C-Glycosylated Phenylalanine Synthesis by Palladium-Catalyzed Cross-Coupling Reactions

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Abstract: A new and convergent synthesis of a *C*-glycosylated phenylalanine derivative using palladium-catalyzed Stille and Neghishi cross-coupling reactions is described. The coupling product constitutes a precursor of a natural glycosylated tyrosine mime.

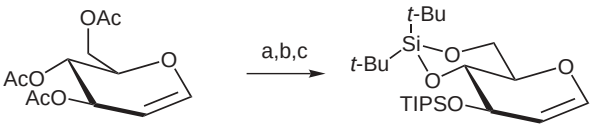
Key words: tin, zinc, carbohydrates, amino acids, cross-coupling, palladium

The importance of glycoproteins in number of biological processes as cell adhesion, cell differentiation or regulation of cell growth is now well established.[1] Almost all of the naturally occurring glycosidic linkages can be divided into *N*-glycosides, mostly attached to asparagine and *O*-glycosides often attached to serine or threonine. However *O*-glycosylation of phenolic units is also frequently encountered.[2] For example a tyrosine residue was glycosylated in glycopeptide antibiotics such as mannopeptimycin or vancomycin.[3] In order to understand the biological mechanisms it is always attractive to have *C*-glycosylated aminoacids[4] due to their stability. They can be used as tools incorporated into more relevant frameworks through supported peptidic synthesis.

Few syntheses of *C*-glycosylated tyrosine or analogues are reported.[2c,5] We chose to use palladium-catalyzed cross-coupling reactions in order to achieve the carbon-carbon bond formation. We describe herein a convergent synthesis of such compounds involving organometallic species produced from the silylated glucal **2** and the protected iodophenylalanine **4**.

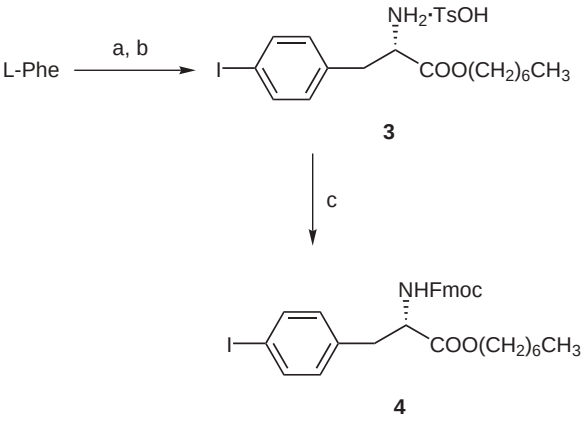
Protective groups on both compounds were chosen in order to be orthogonal and compatible with a future solid-phase peptide synthesis. Sugar protection by silylated groups was proved to be adequate with further C-1 deprotonation.[6] In addition, the protection of the 4,6-position as di-*tert*-butylsilylidene liberates the anomeric position for sterical and conformational reasons.[7] Thus, derivative **2** was prepared from tri-*O*-acetyl-D-glucal **1** according to Scheme 1.

On the other hand, 4-iodophenylalanine derivative **4** was prepared from L-phenylalanine (Scheme 2). Iodination was performed as described by Schwabacher et al.[8] and the resulting product was then esterified with heptanol.[9] Finally, the amino group was protected with 9-fluorenylmethoxycarbonylsuccinimide (FmocOSu) leading to the Fmoc-Phe-(4-I)-OHep (**4**) in 25% overall yield, due essentially to the difficulty of the iodination step. Although the class[10] of compound **4** was previously prepared, in our case this pathway allowed to obtain the compound **4** in large scale.



1 **2**

Scheme 1 (a) K_2CO_3 (0.01 equiv), MeOH (99%); (b) $(t\text{-Bu})_2Si(OTf)_2$ (1 equiv), 2,6-lutidine (2.6 equiv), DMF, –20 °C to 0 °C (64%); (c) TIPSCl (1.1 equiv), imidazole (1.7 equiv), DMF (75%).



Scheme 2 (a) I_2 (0.4 equiv), $NaIO_3$ (0.2 equiv), H_2SO_4 (2.2 equiv), HOAc, 70 °C (50%); (b) $CH_3(CH_2)_6OH$ (5 equiv), TsOH (1.5 equiv), benzene, reflux (50%); (c) $NaHCO_3$ then FmocOSu (0.83 equiv), Na_2CO_3 (2 equiv), dioxane–water (98%).

The coupling of the sugar and amino acid moieties was initially investigated using Stille conditions. The glucal **2** was thus transformed into the stannylated derivative **2′a** ($Z = SnBu_3$) by deprotonation with *t*-BuLi and then quenching with tributyltin chloride. As the coupling reaction of a stannylated glucal with simple aryl bromides had been described,[11] we tested some similar catalytic conditions involving the iodophenylalanine derivative **4** (Scheme 3).

In order to establish the best reaction conditions, we first tested different solvents with $Pd(PPh_3)_4$ as the catalyst. As it is shown in Table 1, toluene proved to be the best sol-

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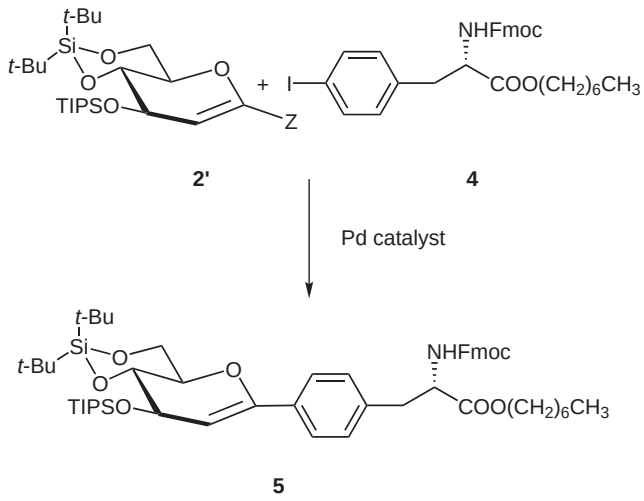


Scheme 3

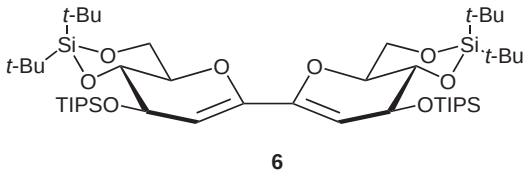


Figure 1

vent especially when a catalytic amount of copper iodide is added in the medium. The use of copper salts favoring the Sn/Cu transmetallation was often described as efficient[12] especially in the case of Stille type reactions involving bulky stannanes.[13] In our case the desired coupled product **5** is obtained along with a byproduct corresponding to the dimer **6** (Figure 1), which can be easily separated by flash chromatography (entry 2).

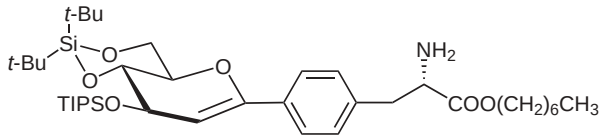
The use of a more polar solvent such as DMF or *N*-methylpyrrolidinone, which are known to favor this type of couplings[12] failed, leading exclusively to the formation of **6** (entries 9 and 10). Changing the source of palladium and using a bulky phosphine (entries 5 and 6) or triphenylarsine (entries 7 and 8) allowed us to avoid the formation of the dimer, but the coupled product **5** was obtained in lower yields than in toluene.

Then we decided to change the metal at glucal **2** choosing to use an organozinc derivative in a Neghishi type coupling reaction with iodophenylalanine derivative **4**. For this purpose **2′b** (Z = ZnCl) was formed in situ by deprotonation with *t*-BuLi and reaction with zinc dichloride and directly engaged in the reaction with Fmoc-Phe-(4-I)-OHep **4** in presence of a catalytic amount of palladium. When $PdCl_2(PPh_3)_2$ in the presence of DIBAL was used[14] in THF at room temperature the coupled product **5** was isolated in 30% yield. In order to increase this yield, the reaction was performed in a 1/1 THF/DMA mixture.[15] In this case the coupling led to the unprotected compound **7** in 61% yield (Figure 2). More interestingly, the desired product was obtained in 69% yield when a complex obtained from $Pd_2dba_3{\cdot}CHCl_3$ and the bulky tri-*o*-tolylphosphine was used.[16] It is noteworthy that in all these experiments realized with the glucal zinc derivative no dimer from the homocoupling of the sugar moiety was detected.

Table 1 Catalyzed Coupling Reaction between **2′** and **4**

Entry	Z	Catalyst[a]	Additive	Solvent	T (°C)	t (h)	**5** Yield (%)[b]	**6** Yield (%)
1	$SnBu_3$	$Pd(PPh_3)_4$		Toluene	90	24	38	0
2	$SnBu_3$	$Pd(PPh_3)_4$	CuI 0.2 equiv	Toluene	90	16	50	42
3	$SnBu_3$	$Pd(PPh_3)_4$		THF	reflux	48	38	24
4	$SnBu_3$	$Pd(PPh_3)_4$	LiCl 3 equiv	THF	reflux	48	27	45
5	$SnBu_3$	$Pd_2(dba)_3{\cdot}CHCl_3$, $(o\text{-tol})_3P$		THF	50	16	24	0
6	$SnBu_3$	$Pd_2(dba)_3{\cdot}CHCl_3$, $(o\text{-tol})_3P$		Dioxane	70	16	35	0
7	$SnBu_3$	$Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3As		THF	50	16	29	0
8	$SnBu_3$	$Pd_2(dba)_3{\cdot}CHCl_3$, Ph_3As		Dioxane	70	16	35	0
9	$SnBu_3$	$Pd(PPh_3)_4$		DMF	60	16	0	48
10	$SnBu_3$	$Pd(PPh_3)_4$		NMP	60	16	0	48
11	ZnCl	$PdCl_2(PPh_3)_2$, DIBAL		THF	20	16	30	0
12	ZnCl	$PdCl_2(PPh_3)_2$, DIBAL		THF/DMA	20	5	61[c]	0
13	ZnCl	$Pd_2(dba)_3.CHCl_3$, $(o\text{-tol})_3P$		THF	20	3	69	0

[a] 10 mol%.
[b] Yield after purification by flash chromatography.
[c] Yield of the deprotected product **7**.



7

Figure 2

In conclusion, we have developed a convergent synthesis of *C*-glycosylated aminoacids by carbon-carbon bond formation according to a palladium catalyzed cross-coupling procedure involving a stannyl or a zinc glucal and a phenylalanine derivative. The functionalization of the coupled product in order to obtain the *C*-glycosylated tyrosine mime is under investigation in the laboratory.

Preparation of 4-Iodo-L-phenylalanine.
In a solution of L-phenylalanine (10 g, 60 mmol) dissolved in acetic acid (55 mL) and concentrated sulfuric acid (7 mL), iodine (6.15 g, 24 mmol) and sodium iodate (2.54 g, 6.29 mmol) were added. The mixture was stirred vigorously and heated at 70 °C during 21 h. Then $NaIO_4$ was introduced (2 × 0.25 g). At the end of the reaction, the solution became orange. Acetic acid was removed in vacuo and the crude was diluted in H_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 25 mL) and CH_2CL_2 (2 × 25 mL). The combined organic layers were decolored by norite (1.25 g), then filtrated. pH was increased to 5 with aq concd NaOH. The precipitate was filtered, washed with H_2O (200 mL) and EtOH (75 mL) yielding 4-iodophenylalanine as a white solid, 9.4 g (53%), mp 255–265 °C, used in the next step without purification.

Preparation of 4-Iodo-L-phenylalanine Heptyl Ester *p*-Toluenesulfonate (3).
A solution of 4-iodophenylalanine (7.5 g, 25.7 mmol) and *p*-toluenesulfonic acid (7.3 g, 38.5 mmol) in benzene (125 mL) and heptanol (18.7 mL) was refluxed until H_2O was separated. The solution was concentrated in vacuo and the product was crystallized in Et_2O. The filtration furnished the compound as a white solid, 7.817 g (53%), mp 118–121 °C. $[\alpha]_D^{20}$ +19.1 (*c* 1, $CHCl_3$). R_f = 0.92 (CH_2Cl_2/MeOH 8/2), ninhydrine. IR (KBr): 1744, 3015, 3403 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.75 [t, 3 H, C*H*$_3$-(CH$_2$)$_5$], 1.01–1.27 [m, 10 H, (C*H*$_2$)$_5$], 2.3 (s, 3 H, C*H*$_3$-Ph), 2.90–3.00 (m, 1 H, C*H*$_2$-CH), 3.10 (m, 1 H, C*H*$_2$-CH), 3.80 (m, 2 H, C*H*$_2$-O), 4.20 (s, 1 H, CH$_2$-C*H*), 6.80 (d, 2 H, H_{ar}, *J* = 10 Hz), 7.10 (d, 2 H, H_{ar} *J* = 7.5 Hz), 7.40 (d, 2 H, H_{ar}, *J* = 7.5 Hz), 7.60 (d, 2 H, H_{ar}, *J* = 10 Hz), 8.20 (brs, 3 H, NH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14 [C*H*$_3$-(CH$_2$)$_5$], 21.3 (C*H*$_3$-Ph), 22.6, 25.5, 28.0, 28.8, 31.6 [(C*H*$_2$)$_5$], 35.7 (C*H*$_2$-CH). 53.8 (CH$_2$-C*H*), 66.3 (C*H*$_2$-O), 92.0, 126.0, 128.9, 131.2, 134.1, 136.9, 137.4, 137.5, 141.2 (C_{ar}), 174.8 (CO).

Preparation of *N*-Fmoc-4-iodo-L-phenylalanine Heptyl Ester (4).
A solution of 4-iodo-L-phenylalanine heptyl ester, TsOH **3** (7.8 g, 13.5 mmol) in CH_2Cl_2 (100 mL) was washed with 10% $NaHCO_3$ (2 × 100 mL). The organic layer was dried on Na_2SO_4. After filtration and evaporation under reduced pressure, 4-iodo-L-phenylalanine heptyl ester was obtained as a colorless syrup (6.33 g, 100%). R_f = 0.85 (CH_2Cl_2/MeOH 8/2).

4-Iodo-L-phenylalanine heptyl ester (6.16 g, 16 mmol) was added in a 10% Na_2CO_3 solution cooled at 0 °C. The mixture was stirred during 15 min and a solution of 9-fluorenylmethoxycarbonyl succinimide (4.512 g, 13.4 mmol) in dioxane (37.5 mL) was added dropwise. The mixture was stirred at r.t. and the reaction was monitored by TLC [R_f = 0.49 (HOAc/toluene 1/9)].

The mixture was diluted in H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried on Na_2SO_4 and evaporated. *N*-Fmoc-4-iodo-L-phenylalanine heptyl ester **4** was obtained as a white solid (8.34 g, 86%), mp 54–55 °C. $[\alpha]_D^{20}$ +22.8 (*c* 1.1, $CHCl_3$). IR (KBr): 1690, 1726, 2924, 3321 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90 [t, 3 H, *J* = 6.4 Hz, C*H*$_3$-(CH$_2$)$_5$], 1.30 [m, 8 H, (C*H*$_2$)$_5$], 1.60 [m, 2 H, (C*H*$_2$)$_5$], 3.00 (m, 2 H, C*H*$_2$-CH), 4.06–4.10 (m, 2 H, O-C*H*$_2$ Fmoc), 4.13–4.22 (m, 1 H, H-9 Fmoc), 4.36–4.43 (m, 2 H, C*H*$_2$-OCO), 4.5 (m, 1 H, CH$_2$-C*H*), 5.30 (d, 1 H, NH, *J* = 7.8 Hz), 6.80 (d, 2 H, H_{ar}, *J* = 8 Hz), 7.25–7.50 (m, 4 H, H_{ar} Fmoc), 7.55 (d, 2 H, *J* = 7 Hz, H_{ar} Fmoc), 7.65 (d, 2 H, *J* = 8 Hz, H_{ar}), 7.70 (d, 2 H, *J* = 7.4 Hz, H_{ar} Fmoc). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0 [C*H*$_3$-(CH$_2$)$_5$], 22.5, 25.7, 28.4, 28.8, 31.6 [(C*H*$_2$)$_5$], 37.8 (C*H*$_2$-CH), 47.1 (C*H* C-9 Fmoc), 54.5 (CH$_2$-C*H*), 65.8 (C*H*$_2$-OCO), 66.8 (O-C*H*$_2$ Fmoc), 92.5, 119.9, 127.7–127.0-125.0, 131.3, 135.4, 137.5, 141.3, 143.7 (C_{ar}), 155.4 (CON), 171.2 (COO). Anal. Calcd for $C_{31}H_{34}NO_4I$: C, 60.89; H, 5.60; N, 2.29. Found: C, 60.94; H, 5.68; N, 2.31.

Preparation of (1,5-Anhydro-2-deoxy-4,6-tri-*O*-di-(*tert*-butyl)silanediyl-3-*O*-triisopropylsilyl-d-arabino-hex-1-enitolyl)-*N*-(9-fluorenylmethoxycarbonyl)-l-phenylalanine Heptyl Ester (5).
Tin-mediated Procedure: In a Schlenk tube, *t*-BuLi (1.7 M, 1.6 mL) was slowly added to a solution of the protected glucal **2** (300 mg, 0.68 mmol) in freshly distilled THF (2.7 mL) stirred at –78 °C. The solution was then stirred during 30 min at 0 °C. Tributyltin chloride (0.46 mL, 1.7 mmol) was added at –78 °C and the mixture was stirred for 1 h at 0 °C. After hydrolysis at 0 °C, the aqueous phase was extracted with Et_2O. Combined organic extracts were washed with H_2O and brine, then dried over $MgSO_4$. Purification by flash chromatography (pure hexane) afforded the product **2′a** (260 mg, 52%). This compound was dissolved in anhydrous toluene (4 mL) and iodophenylalanine **4** (324 mg, 0.53 mmol) was added. This mixture was then transferred by cannula into a solution of $Pd(PPh_3)_4$ (34 mg, 0.04 mmol) and CuI (13 mg, 0.07 mmol) in toluene (4 mL) and heated at 90 °C for 16 h. After cooling at r.t. the solvent was removed and the residue was purified by flash chromatography (pure hexane) affording a mixture of **5** (164 mg, 50%) and **6** (130 mg, 42%).

Zinc-mediated Procedure: In a Schlenk tube, *t*-BuLi (1.7 M, 540 μL) was slowly added to a solution of the protected glucal **2** (216 mg, 0.49 mmol) in freshly distilled THF (2.7 mL) stirred at –78 °C. The solution was then stirred during 30 min at r.t. In another Schlenk tube, $ZnCl_2$ (164 mg, 1.2 mmol) was heated under reduced pressure during 15 min. Then, THF (2.7 mL) was added. This second solution was transferred into the first one and was stirred 1 h at r.t. In another Schlenk tube, a solution of the catalyst was prepared by dissolving $Pd_2(dba)_3{\cdot}CHCl_3$ (14 mg, 0.014 mmol), tri-(*o*-tolyl)phosphine (30 mg, 0.1 mmol) in THF (2.3 mL). A solution of iodophenylalanine **4** (160 mg, 0.26 mmol) in THF (2.3 mL) was slowly added at r.t. Finally, the solution of the organozinc compound was transferred by cannula into the solution containing the catalyst and the aryl iodide. The mixture was stirred during 3 h. The mixture was diluted in brine (6 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (6 mL), dried on Na_2SO_4 and evaporated under reduced pressure. Purification by flash chromatography (cyclohexane–EtOAc 98/2) afforded the product **5** (166 mg, 69%) mp 58–62 °C. $[\alpha]_D^{20}$ +5.6 (*c* 1, $CHCl_3$). R_f = 0.41 (cyclohexane/EtOAc 9/1). IR (KBr): 1732, 2933, 3356 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.40 [m, 52 H, CH$_3$-(CH$_2$)$_5$, (CH$_3$)$_3$C, (CH$_3$)$_2$CH)], 3.10 (m, 2 H, C*H*$_2$-CH), 4.00–4.18 (7 H, m, H_4, H_5, $H_{6,6'}$, O-C*H*$_2$ Fmoc, H-9 Fmoc), 4.20–4.30 [m, 1 H, O-C*H*H-(CH$_2$)$_4$], 4.27–4.40 [m, 1 H, O-C*H*H-(CH$_2$)$_4$], 4.60 (dd, 1 H, H_3, *J* = 2.3 Hz, *J* = 6.5 Hz), 4.60–4.80 (m, 1 H, CH$_2$-

C*H*), 5.20 (d, 1 H, H_2, *J* = 2.3 Hz), 5.30 (d, 1 H, NH, *J* = 8 Hz), 7.00 (d, 2 H, H_{ar}, *J* = 8 Hz), 7.20–7.4 (m, 6 H, H_{ar} Fmoc), 7.50 (d, 2 H, H_{ar}, *J* = 8 Hz), 7.70 (d, 2 H, *J* = 7.4 Hz, H_{ar} Fmoc). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.4 [(*C*H_3)$_2$CH], 13.9 [*C*H_3-(CH$_2$)$_5$], 18.0 [(CH$_3$)$_2$*C*H], 19.7 [(CH$_3$)$_3$*C*], 22.4 (*C*H_2-CH$_3$), 22.6 [(CH$_3$)$_3$*C*], 25.7 [(*C*H$_2$)$_5$], 26.8–27.4 [(*C*H$_3$)$_3$C], 28.3, 28.7, 31.5 [(CH$_2$)$_5$], 37.9 (Ph-*C*H$_2$-CH), 47.0 (*C*H C-9 Fmoc), 54.6 (Ph-CH$_2$-*C*H), 65.6 (C_6), 66 (*C*H$_2$-OCO), 66.8 (O-*C*H$_2$ Fmoc), 71.6 (C_5), 72.8 (C_4), 77.4 (C_3), 101.0 (C2), 119.9, 124.9, 125.0, 126.9, 127.6, 129.0, 132.0, 136.0, 141.0, 143.0 (C_{ar}), 150.5 (C_1), 155.4 (CON), 171.4 (COO). Anal. Calcd for $C_{54}H_{79}NO_8Si_2$: C, 70.01; H, 8.60; N, 1.51. Found: C, 70.02; H, 8.56; N, 1.48.

Homocoupling product **6**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90–1.10 [m, 78 H, (CH$_3$)$_3$C, (CH$_3$)$_2$CH], 3.92 (2 H, ddd, $H_{5'}$ *J* = 2.5 Hz, *J* = 4.9 Hz, *J* = 9.9 Hz), 4.00–4.15 (4 H, m, H_4, H_6), 4.25 (2 H, dd, H_6, *J* = 10.5 Hz), 4.50 (2 H, dd, H_3, *J* = 6.6 Hz, *J* = 2.4 Hz), 5.17 (2 H, d, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.5 [(*C*H$_3$)$_2$CH], 18.2 [(CH$_3$)$_2$*C*H], 19.8 [(CH$_3$)$_3$*C*], 22.7 [(CH$_3$)$_3$*C*], 26.9 [(*C*H$_3$)$_3$C], 29.6 [(*C*H$_3$)$_3$C], 66.1 (C_6), 71.7 (C_5), 72.9 (C_4), 76.5 (C_3), 101.2 (C_2), 151.0 (C_1).

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