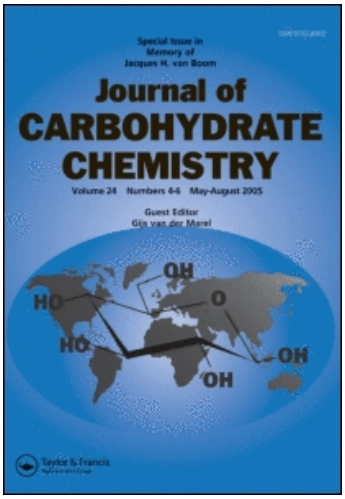

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SYNTHESIS OF UNSATURATED *C*-GLYCOSYL GLYCINES

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SYNTHESIS OF UNSATURATED *C*-GLYCOSYL GLYCINES

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ABSTRACT

Palladium(0)-catalyzed alkylation of 2,3-unsaturated aryl glycoside with ethyl nitroacetate or *N*-(diphenylmethylene)glycine ethyl ester in the presence of *N*,*O*-bis(trimethylsilyl)acetamide/KOAc afforded ethyl 2-(4,5-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-nitroacetate (**2**) and ethyl 2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-[(*N*-diphenylmethylene)amino)]acetate (**7**), respectively. Hydrogenation of compound **2** afforded the saturated aminoesters, while compound **7** was readily transformed into 2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-glycine (**10**) by acidic hydrolysis followedby saponification.

INTRODUCTION

O-Linked glycopeptides represent an important group of glycoconjugates which are involved in various cellular and biological processess.[1,2] However, since glycopeptides contain the natural *O*- or *N*-glycosidic linkage, they are chemically and enzymatically unstable, and these drawbacks sometimes limit their uses. Consequently, there is a need to have access to *C*-analogues of *O*-glycosylated aminoacids in order to increase their stability towards hydrolysis. These analogues can also be used to probe and understand the mechanisms of a number of key cel-

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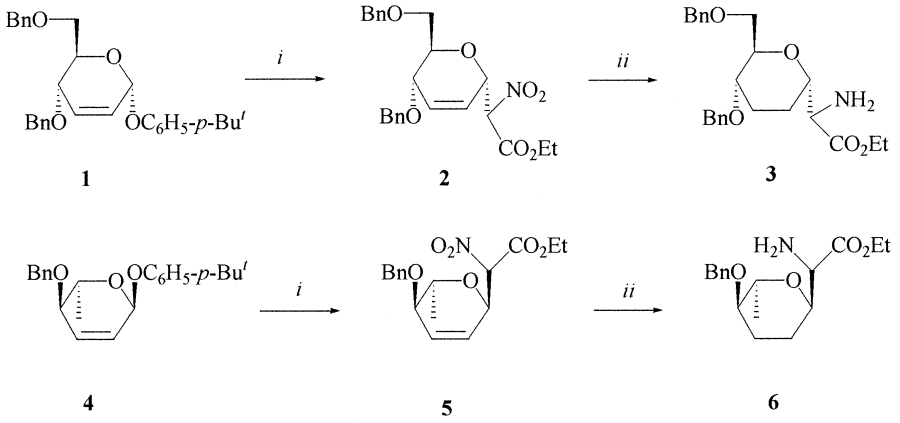
lular processes; effectively a simple modification could provide useful information on the specific role of the carbohydrate moiety of glycopeptides. They can also be readily incorporated into larger and biologically more relevant molecular frameworks. Much effort has therefore been invested in developing new methodologies for the construction of *C*-glycosyl aminoacids. Different approaches to *C*-glycosyl glycine,[3–8] *C*-glycosyl alanine,[9–12] *C*-glycosyl serine,[13–28] *C*-glycosyl asparagine,[21, 28–30] *C*-glycosyl tyrosine,[31] as well as more complex *C*-glycosyl aminoacids[29, 32–34] have been described.

We have previously described the stereoselective synthesis of various functionalized unsaturated *C*-glycosides via palladium(0)-catalyzed alkylation of 2,3-unsaturated *O*-aryl glycosides with various active methylene compounds.[35, 36] We expect that these compounds could be suitable precursors to unsaturated *C*-glycosyl amino acids given a judicious choice of the active methylene compound. We describe in this paper the application of this methodology to the synthesis of unsaturated *C*-glycosyl glycines using ethyl nitroacetate and *N*-(diphenylmethylene)glycine ethyl ester as the nucleophiles.

RESULTS AND DISCUSSION

We have previously shown that palladium(0)-catalyzed alkylation of the unsaturated carbohydrate **1** occurs regio and stereospecifically at the anomeric center to give the α-anomer **2** as the sole product (Scheme 1).[35] However, the reaction is not stereoselective at C-2, a mixture of epimers in a ratio of 75/25 being obtained. In order to increase this selectivity, we attempted some palladium(0)-catalyzed coupling reaction in the presence of the chiral diphosphines *(S,S)*-DIOP [*(S,S)*-(2,3)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane], *(S,S)*-BDPP [*(S,S)*-(2,4)-bis(diphenylphosphinohexane], and *(S)*-Prophos [*(S)*-1,2-bis(diphenylphos-



Reagents and conditions: *(i)* Pd_2dba_3, dppb, $CH_2(NO_2)(CO_2C_2H_5)$, THF, 70 °C; *(ii)* H_2, Pd/C (10%)

Scheme 1.

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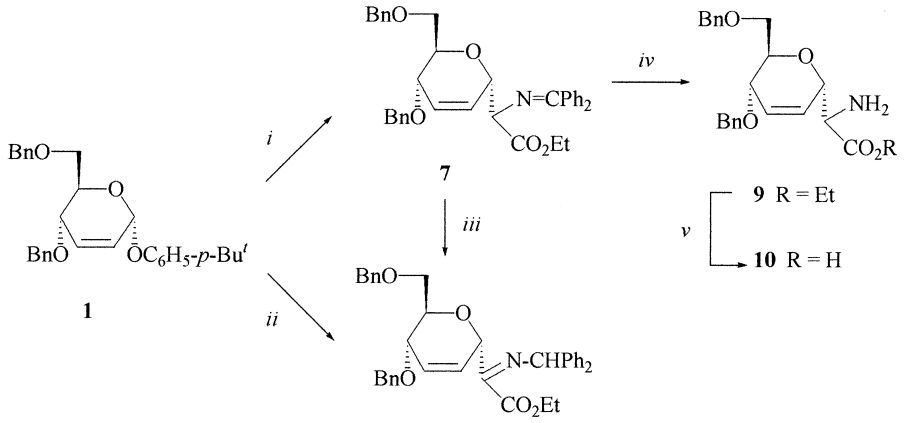

Reagents and conditions: *(i)* Pd_2dba_3, dppb, BSA, KOAc, $CH_2(N{=}CPh_2)CO_2C_2H_5$, THF, 70 °C; *(ii)* Pd_2dba_3, dppb, NaH, $CH_2(N{=}CPh_2)CO_2C_2H_5$, THF, 70 °C; *(iii)* NaH, 70 °C; *(iv)* H_2O, HCl, 25 °C; *(v)* KOH, CH_3OH, H_2O, 25 °C.

Scheme 2.

phino)propane], at 60°C in THF as the solvent; unfortunately we obtained a quite similar ratio of the two epimers: 76/24, 75/25, and 72/28, respectively.

The alkylation reaction was extended to *p-tert*-butylphenyl 4-*O*-benzyl-6-deoxy-2,3-dideoxy-α-L-*erythro*-hex-2-enopyranoside[37] (**4**) using ethyl nitroacetate as the nucleophile; the corresponding unsaturated α-*C*-glycoside **5** was obtained in 90% yield as a 65/35 mixture of the two epimers at C-2 (Scheme 1).

The unsaturated *C*-glycosides **2** and **5** were stirred in ethanol under a hydrogen atmosphere in the presence of Pd/C (10%) in order to access the *C*-glycosidic amino esters (Scheme 1). The corresponding saturated amino esters **3** and **6** were obtained in 30% yield as mixtures of the two epimers (70/30 for **3** and 55/45 for **6**).

We then examined the use of *N*-(diphenylmethylene)glycine ethyl ester as the nucleophile in this palladium(0)-catalyzed alkylation reaction (Scheme 2). No reaction was observed when the condensation between the unsaturated carbohydrate **1** and *N*-(diphenylmethylene)glycine ethyl ester was performed in the absence of a base at 70°C. We therefore used the anion of *N*-(diphenylmethylene)glycine ethyl ester obtained by treating this iminoester with NaH. We observed the formation of a single compound **8** in 52% yield; the structure of this compound was confirmed by NMR using COSY and HMBC sequences, altough the *E/Z* stereochemistry of the double bond was not determined.

We next performed the coupling reaction using *N*,*O*-bis(trimethylsilyl)acetamide (BSA) as the base and KOAc. Under identical conditions, the unsaturated α-*C*-glycoside **7** was obtained in 60% yield as a 50/50 mixture of the two epimers. It is to be noticed that heating compound **7** in THF in the presence of one equivalent of NaH afforded quantitatively the isomerized *C*-glycoside **8**. The conversion to the aminoacid was performed according to the litterature.[38] Treatment of compound **7** by HCl 10% gave the unsaturated amino ester **9** in 69% yield as a 80/20

mixture of the two epimers, that was readily transformed by saponification in 74% yield into the unsaturated *C*-glycosyl glycine **10**.

CONCLUSION

In conclusion, we have shown that palladium(0)-catalyzed alkylation of 2,3-unsaturated aryl glycoside with *N*-(diphenylmethylene)glycine ethyl ester in the presence of *N*,*O*-bis(trimethylsilyl)acetamide and KOAc afforded ethyl 2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-[(*N*-diphenylmethylene)amino]acetate. This compound was readily transformed into 2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-glycine by acidic hydrolysis followed by saponification.

EXPERIMENTAL

General Methods. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (60 F-254, Merck). Compounds were visualized under UV light (254 nm) or by spraying with an H_2SO_4 solution and heating. Column chromatography was performed on silica gel 60 (40–63 mesh, Merck). NMR spectra were recorded on Bruker AC 200 and AM 300 spectrometers, and chemical shifts are given in ppm on the δ scale from internal tetramethylsilane. Reactions involving palladium complexes were carried out in a Schlenk tube under a nitrogen atmosphere. THF was distilled from sodium/benzophenone and stored under a nitrogen atmosphere. Ethyl 2-(4,5-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-nitroacetate (**2**) has already been described.[35]

Ethyl 2-(4-*O*-Benzyl-2,3,6-trideoxy-α-L-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-nitroacetate (5). A solution of 22.9 mg (0.025 mmol) of $Pd_2(dba)_3$ and 40 mg (0.1 mmol) of dppb in tetrahydrofuran (5 mL) was added under argon to a Schlenk tube containing 176.5 mg (0.5 mmol) of the unsaturated carbohydrate **4**[37] and 99.8 mg (0.75 mmol) of ethyl nitroacetate in tetrahydrofuran (5 mL). The solution was stirred at 70°C and the reaction followed by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure to give an oil that was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4/1) as the eluent to give 151 mg of the unsaturated *C*-alkylated carbohydrate **5** (as a 65/35 mixture of the two epimers) (90% yield). Oil; R_f 0.66; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 0.35 × 3H, J = 5.7 Hz, CHCH_3), 1.27 (d, 0.75 × 3H, J = 5.7 Hz, CHCH_3), 1.30 (t, 0.65 × 3H, J = 7.1 Hz, CH_2CH_3), 1.32 (t, 0.35 × 3H, J = 7.1 Hz, CH_2CH_3), 3.67 (m, 1H, H-4), 3.72 (dq, 1H, J = 7.5, 5.8 Hz, H-5), 4.29 (q, 0.65 × 2H, J = 7.1 Hz, OCH_2CH$_3$), 4.30 (q, 0.35 × 2H, J = 7.1 Hz, OCH_2CH$_3$), 4.56 (d, 0.65 × 1H, J = 11.5 Hz, CH_2Ph), 4.57 (d, 0.35 × 1H, J = 11.5 Hz, CH_2Ph), 4.66 (d, 0.35 × 1H, J = 11.5 Hz, CH_2Ph), 4.67 (d, 0.65 × 1H, J = 11.5 Hz, CH_2Ph), 4.92–4.98 (m, 1H, H-1), 5.27 (d, 0.35 × 1H, J = 8.5

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Hz, $CHNO_2$), 5.34 (d, 0.65 × 1H, J = 8.5 Hz, $CHNO_2$), 5.91 (ddd, 1H, J = 10.4, 3.0, 1.3 Hz, H-3), 6.15 (bd, 1H, J = 10.4 Hz, H-2), 7.27–7.39 (m, 5H, H_{ar}); ^{13}C (50 MHz, $CDCl_3$) δ maj (65%) 13.8 (CH_3), 18.0 (CH_3), 63.3 (OCH_2), 69.0 (C-4), 70.8 (C-1), 71.4 (CH_2Ph), 75.0 (C-5), 88.5 ($CHNO_2$), 124.4, 127.9, 128.0, 130.6, 137.8 (C-2, C-3, C_{ar}), 161.9 (CO_2); δ min (35%) 13.9 (CH_3), 17.8 (CH_3), 63.2 (OCH_2), 69.8 (C-4), 70.2 (C-1), 71.0 (CH_2Ph), 74.4 (C-5), 88.4 ($CHNO_2$), 124.8, 128.5, 129.7, 137.9 (C-2, C-3, C_{ar}), 162.5 (CO_2).

Anal. Calcd for $C_{17}H_{21}NO_6$ (335.36): C, 60.89; H, 6.31. Found: C, 61.85; H, 6.67.

Ethyl 2-(4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-[(*N*-diphenylmethylene)amino]acetate (7). A solution of 22.9 mg (0.025 mmol) of $Pd_2(dba)_3$ and 40 mg (0.1 mmol) of dppb in tetrahydrofuran (5 mL) was added under argon to a Schlenk tube containing 230 mg (0.5 mmol) of the unsaturated carbohydrate **1** and 400 mg (1.5 mmol) of *N*-(diphenylmethylene)-glycine ethyl ester in the presence of 304 mg (1.5 mmol) of *N,O*-bis(trimethylsilyl)acetamide and 147 mg (1.5 mmol) of KOAc in tetrahydrofuran (5 mL). The solution was stirred at 70°C and the reaction followed by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure to give an oil that was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4/1) as the eluent to give 172 mg of the unsaturated *C*-alkylated carbohydrate **7** as a 50/50 mixture of the two epimers (60% yield). Oil; isomer R_f 0.44; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.2 Hz, CH_3), 3.57 (dd, 1H, J = 11.1, 3.3 Hz, H-6), 3.62 (dd, 1H, J = 11.1, 4.0 Hz, H-6), 3.69 (ddd, 1H, J = 7.4, 4.0, 3.3 Hz, H-5), 4.08 (m, 2H, CH_2CH_3), 4.10 (dd, 1H, J = 7.3, 1.5 Hz, H-4), 4.39 (d, 1H, J = 7.4 Hz, CHN), 4.45 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.46 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.54 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.56 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.95 (dd, 1H, J = 7.4, 1.8 Hz, H-1), 5.98 (dd, 1H, J = 10.4, 1.8 Hz, H-2), 6.04 (dd, 1H, J = 10.4, 1.5 Hz, H-3), 7.10–7.70 (m, 20H, H_{ar}); ^{13}C (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 61.1 (CH_2CH_3), 68.9 (CHN), 69.4 (C-6), 69.9 (C-1), 70.6 (CH_2Ph), 73.4 (CH_2Ph), 72.5 (C-5), 74.0 (C-4), 127.5–129.0, 130.5, 130.6, 136.0, 136.1, 138.5, 139.4, 139.7 (C-2, C-3, C_{ar}), 170.1 (N=C), 171.3 (CO_2); isomer R_f 0.40; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz, CH_3), 3.60 (dd, 1H, J = 11.1, 3.3 Hz, H-6), 3.67 (dd, 1H, J = 11.1, 4.0 Hz, H-6), 3.68–3.77 (m, 1H, H-5), 3.99–4.27 (m, 3H, CH_2CH_3, H-4), 4.32 (d, 1H, J = 5.9 Hz, CHN), 4.45 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.46 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.54 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.56 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.87 (dd, 1H, J = 5.9, 2.6 Hz, H-1), 5.73 (ddd, 1H, J = 10.7, 2.6, 1.8 Hz, H-2), 6.07 (dd, 1H, J = 10.7, 1.8 Hz, H-3), 7.13–7.73 (m, 20H, H_{ar}); ^{13}C (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 61.1 (CH_2CH_3), 69.0 (CHN), 69.3 (C-6), 69.8 (C-1), 70.8 (CH_2Ph), 73.4 (CH_2Ph), 72.6 (C-5), 74.4 (C-4), 128.0–129.2, 130.1, 130.4, 132.5, 136.1, 136.2, 138.3, 138.5, 139.3 (C-2, C-3, C_{ar}), 170.1 (N=C), 172.1 (CO_2).

Anal. Calcd for $C_{37}H_{37}NO_5$ (575.71): C, 77.19; H, 6.48. Found: C, 77.02; H, 6.32.

Ethyl 2-(4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-(benzhydrylimino)acetate (8). A solution of 22.9 mg (0.025 mmol) of $Pd_2(dba)_3$ and 40 mg (0.1 mmol) of dppb in tetrahydrofuran (5 mL) was added under argon to a Schlenk tube containing 230 mg (0.5 mmol) of the unsaturated carbohydrate **1** and 400 mg (1.5 mmol) of *N*-(diphenylmethylene)glycine ethyl ester in the presence of 36 mg (1.5 mmol) of NaH in tetrahydrofuran (5 mL). The solution was stirred at the desired temperature and the reaction followed by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure to give an oil that was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (4/1) as the eluent to give 150 mg of the unsaturated *C*-alkylated carbohydrate **8** (52% yield). Oil; R_f 0.39; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, 3H, J = 7.0 Hz, CH_3), 3.48 (dd, 1H, J = 14.8, 5.5 Hz, H-6), 3.51 (dd, 1H, J = 14.8, 6.3 Hz, H-6), 3.95 (m, 1H, H-5), 4.10 (m, 2H, CH_2CH$_3$), 4.23 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.38 (dd, 1H, J = 10.3, 5.2 Hz, H-4), 4.49 (d, 1H, J = 14.7 Hz, CH_2Ph), 4.50 (d, 1H, J = 14.7 Hz, CH_2Ph), 4.51 (d, 1H, J = 11.8 Hz, CH_2Ph), 5.68 (dd, 1H, J = 10.3, 10.3 Hz, H-3), 6.57 (dd, 1H, J = 12.5, 10.3 Hz, H-2), 6.69 (d, 1H, J = 12.5 Hz, H-1), 7.15–7.60 (m, 20H, H_{ar}), 7.79 (d, 1H, J = 7.4 Hz, $CHPh_2$); ^{13}C (75 MHz, $CDCl_3$) δ 14.3 (CH_3), 61.1 (CH_2CH_3), 70.3 (CH_2Ph), 70.7 (C-6), 72.6 (C-5), 73.5 (CH_2Ph), 74.6 (C-4), 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.8, 129.3, 131.3, 131.9,138.0, 141.4 (C-2, C-3, C_{ar}), 138.0 (C=N), 171.6 (CO_2).

Anal. Calcd for $C_{37}H_{37}NO_5$ (575.71): C, 77.19; H, 6.48. Found: C, 76.84; H, 6.47.

Isomerization of Compound 7. A solution of 130 mg (0.23 mmol) of the iminoester **7** and 64 mg (2.66 mmol) of NaH in tetrahydrofuran (6 mL) was stirred under nitrogen at 60°C for 5h. The solution was diluted with water (2 mL), and the organic product was extracted with CH_2Cl_2 (2 × 10 mL). Evaporation of the solvent gave quantitatively an oil that was identical to compound **8**.

Hydrogenation of Nitrocompounds 2 and 5. A solution of 1 mmol of the glycosidic nitroester **2** or **5** in 15 mL of ethanol was stirred for 24 h under hydrogen (1 atm) in the presence of 10% Pd/C (10%). After filtration, the solvent was evaporated and the residue purified on silica using methanol as the eluent to afford the aminoester **3** or **6**, respectively.

Ethyl 2*(R,S)*-amino-2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hexopyranosyl)acetate (3) (as a 70/30 mixture). Yield 30%; oil; R_f 0.50 (methanol); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18–1.28 (m, 2H, H-2, H-3), 1.22 (t, 3H, J = 7.1 Hz, CHCH_3), 1.50–1.61 (m, 2H, H-2, H-3), 2.14–2.45 (m, 2H, NH_2), 3.38–3.79 (m, 6H, H-1, H-4, H-5, H-6, CHNH$_2$), 4.15 (q, 0.3 × 2H, J = 7.1 Hz, CH_2CH$_3$), 4.16 (q, 0.7 × 2H, J = 7.1 Hz, CH_2CH$_3$), 4.42 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.52 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.57 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.60 (d, 1H, J = 11.2 Hz, CH_2Ph), 7.28–7.32 (m, 10H, H_{ar}); ^{13}C (50 MHz, $CDCl_3$) δ 14.2 (CH_3), 24.0 and 28.8 (C-2, C-3 maj), 25.0 and 29.7 (C-2, C-3 min), 61.1 (OCH_2 min), 61.2

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(OCH_2 maj), 69.0 (C-6 min), 69.8 (C-6 maj), 70.6 (CH_2Ph min), 71.0 (CH_2Ph maj), 72.1 (C-4), 73.0 (C-5), 73.3 (CH_2Ph), 74.5 (C-1), 80.8 ($CHNH_2$), 127.5, 127.6, 127.7, 127.8, 128.3, 138.3, 138.4 (C_{ar}), 162.5 (CO_2).

Ethyl 2*(R,S)*-amino-(4-*O*-benzyl-2,3,6-trideoxy-α-L-*erythro*-hexopyranosyl)acetate (6) (as a 55/45 mixture). Yield 30%; oil; R_f 0.31 (ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (m, 3H, $CHCH_3$), 1.25 (d, 3H, J = 5.7 Hz, $CHCH_3$), 1.40–2.10 (m, 4H, H-2, H-3), 2.20–2.40 (m, 2H, NH_2), 2.90 (3.40 (m, 2H, H-4, H-5), 3.60–4.05 (m, 2H, H-1, H-2), 4.20 (q, 2H, J = 7.0 Hz, OCH_2CH_3), 4.51 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.56 (d, 1H, J = 12.0 Hz, CH_2Ph), 7.32–7.44 (m, 5H, H_{ar}); ^{13}C (50 MHz, $CDCl_3$) δ 14.2 (CH_3), 17.1 (CH_3 maj), 18.6 (CH_3 min), 22.0 and 29.7 (C-2, C-3 min), 23.1 and 28.8 (C-2, C-3 maj), 61.0 (CH_2CH_3), 70.4 (CH_2Ph min), 71.0 (CH_2Ph maj), 71.4 (C-4), 76.3 (C-5), 76.5 (C-1 min), 77.4 (C-1 maj), 77.7 ($CHNH_2$ min), 78.7 ($CHNH_2$ maj), 127.6, 127.7, 128.4, 135.6 (C_{ar}), 161.9 (CO_2).

Anal. Calcd for $C_{17}H_{25}NO_4$ (307.39): C, 66.43; H, 8.20. Found: C, 66.33; H, 8.52.

Ethyl 2(*R,S*)-Amino-2-(4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)acetate (9). A solution of 262 mg (0.46 mmol) of the iminoester 7 in diethyl ether (5 mL) was stirred at room temperature in the presence of a solution of HCl (10%, 2.5 mL). After 1 h, the organic layer was separated, the aqueous phase was washed with diethyl ether and neutralized with sodium hydrogencarbonate. The organic substrate was extracted with diethyl ether (10 mL). Evaporation of the solvent gave a residue that was purified by chromatography using methanol as the eluent to give 131 mg of compound **9** (as a 80/20 mixture of the two epimers) as an oil (69% yield). R_f 0.74 (methanol); *major isomer* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz, CH_3), 1.92 (bs, 2H, NH_2), 3.54–3.72 (m, 3H, H-5, H-6), 3.92 (m, 1H, $CHNH_2$), 4.01 (dd, 1H, J = 10.3, 4.8 Hz, H-4), 4.10–4.26 (m, 2H, CH_2CH_3), 4.39 (ddd, 1H, J = 5.9, 4.4, 2.2 Hz, H-1), 4.51 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.52 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.58 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.60 (d, 1H, J = 11.8 Hz, CH_2Ph), 5.92 (ddd, 1H, J = 10.7, 2.2, 1.5 Hz, H-2), 6.08 (ddd, 1H, J = 10.7, 2.6, 2.6 Hz, H-3), 7.23–7.38 (m, 10H, H_{ar}); ^{13}C (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 57.7 (CHN), 61.3 (C-6), 69.1 (CH_2Ph), 69.3 (C-1), 70.8 (CH_2CH_3), 72.8 (C-5), 73.4 (CH_2Ph), 73.5 (C-4), 127.2, 127.7, 127.8, 127.9, 128.4, 128.5, 138.1, 138.2 (C-2, C-3, C_{ar}), 172.8 (CO_2); *minor isomer* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz, CH_3), 1.79 (bs, 2H, NH_2), 3.54–3.68 (m, 3H, H-5, H-6), 3.92 (m, 1H, $CHNH_2$), 3.96–4.05 (m, 1H, H-4), 4.10–4.26 (m, 2H, CH_2CH_3), 4.35 (ddd, 1H, J = 5.5, 4.4, 2.2 Hz, H-1), 4.50 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.51 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.59 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.60 (d, 1H, J = 11.8 Hz, CH_2Ph), 5.84 (ddd, 1H, J = 10.3, 2.2, 1.5 Hz, H-2), 6.08 (ddd, 1H, J = 10.3, 2.2, 2.2 Hz, H-3), 7.23–7.38 (m, 10H, H_{ar}); ^{13}C (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 58.1 (CHN), 61.1 (C-6), 70.9 (CH_2Ph), 69.3 (C-1), 70.9 (CH_2CH_3), 73.0 (C-5), 73.4 (CH_2Ph), 73.7 (C-4), 127.2, 127.7, 127.8, 127.9, 128.4, 128.7, 138.1, 138.2 (C-2, C-3, C_{ar}), 173.6 (CO_2). HRMS calcd for $C_{24}H_{29}NO_5$ (CI) 412.2124. Found: 412.2122.

2-(4,6-Di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2*(R,S)*-glycine (10). A solution of 68 mg (0.17 mmol) of the aminoester **9** in methanol (0.5 mL) and aqueous sodium hydroxide 1N (0.5 mL) was stirred for 2 h at room temperature. After filtration on a Dowex 50WX4 (1 g), the residue was dissolved in methanol. Evaporation of the solvent gave 47 mg of the aminoacid **10** as an oil (74% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 2H, NH_2), 3.30–3.70 (m, 3H, H-5, H-6), 3.86 (dm, 1H, J = 9.5 Hz, H-4), 4.10 (m, 1H, C*H*NH_2), 4.25–4.75 (m, 5H, H-1, CH_2Ph), 5.92 (bd, 1H, J = 11.4 Hz, H-2), 6.05 (bd, 1H, J = 11.4 Hz, H-3), 7.10–8.05 (m, 10H, H_{ar}), 10.0 (bs, 1H, CO_2H); ^{13}C (75 MHz, $CDCl_3$) δ 68.5, 68.7, 70.5, 70.7, 77.3 (CHN, C-1, C-4, C-5, C-6), 73.2 (CH_2Ph), 127.0, 127.6, 127.8, 128.0, 128.1, 128.4, 128.5, 129.0, 129.8, 137.9, 138.0 (C-2, C-3, C_{ar}), 171.3 (CO_2). Mass spectra for $C_{22}H_{25}NO_5$ (CI): 340 (100%) (MH^+ - CO_2).

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REFERENCES

1. Dwek, R.A. Glycobiology: Toward Understanding of the Function of Sugars. Chem. Rev. **1996**, *96* (2), 683–720.
2. Marcaurelle, L.A.; Bertozzi, C.R. New Directions in the Synthesis of Glycopeptides Mimetics. Chem. Eur. J. **1999**, *5* (5), 1384–1390.
3. Garner, P.; Park, J.M. Glycosyl α-Amino Acids via Stereocontrolled Buildup of a Penaldic Acid Equivalent. A Novel Synthetic Approach to the Nucleosidic Component of the Polyoxins and Related Substances. J. Org. Chem. **1990**, *55* (12), 3772–3787.
4. Barrett, A.G.M.; Lebold, S.A. (Phenylthio)nitromethane in the Total Synthesis of Polyoxin C. J. Org. Chem. **1990**, *55* (12), 3853–3857.
5. Simchen, G.; Pürkner, E. Synthese α-*C*-Glucosylierter α-Aminocarbonsäure-Derivative. Synthesis **1990**, (6), 525–527.
6. Colombo, L.; Casiraghi, G.; Pittalis, A.; G. Rassu, G. Stereoselective Synthesis of *C*-Glycosyl α-Amino Acids. J. Org. Chem. **1991**, *56* (12), 3897–3900.
7. Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. Total Synthesis of 6-Deoxy-6-aminoheptopyranuronic Acid Derivatives. J. Org. Chem. **1991**, *56* (23), 6523–6527.
8. Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. Diastereoselective Synthesis of α-*C*-Arabinofuranosyl Glycine. Tetrahedron: Asymmetry **1995**, *6* (2), 371–374.
9. Kessler, H.; Wittmann, V.; Köch, M; Kottenhahn, M. Synthesis of *C*-Glycopeptides via Free Radical Addition of Glycosyl Bromides to Dehydroalanine Derivatives. Angew. Chem., Int. Ed. Engl. **1992**, *31* (7), 902–904.
10. M. K. Gurjar, M.K.; Mainkar, A.S.; Syamala, M. Synthesis of *C*-α-D-Glucosyl-α-Amino Acids. Tetrahedron: Asymmetry **1993**, *4* (11), 2343–2346.
11. Axon, J. R.; Beckwith, A.L.J. Diastereoselective Radical Addition to Methyleneoxazolidinones: an Enantioselective Route to α-Amino Acids. J. Chem. Soc., Chem. Commun. **1995**, (5), 549–550.
12. Vincent, S.P.; Schleyer, A.; Wong, C.-H. Asymmetric Strecker Synthesis of *C*-Glycopeptide. J. Org. Chem. **2000**, *65* (14), 4440–4443.

13. Petrus, L.; BeMiller, J.N. Synthesis of a *C*-Glycosyl Amino Acid Analogue of *O*-(β-D-Xylopyranosyl)serine. Carbohydr. Res. **1992**, *230* (1), 197–200.
14. Bertozzi, C.R.; Hoeprich Jr.,P.D.; Bednarski, M.D. Synthesis of Carbon-Linked Glycopeptides as Stable Glycopeptide Models. J. Org. Chem. **1992**, *57* (23), 6092–6094.
15. Bertozzi, C.R.; Cook, D.G.; Kobertz, W.R.; Gonzales-Scarano, F.; Bednarski, M.D. Carbon-Linked Galactosphingolipid Analogs Bind Specifically to HIV-1 gp120. J. Am. Chem. Soc. **1992**, *114* (26), 10639–10641.
16. Dorgan, B.J.; Jackson, R.F.W. Synthesis of *C*-Linked Glycosyl Amino Acid Derivatives using Organozinc Reagents. Synlett **1996**, (9), 859–861.
17. Herpin, T.F.; Motherwell, W.B.; Weibel, J.-M. Two Free Radical Routes for the Preparation of Novel Difluoromethylene-Linked Serine-*O*-Glycopeptide Analogues. Chem. Commun. **1997**, (10), 923–924.
18. Debenham, S.D.; Debenham, J.S.; Burk, M.J.; Toone, E.J. Synthesis of Carbon-Linked Glycopeptides through Catalytic Asymmetric Hydrogenation. J. Am. Chem. Soc. **1997**, *119* (41), 9897–9898.
19. Dondoni, A.; Marra, A.; Massi, A. Synthesis of Methylene Isosteres of α- and β-D-Galactopyranosyl-L-Serine. Chem. Commun. **1998**, (7), 1741–1742.
20. Dondoni, A.; Marra, A.; Massi, A. Stereoselective Synthesis of the *C*-Linked Analogue of β-D-Galactopyranosyl-L-Serine. Tetrahedron **1998**, *54* (12), 2827–2832.
21. Dondoni, A.; Massi, A.; Marra, A. Synthesis of Ethylene Isosteres of β-D-Galactosyl- and β-D-Glucosyl-L-Asparagine. Tetrahedron Lett. **1998**, *39* (36), 6601–6604.
22. Dondoni, A.; Marra, A.; Massi, A. Design and Use of an Oxazolidine Silyl Enol Ether as a New Homoalanine Carbanion Equivalent for the Synthesis of Carbon-Linked Isosteres of *O*-Glycosyl Serine and *N*-Glycosyl Asparagine. J. Org. Chem. **1999**, *64* (3), 933–944.
23. Lay, L.; Meldal, M.; Nicotra, F.; Panza, L.; Russo, G. Stereoselective Synthesis of the *C*-Analogue of β-D-Glucopyranosyl Serine. Chem. Commun. **1997**, (15), 1469–1470.
24. Tedebark, U.; Meldal, M.; Panza, L.; Bock, K. *C*-Linked Glycosyl Azido Acid in Novel Solid-Phase *C*-Glycopeptide Synthesis. Tetrahedron Lett. **1998**, *39* (13), 1815–1818.
25. Urban, D.; Skrydstrup, T.; Beau, J.-M. First Synthesis of a *C*-Glycoside Analogue of a Tumor-Associated Carbohydrate Antigen Employing Samarium Diiodide Promoted *C*-Glycosylation. Chem. Commun. **1998**, (9), 955–956.
26. Fuchss, T.; Schmidt, R.R. Synthesis of the *C*-Analog of 2-Acetylamino-2-deoxy-β-D-Glucopyranosyl L- and D-Serine. Synthesis, **1998**, (5), 753–758.
27. Arya, P.; Ben, R.N.; Qin, H. Remote Asymmetric Induction: Synthesis of *C*-Linked α-Galactoserine and Homoserine Derivatives by Electrophilic Amination. Tetrahedron Lett. **1998**, *39* (34), 6131–6134.
28. Campbell, A.D.; Paterson, D.E.; Raynham, T.M.; Taylor, R.J.K. *exo*-Glycal Approaches to *C*-Linked Glycosyl Amino Acids Synthesis. Chem. Commun. **1999**, (16), 1599–1600.
29. Burkhart, F.; Hoffmann, M.; Kessler, H. Stereoselective Synthesis of a *C*-Glycosidic Analog of *N*-Glucoasparagine. Angew. Chem., Int. Ed. Engl. **1997**, *36* (11), 1191–1192.
30. Dondoni, A.; Mariotti, G.; Marra, A. General, Stereoselective Synthesis of Ethylene Isosteres of α- and β-Glycosylasparagines. Tetrahedron Lett. **2000**, *41* (18), 3483–3487.

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31. Pearce, A.J.; Ramaya, S.; Thorn, S.N.; Bloomberg, G.B.; Walter, D.S.; Gallagher, T. *C*-Glycosyl Tyrosines. Synthesis and Incorporation into *C*-Glycopeptides. J. Org. Chem. **1999**, *64* (15), 5453–5462.
32. Hoffmann, M.; Burkhart, F.; Hessler, F.; Kessler, G. *C*-Glycoside Analogues of N^4-(2-Acetamido-2-deoxy-glucopyranosyl)-L-asparagine: Synthesis and Conformational Analysis of a Cyclic *C*-Glycopeptide. Helv. Chim. Acta **1996**, *79* (6), 1519–1532.
33. Wang, L.-X.; Fan, J.-Q.; Lee, Y.C. Chemoenzymatic Synthesis of a High-Mannose-Type *N*-Glycopeptide Analog with *C*-Glycosidic Linkage. Tetrahedron Lett. **1996**, *37* (12), 1975–1978.
34. Lowary, T.; Meldal, M.; Helmboldt, A.; Vasella, A.; Bock, K. Novel Type of Rigid *C*-Linked Glycosylacetylene-Phenylalanine Building Blocks for Combinatorial Synthesis of *C*-Linked Glycopeptides. J. Org. Chem. **1998**, *63* (26), 9657–9668.
35. Brakta, M.; Lhoste, P.; Sinou, D. Palladium(0)-Based Approach to Functionalized *C*-Glycopyranosides. J. Org. Chem. **1989**, *54* (8), 1890–1896.
36. Chaguir, B.; Brakta, M.; Bolitt, V.; Lhoste, P.; Sinou, D. Functionnalized *C*-Glycosyl Compounds. III. Reaction of Tertiary Nucleophiles with Unsaturated Carbohydrates. Mechanism of the Anomerization. J. Carbohydr. Chem. **1992**, *11* (5), 609–625.
37. Frappa, I.; Sinou, D. An Easy and Efficient Preparation of Aryl α-*O*-Δ^2-Glycosides. Synthetic Commun. **1995**, *25* (9), 2941–2951.
38. Cazes, B.; Djahambini, D.; Goré, J.; Genêt, J.P.; Gaudin, J.M. Palladium-Catalyzed Synthesis of γ-Allenic α-Amino Acids. Synthesis **1988**, (12), 983–985.

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