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GLYCOSYLATION-INDUCED ASYMMETRIC SYNTHESIS OF 1-SUBSTITUTED TETRAHYDROISOQUINOLINES

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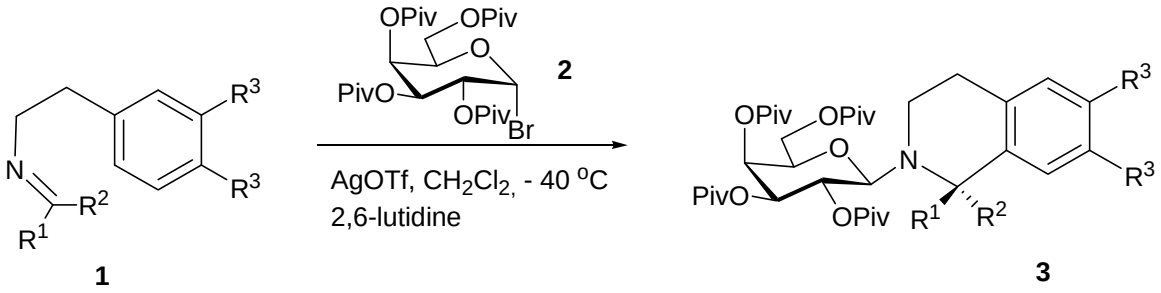
Abstract – Activation of imines by *N*-glycosylation and simultaneous diastereodifferentiation in reactions of the formed *N*-glycosyl iminium ions provide new stereoselective routes to 1-substituted tetrahydroisoquinolines. Pictet-Spengler reactions induced by *N*-galactosylation of β-arylethyl imines of aromatic aldehydes give 1-aryl tetrahydroisoquinolines with high stereoselectivity. Glycosylation-induced addition of dialkylzinc reagents to 3,4-dihydroisoquinoline furnish 1-alkyl-tetrahydroisoquinolines with excellent diastereoselectivity.

Tetrahydroisoquinolines constitute privileged pharmacophoric structures occurring in numerous biologically active natural products, in particular, in alkaloids.[1] Due to their interesting biological effects including antitumor activities their stereoselective synthesis received increasing attention during the past decades.[2] The Pictet-Spengler reaction,[3] an intramolecular α-aminoalkylation of Schiff bases of β-aryl ethylamines, provides a most useful and general synthetic access to tetrahydroisoquinolines. Stereoselective Pictet-Spengler reactions, therefore, are of particular interest for both, the total synthesis of natural tetrahydroisoquinolines[2] and the preparation of synthetic drugs.[4] In stereoselective Pictet-Spengler reactions stereodifferentiation was achieved by the stereogenic center contained in the phenylalanine- and tyrosine-derived substrate to give 1,3-disubstituted derivatives.[5] In auxiliary-supported diastereoselective Pictet-Spengler reactions, the chiral auxiliary was either N-linked to the β-arylethylamine[6] or to the aldehyde.[7] Recently, efficient enantioselective catalysis of the Pictet-Spengler cyclization was achieved using chiral hydrogen bond donor or Binol-derived Brønstedt acid catalysts.[8]

An alternative mode of achieving stereoselectivity in the Pictet-Spengler reactions is based on chiral reagents which activate the *N*-β-arylethyl imines and simultaneously induce stereoselectivity in their aminoalkylating attack at the aromatic ring. In this sense, *N*-acylamino acid chlorides have successfully been applied as the activating and stereodifferentiating reagents in Pictet-Spengler reactions.[9]

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

We here describe *N*-glycosylation of the *N*-(β-phenyl)ethyl imines as a simultaneously activating and diastereodifferentiating principle in Pictet-Spengler reactions. Imines **1** obtained from the corresponding aldehydes and β-aryl ethylamines reacted with 2,3,4,6-tetra-*O*-pivaloyl-D-galactosyl bromide[10] **2** promoted by silver trifluoromethanesulfonate (triflate) (Scheme 1, Table 1).



Scheme 1. Piv = tBu-CO-; Tf = trifluoromethanesulfonate; de = excess of diasteromer

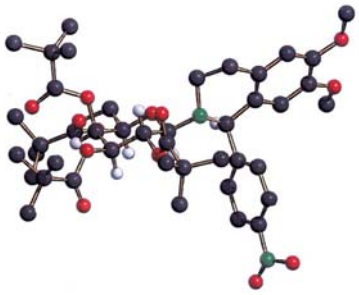
As a rule the reaction was carried out in dichloromethane, started at -40 °C and allowed to warm up to room temperature within 20 h. Excess of the galactosylating reagent **2** / AgOTf (1.2-1.5 equiv.) and 2 equivalents of the base 2,6-lutidine (based on **2**) were applied. The ratio of diastereomers (diastereomeric excess de) was determined by analytical HPLC on reversed phase (RP-18) in methanol/water mixtures. The rate (yield) and the diastereoselectivity of the glycosylation-induced asymmetric synthesis of the 1-substituted tetrahydroisoquinolines **3** distinctly depend upon the structure of the imines **1** (Table 1).

Table 1. Glycosylation-induced Pictet-Spengler reaction according to Scheme 1

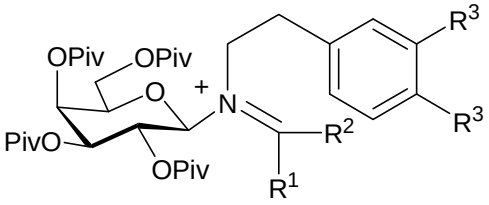
Imine	R^1	R^2	R^3	Product **3**	Yield %	de (%)
1a	Ph	H	OMe	**3a**	74	>98
1b	3,4-di-OMe-Ph	H	OMe	**3b**	27	36
1c	4-NO_2-Ph	H	OMe	**3c**	73	82
1d	Ph	H	H	**3d**	50	64
1e	*t*-Bu	H	OMe	**3e**	31	94
1f	Bn	CO_2H	OMe	**3f**	28	>95[a)]
1g	CO_2Et	H	OMe	**3g**	43	53[b)]
1h	Ph-$C(OMe)_2$	H	OMe	**3h**	40	83[b)]

a) Major diastereomer has (*R*)-configuration due to priority of COOH over C_{arom}; b) Major diastereomer has (*S*)-configuration.

As is shown in Scheme 1 and Table 1 the major diastereomers formed in these Pictet-Spengler reactions have (*R*)-configuration (or analogous stereochemistry, **1g**, **1h**) as was confirmed by an X-ray analysis of the major diastereomer of 1-(4-nitrophenyl)tetrahydroquinoline **3c** (Figure 1)



a

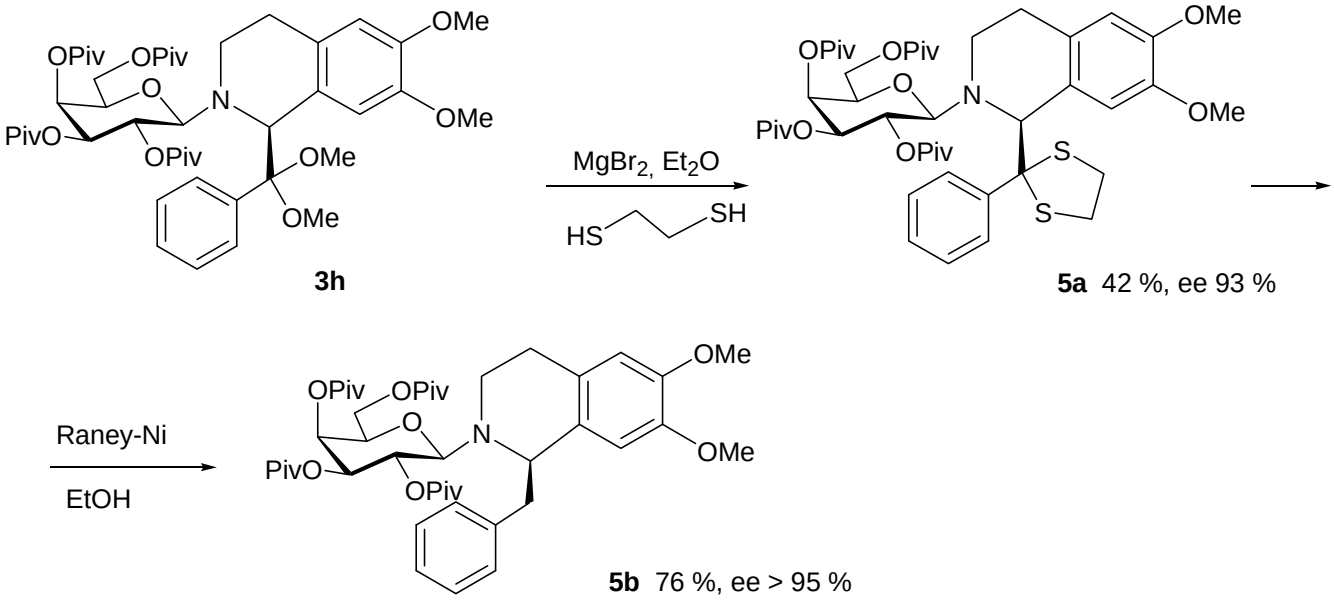


4

b

Figure 1. a) X-Ray analysis of **3c;** b) Reactive *N*-glycosyl iminium intermediate

A high diastereoselectivity is achieved, if the intermediate *N*-galactosyl iminium cation **4** exhibits sufficient electrophilicity (**1a, 1c, 1e, 1f, 1h**). High yields of **3** are obtained, if no sterical hinderance occurs during the electrophilic aromatic substitution reaction (**1a**, **1c**). Effects stabilizing the galactosyl iminium ion **4** favor side reactions and cis to trans isomerization at the iminium salt and, thus, reduce the stereoselectivity of the reaction (**1b**). A lower reactivity of the attacked aromatic ring (**1d** having no electrondonating MeO groups) also results in lower yields and stereoselectivity. The tetrahydroisoquinoline **3h** is of interest as a precursor of the corresponding 1-benzyltetrahydroisoquinoline. Its treatment with ethane-1,2-dithiol promoted by $MgBr_2$ gave the dithioacetal **5a** (Scheme 2).



3h

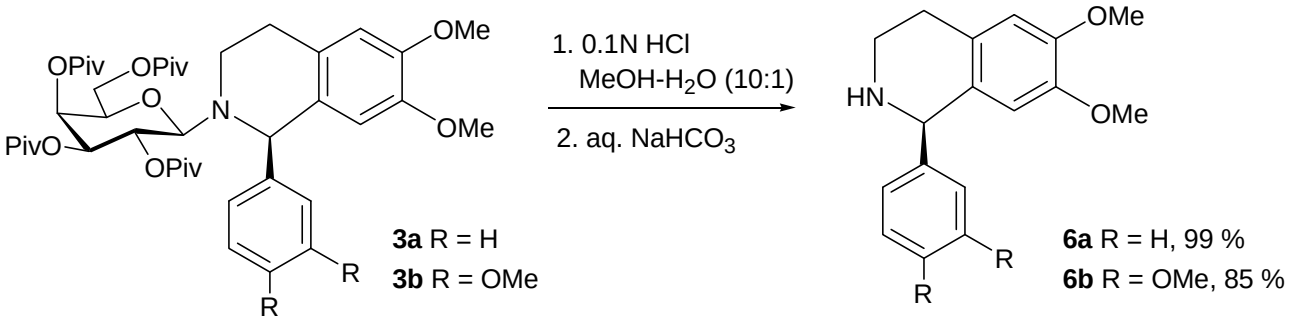
5a 42 %, ee 93 %

5b 76 %, ee > 95 %

Scheme 2

Desulfurization with H_2/Raney-nickel furnished 1-benzyl-tetrahydroquinoline **5b** which after chromatography was isolated with a diastereomeric excess of 93% (*R*:*S* > 96:4).

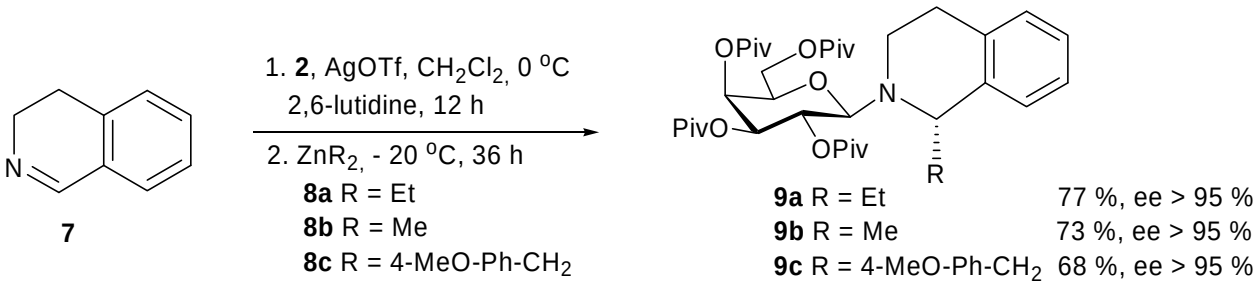
The carbohydrate group can readily be removed from the products **3** by treatment with dilute HCl in methanol as is shown for **3a** and **3b** in Scheme 3. 1(*R*)-Phenyltetrahydroquinoline **6a** was quantitatively isolated in enantiomercally pure form. The corresponding 1-(3,4-dimethoxy)phenyl derivative (Norcryptostyline[11]) **6b** was obtained from a diastereomeric mixture of **3b** (65:35) and showed a positive optical rotation value confirming the (*R*)-configuration of the prevailing diastereomer.



Scheme 3

The reported glycosylation-induced Pictet-Spengler reaction is limited to aldehydes not bearing an α-CH-group. Imines of aliphatic aldehydes are converted to enamines which could not be activated under the conditions described.

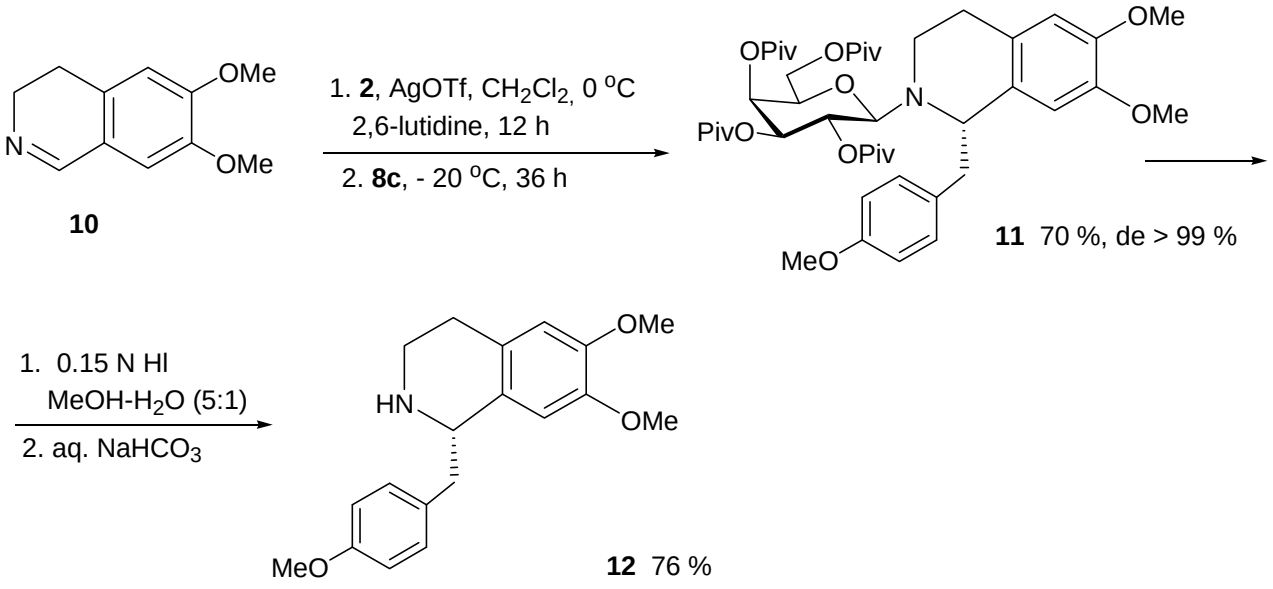
However, an alternative glycosylation-induced reaction proved efficient in the stereoselective preparation of 1-alkyl-tetrahydroisoquinolines. This reaction constitutes of an addition of C-nucleophiles to 3,4-dihydroisoquinolines similar to the Mannich reaction with ester enolates.[12] Stereoselective addition reactions of auxiliary-linked organometallic compounds to 3,4-dihydroisoquinoline **7** have been reported in the literature.[13] Similarly, an asymmetric formation of Reissert compounds from isoquinoline by *N*-acylation with *N*-protected amino acid fluorides and subsequent addition of cyanide has been described.[14] The galactosylation-induced diastereoselective addition of dialkylzinc compounds to 3,4-dihydroisoquinoline **7** was achieved by initial reaction of **7** with galactosyl bromide **2** and AgOTf in the presence of 2 equiv. of 2,4-lutidine in dichloromethane at 0 °C and subsequent dropwise addition of a solution of dialkylzinc at -20 °C (Scheme 4). Diethyl- (**8a**) and dimethyl zinc **8b** were applied as 1M solutions in n-heptane. Di-(4-methoxybenzyl)zinc **8c** was freshly prepared from the Grignard compound in diethyl ether and, after addition of dichloromethane to improve the solubility, immediately used.



Scheme 4

In all cases the (*S*)-configured 1-alkyl tetrahydroisoquinolines **9** were obtained in good yield and excellent diastereoselectivity.

In order to confirm the (*S*)-configuration of compounds **9**, 6,7-dimethoxy-3,4-dihydroisoquinoline[15] **10** was subjected to the glycosylation-induced addition of di-(4-methoxybenzyl)zinc **8c**. The *N*-galactosyl-1(*S*)-(4-methoxybenzyl)tetrahydroquinoline **11** was obtained in a yield of 70% and in diastereomerically pure form (Scheme 5).



Scheme 5

As has been demonstrated for products **3** of the Pictet-Spengler reaction, the carbohydrate auxiliary is readily detached from the tetrahydroisoquinolines **9** and **11**. Treatment of **11** with 0.15N HCl in methanol/water (5:1) and subsequent treatment with aqueous potassium carbonate gave 1-(4-methoxybenzyl)-6,7-dimethoxytetrahydroisoquinoline **12** as the free base in enantiomerically pure form (Scheme 5). Compound **12** is a precursor of coclaurine. Its racemate exhibits vasodilatory effects. The comparison of its optical rotation value with the one reported in the literature[16] confirms the

(*S*)-configuration of the synthesized product.

In conclusion, glycosylation-induced activation of imines provides two efficient stereoselective routes to 1-substituted tetrahydroisoquinolines which are prominent substructures of a large group of alkaloids. While 1-aryl-substituted tetrahydroisoquinolines are accessible with high diastereoselectivity via a glycosylation-induced Pictet-Spengler cyclization, the 1-alkyl-substituted analogues are obtained with excellent diastereoselectivity by glycosylation-induced addition of dialkylzinc reagents to 3,4-dihydroisoquinoline derivatives. The scope of these stereoselective syntheses of 1-substiuted tetrahydroisoquinolines by glycosylation-induced activation of imines can be extended if 2,3,4-tri-*O*-pivaloyl-β-D-arabinopyranosyl bromide accessible in analogy to the tetra-*O*-pivaloyl-D-glucopyranosyl bromide[17] is used as the activating reagent. As shown for reactions of glycosylamines[18] the opposite enantiomers will be obtained in the Pictet-Spengler reaction (compounds **6**) as well as in the addition of dialkylzinc (compound **12**).

EXPERIMENTAL

NMR spectra were recorded on Bruker AM 400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) and Bruker WT 200 (200 MHz ^{1}H) NMR spectrometers. Chemical shifts are given in ppm relative to TMS. Analytical HPLC was carried out using a Knauer system (Knauer MaxiStar K1000 pump and DAD2062 for diode array detection), flow rate: 1 cm^3/min. Preparative HPLC was performed using two Knauer Ministar K500 pumps. Columns: A: Eurospher 100, C8, 5 μ, 250x4 mm, Knauer, B: Kromasil C18, 5 μ 250x4 mm, Knauer; flow rate: 1 cm^3/min. Thin layer chromatography (TLC) was performed on Merck silica gel 60_{F254}, column chromatography on silica gel 60 (0.6-0.2 mm, Baker), flash-chromatography on silica (0.0063-0.04 mm, Merck, Darmstadt, Germany). FAB mass spectra were measured on a Finnigan MAT 95 spectrometer, ESI mass spectra on a Thermoquest Navigator instrument and optical rotations on a Perkin Elmer 241 polarimeter. Melting points were taken on a Büchi Dr. Tottoli apparatus and are uncorrected. Aldimines **1** were prepared form β-aryl ethylamines and the corresponding aldehydes by stirring the components at room temp for 1 h and subsequent removal of the formed water at 100 °C in vacuo. The imine **1f** of phenyl pyruvic acid was formed in dichloromethane in the presence of molecular sieves immediately prior to the Pictet-Spengler reaction (see procedure). Imines **1c**, **1g** and **1h** were obtained by stirring of equimolar amounts of the corresponding aldehyde and β-(6,7-dimethoxyphenyl)ethylamine in toluene and removal of water and solvent in vacuo.

1(*R*)-Phenyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 3a

Silver trifluoromethanesulfonate (0.38 g, 1.13 mmol), 2,3,4,6-tetra-*O*-pivaloyl-α-D-galactopyranosyl

bromide[10,17] (0.65 g, 1.13 mmol) and 2,6-lutidine (0.26 mL, 2.26 mmol) were stirred in CH_2Cl_2 (10 mL) and cooled to -40 °C. To this mixture, *N*-phenylmethylene-2-(3,4-dimethoxyphenyl)ethylamine **1a** (0.18 g, 0.75 mmol) in CH_2Cl_2 (10 mL) was added through a syringe. The cooling was removed and the stirring continued for 20 h. Silver bromide was filtered off, and the solvent was evaporated in vacuo. The remaining residue was purified by column chromatography in light petroleum/EtOAc (10:1). Yield: 428 mg (74%), colorless solid, R_f = 0.47 (light petroleum/EtOAc 4:1), mp 84 °C; $[\alpha]_D^{22}$ -32.1 (c 1, $CHCl_3$)

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.28 (m, 3H, arom.); 7.18 (m, 2H, arom.); 6.55 (s, 1H, arom); 6.00 (s, 1H, arom.); 5.52 (t, $J_{2,3}$ = 9.7 Hz, 1H, H-2); 5.27 (d, $J_{4,3}$ = 2.8 Hz, 1H, H-4); 5.08 (s, 1H, α-CH); 4.87 (dd, $J_{3,4}$ = 3.2 Hz, $J_{2,3}$ = 10.0 Hz, 1H, H-3); 4.00 (m, 1H, H-5); 3.94 (dd, $J_{6,5}$ = 6.5 Hz, 1H, H-6); 3.92 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1); 3.81 (s, 3H, -OCH_3); 3.64 (dd, $J_{6',5}$ = 6.9 Hz, 1H, H-6'); 3.50 (s, 3H, -OCH_3); 2.88 (m, 2H, -CH_2-); 2.63 (m, 2H, -CH_2-); 1.25-1.05 (4s, 36H, CH_3-Piv).

100.6 MHz ^{13}C-NMR ($CDCl_3$): δ = 177.9, 177.4, 177.2, 176.7 (C=O); 147.4 (arom. C-O); 143.2 (arom. C_{ipso}); 130.9, 127.6 (arom. C_{ipso}); 129.9, 128.4, 127.8 (arom. C); 111.9, 110.9 (arom. C); 88.7 (C-1); 72.3, 71,9 (C-3, C-5); 67.5 (α-C); 65.1, 64.8 (C-2, C-4); 61.8 (C-6); 55.80, 55.77 (-OCH_3); 42.0 (-CH_2-); 39.07, 38.72, 38.69 (Piv-$C_{quart.}$); 29.7 (-CH_2-); 27.32, 27.23, 27.16, 27.06 (Piv-CH_3).

Anal. Calcd for $C_{43}H_{61}NO_{11}$ (768.0): C 67.25, H 8.01, N 1.82. Found: C 67.36, H. 8.32, N 1.72.

1-(3,4-Dimethoxyphenyl)-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-*D*-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3b

The reaction was carried out as described for **3a**, however, in the presence of 40 mg of molecular sieves 4Å, using 0.98 mg (1.7 mmol) of **2**, 0.57 g (1.7 mmol) of AgOTf, 0.39 mL (3.4 mmol) of 2,6-lutidine and 0.26 g (0.8 mmol) of *N*-(3,4-dimethoxyphenyl)methylene-2-(3,4-dimethoxyphenyl)ethylamine **1b**. After the purification by column chromatography, preparative HPLC (column B) in MeOH/water (85:15) was carried out. Separation of diastereomers was not achieved. Yield: 182 mg (27%); colorless solid, mp 72 °C, R_f = 0.36 (light petroleum/EtOAc 4:1), $[\alpha]_D^{22}$ +10.2 (c1, $CHCl_3$). Diastereomeric excess (d.e) 36% (anal. HPLC).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.75-6.59 (5s, 5H, arom.); 5.82 (dd, $J_{2,3}$ = 10.2 Hz, 1H, H-2); 5.52 (d, $J_{1,2}$ = 6.9 Hz, 1H, H-1); 5.49 (d, $J_{4,3}$ = 4.0 Hz, 1H, H-4); 5.14 (dd, $J_{3,4}$ = 4.0 Hz, $J_{3,2}$ = 10.3 Hz, 1H, H-3); 4.44 (m, 1H, H-5); 3.69 (dd, $J_{6,5}$ = 6.1 Hz, 2H, H-6,6'); 3,91 (s, 1H, α-CH); 3.87-3.78 (4s, 12H, -OCH_3); 3.35 (m, 1H, -CH_2-); 2.64 (m, 2H, -CH_2-); 1.23-1.04 (4s, 36H, CH_3-Piv):

100.6 MHz ^{13}C-NMR ($CDCl_3$): δ = 177.73, 177.69, 177.3, 177.0 (C=O); 148.2, 147.9, 147.3 (arom. C-O); 135.9 (arom. C_{ipso}); 128.2, 128.0 (arom. C_{ipso}); 111.6, 111.5, 111.3, 111.1, 110.8 (arom. C); 82.6 (C-1); 70.4, 68.9 (C-3, C-5); 68.6 (α-C); 68.4, 66.6 (C-2, C-4); 61.9 (C-6); 56.03, 55.90, 55.84 (-OCH_3); 39.0 (-CH_2-); 38.67, 38,62, 38.57, 38.51 (Piv-$C_{quart.}$); 27.99 (-CH_2-); 25.2, 27.1, 27.0 (Piv-CH_3).

1-Nitrophenyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 3c

Compound **3c** was synthesized according to the procedure described for **3a** starting from *N*-(4-nitrophenyl)methylene-2-(3,4-dimethoxyphenyl)ethylamine **1c** (0.24 g, 0.75 mmol). Yield: 207 mg (73%); de = 82%; colorless solid; mp 187 °C; R_f = 0.38 (light petroleum/EtOAc 4:1); $[\alpha]_D^{22}$ -40.7 (c1, $CDCl_3$). The diastereoisomers were separated by preparative HPLC (column B) in MeOH/water 9:1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, 2H, J = 7.5 Hz, arom.); 7.39 (d, 2H, J = 7.5 Hz, arom); 6.58 (s, 1H, arom.); 5.92 (s, 1H, arom.); 5.55 (t, $J_{2,3}$ = 9.8 Hz, 1H, H-2); 5.29 (d, $J_{4,3}$ = 2.4 Hz, 1H, H-4); 5.25 (s, 1H, α-CH); 4.90 (dd, $J_{3,4}$ = 2.9 Hz, $J_{3,2}$ = 9.8 Hz, 1H, H-3); 4.12 (m, 1H, H-5); 3.91 (dd, $J_{6,5}$ = 6.8 Hz, 1H, H-6); 3.82 (s, 3H, -OCH_3); 3.67 (d, $J_{1,2}$ = 9.8 Hz, 1H, H-1); 3.53 (s, 3H, -OCH_3); 3.44 (dd, $J_{6',5}$ = 6.8 Hz, $J_{6',6}$ = 14.2 Hz, 1H, H-6'); 2.98-2.60 (m, 4H, CH_2-CH_2-N-); 1.25-1.06 (4s, 36H, Piv-CH_3).

100.6 MHz ^{13}C-NMR ($CDCl_3$): δ = 177.8, 177.1, 177.0, 176.6 (C=O); 152.3 (arom. C_{ipso}); 147.9 (C-NO_2); 147.7, 147.4 (arom. C-O); 130.5, 128.9, 127.2 (arom. C.); 123.7 (arom. C_{ipso}); 111.5, 111.3 (arom. C); 89.2 (C-1); 72.14, 72.10 (C-3, C-5); 67.3 (α-C); 64.8, 64.2 (C-2, C-4); 61.6 (C-6); 55.96, 55.82 (-OCH_3); 41.7 (-CH_2-); 39.07, 38.73, 38.70 (Piv-$C_{quart.}$): 29.6 (-CH_2-); 27.33, 27.21, 27.14, 27.05 (Piv-CH_3).

Anal. Calcd for $C_{43}H_{60}N_2O_{13}$ (813.0): C 63.53, H 7.44, N 3.45. Found: C 63.14, H 7.41, N 3.21.

Crystal data: mol weight: 812.9 $gmol^{-1}$, crystal size: 0.1x0.3x0.9 mm^3; absorption μ = 0.68 mm^{-1}, space group: $P2_12_12_1$, orthorhombic; lattice parameters: *a* = 11.0836 (5) Å, *b* = 12.8833 (4) Å, *c* = 6217 (10) Å, V = 4801.0 (3) Å, z = 4, F(000) = 1744, diffractometer: Turbo-CAD4 (Enraf-Nonius), irradiation K_α graphite monochromator, 10737 reflextions measured (incl. Friedel pairs, wR2 = 0.3973, R_1 = 0.1084 for observed reflexes, 0.1530 for all reflexes). CCDC reference number: 166867.

1-Phenyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-1,2,3,4-tetrahydroisoquinoline 3d

Compound **3d** was prepared according to the procedure for **3a**, however, in the presence of 40 mg molecular sieves 4 Å starting form *N*-(phenylmethylene)-2-phenylethylamine (157 mg, 0.75 mmol). Yield: 261 mg (50%); de = 64%; colorless crystals, mp 104-106 °C, R_f = 0.47 (light petroleum/EtOAc 4:1); $[\alpha]_D^{22}$ 16.0 (c1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (m, 4H, arom.) 7.15 (m, 5H, arom.); 5.37 (d, $J_{4.3}$ = 3.0 Hz, 1H, H-4); 5.12 (dd, $J_{3,4}$ = 3.4 Hz, $J_{3,2}$ = 10.3 Hz, 1H, H-3); 5.00 (dd, $J_{2,3}$ = 10.2 Hz, $J_{2,1}$ = 8.9 Hz, 1H, H-2); 4.12 (m, 1H, H-5); 4.07 (d, $J_{1,2}$ = 8.9 Hz, 1H, H-1); 3.96 (dd, $J_{6,5}$ = 7.0 Hz, $J_{6,6'}$ = 10.8 Hz, 1H, H-6); 3.86 (t, $J_{6',5}$ = 6.9 Hz, 1H, H-6'); 3.45 (s, 1H, α-CH); 3.13 (m, 1H, -CH_2-); 2.83 (m, 1H, -CH_2-); 2.69 (m, 2H, -CH_2-); 1.23-1.07 (4s, 36H, CH_3-Piv).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.5, 177.1, 176.8 (C=O); 139.67, 139.33 (arom. C_{ipso}); 128.9, 128.6, 127.9, 126.2, 126.0 (arom. C); 89.8 (C-1); 71.4, 71.3 (C-3, C-5); 68.4 (α-C); 67.9, 67.2

(C-2, C-4); 61.3 (C-6); 46.9 (-CH_2-); 38.9, 38.6 (Piv-$C_{quart.}$); 37.1 (-CH_2-); 27.1, 26.9, 26.8 (Piv-CH_3).
Anal. Calcd for $C_{41}H_{57}NO_9$ (707.9): C 69.56, H 8.12, N 1.98. Found: C 69.70. H 8.79, N 1.84.

1-*tert*-Butyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline 3e

Compound **3e** was synthesized form *N*-(neopentylidene-2-(3,4-dimethoxyphenyl)ethylamine **1e** (187 mg, 0.75 mmol). Yield: 174 mg (31%); de = 94%; colorless solid, mp 58 °C; R_f = 0.46 (light petroleum/EtOAc 4:1); $[\alpha]_D^{22}$ 20.8 (c 1, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.57 (s, 1H, arom.); 6.51 (s, 1H, arom; 5.63 (t, $J_{2,3}$ = 9.7 Hz, 1H, H-2); 5.31 (d, $J_{4,3}$ = 3.0 Hz, 1H, H-4); 5.07 (dd, $J_{3,4}$ = 3.0 Hz, $J_{3,2}$ = 10.0 Hz, 1H, H-3); 4.43 (d, $J_{1,2}$ = 9.4 Hz, 1H, H-1); 3.98-3.86 (m, 3H, H-5,, H-6, H-6'); 3.83 (s, 3H, -OCH_3); 3.80 (s, 3H, -OCH_3); 3.25 (m, 1H, -CH_2-); 3.63 (s, 1H, α-CH); 2.90 (m, 1H, -CH_2-); 2.72 (m, 1H, -CH_2-); 2.46 (m, 1H, -CH_2-); 1.23-1.10 (4s, 36H, CH_3-Piv); 0.84 (s, 9H, -CH_3).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.4, 177.2, 176.7 (C=O); 147.4, 146.0 (arom. C-O); 130.2, 128.6 (arom. C_{ipso}): 113.7, 110.5 (arom. C); 95.4 (C-1); 73.1, 71.8 (C-3, C-5); 69.9 (α-C); 67.6, 66.5 (C-2, C-4); 61.5 (C-6); 56.0, 55.8 (-OCH_3); 41.0 (-CH_2-); 39.04, 39.01, 38.88, 38.77, 38.64 (Piv-$C_{quart.}$, $C_{quart.}$ tBu); 29.3 (-CH_2-); 27.65, 27.39, 27.18, 27.14, 27.07 (Piv-CH_3, CH_3 tBu).
Anal. Calcd for $C_{41}H_{65}NO_{11}$ (748.0): C 65.84, H 8.76, N 1.87. Found: C 65.67, H. 8.76, N 1.42.

1-Benzyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline-1-carboxylic acid 3f

Phenylpyruvic acid (0.25 g, 1.5 mmol), homoveratrylamine (0.25 mL, 1.5 mmol) and molecular sieves 4 Å (50 mg) in CH_2Cl_2 were stirred for 1h. To this mixture was added at -40 °C a solution of AgOTf (0.5 g, 1.5 mmol), galactosyl bromide **2** (0.7 g, 1.5 mmol) and 2,6-lutidine (0.17 mL, 1.5 mmol) in CH_2Cl_2 (10 mL). After stirring for 3 d at 0 °C, filtration and evaporation of the solvents, the product was purified by column chromatography and subsequent preparative HPLC (column B, MeOH/water 80:20). Yield: 280 mg (28%), de. >95%, colorless oil, R_f = 0.46 (light petroleum/EtOAc 4:1); $[\alpha]_D^{22}$ +14.7 (c 1, $CHCl_3$).
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.37 (2s, 2H, arom.); 7.27 (2s, 2H, arom.); 7.18 (s, 1H, arom.); 6.55 (d, J = 1.8 Hz, 1H, arom.); 6.46 (d, J = 1.8 Hz, 1H, arom.); 5.78 (d, $J_{1,2}$ = 8.4 Hz, 1H, H-1); 5.47 (d, $J_{4,3}$ = 3.8 Hz, 1H, H-4); 5.44, (dd, $J_{2,1}$ = 8.4 Hz, 1H, H-2); 5.22 (dd, $J_{3,4}$ = 3.3 Hz, $J_{3,2}$ = 10.5 Hz, 1H, H-3); 4.16 (t, $J_{6,5}$ = 6.5 Hz, H-6, H-6'); 4.06 (m, 1H, H-5); 3.80 (s, 3H, -OCH_3); 3.76 (s, 3H, -OCH_3); 3.01 (m, 2H, -CH_2-); 2.58 (m, 2H, -CH_2-); 1.27-1.06 (4s, 36H, CH_3-Piv).
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.7, 177.1, 176.80, 176.75 (C=O); 165.0 (COOH); 149.0, 147.6 (arom. C-O); 135.5 (arom. C_{ipso}); 133.1, 131.6 (arom. C_{ipso}); 129.4, 128.1, 127.3 (arom, C (R)); 112.0, 111.5 (arom. C); 93.5 (C-1); 72.3, 70.6 (C-3, C-5); 67.9, 66.6 (C-2, C-4); 60.7 (C-6); 55.9, 55.8 (-OCH_3); 47.9 (-CH_2-); 39.1, 38.84, 38.77, 38.71 (Piv-$C_{quart.}$); 35.9 (-CH_2, -CH_2-Ph); 27.19, 27.06, 26.96

(Piv-CH_3).

Anal. Calcd for $C_{45}H_{64}NO_{13}$ (827.0): C 65.35, H 7.80, N 1.69. Found: C 65.98, H 7.91, N 1.68.

Ethyl *N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate 3g

Compound **3g** was synthesized according to the procedure for **3a** starting form *N*-(ethoxycarbonylmethylene)-2-(3,4-dimethoxyphenyl)ethylamine **1g** (200 mg, 0.75 mmol). Yield 275 mg (48%), colorless solid, mp 76-78 °C, R_f = 0.29 (light petroleum/EtOAc 4:1). Anal. Calcd for $C_{40}H_{61}NO_{13}$ (763.9): C 62.93, H. 8.05, N 1.90. Found: C 62.97, H 8.01, N 1.79. The diastereomers were separated by preparative HPLC in MeOH/water (9:1, column B).

(1*S*)-diastereomer: 185 mg, R_t = 15.07 min; $[\alpha]_D^{22}$ -130.8 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.63 (s. 1H, arom.) 6.53 (s, 1H, arom.); 5.59 (t, $J_{2,3}$ = 9.7 Hz, 1H, H-2); 5.36 (d, $J_{4,3}$ = 2.9 Hz, 1H, H-4); 5.12 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 10.0 Hz, 1H, H-3); 4.77 (s, 1H, α-CH); 4.27 (d, $J_{1,2}$ = 9.4 Hz, 1H, H-1); 4.08 (m, 3H, H-5, H-6); 3.88 (m, J = 7.3 Hz, 2H, -OCH_2); 3.79, 3.77 (2s, 2x3H, OCH_3); 2.86 (m, 2H, CH_2); 1.28-1.03 (m, Piv-CH_3, CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.2, 176.8, 172.9 (C=O); 148.1, 147,3 (arom. C-O); 124.0 (arom. C_{ipso}); 111.6, 109.2 (arom. C); 93.4 (C-1); 72.1 (C-3, C-5); 67.2 (α-C); 64.8 (C-2, C-4); 61.22 (C-6); 61.18 (-OCH_2-); 55.9, 55.7 (-OCH_3); 42.8 (-CH_2-); 39.1, 38.72, 38.66 (Piv-$C_{quart.}$); 28.8 (-CH_2-); 27.2, 27.1, 27.0 (Piv-CH_3); 14.2 (-CH_3).

(1*R*)-diastereomer: 63 mg, R_t = 17.18 min, $[\alpha]_D^{22}$ +28.5 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.54 (s, 2H, arom.); 5.39 (m, $J_{2,3}$ = 9.7 Hz, $J_{4,3}$ = 2.9 Hz, 2H, H-2, H-4); 5.14 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 10.0 Hz, 1H, H--3); 4.47 (s, 1H, α-CH); 4.35 (d, $J_{1,2}$ = 9.4 Hz, 1H, H-1); 4.10 (m, 2H, H-5, H-6); 3.88 (m, 2H, -OCH_2-); 3.81 (s, 3H, -OCH_3); 3.77 (s, 3H, -OCH_3); 3.52 (m, 1H, H-6'); 3.11 (m, 1H, -CH_2-N-); 2.74 (m, 1H, -CH_2-); 2.55 (m, 1H, -CH_2-); 1.23-1.07 (m, 39H, Piv-CH_3-+CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.13, 177.10, 176.6, 172.7 (C=O); 148.2, 147.2)arom. C-O); 123.9 (arom. $C_{quart.}$); 111.6, 109.1 (arom. C); 92.9 (C-1); 71.8, 71.6 (C-3, C-5); 67.0, 65.4 (C-2, C-4); 63.3 (α-C); 60.9 (C-6); 60.6 (-OCH_2-); 55.9, 55.7 (-OCH_3); 39.2, 39.1, 38.6 (Piv-Cquart.); 28.0 (-CH_2-); 27.2, 27.1, 27.0, 26.9 (Piv-CH_3); 14.18 (-CH_3).

1-(α,α-Dimethoxybenzyl)-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 3h

Compound **3h** was synthesized according to the procedure for **3a** starting from *N*-(α,α-dimethoxy)phenylmethylene-2-(3,4-dimethoxyphenyl)ethylamine **1h** (0.34 g, 1.0 mmol) and 2,6-lutidine (0.35 mL, 3.0 mmol) in CH_2Cl_2 (10 mL) cooled to -40 °C. After addition of AgOTf (0.5 g,

1.5 mmol) the mixture was stirred for 48 h. For work-up, see **3a**. Yield: 253 mg (40%), de = 83%, colourless solid; mp 92-94 °C. Anal. Calcd for $C_{46}H_{67}NO_{13}$ (842.1): C 65.61, H 8.02, N 1.66. Found: C 65.59, H 8.09, N 1.60.

The (*S*)-diastereomer was separated by preparative HPLC (column B) in MeOH/water 9:1: $[\alpha]_D^{22}$ -32.3 (c 1, $CHCl_3$); R_t = 13.89 min. (R_t of (*R*)-diastereomer = 12.41 min).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16 (m, 5H, arom.); 6.94 (s, 1H, arom.); 6.24 (s, 1H, arom.) 5.57 (t, $J_{2,3}$ = 9.8 Hz, $J_{2,1}$ = 9.4 Hz, 1H, H-2); 5.30 (d, $J_{4,3}$ = 3.1 Hz, 1H, H-4); 5.13 (dd, $J_{3,2}$ = 9.8 Hz, 1H, H-3); 4.73 (d, $J_{1,2}$ = 9.4 Hz, 1H, H-1); 4.44 (s, 1H, α-CH); 3.85 (s, 3H, -OCH_3); 3.82 (m, 3H, H-5, H-6); 3.77 (s, 3H, -OCH_3); 3.34 (s, 3H, -OCH_3); 3.17 (s, 3H, -OCH_3); 2.78 (m, 1H, -CH_2-N-); 2.57 (m, 1H, -CH_2-N-); 2.21 (m, 1H, -CH_2-); 1.39 (m, 1H, -CH_2-); 1.30-1.09 (4s, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.5, 177.2, 176.7 (C=O); 147.5, 145.9 (arom. C-O); 138.0 (arom. C_{ipso}); 130.7 (arom.C_{ipso}); 128.5, 127.5, 126.7 (arom. C); 126.3 (arom. C_{ipso}); 113.0, 109.9 (arom. C); 105.4 ($C(OCH_3)_2$); 94.8 (C-1); 73.3, 71.7 (C-3, C.5); 67.7 (α-C); 65.9, 63.2 (C-2, C-4); 61.9 (C-6); 55.8, 55.6, 49.3, 49.1 (-OCH_3); 39.7 (-CH_2-); 39.0, 38.8, 38.6 (Piv-$C_{quart.}$); 27.7 (-CH_2-); 27.4, 27.2, 27.0, 26.9 (Piv-CH_3).

1-(2-Phenyl-1,3-dithiolan-2-yl)-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5a

1-Dimethoxybenzyltetrahydroisoquinolinone **3h** (*S/R* mixture, 83% de, 253mg, 0.3 mmol), ethane-1,2-dithiol (0.02 mL, 0.33 mmol) and dry $MgBr_2$ (184 mg, 0.63 mmol) in Et_2O (5 mL) were stirred for 20 h. The solution was diluted with Et_2O (20 mL) and washed with water. After drying with Na_2SO_4 and evaporation of the solvent, the product **5a** was purified by column chromatography in light petroleum/EtOAc (10:1).Yield: 109 mg (42%); de = 93%; colorless solid; mp 107-110 °C; R_f = 0.36 (light petroleum/EtOAc 4:1). Anal. Calcd for $C_{46}H_{65}NO_{11}S_2$ (872.2): C 63.35, H 7.51, N 1.61, S 7.35. Found: C 63.33, H 7.40, N 1.61, S 7.38.

The (*S*)-diastereomer was separated by preparative HPLC (column B) in MeCN/water 9:1). R_t = 21.32 min (R_t of (*R*)-diastereomer = 20.20 min). $[\alpha]_D^{22}$ +48.0 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.32-7.0 (m, 6H, arom.); 6.29 (s, 1H, arom.); 5.50 (t, $J_{2,1}$ = 9.3 Hz, 1H, H-2); 5.27 (d, $J_{4,3}$ = 3.1 Hz, 1H, H-4); 5.02 (dd, $J_{3,4}$ = 3.1 Hz, $J_{3,2}$ = 9.8 Hz, 1H, H-3); 4.85 (s, 1H, α-CH); 4.83 (d, $J_{1,2}$ = 9.3 Hz, 1H, H-1); 3.88 (s, 3H, -OCH_3); 3.84 (m, 3H, H-5, H-6); 3.70 (s, 3H, -OCH_3); 3.23-2.78 (m, 6H, -CH_2-N, -CH_2-S); 1.33-1.09 (4s, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.9, 177.5, 177.4, 176,7 (C=O); 147.9, 156.2 (arom. C_{ipso}); 131.0 (arom. C_{ipso}); 129.8, 127.1, 126.7 (arom, C); 127.0 (arom. $C_{quart.}$); 112.3, 109.8 (arom. C); 94.6 (C-1); 84.1 (-S-C-S-); 73.2, 72.4 (C-3, C-5); 71.7 (α-C); 67.5, 66.3 (C-2, C-4); 61.6 (C-6); 55.9, 55.7 (-OCH_3); 40.7, 39.1 (-CH_2-); 39.0, 38.8, 38.7, 37.9 (Piv-$C_{quart.}$); 27.4 (-CH_2-); 27.6, 27.2, 27.1, 26.9 (Piv-CH_3).

1(*R*)-Benzyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline 5b

To 1-dithiolanylbenzyltetrahydroisoquinoline **5a** (109 mg, 0.125 mmol) in dry EtOH (10 mL) Raney-nickel (20 mg) was added. The mixture was stirred under hydrogen atmosphere for 2 d. After filtration and evaporation of the solvent, the product **5b** was purified by column chromatography in light petroleum/EtOAc (10:1). The diastereomeric excess was measured by analytical HPLC (column B, MeOH/water 85:15 to 100:0). Yield: 74 mg (76%), de >95%; colorless solid, mp 85°C; R_f = 0.40 (light petroleum/EtOAc 4:1), R_t = 23.50 min. $[\alpha]_D^{22}$ -23.3 (c 1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.19 (m, 3H, arom.); 6.99 (d, J = 8.5 Hz, 2H, arom.); 6.49 (s, 1H, arom.); 5.62 (m, $J_{2,3}$ = 9.8 Hz, 1H, H-2); 5.60 (s, 1H, arom.); 5.37 (d, $J_{3,4}$ = 2.9 Hz, 1H, H-4); 5.14 (dd, $J_{3,4}$ = 2.9 Hz, $J_{3,2}$ = 9.8 Hz, 1H, H-3); 4.47 (d, $J_{1,2}$ = 9.3 Hz, 1H, H-1); 4.13 (m, 1H, α-H); 4.02-3.85 (m, 3H, H-5,6,6'); 3.77 (s, 3H, -OCH_3); 3.30 (s, 3H, -OCH_3); 3.24 (m, 2H, -CH_2-N, Bn-CH_2-); 2.99 (m, 1H, -CH_2-N-); 2.74-2.63 (m, 3H, -CH_2-Ph, Bn-CH_2-); 1.25-0.92 (4s, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHZ, $CDCl_3$): δ = 177.8, 177.3, 177.2, 176.8 (Piv-C=O); 147.0, 145.6, 139.6 (arom. C_{ipso}); 129.9 (arom. C); 129.7 (arom $C_{quart.}$); 128.2 (arom. C); 128.1 (arom C_{ipso}); 126.1, 110.9, 110.7 (arom. C); 93.7 (C-1); 72.4, 71.9, (C-3, C-5); 67.5, 65.3 (C-2, C-4); 61.5 (α-C); 61.3 (C-6); 55.7, 55.1 (-OCH_3); 45.2, 41.2 (-CH_2-); 39.1, 38.8, 38.7 (Piv-$C_{quart.}$); 29.1 (-CH_2-); 27.4, 27.2, 27.1, 27.0 (Piv-CH_3).

Anal. Calcd for $C_{44}H_{62}NO_{11}$ (781.0); C 67.67, H 8.00, N 1.79. Found: C 67.65, H 7.99; N 1.81.

1-(*R*)-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 6a

N-Galactosylated 1-phenyltetrahydroisoquinoline **3a** (580 g, 0.76 mmol) was stirred in MeOH (13 mL) and aq. 1N HCl (1.3 mL) at room temperature for 20 h. After concentration of the solution in vacuo, CH_2Cl_2 (50 mL) and water (50 mL) were added. The mixture was stirred for 15 min. The aqueous layer was separated and washed three times with CH_2Cl_2 (30 mL each). To the aqueous solution sat. aq. $NaHCO_3$ was added (pH 12). The alkaline solution was extracted with CH_2Cl_2 (3 times 50 mL). The combined organic solutions were dried with $MgSO_4$, and the solvent was evaporated in vacuo. Yield: 203 mg (99%); colorless crystalline solid, mp 94 °C, $[\alpha]_D^{22}$ +20.4 (c 1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.32-7.24 (5s, 5H, arom.)6.64 (s, 1H, arom.); 6.25 (s, 1H, arom.); 5.05 (s, 1H, α-CH); 3.87 (s, 3H, -OCH_3); 3.63 (s, 3H, -OCH_3); 3.27-2.68 (m, 4H, -CH_2-); 1.95 (s, 1H, NH).

1(*R/S*)-(3,4-Dimethyoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5b

(Norcryptostylin) was obtained in analogous procedure from **3b** (a charge formed by promotion of the galactosylation with $Hg(CN)_2$ was used, de 30%, 65 mg, 0.079 mmol). Yield: 22 mg (85%), colorless

crystalline solid, mp 110-113 °C; $[\alpha]_D^{22}$ +9.3 (c 1, $CHCl_3$), lit.,[11b] mp 114-115 °C, $[\alpha]_D^{25}$ +33.5 (c 1, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.80-6.69 (5s, 5H. arom.); 3.97 (s, 1H, α-H); 3.84-3.62 (4s, 12H, $-OCH_3$); 2.96-265 (m, 4H, $-CH_2-$); 1.95 (s, 1H, NH).

Glycosylation-induced addition of dialkylzinc to 3,4-dihydroisoquinoline - General procedure

3,4-Dihydroisoquinoline[19] **7** (0.1 g, 0.75 mmol), galactosyl bromide **2** (0.45 g, 0.8 mmol) and 2,6-lutidine (0.18 mL, 1.6 mmol) in CH_2Cl_2 (10 mL) were stirred at 0 °C. AgOTf (0.5 g, 1.6 mmol) was added and the mixture stirred without cooling for 12h. Additional 10 mL of dry CH_2Cl_2 were added and the mixture cooled to -20 °C. To this mixture, 5 mmol of the dialkylzinc reagent **8** were added. After stirring for 3 d, the mixture was filtered, the solvent evaporated in vacuo, and the remaining residue was purified by flash-chromatography in light petroleum/EtOAc (15:1).

1(*S*)-Ethyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-1,2,3,4-tetrahydroisoquinoline 9a

was synthesized accordingly to the general procedure using 5 mL of diethylzinc (1 M in *n*-heptane). Yield: 374 mg (77%); colorless solid; mp 75-78 °C; R_f = 0.61 (light petroleum/EtOAc 4:1); R_t (column B) = 21.9 min (MeCN/water 93:7 → (40 min)100:0; $[\alpha]_D^{22}$ -3.4 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.98 (m, 4H, arom.); 5.39 (t, $J_{2,3}$ = 9.4 Hz, 1H, H-2); 5.35 (d, $J_{4,3}$ = 3.2 Hz, 1H, H-4); 5.10 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 10.0 Hz, 1H, H-3); 4.31 (d, $J_{1,2}$ = 9.1 Hz, 1H, H-1); 3.90 (m, 3H, H-5,6,6'); 3.73 (t, J = 6.2 Hz, 1H, α-H); 3.21 (m, 1H, $-CH_2$-Ph); 3,06 (m, 1H, $-CH_2$-Ph); 2.83 (m, 1H, $-CH_2$-N); 2.60 (m, 1H, $-CH_2$-N); 1.91 (m, 1H, β-CH_2-); 1.69 (m, 1H, β-CH_2-); 1.25-0.89 (m, 39H, Piv-CH_3, $-CH_3$).

^{13}C-NMR (100.6 MHz $CDCl_3$): δ = 177.7, 177.0 176.9, 176.5 (Piv-C=O); 139.4, 134.6 (arom. C_{ipso}); 128.6, 126.6, 125.7, 124.6 (arom. C); 93.4 (C-1); 71.9, 71.7 (C-3, C-5); 67.4, 65.8 (C-2, C-4); 63.0 (α-C); 62.0 (C-6); 38.9 ($-CH_2$-N); 38.7, 38.6, 38.5, 38.4 (Piv-$C_{quart.}$); 28.7, 28.3 ($-CH_2-$); 27.1, 26.94, 26.91, 26.7 (Piv-CH_3); 11.8 ($-CH_3$).

Anal. Calcd for $C_{37}H_{57}NO_9$ (659.9): C 67.34, H 8.71, N 2.17. Found: C 66.90, H 8.76, N 2.08.

1(*S*)-Methyl-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-1,2,3,4-tetrahydroisoquinoline 9b

was synthesized according to the general procedure using 50 mL of dimethylzinc (1 M in *n*-heptane). Yield: 352 mg (73%); colorless solid; mp 80-81 °C; R_f = 0.61 (light petroleum/EtOAc 4:1); R_t = 15.92 min (conditions as given for **9a**); $[\alpha]_D^{22}$ -2.2 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.03 (m, 3H, arom.); 6.96 (m, 1H, arom.); 5.40 (t, $J_{2,3}$ = 10.0 Hz, $J_{2,1}$ = 9.4 Hz, 1H, H-2); 5.37 (d, $J_{4,3}$ = 3.2 Hz, 1H, H-4); 5.12 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3.2}$ = 10.0 Hz, 1H, H-3); 4.25 (d,

$J_{1,2}$ = 9.1 Hz, 1H, H-1); 4.05 (q, J = 6.8 Hz, 1H, α-CH); 3.95 (m, 3H, H-5,6,6); 3.05 (m, 2H, -CH_2-Ph); 2.80 (m, 1H, -CH_2-N); 1.36 (d, J = 6.8 Hz, 3H, CH_3); 1.25-0.93 (m, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.1, 176.7 (Piv-C=O); 140.5, 134.4 (arom. C_{ipso}); 128.7, 126.3, 125.7, 125.1 (arom, C); 93.2 (C-1); 72.0, 71.7 (C-3, C-5); 67.5, 65.5 (C-2, C-4); 61.1 (C-6); 57.5 (α-C); 39.0, 38.62, 38.57, 38.51 (Piv-$C_{quart.}$); 36.6 (-N-CH_2-); 28.9 (-CH_2-); 27.2, 27.01, 26.95, 26.8 (Piv-CH_3); 21.0 (β-CH_3).

Anal. Calcd for $C_{36}H_{55}NO_9$ (645.8): C 66.95, H 8.58, N 2.17. Found: C 66.78, H 8.65, N 2.09.

1(*S*)-(4-Methoxy-benzyl)-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-1,2,3,4-tetrahydroisoquinoline 9c

was synthesized according to the general procedure. Di-(4-methoxylbenzyl)zinc (**8c**) solution in THF was freshly prepared from 4-methoxybenzyl chloride (1.4 mL, 10 mmol) and magnesium (0.25 g, 10 mmol) in THF (25 mL). The solution of the formed Grignard compound was given to dry zinc chloride (0.78 g, 5 mmol) and the mixture stirred for 14 h. The obtained solution was reacted with **7** as described. Yield: 385 mg (68%); colorless solid; mp 87-89 °C; R_f = 0.58 (light petroleum/EtOAc 4:1) R_t = 16.4 min (conditions, see **9a**); $[\alpha]_D^{22}$ +16.4 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.98 (m, 4H, arom.); 6.82-674 (m, 3H, arom.); 6.28 (d, J = 7.6 Hz, 1H, arom.); 5.43 (t, $J_{2,3}$ = 10.0 Hz, $J_{2,1}$ = 9.4 Hz, 1H, H-2); 5.33 (d, $J_{4,3}$ = 2.9 Hz, 1H, H-4); 5.08 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 10.3 Hz, 1H, H-3); 4.26 (d, $J_{2,1}$ = 9.1 Hz, 1H, H-1); 4.09 (dd, J = 4.7 Hz, 1H, α-CH); 3.94 (m, $J_{6,5}$ = 7.0 Hz, 1H, H-6); 3.85 (m, $J_{6,5}$ = 7.0 Hz, 1H, H-6'); 3.76 (s, 3H, -OCH_3); 3.72 (t, $J_{5,6}$ = 7.0 HZ, 1H, H-5); 3.20 (m, 2H, -CH_2-N-, Bn-CH_2-); 3.08 (q, J = 6.5 HZ, 1H, -CH_2-N-); 2.88-2.79 (m, 2H, -CH_2-Ph, Bn-CH_2-); 2.60 (m, 1H, -CH_2-Ph), 1.24-0.89 (4s, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.2, 177.1, 176.7 (Piv-C=O); 158.0, 138.2, 134.5, 131.8 (arom. C_{ipso}): 130.6, 128.6, 127.2, 125.9, 124.3, 113.5 (arom. C); 93.4 (C-1); 71.8, 71.7 (C-3, C-5); 67.4, 65.8 (C-2, C-4); 63.9 (α-C); 61.7 (C-6); 55.1 (-OCH_3); 41.5, 39.0 (CH_2-CH_2-N); 38.7, 38.6, 38.5, 38.4 (Piv-$C_{quart.}$); 28.5 (-CH_2-): 27.2, 27.0, 26.8 (Piv.CH_3).

Anal. Calcd for $C_{43}H_{61}NO_{10}$ (752.0): C 68.68, H 8.18, N 1.86. Found: C 68.55, H 8.19, N 1.76.

1(*S*)-(4-Methoxy-benyzl)-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 11

The synthesis of **11** was carried out according to the general procedure, however using 6,7-dimethoxy-3,4-dihydroisoquinoline[20] **10** (0.14 g, 0.75 mmol) as the imine compound. After a reaction time of 3 d, filtration and evaporation of the solvents, the product **11** was purified by flash-chromatography in light petroleum/EtOAc (10:1) and, subsequently, by preparative HPLC (column B) using acetonitrile/water 93:7 (within 90 min to 100:0). Yield: 429 mg (70%); colorless solid; mp

91-94 °C; R_f = 0.33 (light petroleum/EtOAc 4:1); R_t = 34.4 min (MeCN/water 70:30, within 40 min to 100:0 (column B); $[\alpha]_D^{22}$ +27.6 (c 1, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, J = 8.5 Hz, 2H, arom.); 6.75 (d, J = 8.5 Hz, 2H, arom.); 6.45 (s, 1H, arom.); 5.52 (s, 1H, arom.); 5.44 (t, $J_{2,3}$ = 9.7 Hz, 1H, H-2,); 5.33 (d, $J_{4,4}$ = 3.2 Hz, 1H, H-4); 5.11 (dd, $J_{3,4}$ = 3.2 Hz, $J_{3,2}$ = 9.7 Hz, 1H, H-3); 4.30 (d, $J_{1,2}$ = 8.8 Hz, 1H, H-1); 3.95 (dd, J = 1.8 Hz, 1H, α-CH); 3.90 (m, $J_{6,5}$ = 7.0 Hz, 2H, H-6,6'); 3.82 (t, $J_{5,6}$ = 6.9 Hz, 1H, H-5); 3.75 (s, 3H, -OCH_3); 3.71 (s, 3H, -OCH_3); 3.32 (s, 3H, -OCH_3); 3.26-3.14 (m, 2H, -CH_2-N-, Bn-CH_2-); 3.07 (m, 1H, CH_2-N-); 2.83-2.71 (m, 2H, -CH_2-Ph, Bn-CH_2-); 2.48 (m, 1H, -CH_2-Ph); 1.22-0.91 (4s, 36H, Piv-CH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 177.8, 177.1, 176.6 (Piv-C=O); 158.0, 147.1, 145.3 (arom, C_{ipso}); 130.9 (arom. C): 129.9, 126.3 (arom. C_{ipso}); 113.6, 111.1, 110.6 (arom. C); 93.6 (C-1); 71.9, 71.7 (C-3, C-5); 67.4, 65.6 (C-2, C-4); 63.2 (α-C); 61.8 (C-6); 55.6, 55.2, 55.1 (-OCH_3); 41.3 (-CH_2-N); 39.0, 38.6, 38.5 (Piv-$C_{quart.}$); 31.8, 28.2, (-CH_2-); 27.16, 27.02, 26.98, 26.83 (Piv-CH_3).

Anal. Calcd for $C_{45}H_{65}NO_{12}$ (812.0): C 66.56, H 8.07, N 1.73. Found: C 66.16, H 7.99, N 1.66.

1(*S*)-(4-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 12

N-Galactosylated tetrahydroisoquinoline **11** (100 mg, 0.123 mmol) was stirred in MeOH (50 mL) and 1N HCl (10 mL) at rt for 2 d. The solution was concentrated in vacuo, diluted with water (50 mL), washed with dichloromethane (2x50 mL), and the aqueous solution was evaporated in vacuo. The remaining hydrochloride was stirred with 1M aq. K_2CO_3 solution and the free amine **12** extracted with CH_2Cl_2. Yield: 24 mg (76%); slightly yellow solid; mp 92-94 °C, $[\alpha]_D^{22}$ -19.9 (c 1, $CHCl_3$); lit.,[16] $[\alpha]_D^{21}$ -19.1 (c 1.37, $CHCl_3$).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.04 (d, J = 8.3 Hz, 2H, arom.); 6.84 (d, J = 8.3 Hz, 2H. arom.); 6.74 (s, 1H, arom.); 6.34 (s, 1H, arom.); 4.56 (t, J = 7.8 Hz, 1H, α-CH); 3.68 (s, 6H, -OCH_3); 3.51 (s, 3H, -OCH_3); 3.45-3.35 (m, 1H, -CH_2-N-); 3.29-3.12 (m, 2H, -CH_2-N-, Bn-CH_2-); 3.00-2.91 (m, 3H, -CH_2-Ph, Bn-CH_2-).

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