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Note

Stereoselective synthesis of sugar–amino acid conjugates. A novel class of amino sugars †

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The high abundance and paramount biological importance of 2-amino-2-deoxy mono- and poly-saccharide-containing natural products has been widely recognized and need little, if any, introduction[1]. In addition, there is an increasing interest for the synthesis, biological evaluation, and chemotherapeutic applications of a variety of nonnatural derivatives of amino sugars[2–4]. In this report we introduce a new class of pharmacologically interesting "unnatural" amino sugars, namely "sugar–amino acid conjugates" that combine the structures of an amino acid and an amino sugar in a single molecule sharing the same *N*-atom. The key intermediates in our synthetic route were α- and β-pyranulosides **3a** and **3b**, which were derived from D-glucal (**1**). Hydrolytic transformation[5] and selective protection of **1** yielded compound **2**, which after oxidative rearrangement[6–9], methylation, and chromatographic separation afforded anomers **3a** and **3b**[10].

Michael-type addition of L-phenylalanine methyl ester to enone **3a** (or **3b**) provided adducts **4** and **5** as an entry to this novel class of compounds. In order to optimize the chemical yields as well as the stereoselectivity of the addition, special control of the reaction parameters was necessary to direct stereocontrol of the nucleophilic attack.

Amino sugars **4** and **5** were impossible to isolate in satisfactory yield due to a fast retro-Michael reaction taking place during the isolation and purification processes. This problem was circumvented by stabilizing the adducts by a reduction in situ of the carbonyl moiety with sodium borohydride. Thus, D-*ribo* and D-*lyxo* 2,3-dideoxy-conjugates **6b** and **7a** were prepared in one step from **3b** and **3a**, respectively, in satisfactory total yield. A crucial factor during this reaction sequence was to maintain the pH around pH 8.5. Optimum yields were obtained in polar solvents using a large excess of the amino acid. Table I summarizes the

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TABLE I

Correlation of the reaction parameters with the yields [a] of products **6a**, **7a**, and **8a** for substrate **3a**

Solvent	pH	Equiv of amino acid	Yields (%)			Ratio [b] **4a**:**5a**	Ratio **8a**:**7a**
			6a	**7a**	**8a**		
MeOH or DMF	8.5	5	14	58	17	1:5	1:3.5
CH_2Cl_2	8.5	5	6	20	6	1:4.5	1:3
EtOEt	8.5	5	traces				
MeOH	5.0	5	10	40	14	1:5.5	1:3
MeOH	7.0	5	12	52	15	1:5.5	1:3.5
MeOH	10.5	5	11	40	12	1:5	1:3.5
MeOH	8.5	1	traces				
MeOH	8.5	3	10	38	12	1:5	1:3

[a] Yields are quoted for isolated compounds. [b] Ratio **4a**:**5a** is based on the ratio **6a**:**7a**+**8a**.

relation of the reaction yield with the pH, the amount of the amino acid, and the polarity of the solvent.

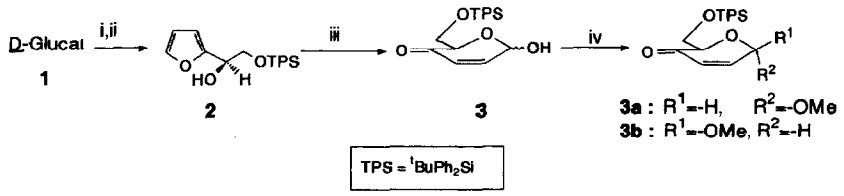
Selectivity towards the thermodynamically favored adduct **4b** was observed using as Michael acceptor the β anomer **3b** (3:1 ratio) (see Scheme 1). Though prolonged reaction time favored the ratio towards **4b**, the total yield was redused. The kinetic product **5a** was synthesized with a better selectivity (5:1 ratio) using the α anomer **3a** as substrate. Furthermore, the reduction of the carbonyl moiety was highly stereoselective for both β anomers **4b** and **5b** (less than 5% of the D-*arabino* isomer was isolated) affording the D-*ribo* analogue **6b** in 62% total yield (based on **3b**), while in the case of α anomers **4a** in **5a** the ratio of the products **6a**, **7a**, and **8a** was 1:4:1 (58% total yield for the D-*lyxo* analogue **7a**).

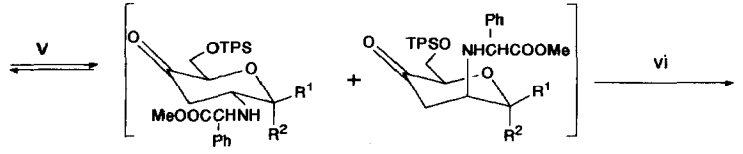
The observed stereochemistry of the above Michael additions is in accordance with previous findings where the attack of the nucleophile to related enone systems takes place from the opposite site of the anomeric substitutent[11–14]. The stereochemistry of the carbonyl reduction mainly depends on the orientation of the C-2 substituent. When the bulky amino acid substituent is in the equatorial position, the reduction yields exclusively the thermodynamically favored product (i.e., **4** → **6**). On the other hand, when it possesses an axial orientation, a syn–axial attack of the hydride anion is hindered. Thus, reduction of ketone **5b** afforded exclusively alcohol **7b**, and reduction of **5a** yielded selectively **7a**, while a small amount of **8a** was also isolated (ratio between **7a**:**8a** was 4:1).

The characteristic coupling constants of all new compounds gave sound proof for the presented conformations. Table II summarizes the chemical shifts and coupling constants of protons at C-1–C-4.

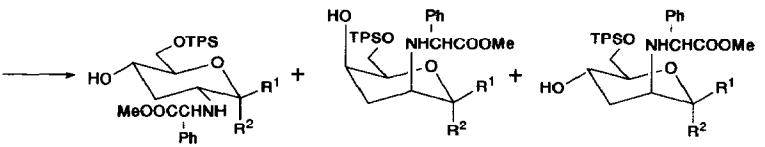
EXPERIMENTAL

General methods.—Infrared spectra were recorded with a Perkin–Elmer 283B spectrophotometer. Specific rotations were determined in MeOH with a Perkin–





	R^1	R^2	4	5	4 : 5
a	-H	-OMe	15%	75%	1 : 5
b	-OMe	-H	75%	25%	3 : 1



	R^1	R^2	6	7	8	6 : 7 : 8
a	-H	-OMe	14%	58%	17%	1 : 4 : 1
b	-OMe	-H	62%	22%	0%	3 : 1 : 0

Scheme 1. **Reagents and conditions:** (i) $HgSO_4$, 2.0 mM H_2SO_4; (ii) $^tBuPh_2SiCl$, imidazole, DMF 3 h, 0°C, 87%; (iii) *N*-bromosuccinimide, 4:1 THF–water, 5 min, 0°C, quant; (iv) MeI, Ag_2O, Me_2CO, overnight, room temp; **3a**, 61%; **3b**, 22%; (v) $PhCH(NH_2)CO_2Me \cdot HCl$, Et_3N, MeOH, (pH 8.5), 15 min, room temp; (vi) $NaBH_4$ (excess), MeOH, AcOH, (pH 8.5), 1 h, 0°C.

TABLE II

Selected physicochemical data of the sugar–amino acid conjugates [a]

Entry	$[\alpha]_D$	HRMS	H-1	H-2	$J_{1,2}$	H-3*e*	$J_{3e,4}$	H-3*a*	$J_{3a,4}$	H-4
6a	36.8	710.1918	4.49 d	2.56 dt	3.4	1.95 dt	4.8	1.43 m	11.8	3.70 m
7a	−7.1	710.1918	4.50 d	2.74 m	< 1	1.96 dt	2.5	1.69 m	3.2	3.65 m
8a	10.2	710.1922	4.27 d	2.62 m	< 1	1.82 m	4.2	1.70 dt	10.3	3.45 m
6b	−21.2	710.1924	4.00 d	2.40 dt	7.3	2.11 dt	4.5	1.35 m	10.6	3.60 m
7b	−40.8	710.1924	4.43 d	2.90 m	2.2	2.12 dt	2.4	1.55 dt	3.0	3.65 m

[a] Measurements of $[\alpha]_D$ at 25°C in methanol. HRMS molecular ion of $[M+Cs^+]$ (theoretical value of $C_{33}H_{43}NO_6Si + Cs = 577.2859 + 132.9051 = 710.1911$). ^1H NMR spectra (360 MHz) were recorded using $CDCl_3$ as solvent. Chemical shifts are given in δ-units and coupling constants in Hz.

Elmer 141 polarimeter using a 10-cm cell. ^{1}H NMR spectra were recorded on a Bruker AM-360 or a Varian 60 MHz (model 360 M) spectrometer in $CDCl_3$ containing Me_4Si as the internal reference. R_f values refer to TLC performed on Silica Gel-60F_{254} (E. Merck). Flash column chromatography performed with Silica Gel-60 (32–63 μm, E. Merck). HRMS molecular ion is that of [M + Cs^+] (theoretical value of $C_{33}H_{43}NO_6Si$ + Cs = 710.1911). (1*R*)-1-(2-Furanyl)-1,2-dihydroxyethane was prepared from D-glucal according to ref. 5.

*Preparation of (1*R*)-2-O-(*tert*-butyldiphenylsilyl)-1-(2-furanyl)-1,2-ethanediol* (**2**). —To a solution of (1*R*)-1-(2-furanyl)-1,2-ethanediol (2.00 g, 15.6 mmol) in dry DMF (20 mL) were added *tert*-butylchlorodiphenylsilane (5.57 g, 20.2 mmol) and imidazole (1.60 g, 23.5 mmol), and the mixture was stirred for 3 h at 0°C. Then, 30 mL of a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with ethyl ether (2 × 100 mL). The organic layer was washed with water (2 × 50 mL), dried over $MgSO_4$, and the mixture was concentrated under reduced pressure. Flash column chromatography of the residue (9:1 hexane–ethyl ether) yielded the disilylated byproduct (0.5 g, 9%) and **2** as a colorless oil (5.15 g, 90%): R_f 0.59 (5:2 hexane–ethyl ether); $[\alpha]_D^{25}$ + 4.6° (MeOH); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.07 (s, 9 H, *tert*-Bu), 2.89 (br, 1 H, OH), 3.93 (d, 2 H, *J* 5.4 Hz, CH_2O), 4.83 (t, 1 H, *J* 5.4 Hz, CHO), 6.29 (m, 2 H, H-3′ and H-4′), 7.20–7.85 (m, 11 H, H-5′ and Ph). Anal. Calcd for $C_{22}H_{26}O_3Si$: C, 72.09; H, 7.15. Found: C, 72.20; H, 7.09.

Compound **2** has been reported[15]; however, no physicochemical data were provided.

*6-O-[(*tert*-Butyldiphenyl)silyl]-2,3-dideoxy-α,β-*D*-glycero-hex-2-enopyranos-4-ulose* (**3**).—A solution of **2** (3.4 g, 9.3 mmol) in 50 mL of 4:1 THF–water was cooled to 0°C and a stoichiometric amount of *N*-bromosuccinimide was added portionwise. When the reaction was completed, ethyl ether (200 mL) was added, and the mixture was succesively washed with 10% aq KI, 15% aq $Na_2S_2O_3$ and 10% aq $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography of the residue (3:2 hexane–ethyl ether) yielded **3** as a pale yellow oil (3.45 g, 97%): R_f 0.35 (3:2 hexane–ethyl ether); $[\alpha]_D^{25}$ −15.3° (MeOH); ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.03 (s, 9 H, *tert*-Bu), 4.11 (m, 3 H, OH and CH_2O), 4.60 (t, 1 H, *J* 3.4 Hz, H-5), 5.78 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 6.21 (d, 1 H, $J_{3,1}$ 0.6 Hz, H-3), 6.88 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 7.22–7.90 (m, 10 H, Ph). Anal. Calcd for $C_{22}H_{26}O_4Si$: C, 69.07; H, 6.85. Found: C, 69.18; H, 6.76.

*Methyl 6-O-[(*tert*-butyl-diphenyl)silyl]-2,3-dideoxy-α-*D*-glycero-hex-2-enopyranosid-4-ulose (**3a**) and methyl 6-O[(*tert*-butyl-diphenyl)silyl]-2,3-dideoxy-β-*D*-glycero-hex-2-enopyranosid-4-ulose* (**3b**).—To a solution of **3** (3.82 g, 10.0 mmol) in acetone (80 mL) were added silver oxide (3.25 g, 14.0 mmol) and iodomethane (3.25 mL). The mixture was stirred overnight in the dark at ambient temperature. On conventional processing, followed by flash column chromatography (3:1 hexane–ethyl ether), two products were isolated in the following order:

Compound **3a**: 0.87 g (yield 22%): R_f 0.32 (5:2 hexane–ethyl ether), $[\alpha]_D^{25}$ −3.8° (MeOH); ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.98 (s, 9 H, *tert*-Bu), 3.46 (s, 3 H, CH_3O), 4.02 (d, 2 H, *J* 3.8 Hz, CH_2), 4.42 (t, 1 H, *J* 3.8 Hz, H-5), 5.15 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 6.08 (d, 1 H, $J_{3,1}$ 0.6 Hz, H-3), 6.80 (dd, 1H, $J_{2,3}$ 10.2 Hz, H-2), 7.26–7.66 (m, 10 H, Ph). Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.54; H, 7.20.

Compound **3b**: 2.42 g (yield 61%): R_f 0.27 (5:2 hexane–ethyl ether); $[\alpha]_D^{25}$ +22.0° (MeOH); ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.98 (s, 9 H, *tert*-Bu), 3.53 (s, 3 H, CH_3O), 4.03 (d, 2 H, *J* 3.7 Hz, CH_2), 4.23 (t, 1 H, *J* 3.7 Hz, H-5), 5.20 (m, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 6.07 (dd, 1 H, $J_{3,1}$ 1.1 Hz, H-3), 6.83 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2), 7.28–7.68 (m, 10 H, Ph). Anal Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.74; H, 7.03.

N-*[Methyl 6-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α-*D*-*ribo*-hexopyranosid-2-yl]-*L*-phenylalanine methyl ester* (**6a**), N-*[methyl 6-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α-*D*-lyxo-hexopyranosid-2-yl]-*L*-phenylalanine methyl ester* (**7a**), N-*[methyl 6-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-α-*D*-arabino-hexopyranosid-2-yl]-*L*-phenylalanine methyl ester* (**8a**).—To a minimum volume of MeOH, L-phenylalanine methyl ester hydrochloride (2.96 g, 13.7 mmol) and Et_3N (1.42 g, 14.1 mmol) were dissolved, the pH being adjusted to pH 8.5. A methanolic solution (5 mL) of **3a** (1.09 g, 2.7 mmol) was added. After stirring for 15 min the mixture was cooled to 0°C, and small quantities of sodium borohydride and acetic acid were alternatively added. The pH was occasionally monitored and found to be around pH 8.5. The end of the reaction was checked by TLC, the mixture was extracted with EtOAc and dried ($MgSO_4$), and the solvent was evaporated in vacuo yielding a yellow oily residue. Flash column chromatography (2:4 EtOAc–hexane) afforded compounds **6a** [0.22 g, 14% yield, R_f 0.36 (4:2 hexane–EtOAc, two passes)], **7a** (0.92 g, 58% yield, R_f 0.49), and **8a** (0.27 g, 17% yield, R_f 0.42) as colorless oils. See Table II for physicochemical data.

N-*[Methyl 6-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-*D*-*ribo*-hexopyranosid-2-yl]-*L*-phenylalanine methyl ester* (**6b**), N-*[methyl 6-O-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-β-*D*-lyxo-hexopyranosid-2-yl]-*L*-phenylalanine methyl ester* (**7b**).—Reaction of **3b** (1.09 g, 2.7 mmol) L-phenylalanine methyl ester hydrochloride (2.96 g, 13.7 mmol), and Et_3N (1.42 g, 14.1 mmol) as described above afforded compounds **6b** [0.98 g, 62% yield, R_f 0.30 (4:2 hexane–EtOAc, acetate, two passes)] and **7b** (0.35 g, 22% yield, R_f 0.44). See Table II for physicochemical data.

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