Enantioselective Syntheses of 2-Alkyl-, 2,6-Dialkylpiperidines and Indolizidine Alkaloids Through Diastereoselective Mannich–Michael Reactions

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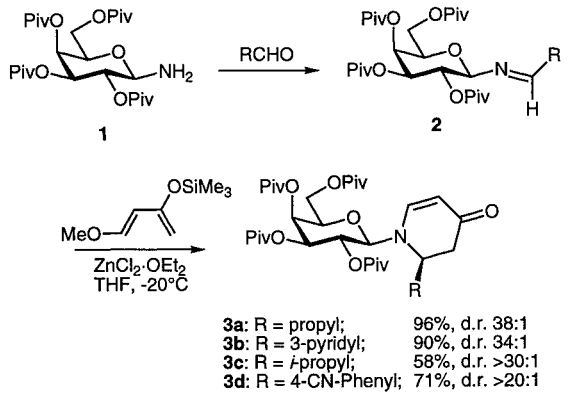
Aldimines of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine react with 1-methoxy-3-trimethylsilyloxybuta-1,3-diene in a Mannich–Michael condensation reaction sequence to give 2-substituted *N*-galactosyl-5,6-dehydropiperidin-4-ones **3** with high diastereoselectivity. The X-ray analysis of the 2-propyl derivative **3a** proved (*R*)-configuration of the major diastereomer and led to the correction of our earlier assignment of configuration for (−)-coniine hydrochloride **9a** obtained from this intermediate. Despite their low reactivity, these enaminones **3** can be converted into chiral 2,6-*cis*-disubstituted piperidinones **12** with high stereoselectivity by reaction with organocuprates in combination with hard electrophiles. Enantiomerically pure alkaloids such as (−)-dihydropinidine and gephyrotoxine 167B have been synthesized according to this methodology.



Scheme 1

Numerous natural products and drugs contain chiral nitrogen heterocycles as structural elements. A series of alkaloids belong to the class of 2-alkyl- and 2,6-dialkylpiperidines.[1] Because these compounds often exhibit marked pharmacological effects and new members of this class are continuously discovered in nature,[2] stereoselective syntheses of chiral piperidines are receiving increasing interest. Asymmetric syntheses of these compounds have been achieved by cyclizations of 1,5-dicarbonyl compounds[3] of functionalized chiral amines,[4] by nucleophilic addition reactions of *N*-alkyl- or *N*-acylpyridinium salts[5] and by reactions of 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (Danishefsky diene)[6] with chiral imines.[7] In an analogous manner, chiral chromium-carbonyl complexes of imines of aromatic aldehydes have recently been used for reactions with the Danishefsky diene.[8]

The aldimines **2** of tetra-*O*-pivaloyl-β-D-galactosylamine **(1)** used for enantioselective syntheses of 2-substituted piperidines gave high yields and high diastereoselectivities in their reactions with the Danishefsky diene.[7a] In addition, the auxiliary can be recovered almost quantitatively after simple acidic cleavage of the *N*-glycosidic bond. It was revealed in more detailed investigations that the galactosyl imines **2** react with isoprene in the presence of zinc chloride via a concerted aza Diels–Alder reaction,[7b] whereas the reaction with the Danishefsky diene proceeds via an initial Mannich reaction (Scheme 1).[7a]

As a rule, the 2-substituted dehydropiperidinones **3** were formed with excellent diastereoselectivity. Pure diastereomers of the chiral piperidinone derivatives were obtained after simple recrystallization or flash chromatography. In order to assign the absolute configuration of compounds **3**, we converted **3a** into coniine[7a] and **3b** into anabasine.[7a,b] Since the hydrochloride of the obtained coniine showed a negative optical rotation, comparison with data reported in the literature[9] implied the product to have the (*S*)-configuration.[7a] However, this was in contradiction to the observed (*S*)-configuration of the anabasine formed in analogous conversion from **3b**[7a,b] and also to other assignments of the configuration of coniine reported in the literature.[3,4,5,7d,e]

Because all the assignments of the configuration of coniine reported in the literature themselves were based on the comparison of optical rotation values with that given in earlier reports,[9,10] we searched for an independent unequivocal elucidation of the absolute configuration of the 2-alkylpiperidines synthesized according to Scheme 1. In one approach to this aim, dehydropiperidinones **3** are planned to be converted into 2,6-disubstituted piperidine alkaloids, although these enaminones **3** had shown marked resistance to reactions with strong nucleophiles like Grignard compounds or organocuprates. However, it can be stated beforehand, that the unambiguous clarification of the absolute configuration of the coniine formed from **3a** became possible when we succeeded in the isolation of suitable crystals of **3a** and their X-ray analysis (Figure 1).

The X-ray structural analysis (Figure 1) shows the coniine precursor **3a** to have (*R*)-configuration. These results disprove the data given for coniine hydrochloride in the literature,[9] and therefore our earlier assignment of the structure of coniine hydrochloride formed from **3a** as well as that for a coniine produced in an analogous reaction sequence from imines of amino acid esters.[7c] As a consequence, the interpretation of the diastereofacial differentiation occurring at the zinc complex **4** of the *N*-galactosyl butyraldimine has to be corrected (Figure 2).

The silyl dienol ether does not attack the imine at the *Re*-face occupied by the coordinated zinc as is the case

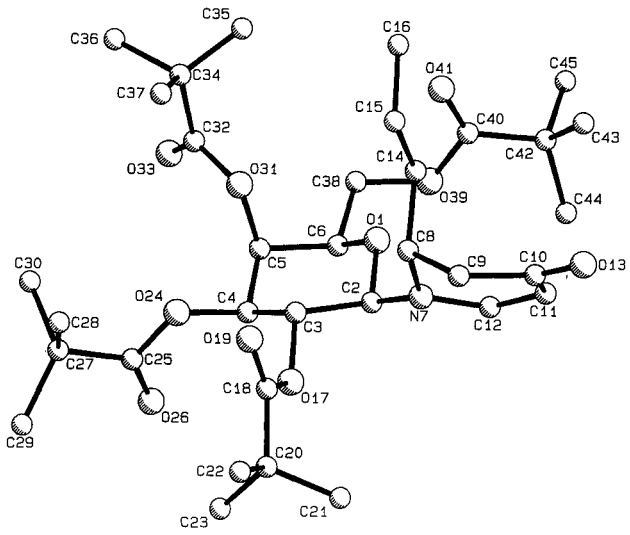


Figure 1. X-Ray Structure of **3a**.

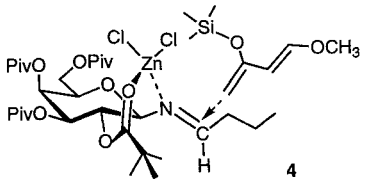
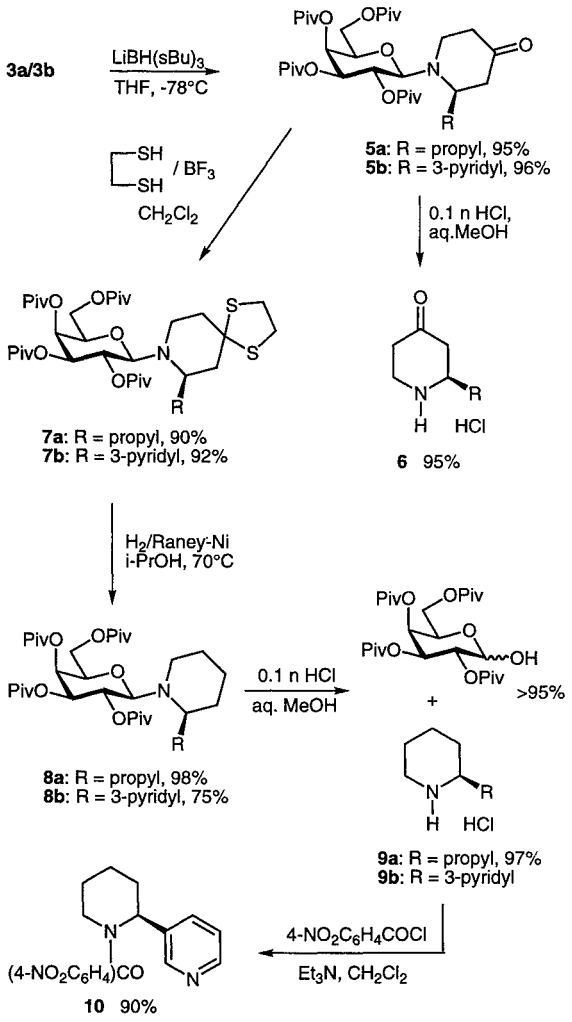


Figure 2. Proposed Mechanism of Stereoselective Mannich Reaction of 1-Methoxy-3-trimethylsiloxybuta-1,3-diene with *N*-Galactosyl Imines.

in a Strecker reaction of **2** with trimethylsilyl cyanide in chloroform.[11] Instead the attack proceeds at the sterically less shielded *Si*-face of the galactosyl imine-Lewis acid complex (Figure 2) as was also observed in the corresponding Ugi reactions[12] and reactions with allylsilanes and allylstannanes.[13]

The conversion of the precursors **3a** and **3b** into the alkaloids (*R*)-coniine and (*S*)-anabasine was carried out according to the preliminarily described reaction sequences.[7a,b] Treatment of **3a** and **3b** with lithium tris-(*s*-butyl)borohydride[14] in tetrahydrofuran at −78 °C resulted in almost quantitative formation of the 2-substituted piperidinones **5a** and **5b**. Acidolytic cleavage of of the *N*-glycosidic bond of **5a** gave the hydrochloride of (*R*)-2-propylpiperidin-4-one **(6)** in the form of a monohydrate which is obviously stabilized by an intramolecular hydrogen bridge (Scheme 2). The isolation of the free ketone **6** required codistillation with acetonitrile and lyophilization in high vacuum. It is interesting to note that the reaction of **6** with 1,2-ethanedithiol in the presence of boron trifluoride exclusively furnished the monothioacetal. It is resistant to dehydration and transformation into the corresponding dithiolane due to a transannular stabilization. Therefore, the dithiolanes **7** were formed from the *N*-galactosylpiperidinones **5** by reaction with ethane-1,2-dithiol and subsequently subjected to desulfurization with Raney nickel to give the *N*-galactosylated alkaloids **8**. The yield of anabasine derivative **8b** is lower because of its persistent adsorption on nickel.



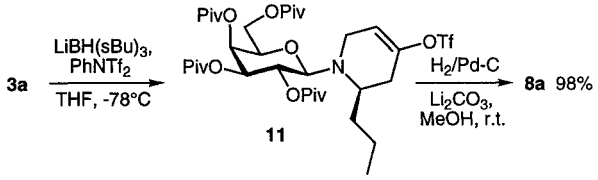
Scheme 2

The release of the enantiomerically pure alkaloids (*R*)-coniine **(9a)** and (*S*)-anabasine **(9b)** from the carbohydrate-linked precursors **8** was achieved by mild acidolysis with dilute hydrochloric acid in aqueous methanol (Scheme 2). The carbohydrate auxiliary was recovered almost quantitatively by simple extraction with pentane. Both alkaloids were isolated as their hydrochlorides, but for comparison of its analytical data with those reported in the literature,[15] anabasine **9b** was converted into its *N*-(4-nitrobenzoyl) derivative **10**.

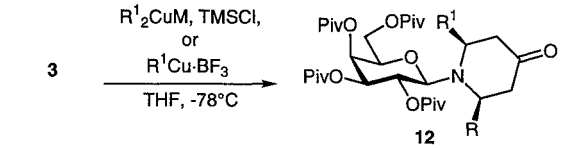
An alternative conversion of the enaminone **3a** into the *N*-galactosyl coniine **8a** consists of trapping the lithium enolate generated during reduction with lithium tris-(*s*-butyl)borohydride by *N*,*N*-bis(trifluormethanesulfonyl)aniline[16] and subsequent hydrogenation of the formed enol triflate **11** (Scheme 3).

The use of the chiral heterocycles **3** of now clarified configuration for further transformations failed at first because of the low reactivity of their vinylogous amide

structure. Even organolithium compounds did not attack the enaminone ring. With lower-order as well as with higher-order organocuprates only slow reactions occurred. After several days a conversion of at best 30% was achieved. However, the formed products did not have the desired structure of 2,6-disubstituted piperidinones. Only the application of organocuprates in combination with hard electrophiles such as trimethylsilyl chloride[17] (TMSCl) or boron trifluoride–diethyl ether complex[18] resulted in 1,4-addition reactions to enaminones **3** and gave 2,6-*cis*-disubstituted piperidinones **12** in useful yields and high diastereoselectivity (Scheme 4, Table 1).

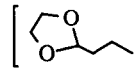
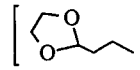


Scheme 3



Scheme 4

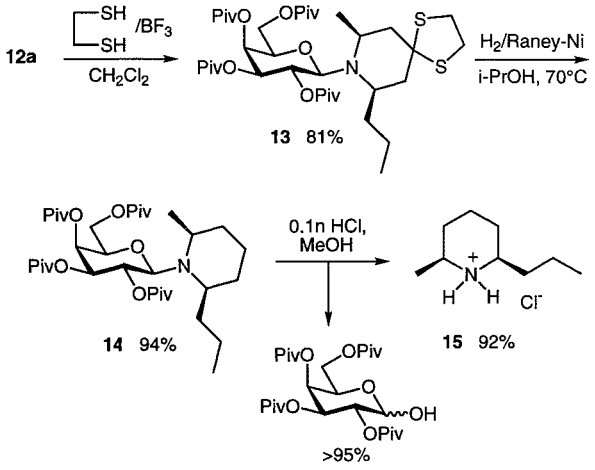
Table. Diastereselective Synthesis of 2,6-Disubstituted Piperidinones **12** from *N*-Galactosyldehydropiperidinones **3**

	Starting Materials	Product	Yield (%)	dr[a]
Ketone	R^1Cu-Complex			
3a	$Me_2CuLi/TMSCl$[b]	**12a**	71	> 10 : 1
3b	$(EEOCH_2CH_2CH_2)_2$ CuMgBr/TMSCl[b,c]	**12b**	82[d]	3 : 1
3c	$(i\text{-}C_3H_7)Cu \cdot BF_3$	**12c**	63	> 20 : 1
3d	 Cu·BF_3	**12d**	65[e]	> 15 : 1
3e	 Cu·BF_3	**12e**	64[e]	> 10 : 1

[a] Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.
[b] Conjugated addition was followed by treatment with TBAF.
[c] EE = 1-Ethoxyethyl.
[d] CuBr · SMe_2 was used.
[e] Cuprate formation was performed in the presence of substrate **3**.

The introduction of non-functionalized alkyl groups proceeded smoothly at −78 °C in tetrahydrofuran with the lithium cuprate/TMSCl combination **(12a)** as well as with the Yamamoto complex[18] formed from isopropylmagnesium bromide, copper iodide and boron trifluoride **(12c)**. The 1,4-addition reaction of functionalized cuprate-BF_3 complexes to the 2-propyl-substituted enaminone **3a** was insufficient independent of the applied copper salt CuI or CuBr · SMe_2. In contrast, the same substrate **3a** efficiently reacted with TMSCl and 3-(1-ethoxy)ethoxypropylcuprate obtained from the corresponding Grignard compound to yield the desired 2,6-disubstituted piperidine derivative **12b**. The stereoselectivity was only moderate. After both TMSCl-promoted reactions of **3a**, the primarily formed silyl enol ether was subsequently cleaved using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran to furnish the piperidinone **12a** or **12b**, respectively. The 2-isopropyl- **(3c)** as well as the 2-aryldihydropyridinone **3d** reacted with functionalized organocuprate-BF_3 complexes generated in situ in the presence of the substrate to furnish the 2,6-disubstituted piperidinones **12d** and **12e** in good yield and high diastereoselectivity. These reactions illustrate the general applicability of this method for the stereoselective synthesis of 2,6-disubstituted piperidines.

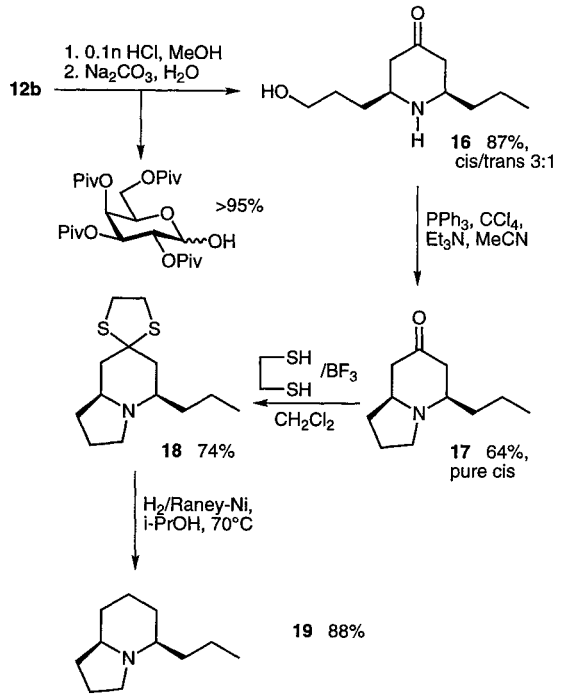
Without further purification, the isolated 2-propyl-6-methylpiperidinone derivative **12a** was subjected to conversion into the dithiolane **13** and subsequent desulfurization using Raney nickel to give the *N*-galactosyl dihydropinidine **14** in an overall yield of 78%. Treatment of **14** with hydrogen chloride in aqueous methanol resulted in the cleavage of the *N*-glycosidic bond. (−)-Dihydropinidine **(15)**, which earlier had been synthesized by different strategies,[3a,19] was isolated in high yield and enantiomerically pure form (Scheme 5). The scissioned carbohydrate auxiliary was recollected almost quantitatively after extraction with diethyl ether.



Scheme 5

The side chain functionalized 2,6-disubstituted dihydropyridine **12b** was used for an enantioselective synthesis of gephyrotoxine 167B which belongs to the minor alkaloids of skin secretions of Central and South American frogs *Dendrobates pumilio*.[20] Up to now, enantioselective syntheses of the indolizidine alkaloid 167B had been achieved either using a non-recoverable auxiliary[21] or in ex-chiral pool syntheses starting from optically active amino acids.[22] Simultaneous acidic cleavage of the *N*-glycosidic bond and of the 1-ethoxyethyl protecting group gave 2-(3-hydroxypropyl)-6-propylpiperidinone **(16)** and the carbohydrate auxiliary, both isolated in high yield. According to its ^{1}H NMR spectrum, the crude

piperidinone **16** showed the same ratio of diastereomers (3:1) as was found for the *N*-glycosyl derivative **12b** (Scheme 6).



Scheme 6

The crude piperidinone **16** was subjected to an Appel reaction[23] with triphenylphosphine/carbon tetrachloride in acetonitrile in the presence of triethylamine which resulted in sequential nucleophilic substitution and cyclization in one step.[24] Surprisingly, only the pure *cis*-diastereomer **17** of the indolizidinone was isolated. It is possible that the corresponding *trans*-isomer has similar chromatographic properties as triphenylphosphine oxide and was separated together with this product during chromatography. However, it seems more likely that the *trans*-isomer is more resistant to substitution and cyclization. This conclusion is supported by the observation that amino alcohol was detectable by TLC even after a reaction time of 24 hours. After conversion of **17** into the dithiolane **18** and subsequent desulfurization using Raney nickel, enantiomerically pure (5*R*, 8a*R*)-gephyrotoxine 167B **(19)** was obtained without any additional purification.

Both enantioselective syntheses of alkaloids (5*R*, 8a*R*)-gephyrotoxine 167B **(19)** and (−)-dihydropinidine **(15)** show that the diastereoselective domino Mannich–Michael reaction of *N*-galactosyl imines **2** with silyldienol ethers of the Danishefsky diene-type in combination with a subsequent 1,4-addition reaction of the obtained dehydropiperidinones **3** with organocuprates in the presence of hard electrophiles, e.g., boron trifluoride or trimethylsilyl chloride, provide an efficient enantioselective access to pharmacologically interesting chiral heterocycles.[33] The clarification of the configuration of the coniine precursor **3a** by means of X-rays analysis ascertains the stereochemical course of these reactions. The potential of these stereoselective syntheses is further extended by the fact that the corresponding *N*-(D-arabinosyl)imines allow the synthesis of the opposite enantiomers by application of the same sequence of reactions.[25]

Reagents and solvents were distilled before use: THF, dioxane, and Et_2O were distilled from potassium/benzophenone ketyl. CH_2Cl_2 was distilled from CaH_2. Light petroleum ether refers to bp 60–80 °C. All reactions and distillations were carried out in flame-dried glassware under argon atmosphere.

TLC was performed on silica gel 60 F_{254} (E. Merck, Darmstadt, Germany). Flash chromatography was carried out on silica gel MN 60 (0.04–0.063 mm), Macherey und Nagel, for chromatography under atmospheric pressure, silica gel 60 (0.06–0.2 mm) (Baker) was used. Analytical HPLC was carried out in MeOH/H_2O mixtures using a LKB 2150 unit equipped with diode array detection (LKB 2140). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 or an Bruker AC-400 NMR spectrometer. Optical rotation values were measured with a Perkin-Elmer 241 polarimeter. FAB-MS-spectra were recorded on a Finnigan-MAT-95-spectrometer. Schiff bases **2** of commercially available amine **1** (Merck-Schuchard) were prepared according to known procedures.[26]

N-Galactosyldehydropiperidinones 3: General Procedure:
To a solution of glycosyl imine **2** (10 mmol) in THF (50 mL) was added a solution of $ZnCl_2$ (1.5 g, 11 mmol) in THF/CH_2Cl_2 (1:1, 11 mL) at −78 °C and stirred for 10 min. 1-Methoxy-3-trimethylsilyloxybuta-1,3-diene (2.5 mL, 12.5 mmol) was added. After stirring for 30 min, the mixture was allowed to warm up to −20 °C. After 24–48 h (TLC monitoring), the reaction was terminated by addition of 1 N HCl (10 mL). THF was evaporated in vacuo, THF (200 mL) was added, and the organic layer was separated, washed with satd aq $NaHCO_3$ (2 × 50 mL), 10% aq Titriplex®III (2 × 50 mL), and with brine, dried ($MgSO_4$), and concentrated to give the crude product which was purified by recrystallization or chromatography.

(2R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-5,6-dehydropiperidin-4-one **(3a)**:

Purification by chromatography (petroleum ether/EtOAc, 3:1); yield: 72% (based on amine **1**); mp 171 °C; $[\alpha]_D^{22}$ −73.5 (*c* = 1, $CHCl_3$); R_f 0.26 (petroleum ether/EtOAc, 2:1); diastereomeric ratio (dr) »15:1.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, *J* = 7.2 Hz, propyl-CH_3), 1.08–1.50 (m, 38 H, Piv-CH_3, CH_2), 1.59 (m, 1 H, CH_2), 1.86 (m, 1 H, CH_2), 2.32 (d, 1 H, *J* = 16.5 Hz, CH_2C=O), 2.58 (dd, 1 H, *J* = 6.2, 16.6 Hz, CH_2C=O), 3.71 (m, 1 H, CHN), 3.92 (dd, 1 H, *J* = 6.5, 9.8 Hz, H-6a), 4.02 (dd, 1 H, *J* = 6.4, 6.1 Hz, H-5), 4.17 (dd, 1 H, *J* = 5.9, 9.7 Hz, H-6b), 4.54 (d, 1 H, *J* = 9.0 Hz, H-1), 4.92 (d, 1 H, *J* = 7.6 Hz, NCH=C*H*), 5.14 (dd, 1 H, *J* = 3.0, 10.1 Hz, H-3), 5.40 (d, 1 H, *J* = 2.9 Hz, H-4), 5.51 (dd, 1 H, *J* = 9.3, 9.8 Hz, H-2), 6.88 (d, 1 H, *J* = 7.7 Hz, NC*H*=CH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.74 (propyl-CH_3), 18.88 (CH_2), 27.00, 27.10, 27.14 (Piv-CH_3), 32.97 (CH_2), 38.68, 38.74, 38.88, 39.04 (Piv-C_{quart}), 39.17 (CH_2C=O), 53.37 (CHN), 60.84 (C-6), 65.38, 66.56, 71.36, 72.95 (C-2, C-3, C-4, C-5), 91.57 (C-1), 100.07, 149.62 (CH=CH), 176.49, 176.99, 177.09, 177.68 (PivC=O), 192.02 (C=O).

$C_{34}H_{55}NO_{10}$	calc.	C 64.03	H 8.69	N 2.20
(637.8)	found	64.23	8.73	2.00

X-ray Analysis of **3a**: monoclinic, space group $P2_1$, a = 12.5889(7)Å, b = 10.5598(4)Å; c = 14.7355(5)Å, β = 96.900(5)°, V = 1944.7(2)Å^3, Z = 2, ϱ_{calc} = 1.089 gcm^{-3}, μ(CuKα) = 0.65 mm^{-1}, crystal dimensions = 0.64 × 0.160 × 0.160 m, 8321 intensities were collected with 1.5° ≤ Θ ≤ 75° at 298 K on a Enraf Nonius CAD4 diffractometer with graphite monochromated CuKα radiation (λ = 1.5418Å), 7530 symmetry independent reflections (R_{int} = 0.033), no absorption correction, 5521 reflections with F/s(F) > 4.0 were treated as observed. The structure was solved by direct methods (SIR-92).[27] Refinement on F^2 (ShelXLS-93)[28] converged at R1 = 0.0572, wR2 = 0.1734

and goodness-of-fit = 1.032 (data to parameter ratio = 17), absolute configuration proved by measuring Friedel pairs and Flack[29] parameter 0.0(2).[34]

(2S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-5,6-dehydropiperidin-4-one (**3b**):

Purification by flash chromatography (petroleum ether/EtOAc, 1:1); yield: 90%; mp 176°C (pentane); $[\alpha]_D^{20}$ +19.6 (c = 3, $CHCl_3$); R_f 0.25 (petroleum ether/EtOAc, 1:2); dr >95:5.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (s, 9H, Piv-CH_3), 1.10 (s, 9H, Piv-CH_3), 1.13 (s, 9H, Piv-CH_3), 1.21 (s, 9H, Piv-CH_3), 2.58 (dd, 1H, J = 5.6, 16.5 Hz, CH_2C=O), 2.92 (dd, 1H, J = 6.5, 16.5 Hz, CH_2C=O), 3.66–3.86 (m, 3H, H-5, H-6a, H-6b), 4.48 (d, 1H, J = 9.2 Hz, H-1), 4.91 (t, 1H, J = 6.0 Hz, ArCHN), 5.07 (dd, 1H, J = 3.0, 10.0 Hz, H-3), 5.15 (d, 1H, J = 7.9 Hz, NCH=C*H*), 5.31 (d, 1H, J = 3.0 Hz, H-4), 5.56 (dd, 1H, J = 9.8, 9.4 Hz, H-2), 7.20 (m, 1H, Ar), 7.21 (d, 1H, J = 7.9 Hz, NC*H*=CH), 7.63, 8.51 (m, 1H, Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.94, 26.97, 27.11 (Piv-CH_3), 38.57, 38.70, 38.90, 38.96 (Piv-C_{quart}), 42.94 (CH_2C=O), 55.90 (ArCHN), 60.68 (C-6), 65.47, 66.47, 71.11, 72.80 (C-2, C-3, C-4, C-5), 90.21 (C-1), 102.46 (CH=CH), 123.21, 134.12, 135.24, 148.33, 149.41 (Ar), 150.09 (CH=CH), 176.29, 176.92, 177.14, 177.50 (Piv-C=O), 190.19 (C=O).

$C_{36}H_{52}N_2O_{10}$	calc.	C 64.27	H 7.79	N 4.16
(672.8)	found	64.23	7.86	3.97

(2R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-isopropyl-5,6-dehydropiperidin-4-one (**3c**):

Purification by chromatography (petroleum ether/EtOAc, 3:1); yield: 58% (based on amine **1**); $[\alpha]_D^{22}$ −69.8 (c = 1, $CHCl_3$); R_f 0.15 (petroleum ether/EtOAc, 3:1); dr 33.5:1 (HPLC).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, 6H, J = 6.8 Hz, CH_3), 1.06 (s, 9H, Piv-CH_3), 1.07 (s, 9H, Piv-CH_3), 1.12 (s, 9H, Piv-CH_3), 1.23 (s, 9H, Piv-CH_3), 2.23 (m, 1H, $CHMe_2$), 2.37 (dd, 1H, J = 6.8, 16.9 Hz, CH_2C=O), 2.56 (dd, 1H, J = 7.3, 16.8 Hz, CH_2C=O), 3.51 (m, 1H, CHN), 3.95 (m, 2H, H-5, H-6a), 4.12 (dd, 1H, J = 5.6, 9.2 Hz, H-6b), 4.57 (d, 1H, J = 9.2 Hz, H-1), 4.90 (d, 1H, J = 7.7 Hz, NC*H*=CH), 5.13 (dd, 1H, J = 10.0, 3.0 Hz, H-3), 5.36 (d, 1H, J = 2.9 Hz, H-4), 5.53 (dd, 1H, J = 9.3, 9.7 Hz, H-2), 6.97 (d, 1H, J = 7.8 Hz, NC*H*=CH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.71, 19.63 (CH_3), 26.98, 27.08, 27.10 (Piv-CH_3), 31.76 ($CHMe_2$), 35.71 (CH_2C=O), 38.65, 38.72, 38.87, 39.03 (Piv-C_{quart}), 58.93 (CHN), 60.95 (C-6), 65.59, 66.56, 71.61, 72.78 (C-2, C-3, C-4, C-5), 90.98 (C-1), 100.58, 149.94 (CH=CH), 176.48, 176.98, 177.13, 177.72 (PivC=O), 192.48 (C=O).

$C_{34}H_{55}NO_{10}$	calc.	C 64.03	H 8.69	N 2.20
(637.8)	found	63.82	8.56	2.12

(2S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-cyanophenyl)-5,6-dehydropiperidin-4-one (**3d**):

Purification by chromatography (petroleum ether/EtOAc, 3:1); yield: 71%; mp 121°C; $[\alpha]_D^{22}$ +22.2 (c = 1, $CHCl_3$); R_f 0.44 (petroleum ether/EtOAc, 1:1); dr >20:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 (s, 9H, Piv-CH_3), 1.11 (s, 9H, Piv-CH_3), 1.15 (s, 9H, Piv-CH_3), 1.21 (s, 9H, Piv-CH_3), 2.54 (dd, 1H, J = 4.6, 16.5 Hz, CH_2C=O), 2.96 (dd, 1H, J = 7.0, 16.5 Hz, CH_2C=O), 3.75 (m, 3H, H-5, H-6a, H-6b), 4.54 (d, 1H, J = 9.1 Hz, H-1), 4.39 (dd, 1H, J = 4.9, 6.5 Hz, ArC*H*N), 5.11 (m, 2H, CH=CH, H-3), 5.32 (d, 1H, J = 2.9 Hz, H-4), 5.55 (dd, 1H, J = 9.5, 9.8 Hz, H-2), 7.21 (d, 1H, J = 7.9 Hz, CH=CH), 7.39 (d, 2H, J = 8.3 Hz, Ar), 7.57 (d, 2H, J = 8.2 Hz, Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.88, 26.91, 27.06 (Piv-CH_3), 38.52, 38.65, 38.87 (Piv-C_{quart}), 42.67 (CH_2C=O), 57.09 (ArCHN), 60.58 (C-6), 65.48, 66.35, 70.92, 72.74 (C-2, C-3, C-4, C-5); 90.48 (C-1), 102.12 (CH=CH), 111.85, 118.14, 127.24, 132.23 (Ar), 145.05 (CN), 150.13 (CH=CH), 176.14, 176.87, 177.17, 177.46 (PivC=O), 189.84 (C=O).

$C_{38}H_{52}N_2O_{10}$	calc.	C 65.50	H 7.52	N 4.02
(696.8)	found	65.52	7.53	3.87

Conversion of Enaminones 3 into the *N*-Glycosylpiperidinones 5; General Procedure:

To a solution of dehydropiperidinone **3** (10 mmol) in THF (90 mL) was added dropwise a 1 M THF solution of L-Selectride®[14] at −78°C during 5 min. After conversion of the starting material (monitoring by TLC), the solution was warmed up to r.t., and the THF was evaporated in vacuo. The residue was dissolved in pentane (100 mL), washed with H_2O and dried ($MgSO_4$). Concentration of the organic layer in vacuo gave the crude product which was purified by flash chromatography.

(2R)-N-(2,3,4,6-Tetra-O-pivalyl-β-D-galactopyranosyl)-2-propylpiperidin-4-one (**5a**):

Yield: 95%; oil; $[\alpha]_D^{20}$ +0.5 (c = 3, $CHCl_3$); R_f 0.70 (petroleum ether/EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, 3H, J = 7.2 Hz, propyl-CH_3), 1.10–1.35 (m, 3H, CH_2), 1.43 (m, 1H, CH_2), 2.15 (m, 2H, CH_2), 2.47 (m, 1H, CH_2), 2.62 (dd, 1H, J = 5.2, 13.9 Hz, CH_2), 3.16 (m, 3H, CHN, CH_2), 3.89 (m, 2H, H-5, H-6a), 4.01 (dd, 1H, J = 6.8, 10.6 Hz, H-6b), 4.35 (d, 1H, J = 9.1 Hz, H-1) 5.11 (dd, 1H, J = 3.1, 10.1 Hz, H-3), 5.33 (d, 1H, J = 3.0 Hz, H-4), 5.42 (t, 1H, J = 9.6 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.90 (propyl-CH_3), 19.17 (CH_2), 27.03, 27.16 (Piv-CH_3), 35.53 (CH_2), 38.64, 38.70, 39.02 (Piv-C_{quart}), 41.63, 41.97, 46.58 (CH_2), 59.76 (CHN), 61.80 (C-6), 65.51, 67.26, 72.03 (C-2, C-3, C-4, C-5), 92.96 (C-1), 176.64, 177.00, 177.16, 177.77 (PivC=O), 209.66 (C=O).

$C_{34}H_{57}NO_{10}$	calc.	C 63.83	H 8.98	N 2.19
(639.81)	found	63.81	9.01	2.28

(2S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)piperidin-4-one (**5b**):

Yield: 96%; amorphous; $[\alpha]_D^{20}$ −9.2 (c = 4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (m, 2H, CH_2), 2.50 (dd, 1H, J = 3.6, 14.8 Hz, CH_2), 2.59 (dd, 1H, J = 14.8 Hz, CH_2), 2.97 (ddd, 1H, J = 5.3, 10.1, 12.4 Hz, NCH_2), 3.49 (m, 1H, H-5), 3.59 (ddd, 1H, J = 5.4, 9.3, 12.3 Hz, NCH_2), 3.82 (d, 1H, J = 9.4 Hz, H-1), 3.90 (dd, 1H, J = 6.7, 11.1 Hz, H-6a), 3.98 (dd, 1H, J = 6.8, 11.2 Hz, H-6b), 4.15 (dd, 1H, J = 4.0, 10.6 Hz, NCH), 4.87 (dd, 1H, J = 3.1, 10.0 Hz, H-3), 5.24 (d, 1H, J = 2.5 Hz, H-4), 5.44 (t, 1H, J = 9.7 Hz, H-2), 7.58 (m, 1H, Ar), 8.51 (d, 1H, J = 1.9 Hz, Ar), 8.59 (dd, 1H, J = 1.5, 4.7 Hz, Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.00, 27.08, 27.16, 27.35 (Piv-CH_3), 38.67, 38.83, 39.01 (Piv-C_{quart}), 41.51, 43.46, 48.50 (CH_2), 61.40 (C-6), 61.57 (CHN), 65.05, 67.11, 71.67, 72.04 (C-2, C-3, C-4, C-5), 88.33 (C-1), 123.81, 135.25, 135.48, 149.49, 149.86 (Ar), 176.51, 177.04, 177.19, 177.74 (PivC=O), 206.79 (C=O).

$C_{36}H_{54}N_2O_{10}$	calc.	C 64.08	H 8.07	N 4.15
(674.8)	found	64.12	8.01	4.21

Dithioacetals 7: General Procedure:

To a suspension of piperidinone **5** (6.5 mmol), ethane-1,2-dithiol (0.7 mL, 8 mmol) and molecular sieves 5Å (5 g) in CH_2Cl_2 (30 mL) was added $BF_3{\cdot}OEt_2$ (3.25 mL, 26 mmol) at 0°C. After 1 h the mixture was warmed up to r.t. and stirring was continued for additional 12 h. The suspension was diluted with CH_2Cl_2 (70 mL), filtered and extracted with satd aq $NaHCO_3$ (2 × 50 mL). The organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography to yield **7** as a colorless amorphous solid.

(2R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propylpiperidin-4-one Ethane-1,2-diyl Dithioacetal (**7a**):

Yield: 90%; mp 133°C; $[\alpha]_D^{20}$ −18.6 (c = 2, $CHCl_3$); R_f 0.49 (petroleum ether/EtOAc, 4:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, 3H, J = 6.5 Hz, propyl-CH_3), 1.07 (s, 9H, Piv-CH_3), 1.11 (s, 9H, Piv-CH_3), 1.14 (s, 9H, Piv-CH_3), 1.21 (s, 9H, Piv-CH_3), 1.17–1.46 (m, 4H, CH_2), 1.71 (dd, 1H, J = 13.0 Hz, CH_2), 1.84 (dd, 1H, J = 3.6, 14.8 Hz, CH_2), 2.02 (m, 2H, CH_2), 2.79 (m, 1H, CHN), 3.16 (m, 1H, NCH_2), 3.24 (m, 4H, SCH_2CH_2S), 3.80 (t, 1H, J = 6.7 Hz, H-5), 3.91 (dd, 1H, J = 6.5, 10.8 Hz, H-6a), 4.08 (dd, 1H, J = 6.9, 10.8 Hz, H-6b),

4.30 (d, 1H, $J = 9.2$ Hz, H-1), 5.09 (dd, 1H, 3.1, 10.0 Hz, H-3), 5.32 (d, 1H, $J = 2.9$ Hz, H-4), 5.41 (t, 1H, $J = 9.6$ Hz, H-2).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 14.48$ (propyl-CH_3), 18.40 (CH_2), 27.06, 27.09, 27.21, 27.29 (Piv-CH_3), 34.74 (CH_2), 37.85 (CH_2), 38.66, 38.69, 38.72, 38.82 (Piv-C_{quart}), 39.06 (CH_2), 42.57, 44.23 (SCH_2CH_2S), 48.14 (CHN), 57.19 (NCH_2), 61.60 (C-6), 64.82 (CS_2), 66.98, 67.32, 71.80, 72.22 (C-2, C-3, C-4, C-5), 86.96 (C-1), 176.79, 176.94, 177.23, 177.86 (PivC=O).

$C_{36}H_{61}NO_9S_2$	calc.	C 60.39	H 8.59	N 1.96
(716.0)	found	60.45	8.59	1.89

(2S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)-4-piperidin-4-one Ethane-1,2-diyl Dithioacetal (**7b**):

Yield: 92%; $[\alpha]_D^{20}$ −3.9 ($c = 3$, $CHCl_3$); R_f 0.66 (petroleum ether/EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.19$ (m, 4H, CH_2), 2.83 (m, 1H, NCH_2), 3.24 (m, 4H, SCH_2CH_2S), 3.35 (m, 1H, NCH_2), 3.43 (m, 1H, H-5), 3.70 (d, 1H, $J = 9.4$ Hz, H-1), 3.88 (dd, 1H, $J = 7.1$, 11.2 Hz, H-6a), 3.92 (dd, 1H, $J = 3.1$, 11.0 Hz, CHN), 4.03 (dd, 1H, $J = 6.8$, 11.2 Hz, H-6b), 4.78 (dd, 1H, $J = 3.1$, 10.0 Hz, H-3), 5.19 (d, 1H, $J = 2.5$ Hz, H-4), 5.40 (t, 1H, 9.7 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 27.04$, 27.15, 27.20, 27.40 (Piv-CH_3), 38.68, 38.70, 38.80 (Piv-C_{quart}), 37.90, 39.03, 41.93, 44.15, 51.17 (CH_2), 61.15 (C-6), 61.55 (CHN), 66.09 (CS_2), 64.62, 67.19, 71.80 72.01 (C-2, C-3, C-4, C-5), 87.85 (C-1), 123.65, 135.42, 136.50, 149.64, 149.89 (Ar), 176.62, 177.00, 177.09, 177.79 (PivC=O).

$C_{38}H_{58}N_2O_9S_2$	calc.	C 60.77	H 7.78	N 3.73
(751.0)	found	60.71	7.79	3.53

Reductive Desulfurization of 7 to give 8: General Procedure:

To a solution of dithioacetal **7** (3 mmol) in *i*-PrOH (50 mL) was added Raney nickel (10 g). The resulting mixture was vigorously stirred under H_2 atmosphere at 70°C. After completion of the reaction (monitoring by TLC), the mixture was filtered through Celite and the filtrate concentrated in vacuo to yield pure **8** as a colorless amorphous solid.

(2R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propylpiperidine (**8a**):

Yield: 98%; amorphous; $[\alpha]_D^{20}$ −2.7 ($c = 2$, $CHCl_3$); R_f 0.57 (petroleum ether/EtOAc, 4:1).

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.8$ Hz, propyl-CH_3), 1.08 (s, 9H, Piv-CH_3), 1.13 (s, 9H, Piv-CH_3), 1.15 (s, 9H, Piv-CH_3), 1.18–1.58 (m, 19H, Piv-CH_3, CH_2), 2.44, 2.66, 3.12 (m, 3H, CHN, NCH_2), 3.79 (t, 1H, $J = 6.7$ Hz, H-5), 3.92 (dd, 1H, $J = 6.5$, 10.9 Hz, H-6a), 4.08 (dd, 1H, $J = 7.0$, 10.9 Hz, H-6b), 4.31 (d, 1H, $J = 9.2$ Hz, H-1), 5.08 (dd, 1H, $J = 3.1$, 10.0 Hz, H-3), 5.33 (d, 1H, $J = 2.9$ Hz, H-4), 5.45 (t, 1H, $J = 9.6$ Hz, H-2).

^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 14.56$ (propyl-CH_3), 19.00, 23.85, 26.20 (CH_2), 27.28, 27.21, 27.10 (Piv-CH_3), 31.49, 34.78 (CH_2), 38.65, 38.70, 38.73, 39.06 (Piv-C_{quart}), 45.02 (NCH_2), 57.53 (CHN), 61.78 (C-6), 64.98, 67.54, 71.69, 72.52 (C-2, C-3, C-4, C-5), 89.30 (C-1), 176.84, 177.30, 177.91 (PivC=O).

$C_{34}H_{59}NO_9$	calc.	C 65.25	H 9.50	N 2.24
(625.8)	found	65.30	9.38	2.38

(2S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)piperidine (**8b**):

Yield: 75%; amorphous; $[\alpha]_D^{20}$ −4.6 ($c = 2$, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.80$–1.25 (m, 6H, CH_2), 2.58 (dd, 1H, $J = 9.8$, 11.7 Hz, NCH_2), 3.30 (d, 1H, $J = 11.6$ Hz, NCH_2), 3.41 (m, 1H, H-5), 3.69 (dd, 1H, $J = 2.3$, 11.3 Hz, CHN), 3.71 (d, 1H, $J = 9.3$ Hz, H-1), 3.98 (dd, 1H, $J = 7.0$, 11.2 Hz, H-6a), 3.99 (dd, 1H, $J = 6.7$, 11.2 Hz, H-6b), 4.76 (dd, 1H, $J = 3.1$, 10.0 Hz, H-3), 5.19 (d, 1H, $J = 2.5$ Hz, H-4), 5.45 (t, 1H, $J = 9.7$ Hz, H-2), 7.23 (dd, 1H, $J = 4.9$, 7.5 Hz, Ar), 7.55 (m, 1H, Ar), 8.47 (d, 1H, $J = 1.7$ Hz, Ar), 8.52 (d, 1H, $J = 1.6$ Hz, Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 27.02$, 27.12, 27.16, 27.36 (Piv-CH_3), 38.66, 38.77, 39.01 (Piv-C_{quart}), 24.87, 25.92, 35.74, 44.82 (CH_2), 61.67 (CHN), 62.08 (C-6), 64.56, 67.36, 71.71, 72.20 (C-2, C-3, C-4, C-5), 88.55 (C-1), 123.52, 135.30, 138.26, 149.18, 149.76 (Ar), 176.61, 176.88, 177.12, 177.81 (PivC=O).

$C_{36}H_{56}N_2O_9$	calc.	C 65.43	H 8.54	N 4.24
(660.8)	found	65.36	8.68	4.21

***N*-Galactosylconiine (8a):**

(6R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-6-propylpiperidine-3-en-4-yl Trifluoromethanesufonate (**11**):

To a solution of dehydropiperidinone **3a** (1.28 g, 2.0 mmol) in THF (30 mL) was added dropwise a 1 M THF solution of L-Selectride®[14] (5 mL, 2.5 equiv) at −78°C. After consumption of the starting material (TLC monitoring), *N*,*N*-bis(trifluoromethanesufonyl))aniline[16] (1.0 g, 3 mmol) was added under N_2 atmosphere. The stirring was continued for 1.5 h and the mixture was allowed warm up to r.t. The solvent was evaporated in vacuo, the residue was dissolved in Et_2O (50 mL), washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford crude **11** which was purified by chromatography (petroleum ether/EtOAc, 6:1); yield: 0.73 g (47%); colorless, amorphous solid; R_f 0.40 (petroleum ether/EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 7.1$ Hz, propyl-CH_3), 1.07 (s, 9H, Piv-CH_3), 1.09 (s, 9H, Piv-CH_3), 1.14 (s, 9H, Piv-CH_3), 1.16–1.38 (m, 11H, Piv-CH_3, CH_2), 1.57 (m, 1H, CH_2), 2.03 (d, 1H, $J = 16.3$ Hz, CH_2), 2.55 (dd, 1H, $J = 2.4$, 16.3 Hz, CH_2), 3.15 (m, 1H, CHN), 3.41 (d, 1H, $J = 17.6$ Hz, NCH_2), 3.57 (dd, 1H, $J = 2.4$, 17.6 Hz, NCH_2), 3.83 (t, 1H, $J = 6.7$ Hz, H-5), 3.89 (dd, 1H, $J = 6.8$, 10.8 Hz, H-6a), 4.04 (dd, 1H, $J = 6.6$, 10.8 Hz, H-6b), 4.20 (d, 1H, $J = 9.2$ Hz, H-1), 5.09 (dd, 1H, $J = 3.1$, 10.1 Hz, H-3), 5.34 (t, 1H, $J = 9.6$ Hz, H-2), 5.35 (d, 1H, $J = 3.0$ Hz, H-4), 5.66 (s, 1H, CH=COTf).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 14.06$ (propyl-CH_3), 19.90 (CH_2), 27.04, 27.15 (Piv-CH_3), 32.79, 33.65 (CH_2), 38.67, 38.72, 39.03 (Piv-C_{quart}), 41.76 (NCH_2), 55.42 (CHN), 61.55 (C-6), 65.47, 67.18, 71.90 (C-2, C-3, C-4, C-5), 92.63 (C-1), 116.15 (*C*H=COTf), 146.62 (CH=COTf), 176.65, 177.09, 177.18, 177.81 (PivC=O).

Conversion of **11** *to* **8**: To the enol triflate **11** (0.66 g, 0.86 mmol) in MeOH (20 mL) were added Li_2CO_3 (100 mg) and Pd/C (5%, 46 mg). The mixture was vigorously stirred under a H_2 atmosphere (20 h). After filtration, the solvent was removed in vacuo and the remaining residue dissolved in Et_2O (50 mL). The organic layer was washed with brine (2 × 25 mL), dried ($MgSO_4$) and evaporated to dryness to yield pure **8a** (0.54 g, 98%) as a colorless solid.

Release of the Enantiomerically Pure Piperidines from the Carbohydrate Auxiliary; General Procedure:

The *N*-glycosylpiperidine or *N*-glycosylpiperidin-4-one (3 mmol) was dissolved in MeOH (30 mL) and treated with aq 1 N HCl (1.5 equiv). The solution was stirred at r.t. until completion of the reaction (monitoring by TLC). The solvent was evaporated in vacuo, the residue dissolved in pentane (60 mL) and the organic layer extracted with H_2O (3 × 30 mL). The carbohydrate auxiliary 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranose was recovered by concentration of the organic phase to dryness. To the combined aqueous layer was added Na_2CO_3, the solution was extracted with Et_2O (3 × 60 mL). The organic layer was concentrated to a volume of 20 mL. A saturated solution of anhyd HCl in Et_2O (1 mL) was added and the hydrochloride of the piperidine derivative was isolated by filtration.

(2R)-2-Propylpiperidin-4-one Hydrochloride (**6**):

Yield: 95%; mp 147°C; colorless crystals; $[\alpha]_D^{20}$ −23.4 ($c = 2$, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.22$ (m, 1H, CHN), 3.42 (m, 1H, NCH_2), 3.72 (m, 1H, NCH_2), 10.21 (s, 1H, NH), 11.11 (s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 13.50$ (CH_3), 18.27, 34.92, 37.27, 34.91 (CH_2), 43.34 (NCH_2), 56.61 (CHN), 201.53 (C=O).

$C_8H_{16}ClNO$	calc.	C 54.08,	H 9.08	N 7.88
(177.68)	found	53.56	9.02	7.59

*(2R)-2-Propylpiperidine Hydrochloride (***9a***; Coniine Hydrochloride)*:

Yield: 97%; colorless crystals; mp 214–216°C; $[\alpha]_D^{20}$ −6.8 (c = 3.5, EtOH); $[\alpha]_D^{22}$ −6.8 (c = 0.6, MeOH) [Lit.[30] mp 221°C; Lit.[3a] $[\alpha]_D^{22}$ −5.8 (c = 1.0, MeOH)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, 3H, J = 7.1 Hz, CH_3), 1.12–1.90 (m, 10H, CH_2), 3.40 (m, 2H, CHN, NCH_2), 3.40 (m, 1H, NCH_2), 9.13 (s, 1H, NH), 9.39 (s, 1H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 13.65 (CH_3), 18.55, 22.17, 22.40, 28.15, 35.32 (CH_2), 44.73 (NCH_2), 57.11 (CHN).

*(2S)-N-4-Nitrobenzoyl-2-(3-pyridyl)piperidine (***10***, N-4-Nitrobenzoylanabasine)*:

The release of anabasine hydrochloride **9b** from the carbohydrate auxiliary was achieved as described for **9a** by treatment of **8b** with 1 N aq HCl (2 equiv). Crude **9b** (3 mmol) was dissolved in CH_2Cl_2 (10 mL), treated with Et_3N (4 mL) and 4-nitrobenzoyl chloride (0.75 g, 4 mmol) and stirred at r.t. for 2 h. Additional CH_2Cl_2 (50 mL) was added, and the organic layer was washed with H_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (EtOAc) to afford **10** (90%) as colorless crystals; mp 122°C; $[\alpha]_D^{20}$ −130.8 (c = 1.2, MeOH); R_f 0.45 (EtOAc) [Lit.[15] mp 127–128°C; $[\alpha]_D$ −130.0 (c = 3, MeOH)].

Trimethylchlorosilane-Mediated Addition of Diorganocuprates to Enaminones 3; Typical Procedures:

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-6-methylpiperidin-4-one **(12a)**:

To a stirred suspension of CuI (1.43 g, 7.5 mmol) in THF (50 mL) at −34°C was added dropwise a 1.6 M Et_2O solution of MeLi (9.4 mL, 2 equiv). The mixture was stirred at −25°C for 1.5 h and then cooled to −78°C. To this mixture was added dropwise a solution of **3a** (3.0 g, 4.7 mmol) and TMSCl (1.9 mL, 15 mmol) in THF (100 mL) via a syringe. After 2 h at −78°C (monitoring by TLC), the reaction was terminated by the addition of 20% aq NH_4OH/NH_4Cl (50:50, 30 mL). Et_2O (300 mL) was added, and the organic layer separated. After washing with additional NH_4OH/NH_4Cl solution (50 mL), the organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to yield the crude silyl enol ether as a colorless amorphous solid. It was dissolved in THF (15 mL) and treated with a 1 M THF solution of Bu_4NF (7 mL, 1.5 equiv) at 0°C. The resulting mixture was stirred at r.t. until completion of the reaction (monitoring by TLC). The mixture was concentrated in vacuo and diluted with Et_2O (100 mL). After washing with brine, the organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by chromatography (petroleum ether/EtOAc, 3:1) yielded **12a** (2.18 g, 71%) as a colorless amorphous solid; $[\alpha]_D^{22}$ 22.2 (c = 1.0, $CHCl_3$); R_f 0.55 (petroleum ether/EtOAc; 3:1); dr >10:1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, 3H, J = 7.2 Hz, CH_3), 1.07–1.37 (m, 42H, Piv-CH_3, CH_3, CH_2), 1.58 (m, 1H, CH_2), 2.18 (d, 1H, J = 15.4 Hz, CH_2), 2.24 (dd, 1H, J = 6.6, 15.5 Hz, CH_2C=O), 2.57 (dd, 1H, J = 5.9, 15.3 Hz, CH_2C=O), 2.73 (dd, 1H, J = 6.8, 15.2 Hz, CH_2C=O), 3.32 (m, H, CHN), 3.75 (m, H, CHN′), 3.82–3.93 (m, 2H, H-5, H-6a), 4.06 (m, 1H, H-6b), 4.34 (d, 1H, J = 9.2 Hz, H-1), 5.08 (dd, 1H, J = 3.1, 9.9 Hz, H-3), 5.33 (d, 1H, J = 3.0 Hz, H-4), 5.43 (t, 1H, J = 9.6 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.87 (CH_3), 19.88 (CH_2), 24.36 (CH_3), 27.04, 27.17, 27.19 (Piv-CH_3), 38.67, 38.70, 39.01 (Piv-C_{quart}), 40.08 (CH_2), 44.37, 47.21 (CH_2C=O), 58.65 (CHN), 61.73 (C-6), 66.05, 67.28, 72.05, 72.44 (C-2, C-3, C-4, C-5), 94.28 (C-1), 176.64, 176.78, 177.24, 177.77 (PivC=O).

$C_{35}H_{59}NO_{10}$	calc.	C 64.29	H 9.09	N 2.14
(653.9)	found	64.29	9.03	2.04

(2S,6R)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-(1-ethoxyethoxy)propyl)-6-propylpiperidin-4-one **(12b)**:

To magnesium (0.48 g, 20 mmol) in THF (6 mL) was added 3-bromopropyl (1-ethoxy)ethyl ether (4.4 g, 20 mmol) at r.t. The suspension was gently warmed until the reaction started and then immediately cooled in an ice bath. The mixture was stirred for 1 h and diluted with THF (6 mL). The formation of the Grignard compound was complete after stirring for additional 2 h at <15°C. The resulting solution was added dropwise to a cooled (−70°C) suspension of CuBr·SMe_2 (1.85 g, 9.0 mmol) in THF (100 mL). After stirring for 2 h (−45°C), the red-brown suspension was cooled to −78°C. Slowly, a solution of **3a** (1.9 g, 3.0 mmol) and TMSCl (2.79 mL, 22 mmol) in THF (200 mL) was added and the mixture was stirred for 12 h. The workup was carried out as described for **12a**. The crude silyl enol ether thus obtained was converted to **12b** by treatment with a 1 M THF solution of Bu_4NF (4.5 mL, 1.5 equiv) at r.t. Isolation of **12b** was achieved according to the procedure described for **12a**. Chromatography (petroleum ether/EtOAc, 5:1) gave **12b**; yield: 1.9 g 82%; colorless oil; $[\alpha]_D^{22}$ −6.9 (c = 1.3, $CHCl_3$); R_f 0.37 (petroleum ether/EtOAc, 3:1); dr 3:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (t, 3H, J = 7.1 Hz, CH_3), 1.08 (s, 9H, Piv-CH_3), 1.13 (s, 9H, Piv-CH_3), 1.14 (s, 9H, Piv-CH_3), 1.15–1.70 (m, 23H, Piv-CH_3, CH_2), 2.14–2.38 (m, 2H, CH_2C=O), 2.61 (dd, 1H, J = 5.8, 16.0 Hz, CH_2C=O), 2.69 (dd, 1H, J = 6.8, 16.0 Hz, CH_2C=O), 3.24–3.70 (m, 6H, OCH_2, CHN, CHN′), 3.90 (m, 2H, H-6a, H-5), 4.07 (dd, 1H, J = 9.3, 12.9 Hz, H-6b), 4.38 (d, 1H, J = 9.2 Hz, H-1), 4.62 (q, 1H, J = 5.4 Hz, OC*H*MeO), 5.08 (dd, 1H, J = 2.9, 10.0 Hz, H-3), 5.36 (d, 1H, J = 2.9 Hz, H-4), 5.43 (t, 1H, J = 9.6 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.82, 15.22 (CH_3), 19.56 (CH_2), 19.74 (CH_3), 26.99, 27.01, 27.12 (Piv-CH_3), 27.94, 30.36, 34.41 (CH_2), 38.63, 38.68, 38.98, 39.94 (Piv-C_{quart}), 43.97, 44.33 (CH_2C=O), 61.61, 61.64 (CH_2, C-6), 66.30, 67.16, 71.96, 72.35 (C-2, C-3, C-4, C-5), 94.25 (C-1), 99.40 (OCHMeO), 176.55, 177.22, 177.50, 177.73 (PivC=O), 209.91 (C=O).

$C_{41}H_{71}NO_{12}$	calc.	C 63.95	H 9.29	N 1.82
(770.0)	found	63.92	9.41	1.48

Conjugated Addition of $R^1Cu \cdot BF_3$ Complexes to Enaminones 3; Typical Procedures:

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2,6-diisopropylpiperidin-4-one **(12c)**:

To a suspension of CuI (0.95 g, 5.0 mmol) in THF (15 mL) was added dropwise a 2 M Et_2O solution of isopropylmagnesium chloride (10 mL, 1 equiv) at −65°C. After 1.5 h the yellow mixture was cooled to −78°C. $BF_3 \cdot OEt_2$ (0.6 mL, 5.0 mmol) was added, and the mixture was stirred for 15 min. After dropwise addition of a solution of **3c** (0.64 g, 1.0 mmol) in (30 mL) through a syringe, the mixture was stirred at −78°C for 6 h. 20% aq NH_4OH/NH_4Cl (50:50, 15 mL) was added and the mixture was extracted with Et_2O (100 mL). The Et_2O solution was washed with NH_4OH/NH_4Cl solution (25 mL) and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue purified by chromatography (petroleum ether/EtOAc, 4:1) to afford **12c** (0.43 g, 63%) as a colorless amorphous solid; $[\alpha]_D^{22}$ −41.4 (c = 1, $CHCl_3$); R_f 0.59 (petroleum ether/EtOAc, 2:1); dr >20:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (d, 3H, J = 6.6 Hz, CH_3), 0.85 (d, 3H, J = 6.9 Hz, CH_3), 0.90 (d, 3H, J = 6.9 Hz, CH_3), 0.91 (d, 3H, J = 6.6 Hz, CH_3), 1.11–1.26 (m, 36H, Piv-CH_3), 1.48 (m, 1H, $CHMe_2$), 1.91 (m, 1H, $CHMe_2$), 2.32 (d, 2H, J = 8.6 Hz, CH_2C=O), 2.57 (dd, 1H, J = 1.8, 17.3 Hz, CH_2C=O), 2.86 (dd, 1H, J = 5.7, 17.3 Hz, CH_2C=O), 3.00 (m, 1H, CHN), 3.20 (ddd, 1H, J = 4.2, 8.4, 17.0 Hz, CHN′), 3.84–3.95 (m, 2H, H-5, H-6a), 4.09 (dd, 1H, J = 9.3, 12.8 Hz, H-6b), 4.50 (d, 1H, J = 9.2 Hz, H-1), 5.05 (dd, 1H, J = 2.8, 9.4 Hz, H-3), 5.29 (d, 1H, J = 2.3 Hz, H-4), 5.33 (t, 1H, J = 9.3 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.50, 19.76, 20.08, 21.07 (CH_3), 27.04, 27.08, 27.20, 27.25 (Piv-CH_3), 31.67, 34.06 ($CHMe_2$), 37.85 (CH_2C=O), 38.71, 38.78, 38.86, 39.06 (Piv-C_{quart}), 42.59 (CH_2C=O′), 58.24, 61.32 (CHN, CHN′), 61.62 (C-6), 67.25, 67.35, 77.97, 73.86 (C-2, C-3, C-4, C-5), 93.19 (C-1), 176.43, 176.66, 177.56, 177.77 (PivC=O), 210.86 (C=O).

$C_{37}H_{63}NO_{10}$	calc.	C 65.17	H 9.31	N 2.05
(681.9)	found	64.98	9.42	2.00

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(4-cyanophenyl)-6-[2-(1,3-dioxolan-2-yl)ethyl]piperidin-4-one (**12e**):

To a suspension of magnesium (0.18 g, 7.5 mmol) in THF (10 mL) was added 2-(2-bromoethyl)-1,3-dioxolane (0.84 mL, 7.0 mmol) at r.t. The suspension was gently warmed until the reaction started and then immediately cooled in an ice bath. The mixture was stirred for 2.5 h keeping the temperature below 10 °C. The resulting Grignard reagent was added dropwise to a cooled (−78 °C) suspension of CuI (1.33 g, 7 mmol) and enaminone **3d** (0.7 g, 1.0 mmol) in THF (100 mL). Within 1 h, the vigorously stirred suspension was allowed to warm up to −55 °C. After cooling to −78 °C, $BF_3 \cdot OEt_2$ (1.84 mL, 15 mmol) was added and the stirring was continued for 14 h. Workup and purification was conducted as described for **12c**; yield: 0.51 g (64%); amorphous; $[\alpha]_D^{22}$ −34.1 (c = 0.25, $CHCl_3$); R_f 0.16 (petroleum ether/EtOAc, 3:1); dr >10:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.02–1.27 (m, 36H, Piv-CH_3), 1.34–1.61 (m, 4H, CH_2), 2.49–2.61 (m, 3H, CH_2C=O, CH_2C=O′), 2.89 (dd, 1H, J = 5.4, 16.9 Hz, CH_2C=O′), 3.62 (m, 1H, AlkylC*H*N), 3.72–3.96 (m, 6H, OCH_2CH_2O, H-6a, H-5), 4.07 (d, 1H, J = 9.6 Hz, H-1), 4.14 (dd, 1H, J = 7.0, 11.0 Hz, H-6b), 4.63 (dd, 1H, J = 4.7, 11.6 Hz, ArC*H*N), 4.77 (t, 1H, J = 2.7, 4.4 Hz, OCHO), 4.85 (dd, 1H, J = 2.9, 10.5 Hz, H-3), 5.28 (d, 1H, J = 2.7 Hz, H-4), 5.50 (t, 1H, J = 9.6 Hz, H-2), 7.44 (d, 2H, J = 8.3 Hz, Ar), 7.63 (d, 2H, J = 8.2 Hz, Ar).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.00, 27.12, 27.18, 27.34 (Piv-CH_3), 30.90, 33.73 (CH_2), 38.65, 38.96 (Piv-C_{quart}), 42.59, 46.39 (CH_2C=O, CH_2C=O′), 51.04 (Alkyl*C*HN), 59.05 (Ar*C*HN), 61.38 (C-6), 64.66, 64.75 (OCH_2CH_2O), 65.68, 67.15, 72.15, 72.80 (C-2, C-3, C-4, C-5), 91.13 (C-1), 103.96 (OCHO), 111.97, 118.32, 128.20, 132.56 (Ar), 147.97 (CN), 176.44, 176.52, 177.28, 177.67 (PivC=O), 207.44 (C=O).

$C_{43}H_{62}N_2O_{12}$	calc.	C 64.64	H 7.82	N 3.51
(799.0)	found	63.95	7.80	3.29

The compound contained traces of inorganic material.

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-isopropyl-6-[2-(1,3-dioxolan-2-yl)ethyl]piperidin-4-one (**12d**):

Piperidinone **12d** was prepared from **3c** (0.64 g, 1 mmol) in close analogy to the synthesis of **12e**; yield: 0.48 g (65%); amorphous; $[\alpha]_D^{22}$ −27.8 (c = 0.35, $CHCl_3$); R_f 0.35 (petroleum ether/EtOAc, 3:1); dr >15:1.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80–0.89 (m, 6H, CH_3), 1.09 (s, 9H, Piv-CH_3), 1.13 (s, 9H, Piv-CH_3), 1.15 (s, 9H, Piv-CH_3), 1.24 (s, 9H, Piv-CH_3), 1.33–1.85 (m, 5H, CH_2, C*H*Me_2), 2.38 (m, 3H, CH_2C=O, CH_2C=O′), 2.76 (dd, 1H, J = 6.1, 17.2 Hz, CH_2C=O), 3.12 (m, 1H, CHN), 3.45 (m, 1H, CHN′), 3.74–3.94 (m, 7H, OCH_2CH_2O, H-6a, H-6b, H-5), 4.37 (d, 1H, J = 9.3 Hz, H-1), 4.79 (t, 1H, J = 3.8 Hz, OCHO), 5.06 (dd, 1H, J = 2.7, 9.8 Hz, H-3), 5.32 (d, 1H, J = 2.6 Hz, H-4), 5.48 (t, 1H, J = 9.5 Hz, H-2).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 16.91, 19.82 (CH_3), 27.02, 27.09, 27.18, 27.25 (Piv-CH_3), 31.45 (*C*HMe_2), 31.69, 33.08 (CH_2), 38.50, 38.68, 38.74, 39.02 (Piv-C_{quart}), 43.35 (CH_2C=O), 51.55 (CHN), 61.51 (C-6), 62.10 (CHN′), 64.73, 64.80 (OCH_2CH_2O), 66.02, 67.22, 71.98, 72.90 (C-2, C-3, C-4, C-5), 93.15 (C-1), 104.20 (OCHO), 176.67, 177.42, 177.79 (PivC=O), 210.63 (C=O).

$C_{39}H_{65}NO_{12}$	calc.	C 63.31	H 8.85	N 1.89
(739.9)	found	63.33	8.85	1.89

(−)-Dihydropinidine Hydrochloride (15):

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-6-methylpiperidin-4-one Ethane-1,2-diyl Dithioacetal (**13**):

To a suspension of piperidinone **12a** (1 g, 1.53 mmol) and ethane-1,2-dithiol (0.25 mL, 3 mmol) in CH_2Cl_2 (10 mL) was added dropwise $BF_3 \cdot OEt_2$ (0.94 mL, 5 equiv) at 0 °C. After 1 h, the mixture was warmed up to r.t. and the stirring was continued for 24 h. The suspension was diluted with CH_2Cl_2 (20 mL) and washed with satd aq $NaHCO_3$ (2 × 20 mL). The organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography (petroleum ether/EtOAc, 8:1) to yield **13** (0.91 g, 81%) as a colorless amorphous solid; $[\alpha]_D^{22}$ 4.9 (c = 1.2, $CHCl_3$); R_f 0.55 (petroleum ether/EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3H, J = 7.2 Hz, CH_3), 1.08–1.29 (m, 39H, Piv-CH_3, CH_3), 1.32–1.42 (m, 4H, CH_2), 1.92–2.12 (m, 4H, CH_2), 2.85 (m, 1H, CHN), 3.09 (m, 1H, CHN′), 3.24 (m, 4H, SCH_2CH_2S), 3.84 (t, 1H, J = 6.8 Hz, H-5), 3.94 (dd, 1H, J = 6.6, 10.8 Hz, H-6a), 4.11 (dd, 1H, J = 7.2, 10.9 Hz, H-6b), 4.41 (d, 1H, J = 9.5 Hz, H-1), 4.96 (dd, 1H, J = 3.1, 9.8 Hz, H-3), 5.36 (d, 1H, J = 3.0 Hz, H-4), 5.53 (t, 1H, J = 9.6 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.21 (CH_3), 19.97 (CH_2), 21.83 (CH_3), 27.10, 27.14, 27.18, 27.32 (Piv-CH_3), 38.57, 38.72, 38.96 (Piv-C_{quart}), 49.75 (CH_2), 59.24 (CHN), 61.72 (C-6), 67.44, 67.84, 72.44, 73.01 (C-2, C-3, C-4, C-5), 88.36 (C-1), 176.84, 177.40, 177.90 (PivC=O).

$C_{37}H_{63}NO_9S_2$	calc.	C 60.88	H 8.70	N 1.92
(730.0)	found	60.87	8.76	1.86

(2R,6S)-N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-propyl-6-methylpiperidine (**14**):

N-Glycosyldihydropinidine **14** was prepared similar to **8** starting from **13** (0.74 g, 1 mmol); yield: 0.61 g (96%); amorphous; $[\alpha]_D^{22}$ 10.6 (c = 0.7, $CHCl_3$); R_f 0.61 (petroleum ether/EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, 3H, J = 7.3 Hz, CH_3), 1.07–1.49 (m, 45H, Piv-CH_3, CH_3, CH_2), 1.66 (m, 4H, CH_2), 2.93 (m, 1H, CHN), 3.15 (m, 1H, CHN′), 3.81 (t, 1H, J = 6.8 Hz, H-5), 3.90 (dd, 1H, J = 6.7, 10.9 Hz, H-6a), 4.07 (dd, 1H, J = 6.9, 10.9 Hz, H-6b), 4.22 (d, 1H, J = 9.3 Hz, H-1), 5.04 (dd, 1H, J = 3.2, 9.9 Hz, H-3), 5.32 (d, 1H, J = 2.8 Hz, H-4), 5.43 (t, 1H, J = 9.5 Hz, H-2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.34 (CH_3), 15.23, 21.61 (CH_2), 22.27 (CH_3), 27.08, 27.14, 27.30 (Piv-CH_3), 28.49, 31.56 (CH_2), 38.36, 38.67, 38.99 (Piv-C_{quart}), 62.06 (C-6), 65.65, 67.52, 71.54, 72.81 (C-2, C-3, C-4, C-5), 96.48 (C-1), 176.67, 176.84, 177.29, 177.94 (PivC=O).

$C_{35}H_{61}NO_9$	calc.	C 65.70	H 9.61	N 2.19
(639.9)	found	65.70	9.51	2.13

(−)-(2R,6S)-2-Propyl-6-methylpiperidine Hydrochloride [**15**, *(−)-Dihydropinidine Hydrochloride*]:

The release of **15** from the carbohydrate auxiliary was carried out as described for **9**, starting from **14** (0.50 g, 0.86 mmol); yield: 92%; colorless crystals; mp 206–208 °C; $[\alpha]_D^{22}$ −11.1 (c = 1.0, EtOH) [Lit.[31] mp 215–220 °C; Lit.[19c], $[\alpha]_D^{22}$ −11.6 (c = 1.03, EtOH)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (t, 3H, J = 7.1 Hz, CH_3), 1.05–1.92 (m, 10H, CH_2), 1.44 (d, 3H, J = 5.6 Hz, CH_3), 2.81 (m, 1H, CHN), 3.00 (m, 1H, CHN′), 8.84 (s, 1H, NH), 9.14 (s, 1H, NH).

^{13}C NMR (50.6 MHz, $CDCl_3$): δ = 13.61 (CH_3), 18.68, 19.33, 22.83, 27.41, 30.56, 35.09 (CH_2, CH_3), 54.37, 58.22 (CHN, CHN′).

These data are in agreement with the spectra reported in the literature.[32]

Gephyrotoxine 167B (19):

(2S,6R)-2-(3-Hydroxypropyl)-6-propylpiperidin-4-one (**16**):

To a solution of *N*-glycosylpiperidin-4-one **12b** (2.0 g, 2.6 mmol) in MeOH (80 mL) was added 1 N aq HCl (5.5 mL). The mixture was stirred at r.t. until completion of the reaction (monitoring by TLC). The solvent was evaporated in vacuo, the residue dissolved in Et_2O (80 mL) and washed with H_2O (5 × 20 mL). The carbohydrate auxiliary was recovered by concentration of the organic phase. The combined aqueous solution was adjusted to pH 10 by addition of Na_2CO_3, stirred for 20 min and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated to dryness in vacuo to afford crude **16** (87%) as a pale yellow oil; yield: 87%; dr 3:1.

major diastereomer:

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, 3H, J = 6.8 Hz, CH_3), 1.29–1.71 (m, 8H, CH_2), 1.98 (dd, 1H, J = 12.0, 14.0 Hz, CH_2C=O), 2.10 (dd, 1H, J = 13.2, 13.4 Hz, CH_2C=O), 2.34 (m, 1H, CH_2C=O), 2.44 (dd, 1H, J = 4.9, 14.9 Hz, CH_2C=O), 2.82

(m, 1 H, CHN), 3.08 (m, 2 H, OH, NH), 3.25 (m, 1 H, CHN'), 3.57 (m, 2 H, CH_2).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.90 (CH_3), 18.86, 29.69, 34.97, 39.08 (CH_2), 48.38, 48.62 (CH_2C=O), 56.35 (CHN), 56.69 (CHN'), 62.50 (CH_2), 208.77 (C=O).

minor diastereomer:

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.81 (CH_3), 19.17, 30.06, 32.86, 36.91 (CH_2), 47.78, 48.46 (CH_2C=O), 52.30 (m, 1 H, CHN), 52.78 (m, 1 H, CHN'), 62.50 (CH_2), 209.02 (C=O).

(5R,8aS)-5-Propyloctahydroindolizidin-7-one **(17)**:

A solution of Et_3N (0.31 mL, 2.2 mmol) in CCl_4 (0.31 mL, 3.2 mmol) was added to crude **16** (0.43 g, 2.15 mmol) dissolved in MeCN (5 mL). The resulting solution was cooled to 0 °C, and Ph_3P (0.68 g, 2.0 mmol) was added. After 45 min the mixture was allowed to warm up to r.t. and the stirring was continued for 22 h. After addition of satd aq $NaHCO_3$ (20 mL) and Et_2O (80 mL), the separated organic layer was washed with brine and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue purified by chromatography (petroleum ether/EtOAc, 1:2) to afford **17** (0.25 g, 64%) as a pale yellow oil; $[\alpha]_D^{22}$ −20.4 (c = 2.2, $CHCl_3$); R_f 0.15 (petroleum ether/EtOAc, 1:2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (t, 3 H, J = 7.1 Hz, CH_3), 1.10–1.94 (m, 8 H, CH_2), 1.99–2.44 (m, 7 H, NCH_2, NCH, CH_2C=O), 3.20 (dt, 1 H, J = 2.4, 8.4 Hz, NCH').

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.17 (CH_3), 18.07, 21.32, 30.68, 36.94 (CH_2), 45.51, 47.04 (CH_2C=O), 50.12 (NCH_2), 60.90, 63.81 (NCH, NCH'), 209.38 (C=O).

FAB-MS (pos.; NBA): m/z = 182.3 ($M+H^+$, 100%).

(5R,8aS)-5-(Propyl)octahydroindolizidin-7-one Ethane-1,2-diyl Dithioacetal **(18)**:

A solution of indolizidinone **17** (0.2 g, 1.1 mmol) and ethane-1,2-dithiol (0.2 mL, 2.4 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.18 mL, 1.43 mmol) was added. After 30 min the mixture was warmed up to r.t. and stirred for an additional 12 h. The suspension was diluted with CH_2Cl_2 (30 mL), filtered and washed with satd aq $NaHCO_3$ (2 × 20 mL) and brine, dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by chromatography (petroleum ether/EtOAc, 1:1) to yield **18** (0.21 g, 74%) as a colorless oil; $[\alpha]_D^{22}$ −54.8 (c = 1.2, $CHCl_3$); R_f 0.44 (petroleum ether/EtOAc, 1:2).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (t, 3 H, J = 6.7 Hz, CH_3), 1.12–1.86 (m, 10 H, CH_2), 1.92–2.22 (m, 5 H, NCH_2, NCH, CH_2), 3.15 (dt, 1 H, J = 2.8, 8.5 Hz, NCH'), 3.23 (s, 4 H, SCH_2CH_2S).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.35 (CH_3), 18.68, 20.79, 29.94, 36.24, 37.72, 39.10 (CH_2), 47.30, 47.40 (SCH_2CH_2S), 50.55 (NCH_2), 61.80, 63.84 (NCH, NCH'), 66.83 (CS_2).

FAB-MS (pos.; NBA): m/z (%) = 258.6 ($M+H^+$, 100%), 214.5 ($M-C_3H_7^+$, 35.1%).

$C_{13}H_{23}NS_2$	calc.	C 60.65	H 9.00	N 5.44
(257.5)	found	59.99	9.06	5.29

*(5R,8aR)-5-(Propyl)octahydroindolizidine (***19***, Gephyrotoxine 167B)*:

Desulfurization of **18** (0.1 g, 0.388 mmol) was carried out as described for **8**; yield: 88%; pale yellow and volatile oil; $[\alpha]_D^{22}$ −99.2 (c = 0.3, hexane) [Lit.[22a] $[\alpha]_D^{20}$ −106.3 (c = 0.8, hexane)].

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (t, 3 H, J = 6.9 Hz, CH_3), 1.02–1.47 (m, 7 H, CH_2), 1.49–2.02 (m, 10 H, NCH_2, NCH, CH_2), 3.22 (dt, 1 H, J = 2.3, 8.5 Hz, NCH').

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.51 (CH_3), 19.18, 20.40, 24.68, 30.52, 30.80, 30.91, 36.86 (CH_2), 51.46 (NCH_2), 63.72, 65.08 (NCH, NCH').

These data are in agreement with the spectra reported in the literature.[22a]

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