO_2, the disaccharide derivative was isolated. The results are presented in Table I.

Special attempts were made to detect the formation of isomeric disaccharides with 1,2-*trans*-linkages by NMR spectroscopy of *the whole* disaccharide fraction: the signals characteristic of 1,2-*trans*-glycosides at 100–102 ppm in the ^{13}C NMR spectra were absent and probably these isomers are not formed at all. Hence, the

* Partial detritylation of the acceptor takes place during the reaction (cf. refs. 2 and 3) and acetylation of the reaction mixture simplifies the isolation of the disaccharide derivatives formed.

TABLE I

The glycosylation of **2**, **3**, and **4** by glycosyl thiocyanate **1**

Run	Acceptor	Donor/acceptor	Disaccharide derivative [a]		$[\alpha]_D^{28}$ (c, $CHCl_3$)	Yield (%)
1	**2**	1.1/1		**(5)**	+162° (1.02)	81
2	**3**	1.4/1		**(6)**	+42° (1.02)	73
3	**4**	1.5/1		**(7)**	+98° (1.05)	72

[a] For NMR data, see Table II.

new glycosylation reaction proceeds stereospecifically for azido sugars, as has been shown for synthesis of 2′-*O*-benzyl derivatives[2,3]. For an explanation of the complete stereospecificity, which is unusual for 1,2-*cis*-glycosylation, a concerted

TABLE II

NMR data for disaccharides **5**–**7**

Compound	^{1}H NMR	^{13}C NMR [a]					
	H-1 ($J_{1,2}$, Hz)	C-1	C-2	C-3	C-4	C-5	C-6
	H-1′ ($J_{1',2'}$, Hz)	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
5	4.97 (4.0)	97.78	71.02	70.14	69.36	67.92	61.97
	5.00 (3.5)	96.65	61.05	70.39	68.58	67.92	66.87
6	4.31 (8.0)	101.72	72.28	80.99	69.07	71.93	62.12
	5.04 (3.5)	98.97	62.00	70.76	67.84	68.78	61.09
7	4.50 (8.0)	103.87	75.52	73.18	68.98	71.71	61.95
	5.54 (3.5)	97.02	60.85	70.08	68.29	68.08	61.57

[a] Additional signals are present in all spectra: 169.4–170.0 (C=O), 55.55 (α-OMe), 56.91–57.38 (β-OMe), and 20.65–21.05 (OAc).

push–pull process, which ensures S_N2 substitution at the anomeric centre with inversion of configuration, was proposed[1]. The azido group substituent at C-2 of the donor serves, as expected[4], as a good non-participating group and, in addition, does not interact with the thiocyanate group. Moreover, the glycosyl thiocyanates containing a neighbouring azido group have no tendency for isomerisation into unreactive glycosyl isothiocyanate derivatives, which is a rather perceptible side reaction during glycosylation by 2-*O*-benzylated glycosyl thiocyanates[2,3].

The data presented show that glycosylation proceeds independently of the locaion of the trityl group in the acceptor, since the 6-, 3-, and 2-*O*-trityl derivatives gave similar results.

The disaccharides synthesised can be easily converted into the corresponding 2-acetamido-2-deoxy derivatives by conventional procedures. For example, the disaccharide **6** (77 mg), after deacetylation (0.1 mL 1 M NaOMe in MeOH, 17 h, 20°C), neutralisation up to pH 6.5, hydrogenation in 4:1 MeOH–EtOAc on 10% Pd–C (50 mg, 3 h, 40°C), and *N*-acetylation in 50% aq MeOH by Ac_2O (1 mL, 16 h, 20°C), gave rise after chromatography to methyl 3-*O*-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-β-D-glucopyranoside (**8**, 88%), $[\alpha]_D^{29}$ +89.4° (*c* 1, MeOH); ^1H NMR data: δ 5.09 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), and 4.10 (d, 1 H, $J_{1,2}$ 8 Hz, H-1); ^{13}C NMR data; δ 105.37 (C-1), 99.63 (C-1′), 85.61 (C-3), 77.77 (C-5), 73.85 (C-2,5′), 73.25 (C-3′), 72.11 (C-4′), 71.42 (C-4), 62.42 (C-6,6′), 57.41 (OMe), 55.59 (C-2′), and 22.87 (NAc).

In summary, the new glycosylation reaction using a 1,2-*trans*-glycosyl thiocyanate containing a 2-azido group as glycosyl donor opens an efficient route to a highly stereospecific synthesis of 1,2-*cis*-glycosides of 2-amino sugars.

REFERENCES

1 N.K. Kochetkov, E.M. Klimov, and N.N. Malysheva, *Tetrahedron Lett.*, 30 (1989) 5459–5462.
2 N.K. Kochetkov, E.M. Klimov, N.N. Malysheva, and A.V. Demchenko, *Carbohydr. Res.*, 212 (1991) 77–91.
3 N.K. Kochetkov, E.M. Klimov, N.N. Malysheva, and A.V. Demchenko, *Bioorg. Khim.*, 16 (1990) 701–710.
4 H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 21 (1982) 155–173.
5 H. Paulsen, A. Wulff, and A.C. Heitman, *Liebigs Ann. Chem.*, (1988) 1073–1078.
6 B. Helferich, W. Klein, and W. Schafer, *Justus Liebigs Ann. Chem.*, 44 (1926) 19–26.
7 Ya.V. Vosney and N.K. Kochetkov, *Carbohydr. Res.*, 54 (1977) 300–303.
8 P.A. Finan and S.D. Warren, *J. Chem. Soc.*, (1962) 3089–3092.
9 S. Brennan and P.A. Finan, *J. Chem. Soc., C*, (1970) 1742–1744.