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2-DEOXY-1-O-SILYLATED-β-HEXOPYRANOSES. USEFUL GLYCOSYL DONORS AND SYNTHETIC INTERMEDIATES.

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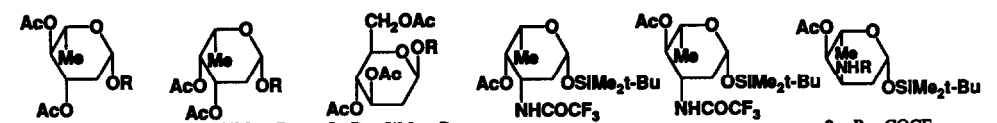
Abstract: Different 2-deoxy-1-O-silylated-β-hexopyranoses were synthesized with high degree of stereoselectivity and in high yield. Their application to direct synthesis of glycosides and glycosyl donors as well as other synthetically useful transformations at the anomeric center have been demostrated.

Glycosylation and functionalization at anomeric center of 2-deoxy carbohydrates continues to be a challenge, hampering synthesis of important natural products and their congeners. One of the possible group of glycosyl donors are hexopyranoses silylated at the anomeric position as demonstrated by Tietze and Qiu[2] for relatively unstable 1-O-trimethylsilylated carbohydrates. In our studies we focused on 1-O-silylated 2-deoxy monosaccharides as glycosyl donors, aiming at the derivatives sufficiently stable to sustain the conditions of most multistep synthesis.



1 - R = $SiMe_2$t-Bu
2 - R = $SiPh_2$t-Bu
3 - R = $SiMe_2$t-Bu
4 - R = $SiPh_2$t-Bu
5 - R = $SiMe_2$t-Bu
6 - R = $SiPh_2$t-Bu
7
8
9 - R = $COCF_3$
10 - R = $COCH_3$

The 1-O-t-butyldimethylsilyl (1-O-TBDMS) and selected examples of 1-O-t-butyldiphenylsilyl ethers of 3,4-di-O-acetyl-2-deoxy-L-rhamnose (**1, 2**), 3,4-di-O-acetyl-2-deoxy-L-fucose (**3, 4**) and 3,4,6-tri-O-acetyl-2-deoxy-D-glucose (**5, 6**), 4-O-acetyl-3-trifluoroacetyl-daunosamine (**7**), -acosamine (**8**) and -ristosamine (**9, 10**) were synthesized by silylation of free anomeric hydroxyl group of acylated glycopyranoses in DMF/imidazol.[3] The β-anomers were formed predominantly with isolated yields ranging between 80-95%. Stereoselectivity was higher for substrates with lyxo configuration or when t-butylchlorodiphenylsilane was used as silylating agent. The α-anomers (0-10%) were detected by analyzing ^{1}H NMR spectra of the reaction mixtures and in some cases isolated by column chromatography.

To demonstrate synthetic usefulness of 1-O-silylated 2-deoxy-monosaccharides, chromatographically pure β anomers were transformed to various products or intermediates (*Scheme 1*). Methyl glycosides of 2-deoxy-L-rhamnose **11**, 2-deoxy-L-fucose **20**, daunosamine **21** and acosamine **12** were obtained in 90-95% yields by treating the respective 1-O-t-butyldimethylsilyl ethers overnight at r.t., with 4:1 mixture of dichloromethane: methanol containing 0.5% HCl.[4]

The 1-O-TBDMS-monosaccharides can also be converted to glycosides in the reaction catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf), in conditions similar to Tietze's acetal-glycosides

synthesis.[2] The 1-O-TBDMS **3** was reacted with cholesterol in the presence of TMSOTf to give α glycoside **22** with 73% yield.

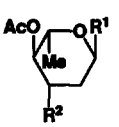
1-O-Acetates of acosamine **13**, daunosamine **23**, and ristosamine **26** were formed in high yields (89--95%) by treating dichloromethane solution of silyl ethers with acetic anhydride/acetic acid containing catalytic amount of $ZnCl_2$.[4]

SCHEME 1

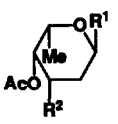
			Products
	TMSOTf / R^1OH	R-OR[1]	**22** (73%)
	0.5% HCl / CH_2Cl_2-MeOH (4:1)	R-OMe	**11** (α,β; 91%); **12** (α,β; 89%); **20** (α,β; 75%); **21** (α,β; 92%); **29** (α,β; 91%)
	Ac_2O-AcOH(4:1) / $ZnCl_2$	R-OAc	**13** (95%); **23** (88%); **26** (α,β; 89%)
R-OSiMe$_2$t-Bu	1N HCl-THF(1:5) / or Bu_4NF	R-OH	**14** (α,β; 92% for H^+; 79% for F^-); **27** (α,β; 93%)
	AcSH / 0.2 eq $ZrCl_4$	R-SAc	**15** (93%); **24** (α>β; 74%); **28** (α>β; 98%); **30** (α>β;90%)
	PhSH / 0.2 eq $ZrCl_4$	R-SPh	**16** (α:β 3:1; 85%); **17** (α:β 4:1; 98%); **25** (α:β > 10:1; 82%)
	TMSBr	R-Br	**18** (85%)

R = 2-deoxy-hexopyranosyl with arabino, lyxo, ribo or xylo configuration

Similar yields were observed for hydrolysis of 1-O-TBDMS derivatives **8** and **10** to 1-OH-acosamine **14** and 1-OH-ristosamine **27**, even though both substrates showed significant difference in the rate of hydrolysis. 1-O-TBDMS of acosamine (**8**) was hydrolyzed in oxolane-1N HCl (5 :1) mixture at r.t. in 48 hr whereas the ristosamine analogue **10** appeared to be stable in this conditions. Compound **10** was hydrolyzed in oxolane: 80% aq. acetic acid (1:1) mixture. Both silyl ethers (**8**, **10**) were easily hydrolyzed by tetrabutylammonium fluoride in oxolane.[4]

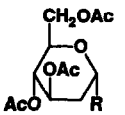


11 - R^1 = OMe; R^2 = OAc
12 - R^1 = OMe; R^2 = NHTFA
13 - R^1 = OAc; R^2 = NHTFA
14 - R^1 = OH; R^2 = NHTFA
15 - R^1 = SAc; R^2 = NHTFA
16 - R^1 = SPh; R^2 = NHTFA
17 - R^1 = SPh; R^2 = OAc
18 - R^1 = Br; R^2 = NHTFA
19 - R^1 = DNM; R^2 = NHTFA



20 - R^1 = OMe; R^2 = OAc
21 - R^1 = OMe; R^2 = NHTFA
22 - R^1 = 3β-cholesteryl; R^2 = OAc
23 - R^1 = OAc; R^2 = NHTFA
24 - R^1 = SAc; R^2 = OAc
25 - R^1 = SPh; R^2 = OAc

26 - R = OAc
27 - R = OH
28 - R = SAc



29 - R = OMe
30 - R = SAc

DNM - daunomycinone
TFA - $COCF_3$

Previously unaccessible[5] 1-α-thioacetates of acosamine (**15**)[6] and ristosamine (**28**)[6] were obtained by a clean transformation using Defaye conditions ($AcSH/ZrCl_4$).[7] Similarly 1-S-acetyl-2-deoxy-1-thio-α-L-fucose (**24**) was prepared in >90 % yields.[6]

Other glycosyl donors could be conveniently generated from 1-O-TBDMS ethers, often under much milder conditions than that from methyl glycosides or 1-O-acyl derivatives. As an example two types of glycosyl donors, glycosyl bromides and thioglycosides[8], were generated from 1-O-TBDMS ethers of 2-deoxy monosaccharides. Phenyl thioglycosides **16**[9], **17**[9] and **25**[9] were generated, respectively, from 1-O-TBDMS-acosamine **8**, -2-deoxy-L-rhamnose **1** and -2-deoxy-L-fucose **3** by using phenylthiol and zirconium chloride as a catalyst.[10] The mixture of α and β anomers was formed with α-anomers as a predominant component. The combine yields of α,β anomers were sometimes as high as 98% (**17** and its β anomer) indicating that 1-O-silyl ethers are excellent substrates for the preparation of thioglycosides.

In a comparably clean reaction, glycosyl bromide **18** was formed by treatment of 1-O-TBDMS-acosamine **8** with bromo trimethylsilane (TMSBr) in dichloromethane under Thiem's conditions.[10] The α-L-arabino-hexopyranosyl bromide **18** was then coupled with daunomycinone in Koenigs-Knorr conditions (HgO, $HgBr_2$ in CH_2Cl_2) to afford as a main component 4'-epi-daunorubicin **19**[4] (84%) confirming the practical usefulness of glycosyl bromides generated in the above conditions.

Further studies on the chemical transformations of 1-O-TBDMS-2-deoxy-monosaccharides as well as other 1-O-silylated carbohydrates are in progress.

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References and Notes

1. On leave from Pharmaceutical Research Institute, Warsaw, Poland.
2. L. F. Tietze, R. Fischer, M. Loegers and M. Beller, *Carbohydr. Res.*, **194**, 155 (1989) and references cited therein; D. Qiu, Y. Wang and M. Cai, *Synth. Commun.*, **19**, 3453 (1989).
3. NMR spectra were recorded for solution in chloroform-d (internal standard Me_4Si) with QE 300 or Nicolet NT 300 spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C nuclei, respectively, unless otherwise stated. All compounds gave correct elemental analysis. Analytical data for selected compounds: Data for **1**: mp 49-50 °C; $[\alpha]^{25}_D$ + 11.5° (c=1.2, CH_2Cl_2); ^1H NMR: δ 4.96 (ddd, 1 H, $J_{2e,3}$ 5.2, $J_{2a,3}$ 11.9, $J_{3,4}$ 9.4 Hz, H-3), 4.83 (dd, 1 H, $J_{1,2a}$ 9.4, $J_{1,2e}$ 2.0 Hz, H-1), 4.74 (t, 1 H, H-4), 3.46 (dq, 1 H, $J_{4,5}$ 9.5 Hz, H-5). Data for **2**: $[\alpha]^{25}_D$ + 4.9° (c=2.3, CH_2Cl_2); ^1H NMR: δ 7.70, 7.40 (m, Ph_2Si), 4.84 (ddd, 1 H, $J_{2e,3}$ 5.2, $J_{2a,3}$ 11.6, $J_{3,4}$ 9.4 Hz, H-3), 4.73 (t, 1 H, H-4), 4.69 (dd, 1 H, $J_{1,2a}$ 9.4, $J_{1,2e}$ 2.0 Hz, H-1), 3.17 (dq, 1 H, $J_{4,5}$ 9.4 Hz, H-5), 1.08 (s, 9 H, t-BuSi); ^{13}C NMR: δ 170.0, 169.7 (OAc), 94.1 (C-1), 74.1, 70.7, 69.7 (C-3, C-4, C-5), 38.8 (C-2), 26.8 (t-BuSi), 20.8, 20.6 (OAc), 19.1 (t-BuSi), 17.4 (C-6). Data for **3**: $[\alpha]^{25}_D$ - 12.9° (c=1.2, CH_2Cl_2); ^1H NMR: δ 5.05 (dd, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ 0.8 Hz, H-4), 4.95 (m, 1 H, ΣJ=20.7 Hz, H-3), 4.79 (m, 1 H, ΣJ=11.6 Hz, H-1), 3.64 (qd, 1 H, H-5); ^{13}C NMR: δ 94.5 (C-1), 69.0, 68.9, 68.3 (C-3, C-4, C-5), 34.2 (C-2), 25.5 (t-BuSi), 20.6, 20.5 (OAc), 17.9 (t-BuSi), 16.3 (C-6), -4.4, -5.3 (Me_2Si). Data for **4**: $[\alpha]^{25}_D$ - 6.1° (c=0.6, CH_2Cl_2); ^1H NMR: δ 7.76, 7.67, 7.40 (m, Ph_2Si), 4.99 (d, 1 H, H-4), 4.79 (ddd, 1 H, $J_{2e,3}$ 5.1, $J_{2a,3}$ 12.5, $J_{3,4}$ 3.2 Hz, H-3), 4.69 (dd, 1 H, $J_{1,2a}$ 9.2, $J_{1,2e}$ 2.3 Hz, H-1), 3.42 (qd, 1 H, $J_{4,5}$ 0.7 Hz, H-5), 2.18, 1.97

(s, 3 H, OAc), 2.02 (ddd, 1 H, H-2a), 1.89 (ddd, 1 H, $J_{2a,2e}$ 12.0 Hz, H-2e), 1.12 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6), 1.09 (s, 9 H, t-BuSi); ^{13}C NMR: δ 170.7, 170.0 (OAc), 94.8 (C-1), 69.1, 69.0, 68.4 (C-3, C-4, C-5), 34.1 (C-2), 26.8 (t-BuSi), 20.8 (OAc), 19.2 (t-BuSi), 16.4 (C-6). Data for **5**: $[\alpha]^{25}_D$ + 5.7° (c=1.1, CH_2Cl_2). Data for: **7**: mp 89-91 °C; $[\alpha]^{25}_D$ - 20.4° (c=1.2, CH_2Cl_2). Data for **8**: mp 63-64 °C; $[\alpha]^{25}_D$ - 12.3° (c=1.3, CH_2Cl_2); ^1H NMR: δ 4.91 (dd, 1 H, $J_{1,2a}$ 8.95, $J_{1,2e}$ 1.85 Hz, H-1), 4.55 (t, 1 H, H-4), 4.14 (m, 1 H, H-3), 3.59 (dq, 1 H, $J_{4,5}$ 9.3 Hz, H-5), 2.33 (ddd, 1 H, $J_{2e,3}$ 4.5, $J_{2a,2e}$ 12.7 Hz, H-2e). Data for **9**: mp 121-122 °C.

4. Products were characterized by ^1H NMR, [α] and mp if applicable. Good agreement with literature data and/or with samples prepared by alternative methods was observed.
5. Previously only β-thioacetate of daunosamine was prepared by I. Pelyvas, A. Hasegawa, and R. L. Whistler, *Carbohyd. Res.*, **146**, 193 (1986).
6. Data for **15**: mp 212-213 °C; ^1H NMR: δ 6.04 (dd, 1 H, H-1), 2.40 (s, 3 H, SAc), 2.37 (ddd, 1 H, $J_{1,2e}$ 1.2, $J_{2e,3}$ 4.6 Hz, H-2e), 2.18 (ddd, 1 H, $J_{1,2a}$ 5.2, $J_{2a,2e}$ 13.7, $J_{2a,3}$ 12.3 Hz H-2a). Data for **24**: ^1H NMR: δ 6.15 (d, 1 H, $J_{1,2a}$ 5.1 Hz, H-1), 5.05 (ddd, 1 H, $J_{2e,3}$ 4.7, $J_{2a,3}$ 12.6, $J_{3,4}$ 3.0 Hz, H-3), 2.38 (s, 3 H, SAc); ^{13}C NMR: δ 192.5 (SAc), 170.1, 169.5 (OAc), 79.2 (C-1), 69.0, 68.7, 67.4 (C-3, C-4, C-5), 30.9, 30.6 (C-2, SAc), 20.4, 20.2 (OAc),16.3 (C-6). Data for **28**: ^1H NMR (C_6D_6): δ 5.70 (t, 1 H, ΣJ 9.8 Hz, H-1), 4.61 (dd, 1 H, $J_{3,4}$ 3.9, $J_{4,5}$ 7.3 Hz, H-4), 1.75 (s, 3 H, SAc), 1.63 (s, 3 H, OAc), 1.01 (d, 3 H, $J_{5,6}$ 6.5 Hz, H-6); ^{13}C NMR: δ 191.9 (SAc), 169.7 (OAc), 156.9 (q, $COCF_3$),115.4 (q, CF_3), 75.0 (C-1), 71.0, 68.3 (C-4, C-5), 45.3 (C-3), 32.6, 30.8 (C-2, SAc), 20.5 (OAc), 16.4 (C-6).
7. J. Defaye, H. Driguez, E. Ohleyer, C. Orgeret, and C. Viet, *Carbohyd. Res.*, **130**, 317 (1984).
8. P. Fugedi, P. J. Garegg, H. Lonn, and T. Norberg, *Glycoconjugate J.*, **4**, 97 (1987).
9. Data for **16**: mp 196-198 °C; $[\alpha]^{25}_D$ - 254.9° (c=1.4, CH_2Cl_2); ^1H NMR: δ 5.59 (d, 1 H, $J_{1,2a}$ 5.4 Hz, H-1), 2.47 (dd, 1 H, $J_{1,2e}$ 0.6, $J_{2e,3}$ 4.5, $J_{2a,2e}$ 13.7 Hz, H-2e), 2.12 (m, 1 H, $J_{2a,3}$ 12.3 Hz, H-2a); ^{13}C NMR: δ 82.9 (C-1), 75.3, 66.7 (C-4, C-5), 48.8 (C-3), 36.3 (C-2). Data for **25**: $[\alpha]^{25}_D$ -292.9° (c=1.4, CH_2Cl_2); ^1H NMR: δ 5.76 (d, 1 H, $J_{1,2a}$ 5.7 Hz, H-1), 2.47 (td, 1 H, $J_{2a,2e} = J_{2a,3}$ =12.7 Hz, H-2a), 2.18, 2.02 (s, 3 H, OAc); ^{13}C NMR: δ 170.4, 169.7 (OAc), 134.5, 130.8, 128.8, 126.9 (phenyl), 83.5 (C-1), 69.5, 67.1, 65.6 (C-3, C-4, C-5), 30.4 (C-2), 20.7, 20.5 (OAc), 16.3 (C-6). Data for **17**: mp 58 °C; $[\alpha]^{25}_D$ - 289.9° (c=1.0, CH_2Cl_2); ^1H NMR: δ 5.60 (d, 1 H, $J_{1,2a}$ 5.6 Hz, H-1), 5.26 (ddd, 1 H, $J_{2e,3}$ 5.2, $J_{2a,3}$ 11.7, $J_{3,4}$ 9.4 Hz, H-3); ^{13}C NMR: δ 82.8 (C-1), 74.7, 69.2, 66.6 (C-3, C-4, C-5), 35.7 (C-2), 20.8, 20.6 (OAc), 17.3 (C-6).
10. J. Thiem and B. Meyer, *Chem. Ber.*, **113**, 3058 (1980).

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