STEREOSELECTIVE SYNTHESIS OF 2-SUBSTITUTED PYRROLIDINES

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

Using *O*-pivaloyl protected D-galactopyranosylamine and D-arabinopyranosylamine, (*S*) or (*R*) configured α-substituted homoallylamines are synthesized with high diastereoselectivity by reaction of the corresponding aldimines with allyltributylstannane. Electrophile-induced *endo*-trig-cyclization of these *N*-glycosylhomoallylamines gave the 2-substituted pyrrolidines of high diastereomeric purity.
Key words: Carbohydrates; Chiral auxiliaries; Homoallylamines; Electrophile-induced cyclization; Pyrrolidines; Nornicotine; Alkaloids; Enantioselective reactions.

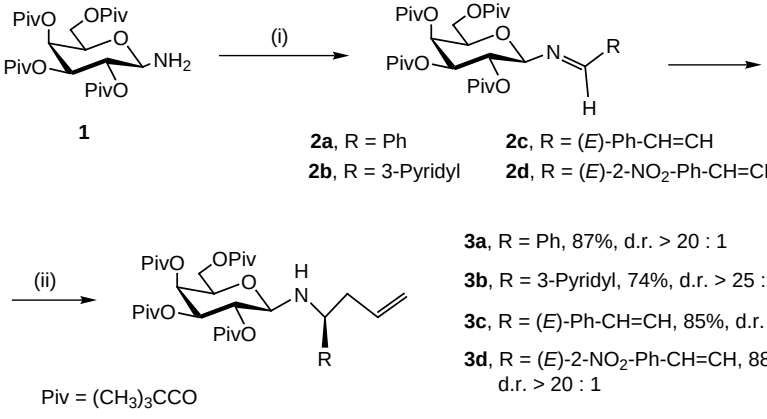
Stereoselective syntheses of chiral nitrogen heterocycles are of particular interest for the organic chemistry of drug design and development[1]. Alkaloids constitute an important class of biologically active natural products[2]. They are considered promising lead structures for the development of drugs. A number of methods for the synthesis of enantiopure nitrogen heterocycles have been reported during the past decade. Some of them are based on ex-chiral-pool strategies using enantiomerically pure starting materials[3]. Other concepts include separations of enantiomers[4]. Auxiliary-based stereoselective syntheses of alkaloids have been performed using α-phenylalkylamines[5], phenylglycinol-[6], camphor-[7] or proline-derived[8] auxiliaries. Asymmetric Mannich reactions have a great potential for the synthesis of chiral heterocycles[9]. Using glycosylamines as the chiral auxiliaries[10] enantiopure piperidine alkaloids have been synthesized by means of asymmetric Mannich reactions with excellent diastereoselectivity[11,12]. Here we report on the stereoselective synthesis of chiral pyrrolidines based on the stereoselective addition of allyltributylstannane to *N*-glycosylimines giving *N*-glycosylhomoallylamines[13,14].

Asymmetric Synthesis of 1-Substituted Homoallylamines

As has been in principle described in previous articles[13,14], (*S*)-1-aryl substituted homoallylamines are synthesized from imines derived from 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**).

The Schiff bases **2** are either formed by reaction of **1** with the aldehyde (benzaldehyde) in propan-2-ol in the presence of catalytic amounts of acetic acid or pyridine-3-carbaldehyde in pentane in the presence of molecular sieves 4Å. The imines **2** can be isolated or directly used for further conversion.

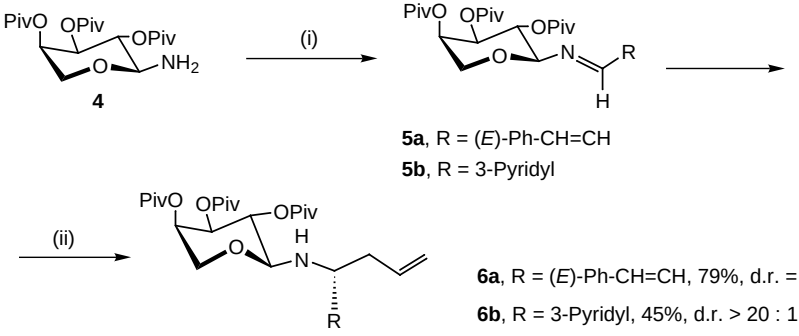
In contrast to earlier work[13], the allylation of imines **2** has been carried out using allyltributylstannane instead of allyltrimethylsilane. To imine **2** and tin tetrachloride (2.2 equivalents) in tetrahydrofuran at –78 °C, allyltributylstannane (1.2 equivalents) is added. The reaction mixture is slowly warmed up to room temperature. After hydrolysis, the corresponding homoallylamines **3** are isolated in high yields and excellent ratios of diastereomers (Scheme 1).



SCHEME 1

For stereoselective reactions of imines giving chiral products of the opposite configuration in comparison with those obtained with the galactosylamine **1**, we successfully used 2,3,4-tri-*O*-pivaloyl-α-D-arabinosylamine[15] (**4**). However, the application of this pseudo-enantiomer to **1** was not successful in the case of the tin tetrachloride-catalyzed allylations using allylsilane or allylstannane derivatives[13b]. Just recently, we found the reason for this astonishing difference in the reactions of imines derived from **1**

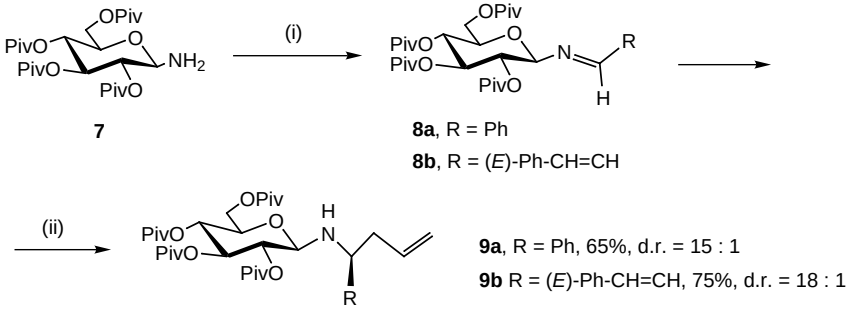
and **4**. In the presence of strong Lewis acids like tin tetrachloride, the *N*-arabinosylimines **5** anomerize more rapidly than the *N*-galactosyl analogues. The β-anomers of **5** (with axial C–N bond) do not react with the allylsilane or allylstannane, but hydrolyze during work-up. This undesired anomerization can be prevented if the reaction temperature in the Lewis acid-catalyzed reactions of the *N*-arabinosylimines with allyltributylstannane is kept below 10 °C (Scheme 2).



(i) R-CHO; (ii) CH_2=$CHCH_2SnBu_3$, $SnCl_4$, THF, -78 °C→ <10 °C

SCHEME 2

Under these conditions, the (*R*)-homoallylamines **6** are obtained with excellent diastereoselectivity. Schiff bases of 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**7**) with allyltributylstannane and tin tetrachloride give (*S*)-homoallylamines **9** like the galactosyl analogues albeit with slightly lower diastereofacial differentiation (Scheme 3).



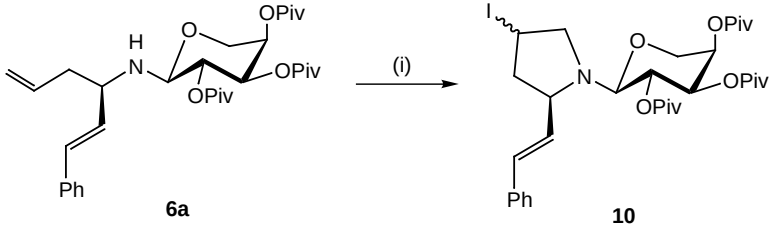
(i) R-CHO; (ii) CH_2=$CHCH_2SnBu_3$, $SnCl_4$, THF, -78 °C→ r.t.

SCHEME 3

Therefore, *N*-galactosylhomoallylamines are preferentially used for further conversion, *e.g.* for the formation of chiral pyrrolidines.

α-*Substituted Pyrrolidines*

Electrophile-induced cyclization of chiral homoallylamines is useful for the synthesis of pyrrolidines. Acid-catalyzed cyclization of 1,5-dienes was successfully applied to the formation of five- or six-membered carbocyclic rings[16]. Unfortunately, treatment of homoallylamine **3a** with formic acid or acetic acid in dichloromethane results in the hydrolytic cleavage of the *N*-glycosidic bond rather than in an acid-catalyzed cyclization. In contrast, the *N*-arabinosylhomoallyamine **6a** reacts with 1.1 equivalents of iodine in dichloromethane–diethyl ether (2 : 1) to form the (*R*)-2-styrylpyrrolidine **10** in high yield (Scheme 4).



6a **10**

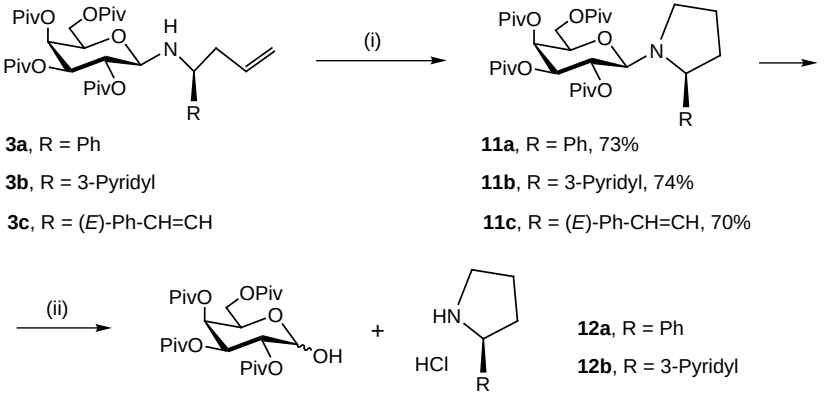
(i) I_2, CH_2CH_2/Et_2O, 63%

SCHEME 4

Stereodifferentiation in the formation of the iodonium intermediate is only low (1.5 : 1). This is considered less important because the iodine is reductively removed during subsequent conversions.

A more general and efficient electrophile-induced cyclization is achieved with mercury salts as initiators[17]. Application of mercury acetate as an electrophile results in varying yields of the cyclized and open-chain products. However, cyclization of the *N*-galactosylhomoallylamines **3** with mercury(II) trifluoroacetate in acetonitrile at 0 °C and subsequent reductive demercuration gives the (*S*)-pyrrolidines **11** in high yield (Scheme 5).

The synthesized chiral heterocycles are readily detached from the carbohydrate auxiliary by treatment of the *N*-galactosyl derivatives **11** with 0.1 M HCl in aqueous methanol to give hydrochlorides **12** of the pyrrolidines almost quantitatively. For confirmation of their absolute configuration, the 2-phenyl derivative **12a** and the 2-(3-pyridyl) derivative **12b** are



3a, R = Ph

3b, R = 3-Pyridyl

3c, R = (*E*)-Ph-CH=CH

11a, R = Ph, 73%

11b, R = 3-Pyridyl, 74%

11c, R = (*E*)-Ph-CH=CH, 70%

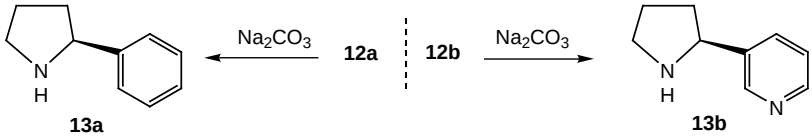
12a, R = Ph

12b, R = 3-Pyridyl

(i) 1. $Hg(OOCCF_3)_2$, CH_3CN; 2. $NaBH_3$, NaOH, H_2O; (ii) 0.1 M HCl/aq. MeOH

SCHEME 5

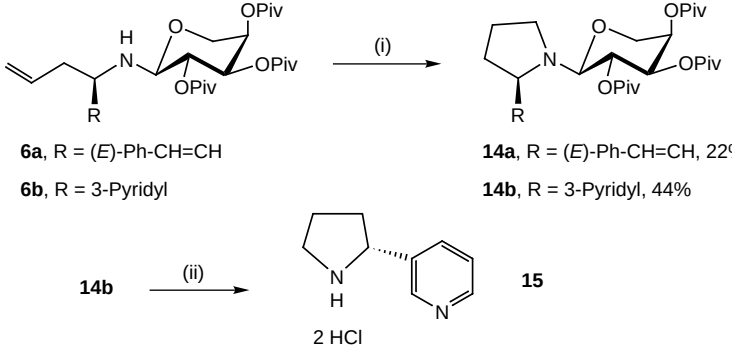
deprotonated to give enantiomerically pure (*S*)-(–)-2-phenylpyrrolidine[18] **(13a)** and (*S*)-(–)-nornicotine[19] (**13b**) (Scheme 6).



13a **13b**

SCHEME 6

2-Substituted pyrrolidines of the opposite configuration are obtained from the *N*-(D-arabinopyranosyl)homoallylamines **6** *via* mercury(II) trifluoroacetate-induced cyclization and subsequent reductive removal of the mercury substituent (Scheme 7).



6a, R = (*E*)-Ph-CH=CH

6b, R = 3-Pyridyl

14a, R = (*E*)-Ph-CH=CH, 22%

14b, R = 3-Pyridyl, 44%

(i) 1. $Hg(OOCCF_3)_2$, CH_3CN; 2. $NaBH_3$, NaOH, H_2O; (ii) 0.1 M HCl/aq. MeOH

SCHEME 7

In both cases, the ratio of diastereomers of **14** is excellent ($R : S > 20 : 1$) according to 400 MHz ^{1}H NMR spectroscopic analysis. Detachment of (*R*)-nornicotine dihydrochloride (**15**) from **14b** is achieved using dilute hydrogen chloride in aqueous methanol. Its opposite enantiomeric configuration compared to **12b** is confirmed by its optical rotation value. The yields of the electrophile-induced cyclization in the *N*-arabinosyl series are lower than those in the *N*-galactosyl series. This is obviously due to the fact, that the *N*-arabinosylhomoallylamines **6** are more prone to anomerization. Their β-anomers (with axial anomeric C–N bond) react more slowly in the electrophile-induced formation of the five-membered ring.

Nevertheless, the combination of the Lewis acid-catalyzed addition of allyltributylstannane to either *N*-(D-galactosyl)- (**2**) or *N*-(D-arabinosyl)imines **5** with the subsequent electrophile-induced *endo*-trig-cyclization of the *N*-glycosylhomoallylamines provides an efficient and highly stereoselective access to 2-substituted pyrrolidines of both enantiomeric configurations.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WT-200 (200 MHz ^{1}H NMR and 50.3 MHz ^{13}C NMR) and a Bruker AM 400 (400 MHz ^{1}H NMR and 100.6 MHz ^{13}C NMR) NMR spectrometer. Chemical shifts (δ) are given in ppm relative to the signal of tetramethylsilane, coupling constants (*J*) are given in Hz. Mass spectra were recorded on a FAB/FD mass spectrometer Finnigan MAT 95. Analytical HPLC was carried out in the reverse phase mode using an LKB 2150 unit with diode array detection (190–370 nm) on Eurospher 100/C18 (5 mμ) from Knauer (Berlin, Germany). Acetonitrile–water mixtures served as eluents. Thin-layer chromatography was carried out using silica gel plates of 60F 254, preparative column chromatography was performed on silica gel 60 (0.06–0.2 mm), flash chromatography was carried out using silica gel (0.04–0.063 mm) all from Merck (Darmstadt, Germany).

N-Alkylidene-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamines[20] **2** and the *N*-alkylidene-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamines[21] **5** have been prepared as previously described.

N-(3-Pyridylmethylidene)-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[20] (**2b**)

Yield 95%, amorphous solid, R_F 0.7 (petroleum ether–ethyl acetate 13 : 7), $[\alpha]_D^{22}$ +8.3 (*c* 1, $CHCl_3$), the compound contains 15% of the α-anomer.

N-[3-(2-Nitrophenyl)prop-2-en-1-ylidene]-2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[20] (**2d**)

Yield 74%, yellowish crystals, m.p. 111–114 °C, $[\alpha]_D^{22}$ –16.7 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (s, 9 H, $C(CH_3)_3$); 1.11 (s, 9 H, $C(CH_3)_3$); 1.15 (s, 9 H, $C(CH_3)_3$); 1.25 (s, 9 H, $C(CH_3)_3$); 4.05 (dd, 1 H, $J_{6a,6b}$ = 10.0, $J_{6a,5}$ = 7.4, H-6a); 4.10 (dd, 1 H, $J_{5,6a}$ = 7.2, $J_{5,6b}$ = 5.6, H-5); 4.22 (dd, $J_{6b.6a}$ = 10.0, $J_{6b,5}$ = 5.5, H-6b); 4.69 (d, 1 H, $J_{1,2}$ = 8.1, H-1); 5.21 (dd, 1 H, $J_{3,2}$ = 10.3, $J_{3,4}$ = 3.0, H-3); 5.27 (dd, 1 H, $J_{2,3}$ = 10.3, $J_{2,1}$ = 8.2, H-2); 5.47 (d, 1 H, $J_{4,3}$ = 2.9, H-4);

6.81 (dd, 1 H, $J_{1',1'}$ = 15.8, $J_{2',3'}$ = 8.8, H-2′); 7.53 (d, 1 H, $J_{1',2'}$ = 15.8, H-1′); 7.49 and 7.43 (2 m, 3 H, H-4″, H-5″, H-6″); 8.00 (d, 1 H, $J_{3'',4''}$ = 8.0, H-3″); 8.18 (d, 1 H, $J_{3',2'}$ = 8.8, H-3′). ^{13}C NMR (100.6 MHz, $CDCl_3$): 94.6 (C-1). For $C_{35}H_{50}N_2O_{11}$ (674.7) calculated: 62.30% C, 7.47% H, 4.15% N; found: 62.50% C, 7.35% H, 3.99% N.

N-(3-Phenylprop-2-en-1-ylidene)-2,3,4-tri-*O*-pivaloyl-α-D-arabinosylamine[21] (**5a**)

Yield 48%, crystals, m.p. 135 °C, $[\alpha]_D^{22}$ +4.3 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.10 (s, 9 H, $C(CH_3)_3$); 1.12 (s, 9 H, $C(CH_3)_3$); 1.26 (s, 9 H, $C(CH_3)_3$); 3.6–3.7 (d, 1 H, $J_{5b,5a}$ = 12.46, H-5b); 4.04–4.15 (dd, 1 H, $J_{5a,4}$ = 1.96, H-5a); 4.5–4.55 (d, 1 H, $J_{1,2}$ = 8.05, H-1); 5.1–5.4 (m, 3 H, H-2, H-3, H-4); 6.8–7.0 (m, 2 H, H-1′, H-2′); 7.3–7.5 (m, 5 H, Ph); 8.1–8.1 (d, $J_{3',2'}$ = 8.3, H-3′). ^{13}C NMR (50.3 MHz, $CDCl_3$): 96.0 (C-1). For $C_{33}H_{49}NO_9$ (603.8) calculated: 67.54% C, 8.01% H, 2.71% N; found: 67.05% C, 8.19% H, 2.51% N.

N-(3-Pyridylmethylidene)-2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine[21] (**5b**)

Yield 44%, crystals, m.p. 131 °C, R_F 0.58 (petroleum ether–ethyl acetate 13 : 7), $[\alpha]_D^{22}$ –11.8 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.11 (s, 9 H, $C(CH_3)_3$); 1.13 (s, 9 H, $C(CH_3)_3$); 1.24 (s, 9 H, $C(CH_3)_3$); 3.78–3.85 (d, 1 H, $J_{5b,5a}$ = 13.30, H-5b); 4.08–4.2 (dd, 1 H, $J_{5a,4}$ = 1.71, $J_{5a,5b}$ = 13.30, H-5a); 4.8–5.4 (m, 4 H, H-1, H-2, H-3, H-4); 7.3 (d, 1 H, $J_{4'',5''}$ = 4.98, H-4″); 8.12 (t, 1 H, $J_{5'',6''}$ = 1.95); 8.45 (s, 1 H, H-1′); 8.65 (d, 1 H, $J_{6'',5''}$ = 1.95, H-6″); 8.85 (s, 1 H, H-2″). ^{13}C NMR (50.3 MHz, $CDCl_3$): 93.3 (C-1).

N-Benzylidene-2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**8a**) and
N-(3-Phenylprop-2-en-1-ylidene)-2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**8b**)

The Schiff bases of the 2,3,4,6-tetra-*O*-pivaloyl-β-D-glucopyranosylamine (**7**; m.p. 110 °C, $[\alpha]_D^{22}$ +21.7 (*c* 1, $CHCl_3$)) were prepared as described[20] for the *N*-galactosyl derivatives **2**.

Compound **8a**. Yield 78%, crystals, m.p. 129 °C, $[\alpha]_D^{22}$ –21.3 (*c* 1, $CHCl_3$). The compound contained 8% of the α-anomer. ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (s, 18 H, $C(CH_3)_3$); 1.14 (s, 9 H, $C(CH_3)_3$); 1.19 (s, 9 H, $C(CH_3)_3$); 3.84–3.92 (m, 1 H, $J_{5,6a}$ = 1.76, $J_{5,6b}$ = 5.28, H-5); 4.1–4.2 (dd, 1 H, $J_{6b,5}$ = 5.28, $J_{6b,6a}$ = 12.63, H-6b); 4.21–4.3 (dd, 1 H, $J_{5,6a}$ = 1.76, $J_{6a,6b}$ = 12.62, H-6a); 4.85–4.9 (t, 1 H, $J_{1,2}$ = 9.10, H-1); 4.98–5.02 (dd, 1 H, $J_{2,1}$ = 9.09, H-2); 5.18–5.23 (t, 1 H, $J_{3,4}$ = 9.69, H-3); 5.4–5.5 (t, 1 H, $J_{4,3}$ = 9.69, H-4); 7.3–7.4 and 7.6–7.7 (2 m, 5 H, Ph); 8.3 (s, 1 H, H-1′). ^{13}C NMR (100.6 MHz, $CDCl_3$): 92.3 (C-1). For $C_{33}H_{49}NO_9$ (603.8) calculated: 65.5% C, 8.18% H, 2.32% N; found: 65.68% C, 8.27% H, 2.24% N.

Compound **8b**. Yield 95%, crystals, m.p. 176 °C, $[\alpha]_D^{22}$ –33.9 (*c* 0.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (s, 9 H, $C(CH_3)_3$); 1.11 (s, 9 H, $C(CH_3)_3$); 1.14 (s, 9 H, $C(CH_3)_3$); 1.20 (s, 9 H, $C(CH_3)_3$); 3.83–4.02 (m, 1 H, $J_{5,6a}$ = 2.2, $J_{5,6b}$ = 4.39, H-5); 4.1–4.3 (2 dd, 2 H, $J_{6b,5}$ = $J_{6a,6b}$ = 12.45, $J_{6a,5}$ = 2.2); 4.63–4.72 (d, 1 H, $J_{1,2}$ = 8.79, H-1); 4.09–5.10 (dd, 1 H, $J_{2,1}$ = 8.83, $J_{2,3}$ = 9.27, H-2); 5.18–5.3 (dd, 1 H, $J_{3,2}$ = 9.27, $J_{3,4}$ = 9.53, H-3); 6.8–7.0 (m, 2 H, $J_{2',1'}$ = 8.54, H-2′, H-3′); 7.3–7.5 (m, 5 H, Ph); 8.1 (d, 1 H, $J_{1',2''}$ = 8.54, H-1′). ^{13}C NMR (100.6 MHz, $CDCl_3$): 94.1 (C-1). For $C_{35}H_{51}NO_9$ (629.7) calculated: 66.75% C, 8.16% H, 2.22% N; found: 66.69% C, 8.06% H, 2.26% N.

1-Substituted *N*-Galactosyl- (**3**) and *N*-Glucosylhomoallylamines (**9**). General Procedure

A solution of *N*-galactosylimine **2** or *N*-glucosylimine **8** (2 mmol) in dry tetrahydrofuran (20 ml) was cooled to –78 °C. Tin tetrachloride (4.4 mmol) was added and the mixture stirred for 2.5 h at –78 °C. Allyltributylstannane (2.4 mmol) was then added. After stirring for 1 h at –78 °C, the mixture was slowly heated up to room temperature and hydrolyzed with 2 M aqueous NaOH (10 ml). Diethyl ether (50 ml) was added, the aqueous layer separated and three times extracted with dichloromethane (15 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The remaining oil was purified by flash chromatography.

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-1(S)-amino-1-phenyl-3-butene[22] (**3a**). Flash chromatography in petroleum ether–ethyl acetate (10 : 1), R_F 0.26, yield 87%, colorless amorphous solid, $[\alpha]_D^{22}$ +4.4 (*c* 1, $CHCl_3$). The compound contains 4% of the (*R*)-diastereomer (ref.[22] gives $[\alpha]_D^{22}$ +2.2 (*c* 1.3, $CHCl_3$) for a mixture of diastereomers 11 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): 3.76 (d, 1 H, $J_{1,2}$ = 8.5, H-1); 5.29 (d, 1 H, $J_{4,3}$ = 3.1, H-4). ^{13}C NMR (100.6 MHz, $CDCl_3$): 86.4 (C-1); 117.8 (C-4′); 134.5 (C-3′).

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-1(S)-amino-1-(3-pyridyl)-3-butene[22] (**3b**). Flash chromatography in petroleum ether–ethyl acetate (2 : 1), R_F 0.16 (petroleum ether–ethyl acetate 3 : 1), yield 74%, colorless amorphous solid, $[\alpha]_D^{22}$ –3.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 3.70 (dd, 1 H, $J_{1,NH}$ = 11.1, $J_{1,2}$ = 8.7, H-1); 4.13 (t, 1 H, $J_{1',2'}$ = 6.8, Pyr-CH-N). ^{13}C NMR (100.6 MHz, $CDCl_3$): 86.3 (C-1). The ratio of diastereomers is >25 : 1 according to the ^{1}H NMR spectrum. The compound described in ref.[22] showed a ratio of diastereomers 11 : 1 and $[\alpha]_D^{22}$ +2.2 (*c* 1.0, $CHCl_3$).

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-3(S)-amino-1(E)-phenyl-1,5-hexadiene[22] (**3c**). Yield 91%, R_F 0.33 (petroleum ether–ethyl acetate 10 : 1), colorless amorphous solid, $[\alpha]_D^{22}$ –5.1 (*c* 1.05, $CHCl_3$), ratio of diastereomers 19 : 1 (ref.[22] gives $[\alpha]_D^{22}$ –3.6 (*c* 1.03, $CHCl_3$), ratio of diastereomers 15 : 1).

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-3-(S)-amino-1(E)-(2-nitrophenyl)-1,5-hexadiene (**3d**). Flash chromatography in petroleum ether–ethyl acetate (4 : 1), R_F 0.40, yield 88%, yellowish amorphous solid, $[\alpha]_D^{22}$ –12.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 (s, 9 H, $C(CH_3)_3$); 1.12 (s, 9 H, $C(CH_3)_3$); 1.15 (s, 9 H, $C(CH_3)_3$); 1.23 (s, 9 H, $C(CH_3)_3$); 1.97 (bs, 1 H, NH); 2.25 (m, 2 H, 2 H-4′); 3.75 (dd, 1 H, $J_{3',2'}$ = 8.3, $J_{3',4'}$ = 6.4, H-3′); 3.97 (m, 2 H, H-5, H-6a); 4.13 (dd, 1 H, $J_{6b,6a}$ = 9.7, $J_{6b,5}$ = 5.7, H-6b); 4.18 (d, 1 H, $J_{1,2}$ = 8.8, H-1); 5.06 (m, 3 H, 2 H-6′, H-2); 5.13 (dd, 1 H, $J_{3,2}$ = 10.3, $J_{3,4}$ = 3.3, H-3); 5.39 (d, 1 H, $J_{4,3}$= 3.1, H-4); 5.74 (m, 1 H, 5-5′); 5.75 (dd, 1 H, $J_{2',1'}$ = 15.6, $J_{2',3'}$ = 8.3, H-2′); 6.88 (d, 1 H, $J_{1',2'}$ = 15.6, H-1′); 7.38 (dt, 1 H, $J_{4'',3''} = J_{4'',5''}$ = 8.4, $J_{4'',6''}$ = 1.4, H-4″); 7.47 (dd, 1 H, $J_{6'',5''}$ = 7.8, $J_{6'',4''}$ = 1.2, H-6″); 7.55 (ddd, 1 H, $J_{5'',4''}$ = 8.5, $J_{5'',6''}$ = 7.5, $J_{5'',3''}$ = 1.0, H-5″); 7.93 (dd, 1 H, $J_{3'',4''}$ = 8.2, $J_{5'',3''}$ = 1.0, H-3″). ^{13}C NMR (100.6 MHz, $CDCl_3$): 86.6 (C-1); 147.8 (C-NO_2). Ratio of diastereomers is >20 : 1 according to the ^{1}H NMR spectrum.

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-glucopyranosyl)-1(S)-amino-1-phenyl-3-butene (**9a**). Flash chromatography in petroleum ether–ethyl acetate (10 : 1), R_F 0.52 (petroleum ether–ethyl acetate 4 : 1), yield 65%, colorless amorphous solid, $[\alpha]_D^{22}$ –12.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.06 (s, 9 H, $C(CH_3)_3$); 1.17 (s, 9 H, $C(CH_3)_3$); 1.18 (s, 9 H, $C(CH_3)_3$); 1.24 (s, 9 H, $C(CH_3)_3$); 2.18 (bs, 1 H, NH); 2.27–2.38 (m, 2 H, 2 H-2′); 3.58–3.61 (m, 1 H, $J_{5,6a}$ = 7.1, $J_{5,6b}$ = 6.6., H-5); 3.77 (d, 1 H, $J_{1,2}$ = 7.7, H-1); 3.94 (dd, $J_{6b,6a}$ = 11.2, $J_{6b,5}$ = 6.6, H-6b); 4.07 (dd, 1 H, $J_{6a,6b}$ = 11.2, $J_{6a,5}$ = 7.1, H-6a); 4.12 (dd, 1 H, $J_{1',2a'}$ = 6.9, $J_{1',2b'}$ = 6.9, H-1′); 5.01 (m, 4 H, H-2, H-3, 2 H-4′); 5.29 (d, $J_{4,3}$ = 2.9, H-4); 5.61 (m, 1 H, H-3′); 7.21–7.29 (m, 5 H, Ph). ^{13}C NMR

(100.6 MHz, $CDCl_3$): 86.1 (C-1). Ratio of diastereomers is 17 : 1 according to the ^1H NMR spectrum. For $C_{36}H_{55}NO_9$ (645.8) calculated: 66.95% C, 8.58% H, 2.17% N; found: 67.17% C, 8.65% H, 2.06% N.

N-(2,3,4,6-Tetra-O-pivaloyl-β-D-glucopyranosyl)-3(S)-amino-1(E)-phenyl-1,5-hexadiene (**9b**). Flash chromatography in petroleum ether–ethyl acetate (7 : 1), R_F 0.53 (petroleum ether–ethyl acetate 6 : 1), yield 75%, colorless amorphous solid, $[\alpha]_D^{22}$ –14.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 1.08 (s, 9 H, $C(CH_3)_3$); 1.10 (s, 9 H, $C(CH_3)_3$); 1.16 (s, 9 H, $C(CH_3)_3$); 1.23 (s, 9 H, $C(CH_3)_3$); 1.85–1.92 (bs, 1 H, NH); 2.08–2.12 (m, 1 H, $J_{4b,4a}$ = 13.69, H-4b); 2.24–2.29 (m, 1 H, $J_{4a,4b}$ = 13.7); 3.58–3.61 (m, 1 H, $J_{5,6b}$ = 6.26, H-5); 3.65–3.70 (m, 1 H, H-3); 3.96–4.01 (dd, 1 H, $J_{6b,5}$ = 6.26, $J_{6b,6a}$ = 12.31, C-6b); 4.1–4.2 (m, 2 H, $J_{6a,5}$ = 1.56, $J_{6a,6b}$ = 12.13, H-6a, H-1); 4.81–4.86 (t, 1 H, $J_{2,1}$ = $J_{2,3}$ = 9.39, H-2); 4.99–5.89 (m, 3 H, $J_{4,3}$ = 9.78, H-4, 2 H-6′); 5.24–5.29 (dd, 1 H, $J_{3,2}$ = 9.39, $J_{3,4}$ = 9.78, H-3); 5.7–5.86 (m, 2 H, $J_{2',1'}$ = 16.04, H-2′, H-5′); 6.42 (d, 1 H, $J_{1',2'}$ = 16.04); 7.2–7.34 (m, 5 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 86.5 (C-1). Ratio of diastereomers is 18 : 1 according to the ^1H NMR spectrum. For $C_{38}H_{57}NO_9$ (671.8) calculated: 67.93% C, 8.55% H, 2.08% N; found: 67.50% C, 8.52% H, 2.00% N.

1-Substituted *N*-(D-Arabinopyranosyl)homoallylamines (**6**). General Procedure

A solution of *N*-arabinosylimine **5** (1.5 mmol) in dry tetrahydrofuran (20 ml) was cooled to –78 °C. Tin tetrachloride (3.3 mmol) was added dropwise, and the mixture was stirred for 3 h at –78 °C. Then, allyltributylstannane (3.1 mmol) was added and the reaction is allowed to warm up to 0–5 °C within 15 h. After stirring for an additional 24 h at this temperature, 2 M aqueous NaOH (15 ml) and, subsequently, ethyl acetate (60 ml) were added. The aqueous layer was separated and extracted twice with ethyl acetate (20 ml). The combined organic layers were washed with 2 M NaOH (30 ml), brine (20 ml) and water, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography.

N-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-3(R)-amino-1(E)-phenyl-1,5-hexadiene (**6a**). Column chromatography in petroleum ether–ethyl acetate (8 : 1), R_F 0.69 (petroleum ether–ethyl acetate 5 : 1), yield 79%, crystals, m.p. 126 °C, $[\alpha]_D^{22}$ –47.0 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): 1.08 (s, 9 H, $C(CH_3)_3$); 1.12 (s, 9 H, $C(CH_3)_3$); 1.16 (s, 9 H, $C(CH_3)_3$); 1.20 (s, 9 H, $C(CH_3)_3$); 1.85–1.92 (bs, 1 H, NH); 2.15 (m, 2 H, H-4′); 3.49–3.51 (d, 1 H, $J_{1,2}$ = 12.62, H-1); 3.65–3.71 (dd, 1 H, $J_{5b,4}$ = 6.75, $J_{5b,5a}$ = 14.6, H-5b); 3.86–3.91 (dd, 1 H, $J_{5a,4}$ = 2.05, $J_{5a,6b}$ = 13.21, H-5a); 4.0 (m, 1 H, H-3′); 4.98–5.1 (m, 5 H, H-2, H-3, H-4, 2 H-6′); 5.68–5.8 (m, 1 H, H-5′); 5.81–5.9 (dd, 1 H, $J_{2',3}$ = 8.22, $J_{2',1'}$ = 15.85, H-2′); 6.43–6.4 (d, 1 H, $J_{1',2''}$ = 16.14, H-1′); 7.2–7.4 (m, 5 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 70.1 (-CH-NH); 87.2 (C-1). According to the ^1H NMR spectrum, the ratio of diastereomers is 19 : 1. For $C_{33}H_{47}NO_7$ (557.7) calculated: 68.85% C, 8.49% H, 2.51% N; found: 68.84% C, 8.42% H, 2.12% N.

N-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-1(R)-amino-1-(3-pyridyl)-3-butene (**6b**). Column chromatography in petroleum ether–ethyl acetate (5 : 2), R_F 0.19, yield 45%, colorless oil, $[\alpha]_D^{22}$ –21.1 (*c* 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): 1.06 ((s, 9 H, $C(CH_3)_3$); 1.16 (s, 9 H, $C(CH_3)_3$); 1.21 (s, 9 H, $C(CH_3)_3$); 2.2–2.4 (m, 2 H, H-2′); 3.28–3.38 (dd, 1 H, $J_{6b,6a}$ = 13.43, $J_{6b,5}$ = 1.05, H-6b); 3.55–3.65 (d, 1 H, $J_{1,2}$ = 8.3); 3.78–3.88 (dd, 1 H, $J_{6a,6b}$ = 13.42, $J_{6a,5}$ = 13.23, H-6a); 4.1-4.2 (t, 1 H, $J_{1',2a'}$ = 6.59, $J_{1',2b'}$ = 7.08, H-1′); 4.93–5.10 (m, 5 H, H-2, H-3, H-4, 2 H-4′); 5.1–5.65 (m, 1 H, H-3′); 7.17–7.24 (dd, 1 H, $J_{5'',3''}$ = 7.81, H-5″); 7.54–7.59 (dd, $J_{4'',5''}$ = 7.81, H-4″); 8.46 (bs, 2 H, H-2″, H-6″). ^{13}C NMR (100.6 MHz, $CDCl_3$): 86.7 (C-1). The

ratio of diastereomers was 13 : 1 according to analytical HPLC. For $C_{29}H_{44}N_2O_7$ (532.7) calculated: 65.39% C, 8.33% H, 5.26% N; found: 65.41% C, 8.37% H, 5.28% N.

2-Substituted 1-Glycosylpyrrolidines (**11**) and (**14**). General Procedure

To a solution of the *N*-glycosylhomoallylamine **3** or **6** (0.5 mmol), in acetonitrile (10 ml) at 0 °C, a solution of mercury(II) trifluoroacetate (324 mg, 0.75 mmol) in acetonitrile (1.5 ml) was added. The solution was stirred for 2 h at 0 °C. Then, sodium borohydride (38 mg, 1.0 mmol) in 3 M NaOH (1.1 ml, 3.2 mmol) was added. After stirring for 30 min at 0 °C (precipitation of mercury) and addition of saturated aqueous $NaHCO_3$ solution (50 ml), the aqueous layer was extracted four times with 30 ml of CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated *in vacuo*. Pyrrolidines **11** and **14** were purified by chromatography.

(S)-1-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-phenylpyrrolidine (**11a**). Flash chromatography in petroleum ether–ethyl acetate (10 : 1), R_F 0.31, yield 73%, colorless crystals, m.p. 160 °C, $[\alpha]_D^{22}$ –24.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 ((s, 9 H, $C(CH_3)_3$); 1.16 (s, 9 H, $C(CH_3)_3$); 1.17 (s, 9 H, $C(CH_3)_3$); 1.25 (s, 9 H, $C(CH_3)_3$); 1.65 (m, 1 H, H-3′); 1.82 (m, 2 H, 2 H-4′); 2.12 (m, 1 H, H-3′); 3.16 (m, 2 H, 2 H-5′); 3.72 (t, 1 H, $J_{5,6a} = J_{5,6b}$ = 6.8, H-5); 3.94 (dd, 1 H, $J_{6a,6b}$ = 11.1, $J_{6a,5}$ = 6.6, H-6a); 4.00 (d, 1 H, $J_{1,2}$ = 9.3, H-1); 4.10 (m, 2 H, H-2′, H-6b); 4.93 (dd, 1 H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.1, H-3); 5.29 (d, 1 H, $J_{4,3}$ = 3.0, H-4); 5.39 (t, 1 H, $J_{2,1} = J_{2,3}$ = 9.6, H-2); 7.21–7.27 (m, 5 H, Ph). Ratio of diastereomers determined by ^{1}H NMR is >20 : 1. For $C_{36}H_{55}NO_9$ (645.8) calculated: 66.95% C, 8.58% H, 2.70% N; found: 66.93% C, 8.53% H, 2.10% N.

(S)-1-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-(3-pyridyl)pyrrolidine (**11b**). Flash chromatography in petroleum ether–ethyl acetate (2 : 1), R_F 0.13 (petroleum ether–ethyl acetate 4 : 1), yield 70%, colorless crystals (pentane), m.p. 126–127 °C, $[\alpha]_D^{22}$ –32.9 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.03 (s, 9 H, $C(CH_3)_3$); 1.11 (s, 9 H, $C(CH_3)_3$); 1.14 (s, 9 H, $C(CH_3)_3$); 1.21 (s, 9 H, $C(CH_3)_3$); 1.63 (m, 1 H, H-3′); 1.80 (m, 2 H, 2 H-4′); 2.13 (m, 1 H, H-3′); 3.17 (t, 1 H, $J_{5',4'}$ = 7.0, 2 H-5′); 3.72 (t, 1 H, $J_{5,6a} = J_{5,6b}$ = 6.7, H-5); 3.91 (dd, 1 H, $J_{5,6a}$ = 6.7, $J_{6a,6b}$ = 11.3, H-6a); 3.94 (d, 1 H, $J_{1,2}$ = 9.4, H-1); 4.07 (dd, 1 H, $J_{5,6b}$ = 6.7, $J_{6a,6b}$ = 11.3, H-6b); 4.11 (t, 1 H, $J_{2'3'}$ = 7.7, H-2′); 4.91 (dd, 1 H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.0, H-3); 5.28 (d, 1 H, $J_{4,3}$ = 2.9, H-4); 5.35 (t, 1 H, $J_{2,1} = J_{2,3}$ = 9.7, H-2); 7.17 (dd, 1 H, $J_{5'',4''}$ = 7.7, $J_{5'',6''}$ = 4.8, H-5″); 7.55 (d, 1 H, $J_{4'',5''}$ = 7.7, H-4″); 8.46 (m, 2 H, H-2″, H-6″). ^{13}C NMR (100.6 MHz, $CDCl_3$): 61.2 (C-2′); 87.4 (C-1). Ratio of diastereomers determined from the ^{1}H NMR spectrum is >20 : 1. For $C_{35}H_{54}N_2O_9$ (646.8) calculated: 64.99% C, 8.41% H, 4.33% N; found: 64.94% C, 8.41% H, 4.30% N.

(E)-(S)-1-(2,3,4,6-Tetra-O-pivaloyl-β-D-galactopyranosyl)-2-styrylpyrrolidine (**11c**). Flash chromatography in petroleum ether–ethyl acetate (10 : 1), R_F 0.29, yield 74%, colorless crystals, m.p. 109–110 °C (pentane), $[\alpha]_D^{22}$ –36.4 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 (s, 9 H, $C(CH_3)_3$); 1.15 (s, 9 H, $C(CH_3)_3$); 1.18 (s, 9 H, $C(CH_3)_3$); 1.24 (s, 9 H, $C(CH_3)_3$); 1.55 (m, 1 H, H-3′); 1.73 (m, 2 H, 2 H-2′); 1.96 (m, 1 H, H-3′); 3.06 (m, 2 H, 2 H-5′); 3.62 (q, 1 H, $J_{2',3'} = J_{2',CH}$ = 8.2, H-2); 3.84 (t, 1 H, $J_{5,6a} = J_{5,6b}$ = 6.8, H-5); 3.95 (dd, 1 H, $J_{6a,6b}$ = 11.0, $J_{6a,5}$ = 6.9, H-6a); 4.13 (dd, 1 H, $J_{6b,6a}$ = 11.0, $J_{6b,5}$ = 6.8, H-6b); 4.22 (d, 1 H, $J_{1,2}$ = 9.3, H-1); 5.04 (dd, 1 H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 3.1, H-3); 5.32 (t, 1 H, $J_{2,1} = J_{2,3}$ = 9.9, H-2); 5.34 (d, 1 H, $J_{3,4}$ = 2.7, H-4); 5.88 (dd, 1 H, $J_{CH=CH}$ = 8.4, CH=); 6.41 (d, 1 H, $J_{CH=CH}$ = 15.8, =CH); 7.19–7.32 (m, 5 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 62.3 (C-2′); 87.3 (C-1). Ratio of diastereomers de-

termined by ^{1}H NMR is >20 : 1. For $C_{38}H_{57}NO_9$ (671.8) calculated: 67.93% C, 8.55% H, 2.08% N; found: 67.97% C, 8.53% H, 1.97% N.

(E)-(R)-1-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-2-styrylpyrrolidine (**14a**). Column chromatography in petroleum ether–ethyl acetate (15 : 1), R_F 0.65 (petroleum ether–ethyl acetate 10 : 1), yield 22%, crystals, m.p. 200 °C, $[\alpha]_D^{22}$ –13.8 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 1.09 (s, 9 H, $C(CH_3)_3$); 1.16 (s, 9 H, $C(CH_3)_3$); 1.25 (s, 9 H, $C(CH_3)_3$); 1.51–1.54 (m, 1 H, H-3′); 1.70–1.74 (m, 2 H, H-4′); 1.91–2.01 (m, 1 H, H-3′); 3.05–3.1 (t, 2 H, $J_{5a',4'}$ = 6.84, $J_{5',4}$ = 7.08, H-5′); 3.59–3.77 (m, 2 H, $J_{2',3'}$ = 8.3, H-2′, H-5b); 3.85–3.98 (dd, 1 H, $J_{5a,5b}$ = 12.94, $J_{5a,4}$ = 2.2, H-5a); 4.15–4.18 (d, 1 H, $J_{1,2}$ = 9.28, H-1); 4.9–5.05 (dd, 1 H, $J_{3,2}$ = 10.0, $J_{3,4}$ = 4.48, H-3); 5.15–5.21 (m, 1 H, H-4); 5.3–5.41 (dd, 1 H, $J_{2,1}$ = 9.28, $J_{2,3}$ = 10.0, H-2); 5.8–6.0 (dd, 1 H, $J_{1'',2'}$ = 8.55, $J_{1'',2''}$ = 8.55, $J_{1'',2''}$ = 15.87, H-1″); 6.4–6.55 (dd, 1 H, $J_{2'',1''}$ = 15.84, H-2″); 7.2–7.43 (m, 5 H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): 62.3 (C-2′); 87.8 (C-1); 131.4 (CH-CH=CH-Ph). Ratio of diastereomers determined by ^{1}H NMR >20 : 1. FD MS: *m/z* 557.6 (M^+).

(R)-1-(2,3,4-Tri-O-pivaloyl-α-D-arabinopyranosyl)-2-(3-pyrridyl)pyrrolidine (**14b**). After evaporation of the solvent, the remaining crude product was recrystallized from acetonitrile, yield 44%, crystals, m.p. 217 °C (decomp.), $[\alpha]_D^{22}$ –12.9 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): 1.06 (s, 9 H, $C(CH_3)_3$); 1.15 (s, 9 H, $C(CH_3)_3$); 1.21 (s, 9 H, $C(CH_3)_3$); 1.54 (m, 1 H, H-3′); 1.72–1.92 (m, 2 H, H-4′); 2.1–2.25 (m, 1 H, H-3′); 3.18–3.25 (m, 2 H, H-5′); 3.4–3.5 (dd, 1 H, $J_{5b,5a}$ = 12.45, H-5b); 3.8–3.98 (m, 2 H, $J_{5a,5b}$ = 12.35, H-5a, H-1); 4.08–4.1 (t, 1 H, $J_{2'3'}$ = 7.57); 4.85–4.95 (dd, 1 H, $J_{3,2}$ = 10.01, $J_{3,4}$ = 3.42, H-3); 5.08–5.18 (m, 1 H, H-4); 5.38–5.5 (t, 1 H, $J_{2,1}$ = 9.52, $J_{2,3}$ = 9.77, H-2); 7.18–7.23 (dd, 1 H, $J_{5'',4''}$ = 7.81, $J_{5'',6''}$ = 4.88, H-5″); 7.55–7.63 (dt, 1 H, $J_{4'',5''}$ = 7.81, H-4″); 8.5 (bs, 2 H, H-2″, H-6″). ^{13}C NMR (50.3 MHz, $CDCl_3$): 61.2 (C-2′); 87.8 (C-1). The ratio of diastereomers was determined by the ^{1}H NMR spectrum >20 : 1. For $C_{29}H_{44}N_2O_7$ (532.7) calculated: 65.34% C, 8.33% H, 5.26% N; found: 65.12% C, 8.32% H, 5.15% N.

(*E*)-(2*R*)-1-(2,3,4-Tri-*O*-pivaloyl-α-D-arabinopyranosyl)-4-iodo-2-styrylpyrrolidine (**10**)

To a solution of *N*-arabinosylhomoallylamine **6a** (100 mg, 0.18 mmol) in diethyl ether–dichloromethane (3 ml, 1 : 2) at 0 °C, iodine (50 mg, 0.19 mmol) was added. The solution was stirred at 0 °C for 2 h. After addition of dichloromethane (20 ml), washing with saturated $NaHCO_3$ solution (20 ml), 0.5 M $Na_2S_2O_3$ solution (20 ml) and water, the organic layer was dried over $MgSO_4$. The solvent was evaporated, the residue dissolved in ethyl acetate (20 ml) and filtered through neutral Al_2O_3. Evaporation of the solvent gave **10** as a yellowish oil. Yield 77 mg (63%), R_F 0.18 (petroleum ether–ethyl acetate 7 : 1), $[\alpha]_D^{22}$ –27.8 (*c* 1.0, $CHCl_3$). According to the ^{1}H NMR analysis, the substance consists of two diastereomers differing in the configuration at C-4 of the pyrrolidine ring.

(–)-(*S*)-2-Phenylpyrrolidine (**13a**)

To a solution of 1-galactosyl-2-phenylpyrrolidine **11a** (234 mg, 0.36 mmol) in methanol (4 ml), 1 M HCl (0.54 ml, 0.54 mmol) was added. After addition of dichloromethane (0.5 ml), the mixture was stirred at room temperature for 20 h and then concentrated *in vacuo*. The residue was dissolved in 1 M HCl (20 ml) and extracted three times with pentane (40 ml). The aqueous solution was evaporated *in vacuo*. The remaining hydrochloride **12a** was dissolved in saturated aqueous Na_2CO_3 solution and extracted with dichloromethane (twice with 20 ml).

The organic layer was dried with $MgSO_4$ and the solvent evaporated *in vacuo* to give 51 mg (96%) of the 2-phenylpyrrolidine **13a**. Brownish oil, R_F 0.25 (petroleum ether–ethyl acetate 3 : 1), $[\alpha]_D^{22}$ –22.9 (*c* 0.3, MeOH) (ref.[18] gives $[\alpha]_D^{22}$ –22.0 (MeOH)). ^{1}H NMR (400 MHz, $CDCl_3$): 1.76 (m, 1 H, H-3); 1.89 (m, 2 H, 2 H-4); 2.18 (m, 1 H, H-3); 3.00 (m, 1 H, H-5); 4.14 (t, 1 H, $J_{2,3}$ = 7.7, H-2); 4.66 (bs, 1 H, NH); 7.27–7.39 (m, 5 H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): 62.6 (C-2).

(*S*)-(–)-Nornicotine (**13b**)

To a solution of the 1-galactosyl-2-(3-pyridyl)pyrrolidine **11b** (152 ml, 0.23 mmol) in methanol (3 ml), 1 M HCl (0.82 ml, 0.82 mmol) was added. Dichloromethane was added to the stirred solution until dissolution of the formed precipitate. The mixture was stirred for 24 h at room temperature, and the solvent evaporated *in vacuo*. The residue was dissolved in 0.5 M HCl (10 ml) and extracted three times with dichloromethane (30 ml). The aqueous solution was evaporated *in vacuo* to give the dihydrochloride **12b** (52 mg), $[\alpha]_D^{22}$ +5.4 (*c* 1, MeOH). The salt was dissolved in saturated aqueous Na_2CO_3 solution and the product extracted with dichloromethane (three times 10 ml). Evaporation of the solvent gave (*S*)-nornicotine as a brownish oil. Yield 34 mg (quantitative), $[\alpha]_D^{22}$ –29.3 (*c* 0.25, MeOH) (ref.[19] gives $[\alpha]_D^{22}$ –34.9 (*c* 0.3, MeOH)). ^{1}H NMR of the dihydrochloride **13b** (400 MHz, $CDCl_3$): 2.38 (bm, 3 H, H-3, 2 H-4); 2.70 (m, 1 H, H-3); 3.63 (m, 2 H, 2 H-5); 4.96 (m, 1 H, H-2); 8.27, 8.94, 9.02, 9.21 (4 s, 4 H, H-2′, H-4′, H-5′, H-6′). ^{13}C NMR (100.6 MHz, D_2O): 25.8 (C-4); 32.5 (C-3); 48.7 (C-5); 62.1 (C-2); 130.5 (C-4′); 137.5 (C-5′); 143.4 (C-3′); 144.6 (C-6′); 148.9 (C-2′).

(*R*)-Nornicotine Dihydrochloride **15**

To a solution of the 1-arabinosyl-2-(3-pyridyl)pyrrolidine (**14b**) (126 mg, 0.19 mmol) in methanol (5 ml) 1 M HCl (2 ml, 2 mmol) was added. After stirring for 1 h at room temperature the mixture was poured into 0.5 M HCl (25 ml) and dichloromethane (25 ml). The organic layer was separated and the aqueous solution extracted twice with dichloromethane (25 ml). After evaporation of the aqueous solution, the dihydrochloride **15** was isolated: yield 35 mg (84%), $[\alpha]_D^{22}$ –3.8 (*c* 1.0, MeOH), EI MS, *m/z*: 148.2 (M + H).

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