Stereoselective Synthesis of Enantiomerically Pure Piperidine Derivatives by *N*-Galactosylation of Pyridones

Ellen Klegraf,[a] Markus Follmann,[a] Dieter Schollmeyer,[a] and Horst Kunz*[a]

Dedicated to Professor Karsten Krohn on the occasion of his 60th birthday

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Stereoselective desymmetrization of 4-pyridone has been achieved through selective *N*-galactosylation, activation of the *N*-(galactosyl)pyridone by *O*-silylation and immediate addition of Grignard compounds. Chiral piperidine derivatives, e.g. (*S*)-(+)-coniine and (5*S*,9*S*)-(+)-indolozidine 167B, were synthesised in enantiomerically pure form using these highly regio- and stereoselective reactions. After *N*-galactosylation of 2-pyridone and *O*-silylation of the *N*-galactosyl-2-pyridone, addition of a Grignard compound proceeded with high 1,4-regioselectivity and complete diastereoselectivity, to furnish 4-substituted 5,6-dehydro-2-piperidones.

Introduction

The piperidine ring is an important structural motif in natural compounds, e.g. in alkaloids,[1] and also in pharmaceuticals.[2,3] Hence, the development of stereoselective syntheses leading to polysubstituted chiral piperidines is of general interest in natural product and medicinal chemistry.[4] Since piperidinones can be smoothly converted into piperidines, they are attractive intermediates for the synthesis of chiral piperidines. The chemistry of chiral piperidinones has been reviewed recently.[5] Apart from enantioselective catalysis, most general routes in asymmetric synthesis are based on the use of chiral auxiliaries[6] or procedures exploiting the chiral pool.[7] We recently reported a desymmetrization reaction at 4-pyridone, for the synthesis of chiral 2-substituted *N*-glycosyl-5,6-didehydro-4-piperidinones,[8] during which the stereodifferentiating tool was introduced by *N*-galactosylation. An analogous procedure was applied to 2-pyridinone and resulted in the unprecedented regio- and stereoselective formation of 4-substituted *N*-galactosyl-5,6-didehydro-2-piperidinones.[9] Further transformations of the thus obtained piperidone derivatives and detailed preparations of two alkaloids are described in this article.

[a] Institut für Organische Chemie, Universität Mainz, Duesbergweg 10−14, 55128 Mainz, Germany
Fax: (internat.) + 49-6131-3924786
E-mail: hokunz@uni-mainz.de
[b] Aventis Pharma Deutschland GmbH, Industriepark Hoechst, G 838, 206 F, 65926 Frankfurt am Main, Germany
E-mail: markus.follmann@aventis.com

Results and Discussion

The *N*-(galactosyl)pyridones **3** and **5** are obtained readily in multigram quantities by the Vorbrüggen reaction[10] starting from *O*-pivaloylated galactosyl fluoride[8,11] **1** and (trimethylsilyloxy)pyridines[12] **2** or **4** (Scheme 1). The choice of the Lewis acid is crucial for the chemoselectivity of the glycosylation reaction between galactosyl fluoride **1** and the *O*-silylated pyridone **2**. While boron trifluoride (BF_3) favours the formation of the α-*O*-galactosylated compound, application of tin tetrachloride ($SnCl_4$) produces a mixture (4:3) of the β-*N*- and α-*O*-galactosylated compounds. In contrast, titanium tetrachloride ($TiCl_4$) quantitatively and selectively promotes the formation of the *N*-glycosylated pyridone **3**. Interestingly, in the series of the 2-pyridones, the use of either $SnCl_4$ or $TiCl_4$ results in quantitative formation of the *N*-glycosylated 2-pyridone **5**.

Syntheses Based on Stereoselective Conjugate Addition Reactions at *N*-Galactosyl-4-pyridone

The initial aim of this work was to study the reactivity of the *N*-galactosyl-4-pyridone **3** towards organomagnesium, -lithium and -copper compounds. However, the pyridone compounds proved to be inert towards all of these reagents. To overcome this problem, the methodology published by Beifuss et al.[13] was adopted. In this way, activation of the *N*-(galactosyl)pyridone **3** was achieved by *O*-silylation using trimethylsilyl trifluoromethanesulfonate (TMSOTf). The intermediate pyridinium salt reacted readily with Grignard reagents at the 2-position (Scheme 2). The addition reaction

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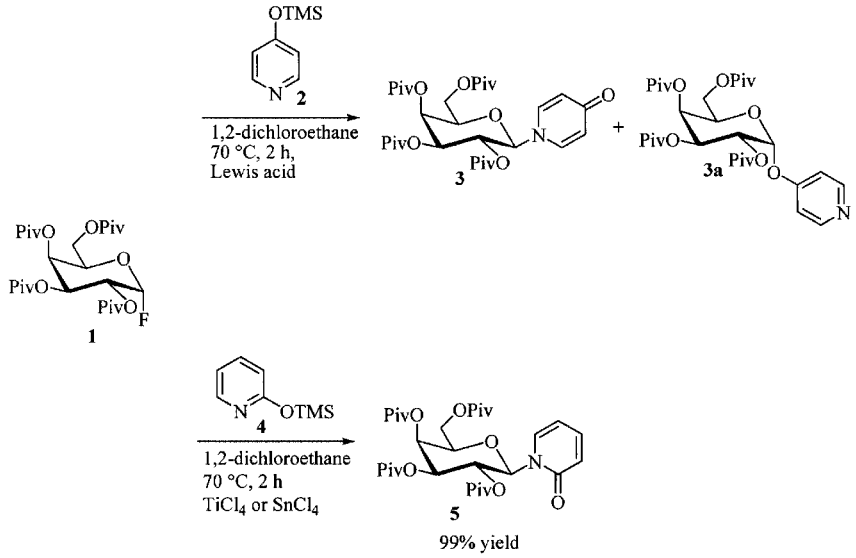
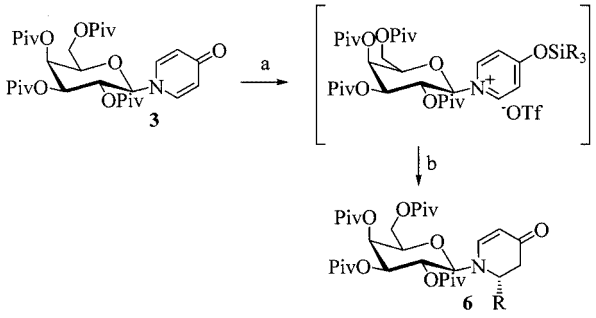


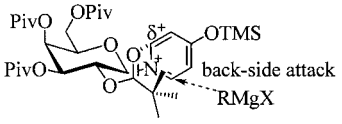
Scheme 1. Chemoselective synthesis of *N*-(galactosyl)pyridones



Scheme 2. Reagents and conditions: (a) TMSOTf, CH_2Cl_2, room temp., 1 h; (b) 2,6-lutidine, RMgX, CH_2Cl_2, room temp., 1−2 h

proceeded with good to excellent diastereoselectivity, thereby desymmetrizing the pyridine (Table 1).

The reason for this differentiation remains open to speculation. It can be assumed from previous experiments[11,14] that the front side of the heterocycle (Scheme 3) is effectively shielded by the 2-pivaloyl group leaving two diastereotopic back-side sites accessible to the addition reaction. An interpretation of the differentiation between these upper and lower back-side sites can be obtained by reference to the X-ray analysis of the products (Figure 1). An electronic participation of the carbonyl oxygen atom of the 2-pivaloyl group might block the upper site favouring addition of the Grignard compound not only to the other face, but also to the lower site.



Scheme 3

The absolute configuration of *N*-(galactosyl)dehydropiperidinones **6** was proven by X-ray analyses of several derivatives of **6** as well as by comparison with analogous compounds obtained in previous work by domino-Mannich−Michael reactions using *N*-(galactosyl)imines,[14] which lead selectively to the opposing diastereomers. As an example, the X-ray structure analysis of compound **6h**

Table 1. Stereoselective synthesis of dehydropiperidinones **6**

Compound	Grignard reagent, RMgX	Yield [%]	Diastereoselectivity (*S*)/(*R*)
6a	MeMgCl	74	95:5
6b	*n*PrMgCl	84	89:11
6c	*i*PrMgCl	89	8:92
6d	*n*BuMgCl	50	> 99:1
6e	*n*DecMgBr	71	79:21
6f	vinylMgBr	51	1:99
6g	1-butenylMgBr	19	> 99:1
6h	PhMgCl	83	< 1:99
6i	*m*-$MeOC_6H_4MgBr$	35	< 1:99
6j	$ClMg(CH_2)_3OMgCl$	30	92:8
6k	$ClMg(CH_2)_3SiPhMe_2$	66	> 99:1

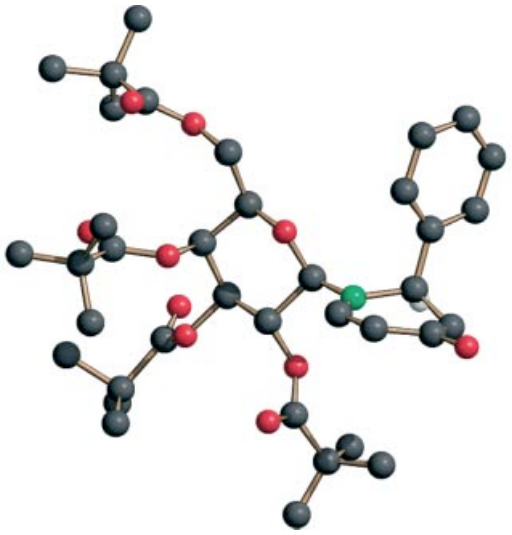
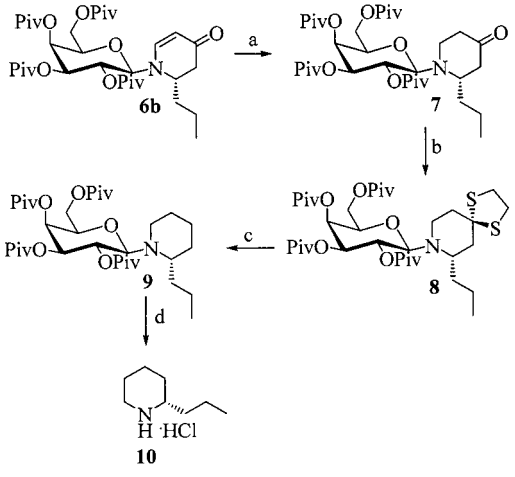


Figure 1. X-ray analysis of 1-galactosyl-2-phenyl-5,6-dehydropiperidinone **6h**

shown in Figure 1 provides evidence that the introduced substituent adopts a pseudo-axial position.

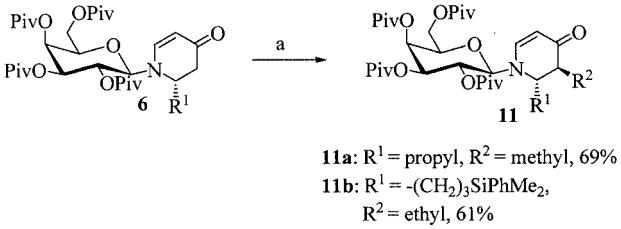
Variation of the silylating reagent influenced neither the yield nor the diastereoselectivity of the reaction. The reactions proceeded with almost identical results when either TMSOTf, triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) or the less expensive trimethylsilyl chloride (TMSCl) was used for activation of the (galactosyl)pyridone **3**. According to this methodology, side chains containing further functional groups can be introduced into the pyridone ring (see, for example, Entries **6f**, **6g**, **6i**–**6k** in Table 1).

In the syntheses of a number of different alkaloids, Comins et al.[6a] have demonstrated the utility of synthons like **6**. According to the strategy outlined here, the synthesis of the (*S*) enantiomer of coniine, a major alkaloid from *conium maculatum* (hemlock), was achieved by the method shown in Scheme 4. This conversion illustrates a general route to chiral 2-substituted piperidines. After introduction of the *n*-propyl chain by Grignard addition, the dehydropiperidinone **6b** was treated with lithium tris(*sec*-butyl)-borohydride (L-Selectride) in THF at −78 °C, affording piperidinone **7** in almost quantitative yield. The dithiolane **8** was formed by reaction of **7** with 1,2-ethanedithiol in the presence of boron trifluoride–diethyl ether ($BF_3{\cdot}OEt_2$) in a yield of 88%. Subsequent desulfurization using Raney nickel yielded the *N*-galactosylated coniine **9** almost quantitatively. The enantiomerically pure (*S*)-(+)-coniine (**10**) was isolated as its hydrochloride in quantitative yield after mild acidolysis of **9** with dilute hydrochloric acid in aqueous methanol. This total synthesis requires 5 steps starting from the *N*-galactosyl-4-pyridone **3** and gave the natural alkaloid in an overall yield of 44%.



Scheme 4. Reagents and conditions: (a) L-Selectride, THF, −78 °C, 2 h, 61%; (b) 1,2-ethanethiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temp., 12 h, 88%; (c) Raney nickel, H_2, isopropyl alcohol, 70 °C, 12 h, 97%; (d) 2 N HCl, methanol, 20 °C, 36 h, quantitative yield

Subsequently, compounds **6** were deprotonated by using lithium hexamethyldisilazane (LiHMDS), and the alkylation of the thus formed enolates was investigated. These alkylation reactions yielded exclusively the *trans*-2,3-disubstituted piperidinones **11** (Scheme 5), which is in agreement with observations reported by Comins et al.[15] and previous results obtained from the analogous diastereomeric *N*-(glycosyl)dehydropiperidinones.[14]



11a: R^1 = propyl, R^2 = methyl, 69%
11b: R^1 = -$(CH_2)_3SiPhMe_2$, R^2 = ethyl, 61%

Scheme 5. Reagents and conditions: (a) 1.2 equiv. LiHMDS, THF, −78 °C, 1 h, 3 equiv. R^2I, −10 °C, 12 h

The absolute configuration of compounds **11** was proven by an X-ray analysis of compound **11a** (see Figure 2), showing both substituents in an antiperiplanar position.

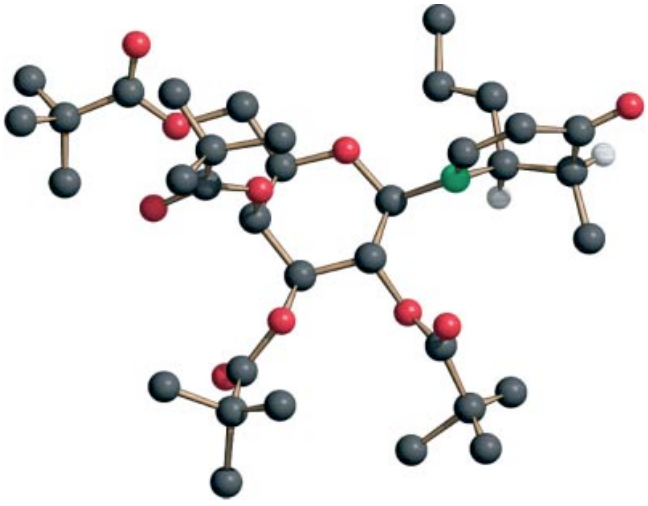
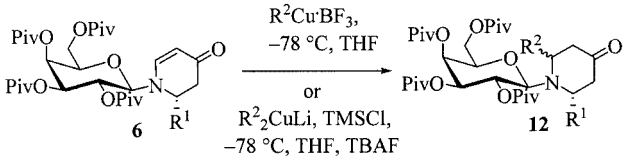


Figure 2. X-ray analysis of the *trans*-2,3-disubstituted 1-galactosyl-5,6-dehydropiperidinone **11a**

Further transformations at the enaminone group of compounds **6** are also of interest. In general, *cis*-2,6-disubstituted 4-piperidinones are important synthons for the synthesis of piperidine alkaloids. To achieve this substitution pattern from precursors like **6**, a diastereoselective 1,4-addition at the vinylogous amide structure of **6** is required. For these conversions organocuprates, in combination with hard electrophiles such as TMSCl[16]or $BF_3{\cdot}OEt_2$,[17] were allowed to react with compounds **6** (Scheme 6) to give 2,6-disubstituted piperidinones **12** in high yields (Table 2).



Scheme 6. Activated addition of organocuprates

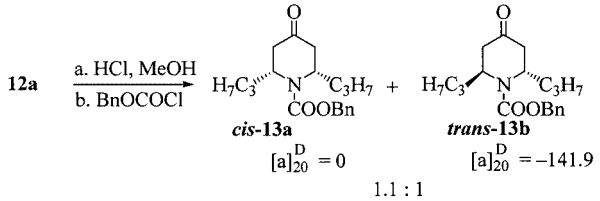
Table 2. Synthesis of 2,6-disubstituted piperidinones **12** according to Scheme 6

Compound	R^1	R^2	Cuprate	Yield [%]	*cis*/*trans* ratio
12a	propyl	propyl	$R^2Cu{\cdot}BF_3$	83	1.5:1
12b	phenyl	phenyl	$R^2Cu{\cdot}BF_3$	99	3:1
12c	methyl	vinyl	$R^2Cu{\cdot}BF_3$	73	2:1
12b	phenyl	phenyl	$R^2_2CuLi/TMSCl$	47	2.7:1

Compared to previous results obtained with the diastereomers of **6**,[14] the opposite configuration at position 2 given in compounds **6** resulted in lower diastereoselectivity (Scheme 6, Table 2).

These reactions obviously represent the mismatched case in which the carbohydrate auxiliary on the one hand and the stereogenic center in the 2-position of the piperidinone **6** on the other hand exhibit opposing influences on the conjugate addition of the cuprates.

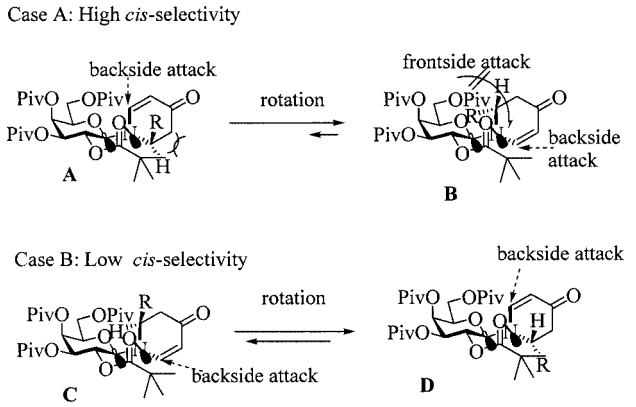
In order to simultaneously prove the existence of two diastereomers in compounds **12** and their absolute configuration, the auxiliary of **12a** was replaced by a nonchiral benzyloxycarbonyl (Z) group and the diastereomers were separated by chromatography (Scheme 7).



Scheme 7. Reagents and conditions: (a) 2 N HCl/methanol (1:5, v/v), 25 °C, 36 h; (b) BnOCOCl, aq. satd. Na_2CO_3, 25 °C, 1 h, 94% (two steps)

On the basis of the optical rotation values of products *cis*-**13a** and *trans*-**13b**, the major diastereomer in **12a** (Scheme 7) was assigned as the *cis* derivative *cis*-**13a** (50%), whereas the minor product (44%) was assigned as the *trans* diastereomer *trans*-**13b**.

The influence of the substituent in 2-position of the piperidone **6** on the side differentiation can be rationalized by the following considerations. For the *N*-(galactosyl)dehydropiperidinones **6**, the axial orientation of substituent R and the existence of rotamers are typical (Scheme 8). The *exo*-anomeric effect[18] stabilizes the two rotamers in which the substituent R could occupy the axial position.



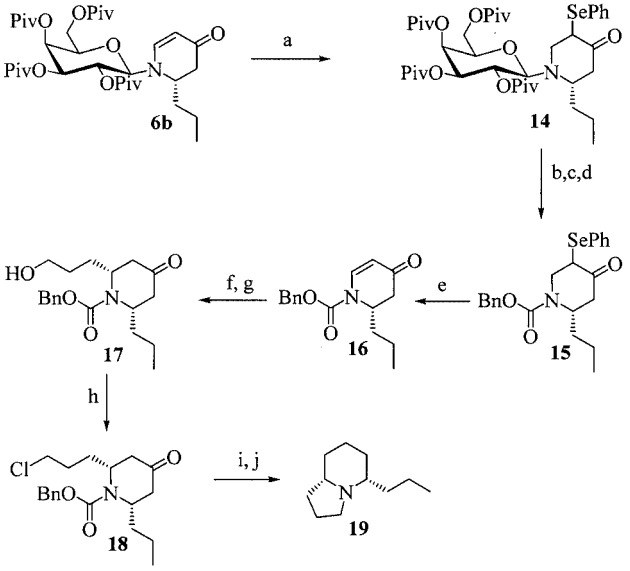
Scheme 8. Possible scenario for the stereochemical addition of organocuprates

Case A represents piperidinone diastereomers obtained by reactions of a Danishefsky diene with galactosylimines.[14,19] Rotamer **A** is destabilized by an unfavourable steric interaction between R and the 2-pivaloyl group. However, this steric interaction, is minimized upon conversion to rotamer **B** and addition of the organocuprate then proceeds from the unhindered back side ("matched case").

In contrast, case B represents the "mismatched" situation in which both rotamers **C** and **D** are not favoured sterically. In **C**, substituent R and the 2-pivaloyl group interfere with each other. The amount of *trans*-2,6-disubstituted product in **12** results from a back-side attack at rotamer **C**. In rotamer **D**, the steric repulsion of substituents is minimized, and a back-side attack should give the *cis*-substituted product. The reason for the limited contribution of rotamer **D** (case B) in the conjugate addition entailing a low *cis* selectivity is more difficult to explain. Obviously, the electrophilic reactivity of the enaminone system in rotamer **D** is reduced (see also, Scheme 3).

As a consequence of these results, the strategy for the synthesis of the 2,6-disubstituted piperidinones from precursors **6** was changed. The mismatching interference by the carbohydrate auxiliary indicates that it should be removed prior to the functionalization of the enone system (Scheme 9). However, acid hydrolysis of the *N*-glycoside bond of compound **6** is not possible because of the acid stability of (vinylogous) *N*-glycosylamides. This problem was circumvented by conjugate hydride addition of **6b** using L-Selectride, and subsequent trapping of the resulting lithium enolate with phenylselenium chloride, affording **14** in a

yield of 70%. After mild acidolysis of the sensitized *N*-glycosidic bond, the piperidone was *N*-protected as benzyl carbamate **15**. Oxidation of this compound to the selenium oxide with H_2O_2·urea complex and subsequent elimination, reinstalled the vinylogous amide **16** in a yield of 53% over three steps.[20]



Scheme 9. Reagents and conditions: (a) L-Selectride, PhSeCl, 70%; (b) 1 N HCl, methanol, 12 h; (c) separation; (d) aq. Na_2CO_3, BnOCOCl, 53% yield over three steps; (e) H_2O_2·urea, CH_2Cl_2/H_2O (20:2), 69%; (f) Mg, THF, $Br(CH_2)_3OEE$ (EE = 1-ethoxyethyl); (g) CuBr·SMe_2, BF_3·OEt_2, THF, −78 °C, 1 h, 73%, *dr* = 2:1; (h) PPh_3, NCS, CH_2Cl_2, −40 to +20 °C, 95%; (i) LiHMDS, THF; (j) 2-amino-5-chloropyridine triflate, Pd/C, H_2, 41% over two steps

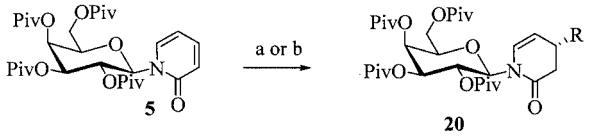
Comins et al. have reported that benzyloxycarbonyl-protected 2,3-dehydropiperidin-4-ones undergo conjugate addition of organocuprates with *cis* diastereoselectivity.[15a,21,22] According to those observations the synthesis of indolizidine 167B **19** (Scheme 9), an alkaloid from the secretions of frogs belonging to the family *dendrobates*,[23] should be possible by introduction of an *O*-protected hydroxypropyl side chain to precursor **16**.[24] However, the conjugate addition of the (1-ethoxyethyl)cuprate−boron trifluoride complex[25] to **16** proceeded with disappointingly low diastereoselectivity (*cis*/*trans* = 2:1). This unexpected result might be due to an interfering coordination of the ethoxyethyl protecting group to the metal ion of this complex. Non-substituted alkylcuprates react with high stereoselectivity under identical conditions.[22,26]

Acidolytic removal of the 1-ethoxyethyl (EE) group gave **17** which was transformed into the chloride **18** by a modified Appel reaction using *N*-chlorosuccinimide/triphenylphosphane.[14] At this stage the diastereomers were separated by column chromatography. Reduction of the carbonyl group was achieved by deprotonation with LiHMDS, trapping the lithium enolate as enol triflate using 2-amino-5-chloropyridine triflate,[27] followed by hydrogenation, which simultaneously effected removal of the *N*-benzyloxycarbonyl group. The ring-closing *N*-alkylation was performed under basic conditions (Li_2CO_3) and furnished the target (+)-indolizidine 167B **19** in an overall yield of 6.3% after nine steps from the *N*-galactosyl-4-pyridone **3**.

Regio- and Stereoselective Conjugate Addition Reactions at N-Galactosyl-2-pyridone

In contrast to the number of stereoselective syntheses of 2-substituted and 2,6-disubstituted piperidines, only a few methods are known for the stereoselective formation of piperidines bearing a substituent at 4-position.[28] We recently reported a stereoselective access to 4-substituted piperidines which resembles the reactions outlined for the *N*-galactosyl-4-pyridones.[9]

Activation of the *N*-galactosyl-2-pyridone **5** with either TMSOTf or TIPSOTf, formed the corresponding 2-(silyloxy)pyridinium triflate which was thus rendered susceptible to nucleophilic addition of Grignard reagents (Scheme 10). However, in contrast to our expectations, the conjugate addition of Grignard compounds took place selectively at 4-position. The same regioselectivity was obtained using organocuprates as nucleophiles. The diastereoselectivity of these conjugate addition reactions is excellent regardless of whether Grignard reagents or organocuprates are used (Table 3).



Scheme 10. Reagents and conditions: (a) R_3SiOTf, 1 h, CH_2Cl_2, room temp., 2,6-lutidine, RMgX, CH_2Cl_2, room temp., 1−2 h; (b) TMSCl, THF, 1 h, room temp., R^2_2CuLi, THF, −78 °C to room temp.

Table 3. Stereoselective addition of Grignard reagents and organocuprates

Compound	Reagent	Yield [%]	Diastereoselectivity (*R*)/(*S*)
20a	EtMgCl	54	> 99:1
20b	*n*PrMgCl	68	> 99:1
20c	*i*PrMgCl	88	< 1:99
20d	*n*BuMgCl	75	> 99:1
20e	*t*BuMgCl	22	< 1:99
20f	*n*DecMgCl	55	> 99:1
20g	cyclohexylMgCl	79	< 1:99
20h	benzylMgCl	34	> 99:1
20i	phenylMgCl	76	> 99:1
20j	butenylMgBr	86	> 99:1
20d	nBu_2CuLi	64	> 99:1
20e	tBu_2CuLi	39	92:8
20k	$nHex_2CuLi$	93	> 99:1

The carbohydrate auxiliary obviously controls both the facial selectivity as well as the regioselectivity during this addition. Only in two experiments (**20c** and **20f**) was the regioisomeric 6-substituted product detectable by ^1H NMR spectroscopy of the crude products. However, they composed less than 5% of the products and could be separated

by flash chromatography. The absolute configuration of the 4-substituted 2-pyridone was determined by X-ray analysis of products **20b** and **20c** showing that the substituent adopts a pseudo-equatorial position (Figure 3).

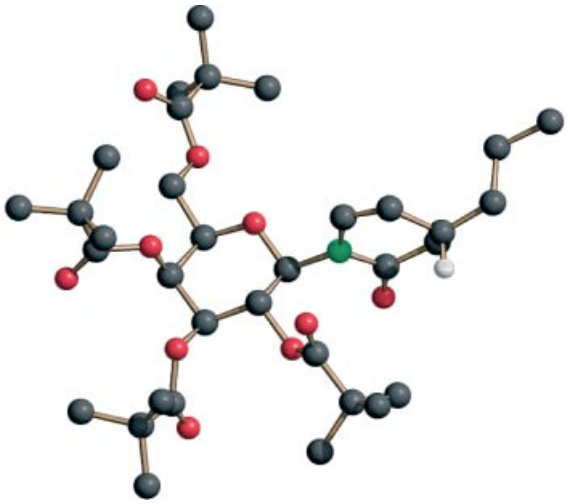
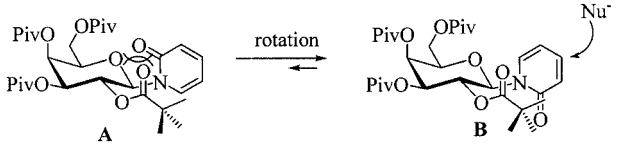


Figure 3. X-ray analysis of 1-galactosyl-4-propyl-5,6-dehydropiperidin-2-one **20b**

The selective formation of one diastereomer can be rationalized in terms of the different stability of rotamers **A** and **B** of the *N*-galactosyl-2-pyridone **5** (Scheme 11). Rotamer **B** is favoured because the electrostatic repulsion between the carbonyl oxygen atom of the lactam and the carbonyl oxygen atom of the 2-pivaloyl group is minimized. After activation by *O*-silylation, any incoming nucleophile preferentially attacks from the less shielded *si*-face (back side).



Scheme 11

It is worth noting that the electrophilic reactivity at 6-position is obviously reduced, probably because of the participation of the carbonyl oxygen atom of the 2-pivaloyl group (see Scheme 8, rotamer D).

Conclusion

The results described are evidence that efficient stereodifferentiation of enantiotopic sites of 4- and 2-pyridone can be achieved in conjugate addition reactions of Grignard and organocuprate reagents to the corresponding *O*-silylated *N*-(galactosyl)pyridinium salts. In the 4-pyridone series these conversions result in an enantioselective desymmetrization giving 2-substituted 5,6-dehydropiperidinones of the opposite configuration compared to those obtained from domino-Mannich−Michael reaction sequences using *N*-(galactosyl)imines.[14] The application of this methodology was demonstrated by total syntheses of enantiomerically pure (*S*)-coniine and (5*S*,9*S*)-indolizidine 167B. Nucleophilic addition reactions of *N*-(galactosyl)pyridinium ions derived from 2-pyridone furnished 4-substituted pyridone derivatives with surprising regioselectivity and excellent stereoselectivity. This class of compounds is of substantial importance for developments in the area of CNS-active drugs.[3]

Experimental Section

Materials and Methods: Reactions were carried out in flame-dried glassware under argon. Solvents were distilled before use. Analytical TLC was performed on aluminium-backed TLC plates coated with silica gel $60F_{254}$ (E. Merck, Darmstadt, Germany). Column chromatography was performed on silica (63−200 μm, Baker or 40−63 μm, E. Merck). Melting points were measured with a Dr. Tottoli apparatus (Büchi) and are uncorrected. Optical rotation values were measured with a Perkin−Elmer 241 polarimeter. NMR spectra were recorded with a Bruker WT-200, a Bruker AC-300 or a Bruker AM 400 spectrometer; chemical shifts given are expressed in δ (ppm) downfield from tetramethylsilane. ESI-MS data were measured with a navigator (Thermo Quest) spectrometer, FD-MS data with a MAT 95-spectrometer (Finnigan). HPLC analyses were performed with a Knauer system equipped with a Luna C-18-2 column (Phenomenex, 250 × 4.6 mm, 5 μm particle size) and a diode array UV detector at a flow rate of 1 mL/min.

1,4-Dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-pyridin-4(1*H*)-one (3): 4-(Trimethylsilyloxy)pyridine (**2**, 9.8 mL, 57.8 mmol) was added slowly to 2,3,4,6-tetra-*O*-pivaloyl-α-D-galactopyranosyl fluoride[11] (**1**, 20 g, 30.8 mmol), dissolved in 1,2-dichloroethane (350 mL) at 70 °C through a syringe. Then $TiCl_4$ (33.8 mL, 308 mmol) was added, turning the previously colourless solution to yellow. The mixture was refluxed for 1 h. After cooling to room temperature, the reaction was terminated by careful addition of aq. satd. $NaHCO_3$ (500 mL). The organic layer was diluted with CH_2Cl_2 (500 mL), the aqueous layer extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic layers were dried with $MgSO_4$. After evaporation of the solvent in vacuo and flash chromatography (ethyl acetate/methanol, 9:1), colourless crystals of **3** were isolated (18.28 g, 30.8 mmol, yield quant.). M.p. 115 °C. R_f = 0.11 (ethyl acetate/light petroleum ether, 4:1). $[\alpha]_D^{20}$ = 3.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97, 1.05, 1.10, 1.26 (4 s, 36 H, piv C*H*$_3$), 3.99 (dd, $J_{6a,6b}$ = 11.0, $J_{6a,5}$ = 7.4 Hz, 1 H, H-6a), 4.11 (dd, $J_{6b,6a}$ = 11.0, $J_{6b,5}$ = 6.7 Hz, 1 H, H-6b), 4.19 (t, $J_{5,6a}$ = 6.7, $J_{5,6b}$ = 7.0 Hz, 1 H, H-5), 4.97 (d, $J_{1,2}$ = 9.4 Hz, 1 H, H-1), 5.21 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 3.1 Hz, 1 H, H-3), 5.45 (m, $J_{2,3}$ = 10.3, $J_{2,1}$ = 8.8, $J_{4,3}$ = 3.0 Hz, 2 H, H-2, H-4), 6.31 (d, *J* = 7.8 Hz, 2 H, N−C*H*=CH−), 7.34 (d, *J* = 7.4 Hz, 2 H, N−CH=C*H*−) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.7, 27.2 (piv *C*H$_3$), 38.7, 38.8, 39.1 (piv $C_{quat.}$), 60.5 (C-6), 66.4, 67.5, 70.8, 74.0 (C-2, C-3, C-4, C-5), 90.9 (C-1), 118.7 (N−CH=*C*H−), 137.2 (N−*C*H=CH−), 176.1, 176.3, 177.0, 177.7 (piv C=O), 179.5 (C=O) ppm. $C_{31}H_{47}NO_{10}$ (593.71): calcd. C 62.71, H 7.98, N 2.36; found C 62.68, H 7.95, N 2.11.

General Procedure for the Preparation of Compounds 6: The *N*-(galactosyl)pyridone **3** in CH_2Cl_2 or toluene (30 mL·g^{-1}) was treated with the corresponding silylating agent (1.2−1.8 equiv.) at ambient

temperature. After stirring for 30 min, 2,6-lutidine (1.2−1.8 equiv.) was added followed by addition of a solution of the corresponding Grignard reagent (1.2−1.8. equiv.). Relevant experimental details and analytical data are given for each compound. After stirring for 10−60 min (until TLC monitoring indicated complete conversion), the reaction was terminated by addition of aq. satd. $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2, the combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. Purification by flash chromatography (light petroleum ether/ethyl acetate) afforded the following compounds.

(2*S*)-2,3-Dihydro-2-methyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6a): Compound **3** (4 g, 6.74 mmol), TIPSOTf (3.27 mL, 12.13 mmol), 2,6-lutidine (1.41 mL, 12.13 mmol), MeMgCl (3 M in THF, 4.1 mL, 12.13 mmol); solvent: CH_2Cl_2; yield 3.03 g (4.96 mmol, 74%); mixture of diastereomers, ratio > 95:5 (^{1}H NMR). Data for the mixture of diastereomers: M.p. 88 °C. R_f = 0.58 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{28}$ = −16.3 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data for the unseparated major (*S*) diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$,): δ = 1.08−1.25 (m, 39 H, piv CH_3, $-CH_3$), 2.19 (d, J_{gem} = 16.1 Hz, 1 H, $-CH_2-C=O$), 2.68 (dd, J_{gem} = 16.2, J_{vic} = 6.6 Hz, 1 H, $-CH_2-C=O$), 3.73 (m, 1 H, NCH), 4.02 (m, 3 H, H-5, H-6a, H-6b), 4.42 (d, $J_{1,2}$ = 9.4 Hz, 1 H, H-1), 5.11 (d, *J* = 7.9 Hz, 1 H, NCH=CH), 5.13 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.37 (t, 1 H, H-2), 5.40 (d, $J_{4,3}$ = 3.2 Hz, 1 H, H-4), 7.05 (d, *J* = 7.9 Hz, 1 H, NCH=C) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 16.3 ($-CH_3$), 27.0, 27.2 (piv CH_3), 38.7, 38.7, 39.1 (piv $C_{quat.}$), 42.9 ($CH_2C=O$), 56.1 (MeCHN), 61.5 (C-6), 66.7, 66.8, 71.4, 73.1 (C-2, C-3, C-4, C-5), 90.4 (C-1), 101.7 (NCH=*C*H), 146.4 (N*C*H=CH), 176.5, 176.6, 177.1, 177.8 (piv C=O), 191.6 (C=O) ppm. MS (FD): *m*/*z* = 610.0 $[M]^+$. $C_{32}H_{51}NO_{10}$ (609.76): calcd. C 62.93, H 8.58, N 2.29; found C 63.12, H 8.63, N 2.23.

(2*S*)-2,3-Dihydro-2-propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one [(*S*)-6b] and (2*R*)-2,3-Dihydro-2-propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one [(*R*)-6b]: 3 (1 g, 1.68 mmol), TIPSOTf (0.73 mL, 2.69 mmol), 2,6-lutidine (0.31 mL, 2.69 mmol), *n*PrMgCl (2 M in diethyl ether, 1.35 mL, 2.69 mmol); solvent: CH_2Cl_2; yield 0.90 g (1.41 mmol, 84%); mixture of diastereomers, ratio 8:1 (^{1}H NMR). The diastereomers were separated by preparative HPLC [Luna 10 μ, Kromasil C-18(2), 250 × 50 mm (Phenomenex), eluent: MeCN/H_2O (85:15), flow 20 mL·min^{-1}, UV detection at 310 nm, R_t [min] = 31.64 [(*S*) isomer], 40.92 [(*R*) isomer]. The minor diastereomer [(*R*) isomer] is identical to the compound obtained from the tandem-Mannich−Michael reaction of galactosylimine.[14] Data for the pure (*S*) isomer: M.p. 161 °C. R_f = 0.70 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{28}$ = 13.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, $-CH_3$), 1.08−1.25 (m, 38 H, piv CH_3), 1.54 (m, 1 H, $-CH_2-$), 1.79 (m, 1 H, $-CH_2-$), 2.34 (d, J_{gem} = 16.0 Hz, 1 H, $-CH_2-C=O$), 2.61 (dd, J_{gem} = 16.0, J_{vic} = 6.7 Hz, 1 H, $-CH_2-C=O$), 3.50 (m, 1 H, NCH), 4.03 (m, 3 H, H-5, H-6a, H-6b), 4.39 (d, $J_{1,2}$ = 9.0 Hz, 1 H, H-1), 5.09 (d, *J* = 8.2 Hz, 1 H, NCH=C*H*), 5.14 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.35 (t, 1 H, H-2), 5.40 (d, $J_{4,3}$ = 3.1, 1 H, H-4), 7.10 (d, *J* = 7.9 Hz, 1 H, NCH=C) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 ($-CH_3$), 18.6 ($-CH_2-$), 27.0, 27.1, 27.2 (piv CH_3), 31.6 ($-CH_2-$), 38.6, 38.7, 38.8, 39.1 (piv $C_{quat.}$), 39.7 (*C*H$_2$C=O), 60.4 (propyl−*C*HN), 61.5 (C-6), 66.8, 67.4, 71.4, 73.2 (C-2, C-3, C-4, C-5), 90.3 (C-1), 101.5 (NCH=*C*H), 146.4 (N*C*H=CH), 176.3, 176.5, 177.1, 177.8 (piv C=O), 191.5 (C=O) ppm. $C_{34}H_{55}NO_{10}$ (637.81): calcd. C 64.03, H 8.69, N 2.20; found C 63.78, H 8.86, N 2.15.

(2*R*)-2,3-Dihydro-2-isopropyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6c): 3 (4.35 g, 7.33 mmol), TMSOTf (2.11 mL, 11.72 mmol), 2,6-lutidine (1.36 mL, 11.72 mmol), *i*PrMgCl (2 M in THF, 5.86 mL, 11.72 mmol); solvent: CH_2Cl_2; yield 4.15 g (6.50 mmol, 89%), mixture of diastereomers, ratio 92:8 (^{1}H NMR). Data for the mixture of diastereomers: R_f = 0.63 (light petroleumether/ethyl acetate, 1:1). $[\alpha]_D^{28}$ = 22.3 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data for the unseparated major (*R*) diastereomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89, 0.93 (2d, *J* = 6.3, *J* = 6.8 Hz, 6 H, $-CH_3$), 1.08, 1.12, 1.13, 1.26 (4s, 36 H, piv CH_3), 2.09 (dd, *J* = 6.3, *J* = 6.8 Hz, 1 H, $(CH_3)_2CH$], 2.44 (d, J_{gem} = 16.6 Hz, 1 H, $-CH_2-C=O$), 2.60 (dd, J_{gem} = 16.6, J_{vic} = 7.8 Hz, 1 H, $-CH_2-C=O$), 3.31 (m, 1 H, NC*H*), 4.03 (m, 3 H, H-5, H-6a, H-6b), 4.36 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 5.05 (d, *J* = 7.8 Hz, 1 H, NCH=C*H*), 5.13 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.33 (t, *J* = 10.2 Hz, 1 H, H-2), 5.41 (d, $J_{4,3}$ = 3.4 Hz, 1 H, H-4), 7.19 (d, *J* = 8.3 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 18.1, 19.2 (2 × methyl), 27.0, 27.0, 27.1, 27.2 (piv CH_3), 31.6 (*C*HMe$_2$), 37.0 (*C*H$_2$C=O), 38.7, 38.8, 38.9, 39.1 (piv $C_{quat.}$), 61.8 (*i*Pr*C*HN), 66.0, 67.0, 68.1, 71.4, 73.3 (C-2, C-3, C-4, C-5, C-6), 89.8 (C-1), 101.0 (NCH=*C*H), 146.8 (N*C*H=CH), 176.3, 177.1, 177.8 (piv C=O), 191.6 (C=O) ppm. MS (FD): *m*/*z* = 638.9 $[M + H]^+$. $C_{34}H_{55}NO_{10}$ (637.81): calcd. C 64.03, H 8.69, N 2.20; found C 63.17, H 8.57, N 1.92.

(2*S*)-2-Butyl-2,3-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6d): 3 (1.62 g, 2.73 mmol), TMSOTf (0.31 mL, 4.09 mmol), 2,6-lutidine (0.74 mL, 4.09 mmol), *n*BuMgCl (2 M in THF, 2.73 mL, 5.46 mmol); solvent: toluene; yield 0.89 g (1.37 mmol, 50%); single diastereomer, ratio > 99:1 (^{1}H NMR). R_f: 0.25 (light petroleum ether/ethyl acetate, 2:1). $[\alpha]_D^{28}$ = 2.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.88 (t, 3 H, $-CH_3$), 1.08−1.27 (m, 40 H, piv CH_3, $-CH_2-$), 1.52 (m, 1 H, $-CH_2-$), 1.86 (m, 1 H, $-CH_2-$), 2.39 (d, J_{gem} = 15.8 Hz, 1 H, $-CH_2-C=O$), 2.63 (dd, J_{gem} = 16.4, J_{vic} = 6.7 Hz, 1 H, $-CH_2-C=O$), 3.50 (m, 1 H, NC*H*), 4.04 (m, 3 H, H-5, H-6a, H-6b), 4.40 (d, $J_{1,2}$ = 9.1 Hz, 1 H, H-1), 5.11 (d, *J* = 7.9 Hz, 1 H, NCH=C*H*), 5.14 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.36 (t, 1 H, H-2), 5.42 (d, $J_{4,3}$ = 3.2 Hz, 1 H, H-4), 7.10 (d, *J* = 7.9 Hz, 1 H, NC*H*=C) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.9 ($-CH_3$), 22.3 ($-CH_2-$), 27.0, 27.1, 27.1, 27.2 (piv CH_3), 27.8, 29.1 ($-CH_2-$), 38.6, 38.7, 38.8, 38.9 (piv $C_{quat.}$), 39.6 (*C*H$_2$C=O), 60.2 (butyl−*C*HN), 61.38 (C-6), 66.6, 67.5, 71.2, 73.0 (C-2, C-3, C-4, C-5), 90.2 (C-1), 101.4 (NCH=*C*H), 146.6 (N*C*H=CH), 176.3, 176.5, 176.9, 177.7 (piv C=O), 191.5 (C=O) ppm. MS (FD): *m*/*z* = 652.0 $[M]^+$; calcd. for $C_{35}H_{57}NO_{10}$ (651.83).

(2*S*)-2-Decyl-2,3-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one [(*S*)-6e] and (2*R*)-2-Decyl-2,3-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one [(*R*)-6e]: 3 (1 g, 1.68 mmol), TMSOTf (0.55 mL, 3.03 mmol), 2,6-lutidine (0.33 mL, 3.03 mmol), *n*DecMgCl (1 M in diethyl ether, 3.03 mL, 3.03 mmol); solvent: CH_2Cl_2; yield 0.88 g (1.19 mmol, 71%); mixture of diastereomers, ratio 3.8:1 (HPLC). R_f = 0.29 (light petroleum ether/ethyl acetate, 4:1). The diastereomers were separated by HPLC {MeCN/H_2O [gradient 88:12 to 100:0 (40 min), flow 1 mL·min^{-1}, UV detection at 310 nm, R_t [min] = 22.28 (major isomer), 27.28 (minor isomer)}. Data given for the pure major (*S*) compound isolated by HPLC: $[\alpha]_D^{20}$ = 3.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.79−1.25 (m, 55 H, piv CH_3, $-CH_2-$, $-CH_3$), 1.49 (m, 1 H, $-CH_2-$), 1.80 (m, 1 H, $-CH_2-$), 2.37 (d, J_{gem} = 16.1 Hz, 1 H, $-CH_2-C=O$), 2.61 (dd, J_{gem} = 16.1, J_{vic} = 6.3 Hz, 1 H, $-CH_2-C=O$), 3.47 (m, 1 H, NC*H*), 4.01 (m,

3 H, H-5, H-6a, H-6b), 4.39 (d, $J_{1,2}$ = 8.8 Hz, 1 H, H-1), 5.12 (m, 2 H, NCH=C*H*, H-3), 5.31 (t, *J* = 9.3 Hz, 1 H, H-2), 5.40 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 7.08 (d, *J* = 7.8 Hz, 1 H, NC*H*=C) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1 (−CH_3), 22.6, 25.5, 25.6 (−CH_2−), 27.0, 27.1, 27.2 (piv CH_3), 29.2, 29.4, 29.5, 31.5, 31.8 (−CH_2−), 38.6, 38.7, 38.8, 39.1 (piv $C_{quat.}$), 39.6 (*C*H_2C=O), 60.7 (decyl−*C*HN), 61.4 (C-6), 66.8, 67.3, 71.4, 73.1 (C-2, C-3, C-4, C-5), 90.2 (C-1), 101.5 (NCH=*C*H), 146.6 (N*C*H=CH), 176.3, 176.5, 177.1, 177.7 (piv C=O), 191.5 (C=O) ppm. $C_{41}H_{70}NO_{10}$ (737.00): calcd. C 66.82, H 9.57, N 1.90; found C 66.83, H 9.43, N 1.96. Data for the minor (*R*) compound separated by HPLC: $[\alpha]_D^{20}$ = −59.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (t, 3 H, −CH_3), 1.06−1.23 (m, 52 H, piv CH_3, −CH_2−), 1.43, 1.78 (m, 2 H, −CH_2−), 2.31 (d, J_{gem} = 16.6 Hz, 1 H, −CH_2−C=O), 2.57 (dd, J_{gem} = 16.6, J_{vic} = 6.8 Hz, 1 H, −CH_2−C=O), 3.79 (m, 1 H, NC*H*), 3.87−4.13 (m, 3 H, H-5, H-6a, H-6b), 4.52 (d, $J_{1,2}$ = 8.8 Hz, 1 H, H-1), 4.90 (d, *J* = 7.3 Hz, 1 H, NCH=C*H*), 5.12 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.38 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 5.48 (t, *J* = 10.3, *J* = 9.3 Hz, 1 H, H-2), 6.86 (d, *J* = 7.8 Hz, 1 H, NC*H*=C) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1 (−CH_3), 22.6, 25.8 (−CH_2−), 27.0, 27.1, 27.2 (piv CH_3), 29.2, 29.4, 29.5, 30.6, 31.8 (−CH_2−), 38.7, 38.7, 38.8 (piv $C_{quat.}$), 39.0 (*C*H_2C=O), 53.7 (decyl−*C*HN), 60.8 (C-6), 65.7, 66.5, 71.3, 72.8 (C-2, C-3, C-4, C-5), 91.5 (C-1), 99.9 (NCH=*C*H), 149.7 (N*C*H=CH), 176.4, 177.0, 177.1, 177.6 (piv C=O), 192.1 (C=O) ppm. $C_{41}H_{70}NO_{10}$ (737.00): calcd. C 66.82, H 9.57, N 1.90; found C 66.81, H 9.46, N 1.91.

(2*R*)-2,3-Dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-vinylpyridine-4(1*H*)-one (6f): 3 (5 g, 8.42 mmol), TMSOTf (2.30 mL, 12.63 mmol), 2,6-lutidine (1.50 mL, 12.63 mmol), vinylMgBr (1 M in THF, 4.1 mL, 12.6 mmol); solvent: CH_2Cl_2; yield 2.65 g (4.26 mmol, 51%); ratio of diastereomers > 99:1 (HPLC). R_f = 0.56 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = −40.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09, 1.14, 1.15, 1.27 (4s, 36 H, piv CH_3), 2.42 (dd, J_{gem} = 16.1, ^4J = 2.6 Hz, 1 H, −CH_2C=O), 2.72 (dd, J_{gem} = 16.3, J_{vic} = 6.9 Hz, 1 H, −CH_2C=O), 3.96−4.09 (m, 4 H, H-5, H-6a, H-6b, NC*H*R), 4.41 (d, $J_{1,2}$ = 9.1 Hz, 1 H, H-1), 5.13 (d, *J* = 7.6 Hz, 1 H, NCH=C*H*), 5.13−5.18 (m, 2 H, H-3, RHC=CH_2), 5.26 (d, J_{trans} = 17.3 Hz, 1 H, RHC=CH_2), 5.39 (t, *J* = 9.6 Hz, 1 H, H-2), 5.41 (d, $J_{4,3}$ = 3.2 Hz, 1 H, H-4), 5.94 (ddd, J_{trans} = 17.2, J_{cis} = 10.3, *J* = 7.0 Hz, 1 H, R*H*C=CH_2), 7.14 (d, *J* = 8.2 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.0, 27.1, 27.2 (piv CH_3), 38.7, 38.8, 38.9, 39.1 (piv $C_{quat.}$), 41.5 (*C*H_2C=O), 61.3, 62.3 (C-6, NCHR), 66.8, 67.2, 71.5, 73.2 (C-2, C-3, C-4, C-5), 89.7 (C-1), 102.1 (NCH=*C*H), 118.1 (H_2C=CHR), 133.7 (H_2C=*C*HR), 146.8 (N*C*H=CH), 176.4, 176.6, 177.2, 177.8 (piv C=O), 191.0 (C=O) ppm. $C_{32}H_{51}NO_{10}$ (621.77): calcd. C 63.75, H 8.27, N 2.25; found C 63.18, H 8.19, N 2.16.

(2*S*)-2-(3-Butenyl)-2,3-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one) (6g): 3 (1.18 g, 1.98 mmol), TIPSOTf (0.81 mL, 2.97 mmol), 2,6-lutidine (0.34 mL, 2.97 mmol), butenylMgBr [freshly prepared from Mg (72 mg, 2.96 mmol) and 4-bromobutene (0.30 mL, 2.99 mmol)]; solvent: CH_2Cl_2; yield 0.25 g (0.38 mmol, 79%); 24% conversion; single diastereomer, ratio >> 99:1 (^{1}H NMR). R_f = 0.62 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = 4.9 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07, 1.10, 1.12, 1.24 (4s, 36 H, piv CH_3), 1.65−1.72 (m, 1 H, −CH_2−), 1.83−1.99 (m, 2 H, −CH_2−), 2.08−2.11 (m, 1 H, −CH_2−), 2.35 (d, J_{gem} = 16.4 Hz, 1 H, −CH_2−CO), 2.61 (dd, J_{gem} = 16.1, J_{vic} = 6.5 Hz, 1 H, −CH_2−CO), 3.52 (m, 1 H, NC*H*), 3.98−4.07 (m, 3 H, H-5, H-6a, H-6b), 4.38 (d, $J_{1,2}$ = 9.4 Hz, 1 H, H-1), 4.91−5.00 (m, 2 H, alkene), 5.09 (d, *J* = 9.1 Hz, 1 H, NCH=C*H*), 5.12 (dd, $J_{3,2}$ = 10.0, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.33 (t, 1 H, H-2), 5.4 (d, $J_{4,3}$ = 3.2 Hz, 1 H, H-4), 5.66 (m, 1 H, alkene), 7.09 (d, *J* = 7.9 Hz, NC*H*=CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.03, 27.22 (piv CH_3), 28.45, 29.78 (−CH_2−), 38.76, 38.81, 38.91, 39.10 (piv $C_{quat.}$), 39.62 (*C*H_2C=O), 59.68 (butenyl *C*HN), 61.54 (C-6), 66.85, 67.31, 71.40, 73.19 (C-2, C-3, C-4, C-5), 90.23 (C-1), 101.69 (NCH=*C*H), 116.00 (*C*=CH_2), 136.91 (C=*C*H_2), 146.58 (N*C*H=CH), 176.39, 176.57, 177.16, 177.83 (piv C=O), 191.42 (C=O) ppm. $C_{35}H_{57}NO_{10}$ (651.81): calcd. C 64.49, H 8.81, N 2.15; found C 63.85, H 8.13, N 2.02.

(2*R*)-2,3-Dihydro-2-phenyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6h): 3 (2 g, 3.37 mmol), TMSOTf (1.10 mL, 6.06 mmol), 2,6-lutidine (0.70 mL, 6.06 mmol), PhMgCl (2 M in THF, 3.03 mL, 6.06 mmol); solvent: CH_2Cl_2; yield 1.87 g (2.78 mmol, 83%). M.p. 173 °C. Single diastereomer, ratio >> 99:1 (HPLC, ^{1}H NMR). R_f = 0.58 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = −65.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07−1.27 (4 s, 36 H, piv CH_3), 2.65 (dd, J_{gem} = 16.1, J_{vic} = 5.8 Hz, 1 H, −CH_2−C=O), 2.84 (dd, J_{gem} = 16.1, J_{vic} = 6.8 Hz, 1 H, −CH_2−C=O), 3.74 (m, 1 H, H-5), 3.95 (m, 2 H, H-6a, H-6b), 4.34 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 4.69 (m, 1 H, NC*H*), 5.01 (dd, $J_{3,2}$ = 10.3, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.22 (d, *J* = 8.3 Hz, 1 H, NCH=C*H*), 5.34 (d, $J_{4,3}$ = 2.9, 1 H, H-4), 5.43 (t, 1 H, H-2), 7.30 (m, 5 H, ar.), 7.36 (d, *J* = 7.8 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.0, 27.1 27.2 (piv CH_3), 38.6, 38.7, 38.8, 39.0 (piv $C_{quat.}$), 44.0 (*C*H_2C=O), 61.0 (phenyl−*C*HN), 63.3 (C-6), 66.7, 67.7, 71.6, 73.1 (C-2, C-3, C-4, C-5), 88.4 (C-1), 102.1 (NCH=*C*H), 126.7, 128.5, 128.9 (*o*-, *m*-, *p*-C, phenyl), 138.2 (*ipso*-C, phenyl), 147.3 (N*C*H=CH), 176.2, 176.4, 177.1, 177.6 (piv C=O), 190.4 (C=O) ppm. $C_{37}H_{53}NO_{10}$ (671.82): calcd. C 66.15, H 7.95, N 2.08; found C 66.27, H 8.14, N 2.12. Crystal data: size: 0.032 × 0.064 × 0.126 mm; colourless needles; $P2_1$ (monoclinic); *a* = 15.409(3) Å, *b* = 10.767(2) Å, *c* = 24.761(6) Å, β = 96.00(1)°, *V* = 4085(1) Å^3, *Z* = 4, *F*(000) = 1448; *T* = 298 K; ρ = 1.092 g·cm^{-3}. Data collection: Diffractometer: CAD4 (Enraf−Nonius); radiation: Cu-K_α, graphite monochromator; scan-type: ω/2Θ; scan width 0.8 + 0.14·tanΘ and 25% left and right for determination of background; measurement range 1−5° ≤ Θ ≤ 75°; 0 ≤ *h* ≤ 19, 0 ≤ *k* ≤ 13, −31 ≤ *l* ≤ 31; reflections: measured 18201 (with Friedel pairs), independent 16489 (R_{int} = 0.0340), observed 8484 (|*F*|/σ(*F*) > 4.0). CCDC-237631 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

(2*R*)-2,3-Dihydro-2-(3-methoxyphenyl)-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6i): 3 (0.5 g, 0.84 mmol), TMSOTf (0.18 mL, 1.01 mmol), 2,6-lutidine (0.12 mL, 1.01 mmol), 3-$MeOC_6H_4MgBr$ (1 M in THF, 1.01 mL, 1.01 mmol); solvent: CH_2Cl_2; yield 0.28 g (0.4 mmol, 47%); single diastereomer, ratio >> 99:1 (^{1}H NMR). R_f = 0.58 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = −57.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07, 1.11, 1.16, 1.27 (4 s, 36 H, piv CH_3), 2.65 (dd, J_{gem} = 16.1, J_{vic} = 5.8 Hz, 1 H, −CH_2−CO), 2.83 (dd, J_{gem} = 16.1, J_{vic} = 6.8 Hz, 1 H, −CH_2−CO), 3.77 (m, 4 H, −OCH_3, NC*H*−phenyl), 3.97 (d, $J_{6,5}$ = 6.8 Hz, 2 H, H-6a, H-6b), 4.36 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 4.66 (t, 1 H, H-5), 5.02 (dd, $J_{3,2}$ = 10.3, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.24 (d, *J* = 7.8 Hz, 1 H, NCH=C*H*), 5.38 (m, 2 H, H-2, H-4), 6.83 (m, 3 H, ar.), 7.18 (1 H, ar.), 7.35 (d, *J* = 8.8 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.00,

27.07 (piv CH_3), 38.67, 38.78, 38.91, 39.11 (piv $C_{quat.}$), 60.88 (C-6), 63.24, 66.64, 67.78, 71.61, 73.07, 75.52 (C-2, C-3, C-4, C-5, N*C*H-phenyl), 88.38 (C-1), 102.05 (NCH=*C*H), 147.60 (N*C*H=CH), 112.97, 113.42, 118.83, 129.93 (2 × *o*-, *m*-, *p*-C, phenyl), 139.62 (C_{ipso}), 159.95 (MeO−C_{ar}), 176.29, 176.52, 177.20, 177.78 (piv CO), 190.66 C=O) ppm. MS (FD): *m*/*z* = 701.9 $[M]^+$. $C_{38}H_{55}NO_{11}$ (701.85): calcd. C 65.03, H 7.90, N 2.00; found C 64.12, H 8.61, N 1.76.

(2*S*)-2,3-Dihydro-2-(3-hydroxypropyl)-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6j): 3 (1.13 g, 1.90 mmol), TMSOTf (0.447 mL, 2.47 mmol), 2,6-lutidine (0.286 mL, 2.47 mmol). The Grignard reagent was prepared according to the procedure of ref.[29] using 3-chloro-1-propanol (0.83 mL, 10 mmol) in anhydrous THF (10 mL), *i*PrMgCl (5 mL, 2.0 M in THF, 10 mmol), Mg (240 mg, 10 mmol); solvent: CH_2Cl_2; yield 0.315 g (0.48 mmol, 71%), 35% conversion; mixture of diastereomers, ratio >12:1 (^{1}H NMR). R_f = 0.08 (light petroleum ether/ethyl acetate, 1:1). Data given for the mixture of diastereomers: $[\alpha]_D^{20}$ = 3.1 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data given for the unseparated major (*S*) diastereomer: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07, 1.11, 1.13, 1.25 (4s, 36 H, piv CH_3), 1.43−1.87 (m, 4 H, −CH_2−), 2.02 (br. s, 1 H, OH), 2.36 (m, 3 H, NC*H*, −CH_2−OH), 4.05 (m, 3 H, H-5, H-6a, H-6b), 4.46 (d, $J_{1,2}$ = 8.8 Hz, 1 H, H-1), 5.10 (d, *J* = 7.3 Hz, 1 H, NCH=C*H*), 5.13 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.32 (t, 1 H, H-2), 5.40 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 7.10 (d, *J* = 7.8 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 26.17 (−CH_2−), 27.05, 27.10, 27.22 (piv CH_3), 28.31 (−CH_2−), 38.70, 38.76, 38.84, 39.11 (piv $C_{quat.}$), 39.82 (−*C*H$_2$C=O), 60.23 (propyl−*C*HN), 61.28 (C-6), 62.19 (−*C*H$_2$−OH), 66.80, 67.39, 71.46, 73.06 (C-2, C-3, C-4, C-5), 90.13 (C-1), 101.56 (NCH=*C*H), 146.79 (N*C*H=CH), 176.52, 176.58, 177.19, 177.87 (piv CO), 191.68 (C=O) ppm. MS (FD): *m*/*z* = 653.9 $[M]^+$.

(2*S*)-2,3-Dihydro-2-{3-[dimethyl(phenyl)silyl]propyl}-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (6k): 3 (5 g, 8.42 mmol), TIPSOTf (3.4 mL, 12.63 mmol), 2,6-lutidine (1.47 mL, 12.63 mmol); Mg (0.48 g, 20 mmol), anhydr. THF (10 mL), 1,2-dibromomethane (0.57 mL, 3.16 mmol), 3-[dimethyl(phenyl)silyl]propyl chloride (3.58 mL, 16.8 mmol) (prepared according to ref.[30]); solvent: CH_2Cl_2; yield 4.3 g (5.57 mmol, 66%); single diastereomer, ratio >> 99:1 (^{1}H NMR). R_f = 0.68 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = −11.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.25 (s, 6 H, Si−Me), 0.67 (t, 2 H, −Si−CH_2−), 1.03−1.19 (m, 38 H, piv CH_3, −CH_2−), 1.35−1.98 (m, 2 H, −CH_2−), 2.33 (d, J_{gem} = 16.1 Hz, 1 H, −CH_2−CO), 2.60 (dd, J_{gem} = 16.6, J_{vic} = 6.8 Hz, 1 H, −CH_2−CO), 3.47 (m, 1 H, NC*H*), 3.89−4.15 (m, 3 H, H-5, H-6a, H-6b), 4.25 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 5.08−5.14 (m, 2 H, NCH=C*H*, H-3), 5.27 (t, 1 H, H-2), 5.39 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 7.07 (d, *J* = 8.3 Hz, 1 H, NC*H*=CH), 7.31−7.49 (m, 5 H, phenyl) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = −3.23, −3.07 (Si−CH_3), 15.69, 19.85 (−CH_2−), 26.17 (−CH_2−), 27.06, 27.24 (piv CH_3), 32.73 (−CH_2−), 38.71, 38.79, 38.84, 39.11 (piv $C_{quat.}$), 39.50 (−*C*H$_2$C=O), 60.27 (*C*HN), 61.30 (C-6), 66.75, 67.30, 71.38, 72.99 (C-2, C-3, C-4, C-5), 90.18 (C-1), 101.54 (NCH=*C*H), 127.78, 129.04, 133.52 (*o*-, *m*-, *p*-C, phenyl), 138.98 (C_{ipso}), 146.56 (N*C*H=CH), 176.39, 176.57, 177.20, 177.76 (piv CO), 191.50 (C=O) ppm. MS (FD): *m*/*z* = 772.1 $[M]^+$. $C_{42}H_{65}NO_{10}Si$ (772.07): calcd. C 65.34, H 8.49, N 1.81; found C 65.31, H 8.44, N 1.84.

The following intermediates in the synthesis of (*S*)-coniine were prepared according to the method for their stereoisomeric analogues obtained in the published synthesis of (*R*)-coniine.[14]

(2*S*)-2-Propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-piperidin-4-one (7): Dehydropiperidinone **6b** (1.07 g, 1.67 mmol) in dry THF (30 mL), L-Selectride (2.09 mL, 1 M in THF, 2.09 mmol); yield 0.65 g (1.01 mmol, 61%). R_f = 0.60 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = 3.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, −CH_3), 1.02−1.60 (m, 40 H, piv CH_3, −CH_2−), 2.29−2.57 (m, 2 H, −CH_2−), 3.13−3.42 (m, 3 H, −CH_2−, NC*H*), 3.92−4.11 (m, 3 H, H-5, H-6a, H-6b), 4.38 (d, $J_{1,2}$ = 8.8 Hz, 1 H, H-1), 5.13 (dd, $J_{3,2}$ = 10.3, $J_{3,4}$ = 3.0 Hz, 1 H, H-3), 5.37 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 5.45 (t, 1 H, H-2) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.0 (−CH_3), 19.8 (−CH_2−), 27.0, 27.1, 27.2 (piv CH_3), 34.5 (−CH_2−), 38.7, 39.0 (piv $C_{quat.}$), 41.8, 43.5, 46.6 (−CH_2−), 59.0 (propyl*C*HN), 62.0 (C-6), 65.3, 67.3, 71.9, 72.1 (C-2, C-3, C-4, C-5), 92.7 (C-1), 176.7, 177.0, 177.2 (piv C=O), 210.0 (C=O) ppm. $C_{34}H_{57}NO_{10}$ (639.81): calcd. C 63.83, H 8.98, N 2.19; found C 63.74, H 9.01, N 2.21.

(2*S*)-4-(1,3-Dithiolan-2-yl)-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-2-propylpiperidine (8): Piperidinone **7** (0.65 g, 1.01 mmol), 1,2 ethanedithiol (0.176 mL, 2.13 mmol) in dry dichloromethane (10 mL), boron trifluoride diethyl ether (0.63 mL, 5.05 mmol); yield 0.64 g (0.87 mmol, 88%). R_f: 0.81 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = 1.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, −CH_3), 1.04−1.21 (m, 40 H, piv CH_3, −CH_2−), 1.74−2.17 (m, 5 H, −CH_2−), 2.60−2.90 (m, 3 H, −CH_2−), 3.20 (m, 4 H, −SCH_2−), 3.70−4.10 (m, 4 H, NC*H*, H-5, H-6a, H-6b), 4.25 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 5.04 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 3.0 Hz, 1 H, H-3), 5.28 (d, $J_{4,3}$ = 2.5 Hz, 1 H, H-4), 5.40 (t, 1 H, H-2) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.1 (−CH_3), 19.7 (−CH_2−), 27.0, 27.1, 27.2 (piv CH_3), 34.0, 38.1, 38.2 (−CH_2−), 38.6 (piv $C_{quat.}$), 42.5 (−CH_2−), 44.8, 45.8 (−SCH_2−), 59.2 (propyl*C*HN), 62.1 (CS_2), 65.1 (C-6), 67.2, 67.4, 71.7, 72.2 (C-2, C-3, C-4, C-5), 89.2 (C-1), 176.7, 176.8, 177.2, 177.9 (piv C=O) ppm. No correct elemental analysis was obtained.

(2*S*)-2-Propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)piperidine (9): *N*-(Galactosyl)piperidine **8** (0.64 g, 0.89 mmol), dry 2-propanol (50 mL), Raney-nickel (3 g), hydrogen, 70 °C, 9 h; yield 0.54 g (0.86 mmol, 97%). R_f = 0.95 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = 4.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, −CH_3), 1.03−1.69 (m, 46 H, piv CH_3, −CH_2−), 2.72−2.83 (m, 3 H, −NCH_2−, NC*H*), 3.78−3.99 (m, 3 H, H-5, H-6a, H-6b), 4.04 (d, $J_{1,2}$ = 8.7 Hz, 1 H, H-1), 5.04 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 2.9 Hz, 1 H, H-3), 5.26−5.35 (m, 2 H, H-2, H-4) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.3 (−CH_3), 20.0, 20.2, 25.8 (−CH_2−), 26.9, 27.0, 27.1 (piv CH_3), 29.6, 31.0, 31.8 (−CH_2−), 38.5, 38.6, 39.0, 40.5 (piv $C_{quat.}$), 60.1 (propyl*C*HN), 62.0 (C-6), 65.2, 67.4, 71.5, 72.0 (C-2, C-3, C-4, C-5), 93.8 (C-1), 176.7, 177.2, 177.9 (piv C=O) ppm. $C_{34}H_{59}NO_9$ (625.84): calcd. C 65.25, H 9.50, N 2.04; found C 64.26, H 9.67, N 2.04.

(*S*)-(+)-Coniine·HCl (10): Piperidine **9** (0.38 g, 0.61 mmol) in methanol (10 mL), 2 N HCl (1 mL), 48 h; yield 0.1 g (0.61 mmol, 100%). M.p. 214−215 °C (ref.[14] 221 °C). $[\alpha]_D^{22}$ = 6.8 (*c* = 1.0, MeOH) {ref.[14] $[\alpha]_D^{25}$ = −6.8 (*c* = 0.6, MeOH) (enantiomer)}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.80 (t, 3 H, −CH_3), 1.0−2.10 (m, 10 H, −CH_2−), 2.72−3.00 (m, 2 H, NCH_2), 3.40 (m, 1 H, NCH), 9.13, 9.39 (2 s, 2 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.7 (CH_3), 18.5, 22.2, 22.4, 28.1, 35.3 (CH_2), 44.8 (NCH_2), 57.1 (propyl*C*HN) ppm.

(2*S*,3*S*)-2,3-Dihydro-3-methyl-2-propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (11a): A solution of **6b** (1.01 g, 1.58 mmol) in THF (10 mL) was added slowly through a

syringe to a solution of LiHMDS (0.32 g, 1.90 mmol) in THF (50 mL) at −78 °C. Stirring was continued for 1 h before methyl iodide (0.296 mL, 4.75 mmol) was added, and the mixture was warmed up to −10 °C. After stirring at this temperature for 12 h, the reaction was terminated by addition of aq. satd. NH_4Cl (150 mL). The mixture was extracted three times with diethyl ether (200 mL). The combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. Flash chromatography (light petroleum ether/ethyl acetate, 1:1) yielded **11a** together with some unreacted starting material. The compounds were separated by preparative HPLC [Luna 10 μ, Kromasil C-18(2), 250 × 50 mm (Phenomenex), eluent: MeCN/H_2O, 85:15, flow: 20 mL·min^{-1}, UV detection at 310 nm, R_t [min]: 41.92 (**6b**), 49.70 (**11a**)]; yield 0.99 g (69%), 69% conversion. M.p. 115 °C. Single diastereomer, ratio >> 99:1 (^{1}H NMR, HPLC). R_f = 0.78 (light petroleum ether/ethyl acetate, 1:1). Data for the pure (2*S*,3*S*) diastereomer: $[\alpha]_D^{25} = -61.3$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, CH_3), 1.10−1.27 (m, 41 H, piv CH_3, CH_2, CH_3), 1.39−1.89 (m, 2 H, CH_2), 2.34 (m, 1 H, −C*H*Me), 3.24 (br. d, *J* = 10.3 Hz, 1 H, NC*H*), 4.03 (m, 3 H, H-5, H-6a, H-6b), 4.47 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 5.00 (d, *J* = 7.8 Hz, 1 H, NCH=C*H*), 5.13 (dd, $J_{3,2}$ = 10.2, $J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.38 (t, 1 H, H-2), 5.40 (d, $J_{4,3}$ = 3.4 Hz, 1 H, H-4), 7.04 (d, *J* = 7.8 Hz, 1 H, NC*H*=C) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9, 17.8 (−CH_3), 18.6 (−CH_2−), 27.0, 27.1 (piv CH_3), 31.8 (−CH_2−), 38.6, 38.7, 38.8, 39.0 (piv $C_{quat.}$), 42.9 (*C*HMeC=O), 61.4 (propyl−*C*HN), 64.5 (C-6), 66.7, 66.8, 71.9, 72.7 (C-2, C-3, C-4, C-5), 90.4 (C-1), 99.4 (NCH=*C*H), 146.7 (N*C*H=CH), 176.4, 176.5, 177.2, 177.8 (piv C=O), 196.6 (C=O) ppm. MS (FAB): *m*/*z* = 652.6 [M + H]$^+$. $C_{35}H_{57}NO_{10}$ (651.83): calcd. C 64.49, H 8.81, N 2.15; found C 63.79, H 8.67, N 2.07. Crystal data: Size: 0.128 × 0.256 × 0.512 mm; colourless crystal; $P2_1$ (monoclinic); *a* = 13.243(2) Å, *b* = 10.4162(6) Å, *c* = 15.703(2) Å, β = 112.477(7)°, *V* = 2001.6(5) Å^3, *Z* = 2, *F*(000) = 708; *T* = 295 K; ρ = 1.082 g·cm^{-3}. Data collection: diffractometer: CAD4 (Enraf-Nonius); radiation: Cu-K_α, graphite monochromator, scan-type: ω/2Θ; scan-width: 0.8 + 0.14·tan(Θ) and 25% left and right for determination of background; measurement range: 1.5° ≤ Θ ≤ 74°; 0 ≤ *h* ≤ 16 0 ≤ *k* ≤ 12 −19 ≤ *l* ≤ 19; reflections: measured 8664 (with Friedel pairs), independent 7808 (R_{int} = 0.0468), observed 3185 ($|F|/\sigma(F) > 4.0$). CCDC-237632 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

(2*S*,3*S*)-2-{[Dimethyl(phenyl)silyl]propyl}-3-ethyl-2,3-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-4(1*H*)-one (11b): Procedure see above; dehydropiperidinone **6k** (3.4 g, 4.40 mmol) in dry THF (50 mL), LiHMDS (1.1 g, 6.60 mmol) in dry THF (10 mL), EtI (1.05 mL, 13.2 mmol); yield 2.84 g (3.55 mmol, 81%); single diastereomer, only *trans* (HPLC). R_f = 0.68 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20} = -25.4$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.22 (s, 6 H, Si−CH_3), 0.66 (t, 2 H, −Si−CH_2−), 0.88 (t, *J* = 7.3 Hz, 3 H, −CH_3), 1.09−1.22 (m, 40 H, piv CH_3, −CH_2−), 1.33−1.54 (m, 3 H, −CH_2−), 2.01−2.03 [m, 2 H, −C*H*(Et)−CO, −CH_2−], 3.38−3.41 (m, 1 H, NC*H*), 3.93−4.09 (m, 3 H, H-5, H-6a, H-6b), 4.39 (d, $J_{1,2}$ = 9.4 Hz, 1 H, H-1), 4.95 (d, *J* = 7.7 Hz; 1 H, NCH=C*H*), 5.09 (dd, $J_{3,2}$ = 9.7, $J_{3,4}$ = 3.3 Hz, 1 H, H-3), 5.32 (t, 1 H, H-2), 5.37 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 6.94 (d, *J* = 7.9 Hz, 1 H, NC*H*=CH), 7.31−7.47 (m, 5 H, phenyl) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = −3.66 (Si−CH_3), 15.67, 19.71, 24.29 (−CH_2−), 26.36, 26.47, 27.45 (piv CH_3), 32.65 (−CH_2−), 38.38, 38.60, 38.73, 38.97 (piv $C_{quat.}$), 49.76 [−*C*H(Et)C=O], 59.65 (*C*HN), 61.39 (C-6), 66.51, 66.79, 72.08, 72.47 (C-2, C-3, C-4, C-5), 90.45 (C-1), 99.34 (NCH=*C*H), 127.65, 128.88, 133.89 (*o*-, *m*-, *p*-C, phenyl), 138.90 (C_{ipso}), 147.49 (N*C*H=CH), 176.29, 176.44 (piv CO), 195.50 (C=O) ppm. MS (FD): *m*/*z* = 800.1 [M]$^+$.

General Procedure for the Cuprate Addition: A solution of the Grignard reagent (1 mmol) in diethyl ether or THF was added dropwise to a suspension of CuI (1 mmol) in THF (10 mL) at the temperature quoted for each compound. After stirring for 1 h, BF_3·OEt_2 (1 mmol) was added, and stirring was continued for an additional 15 min. Then a solution of the corresponding enaminone **6** in THF (20 mL mmol^{-1}) was added through a syringe and stirring was continued at −78 °C until TLC showed complete conversion (1−10 h). The reaction was terminated by addition of concd. NH_4OH/aq. satd. NH_4Cl (1:1) (100 mL), the mixture was warmed up to ambient temperature and was extracted twice with diethyl ether (200 mL). The combined organic layers were washed with aq. satd. NH_4Cl (100 mL) and dried with $MgSO_4$. Evaporation of the solvent in vacuo and purification of the residue by flash chromatography afforded the following compounds.

(2*S*)-2,6-Dipropyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-piperidin-4-one (12a): 6b (1.36 g, 2.31 mmol), 4.6 equiv. RCu·BF_3 (propylMgCl, 2 M in THF); temperature, time: −78 °C, 2 h; yield 1.31 g (1.92 mmol, 83%); mixture of diastereomers, ratio: 1.1:1 (^{1}H NMR). R_f = 0.74 (light petroleum ether/ethyl acetate, 8:1). Only characteristic signals are given for the mixture: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.38 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1$_{minor}$), 4.58 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1$_{major}$), 5.45 (t, *J* = 9.8 Hz, 1 H, H-2$_{minor}$), 5.61 (t, *J* = 9.8 Hz, 1 H, H-2$_{major}$) ppm. $C_{37}H_{63}NO_{10}$ (681.90): calcd. C 65.17, H 9.31, N 2.05; found C 64.94, H 9.28, N 2.07.

(2*R*)-2,6-Diphenyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)piperidin-4-one (12b): 6h (2.15 g, 2.97 mmol), 4.3 equiv. RCu·BF_3 (phenylMgCl, 2 M inTHF); temperature, time: −78 °C, 18 h; yield 2.2 g (2.94 mmol, 99%); mixture of diastereomers, ratio: 3:1 (^{1}H NMR). R_f = 0.60 (light petroleum ether/ethyl acetate, 6:1). Only characteristic signals are given for the mixture. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.33 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1$_{major}$), 4.40 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1$_{minor}$), 4.87 (dd, $J_{3,2}$ = 9.8, $J_{3,4}$ = 3.4 Hz, 1 H, H-3$_{major}$), 5.74 (t, *J* = 9.8 Hz, 1 H, H-2$_{major}$) ppm. $C_{43}H_{59}NO_{10}$ (747.91): calcd. C 68.87, H 7.93, N 1.87; found C 68.94, H 7.65, N 1.59.

(2*S*)-2-Methyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6-vinylpiperidin-4-one (12c): 6a (2.43 g, 3.97 mmol), 5.0 equiv. RCu·BF_3 (vinylMgCl, 1 M in THF); temperature, time: −78 °C, 5 h; yield 1.85 g (2.9 mmol, 73%); mixture of diastereomers, ratio ca. 2:1 (^{1}H NMR). R_f = 0.37 (light petroleum ether/ethyl acetate, 4:1). Only characteristic signals are given for the mixture: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.47 (t, *J* = 9.8 Hz, 1 H, H-2$_{major}$), 6.07 (d, J_{trans} = 15.6 Hz, 1 H, vinyl$_{major}$), 7.02 (dd, J_{trans} = 15.6, J_{cis} = 11.2 Hz, 1 H, vinyl$_{major}$) ppm. MS (FAB): *m*/*z* = 638.5 [M + H]$^+$. $C_{34}H_{55}NO_{10}$ (637.81): calcd. C 64.03, H 8.69, N 2.20; found C 63.54, H 8.62, N 2.18.

(2*R*)-2,6-Diphenyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)piperidin-4-one (12b): CuI (1 mmol) in dry Et_2O (10 mL) and PhLi (2 mmol, 1.7 M in cylohexane) were stirred at 0 °C for 10 min. The solution was cooled to −78 °C, and a mixture of **6h** (0.5 g, 0.74 mmol) and TMSCl (6 mmol, 4.3 mL) in Et_2O was added slowly through a syringe. After 18 h, TLC showed complete conversion, and the reaction was terminated by addition of 1.5 mL of a TBAF solution (1 M in THF). The aqueous layer was separated

and extracted with Et_2O (2 × 50 mL). After combination of the organic layers and drying with $MgSO_4$, the solvent was evaporated in vacuo. Further purification was carried out by flash chromatography. Yield 0.26 g (0.35 mmol, 47%); mixture of diastereomers, ratio 2.7:1 (^{1}H NMR). R_f = 0.60 (light petroleum ether/ethyl acetate, 6:1). Analytical data are identical to those obtained from cuprate addition using RCu·BF_3 (see above).

(2*S*,6*R*)-1-(Benzyloxycarbonyl)-2,6-dipropylpiperidin-4-one (*cis*-13a) and (2*S*,6*S*)-1-(Benzyloxycarbonyl)-2,6-dipropylpiperidin-4-one (*trans*-13b): Piperidine **12a** (0.78 g, 1.14 mmol) was dissolved in MeOH (10 mL) and treated with aq. HCl (2 N, 2 mL). After stirring overnight, the solvent was evaporated yielding a colourless residue which was dissolved in a mixture of water (50 mL) and diethyl ether (50 mL). The phases were separated and the aqueous layer was extracted twice with diethyl ether (50 mL). The aqueous layer containing the heterocycle as its hydrochloride was concentrated to dryness in vacuo. The residue was dissolved in water (10 mL) and treated, whilst stirring, with aq. satd. Na_2CO_3 (10 mL). After 1 h, benzyl chloroformate (0.25 mL, 0.17 mmol) was added, and stirring was continued for 1 h. The reaction mixture was extracted twice with diethyl ether (50 mL), the combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. Purification by flash chromatography (light petroleum ether/ethyl acetate, 20:1) yielded **13a** and **13b** as colourless oils (0.18 g, 0.57 mmol, 50%, *cis*-**13a** and 0.16 g, 0.5 mmol, 44%, *trans*-**13b**). MS (FAB): *m*/*z* = 318.0 $[M + H]^+$; calcd. for $C_{19}H_{27}NO_3$ 317.42. ***cis*-13a:** R_f = 0.68 (ethyl acetate/light petroleum ether, 4:1). $[\alpha]_D^{28}$ = 0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.86 (t, *J* = 7.3, *J* = 6.7 Hz, 6 H, propyl CH_3), 1.23−1.46 (m, 8 H, $-CH_2-$), 2.31 (dd, J_{gem} = 15.1, *J* = 2.4 Hz, 2 H, H-3a, H-5a), 2.64 (dd, J_{gem} = 15.1, J_{vic} = 7.8 Hz, 2 H, H-3b, H-5b), 4.63 (m, 2 H, NC*H*), 5.13 (s, 2 H, $PhCH_2-$), 7.25−7.33 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.7 ($-CH_3$), 20.0, 38.8 ($-CH_2-$), 43.6 ($-CH_2-C=O$), 52.9 (N*C*H), 67.6 (Ph*C*H_2), 127.5, 128.0, 128.1, 136.4 (Ph), 155.7 (OC=O), 208.2 (C=O) ppm. ***trans*-13b:** R_f = 0.51 (ethyl acetate/light petroleum ether, 4:1). $[\alpha]_D^{28}$ = −141.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.83 (t, *J* = 7.3, *J* = 6.8 Hz, 6 H, propyl CH_3), 1.22−1.35 (m, 6 H, $-CH_2-$), 1.71−1.75 (m, 2 H, $-CH_2-$), 2.48 (dd, J_{gem} = 18.1, *J* = 2.4 Hz, 2 H, H-3a, H-5a), 2.67 (dd, J_{gem} = 18.1, J_{vic} = 4.9 Hz, 2 H, H-3b, H-5b), 4.17 (m, 2 H, NC*H*), 5.08 (d, J_{gem} = 12.2 Hz, 1 H, phenylCH_2-), 5.20 (d, J_{gem} = 12.2 Hz, 1 H, PhCH_2-), 7.28−7.35 (m, 5 H, phenyl) ppm. ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 13.7 ($-CH_3$), 19.8, 39.0 ($-CH_2-$), 41.5 ($-CH_2-C=O$), 51.2 (N*C*H), 67.2 (Ph*C*H_2), 128.0, 128.5, 136.5 (Ph), 155.3 (OC=O), 207.6 (C=O) ppm.

Synthesis of *ent*-Indolizidine 167B

(2*S*)-1-(Benzyloxycarbonyl)-2,3-dihydro-2-propylpyridine-4(1*H*)-one (16)

(2*S*)-5-(Phenylselenyl)-2-propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)piperidin-4-one (14): A solution of enaminone **6b** (2.17 g, 3.40 mmol) in THF (50 mL) at −78 °C was treated with L-Selectride (1 M in THF, 3.74 mL, 3.74 mmol). The solution was maintained at this temperature for 40 min, then the intermediate lithium enolate was trapped by the addition of PhSeCl (0.78 g, 4.08 mmol) in THF (5 mL). Stirring was continued for 2 h before the reaction was terminated by addition of aq. satd. $NaHCO_3$ (50 mL). After extracting with diethyl ether (3 × 80 mL), the combined organic fractions were dried with $MgSO_4$. After evaporation of the solvent, purification by flash chromatography (light petroleum ether/ethyl acetate, 10:1) yielded **14** as a slightly yellow amorphous solid (1.90 g, 70%) composed of an inseparable mixture of diastereomers, ratio ca. 3:1 (^{1}H NMR). R_f = 0.49 (light petroleum ether/ethyl acetate, 4:1). MS (FD): *m*/*z* = 796.1 $[M,^{80}Se]^+$; calcd. for $C_{40}H_{61}NO_{10}Se$ 795.83. The product was used in the next step without further purificaton.

(2*S*)-1-(Benzyloxycarbonyl)-5-phenylselenyl-2-propylpiperidin-4-one (15): HCl (1 mL, 1 N) was added to **14** (460 mg, 0.58 mmol), dissolved in methanol (10 mL). TLC showed complete conversion after 12 h. The solvent was evaporated in vacuo. After addition of diethyl ether (50 mL) and water (50 mL) and thorough extraction, the layers were separated and extracted again until TLC showed complete separation. The aqueous layer was concentrated in vacuo to a volume of 10 mL, and satd. Na_2CO_3 (1 mL) was added. Benzyl chloroformate (0.16 mL, 1.13 mmol) was added under vigorous stirring. After 2 h, the reaction mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography yielded **15** as a yellow oil; yield 0.133 g (0.31 mmol, 53%, two steps). R_f = 0.47 (light petroleum ether/ethyl acetate, 4:1). MS (FD): *m*/*z* = 431.6 $[M,^{80}Se]^+$; calcd. for $C_{22}H_{25}NO_3Se$ 431.10. This product was used for the oxidation without further purification.

(2*S*)-1-(Benzyloxycarbonyl)-2,3-dihydro-2-propylpyridine-4(1*H*)-one (16): The piperidinone **15** (133 mg, 0.31 mmol) was dissolved in CH_2Cl_2/water (20:1) (10 mL). Under vigorous stirring H_2O_2/urea complex (80 mg, 0.85 mmol) was added. The stirring was continued for 2 h until TLC showed complete conversion. The reaction mixture was extracted with aq. satd. $NaHCO_3$ (10 mL), and the layers were separated. After extraction of the aqueous solution with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried with $MgSO_4$, and the solvent was evaporated in vacuo. Flash chromatography (light petroleum ether/ethyl acetate, 5:1) yielded **16** as a colourless oil; yield 58 mg (69%). R_f = 0.23 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{20}$ = 122.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ =. 0.84 (t, 3 H, $-CH_3$), 1.20 (m, 2 H, $-CH_2-$), 1.58 (q, 2 H, $-CH_2-$), 2.40 (d, J_{gem} = 16.6 Hz, 1 H, $-CH_2-C=O$), 2.75 (dd, J_{gem} = 16.6, J_{vic} = 6.8 Hz, 1 H, $-CH_2-C=O$), 4.58 (m, 1 H, NCH propyl), 5.22 (s, 2 H, PhCH_2), 5.27 (d, *J* = 8.0 Hz, 1 H, NCH=C*H*), 7.35 (m, 5 H, Ph), 7.72 (d, *J* = 7.8 Hz, 1 H, NC*H*=C) ppm. ^{13}C NMR (50.3 MHz $CDCl_3$): δ = 13.7 ($-CH_3$), 18.9, 32.6 ($-CH_2-$), 39.6 (*C*H_2C=O), 53.2 (propyl*C*HN), 68.9 (Ph*C*H_2-), 107.1 (NCH=*C*H), 126.9, 127.5, 128.7 (*o*-, *m*-, *p*-Ph), 135.0 (*ipso*-C), 141.5 (N*C*H=CH), 152.5 (NCO), 193.1 (C=O) ppm. MS (FD): *m*/*z* = 273.4 $[M]^+$; calcd. for $C_{16}H_{19}NO_3$ 273.33.

(2*S*)-1-(Benzyloxycarbonyl)-6-(3-hydroxypropyl)-2-propylpiperidin-4-one (17): Preparation of the Grignard reagent: Mg filings (0.42 g, 17.2 mmol) in THF (15 mL) were treated with 1,2-dibromoethane (0.1 mL, 8.61 mmol) at ambient temperature. After the violent reaction had ceased, the solvent was taken up in a syringe and THF (10 mL) was added. This washing process was repeated three times. To this activated Mg in THF (10 mL) was added 3-(1-ethoxyethoxy)propyl bromide[24](1.13 mL) and the mixture was stirred until the metal was consumed (2 h). Cuprate addition: BF_3·OEt_2 (1.51 mL, 2.39 mmol) was added to a suspension of enaminone **16** (218 mg, 0.79 mmol) and CuBr·SMe_2 (0.49 g, 2.39 mmol) in THF (15 mL) at −78 °C, and stirring was continued for 10 min. Subsequently, the previously prepared Grignard reagent (3.8 mL) was added through a syringe, and the reaction mixture was stirred at −78 °C. After 5 h, a mixture of aq. satd. NH_4Cl and concd. NH_4OH (1:1, 30 mL) was added to the cold reaction mixture, and it was warmed to ambient temperature. Separation of the phases, extraction of the aqueous layer with diethyl ether (3 × 50 mL), drying of the combined organic layers with $MgSO_4$ and evapor-

ation of the solvent yielded a colourless oil. The residue was dissolved in THF (10 mL) and treated with aq. HCl (2 N, 0.5 mL). After 20 min, the mixture was neutralized by addition of aq. satd. $NaHCO_3$ and extracted twice with diethyl ether (50 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated in vacuo. Flash chromatography (light petroleum ether/ethyl acetate, 4:1) gave **17** (193 mg, colourless oil, 73%) as a mixture of diastereomers, ratio 2:1 (^{1}H NMR). R_f = 0.24 (light petroleum ether/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = −34.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (t, 3 H, $-CH_3$), 1.1−1.7 (m, 8 H, $-CH_2$-, −OH), 2.1−2.7 (m, 5 H, $-CH_2-$), 3.5 (m, 2 H, $-CH_2OH$), 4.15, 4.6 (2 m, 2 H, NCH), 5.15 (m, $PhCH_2$), 7.35 (m, Ph) ppm. ^{13}C NMR (50.3, MHz $CDCl_3$): δ = 13.7 ($-CH_3$), 19.8, 20.0 ($-CH_2$), 29.1, 29.4 ($-CH_2-$), 33.0, 33.3 ($-CH_2-$), 38.8, 39.0 ($-CH_2-$), 41.4, 43.7 ($-CH_2-$), 50.8, 51.2, 52.7, 52.9 (*C*HN), 61.7 ($-CH_2O-$), 67.4, 67.7 (benzyl $-CH_2-$), 128.1, 128.3 (*o*-, *m*-, *p*-Ph), 136.2, 136.3 (*ipso*-C), 155.5, 155.8 (NCO), 207.4, 208.0 (C=O) ppm. MS (FD): *m*/*z* = 333.7 $[M]^+$; calcd. for $C_{19}H_{27}NO_4$ (333.42).

(2*S*,6*R*)-*cis*-1-(Benzyloxycarbonyl)-6-(3-chloropropyl)-2-propylpiperidin-4-one (*cis*-18) and (2*S*,6*S*)-*trans*-1-(Benzyloxycarbonyl)-6-(3-chloropropyl)-2-propylpiperidin-4-one (*trans*-18): The *N*-(galactosyl)piperidinones **17** (183 mg, 0.55 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to −40 °C. Subsequently, PPh_3 (216 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) and *N*-chlorosuccinimide in CH_2Cl_2 (10 mL) were added slowly through a syringe. The reaction mixture was stirred overnight and slowly warmed to room temperature. The reaction was terminated by addition of methanol (10 mL) and the mixture stirred for an additional 15 min. Evaporation of the solvent in vacuo and purification of the residue by flash chromatography (light petroleum ether/ethyl acetate, 4:1) yielded two separable products [126 mg, *cis*-**18**; R_f = 0.76 (light petroleum ether/ethyl acetate, 1:1) and 58 mg, *trans*-**18**; R_f = 0.87 (light petroleum ether/ethyl acetate, 1:1)]; overall yield 95%. ***cis*-18:** $[\alpha]_D^{20}$ = −2.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, 3 H, $-CH_3$), 1.19−1.80 (m, 8 H, $-CH_2-$), 2.23 (t, J_{gem} = 13.5 Hz, 2 H, $-CH_2-C=O$), 2.61−2.69 (m, 2 H, $-CH_2-C=O$), 3.45 (m, 2 H, $-CH_2Cl$), 4.62 (m, 2 H, NCH), 5.12 (s, 2 H, $PhCH_2$), 7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.7 ($-CH_3$), 19.8, 29.7, 34.0, 38.8, 43.5, 43.8, 44.3 ($-CH_2-$), 52.4, 52.9 (*C*HN), 67.7 ($PhCH_2-$), 128.1, 128.2 (*o*-, *m*-, *p*-Ph), 136.2 (*ipso*-C), 155.6 (NCO), 207.4 (C=O) ppm. MS (FD): *m*/*z* = 351.5 $[M]^+$; calcd. for $C_{19}H_{26}ClNO_3$ 351.87. ***trans*-18:** $[\alpha]_D^{20}$ = −68.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, $-CH_3$), 1.20−1.92 (m, 8 H,$-CH_2-$), 2.49 (t, 2 H, $-CH_2-C=O$), 2.54 (m, 2 H, $-CH_2-C=O$), 3.42 (m, 2 H, $-CH_2Cl$), 4.09 (m, 2 H, NCH), 5.08 (d, J_{gem} = 12.0 Hz, 1 H, $PhCH_2$), 5.19 (d, J_{gem} = 12.3 Hz, 1 H, $PhCH_2$), 7.29−7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.7 ($-CH_3$), 19.8, 29.6, 34.4, 38.9, 41.5, 41.8, 44.3 ($-CH_2-$), 50.8, 51.3 (CHN), 67.4 ($PhCH_2-$), 128.2, 128.6 (*o*-, *m*-, *p*-Ph), 136.3 (*ipso*-C), 155.3 (NCO), 207.0 (C=O) ppm. MS (FD): *m*/*z* = 351.5 $[M]^+$; calcd. for $C_{19}H_{26}ClNO_3$ 351.87.

(5*S*,9*S*)-(+)-Indolizidine 167B (*ent*-19): Synthesis of the vinyl triflates: A solution of LiHMDS (69.5 mg, 0.42 mmol) in THF (5 mL) was added dropwise to a solution of ketone **18** (97.9 mg, 0.27 mmol) in THF (7 mL) at −78 °C with stirring. After 1 h, the enolates were trapped by addition of a solution of 2-amino-5-chloro-*N*,*N*-bis(trifluoromethylsulfonyl)pyridine[27] (163.4 mg, 0.42 mmol) in THF (1 mL). The mixture was warmed to ambient temperature overnight. Addition of aq. satd. NH_4Cl (10 mL), separation of the layers, extraction of the aqueous phase with diethyl ether (10 mL), subsequent drying of the combined organic layers with $MgSO_4$ and evaporation of the solvent in vacuo gave a colourless oil. The residue was purified by passing it through a short plug of silica which gave a mixture of regioisomers of the vinyl triflates (102 mg, 76%). R_f = 0.69 (0.87 (light petroleum ether/ethyl acetate, 4:1). Reduction and ring closure: The crude vinyl triflates (100 mg, 0.20 mmol) were dissolved in ethyl acetate (20 mL). Li_2CO_3 (30 mg, 0.4 mmol) and Pd/C (10%, 30 mg) were added. Hydrogen was bubbled through the solution for 1 h. After TLC showed complete consumption of the vinyl triflates, the mixture was passed through a plug of Celite, which was then washed several times with CH_2Cl_2. The volume of the combined solutions was reduced in vacuo and the resulting residue was dissolved in methanol (10 mL), treated with Li_2CO_3 (30 mg) and stirred overnight. The solvents were evaporated to dryness in vacuo, the residue dissolved in CH_2Cl_2 (10 mL) and the solution washed with aq. satd. NaCl (10 mL). The organic layer was dried with $MgSO_4$, the solvent was evaporated in vacuo and the residue was purified by flash chromatography (ethyl acetate/methanol, 9:1) to yield a clear, volatile oil; yield 24.3 mg, 70%. R_f = 0.07 (ethyl acetate/methanol, 9:1). $[\alpha]_D^{20}$ = 101.4 (*c* = 0.22, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, $-CH_3$), 1.02−1.52 (m, 7 H), 1.52−2.02 (m, 10 H), 3.26 (td, *J* = 8.3 Hz, 2.0 Hz, 1 H, NC*H*) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.5 ($-CH_3$), 19.1, 20.4, 24.6, 30.5, 30.8, 30.9, 36.8, 51.5 (NCH_2), 63.7, 65.0 (N*C*HR) ppm. GC-MS (MS-Finnigan ion-trap): *m*/*z* = 166 $[M - H]^-$; calcd. for $C_{11}H_{21}N$ 167.29.

1,2-Dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-pyridin-2(1*H*)-one (5): 2,3,4,6-Tetra-*O*-pivaloyl-α-D-galactopyranosyl fluoride[11] (**1**) (36.7 g, 71 mmol) in 1,2-dichloroethane (200 mL) was heated to 70 °C. Then, 2-(trimethylsilyloxy)pyridine (**4**, 17.66 mL, 105 mmol) was added slowly through a syringe. To this solution $TiCl_4$ (14 mL, 128 mmol) was added. The colour of the solution turned to red. The mixture was refluxed for 2 h. After cooling to room temperature, aq. satd. $NaHCO_3$ (500 mL) was added carefully. The mixture was diluted with CH_2Cl_2 (500 mL), the aqueous layer extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic layers were dried with $MgSO_4$. Evaporation of the solvent in vacuo and flash chromatography (light petroleum ether/ethyl acetate, 2:1) yielded **5** as colourless crystals (40.6 g, 97%). M.p. 120 °C. R_f = 0.48 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{27}$ = 73.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97, 1.08, 1.13, 1.28 (4 s, 36 H, piv CH_3), 4.0−4.22 (m, 3 H, H-6a, H-6b, H-5), 5.31 (dd, $J_{3,2}$ = 10.25, $J_{3,4}$ = 2.93 Hz, 1 H, H-3), 5.44 (t, $J_{2,3}$ = 10.3, $J_{2,1}$ = 9.28 Hz, 1 H, H-1), 5.51 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 6.21 (t, *J* = 6.83 Hz, 1 H, N−CH=C*H*), 6.37 (d, $J_{1,2}$ = 9.28 Hz, 1 H, H-1), 6.45 (d, *J* = 9.27 Hz, 1 H, OC−C*H*), 7.22−7.34 (m, 2 H, OC−CH=C*H*−, N−C*H*=CH−) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.03 (piv CH_3), 38.70, 38.75, 38.81, 39.11 (piv $C_{quat.}$), 60.72 (C-6), 66.88, 67.76, 71.22, 74.01 (C-2, C-3, C-4, C-5), 79.52 (C-1), 106.55 (N−CH=C*H*−), 120.57 (OC−*C*H), 132.66 (N−*C*H), 139.89 (OC−CH=*C*H−), 161.72 (NCO), 176.42, 176.88, 177.0, 177.76 (piv C=O) ppm. FD-MS: *m*/*z* $[M^+]$ found: 594.0. $C_{31}H_{47}NO_{10}$ (593.71): calcd. C 62.71, H 7.98, N 2.36; found C 62.70, H 8.13, N 2.30.

General Procedure for the Regioselective Addition of Grignard Compounds To Furnish Compounds 20: The 1,2-dihydropyridin-2-one derivative **5** (1 g, 1.68 mmol) in dry CH_2Cl_2 (20 mL) was treated with 2.0 equiv. (3.36 mmol) of the corresponding silylating reagent at room temperature. After stirring for 1 h, 2.0 equiv. of 2,6-lutidine (0.39 mL, 3.36 mmol) was added. Subsequently, 1.5 equiv. (2.52 mmol) of a solution of the corresponding Grignard reagent (in THF or Et_2O) was added slowly through a syringe. Details are given for each compound. After stirring for 2 h (until TLC indicated complete conversion), satd. NH_4Cl (10 mL) was added, the

mixture was diluted with CH_2Cl_2 (20 mL) and the layers were separated. After extraction of the aqueous solution with CH_2Cl_2 the combined organic layers were dried with $MgSO_4$, filtered and the solvent was removed in vacuo. Further purification was carried out by flash chromatography and afforded the compounds **20**.

(4*R*)-4-Ethyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20a): TMSOTf (3.36 mmol, 0.61 mL), EtMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.56 g (0.91 mmol, 54%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 124 °C. R_f = 0.31 (light petroleum ether/ethyl acetate, 8:1). $[\alpha]_D^{23}$ = 40.60 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (m, 3 H, $-CH_3$), 1.07, 1.08, 1.13, 1.25 (4 s, 36 H, piv CH_3), 1.40 (m, 2 H, $-CH_2-$Me), 2.25−2.52 (m, 3 H, $-CH_2CO$, $-CH-$ethyl), 3.89−4.12 (m, 3 H, H-6a, H-6b, H-5), 5.18−5.23 (m, 2 H, H-3, N−CH=C*H*), 5.27 (t, $J_{2,1}$= 8.79 Hz, 1 H, H-2), 5.43 (d, $J_{4,3}$ = 2.92 Hz, 1 H, H-4), 5.87 (d, $J_{1,2}$ = 8.79 Hz, 1 H, H-1), 6.21 (dd, J_{olef} = 8.3 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 10.82 ($-CH_3$), 27.05, 27.24 (piv CH_3), 27.29 ($-CH_2$-Me), 32.75 (CH−ethyl), 37.42 ($CO\mathit{C}H_2-$), 38.71, 38.75, 39.08 (piv $C_{quat.}$), 60.85 (C-6), 66.27; 66.85, 71.57, 73.06 (C-2, C-3, C-4, C-5), 78.45 (C-1), 112.68 (NCH=*C*H), 122.88 (N*C*H=CH), 169.69 (NC=O), 176.55; 176.80, 177.03, 177.79, (piv C=O) ppm. MS (FD): *m*/*z* = 624.4 [M^+]. $C_{33}H_{53}NO_{10}$ (623.77): calcd. C 63.54, H 8.56, N 2.25; found C 63.54, H 8.54, N 2.21.

(4*R*)-3,4-Dihydro-4-propyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20b): TIPSOTf (3.36 mmol, 0.68 mL), *n*PrMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.73 g (1.14 mmol, 68%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 118 °C. R_f = 0.42 (light petroleum ether/ethyl acetate, 8:1). $[\alpha]_D^{27}$ = 49.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (m, 3 H, $-CH_3$), 0.98, 1.07, 1.08, 1.14 (4s, 36 H, piv CH_3), 1.19−1.33 (m, 4 H, $-CH_2-CH_2-$), 2.15−2.65 (m, 3 H, $-CH_2CO$, $-CH$propyl), 3.90−4.10 (m, 3 H, H-5, H-6a, H-6b), 5.16−5.27 (m, 2 H, H-3, N−CH=C*H*), 5.36 (t, $J_{2,3}$ = 10.26 Hz, $J_{2,1}$= 8.79 Hz, 1 H, H-2), 5.43 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 5.87 (d, $J_{1,2}$ = 9.28 Hz, 1 H, H-1), 6.20 (d, J_{olef} = 8.3 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz,$CDCl_3$): δ = 13.91 ($-CH_3$), 19.52 ($-CH_2CH_3$), 27.05, 27.22 (piv CH_3), 30.93 ($-CH_2-$ethyl), 37.76 (*C*Hpropyl), 38.70 ($CO-CH_2-$), 38.73, 38.81, 39.07 (piv $C_{quat.}$), 60.83 (C-6), 66.29, 66.85, 71.54, 73.04 (C-2, C-3, C-4, C-5), 78.44 (C-1), 113.05 (NCH=*C*H−), 122.75 (N*C*H=CH), 169.64 (NC=O), 176.52, 176.73, 176.77, 177.00 (piv C=O) ppm. MS (FD): *m*/*z* = 638.1 [M^+]. $C_{34}H_{55}NO_{10}$ (637.81): calcd. C 64.03, H 8.69, N 2.20; found C 66.30, H 8.66, N 2.16. Crystal data: $P2_12_12_1$, (orthorhombic), *a* = 6.34549(4) Å, *b* = 24.4408 (14) Å, *c* = 24.5635(13) Å, *V* = 3815.1(4) Å^3, *Z* = 4, *F*(000) = 1384, Turbo CAD4, Cu-K_α, SIR92, SHELXL-97. CCDC-165221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

(4*S*)-3,4-Dihydro-4-isopropyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20c): TMSOTf (3.36 mmol, 0.61 mL), *i*PrMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.95 g (1.49 mmol, 88%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 74 °C. R_f = 0.34 (light petroleum ether/ethyl acetate, 8:1). $[\alpha]_D^{23}$ = 32.20 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, 6 H, $-CH_3$), 1.07, 1.08, 1.13, 1.25 (4 s, 36 H, piv CH_3), 1.27 [m, 1 H,C*H*$(CH_3)_2$], 2.14−2.56 (m, 3 H, $-CH_2CO$, $-CH-i$Pr), 3.39−4.25 (m, 3 H, H-6a, H-6b, H-5), 5.16−5.23 (m, 2 H, H-3, N−CH=C*H*), 5.32 (t, $J_{2,1}$ = 9.78 Hz, 1 H, H-2), 5.43 (d, $J_{4,3}$ = 2.35 Hz, 1 H, H-4), 5.87 (d, $J_{1,2}$ = 9 Hz, 1 H, H-1), 6.24 (dd, J_{allyl} = 1.96, J_{olef} = 8.22 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.12 ($-CH_3$), 19.44 ($-CH_3$), 26.98, 27.05, 27.24 (piv CH_3), 31.33 [*C*H$(CH_3)_2$], 35.06 ($CO-CH_2-$), 37.82 (*C*H−*i*Pr), 38.75, 38.83, 39.08 (piv $C_{quat.}$), 60.94 (C-6), 66.21, 66.88, 71.70, 73.0 (C-2, C-3, C-4, C-5), 78.45 (C-1), 111.80 (NCH=*C*H), 123.398 (N*C*H=CH), 169.93 (NC=O), 176.55, 176.84, 177.03, 177.81 (piv C=O) ppm. MS (FD): *m*/*z* = 638.1 [M^+]. $C_{34}H_{55}NO_{10}$ (637.81): calcd. C 64.03, H 8.69, N 2.20; found C 64.02, H 8.66, N 2.16.

(4*R*)-4-Butyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20d): TMSOTf (3.36 mmol, 0.61 mL), *n*BuMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.824 g (1.26 mmol, 75%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 57 °C. R_f = 0.21 (light petroleum ether/ethyl acetate, 6:1). $[\alpha]_D^{27}$ = 59.71 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (m, 3 H, $-CH_3$), 1.06, 1.07, 1.14, 1.25 (4 s, 36 H, piv CH_3), 1.28 (m, 6 H, $-CH_2-$), 2.24−2.65 (m, 3 H, $-CH_2CO$, C*H*−butyl), 3.95−4.14 (m, 3 H, H-5, H-6a, H-6b), 5.16−5.27 (m, 2 H, H-3, NCH=C*H*), 5.31 (t, 1 H, H-2), 5.44 (d, $J_{4,3}$ = 2.93 Hz, 1 H, H-4), 5.85 (d, $J_{1,2}$ = 8.79 Hz, 1 H, H-1), 6.20 (d, J_{olef} = 7.79 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.95 ($-CH_3$), 22.56 ($-CH_2-CH_3$), 27.05, 27.24 (piv CH_3), 31.18 (*C*H−butyl), 34.09 ($-CH_2-$Et), 37.80 ($CO\mathit{C}H_2-$), 38.73, 38.81, 39.08 (piv $C_{quat.}$), 60.83 (C-6), 66.29, 66.83, 71.56, 73.04 (C-2, C-3, C-4, C-5), 78.45 (C-1), 113.11 (NCH=*C*H), 122.74 (N*C*H=CH), 169.67 (NC=O), 176.53, 176.79, 177.01 (piv C=O) ppm. MS (FD): *m*/*z* = 652.3 [M^+]. $C_{35}H_{57}NO_{10}$ (651.3): calcd. C 64.49, H 8.81, N 2.15; found C 63.81, H 8.83, N 2.13.

(4*R*)-4-*tert*-Butyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20e): TMSOTf (3.36 mmol, 0.61 mL), *t*BuMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.243 g (0.37 mmol, 22%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 82 °C. R_f = 0.23 (light petroleum ether/ethyl acetate, 15:1). $[\alpha]_D^{23}$ = 18.38 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9 H, $-CH_3$), 0.98, 1.07, 1.08, 1.14 (4 s, 36 H, piv CH_3), 1.19−1.33 (m, 4 H, $-CH_2-$), 2.04−2.56 (m, 3 H, $-CH_2CO$, $-CH-t$Bu), 3.90−3.98 (m, 1 H, H-6a), 4.02−4.08 (m, 2 H, H-5, H-6b), 5.17−5.25 (m, 2 H, H-3, N−CH=C*H*), 5.31 (t, $J_{2,3}$ = 10.17 Hz, $J_{2,1}$ = 9.39 Hz, 1 H, H-2), 5.42 (d, $J_{4,3}$ = 2.7 Hz, 1 H, H-4), 5.86 (d, $J_{1,2}$ = 9.3 Hz, 1 H, H-1), 6.20 (dd, J_{olef} = 8.21, J_{allyl} = 1.95 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.72 ($-CH_3$), 27.02, 27.22 (piv CH_3), 33.09 ($CO\mathit{C}H_2-$), 38.67 (*t*Bu $C_{quat.}$), 38.72, 38.78, 39.05 (piv $C_{quat.}$), 41.78 (*C*H−*t*Bu), 60.98 (C-6), 66.09, 66.86, 71.47, 73.04 (C-2, C-3, C-4, C-5), 78.33 (C-1), 110.03 (NCH=*C*H), 123.48 (N*C*H=CH), 170.02 (NC=O), 176.54, 176.82, 176.98, 177.01 (piv C=O) ppm. MS (FD): *m*/*z* = 652.2 [M^+]. $C_{35}H_{57}NO_{10}$ (651.83): calcd. C 64.49, H 8.81, N 2.15; found C 64.36, H 8.76, N 2.04.

(4*R*)-4-Decyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20f): TMSOTf (3.36 mmol, 0.61 mL), *n*-decylMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.70 g (0.95 mmol, 55%); mixture of diastereomers, ratio 96:4 (^{1}H NMR). R_f = 0.82 (light petroleum ether/ethyl acetate, 8:1); the diastereomers were separated by HPLC [MeCN/H_2O (gradient: 80:20 to 100:0 (80 min); flow: 20 mL·min^{-1}; UV detection at 200 nm; R_t [min]: 57.417 (major isomer), 65.565 (minor isomer)]. Analytical data for the pure major (*R*) diastereomer separated by prepatrative HPLC: $[\alpha]_D^{25}$ = 48.82 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (t, 3 H, $-CH_3$), 1.03−1.41 (m, 54 H, piv CH_3), 2.11−2.48 (m, 3 H, $-CH_2CO$, C*H*−decyl), 3.93−4.09 (m, 3 H, H-5, H-6a, H-6b), 5.15−5.33 (m, 3 H, H-2, H-3, NCH=C*H*), 5.40

(d, $J_{4,3}$ = 2.4 Hz, 1 H, H-4), 5.84 (d, $J_{1,2}$ = 8.8 Hz, 1 H, H-1), 6.17 (d, J = 7.8 Hz, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.04 (−CH_3), 23.86, 25.56 (−CH_2−), 26.36, 26.63, 26.89, 27.19 (piv CH_3), 29.63−39.02 (−CH_2−, piv $C_{quat.}$), 31.49 (*C*H−decyl), 60.77 (C-6), 66.29, 66.79, 71.53, 72.99 (C-2, C-3, C-4, C-5), 78.40 (C-1), 113.08 (NCH=*C*H), 122.70 (N*C*H=CH), 169.61 (NCO), 176.45, 176.66, 176.93, 177.68 (piv CO) ppm. MS (FD): *m*/*z* = 736.8 [M + H^+]. $C_{41}H_{69}NO_{10}$ (735.49): calcd. C 66.91, H 9.45, N 1.90; found C 66.92, H 9.44, N 1.88.

(4*S*)-4-Cyclohexyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20g): TMSOTf (3.36 mmol, 0.61 mL), cyclohexylMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.9 g (1.33 mmol, 79%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 114 °C. R_f = 0.24 (light petroleum ether/ethyl acetate, 15:1). $[\alpha]_D^{23}$ = 74.48 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07, 1.08, 1.14, 1.26 (4 s, 36 H, piv CH_3), 1.66 (br. s, 11 H, cyclohexyl CH_2− and C*H*−), 2.17−2.49 (m, 3 H, −CH_2CO, −C*H*−cyclohexyl), 3.96−4.26 (m, 3 H, H-6a, H-6b, H-5), 5.16−5.24 (m, 2 H, H-3, N−CH=C*H*), 5.32 (t, $J_{2,1}$ = 9.28 Hz, $J_{2,3}$ = 10.25 Hz, 1 H, H-2), 5.42 (d, $J_{4,3}$ = 2.93 Hz, 1 H, H-4), 5.86 (d, $J_{1,2}$ = 9.28 Hz, 1 H, H-1), 6.20 (dd, J_{olef} = 8.3, J_{allyl} = 1.95 Hz, 1 H, NC*H*=CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.33 (C-4 cyclohexyl), 27.05, 27.24 (piv CH_3), 29.44, 29.59 (C-2, C-3, C-5, C-6 cyclohexyl), 34.69 (C-3), 36.90 (C-1 cyclohexyl), 38.71, 38.81, 39.08 (piv $C_{quat.}$), 41.40 (C-4), 60.93 (C-6), 66.21, 66.87, 71.54, 73.06 (C-2, C-3, C-4, C-5), 78.44 (C-1), 111.15 (NCH=*C*H), 123.14 (N*C*H=CH), 169.93 (NC=O), 176.55, 176.82, 177.01, 177.81 (piv C=O) ppm. MS (FD): *m*/*z* = 678.2 [M^+]. $C_{37}H_{59}NO_{10}$ (677.87): calcd. C 65.56, H 8.77, N 2.07; found C 65.49, H 8.78, N 2.05.

(4*R*)-4-Benzyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20h): TMSOTf (3.36 mmol, 0.61 mL), benzylMgCl (1 M in THF, 2.52 mL, 2.52 mmol); yield 0.392 g (0.57 mmol, 34%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 137 °C. R_f = 0.24 (light petroleum ether/ethyl acetate, 8:1). $[\alpha]_D^{23}$ = 56.62 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15, 1.17, 1.23, 1.34 (4 s, 36 H, piv CH_3), 2.38−2.44 (m, 1 H, −CH*H*^{b}−phenyl), 2.53 (dd, J_{vic} = 5.47, J_{gem} = 16.04 Hz, 1 H, −CH*H*^{a}−phenyl), 2.67−2.82 (m, 3 H, −CH_2CO, −C*H*−benzyl), 4.03−4.09 (m, 1 H, H-6b), 4.14−4.21 (m, 2 H, H-6a, H-5), 5.28−5.33 (m, 2 H, H-3, N−CH=C*H*), 5.32 (t, $J_{2,1}$ = 9.39 Hz, $J_{2,3}$ = 10.17 Hz, 1 H, H-2), 5.42 (d, $J_{4,3}$ = 2.74 Hz, 1 H, H-4), 5.96 (d, $J_{1,2}$ = 9.39 Hz, 1 H, H-1), 6.32 (dd, J_{olef} = 7.83, J_{allyl} = 0.78 Hz, 1 H, NC*H*=CH), 7.19−7.44 (m, 5 H, phenyl H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.02, 27.21 (piv CH_3), 33.11 (C-3), 37.26 (−*C*H_2−phenyl), 38.72, 38.79, 39.05 (piv $C_{quat.}$), 40.37 (*C*H−benzyl), 60.78 (C-6), 66.27, 66.76, 73.02 (C-2, C-3, C-4, C-5), 78.41 (C-1), 112.10 (NCH=*C*H), 123.17 (N*C*H=CH), 126.45, 126.95, 127.62, 128.51, 129.03 (2 × *o*-, *m*-, *p*-C, phenyl), 138.54 (*ipso*-C, phenyl), 169.23 (NC=O), 176.53, 176.82, 177.01, 177.79 (piv C=O) ppm. MS (FD): *m*/*z* = 686.3 [M^+]. $C_{38}H_{55}NO_{10}$ (685.84): calcd. C 66.55, H 8.08, N 2.04; found C 66.12, H 8.69, N 1.96.

(4*R*)-3,4-Dihydro-4-phenyl-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20i): TIPSOTf (3.36 mmol, 0.68 mL), PhMgCl (1 M in THF, 2.52 mL, 2.52 mmol); reaction time 12 h; yield 0.86 g (1.28 mmol, 76%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 145 °C. R_f = 0.73 (light petroleum ether/ethyl acetate, 4:1). $[\alpha]_D^{28}$ = 76.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10, 1.12, 1.15, 1.27 (4 s, 36 H, piv CH_3), 2.64 (dd, J_{gem} = 16.1, J_{vic} = 10.3 Hz, 1 H, CH_2CO), 2.74 (dd, J_{gem} = 16.1, J_{vic} = 6.1 Hz, 1 H, CH_2CO), 3.58 (m, 1 H, CHPh), 4.01−4.13 (m, 3 H, H-5, H-6a, H-6b), 5.24 (dd, $J_{3,2}$ = 10.9, $J_{3,4}$ = 3.2 Hz, 1 H, H-3), 5.34−5.41 (m, 2 H, H-2, NCH=C*H*), 5.46 (d, $J_{4,3}$ = 2.9 Hz, 1 H, H-4), 5.92 (d, $J_{1,2}$ = 9.4 Hz, 1 H, H-1), 6.39 (dd, J_{olef} = 7.9, ^4J = 2.1 Hz, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.05, 27.26, 27.37 (piv CH_3), 37.81 (*C*H−phenyl), 38.74, 38.90, 39.10, (piv $C_{quat.}$), 40.60 (−CH_2−), 60.90 (C-6), 66.36, 66.84, 71.50, 73.18 (C-2, C-3, C-4, C-5), 78.57 (C-1), 111.83 (NCH=*C*H), 123.91 (N*C*H=CH), 127.02, 127.12, 128.90 (*o*-, *m*-, *p*-C, phenyl), 142.31 (*ipso*-C, phenyl), 169.43 (NCO), 176.56, 176.95, 177.83 (piv CO) ppm. MS (ESI): *m*/*z* = 694.4 [M + Na^+]. $C_{37}H_{53}NO_{10}$ (671.82): calcd. C 66.15, H 7.95, N 2.08; found C 66.20, H 7.98, N 2.07.

(4*R*)-4-(3-Butenyl)-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridine-2(1*H*)-one (20j): TIPSOTf (4.2 mmol, 0.85 mL, 2.5 equiv.), 2,6-lutidine (4.2 mmol, 0.48 mL, 2.5 equiv.), butenylMgBr [freshly prepared from Mg (4.2 mmol), butenyl bromide (4.2 mmol) in THF]; yield 0.93 g (1.44 mmol, 86%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). R_f = 0.44 (light petroleum ether/ethyl acetate, 6:1). $[\alpha]_D^{25}$ = 33.14 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16, 1.23, 1.35 (4 s, 36 H, piv CH_3), 1.6 (m, 2 H, −CH_2−), 2.25 (m, 2 H, −CH_2−), 2.30−2.65 (m, 3 H, CH_2CO, C*H*−butenyl), 4.03−4.21 (m, 3 H, H-5, H-6a, H-6b), 5.02−5.13 (m, 2 H, CH=CH_2), 5.32 (m, 2 H, H-3, NCH=C*H*), 5.41 (t, $J_{2,1}$ = 9.78, $J_{2,3}$ = 9.79 Hz, 1 H, H-2), 5.54 (d, $J_{4,3}$ = 2.35 Hz, 1 H, H-4), 5.77−5.89 (m, 1 H, C*H*=CH_2), 5.98 (d, $J_{1,2}$ = 9.39 Hz, 1 H, H-1), 6.39 (dd, J_{olef} = 8.21, ^4J = 1.95 Hz, NC*H*=CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.99, 27.19 (piv CH_3), 30.39 (−CH_2−), 30.45 (*C*H−butenyl), 33.36 (−CH_2−), 37.53 (−CH_2−CO), 38.94, 38.76, 39.04, (piv $C_{quat.}$), 60.77 (C-6), 66.23, 66.74, 71.44, 73.01 (C-2, C-3, C-4, C-5), 78.34 (C-1), 112.66 (NCH=*C*H), 115.23 (CH=*C*H_2), 122.90 (N*C*H=CH), 137.60 (*C*H=CH_2), 169.41 (NCO), 176.50, 176.77, 176.98, 177.76 (piv CO) ppm. MS (ESI): *m*/*z* = 672.6 [M + Na^+] for $C_{35}H_{55}NO_{10}$ (649.38): calcd. C 64.69, H 8.53, N 2.16; found C 64.46, H 8.05, N 2.01.

General Procedure for the 1,4-Addition of Activated Organocuprates to *N*-Galactosyl-2-pyridone 5

A) Formation of Organocuprate: A suspension of CuI in dry THF was cooled to −35 °C, and the corresponding organolithium compound was added. The reaction mixture was warmed up during 1.5 h until the solution became clear. Details are given for each compound. After formation of the organocuprate, the reaction mixture was cooled to −78 °C.

B) 1,4-Addition: The 1,2-dihydropyridin-2-one **5** was dissolved in dry THF at ambient temperature and treated with TMSCl. After stirring for 30 min, this solution was added to the solution of the organocuprate through a syringe. The reaction mixture was warmed up overnight. After hydrolysis with 100 mL of concd. NH_4OH/satd.NH_4Cl (1:1, v/v) and addition of 100 mL of diethyl ether, the aqueous layer was separated and extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. Evaporation of the solvent in vacuo and flash chromatography (light petroleum ether/ethyl acetate) yielded compounds **19**.

(4*R*)-4-Butyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridin-2(1*H*)-one (20d): CuI (1.603 g, 8.42 mmol), dry THF (55 mL), *n*BuLi (10.51 mL, 16.84 mmol, 1.6 M in pentane); temperature, time for formation of organocuprate: −35 °C to −20 °C, 1.5 h; galactosyl-2-pyridone **5** (1 g, 1.68 mmol), dry THF (50 mL), TMSCl (3.23 mL, 25.26 mmol); yield 0.7 g (1.07 mmol, 64%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC).

The product is identical to the compound obtained from the Grignard addition method for **20d** (see above).

(4*S*)-4-*tert*-Butyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridin-2(1*H*)-one (20e): CuI (1.603 g, 8.42 mmol), dry THF (55 mL), *t*BuLi (9.9 mL, 16.84 mmol, 1.7 M in pentane); temperature, time for formation of organocuprate: −35 to −20 °C, 1.5 h; galactosyl-2-pyridone **5** (1 g, 1.68 mmol), dry THF (50 mL), TMSCl (3.23 mL, 25.26 mmol); yield 0.42 g (0.65 mmol, 39%); mixture of diastereomers, ratio 92:8 (^{1}H NMR and HPLC). R_f = 0.36 (light petroleum ether/ethyl acetate, 8:1). The major diastereomer is identical to the major diastereomer obtained from the Grignard addition to **20e** (see above).

(4*R*)-4-Hexyl-3,4-dihydro-1-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)pyridin-2(1*H*)-one (20k): CuI (1.603 g, 8.42 mmol), dry THF (55 mL), *n*-hexylLi (7.3 mL, 16.84 mmol, 2.3 M in pentane); formation of organocuprate: temperature, time: −35 to −20 °C, 1.5 h; galactosyl-2-pyridone **5** (1 g, 1.68 mmol), dry THF (50 mL), TMSCl (3.23 mL, 25.26 mmol); yield 1.07 g (1.57 mmol, 93%); single diastereomer, ratio >> 99:1 (^{1}H NMR and HPLC). M.p. 88 °C. $[\alpha]_D^{25}$ = 44.51 (*c* = 1.0 g/mL, $CHCl_3$). R_f = 0.67 (light petroleum ether/ethyl acetate, 4:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, $-CH_3$), 1.03−1.49 (m, 57 H, piv CH_3, $-CH_2-$), 2.13−2.68 (m, 3 H, $-CH_2CO$, CH−hexyl), 3.89−4.16 (m, 3 H, H-5, H-6a, H-6b), 5.15−5.29 (m, 2 H, H-3, NCH=C*H*), 5.32 (t, $J_{2,1}$ = 9.28, $J_{2,3}$ = 10.26 Hz, 1 H, H-2), 5.45 (d, $J_{4,3}$ = 2.4 Hz, 1 H, H-4), 5.88 (d, $J_{1,2}$ = 8.79 Hz, 1 H, H-1), 6.21 (d, *J* = 7.8 Hz, NC*H*=CH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.03 ($-CH_3$), 22.58, 26.36 ($-CH_2-$), 26.63, 27.05, 27.24 (piv CH_3), 29.65 ($-CH_2-$), 31.18 (*C*H−hexyl), 31.92, 34.39, 37.80 ($-CH_2-$), 38.71, 38.75, 39.01(piv $C_{quat.}$), 60.83 (C-6), 66.31, 66.83, 71.56, 73.06 (C-2, C-3, C-4, C-5), 78.45 (C-1), 113.15 (NCH=*C*H), 122.74 (N*C*H=CH), 169.69 (NCO), 176.53, 176.80, 177.03, 177.79 (piv CO) ppm. MS (FD): *m*/*z* = 680.2 [M^+]. $C_{37}H_{61}NO_{10}$ (679.88): calcd. C 65.36, H 9.04, N 2.06; found C 65.62, H 9.12, N 1.96.

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