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Palladium-catalysed C–C coupling reactions in the enantioselective synthesis of 2,4-disubstituted 4,5-dehydropiperidines using galactosylamine as a stereodifferentiating auxiliary

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Abstract—Stereoselective synthesis of enantiomerically pure 2,4-disubstituted piperidine derivatives, which are considered interesting pharmacophoric structures, was achieved starting with a tandem Mannich–Michael reaction sequence on *O*-pivaloylated *N*-galactosyl aldimines. Subsequent conversion of the thus formed 2-substituted dehydropiperidinones into the corresponding enol triflates was carried out by conjugate hydride addition and trapping the enolate with *N*,*N*-bis(trifluoromethanesulfonyl)aniline. Their Suzuki–Miyaura coupling with aryl and heteroaryl boronic acids was performed under conditions compatible with the carbohydrate structure, in particular, with the sensitive *N*-glycosidic bond.

1. Introduction

Substituted piperidines are important pharmacophoric structures since they enable the development of efficient ligands for quite a number of receptors and enzymes.[1] There have been numerous reports on the synthesis of substituted piperidines in the literature,[2,3] but not surprisingly 1,4-substitution of the piperidine ring dominates due to the ease of synthesis and the absence of complicating stereochemical issues.[4] Over the recent years, several commercial drugs have appeared that possess the 1,4-substitution pattern as the common motif (Fig. 1). Risperdal® (risperidone, **1**) is an antipsychotic drug used for treatment of schizophrenia.[5] Naramig® (naratriptan, **2**), an agonist of serotonin receptors 5-HT_{1D} and 5-HT_{1B}, is applied to treat migraine.[6] Finally, Aricept® (donepezil, **3**), a cholinesterase inhibitor,[7] is currently being prescribed for the treatment of Alzheimer's disease.

In preceding work,[8–10] we described the stereoselective synthesis of 2-substituted 5,6-dehydropiperidin-4-ones using galactosylamine **4** as a diastereodifferentiating auxiliary. As an extension of this methodology, we have developed a general method to install functionality at the 4-position of the piperidine ring structure. As few methods have been reported for the synthesis of 2,4-disubstituted piperidine derivatives,[4,11–15] we considered these attractive compounds, containing additional structural information compared to the 1,4-disubstituted derivatives shown in Figure 1, as interesting targets for stereoselective syntheses.

2. Results and discussion

The synthesis of these 2,4-disubstituted dehydropiperidines begins with the condensation of 2,3,4,6-tetra-*O*-β-D-galactosylamine **4** and an aldehyde to give the corresponding Schiff bases **5** with the *trans* configuration at the imine double bond.[16] This method was extended to halogen-substituted phenyl acetaldehydes that required a variation in the choice of solvent. Instead of pentane, isopropyl alcohol proved to be suitable for the dehydrating reaction conditions commonly used in the synthesis of aliphatic *N*-galactosyl imines **5**. Furthermore, the formation of the undesired enamine was not detected. The aldimines **5** were reacted with 1-methoxy-3-trimethylsilyloxy-butadiene **6** (Danishefsky's

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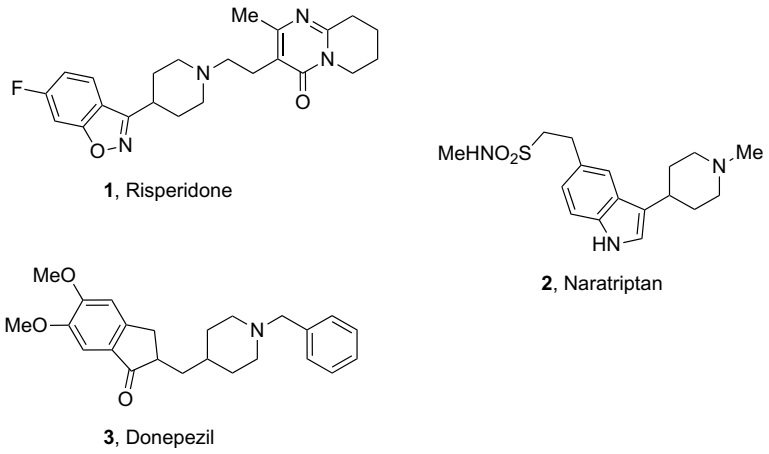
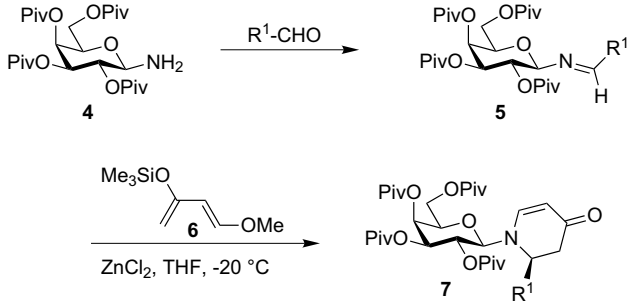


Figure 1. Drug launches containing a 1,4-disubstituted piperidine ring as structural feature.

diene) to form 2-substituted dehydropiperidinones **7** with high diastereoselectivity (Scheme 1).[8,9]



Scheme 1. Diastereoselective synthesis of dehydropiperidinones **7**.

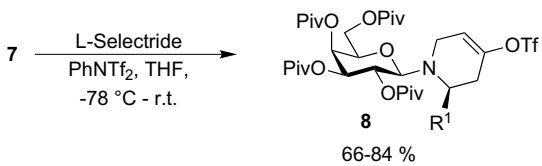
In this tandem Mannich–Michael reaction the Lewis acid plays a decisive role. It increases the electrophilic reactivity of the imine and coordinates both the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group of the carbohydrate auxiliary. This leads to efficient shielding of the (*Re*)-face of the imine. Therefore, the nucleophilic attack occurs preferentially from the less hindered (*Si*)-face. Thus, the 2-substituted dehydropiperidinones **7** were obtained in excellent diastereoselectivity (Table 1). Pure diastereomers of the chiral piperidinone derivatives were obtained following flash chromatography. Diastereoselectivity in the synthesis of the benzyl-substituted dehydropiperidinones **7e**–**g** increases slightly with the size of the halogen substituent. The lower yields obtained for the 2-chloro-**7e** and 2-iodo-benzyl **7g** derivatives resulted from impurities that could not be separated from the phenyl acetaldehydes as the starting materials.

Table 1. Stereoselective synthesis of 2-substituted *N*-galactosyl dehydropiperidinones **7**

Compound	R^1	Yield [%]	D.r.[a] (*S*):(*R*)
7a	*n*Pr	96	3:97[b]
7b	*i*Pr	84	96:4
7c	4-Cl–Ph	89	98:2
7d	3-Pyridyl	63	97:3
7e	2-Cl–Bn	53	10:90[b]
7f	2-Br–Bn	70	6:94[b]
7g	2-I–Bn	32	5:95[b]

[a] Determined by analytical HPLC of the crude product.
[b] Reversal of the configuration due to the lower priority of substituent R.

To target the carbonyl functionality in the 4-position we took advantage of the enone conjugation. Chemoselective hydride transfer to the C=C double bond was carried out using the sterically demanding boron hydride reagent L-Selectride®. Subsequent trapping of the generated enolate with *N*,*N*-bis(trifluoromethanesulfonyl)aniline ($PhNTf_2$) leads to the regioselective formation of *N*-galactosyl 4-triflyl 4,5-dehydropiperidines **8** (Scheme 2). Prior work on the formation of these heterocyclic enol triflates tended to hydrogenate the carbonyl moiety of piperidin-4-ones to obtain saturated 2-substituted piperidines.[9,17] The formation of regioisomers as described by Garbaccio et al. (application of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine as sulfonation reagent) was not observed.[18] Even after warming to ambient temperature to complete sulfonation of the enolate intermediate, that required generation at −78 °C to prevent 1,2-addition, no 3,4-dehydro isomer could be detected. The *N*-galactosyl enol triflates **8** possess an astonishing stability towards hydrolysis. These compounds could be isolated by flash chromatography on silica gel. If no further purification was carried out, following conversions suffered from remaining traces of the sulfonation reagent.

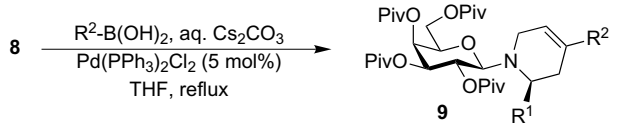


Scheme 2. Regioselective formation of 4-triflyl-4,5-dehydropiperidines **8**.

By this procedure, a variety of enol triflates of *N*-glycosyl piperidine derivatives are accessible, which are suit-

able for transition metal-catalysed C–C-bond formation reactions, particularly for the Suzuki–Miyaura cross-coupling.[19] The cross-coupling of organic triflates is well known,[20–23] and offers a general access to insert aryl-, alkenyl- and even alkyl-substituents.[24]

The coupling of phenyl and heteroaryl boronic acids to *N*-galactosyl enol triflates **8** gave 2,4-disubstituted 4-aryl 4,5-dehydropiperidines **9** (Scheme 3). For all boronic acid derivatives (except 3,5-dimethyl-isoxazol-4-boronic acid) bis(triphenylphosphine)palladium(II) chloride [$Pd(PPh_3)_2Cl_2$] in combination with aqueous caesium carbonate as the base and THF as the solvent proved to be successful and led to the desired cross-coupled products in good yields (Table 2). Several catalytic systems were investigated for the analogous conversion of the isoxazole-derived boronic acid, but none was capable to promote this cross-coupling reaction. Tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] showed low reactivity for the employed substrates. When 1,1′-bis(diphenylphosphino)ferrocene palladium(II) chloride [$Pd(dppf)Cl_2$] was used as the catalyst instead of $Pd(PPh_3)_2Cl_2$ under similar conditions, the yield decreased (see yields in parentheses in Table 2). In general, the reaction of electron-poor heterocyclic boronic acids, such as pyrimidine-5- and pyridine-3-boronic acid, proceeded in high conversion rates. However, the reaction with the electron-rich isoxazole-boronic acid failed.



Scheme 3. Suzuki–Miyaura cross-coupling reaction on *N*-galactosyl enol triflates **8**.

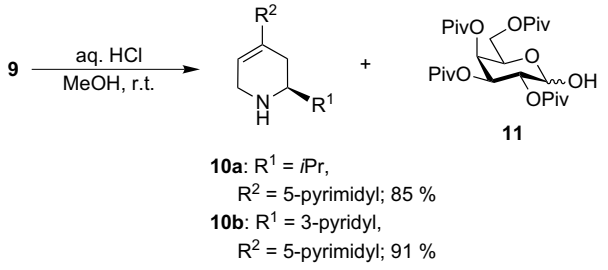
Table 2. Palladium-catalysed cross-coupling to yield 2,4-disubstituted dehydropiperidines **9**

Compound	R^1	R^2	Time [h]	Yield [%]
9a	*n*Pr	5-Pyrimidine	16	83
9b	*n*Pr	8-Chinoline	16	72
9c	*n*Pr	3-Pyridine	19	83
9d	*n*Pr	Ph	16	64
9e	*i*Pr	5-Pyrimidine	22	64
9f	*i*Pr	4-(3,5-dimethyl-isoxazol)	20	—
9g	4-Cl–Ph	5-Pyrimidine	15	69 (38)[a]
9h	4-Cl–Ph	8-Chinoline	21	66 (66)[b]
9i	4-Cl–Ph	4-(3,5-dimethyl-isoxazol)	16	—
9j	3-Pyridyl	5-Pyrimidine	17	90 (71)[b]
9k	3-Pyridyl	8-Chinoline	16	71 (65)[b]
9l	3-Pyridyl	3-Pyridine	19	79
9m	3-Pyridyl	Ph	16	79
9n	2-Cl–Bn	5-Pyrimidine	16	57

[a] Yield in parentheses when $Pd(PPh_3)_4$/LiCl/aq Na_2CO_3 was used as catalytic system.

[b] Yields in parentheses when $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ was used instead of $Pd(PPh_3)_2Cl_2$.

Cleavage of the *N*-glycosidic bond was readily achieved by treatment of the dehydropiperidines **9** with dilute HCl in methanol at ambient temperature (Scheme 4). The heterocycles **10** were separated from the hemiacetal of the carbohydrate auxiliary **11**, which was quantitatively recovered. After neutralisation, the 2,4-disubstituted 4,5-dehydropiperidines **10** were obtained in high yields and in an enantiomerically pure form.



Scheme 4. Detachment of the 2,4-disubstituted piperidine derivatives **10** from the carbohydrate scaffold.

3. Conclusion

The described results show that the efficient diastereodifferentiation achieved with *N*-glycosyl aldimines in tandem Mannich–Michael reaction sequences with silyl dienol ethers giving 2-substituted dehydropiperidinones can be exploited to a highly stereoselective synthesis of enantiomerically pure 2,4-disubstituted piperidine derivatives. Conjugate hydride addition to these dehydropiperidinones and trapping of the intermediate enolate with *N*,*N*-bis(trifluoromethanesulfonyl)aniline gave the enol triflates, which proved efficient components in Suzuki–Miyaura cross-coupling reactions. Neither the carbohydrate structure nor the sensitive *N*-glycosidic bond is affected under the required reaction conditions. The products thus obtained are considered interesting pharmacophoric groups. They are also promising substrates for further derivatisations, for example, at the C=C double bond. The scope of the methodology described herein can be expanded to stereoselective syntheses of piperidine derivatives with opposite enantiomeric configuration by using *O*-pivaloylated D-arabinopyranosylamine as an auxiliary virtually enantiomeric to the D-galactosylamine.[26]

4. Experimental section

4.1. Instruments

^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200, AC-300 and AM-400 spectrometers. Mass spectra were recorded on a Navigator-1 ESI mass spectrometer (ThermoQuest). Accurate mass spectra (HRMS) were measured on a Waters Q-TOF-Ultima 3 with a lockspray interface, using NaICsI clusters as external reference. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter. Thin layer chromatography was performed on Merck TLC plates

silica gel 60 F_{254}. Flash chromatography was carried out on ICN Biomedicals silica gel (40–63 μm mesh). Analytical HPLC runs were performed with a Phenomenex Luna C-18 (2) column (5μ, 250 × 4.6 mm) using MeCN/H_2O mixtures.

4.2. Materials

THF was distilled over potassium benzophenone ketyl. Aldehydes used for imine formation were distilled and stored at 4 °C. Diene **6** was prepared by the procedure of Danishefsky and Kitahara followed by repeated careful distillation at moderate temperature (oil bath temperature has to be kept below 70 °C).[25] Schiff bases **5** were prepared according to known procedures for aliphatic/benzylic and aromatic aldehydes.[16] $Pd(PPh_3)_2Cl_2$ and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ were purchased from Acros Organics. THF and aqueous alkaline solutions applied in Suzuki reactions were degassed in an ultrasonic bath under argon atmosphere for at least 4 h.

4.3. General procedure for the synthesis of *N*-galactosyl dehydropiperidinones 7

To a solution of glycosyl imine **5** (10 mmol) in dry THF (50 mL), a solution of $ZnCl_2$ (1 M in THF/CH_2Cl_2 (1:1), 11 mL) was added at −78 °C and stirred for 10 min. Danishefsky's diene **6** (2.5 mL, 12.5 mmol) was added, and after stirring for 30 min the mixture was allowed to warm up to −20 °C. The reaction was terminated by the addition of 1 M HCl (10 mL) after complete consumption of the starting material (TLC monitoring, 1–2 d). THF was evaporated in vacuo, diethyl ether (200 mL) was added and the layers were separated. The organic layer was washed with saturated aq $NaHCO_3$ (2 × 50 mL), 10% aq Titriplex®III (50 mL), and brine (50 mL), dried over $MgSO_4$ and concentrated.

4.3.1. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-5,6-dehydro-piperidin-4-one 7a. Purification by flash chromatography (petroleum ether/ethyl acetate (3:1)); yield: 96%; orange amorphous solid; R_f = 0.18 (petroleum ether/ethyl acetate (3:1)); Lit.:[9] $[\alpha]_D^{22} = -73.5$ (*c* 1.0, $CHCl_3$); d.r. 3:97 (analytical HPLC); ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.30 (d, 1H, ^3J = 7.4 Hz, NC*H*=CH); 5.53 (t, 1H, ^3J = 9.0 Hz, H-2); 5.47 (d, 1H, ^3J = 3.1 Hz, H-4); 5.33 (dd, 1H, ^3J = 3.1, ^3J = 10.2 Hz, H-3); 5.01 (d, 1H, ^3J = 9.0 Hz, H-1); 4.90 (d, 1H, ^3J = 7.4 Hz, NCH=C*H*); 4.31–4.20 (m, 2H, H-5, H-6b); 4.00 (dd, 1H, ^3J = 6.2, ^2J = 10.6 Hz, H-6a); 3.83–3.80 (m, 1H, CHN); 2.64 (dd, 1H, ^3J = 6.4, ^2J = 16.6 Hz, CH_2C=O); 2.32 (d, 1H, ^2J = 16.8 Hz, CH_2C=O); 1.91–1.87 (m, 1H, CH_2); 1.71–1.68 (m, 1H, CH_2); 1.41–1.38 (m, 1H, CH_2); 1.33–1.21 (m, 10H, PivCH_3, CH_2); 1.17, 1.14, 1.12 (3s, 27H, PivCH_3); 0.94 (t, 3H, ^3J = 7.4 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 193.31 (C=O); 177.56, 177.23, 176.87, 176.56 (PivC=O); 152.57 (N*C*H=CH); 97.76 (NCH=*C*H); 90.83 (C-1); 72.56, 71.28, 66.91, 66.22 (C-2, C-3, C-4, C-5); 60.70 (C-6); 52.37 (CHN); 38.71, 38.54, 38.37, 38.31 (Piv*C*Me_3); 37.93 (*C*H_2C=O); 32.40 (CH_2); 26.24, 26.21, 26.16, 26.04 (PivCH_3); 18.60 (CH_2); 12.85 (CH_3) ppm; MS (ES^+): *m*/*z* 638.5 $[M+H]^+$, 660.5 $[M+Na]^+$.

4.3.2. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-isopropyl-5,6-dehydro-piperidin-4-one 7b. Purification by flash chromatography (cyclohexane/ethyl acetate (3:1)); yield: 84%; yellow amorphous solid; R_f = 0.19 (cyclohexane/ethyl acetate (2:1)); Lit.:[9] $[\alpha]_D^{22} = -69.8$ (*c* 1.0, $CHCl_3$); d.r. 96:4 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.00 (d, 1H, ^3J = 7.8 Hz, NC*H*=CH); 5.56 (t, 1H, ^3J = 9.8 Hz, H-2); 5.42 (d, 1H, ^3J = 2.9 Hz, H-4); 5.16 (dd, 1H, ^3J = 2.9, ^3J = 9.8 Hz, H-3); 4.95 (d, 1H, ^3J = 7.3 Hz, NCH=C*H*); 4.60 (d, 1H, ^3J = 8.8 Hz, H-1); 4.16 (dd, 1H, ^3J = 5.4, ^2J = 8.8 Hz, H-6a); 4.05–3.91 (m, 2H, H-5, H-6a); 3.58–3.49 (m, 1H, CHN); 2.60 (dd, 1H, ^3J = 7.3, ^2J = 17.0 Hz, CH_2C=O); 2.41 (dd, 1H, ^3J = 6.5, ^2J = 17.0 Hz, CH_2C=O); 2.36–2.19 (m, 1H, C*H*$(CH_3)_2$); 1.27, 1.16, 1.11, 1.10 (4s, 36H, PivCH_3); 0.91 (d, 6H, ^3J = 6.8 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 192.48 (C=O); 177.72, 177.13, 176.98, 176.48 (PivC=O); 149.94 (N*C*H=CH); 100.58 (NCH=*C*H); 90.98 (C-1); 72.78, 71.61, 66.56, 65.59 (C-2, C-3, C-4, C-5); 60.95 (C-6); 58.93 (CHN); 39.03, 38.87, 38.72, 38.65 (Piv*C*Me_3); 35.71 (*C*H_2C=O); 31.76 (*C*H$(CH_3)_2$); 27.10, 27.08, 26.98 (PivCH_3); 19.63, 17.71 (CH_3) ppm; MS (ES^+): *m*/*z* 536.7 $[M-PivOH+H]^+$, 558.7 $[M-PivOH+Na]^+$, 638.6 $[M+H]^+$, 660.6 $[M+Na]^+$.

4.3.3. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(4-chlorophenyl)-5,6-dehydro-piperidin-4-one 7c. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 89%; yellow amorphous solid; R_f = 0.27 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = +15.6$ (*c* 1.0, $CHCl_3$); d.r. 98:2 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.31–7.20 (m, 5H, Ar, NC*H*=CH); 5.56 (t, 1H, ^3J = 9.4 Hz, H-2); 5.31 (d, 1H, ^3J = 2.9 Hz, H-4); 5.20 (d, 1H, ^3J = 7.8 Hz, NCH=C*H*); 5.01 (dd, 1H, ^3J = 3.2, ^3J = 10.0 Hz, H-3); 4.80 (dd, 1H, ^3J = 5.9, ^3J = 8.3 Hz, CHN); 4.34 (d, 1H, ^3J = 9.3 Hz, H-1); 3.93–3.70 (m, 3H, H-5, H-6a, H-6b); 2.77 (dd, 1H, ^3J = 5.9, ^2J = 16.6 Hz, CH_2C=O); 2.62 (dd, 1H, ^3J = 8.8, ^2J = 16.6 Hz, CH_2C=O); 1.23, 1.15, 1.14, 1.08 (4s, 36H, PivCH_3) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 191.17 (C=O); 177.72, 177.34, 177.07, 176.44 (PivC=O); 149.74 (N*C*H=CH); 137.28, 134.38 (*ipso*-aryl); 128.47, 129.09 (aryl); 103.26 (NCH=*C*H); 88.72 (C-1); 72.76, 71.39, 66.63, 65.24 (C-2, C-3, C-4, C-5); 61.01 (C-6); 59.05 (CHN); 43.57 (*C*H_2C=O); 39.07, 38.94, 38.78, 38.69 (Piv*C*Me_3); 27.05, 27.18 (PivCH_3) ppm; MS (ES^+): *m*/*z* 706.5 $[M+H]^+$, 728.5 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{37}H_{52}ClNO_{10}$ (706.26): C 62.92, H 7.42, N 1.98; found: C 62.86, H 7.45, N 1.95.

4.3.4. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-5,6-dehydro-piperidin-4-one 7d. Purification by flash chromatography (cyclohexane/ethyl acetate (1:1)); yield: 63%; yellowish amorphous solid; R_f = 0.10 (cyclohexane/ethyl acetate (1:1)); Lit.:[9] $[\alpha]_D^{22} = +19.6$ (*c* 3.0, $CHCl_3$); d.r. 97:3 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.56 (s, 1H, aryl); 8.54 (d,

1H, ^3J = 4.8 Hz, aryl); 7.72 (d, 1H, ^3J = 8.1 Hz, aryl); 7.29 (dd, 1H, ^3J = 5.0, ^3J = 7.9 Hz, aryl); 7.21 (d, 1H, ^3J = 8.1 Hz, NC*H*=CH); 5.56 (t, 1H, ^3J = 9.7 Hz, H-2); 5.32 (d, 1H, ^3J = 2.9 Hz, H-4); 5.16 (d, 1H, ^3J = 7.8 Hz, NCH=C*H*); 5.09 (dd, 1H, ^3J = 2.9, ^3J = 9.9 Hz, H-3); 4.94 (t, 1H, ^3J = 5.9, CHN); 4.52 (d, 1H, ^3J = 9.2 Hz, H-1); 3.85 (t, 1H, ^3J = 6.6 Hz, H-5); 3.77 (dd, 1H, ^3J = 6.4, ^2J = 10.8 Hz, H-6a); 3.68 (dd, 1H, ^3J = 7.4, ^2J = 11.0 Hz, H-6b); 2.96 (dd, 1H, ^3J = 6.6, ^2J = 16.5 Hz, CH_2C=O); 2.59 (dd, 1H, ^3J = 5.1, ^2J = 16.5 Hz, CH_2C=O); 1.22, 1.14, 1.10, 1.08 (4s, 36H, PivCH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 190.36 (C=O); 177.58, 177.20, 176.99, 176.34 (PivC=O); 150.18 (N*C*H=CH); 149.52, 148.36 (aryl); 135.16 (*ipso*-aryl); 134.09, 123.26 (aryl); 102.48 (NCH=*C*H); 90.16 (C-1); 72.73, 71.04, 66.38, 65.39 (C-2, C-3, C-4, C-5); 60.65 (C-6); 55.90 (CHN); 42.97 (*C*H_2C=O); 38.99, 38.93, 38.73, 38.60 (Piv*C*Me_3); 27.14, 26.99, 26.96 (PivCH_3) ppm; MS (ES^+): *m/z* 673.4 $[M+H]^+$, 695.3 $[M+Na]^+$, 736.4 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{36}H_{53}N_2O_{10}$ (M+H): 673.3700; found: 673.3704.

4.3.5. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-chlorobenzyl)-5,6-dehydro-piperidin-4-one 7e. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 53%; yellowish amorphous solid; R_f = 0.13 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -10.2$ (*c* 1.0, $CHCl_3$); d.r. 10:90 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.30 (m, 1H, aryl); 7.19–7.16 (m, 1H, aryl); 7.12–7.09 (m, 1H, aryl); 6.95 (dd, 1H, ^4J = 0.7, ^3J = 7.7 Hz, NC*H*=CH); 5.51 (t, 1H, ^3J = 9.5 Hz, H-2); 5.47 (d, 1H, ^3J = 3.3 Hz, H-4); 5.20 (dd, 1H, ^3J = 3.3, ^3J = 10.3 Hz, H-3); 5.08 (d, 1H, ^3J = 7.7 Hz, NCH=C*H*); 4.60 (d, 1H, ^3J = 9.2 Hz, H-1); 4.22–4.17 (m, 1H, CHN); 4.16 (dd, 1H, ^3J = 6.1, ^2J = 10.1 Hz, H-6a); 4.07 (t, 1H, ^3J = 6.4 Hz, H-5); 3.98 (dd, 1H, ^3J = 7.0, ^2J = 9.9 Hz, H-6b); 3.26 (dd, 1H, ^3J = 4.8, ^2J = 13.2 Hz, CH_2–ClPh); 3.12 (dd, 1H, ^3J = 10.7, ^2J = 13.2 Hz, CH_2–ClPh); 2.46 (dd, 1H, ^3J = 6.3, ^2J = 16.9 Hz, CH_2C=O); 2.10 (d, 1H, ^2J = 16.9 Hz, CH_2C=O); 1.29, 1.15, 1.10, 1.09 (4s, 36H, PivCH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 191.65 (C=O); 177.75, 177.09, 176.96, 176.69 (PivC=O); 149.17 (N*C*H=CH); 134.78, 134.29 (*ipso*-aryl); 132.53, 129.57, 128.37, 127.04 (aryl); 100.51 (NCH=*C*H); 91.86 (C-1); 73.27, 71.23, 66.41, 66.13 (C-2, C-3, C-4, C-5); 60.78 (C-6); 52.12 (CHN); 39.05, 38.90, 38.76, 38.67 (Piv*C*Me_3); 38.17 (*C*H_2C=O); 34.30 (*C*H_2–ClPh); 27.19, 27.16, 27.05, 27.01 (PivCH_3) ppm; MS (ES^+): *m/z* 720.4 $[M+H]^+$, 742.4 $[M+Na]^+$, 783.5 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{55}ClNO_{10}$ (M+H): 720.3515; found: 720.3510.

4.3.6. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-bromobenzyl)-5,6-dehydro-piperidin-4-one 7f. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 70%; yellowish amorphous solid; R_f = 0.15 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -5.0$ (*c* 1.0, $CHCl_3$); d.r. 6:94 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.52 (d, 1H, ^3J = 8.1 Hz, aryl); 7.23 (dt, 1H, ^3J = 1.1, ^3J = 7.4 Hz, aryl); 7.12–7.06 (m, 2H, aryl); 6.95 (d, 1H, ^3J = 7.7 Hz, NC*H*=CH); 5.52 (t, 1H, ^3J = 9.7 Hz, H-2); 5.47 (d, 1H, ^3J = 2.6 Hz, H-4); 5.20 (dd, 1H, ^3J = 3.3, ^3J = 10.3 Hz, H-3); 5.09 (d, 1H, ^3J = 7.7 Hz, NCH=C*H*); 4.61 (d, 1H, ^3J = 9.2 Hz, H-1); 4.24–4.16 (m, 1H, CHN); 4.13 (dd, 1H, ^3J = 5.9, ^2J = 9.9 Hz, H-6a); 4.06 (t, 1H, ^3J = 6.6 Hz, H-5); 3.96 (dd, 1H, ^3J = 6.6, ^2J = 9.9 Hz, H-6b); 3.23 (dd, 1H, ^3J = 5.2, ^2J = 13.2 Hz, CH_2–BrPh); 3.14 (dd, 1H, ^3J = 10.3, ^2J = 13.2 Hz, CH_2–BrPh); 2.48 (dd, 1H, ^3J = 7.0, ^2J = 17.3 Hz, CH_2C=O); 2.11 (d, 1H, ^2J = 16.9 Hz, CH_2C=O); 1.29, 1.25, 1.10, 1.09 (4s, 36H, PivCH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 191.66 (C=O); 177.75, 177.11, 176.96, 176.66 (PivC=O); 148.96 (N*C*H=CH); 136.53 (*ipso*-aryl); 132.89, 132.50, 128.61, 127.64 (aryl); 124.78 (*ipso*-CBr); 100.62 (NCH=*C*H); 91.66 (C-1); 73.27, 71.29, 66.41, 66.10 (C-2, C-3, C-4, C-5); 60.77 (C-6); 52.42 (CHN); 39.05, 38.91, 38.76, 38.67 (Piv*C*Me_3); 38.20 (*C*H_2C=O); 36.55 (*C*H_2–BrPh); 27.25, 27.16, 27.07, 27.02 (PivCH_3) ppm; MS (ES^+): *m/z* 764.2 $[M(^{79}Br)+H]^+$, 766.2 $[M(^{81}Br)+H]^+$, 786.3 $[M(^{79}Br)+Na]^+$, 788.3 $[M(^{81}Br)+Na]^+$, 827.4 $[M(^{79}Br)+CH_3CN+Na]^+$, 829.4 $[M(^{81}Br)+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{54}BrNNaO_{10}$ (M+Na): 786.2829; found: 786.2806.

4.3.7. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-iodobenzyl)-5,6-dehydro-piperidin-4-one 7g. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 32%; yellow amorphous solid; R_f = 0.13 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -0.8$ (*c* 1.0, $CHCl_3$); d.r. 5:95 (analytical HPLC); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80 (d, 1H, ^3J = 7.8 Hz, aryl); 7.26 (t, 1H, ^3J = 7.4 Hz, aryl); 7.10 (dd, 1H, ^4J = 1.4, ^3J = 7.6 Hz, aryl); 6.97 (d, 1H, ^3J = 7.4 Hz, NC*H*=CH); 6.92 (dt, 1H, ^4J = 1.4, ^3J = 7.6 Hz, aryl); 5.53 (t, 1H, ^3J = 9.8 Hz, H-2); 5.45 (d, 1H, ^3J = 3.1 Hz, H-4); 5.19 (dd, 1H, ^3J = 3.3, 10.0 Hz, H-3); 5.11 (d, 1H, ^3J = 7.4 Hz, NCH=C*H*); 4.67 (d, 1H, ^3J = 9.0 Hz, H-1); 4.18–4.12 (m, 1H, CHN); 4.11–4.03 (m, 2H, H-5, H-6a); 3.94 (dd, 1H, ^3J = 6.3, ^2J = 9.8 Hz, H-6b); 3.16 (d, 2H, ^3J = 8.6 Hz, CH_2–IPh); 2.52 (dd, 1H, ^3J = 6.7, ^2J = 16.8 Hz, CH_2C=O); 2.14 (d, 1H, ^2J = 16.8 Hz, CH_2C=O); 1.28, 1.15, 1.11, 1.05 (4s, 36H, PivCH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 191.59 (C=O); 177.76, 177.17, 176.99, 176.61 (PivC=O); 148.32 (N*C*H=CH); 139.93 (*ipso*-aryl); 139.65, 131.52, 128.75, 128.49 (aryl); 100.90 (*ipso*-CI); 100.86 (NCH=*C*H); 91.18 (C-1); 73.26, 71.49, 66.44, 65.99 (C-2, C-3, C-4, C-5); 60.80 (C-6); 53.25 (CHN); 40.73 (*C*H_2C=O); 39.09, 38.94, 38.79, 38.70 (Piv*C*Me_3); 38.30 (*C*H_2–ClPh); 27.32, 27.19, 27.08, 27.04 (PivCH_3) ppm; MS (ES^+): *m/z* 812.6 $[M+H]^+$, 834.6 $[M+Na]^+$, 875.5 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{54}INNaO_{10}$ (M+Na): 834.2690; found: 834.2684.

4.4. General procedure for the conjugated hydride addition and subsequent formation of the enol triflates 8

To a solution of enone **7** (1.0 mmol) and *N*,*N*-bis(trifluoromethanesulfonyl)aniline (1.1 mmol) in dry THF (20 mL), a 1 M solution of L-Selectride® in THF (1.1 mmol) was added dropwise at −78 °C. After 1 h,

the solution was allowed to warm up to ambient temperature and stirred for another hour. The solvent was evaporated in vacuo; the residue was dissolved in diethyl ether (25 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo to give crude **8** which was further purified.

4.4.1. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8a. Purification by flash chromatography (cyclohexane/ethyl acetate (10:1)); yield: 75%; colourless oil; $R_f = 0.62$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -10.5$ (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 5.67 (br s, 1H, CH=COTf); 5.38–5.32 (m, 2H, H-2, H-4); 5.10 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.20 (d, 1H, ^3J = 9.2 Hz, H-1); 4.05 (dd, 1H, ^3J = 6.1, ^2J = 10.5 Hz, H-6a); 3.92–3.82 (m, 2H, H-5, H-6b); 3.57 (dd, 1H, ^3J = 2.6, ^2J = 17.6 Hz, NCH_2); 3.41 (d, 1H, ^2J = 16.9 Hz, NCH_2); 3.16–3.14 (m, 1H, CHN); 2.56 (dd, 1H, ^3J = 2.6, ^2J = 16.5 Hz, $CHCH_2$); 2.04 (d, 1H, ^2J = 16.5 Hz, $CHCH_2$); 1.64–1.50 (m, 1H, CH_2); 1.40–1.26 (m, 3H, CH_2); 1.23, 1.14, 1.10, 1.08 (4s, 36H, $PivCH_3$); 0.88 (t, 3H, ^3J = 7.0 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.82, 177.18, 177.11, 176.66 (PivC=O); 146.58 (CH=*C*OTf); 116.18 (*C*H=COTf); 92.56 (C-1); 71.80, 67.09, 65.41 (C-2, C-3, C-4, C-5); 61.48 (C-6); 55.37 (CHN); 41.71 (NCH_2); 39.00, 38.70, 38.66 (Piv*C*Me_3); 33.61 ($CHCH_2$); 32.74 (CH_2); 27.13, 27.02 ($PivCH_3$); 19.89 (CH_2); 14.08 (CH_3) ppm; MS (ES^+): m/z 622.7 $[M-OTf]^+$, 670.6 $[M-PivOH+H]^+$, 772.7 $[M+H]^+$, 794.6 $[M+Na]^+$, 835.7 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{35}H_{56}F_3NNaO_{12}S$ (M+Na): 794.3373; found: 794.3386.

4.4.2. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-isopropyl-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8b. Purification by flash chromatography (cyclohexane/ethyl acetate (4:1)); yield: 76%; colourless oil; $R_f = 0.59$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -5.8$ (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 5.67 (br s, 1H, CH=COTf); 5.38 (t, 1H, ^3J = 9.4 Hz, H-2); 5.34 (d, 1H, ^3J = 3.1 Hz, H-4); 5.10 (dd, 1H, ^3J = 3.1, ^3J = 9.8 Hz, H-3); 4.24 (d, 1H, ^3J = 9.4 Hz, H-1); 3.99 (dd, 1H, ^3J = 7.0, ^2J = 11.3 Hz, H-6a); 3.92 (dd, 1H, ^3J = 6.3, ^2J = 11.3 Hz, H-6b); 3.85 (t, 1H, ^3J = 6.6 Hz, H-5); 3.59 (d, 1H, ^2J = 17.9 Hz, NCH_2); 3.41 (dd, 1H, ^3J = 2.7, ^2J = 18.4 Hz, NCH_2); 2.67 (m, 1H, CHN); 2.55 (dd, 1H, ^3J = 2.7, ^2J = 16.4 Hz, $CHCH_2$); 2.27 (d, 1H, ^2J = 17.2 Hz, $CHCH_2$); 1.89–1.77 (m, 1H, $CH(CH_3)_2$); 1.23, 1.15, 1.11, 1.09 (4s, 36H, $PivCH_3$); 0.90 (d, 3H, ^3J = 3.1 Hz, CH_3); 0.88 (d, 3H, ^3J = 3.1 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.48, 177.28, 176.87, 176.65 (PivC=O); 146.55 (CH=*C*OTf); 116.43 (*C*H=COTf); 92.41 (C-1); 72.06 (C-3); 71.68 (C-5); 67.11 (C-4); 65.75 (C-2); 64.44 (CHN); 61.73 (C-6); 39.75 (NCH_2); 39.01, 38.72, 38.70 (Piv*C*Me_3); 28.85 ($CHCH_2$); 27.74 ($CH(CH_3)_2$); 27.17, 27.14, 27.04 ($PivCH_3$); 20.72, 18.93 (CH_3) ppm; MS (ES^+): m/z 622.7 $[M-OTf]^+$, 670.7 $[M-PivOH+H]^+$, 772.7 $[M+H]^+$, 794.7 $[M+Na]^+$, 835.8 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{35}H_{56}F_3NNaO_{12}S$ (M+Na): 794.3373; found: 794.3398.

4.4.3. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(4-chlorophenyl)-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8c. Purification by flash chromatography (cyclohexane/ethyl acetate (10:1)); yield: 72%; colourless amorphous solid; $R_f = 0.56$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -13.4$ (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, 2H, ^3J = 8.6 Hz, aryl); 7.21 (d, 2H, ^3J = 8.6 Hz, aryl); 5.82 (br s, 1H, CH=COTf); 5.42 (t, 1H, ^3J = 9.8 Hz, H-2); 5.24 (d, 1H, ^3J = 2.8 Hz, H-4); 4.84 (dd, 1H, ^3J = 2.9, ^3J = 9.9 Hz, H-3); 4.04 (dd, 1H, ^3J = 3.9, ^3J = 9.8 Hz, CHN); 3.99 (dd, 1H, ^3J = 6.6, ^2J = 11.4 Hz, H-6a); 3.88 (dd, 1H, ^3J = 6.6, ^2J = 11.3 Hz, H-6b); 3.82 (d, 1H, ^3J = 9.4 Hz, H-1); 3.75 (dd, 1H, ^3J = 1.9, ^2J = 16.8 Hz, NCH_2); 3.67 (dd, 1H, ^3J = 1.9, ^2J = 16.8 Hz, NCH_2); 3.42 (t, 1H, ^3J = 6.8 Hz, H-5); 2.74–2.68 (m, 1H, $CHCH_2$); 2.43 (d, 1H, ^2J = 16.8 Hz, $CHCH_2$); 1.23, 1.17, 1.16, 1.06 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.85, 177.20, 177.12, 176.52 (PivC=O); 145.04 (CH=*C*OTf); 137.49, 134.48 (*ipso*-aryl); 129.63, 129.21 (aryl); 116.16 (*C*H=COTf); 87.57 (C-1); 71.80 (C-3); 71.61 (C-5); 67.18 (C-4); 64.79 (C-2); 61.59 (C-6); 60.00 (CHN); 41.61 (NCH_2); 39.03, 38.76, 38.69 (Piv*C*Me_3); 36.32 ($CHCH_2$); 27.17, 27.13, 27.10, 27.01 ($PivCH_3$) ppm; MS (ES^+): m/z 690.5 $[M-OTf]^+$, 738.4 $[M-PivOH+H]^+$, 840.4 $[M+H]^+$, 862.4 $[M+Na]^+$, 903.5 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{53}ClF_3NNaO_{12}S$ (M+Na): 862.2827; found: 862.2819.2

4.4.4. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8d. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 84%; colourless amorphous solid; $R_f = 0.25$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -12.7$ (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.62 (dd, 1H, ^4J = 1.2, ^3J = 4.7 Hz, aryl); 8.55 (d, 1H, ^4J = 1.6 Hz, aryl); 7.61 (dd, 1H, ^4J = 1.6, ^3J = 7.8 Hz, aryl); 7.34 (dd, 1H, ^3J = 4.9, ^3J = 8.0 Hz, aryl); 5.85 (br s, 1H, CH=COTf); 5.44 (t, 1H, ^3J = 9.6 Hz, H-2); 5.25 (d, 1H, ^3J = 2.7 Hz, H-4); 4.86 (dd, 1H, ^3J = 3.1, ^3J = 9.8 Hz, H-3); 4.15 (dd, 1H, ^3J = 4.1, ^3J = 9.2 Hz, CHN); 3.96 (dd, 1H, ^3J = 6.4, ^2J = 11.2 Hz, H-6a); 3.91 (dd, 1H, ^3J = 7.0, ^2J = 11.0 Hz, H-6b); 3.83 (d, 1H, ^3J = 9.4 Hz, H-1); 3.79–3.66 (m, 2H, NCH_2); 3.44 (t, 1H, ^3J = 6.8 Hz, H-5); 2.77–2.71 (m, 1H, $CHCH_2$); 2.51 (d, 1H, ^2J = 16.4 Hz, $CHCH_2$); 1.23, 1.17, 1.16, 1.06 (4s, 34H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.81, 177.24, 177.12, 176.49 (PivC=O); 149.91, 149.76 (aryl); 144.88 (CH=*C*OTf); 135.69 (aryl); 134.74 (*ipso*-aryl); 123.86 (aryl); 116.36 (*C*H=COTf); 88.13 (C-1); 71.70, 67.01, 64.81 (C-2, C-3, C-4, C-5); 61.36 (C-6); 58.07 (CHN); 41.76 (NCH_2); 39.02, 38.78, 38.69, 38.66 (Piv*C*Me_3); 35.86 ($CHCH_2$); 27.16, 27.10, 27.08, 26.99 ($PivCH_3$) ppm; MS (ES^+): m/z 657.6 $[M-OTf]^+$, 705.4 $[M-PivOH+H]^+$, 807.6 $[M+H]^+$, 829.6 $[M+Na]^+$, 870.5 $[M+CH_3CN+Na]^+$; HRMS:

calcd for $C_{37}H_{53}F_3N_2NaO_{12}S$ (M+Na): 829.3169; found: 829.3160.

4.4.5. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-chlorobenzyl)-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8e. Purification by flash chromatography (cyclohexane/ethyl acetate (5:1)); yield: 66%; yellow amorphous solid; $R_f = 0.56$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = +10.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.36–7.33$ (m, 1H, aryl); 7.20–7.15 (m, 3H, aryl); 5.78 (t, 1H, $^3J = 2.2$ Hz, CH=COTf); 5.44–5.37 (m, 2H, H-2, H-4); 5.16 (dd, 1H, $^3J = 3.3$, $^3J = 10.3$ Hz, H-3); 4.26 (d, 1H, $^3J = 9.2$ Hz, H-1); 4.08 (dd, 1H, $^3J = 6.4$, $^2J = 10.8$ Hz, H-6a); 3.94 (dd, 1H, $^3J = 7.4$, $^2J = 10.7$ Hz, H-6b); 3.87 (t, 1H, $^3J = 6.8$ Hz, H-5); 3.78–3.68 (m, 2H, CHN, NCH_2); 3.48 (br d, 1H, $^2J = 16.9$ Hz, NCH_2); 3.09 (dd, 1H, $^3J = 3.5$, $^2J = 13.0$ Hz, CH_2–ClPh); 2.91 (dd, 1H, $^3J = 11.0$, $^2J = 13.2$ Hz, CH_2–ClPh); 2.45–2.37 (m, 1H, $CHCH_2$); 1.96 (d, 1H, $^2J = 16.9$ Hz, $CHCH_2$); 1.27, 1.14, 1.12, 1.10 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.81$, 177.18, 177.14, 176.69 (PivC=O); 146.39 (CH=*C*OTf); 136.49, 134.26 (*ipso*-aryl); 131.40, 129.76, 128.03, 126.99 (aryl); 115.91 (*C*H=COTf); 93.40 (C-1); 72.16, 71.65, 67.03, 65.33 (C-2, C-3, C-4, C-5); 61.27 (C-6); 54.34 (CHN); 43.00 (NCH_2); 39.02, 38.72, 38.66 (Piv*C*Me_3); 34.92 (*C*H_2–ClPh); 30.99 (CH*C*H_2); 27.20, 27.17, 27.04, 26.99 ($PivCH_3$) ppm; MS (ES^+): *m*/*z* 704.5 $[M-OTf]^+$, 854.6 $[M+H]^+$, 876.6 $[M+Na]^+$; HRMS: calcd for $C_{39}H_{56}ClF_3NO_{12}S$ (M+H): 854.3164; found: 854.3163.

4.4.6. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-bromobenzyl)-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8f. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 78%; yellowish amorphous solid; $R_f = 0.57$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = +9.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.52$ (d, 1H, $^3J = 7.8$ Hz, aryl); 7.24–7.22 (m, 2H, aryl); 7.11–7.05 (m, 1H, aryl); 5.78 (t, 1H, $^3J = 1.8$ Hz, CH=COTf); 5.43–5.38 (m, 2H, H-2, H-4); 5.16 (dd, 1H, $^3J = 3.1$, $^3J = 10.2$ Hz, H-3); 4.27 (d, 1H, $^3J = 9.4$ Hz, H-1); 4.06 (dd, 1H, $^3J = 6.3$, $^2J = 10.9$ Hz, H-6a); 3.93 (dd, 1H, $^3J = 7.4$, $^2J = 11.0$ Hz, H-6b); 3.85 (t, 1H, $^3J = 6.8$ Hz, H-5); 3.79 (br d, 1H, $^2J = 17.6$ Hz, NCH_2); 3.71–3.68 (m, 1H, CHN); 3.50 (br d, 1H, $^2J = 17.6$ Hz, NCH_2); 3.08 (dd, 1H, $^3J = 3.7$, $^2J = 13.1$ Hz, CH_2–BrPh); 2.93 (dd, 1H, $^3J = 10.8$, $^2J = 13.1$ Hz, CH_2–BrPh); 2.40 (br d, 1H, $^2J = 15.7$ Hz, $CHCH_2$); 1.97 (d, 1H, $^2J = 16.8$ Hz, $CHCH_2$); 1.26, 1.14, 1.11, 1.10 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.81$, 177.21, 177.14, 176.66 (PivC=O); 146.40 (CH=*C*OTf); 138.21 (*ipso*-aryl); 133.10, 131.34, 128.25, 127.62 (aryl); 124.85 (*ipso*-CBr); 115.94 (*C*H=COTf); 93.31 (C-1); 72.12, 71.65, 67.03, 65.32 (C-2, C-3, C-4, C-5); 61.24 (C-6); 54.39 (CHN); 42.84 (NCH_2); 39.03, 38.72, 38.67 (Piv*C*Me_3); 37.34 (*C*H_2–BrPh); 31.01 (CH*C*H_2); 27.26, 27.19, 27.05 ($PivCH_3$) ppm; MS (ES^+): *m*/*z* 748.5 $[M(^{79}Br)-OTf]^+$, 750.5 $[M(^{81}Br)-OTf]^+$, 898.5 $[M(^{79}Br)+H]^+$, 900.4 $[M(^{81}Br)+H]^+$, 920.5 $[M(^{79}Br)+Na]^+$, 922.4 $[M(^{81}Br)+Na]^+$; HRMS: calcd for $C_{39}H_{55}BrF_3NNaO_{12}S$ (M+Na): 920.2478; found: 920.2499.

4.4.7. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-iodobenzyl)-4-(trifluoro-methanesulfonyloxy)-4,5-dehydro-piperidine 8g. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 82%; yellowish amorphous solid; $R_f = 0.66$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = +8.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.81$ (d, 1H, $^3J = 7.7$ Hz, aryl); 7.40–7.34 (m, 1H, aryl); 7.27 (d, 1H, $^3J = 8.3$ Hz, aryl); 6.90 (dt, 1H, $^4J = 2.2$, $^3J = 7.6$ Hz, aryl); 5.79 (br s, 1H, CH=COTf); 5.45–5.39 (m, 2H, H-2, H-4); 5.16 (dd, 1H, $^3J = 3.1$, $^3J = 10.1$ Hz, H-3); 4.29 (d, 1H, $^3J = 9.2$ Hz, H-1); 4.05 (dd, 1H, $^3J = 6.4$, $^2J = 10.8$ Hz, H-6a); 3.92 (dd, 1H, $^3J = 7.5$, $^2J = 10.9$ Hz, H-6b); 3.83 (t, 1H, $^3J = 6.8$ Hz, H-5); 3.78 (d, 1H, $^2J = 17.4$ Hz, NCH_2); 3.70–3.66 (m, 1H, CHN); 3.51 (br d, 1H, $^2J = 17.3$ Hz, NCH_2); 3.08 (dd, 1H, $^3J = 3.7$, $^2J = 13.6$ Hz, CH_2–IPh); 2.92 (dd, 1H, $^3J = 10.7$, $^2J = 13.6$ Hz, CH_2–IPh); 2.41 (dd, 1H, $^3J = 2.2$, $^2J = 16.5$ Hz, $CHCH_2$); 1.98 (d, 1H, $^2J = 16.2$ Hz, $CHCH_2$); 1.25, 1.14, 1.13, 1.10 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.85$, 177.27, 177.21, 176.64 (PivC=O); 146.37 (CH=*C*OTf); 141.51 (*ipso*-aryl); 139.86, 130.33, 129.54, 128.49 (aryl); 116.03 (*C*H=COTf); 101.19 (*ipso*-CI); 93.09 (C-1); 72.01, 71.70, 67.01, 65.30 (C-2, C-3, C-4, C-5); 61.30 (C-6); 55.39 (CHN); 42.72 (NCH_2); 41.86 (CH*C*H_2); 39.03, 38.73, 38.70, 38.67 (Piv*C*Me_3); 31.11 (*C*H_2–IPh); 27.17, 27.04 ($PivCH_3$) ppm; MS (ES^+): *m*/*z* 946.4 $[M+H]^+$, 968.3 $[M+Na]^+$; HRMS: calcd for $C_{39}H_{55}F_3INNaO_{12}S$ (M+Na): 834.2690; found: 834.2704.

4.5. General procedure for the palladium-catalysed Suzuki reactions

A two-necked round bottom flask provided with a septum and a reflux condenser was charged with enol triflate **8** (1 mmol), boronic acid (2 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol %), evaporated and flushed with argon. Degassed THF (10 mL) and 2 M aq Cs_2CO_3 (5 mmol) were added by syringe and the suspension heated to reflux. After completed reaction (TLC monitoring), the accumulated colloidal palladium was filtered off (hyflo gel), the solvent evaporated in vacuo and the residue, dissolved in diethyl ether (50 mL), washed with water (10 mL) and brine (5 mL). Drying over $MgCO_3$ and concentration in vacuo gave the crude products **9**.

4.5.1. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-4-(5-pyrimidyl)-4,5-dehydro-piperidine 9a. Purification by flash chromatography (cyclohexane/ethyl acetate (5:1)); yield: 83%; colourless amorphous solid; $R_f = 0.25$ (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -23.3$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 9.05$ (s, 1H, aryl); 8.66 (s, 2H, aryl); 6.16 (br s, 1H, CH=CAr); 5.45 (t, 1H, $^3J = 9.6$ Hz, H-2); 5.37 (d, 1H, $^3J = 2.9$ Hz, H-4); 5.13 (dd, 1H, $^3J = 3.1$, $^3J = 10.1$ Hz, H-3); 4.31 (d, 1H, $^3J = 9.2$ Hz, H-1); 4.07 (dd, 1H, $^3J = 5.7$, $^2J = 9.8$ Hz, H-6a); 3.94–3.85 (m, 2H, H-5, H-6b); 3.74 (dd, 1H, $^3J = 2.6$, $^2J = 18.4$ Hz, NCH_2); 3.47 (d, 1H, $^2J = 18.8$ Hz,

NCH_2); 3.22–3.17 (m, 1H, CHN); 2.53 (dd, 1H, ^3J = 2.5, ^2J = 16.3 Hz, $CHCH_2$); 2.17 (d, 1H, ^2J = 16.2 Hz, $CHCH_2$); 1.72–1.58 (m, 1H, CH_2); 1.42–1.29 (m, 3H, CH_2); 1.25, 1.14, 1.10, 1.09 (4s, 36H, $PivCH_3$); 0.91 (t, 3H, ^3J = 7.0 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.84, 177.23, 177.08, 176.73 (PivC=O); 157.01, 153.02 (aryl); 134.24 (CH=*C*Ar); 128.43 (*ipso*-aryl); 125.67 (*C*H=CAr); 91.87 (C-1); 72.01, 71.76, 67.30, 65.35 (C-2, C-3, C-4, C-5); 61.65 (C-6); 53.70 (CHN); 44.20 (NCH_2); 39.03, 38.72, 38.66 ($PivCMe_3$); 33.79 ($CHCH_2$); 31.52 (CH_2); 27.17, 27.08, 27.04 ($PivCH_3$); 20.03 (CH_2); 14.32 (CH_3) ppm; MS (ES^+): *m/z* 600.4 $[M-PivOH+H]^+$, 622.3 $[M-PivOH+Na]^+$, 702.4 $[M+H]^+$, 724.4 $[M+Na]^+$, 765.5 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{59}N_3NaO_9$ (M+Na): 724.4149; found: 724.4161; elemental analysis: calcd (%) for $C_{38}H_{59}N_3O_9$ (701.89): C 65.03, H 8.47, N 5.99; found: C 64.94, H 8.47, N 5.98.

4.5.2. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-4-(8-chinolyl)-4,5-dehydro-piperidine 9b. Purification by flash chromatography (cyclohexane/ethyl acetate (10:1)); yield: 72%; yellow amorphous solid; R_f = 0.56 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -15.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.83 (dd, 1H, ^4J = 1.8, ^3J = 4.4 Hz, aryl); 8.08 (dd, 1H, ^4J = 1.7, ^3J = 8.3 Hz, aryl); 7.70–7.65 (m, 1H, aryl); 7.44–7.42 (m, 2H, aryl); 7.33 (dd, 1H, ^3J = 4.1, ^3J = 8.5 Hz, aryl); 5.85 (br s, 1H, CH=CAr); 5.54 (t, 1H, ^3J = 9.6 Hz, H-2); 5.39 (d, 1H, ^3J = 2.9 Hz, H-4); 5.16 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.37 (d, 1H, ^3J = 9.2 Hz, H-1); 4.16 (dd, 1H, ^3J = 6.6, ^2J = 10.7 Hz, H-6a); 3.99–3.87 (m, 2H, H-5, H-6b); 3.81 (dd, 1H, ^3J = 2.7, ^2J = 17.1 Hz, NCH_2); 3.48 (d, 1H, ^2J = 16.9 Hz, NCH_2); 3.29–3.22 (m, 1H, CHN); 2.78 (dd, 1H, ^3J = 2.4, ^2J = 16.4 Hz, $CHCH_2$); 2.49 (d, 1H, ^2J = 16.5 Hz, $CHCH_2$); 1.79–1.64 (m, 2H, CH_2); 1.48–1.30 (m, 2H, CH_2); 1.27, 1.18, 1.15, 1.10 (4s, 36H, $PivCH_3$); 0.94 (t, 3H, ^3J = 7.2 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.93, 177.31, 177.03, 176.88 (PivC=O); 149.32 (aryl); 146.49, 143.14, 136.68 (*ipso*-aryl, CH=*C*Ar); 135.92, 128.37 (aryl); 128.33 (*ipso*-aryl); 126.93, 126.27, 124.03 (aryl); 120.73 (*C*H=CAr); 92.37 (C-1); 72.33, 71.64, 67.50, 65.39 (C-2, C-3, C-4, C-5); 61.77 (C-6); 53.70 (CHN); 44.83 (NCH_2); 39.06, 38.73, 38.67 ($PivCMe_3$); 35.14 ($CHCH_2$); 33.70 (CH_2); 27.19, 27.14, 27.07 ($PivCH_3$); 20.19 (CH_2); 14.49 (CH_3) ppm; MS (ES^+): *m/z* 649.6 $[M-PivOH+H]^+$, 751.7 $[M+H]^+$, 773.7 $[M+Na]^+$; HRMS: calcd for $C_{43}H_{63}N_2O_9$ (M+H): 751.4534; found: 751.4506.

4.5.3. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-4-(3-pyridyl)-4,5-dehydro-piperidine 9c. Purification by flash chromatography (cyclohexane/ethyl acetate (5:1)); yield: 83%; colourless amorphous solid; R_f = 0.38 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -24.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.58 (s, 1H, aryl); 8.43 (d, 1H, ^3J = 3.7 Hz, aryl); 7.58 (d, 1H, ^3J = 8.1 Hz, aryl); 7.20 (dd, 1H, ^3J = 4.8, ^3J = 7.7 Hz, aryl); 6.06 (br s, 1H, CH=CAr); 5.46 (t, 1H, ^3J = 9.6 Hz, H-2); 5.37 (d, 1H, ^3J = 2.9 Hz, H-4); 5.13 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.31 (d, 1H, ^3J = 9.2 Hz, H-1); 4.08 (dd, 1H, ^3J = 5.9, ^2J = 9.9 Hz, H-6a); 3.94–3.84 (m, 2H, H-5, H-6b); 3.72 (dd, 1H, ^3J = 2.8, ^2J = 17.8 Hz, NCH_2); 3.44 (d, 1H, ^2J = 17.4 Hz, NCH_2); 3.20–3.16 (m, 1H, CHN); 2.52 (dd, 1H, ^3J = 2.4, ^2J = 16.4 Hz, $CHCH_2$); 2.18 (d, 1H, ^2J = 17.0 Hz, $CHCH_2$); 1.72–1.59 (m, 1H, CH_2); 1.46–1.30 (m, 3H, CH_2); 1.25, 1.14, 1.10, 1.09 (4s, 36H, $PivCH_3$); 0.90 (t, 3H, ^3J = 7.0 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.84, 177.23, 177.03, 176.75 (PivC=O); 147.81, 146.43 (aryl); 136.88 (CH=*C*Ar); 132.07 (aryl); 131.10 (*ipso*-aryl); 123.82 (aryl); 123.82 (*C*H=CAr); 91.93 (C-1); 72.09, 71.67, 67.33, 65.35 (C-2, C-3, C-4, C-5); 61.65 (C-6); 53.62 (CHN); 44.37 (NCH_2); 39.02, 38.69, 38.64 ($PivCMe_3$); 33.78 ($CHCH_2$); 32.01 (CH_2); 27.16, 27.07, 27.02 ($PivCH_3$); 20.06 (CH_2); 14.34 (CH_3) ppm; MS (ES^+): *m/z* 599.7 $[M-PivOH+H]^+$, 701.7 $[M+H]^+$, 723.8 $[M+Na]^+$, 764.88 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{39}H_{61}N_2O_9$ (M+H): 701.4377; found: 701.4367.

4.5.4. (2*R*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-*n*-propyl-4-phenyl-4,5-dehydro-piperidine 9d. Purification by flash chromatography (cyclohexane/ethyl acetate (8:1)); yield: 64%; colourless amorphous solid; R_f = 0.59 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -28.8$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.34–7.28 (m, 3H, aryl); 7.26–7.18 (m, 2H, aryl); 6.00 (br s, 1H, CH=CAr); 5.48 (t, 1H, ^3J = 9.7 Hz, H-2); 5.37 (d, 1H, ^3J = 2.9 Hz, H-4); 5.13 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.32 (d, 1H, ^3J = 9.2 Hz, H-1); 4.09 (dd, 1H, ^3J = 6.1, ^2J = 10.1 Hz, H-6a); 3.95–3.84 (m, 2H, H-5, H-6b); 3.72 (dd, 1H, ^3J = 2.6, ^2J = 17.6 Hz, NCH_2); 3.42 (br d, 1H, ^2J = 16.9 Hz, NCH_2); 3.20–3.14 (m, 1H, CHN); 2.53 (dd, 1H, ^3J = 1.8, ^2J = 15.8 Hz, $CHCH_2$); 2.22 (br d, 1H, ^2J = 15.8 Hz, $CHCH_2$); 1.72–1.54 (m, 2H, CH_2); 1.39–1.30 (m, 2H, CH_2); 1.26, 1.15, 1.10, 1.09 (4s, 36H, $PivCH_3$); 0.90 (t, 3H, ^3J = 7.2 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.90, 177.28, 177.05, 176.82 (PivC=O); 141.66 (CH=*C*Ar); 133.69 (*ipso*-aryl); 128.25, 126.74, 124.84 (aryl); 121.87 (*C*H=CAr); 91.99 (C-1); 72.21, 71.64, 67.40, 65.38 (C-2, C-3, C-4, C-5); 61.68 (C-6); 53.56 (CHN); 44.59 (NCH_2); 39.05, 38.72, 38.67 ($PivCMe_3$); 33.81 ($CHCH_2$); 32.38 (CH_2); 27.17, 27.08, 27.05 ($PivCH_3$); 20.12 (CH_2); 14.41 (CH_3) ppm; MS (ES^+): *m/z* 598.6 $[M-PivOH+H]^+$, 620.6 $[M-PivOH+Na]^+$, 700.6 $[M+H]^+$, 722.7 $[M+Na]^+$, 763.8 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{40}H_{62}NO_9$ (M+H): 700.4425; found: 700.4415.

4.5.5. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-isopropyl-4-(5-pyrimidyl)-4,5-dehydro-piperidine 9e. Purification by flash chromatography (cyclohexane/ethyl acetate (3:1)); yield: 64%; yellowish amorphous solid; R_f = 0.29 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -25.3$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.04 (s, 1H, aryl); 8.67 (s, 2H, aryl); 6.15 (br s, 1H, CH=CAr); 5.47 (t, 1H, ^3J = 9.7 Hz, H-2); 5.35 (d, 1H, ^3J = 2.9 Hz, H-4); 5.12 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.37 (d, 1H, ^3J = 9.2 Hz, H-1); 4.01–3.85 (m, 3H, H-5, H-6a, H-6b); 3.66 (dd,

1H, ^3J = 2.6, ^2J = 18.8 Hz, NCH_2); 3.58 (dd, 1H, ^3J = 2.8, ^2J = 18.9 Hz, NCH_2); 2.76 (dd, 1H, ^3J = 5.5, ^3J = 11.4 Hz, CHN); 2.51–2.45 (m, 1H, $CHCH_2$); 2.37–2.30 (m, 1H, $CHCH_2$); 2.01–1.90 (m, 1H, $CH(CH_3)_2$); 1.24, 1.11, 1.10, 1.09 (4s, 36H, $PivCH_3$); 0.95 (d, 3H, ^3J = 6.6 Hz, CH_3); 0.88 (d, 3H, ^3J = 6.6 Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.84, 177.30, 177.09, 176.72 (PivC=O); 156.90, 152.99 (aryl); 134.27 (CH=*C*Ar); 128.46 (*ipso*-aryl); 126.05 (*C*H=CAr); 91.09 (C-1); 72.30, 71.65, 67.40, 65.63 (C-2, C-3, C-4, C-5); 61.96 (C-6, CHN); 42.37 (NCH_2); 39.05, 38.73, 38.61 (Piv*C*Me_3); 27.61 ($CHCH_2$); 27.20, 27.17, 27.07, 27.02 ($PivCH_3$); 26.72 ($CH(CH_3)_2$); 21.03 (CH_3); 18.01 (CH_3) ppm; MS (ES^+): *m/z* 600.5 $[M-PivOH+H]^+$, 702.5 $[M+H]^+$, 724.5 $[M+Na]^+$, 765.6 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{38}H_{59}N_3NaO_9$ (M+Na): 724.4149; found: 724.4156.

4.5.6. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(4-chlorophenyl)-4-(5-pyrimidyl)-4,5-dehydropiperidine 9g. Purification by flash chromatography (cyclohexane/ethyl acetate (3:1)); yield: 69%; orange amorphous solid; R_f = 0.23 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -26.8$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.05 (s, 1H, aryl); 8.70 (s, 2H, aryl); 7.35 (d, 2H, ^3J = 8.5 Hz, aryl); 7.26 (d, 2H, ^3J = 8.5 Hz, aryl); 6.30 (br s, 1H, CH=CAr); 5.48 (t, 1H, ^3J = 9.5 Hz, H-2); 5.25 (d, 1H, ^3J = 2.9 Hz, H-4); 4.86 (dd, 1H, ^3J = 2.9, ^3J = 9.9 Hz, H-3); 4.08–3.99 (m, 2H, CHN, H-6a); 3.92 (d, 1H, ^3J = 9.2 Hz, H-1); 3.90–3.84 (m, 3H, H-6b, NCH_2); 3.46 (t, 1H, ^3J = 6.8 Hz, H-5); 2.74–2.65 (m, 1H, $CHCH_2$); 2.52 (d, 1H, ^3J = 15.1 Hz, $CHCH_2$); 1.25, 1.17, 1.15, 1.06 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.87, 177.14, 177.11, 176.58 (PivC=O); 157.02, 152.90 (aryl); 139.29, 134.02 (*ipso*-aryl); 134.00 (CH=*C*Ar); 129.61, 129.09 (aryl); 128.01 (*ipso*-aryl); 125.38 (*C*H=CAr); 87.69 (C-1); 72.01, 71.46, 67.27, 64.90 (C-2, C-3, C-4, C-5); 61.71 (C-6); 59.43 (CHN); 43.84 (NCH_2); 39.05, 38.78, 38.69 (Piv*C*Me_3); 35.81 ($CHCH_2$); 27.20, 27.11, 27.02 ($PivCH_3$) ppm; MS (ES^+): *m/z* 668.5 $[M-PivOH+H]^+$, 690.5 $[M-PivOH+Na]^+$, 770.6 $[M+H]^+$, 792.6 $[M+Na]^+$, 833.5 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{41}H_{56}ClN_3NaO_9$ (M+Na): 792.3603; found: 792.3602.

4.5.7. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(4-chlorophenyl)-4-(8-chinolyl)-4,5-dehydropiperidine 9h. Purification by flash chromatography (cyclohexane/ethyl acetate (10:1)); yield: 66%; yellowish amorphous solid; R_f = 0.54 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -19.4$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.85 (dd, 1H, ^4J = 2.0, ^3J = 4.3 Hz, aryl); 8.09 (dd, 1H, ^4J = 1.6, ^3J = 8.2 Hz, aryl); 7.69 (dd, 1H, ^4J = 1.4, ^3J = 8.0 Hz, aryl); 7.53 (dd, 1H, ^4J = 1.6, ^3J = 7.0 Hz, aryl); 7.45 (t, 1H, ^3J = 7.4 Hz, aryl); 7.36–7.29 (m, 5H, aryl); 6.05 (br s, 1H, CH=CAr); 5.56 (t, 1H, ^3J = 9.8 Hz, H-2); 5.27 (d, 1H, ^3J = 2.7 Hz, H-4); 4.88 (dd, 1H, ^3J = 3.1, ^3J = 9.8 Hz, H-3); 4.31 (dd, 1H, ^3J = 4.1, ^3J = 9.6 Hz, CHN); 4.04 (dd, 1H, ^3J = 6.7, ^2J = 10.9 Hz, H-6a); 3.96 (d, 1H, ^3J = 9.8 Hz, H-1); 3.94–3.91 (m, 2H, H-6b, NCH_2); 3.81 (br d, 1H, ^2J = 16.8 Hz, NCH_2); 3.49 (t, 1H, ^3J = 6.6 Hz, H-5); 2.98–2.85 (m, 2H, $CHCH_2$); 1.26, 1.23, 1.19, 1.08 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.93, 177.20, 177.11, 176.70 (PivC=O); 149.51 (aryl); 146.27, 141.60, 140.61 (CH=*C*Ar, *ipso*-aryl); 136.15 (aryl); 135.99, 133.25 (*ipso*-aryl); 129.87, 128.67, 128.56 (aryl); 128.40 (*ipso*-aryl); 127.23, 126.24, 124.53 (aryl); 120.78 (*C*H=CAr); 88.18 (C-1); 72.28, 71.30, 67.43, 65.05 (C-2, C-3, C-4, C-5); 61.83 (CHN); 59.61 (C-6); 43.80 (NCH_2); 39.48 ($CHCH_2$); 39.04, 38.81, 38.68 (Piv*C*Me_3); 27.24, 27.20, 27.12, 27.04 ($PivCH_3$) ppm; MS (ES^+): *m/z* 717.5 $[M-PivOH+H]^+$, 739.5 $[M-PivOH+Na]^+$, 819.6 $[M+H]^+$, 841.5 $[M+Na]^+$; HRMS: calcd for $C_{46}H_{59}ClN_2NaO_9$ (M+Na): 841.3807; found: 841.3793.

4.5.8. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-(5-pyrimidyl)-4,5-dehydropiperidine 9j. Purification by flash chromatography (cyclohexane/ethyl acetate (1:1)); yield: 90%; colourless amorphous solid; R_f = 0.05 (cyclohexane/ethyl acetate (1:1)); $[\alpha]_D^{22} = -33.9$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.06 (s, 1H, aryl); 8.70 (s, 2H, aryl); 8.62 (dd, 1H, ^4J = 1.5, ^3J = 4.8 Hz, aryl); 8.59 (d, 1H, ^4J = 1.5 Hz, aryl); 7.45 (d, 1H, ^3J = 7.7 Hz, aryl); 7.33 (dd, 1H, ^3J = 4.8, ^3J = 7.7 Hz, aryl); 6.32 (br s, 1H, CH=CAr); 5.51 (t, 1H, ^3J = 9.6 Hz, H-2); 5.26 (d, 1H, ^3J = 2.9 Hz, H-4); 4.87 (dd, 1H, ^3J = 3.3, ^3J = 9.9 Hz, H-3); 4.16 (dd, 1H, ^3J = 3.7, ^3J = 9.9 Hz, CHN); 4.02–3.88 (m, 5H, H-6a, H-6b, H-1, NCH_2); 3.48 (t, 1H, ^3J = 6.6 Hz, H-5); 2.79–2.71 (m, 1H, $CHCH_2$); 2.58 (d, 1H, ^2J = 15.1 Hz, $CHCH_2$); 1.25, 1.17, 1.16, 1.07 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.84, 177.15, 176.55 (PivC=O); 157.28, 152.95, 149.98, 149.80 (aryl); 136.28 (CH=*C*Ar); 135.60 (aryl); 132.92, 128.07 (*ipso*-aryl); 125.35 (aryl); 123.74 (*C*H=CAr); 88.08 (C-1); 71.94, 71.58, 67.15, 64.90 (C-2, C-3, C-4, C-5); 61.54 (C-6); 57.58 (CHN); 43.96 (NCH_2); 39.05, 38.81, 38.70 (Piv*C*Me_3); 35.57 ($CHCH_2$); 27.20, 27.12, 27.10, 27.04 ($PivCH_3$) ppm; MS (ES^+): *m/z* 635.6 $[M-PivOH+H]^+$, 737.6 $[M+H]^+$, 759.7 $[M+Na]^+$, 800.6 $[M+CH_3CN+Na]^+$; HRMS: calcd for $C_{40}H_{57}N_4O_9$ (M+H): 737.4126; found: 737.4155.

4.5.9. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-(8-chinolyl)-4,5-dehydropiperidine 9k. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 71%; yellowish amorphous solid; R_f = 0.18 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -24.4$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.85 (dd, 1H, ^4J = 1.7, ^3J = 4.2 Hz, aryl); 8.67 (br s, 1H, aryl); 8.55 (br s, 1H, aryl); 8.09 (dd, 1H, ^4J = 1.8, ^3J = 8.5 Hz, aryl); 7.77 (d, 1H, ^3J = 8.1 Hz, aryl); 7.70 (dd, 1H, ^4J = 1.5, ^3J = 8.1 Hz, aryl); 7.53 (dd, 1H, ^4J = 1.7, ^3J = 7.2 Hz, aryl); 7.45 (t, 1H, ^3J = 7.5 Hz, aryl); 7.34 (dd, 1H, ^3J = 4.2, ^3J = 8.3 Hz, aryl); 7.28 (dd, 1H, ^3J = 5.5, ^3J = 8.1 Hz, aryl); 6.05 (br s, 1H, CH=CAr); 5.58 (t, 1H, ^3J = 9.7 Hz, H-2); 5.28 (d, 1H, ^3J = 2.6 Hz, H-4); 4.89 (dd, 1H, ^3J = 3.3, ^3J = 9.9 Hz, H-3); 4.38 (dd, 1H, ^3J = 4.4, ^3J = 8.8 Hz, CHN); 4.05–3.93 (m, 4H, H-1, H-6a, H-6b, NCH_2); 3.85–3.79 (m, 1H, NCH_2); 3.51 (t, 1H, ^3J = 6.6 Hz, H-5); 3.06–2.90 (m, 2H, $CHCH_2$); 1.26, 1.23, 1.18, 1.08 (4s, 36H, $PivCH_3$) ppm; ^{13}C NMR ($CDCl_3$,

75.5 MHz): δ = 177.85, 177.20, 177.12, 176.67 (PivC=O); 150.27, 149.50, 149.10 (aryl); 146.31, 141.55, 137.57, 136.15 (*ipso*-aryl, CH=*C*Ar); 136.13, 135.89, 128.58 (aryl); 128.40 (*ipso*-aryl); 127.32, 126.26, 124.49, 123.84 (aryl); 120.84 (*C*H=CAr); 88.73 (C-1); 72.22, 71.44, 67.33, 65.08 (C-2, C-3, C-4, C-5); 61.66 (C-6); 57.78 (CHN); 43.92 (NCH_2); 39.09 ($CHCH_2$); 38.84, 38.69 (Piv*C*Me$_3$); 27.23, 27.20, 27.11, 27.05 (PivCH$_3$) ppm; MS (ES$^+$): *m*/*z* 684.5 [M−PivOH+H]$^+$, 786.6 [M+H]$^+$, 808.7 [M+Na]$^+$, 824.5 [M+K]$^+$; HRMS: calcd for $C_{45}H_{60}N_3O_9$ (M+H): 786.4330; found: 786.4316.

4.5.10. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-(3-pyridyl)-4,5-dehydro-piperidine 9l. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 79%; yellowish amorphous solid; R_f = 0.06 (cyclohexane/ethyl acetate (1:1)); $[\alpha]_D^{22} = -30.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.61–8.59 (m, 3H, aryl); 8.45 (d, 1H, ^3J = 4.1 Hz, aryl); 7.67–7.59 (m, 2H, aryl); 7.32 (dd, 1H, ^3J = 4.8, ^3J = 7.7 Hz, aryl); 7.21 (dd, 1H, ^3J = 4.8,8.0 Hz, aryl); 6.23 (br s, 1H, CH=CAr); 5.52 (t, 1H, ^3J = 9.8 Hz, H-2); 5.26 (d, 1H, ^3J = 2.6 Hz, H-4); 4.87 (dd, 1H, ^3J = 3.3, ^3J = 9.9 Hz, H-3); 4.15 (dd, 1H, ^3J = 3.9, ^3J = 9.7 Hz, CHN); 4.02–3.91 (m, 3H, H-1, H-6a, H-6b); 3.84 (br s, 2H, NCH_2); 3.49–3.44 (m, 1H, H-5); 2.79–2.69 (m, 1H, $CHCH_2$); 2.58 (d, 1H, ^2J = 13.6 Hz, $CHCH_2$); 1.26, 1.17, 1.16, 1.07 (4s, 36H, PivCH$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.81, 177.12, 177.09, 176.57 (PivC=O); 150.00, 149.56, 148.26, 146.37 (aryl); 136.71, 136.36 (*ipso*-aryl, CH=*C*Ar); 135.63, 132.10 (aryl); 130.75 (*ipso*-aryl); 123.67, 123.46, 123.16 (aryl, *C*H=CAr); 88.23 (C-1); 72.00, 71.49, 67.18, 64.91 (C-2, C-3, C-4, C-5); 61.54 (C-6); 57.62 (CHN); 43.92 (NCH_2); 39.03, 38.76, 38.67, 38.64 (Piv*C*Me$_3$); 36.08 ($CHCH_2$); 27.19, 27.08, 27.01 (PivCH$_3$) ppm; MS (ES$^+$): *m*/*z* 634.7 [M−PivOH+H]$^+$, 656.6 [M−PivOH+Na]$^+$, 736.7 [M+H]$^+$, 758.7 [M+Na]$^+$, 799.8 [M+CH$_3$CN+Na]$^+$; HRMS: calcd for $C_{41}H_{58}N_3O_9$ (M+H): 736.4173; found: 736.4166.

4.5.11. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-phenyl-4,5-dehydro-piperidine 9m. Purification by flash chromatography (cyclohexane/ethyl acetate (2:1)); yield: 79%; yellow amorphous solid; R_f = 0.28 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = -34.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.61–8.59 (m, 2H, aryl); 7.68 (dt, 1H, ^4J = 1.7, ^3J = 8.0 Hz, aryl); 7.37–7.29 (m, 4H, aryl); 7.27–7.17 (m, 2H, aryl); 6.17 (br s, 1H, CH=CAr); 5.54 (t, 1H, ^3J = 9.6 Hz, H-2); 5.26 (d, 1H, ^3J = 2.6 Hz, H-4); 4.87 (dd, 1H, ^3J = 3.1, ^3J = 10.1 Hz, H-3); 4.15 (dd, 1H, ^3J = 3.9, ^3J = 9.4 Hz, CHN); 4.02–3.90 (m, 3H, H-1, H-6a, H-6b); 3.81 (br s, 2H, NCH_2); 3.47 (t, 1H, ^3J = 6.8 Hz, H-5); 2.79–2.69 (m, 1H, $CHCH_2$); 2.64–2.58 (m, 1H, $CHCH_2$); 1.26, 1.17, 1.16, 1.07 (4s, 36H, PivCH$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.87, 177.20, 177.12, 176.64 (PivC=O); 149.88, 149.25 (aryl); 139.99, 137.34 (*ipso*-aryl, CH=*C*Ar); 135.89 (aryl); 133.25 (*ipso*-aryl); 128.39, 127.13, 124.67, 123.71 (aryl); 115.46 (*C*H=CAr); 88.44 (C-1); 72.10, 71.47, 67.24, 64.96 (C-2, C-3, C-4, C-5); 61.57 (C-6); 57.69 (CHN); 43.95 (NCH_2); 39.06, 38.78, 38.70, 38.67 (Piv*C*Me$_3$); 36.53 ($CHCH_2$); 27.22, 27.17, 27.10, 27.04 (PivCH$_3$) ppm; MS (ES$^+$): *m*/*z* 633.7 [M−PivOH+H]$^+$, 655.6 [M−PivOH+Na]$^+$, 735.7 [M+H]$^+$, 757.7 [M+Na]$^+$, 798.7 [M+CH$_3$CN+Na]$^+$; HRMS: calcd for $C_{42}H_{59}N_2O_9$ (M+H): 735.4221; found: 735.4198.

4.5.12. (2*S*)-*N*-(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-(2-chlorobenzyl)-4-(5-pyrimidyl)-4,5-dehydro-piperidine 9n. Purification by flash chromatography (cyclohexane/ethyl acetate (4:1)); yield: 57%; colourless amorphous solid; R_f = 0.20 (cyclohexane/ethyl acetate (2:1)); $[\alpha]_D^{22} = +18.2$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.04 (s, 1H, aryl); 8.61 (s, 2H, aryl); 7.30 (dd, 1H, ^3J = 3.9, ^3J = 5.7 Hz, aryl); 7.20–7.10 (m, 3H, aryl); 6.22 (br s, 1H, CH=CAr); 5.51 (t, 1H, ^3J = 9.6 Hz, H-2); 5.44 (d, 1H, ^3J = 2.9 Hz, H-4); 5.19 (dd, 1H, ^3J = 3.3, ^3J = 10.3 Hz, H-3); 4.33 (d, 1H, ^3J = 9.2 Hz, H-1); 4.12 (dd, 1H, ^3J = 6.4, ^2J = 10.5 Hz, H-6a); 4.03–3.88 (m, 3H, H-5, H-6b, NCH_2); 3.79–3.76 (m, 1H, CHN); 3.49 (br d, 1H, ^2J = 17.6 Hz, NCH_2); 3.16 (dd, 1H, ^3J = 3.9, ^2J = 13.1 Hz, CH_2–ClPh); 3.05 (dd, 1H, ^3J = 10.7, ^2J = 12.9 Hz, CH_2–ClPh); 2.35–2.30 (m, 1H, $CHCH_2$); 2.07 (d, 1H, ^2J = 16.9 Hz, $CHCH_2$); 1.30, 1.14, 1.11, 1.09 (4s, 36H, PivCH$_3$) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 177.82, 177.18, 177.08, 176.76 (PivC=O); 157.07, 153.19 (aryl); 137.55, 134.18, 134.11 (*ipso*-aryl, CH=*C*Ar); 131.20, 129.69 (aryl); 128.69 (*ipso*-aryl); 127.71, 126.87 (aryl); 125.09 (*C*H=CAr); 93.46 (C-1); 72.16, 71.83, 67.19, 65.38 (C-2, C-3, C-4, C-5); 61.38 (C-6); 52.60 (CHN); 45.79 (NCH_2); 39.06, 38.73, 38.69 (Piv*C*Me$_3$); 34.29 ($CHCH_2$); 29.60 (CH_2–ClPh); 27.22, 27.05 (PivCH$_3$) ppm; MS (ES$^+$): *m*/*z* 682.5 [M−PivOH+H]$^+$, 704.5 [M−PivOH+Na]$^+$, 784.5 [M+H]$^+$, 806.6 [M+Na]$^+$, 847.6 [M+CH$_3$CN+Na]$^+$; HRMS: calcd for $C_{42}H_{58}ClN_3NaO_9$ (M+Na): 806.3759; found: 806.3767.

4.6. General procedure for the cleavage of the *N*-glycosidic bond to detach the dehydropiperidines 10

To a solution of *N*-galactosyl dehydropiperidine **9** (0.2 mmol) in methanol (6 mL) was added 1 M aq HCl (1.2 mL) and stirred at ambient temperature for 12–24 h (TLC monitoring). The solvent was evaporated in vacuo, the residue dissolved in diethyl ether (10 mL) and the organic layer extracted with water (3 × 5 mL). The hemiacetal of the carbohydrate auxiliary **11** was quantitatively recovered by concentration of the organic layer. The combined aqueous layer was alkalised with Na_2CO_3 and extracted with CH_2Cl_2 (3 × 10 mL) to give the dehydropiperidine **10** after evaporation of the solvent in vacuo.

4.6.1. (2*S*)-2-Isopropyl-4-(5-pyrimidyl)-4,5-dehydropiperidine 10a. Yield: 85%; yellow oil; R_f = 0.08 (ethyl acetate/methanol (9:1)); $[\alpha]_D^{22} = -94.9$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.05 (s, 1H, aryl); 8.71 (s, 2H, aryl); 6.22 (br s, 1H, CH=CAr); 3.68–3.53 (m, 2H, NCH_2); 2.59 (ddd, 1H, ^3J = 4.1, ^3J = 5.9, ^3J = 9.9 Hz, CHN); 2.35 (br d, 1H, ^2J = 15.8 Hz, $CHCH_2$); 2.30–2.19 (m, 1H, $CHCH_2$); 1.78–1.67 (m,

1H, C*H*$(CH_3)_2$); 1.01 (d, 3H, ^3J = 4.8 Hz, CH_3); 0.98 (d, 3H, ^3J = 4.8 Hz, CH_3) ppm; MS (ES^+): *m/z* 204.0 $[M+H]^+$, 245.0 $[M+CH_3CN+H]^+$; HRMS: calcd for $C_{12}H_{18}N_3$ (M+H): 204.1501; found: 204.1508.

4.6.2. (2*S*)-2-(3-Pyridyl)-4-(5-pyrimidyl)-4,5-dehydropiperidine 10b. Yield: 91%; yellow solid; R_f = 0.07 (ethyl acetate/methanol (2:1)); $[\alpha]_D^{22} = -100.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.03 (s, 1H, aryl); 8.70 (s, 2H, aryl); 8.62 (d, 1H, ^4J = 2.2 Hz, aryl); 8.50 (dd, 1H, ^4J = 1.5, ^3J = 4.8 Hz, aryl); 7.74 (dt, 1H, ^4J = 1.8, ^3J = 7.7 Hz, aryl); 7.27 (dd, 1H, ^3J = 4.8, ^3J = 7.7 Hz, aryl); 6.30 (d, 1H, ^3J = 1.5 Hz, CH=CAr); 3.99 (t, 1H, ^3J = 7.0 Hz, CHN); 3.83–3.66 (m, 2H, NCH_2); 2.58–2.56 (m, 2H, CHCH_2) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 157.29, 153.13, 149.19 (aryl); 149.17 (CH=*C*Ar); 148.57 (aryl); 138.93 (*ipso*-aryl); 134.18 (aryl); 129.76 (*ipso*-aryl); 126.26, 123.71 (aryl, *C*H=CAr); 55.31 (CHN); 46.34 (NCH_2); 35.14 (CH*C*H_2) ppm; MS (ES^+): *m/z* 239.4 $[M+H]^+$, 280.3 $[M+CH_3CN+H]^+$; HRMS: calcd for $C_{14}H_{15}N_4$ (M+H): 239.1297; found: 239.1292.

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