Towards Glucosamine Building Blocks: Regioselective One-Pot Protection and Deallylation Procedures

Ramu Enugala, Luísa C. R. Carvalho, M. Manuel B. Marques*

REQUIMTE/CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal
Fax +351(21)2948550; E-mail: mmbmarques@dq.fct.unl.pt
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Abstract: Glucosamine building blocks have been prepared by an efficient regioselective one-pot protection approach. This synthetic route enabled the straightforward preparation of a glucosamine disaccharide in 73% yield. The system $Pd(PPh_3)_4$/TES was investigated as an alternative procedure for anomeric allyl ether deprotection.

Key words: glucosamine, regioselective protection, one-pot procedure, allyl ether deallylation, palladium catalysis

Carbohydrates are well known as important targets for modern therapeutics.[1,2] Among the biologically relevant carbohydrates are the glycoconjugates possessing residues of 2-amino-2-deoxy-β-D-glucopyranosyl (D-glucosamino) series. Some of the most representative examples are: chitin (**1**), a linear homopolymer of 2-acetamido-D-glucosamine (GlcNAc) that is a naturally abundant mucopolysaccharide, and heparin (**2**), a linear sulfated polysaccharide consisting of alternating N-sulfated D-glucosamine and L-iduronic acid units which is the major factor in several biological processes[3] (Figure 1).

Indeed, the most important classes of glycoconjugates and oligosaccharides are those incorporating glucosamine residues.[4–6] Thus, the development of synthetic methods towards glycosides and oligosaccharides containing the glucosamine moiety has been the focus of a significant amount of research.[7–11] The less explored preparation of monomeric building blocks (glycosyl acceptors and donors) usually requires multistep sequences and involves several protecting-group manipulations.[8,12] Given the importance of these glycosides there is a need to develop a highly efficient and regioselective protection methodology.[13] Among the several synthetic strategies developed for the synthesis of carbohydrates and especially for the construction of complex oligosaccharides, the most attractive is a one-pot procedure.[14] Recently, one-pot approaches for glycosylation strategies[15] and for regioselective protection of glucose monosaccharides have been reported.[16,17] Over the past few years, our research interest has been focused on glycopeptide chemistry,[18] particularly in glycosides containing the glucosamine moiety. Despite the work developed by Hung and co-workers on glucose monosaccharides,[19] we investigated a one-pot approach for the construction of glucosamine building blocks, in order to establish a more efficient and rapid methodology towards glucosamine disaccharides. Herein, we report the preliminary results on the synthesis of glucosamine building blocks via a one-pot regioselective protection approach. Such an approach allows the protection of the hydroxy groups with suitable groups while avoiding multistep sequences, laborious workups, separations and purifications, and provides the control for a regioselective glycosylation.

We envisaged that a properly N-protected glucosamine fully silylated at O-3, O-4, and O-6 could be used as key intermediate to achieve glucosamine building blocks, donors and acceptors, with a different substitution pattern, via a one-pot sequential procedure (Scheme 1). Moreover, we planned to explore the possibility of including the

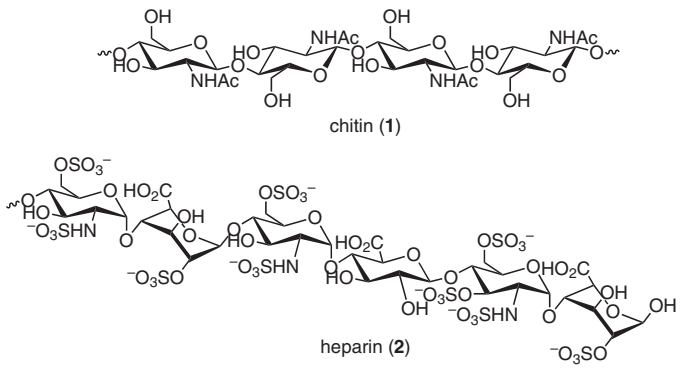

Figure 1 Some representative examples of glycoconjugates composed mainly of glucosamine blocks

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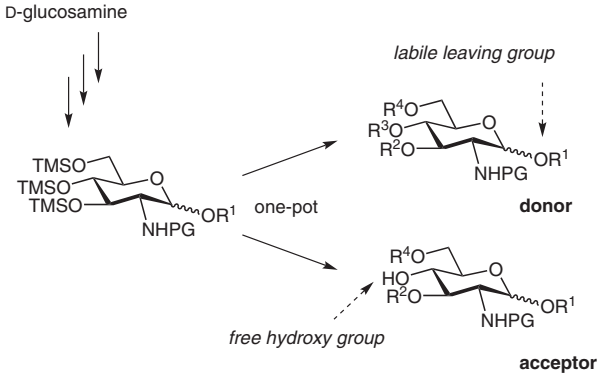
glycosylation as the last step of the one-pot synthetic sequence.

The synthesis started with the crucial choice of the protecting groups, for both the anomeric position and the amine group. It has been reported that glycosylation of aglycones with glycosyl donors bearing a 2-acetamido-2-deoxy functionality is usually not viable.[7,9,11] It is also well demonstrated that the choice of protecting groups can influence the reactivity of the glycosyl acceptor and consequently the glycosylation step.[19] Wong and coworkers[20] have confirmed that the reactivity of 2-amino sugar acceptors can be suitably tuned by the N-protecting group. To overcome these problems several N-protecting groups have been developed.[8,12] Indeed, it was reported that *N*-trichloroethoxycarbonyl-protected (*N*-Troc) glucosamine is 33.7-fold more reactive than the corresponding *N*-phthaloyl-protected (*N*-Phth) glucosamine.

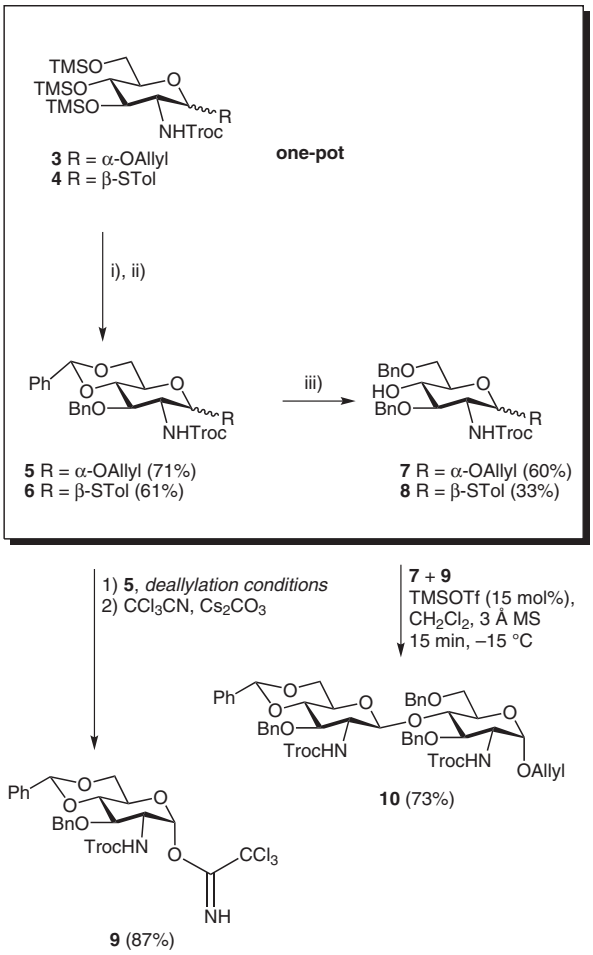


Scheme 1 Proposed strategy for the synthesis of glucosamine building blocks

The use of allyl ether as a protecting group for the anomeric position is of great importance in carbohydrate chemistry, due to its easy formation and stability under different reaction conditions.[21] Alternatively, thioglycosides are widely used as glycosyl donors due to their easy preparation, stability and versatility, and S-*p*-methylphenyl (STol) can be used directly for glycosylation.[20] Therefore, Troc group was used as the nitrogen protecting group, while OAllyl and STol were used as protecting groups for the anomeric position.

Synthesis of the glucosamine building blocks started with the preparation of the key intermediates **3** and **4**. The synthesis involved silylation of the known *N*-Troc allyl[22,23] and *N*-Troc *S*-Tolyl glycosides[20,24] in 88% and 70% yield, respectively.

The synthetic protocol consisted of a one-pot regioselective protection sequence catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf). The strategy involved the following steps: (i) O-6 and O-4 protection with an arylidene acetal; (ii) reductive arylmethylation of O-3 to produce fully protected compounds **5** and **6**; and (iii) regioselective reductive opening of the benzylidene group to produce **7** and **8** with a free O-4 position (Scheme 2). To investigate this approach with glucosamine we decided to use a benzyl ether as the permanent protecting group. Thus, a solution of **3** in dry CH_2Cl_2 at –86 °C with 3 Å MS, was treated with benzaldehyde and TMSOTf as catalyst. The reaction was monitored by TLC,[25] and after formation of the arylidene acetal, benzaldehyde, triethylsilane (TES), and TMSOTf were added. The fully protected glucosamine **5** was formed and the selective benzylidene acetal ring opening could be achieved by sequential addition of TES, and $BF_3{\cdot}OEt_2$.[26,12] Compound **7** was purified and isolated in 60%.[27] Alternatively, compound **5** could be isolated in 71% yield by quenching the reaction at stage ii. Similar reaction conditions were carried out for thioglycoside **4**. However, at stage i at –86 °C the reaction mixture became too viscous to allow stirring, thus conditions were optimized at –20 °C for the next stages (ii and iii). The compound **8** was purified and isolated in 33% yield.[27] Alternatively, fully protected compound **6** could be isolated in 61% yield by quenching the reaction at stage ii. This approach represents a straightforward route to the thioglycosides **6** and **8** that can be used for oligosaccharides synthesis. Indeed, literature report[24] for the synthesis of **8** involved additional protecting-group manipulations such as the installation of a temporary



Scheme 2 Synthesis of a *N*-Troc glucosamine disaccharide via a one-pot procedure for the monosaccharide's preparation. *Reagents and conditions*: i) PhCHO, TMSOTf, CH_2Cl_2, 3 Å MS, –86 °C; ii) PhCHO, TES, TMSOTf; iii) TES, $BF_3{\cdot}OEt_2$.

azide at C-2 to introduce the benzyl group at O-3, followed by Staudinger reaction to restore the amino group. Such a multistep sequence involving many isolation and purification procedures is avoided in the present route.

The next step requires allyl ether cleavage in **5**, but the methods available are not compatible with a one-pot procedure. In our first approach, the iridium complex[28] was used for the isomerization of **5**, using the reported protocol, followed by treatment with I_2 to afford the deallylated compound. The free hydroxy group was treated with Cs_2CO_3 and CCl_3CN, affording the glycosyl trichloroacetimidate **9** in 87% yield. The initial plan involved a one-pot glycosylation, as the last step of the procedure. However, the glycosylation did not proceed at all; probably due to the conditions resulting from the previous step in the sequence. Thus, the glycosylation reaction was performed on isolated **7** and **9** under standard conditions to afford disaccharide **10** in 73% yield.[27]

Common deallylation methods consist of two-step procedures, involving allyl isomerization to a labile prop-1-enyl ether followed by hydrolytic cleavage. Deprotection of the allyl group has been achieved using catalysts, such as iridium,[29] $(Ph_3P)_3RhCl$,[30] $PdCl_2/CuCl/O_2$,[31] Pd/C,[32] Ti(O-*i*-Pr)$_4$/BuMgCl,[33] $Pd(PPh_3)$/TsOH,[34] CP_2Zr,[35] $NaCNBH_3$/TMSCl,[36] *t*-BuLi,[37] and NBS/*hν*.[38] The use of vinyl glycosides directly in the glycosylation was described by Wang and co-workers.[39] However, this methodology did not avoid the use of the expensive iridium complex as catalyst to afford the 1-propenyl glycoside intermediate, which underwent glycosylation promoted by NIS. This approach has not been applied to the glucosamino moieties.

Although the isomerization of the allyl group catalyzed by an iridium complex is usually performed with moderate to high yields, the reaction is highly sensitive, and dependent on the control of the reaction conditions. Thus, alternative approaches to the isomerization of the anomeric allyl group were also investigated. Preliminary studies were performed with *N*-acetyl glucosamine derivative **11**. After treatment of **11** with $Pd(OAc)_2$, *t*-$BuMe_2SiH$, and Et_3N,[40] the reduction product **12** was obtained in 85% yield.

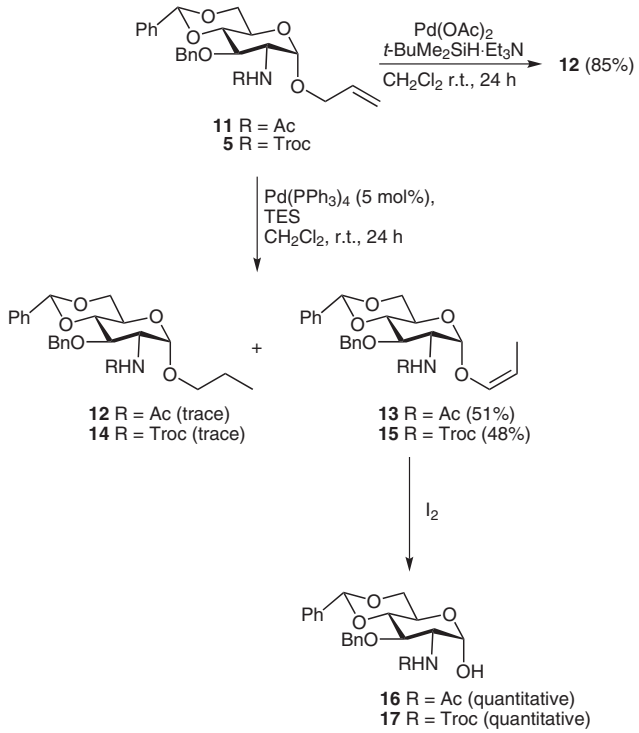
The system Pd(II)-TES has been reported for the reduction and isomerization[41] of olefins under mild conditions. We explored a similar system for the deallylation of **11** (Scheme 3, Table 1).[42]

Thus, to examine the Pd(0)/TES system for the isomerization of *O*-allyl glucosamine derivatives we first attempted the reaction of **11** with $Pd(PPh_3)_4$. Accordingly the conditions were changed to TES and 5 mol% $Pd(PPh_3)_4$, and **13** was observed in 51% yield by ^{1}H NMR (*cis*/*trans* = 2:0.1) and isolated (after deallylation; Table 1, entry 1). The optimized conditions for isomerization were achieved through a series of experiments, consisting of sequential changes of catalyst loading (Table 1). However, applying these conditions to *N*-Troc glucosamine derivative **5**, reaction being carried with 1 mol% of $Pd(PPh_3)_4$, only 32% of the isomerized product **15** was obtained (entry 2). A better result was obtained when the 5 mol% of catalyst was used, and the isomerized product **15** was observed by

Table 1 Isomerization vs. Reduction of *O*-Allyl-Protected Glucosamine **11** and **5** in the Presence of Pd/TES System

Entry	Compound	$Pd(PPh_3)_4$ (mol%)	Solvent	Time (h)	Temp (°C)	Products	Yield (%), *cis*/*trans*[c]
1[a]	**11**	5	CH_2Cl_2	24	r.t.	**12** **13**	trace 51 (2:0.1)
2[a]	**5**	1	CH_2Cl_2	72	r.t.	**14** **15**	trace 32 (2:1)
3[a]	**5**	5	CH_2Cl_2	24	r.t.	**14** **15**	trace 48 (2:1)
4[a]	**5**	5	THF	12	–5	**14** **15**	95 –
5[a]	**5**	20	CD_2Cl_2	24	r.t.	**14** **15**	20 50 (2:1)
6[a]	**5**	20	CH_2Cl_2	24	–5	**14** **15**	19 52 (2:1)
7[b,d]	**5**	20	CH_2Cl_2	12	r.t.	**14** **15**	20 40 (2:1)
8[b,d]	**5**	20	CD_2Cl_2	12	–5	**14** **15**	86 trace
9[a]	**5**	30	CH_2Cl_2	24	r.t.	**14** **15**	20 53 (2:1)

[a] TES addition to a mixture of catalyst and **5**.
[b] Catalyst and TES (stirred for 30 min) followed by **5** addition.
[c] Isolated after deallylation, except in entries 5–7 (yield of **14** determined by ^{1}H NMR).
[d] The reaction was monitored for 24 h; however, after 12 h no evolution was observed.



Scheme 3 Isomerization of the allyl group catalyzed by Pd/TES

^{1}H NMR in 48% yield and isolated (entry 3). Changing the reaction solvent from CH_2Cl_2 to THF, gave almost exclusively the reduction product (entry 4).

Encouraged by these initial results, we decided to monitor the reaction by ^{1}H NMR. Expecting to obtain a reduction in reaction time, we carried out the first experiments using 20 mol% $Pd(PPh_3)_4$. Addition of TES to a mixture of 20 mol% $Pd(PPh_3)_4$ and **5** in CD_2Cl_2, at room temperature, led to the isomerized product **15** in 50% yield and **14** in 20% (entry 5). The characteristic Hb multiplet of **5** could be seen at δ = 5.89 ppm, while in the isomerized product **15**, the Hb signal appeared as a multiplet at δ = 4.66 ppm. Due to the presence of *cis*/*trans* isomers, the Hc proton resonance appeared as a double doublets at δ = 6.03 and 6.12 ppm (2:1; Scheme 4). The reduced compound **14** could also be observed under these conditions, as indicated by proton resonances for Hc at δ = 3.41 and 3.64 ppm.

Further increase in the catalyst loading did not significantly improve the yield of the isomerized product **15**, but promoted the formation of the reduction product **14** (entry 9).

The effect of order of reagents addition and temperature was also investigated. In order to study how the order of addition of reagents influences the reaction outcome, the addition of **5** and TES was inverted. Thus, addition of **5** to a mixture of 20 mol% $Pd(PPh_3)_4$ and TES at room temperature afforded a lower yield of **15** (40%) and the reduced compound **14** (20%) (entry 7). A similar result was obtained when TES was added to a mixture of 20 mol% $Pd(PPh_3)_4$ and **5** at room temperature, afforded **15** (50%) and **14** (20%; entry 5).

Several experiments were carried to investigate the influence of reaction temperature (entries 5 and 6; entries 7 and 8). The formation of **14** is enhanced if the mixture of Pd/TES is allowed to stir previously at –5 °C for 30 minutes, affording **14** with 86% yield (entry 7 vs. entry 8). Thus, we observed that the combination of temperature and order of addition of reagents play a major role in isomerization vs. reduction.

In summary, an efficient regioselective one-pot synthesis of glucosamine building blocks was developed. Currently, this approach is being applied to other glucosamine derivatives. The $Pd(PPh_3)_4$/TES new isomerization method described appears as an alternative to the costly and commonly used metal complexes. Despite the modest yield obtained for the isomerized compound, it represents a step forward in deallylation procedures. It is believed that advances on one-pot syntheses and allyl-deprotection protocols are a valuable contribution to the improvement of the synthetic efficiency in carbohydrate chemistry.

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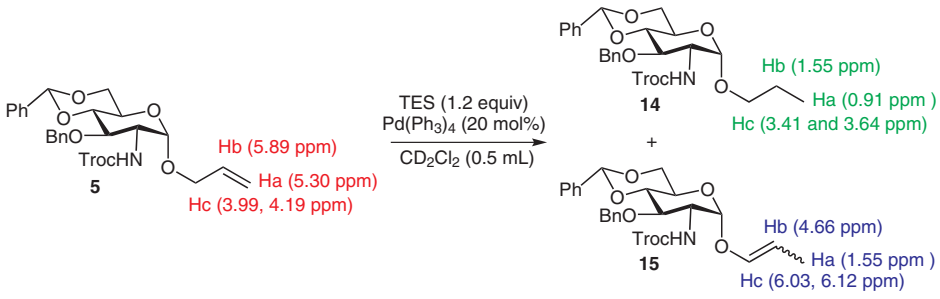

Scheme 4 ^{1}H NMR of reaction of **5** with 20 mol% $Pd(PPh_3)_4$-TES at r.t.

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(27) **Selected Spectroscopic Data**
Compound (**7**): white solid; mp 63–65 °C; $[\alpha]_D^{25}$ +58.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 7.49–7.26 (m, 10 H, Ar*H*), 5.90 (m, 1 H, CH_2CH=CH_2), 5.23 (d, 1 H, *J* = 17.4 Hz, CH_2CH=CH_2), 5.24 (d, 1 H, *J* = 10.1 Hz, CH_2CH=CH_2), 5.16 (d, 1 H, *J* = 9.7 Hz, NH), 4.80–4.70 (m, 3 H, H-1, CH_2CCl_3), 4.67–4.54 (m, 4 H, CH_2Ph), 4.17 (m, 1 H, CH_2CH=CH_2), 4.01–3.98 (m, 2 H, H-2, CH_2CH=CH_2), 3.70–3.60 (m, 5 H, H-4, H-5, H-6a, H-6b, H-3), 2.66 (br s, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 54.4, 68.2, 69.8, 70.2, 71.9, 73.6, 74.4, 74.5, 80.1, 95.3, 96.8, 117.9, 127.6, 127.7, 128.4, 128.5, 133.3, 137.7, 138.2, 154.1. HRMS–FAB: *m/z* calcd for $C_{26}H_{30}NCl_3O_7$: 574.1166; found: 574.1152.
Compound (**8**): white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 7.40–7.26 (m, 12 H, Ar*H*), 7.05 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 5.11 (br s, 1 H, NH), 4.90 (d, 1 H, *J* = 9.7 Hz, H-1), 4.76 (s, 4 H, 2 × CH_2Ph), 4.57 (dd, 2 H, *J* = 11.8, 18.2 Hz, CH_2CCl_3), 3.80–3.75 (m, 3 H, 3-H, 2 × H-6), 3.67 (t, 1 H, *J* = 9.0 Hz, H-4), 3.52–3.50 (m, 1 H, H-5), 3.35 (dd, 1 H, *J* = 9.0 Hz, 17.6 Hz, H-2), 2.78 (br s, 1 H, OH), 2.30 (s, 3 H, SPhCH_3).
Compound (**10**): colorless solid; mp 176–179 °C; $[\alpha]_D^{25}$ +43.3 (*c* 0.12, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 7.49–7.26 (m, 20 H, Ar*H*), 5.89–5.80 (m, 1 H, CH_2CH=CH_2), 5.42 (s, 1 H, C*H*Ph), 5.28–5.20 (m, 2 H, CH_2CH=CH_2), 4.95–4.55 (m, 10 H, H-1, 2 × CH_2Ph, CH_2Ph, 2 × CH_2CCl_3), 4.29 (d, 1 H, *J* = 12.1 Hz, CH_2Ph), 4.13–3.95 (m, 5 H, CH_2CH=CH_2, H-2, H-1′, H-3′), 3.76–3.44 (m, 6 H, H-6′, H-2′, H-4′, H-3, H-5, H-6), 3.20–3.11 (m, 3 H, H-4, H-5′, H-6′). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 54.6, 57.4, 65.4, 66.8, 68.4, 68.5, 70.2, 73.6, 73.9, 74.5, 76.5, 77.7, 78.0, 82.1, 95.4, 95.5, 96.7, 100.9, 101.1, 118.2, 126.0, 127.2, 127.8, 128.2, 128.3, 128.4, 129.0, 129.8, 133.2, 137.2, 137.7, 138.2, 138.9, 154.0, 154.1. HRMS (ESI-TOF): *m/z* calcd for $C_{49}H_{52}Cl_6N_2O_{13}Na$: 1109.1492; found: 1109.1493.
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(42) **General Procedure for the Isomerization**
To a solution of compound **5** or **11** (0.14 mmol) and $Pd(PPh_3)_4$ (8 mg, 5 mol%) in dry CH_2Cl_2 (3.2 mL) was added TES (27 μL, 0.17 mmol). After stirring for 24 h at r.t., the reaction mixture was quenched with sat. aq solution of $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine (1 mL), dried over Na_2SO_4, and

concentrated under reduced pressure.

Selected Spectroscopic Data

Compound (**13**): ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C): δ = 7.52–7.28 (m, 10 H, Ar*H*), 6.01 (d, 1 H, *J* = 4.4 Hz, C*H*=CHCH$_3$), 5.59 (s, 1 H, C*H*Ph), 5.25 (d, 1 H, *J* = 9.3 Hz, NH), 5.04 (d, 1 H, *J* = 3.6 Hz, H-1), 4.95–4.90 (m, 1 H, CH_2Ph), 4.67–4.59 (m, 2 H, CH_2Ph, CH=C*H*CH$_3$), 4.34–4.25 (m, 2 H, H-5, H-6), 3.84–3.74 (m, 4 H, H-3, H-2, H-4, H-6), 1.91 (s, 3 H, COCH_3), 1.54 (d, *J* = 6.9 Hz, 3 H, CH=CHCH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 23 °C): δ = 10.5, 23.2, 52.4, 63.4, 69.7, 68.8, 74.0, 75.4, 82.7, 98.1, 101.2, 104.8, 125.9, 127.6, 127.8, 128.1, 128.2, 128.4, 128.9, 137.2, 138.3, 141.5, 169.9. HRMS–FAB: *m/z* calcd for $C_{25}H_{29}NO_6Na$: 462.1887; found: 462.1658.