Stereoselective Synthesis of $\alpha$-Arylalkylamines by Glycosylation-induced Asymmetric Addition of Organometallic Compounds to Imines

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

Activation of imines of aromatic aldehydes by $N$-glycosylation with $O$-pivaloyl-galactopyranosyl bromide (pivalobromogalactose) and subsequent addition of organotin, organolithium, Grignard, or organozinc reagents afforded $\alpha$-arylalkylamines with moderate to high diastereoselectivity.

Key words: Iminium Salts, Galactosylamine, Carbohydrate Auxiliaries, Arylalkylamines, Organometallic Reagents

Introduction

Arylalkylamines are of interest as building blocks for the synthesis of biologically active compounds and as chiral ligands or chiral auxiliaries in stereoselective syntheses [1]. Their stereoselective synthesis has been achieved by enantioselective reduction of ketimines using chiral reagents [2], as for example Corey’s oxaborolidines [3], or proline-derived triacyloxyborohydrides [4]. Particularly efficient asymmetric syntheses of chiral arylalkylamines have been accomplished by Noyori et al. [5] through enantioselective catalysis of hydrogen transfer reactions using a chiral 1,2-diphenyl-ethylenediamine ruthenium catalyst. Enantioselective transferhydrogenations have also been achieved using a chiral titanocene catalyst [6] or sterically demanding BINOL phosphates [7]. Asymmetric hydrogenation of imines using transition metal catalysts has successfully been used to produce chiral branched amines [8, 9]. An alternative to these reductive procedures consists of the stereoselective addition of organometallic compounds to aldimines [10, 11]. We here report on a new asymmetric addition of organometallic reagents to imines, which is based on the principle of glycosylation-induced asymmetric synthesis [12].

Results and Discussion

Iminium salts exhibit distinctly higher reactivity towards nucleophiles compared to imines [13]. In the approach described here, we tried to utilize the enhanced reactivity of iminium salts in combination with the stereodifferentiating potential of glycosyl substituents, demonstrated already in a number of diastereoselective Mannich-type reactions of glycosyl imines [14, 15], for the stereoselective synthesis of arylalkylamines. Glycosyl imines themselves proved to be not sufficiently reactive for the addition of Grignard compounds, although Takahashi et al. [16] had reported on successful conversions of imines into branched amines using Grignard reagents. For reactions with organometallic reagents, $N$-ethyl benzaldimine (or $N$-benzylidene ethylamine) (1) was used as the model substrate (Scheme 1). It was reacted with 2,3,4,6-tetra-$O$-pivaloyl-$\alpha$-D-galactopyranosyl bromide [17] (2) in dichloromethane in the presence of silver trifluoromethanesulfonate (triflate) and 2,6-lutidine at $0^\circ$C to give the $N$-galactosyliminium salt 3. After completion of the iminium salt formation, the solution was cooled to $-20^\circ$C. At this temperature, the organometallic reagent was added.

Reaction of iminium salt 3 with tetra-$n$-butylan gave $\alpha$-phenylamylamine 4 in a low yield, but the diastereomers were formed in a ratio of 15:1. Usually, organotin reagents are of low nucleophilicity. Their reaction with electrophiles needs the promotion by Lewis acids [18]. In absence of a Lewis acid, which, for example, may also activate the stannane via a chloride bridge, the reactivity of the stannane towards the iminium salt obviously is low and does not lead to a smooth conversion.
On the other hand, application of the much more reactive butyllithium is not sufficiently tolerated by the solvent required for the iminium salt formation. The reaction also produced a low yield, but proceeded with excellent diastereoselectivity (ratio of diastereomers 28:1). The diastereoselectivity of these reactions was detected from the crude product by $^1$H NMR spectroscopy or by analytical reversed phase HPLC.

Reaction of the iminium salt 3 with tributylstannyl cyanide gave the phenylglycinonitrile 5 in distinctly higher yield (Scheme 2). However, in this case the diastereoselectivity was low displaying a diastereomeric ratio of only 3:1.

We concluded from the results shown in Schemes 1 and 2 that the reactivity of the organometallic reagent is of strong influence on the result of the reactions of the galactosyl iminium salt 3 in the solvent dichloromethane. As a consequence, the highly reactive nucleophile butyllithium was substituted by less reactive Grignard compounds (Scheme 3).

In these reactions, the $\alpha$-arylalkylamines 6 were formed in ca. 50% yield (after purification) and with moderate to good diastereoselectivity (diastereomeric ratio 10:1 in case of 6a).

In further extension of these investigations, the reactivity of the nucleophile was even more reduced, and diethylzinc was applied (Scheme 4).

In this process, the $\alpha$-phenylpropylamine 7 was formed in 77% yield and 82% diastereoselectivity. The diastereomers, although distinguishable by analytical HPLC, could not be separated by chromatographic procedures. Repeated recrystallization from dichloro-
methane/methanol resulted in an enrichment of the major (S) diastereomer.

To overcome this disadvantage, the structure of the model imine was modified, and N-benzylidene-p-methoxy-aniline [19] (8) was investigated as the substrate (Scheme 5).

The iminium salt 9 was prepared in dichloromethane under the conditions described for the formation of 3. Conversion of 9 with diethylzinc proceeded under identical conditions as given for the formation of 7 with high yield and excellent diastereoselectivity. The obtained diastereomers of α-phenylpropyl aniline 10 were separated giving 79% of the (S)-diastereomer and 3.5% of the (R)-diastereomer. The amine 10 offers the advantage that the N-(methoxy)phenyl group can be removed by oxidative processes if this is desired.

As has been shown and proven by X-ray analysis of the products for the galactosylation-induced Mannich [12a] and Pictet-Spengler reactions [12b], the N-glycosylation of imines, as for example 1 or 8, is accompanied by a prevailing E to Z isomerization at the C=N double bond.

The nucleophilic attack at the iminium ions, 3 or 9, respectively, is sterically hindered at the front side, and therefore should preferentially proceed at the Si (back) side (Scheme 6) to afford the α-aryalkylamines 4, 6, 7 and 10 in (S)-configuration as the major diastereomers. The electron-delocalizing effect of the N-(4-methoxy)phenyl substituent supports the E to Z isomerization during the galactosylation of imine 8. As a consequence, the iminium salt 9 is more easily formed and can undergo the reaction with the nucleophile diethylzinc more readily and with higher diastereoselectivity compared to the iminium salt 3, although the latter contains the smaller N-substituent.

Further evidence for the stereochemical course of these addition reactions to imines was achieved by transformation of the major diastereomer of N-galactosylamine 10 into a known chiral amine. Treatment of N-glycosylamines with diluted aqueous HCl...
in methanol results in the cleavage of the N-glycosidic bond [20, 21]. In case of N-galactosyl aniline 10, the deglycosylation reaction was carried out with 1N HCl/acetonitrile (1 : 10). After neutralization, the N-(4-methoxy-phenyl) group was removed from the arylalkylamine 11 by subsequent oxidation with ceric ammonium nitrate to afford α-phenylpropylamine 12 in high yield (Scheme 7).

Comparison of the optical rotation value of the obtained product 12 ([α]D22 = +5.82 (c = 2, EtOH)) with that given in the literature [22] ([α]D22 = +5.1 (c = 2.0, EtOH)) confirmed that the major diastereomer of 10 had (S) configuration.

Conclusion

N-Glycosylation of arylaldimines provides a strong activation the C=N double bond in the intermediate N-glycosyl iminium salts and, at the same time, an efficient diastereodifferentiation in their reactions with organometallic nucleophiles to afford α-arylalkylamines. As the N-glycosylation is accompanied by E to Z isomerization at the C=N double bond, π-delocalizing N-substituents in the imine substrates favor both reactivity and diastereodifferentiation in these glycosylation-induced asymmetric addition reactions to imines. The reactivity of the organometallic reagent must be compatible with the solvent used for the formation of the N-glycosyl iminium salt. Diethylzinc gave the best results in these glycosylation-induced asymmetric syntheses of arylalkylamines in terms of yield and diastereoselectivity. Using O-pivaloylated N-galactosyl bromide afforded the stereoselective formation of arylalkylamines with (S)-configuration. According to the principle of quasi-enantiomeric carbohydrates [23], the O-pivaloylated arabinopyranosyl bromide should offer an analogous access to the corresponding (R)-enantiomers of the arylalkylamines.

Experimental Section

General procedures

Reagents and solvents were distilled before use: Tetrahydrofuran, dioxane, and Et2O were distilled from potassium/benzophene ketyl. CH2Cl2 was distilled from CaH2. Light petroleum refers to b. p. 60 – 80 °C (Knauer MaxiStar K1000 pump and DAD2062 for diode array detection); flow rate: 1 cm³ min⁻¹. Preparative HPLC was performed using two Knauer Ministar K500 pumps. Columns: A: Eurospher 100, C8, 5 µ, 250 × 4 mm², Knauer, B: Kromasil C18, 5 µ, 250 × 4 mm², Knauer, flow rate: 1 cm³ min⁻¹. Thin layer chromatography (TLC) was performed on Merck silica gel 60F254, 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. Melting points were taken on a Büchi Dr. Tottoli apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a Bruker AC-200 or a Bruker AC-400 NMR instrument. Optical rotation values were measured with a Perkin-Elmer 241 polarimeter.

Reaction of arylaldimines via N-galactopyranosyl iminium salts with organometallic reagents – General procedure

Under argon atmosphere, the imine 1 or 8 (0.75 mmol), 2,3,4,6-tetra-O-pivaloyl-a-D-galactopyranosyl bromide [17] (0.45 g, 0.8 mmol) and 2,6-lutidine (0.18 mL, 1.6 mmol) were stirred in dichloromethane (10 mL) at 0 °C for 10 min. Silver trifluoromethanesulfonate (0.5 g, 1.6 mmol) was added, and the mixture was stirred at r. t. for 12 h. After dilution with dichloromethane (10 mL) the reaction mixture was cooled to –20 °C. At this temperature, 5 mmol of the organometallic reagent (either neat or in the solvent given) was added dropwise. Stirring was continued while the reaction mixture was allowed to warm up to r. t. After 3 d the solvents were evaporated in vacuo, and the ratio of diastereomers was recorded either by 1H NMR spectroscopy (ma = major, mi = minor diastereomer) or by analytical HPLC. Purification was carried out by flash chromatography in light petroleum-ethyl acetate (15 : 1).

N-Ethyl-N-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-1-phenyl-aminomine (4)

Method a) N-Benzylidene-ethylamine [24] (1) (0.1 g) was used as the imine component and reacted with 1.7 mL of tetrabutyllstannane. The ratio of diastereomers detected by 1H NMR spectroscopy of the crude product was 15 : 1. The mixture of diastereomers 4 was isolated by flash chromatography and by preparative HPLC on a Knauer Kromasil C18 column in MeCN-H2O = 93 : 7 to 100 : 0 within 90 min. Yield: 82 mg, (16 %); colorless solid, m. p. 67 – 69 °C, Rf = 0.69 (light petroleum-ethyl acetate 4 : 1), Rf = 28.20 min. – C39H63NO9 (689.9): calcd. C 67.90, H 9.20, N 2.03; found C 67.84, H 9.26, N 1.99. – 1H NMR (400 MHz, CDCl3); δ = 7.23 (m, 5H, arom. (ma, mi)); 5.39 (t, J 3 = 2.9 Hz, 1H, H-2 (ma, mi)); 5.32 (d, J 3,4 = 2.9 Hz, 1H, H-4 (mi)); 5.25 (d, J 3,4 = 2.9 Hz, 1H, H-4 (ma)); 4.97 (dd, J 3,4 = 2.9 Hz, J 3,2 = 9.7 Hz, 1H, H-3 (mi)); 4.92 (dd, J 3,4 = 2.9 Hz, 1H,
H-3 (ma); 4.37 (d, J = 9.4 Hz, 1H, H-1 (mi)); 4.20 (d, J = 9.1 Hz, 1H, H-5 (ma, mi)); 3.79 (m, 1H, H-6 (ma, mi)); 3.72 (m, 1H, H-6′ (ma, mi)); 3.52 (t, J = 7.0 Hz, 1H, α-CH (ma, mi)); 2.92 (m, 1H, -CH₂-N- (ma, mi)); 2.65 (m, 1H, -CH₂-N- (ma, mi)); 1.74 (m, 2H, β-CH₂- (ma, mi)); 1.25 – 1.02 (m, 36H, Piv-CH₃); 0.78 (t, J = 7.0 Hz, 3H, -CH₃ (ma, mi)).

Method b) N-Benzylidene-ethylamine [24] (I) (0.1 g) was subjected to glycosylation and reacted with 3.2 mL of n-butyl lithium (1.6 M in n-hexane). The ratio of diastereomers detected by ¹H NMR spectroscopy of the crude product amounted to 28:1. The diastereomers 4 were isolated by flash chromatography and by preparative HPLC on a Knauer Kromasil C18 column in MeCN-H₂O = 93:7 to 100:0 within 90 min. Yield: 114 mg (22 %); colorless solid, m. p. 98 – 101 °C, Rᵣ = 0.73 (light petroleum-ethyl acetate = 4 : 1). – ¹H NMR (400 MHz, CDCl₃): δ = 7.22 (m, 5H, arom. (ma, mi)); 5.39 (t, J = 9.3 Hz, H₂, 1H, H-1 (ma, mi)); 5.42 (dd, J = 9.3 Hz, 1H, H-2 (ma, mi)); 5.24 (dd, J, 1.3 Hz, 1H, H-4 (ma)); 4.98 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 4.91 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 1.72 (m, 2H, β-CH₂- (ma, mi)); 1.22 – 0.95 (m, 41H, Piv-CH₃ + -CH₂-N- + -CH₃ (ma, mi)); 0.79 (t, J = 7.3 Hz, 3H, -CH₃ (ma, mi)). – ¹³C NMR (100.6 MHz, CDCl₃): δ = 7.72 (m, 5H, arom. (ma, mi)); 5.93 (t, J = 9.3 Hz, 1H, H-1 (ma, mi)); 5.07 (dd, J, 1.3 Hz, 1H, H-4 mi)); 4.89 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 mi)); 4.91 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 1.72 (m, 2H, β-CH₂- (ma, mi)); 1.22 – 0.95 (m, 41H, Piv-CH₃ + -CH₂-N- + -CH₃ (ma, mi)); 0.79 (t, J = 7.3 Hz, 3H, -CH₃ (ma, mi)). – ¹³C NMR (100.6 MHz, CDCl₃): δ = 7.72 (m, 5H, arom. (ma, mi)); 5.93 (t, J = 9.3 Hz, 1H, H-1 (ma, mi)); 5.07 (dd, J, 1.3 Hz, 1H, H-4 mi)); 4.89 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 mi)); 4.91 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 1.72 (m, 2H, β-CH₂- (ma, mi)); 1.22 – 0.95 (m, 41H, Piv-CH₃ + -CH₂-N- + -CH₃ (ma, mi)); 0.79 (t, J = 7.3 Hz, 3H, -CH₃ (ma, mi)).

N-Ethyl-N-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)-(1-phenyl)ethyamine (6a)

In analogy to the synthesis of 6a, N-benzylidene-ethylamine [24] (1) (0.1 g) was subjected to glycosylation and reacted with 2.5 mL of n-propylmagnesium chloride (2 M in diethyl ether). The diastereomeric excess was determined by ¹H NMR spectroscopy of the crude product 6a (de 82 %). The mixture of diastereomers 6b was purified by flash chromatography and preparative HPLC in MeCN-H₂O = 93:7 on a Knauer Kromasil C18 column. Yield: 264 mg (52 %); colorless solid, m. p. 98 – 101 °C, Rᵣ = 0.73 (light petroleum-ethyl acetate = 4 : 1). – ¹H NMR (400 MHz, CDCl₃): δ = 7.22 (m, 5H, arom. (ma, mi)); 5.39 (t, J = 9.3 Hz, H₂, 1H, H-1 (ma, mi)); 5.42 (dd, J, 1.3 Hz, 1H, H-4 (ma)); 4.98 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 4.91 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 1.72 (m, 2H, β-CH₂- (ma, mi)); 1.22 – 0.95 (m, 41H, Piv-CH₃ + -CH₂-N- + -CH₃ (ma, mi)); 0.79 (t, J = 7.3 Hz, 3H, -CH₃ (ma, mi)). – ¹³C NMR (100.6 MHz, CDCl₃): δ = 7.72 (m, 5H, arom. (ma, mi)); 5.93 (t, J = 9.3 Hz, 1H, H-1 (ma, mi)); 5.07 (dd, J, 1.3 Hz, 1H, H-4 mi)); 4.89 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 mi)); 4.91 (dd, J, 1.3 Hz, 9.7 Hz, 1H, H-3 (ma, mi)); 1.72 (m, 2H, β-CH₂- (ma, mi)); 1.22 – 0.95 (m, 41H, Piv-CH₃ + -CH₂-N- + -CH₃ (ma, mi)); 0.79 (t, J = 7.3 Hz, 3H, -CH₃ (ma, mi)).
0.70 (light petroleum–ethyl acetate = 4 : 1), \( R_f = 16.20 \) min.– C\textsubscript{6}H\textsubscript{12}N\textsubscript{6}O\textsubscript{3} (647.9): calcld. C 66.74, H 8.87, N 2.16; found C 67.08, H 8.76, N 2.02. – \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.26 \) (m, 5H, arom. (ma, mi)), 5.43 (2J, \( J_{2,3} = 9.8 \) Hz, \( J_{1,2} = 9.8 \) Hz, 1H, –H-2 (ma, mi)), 5.31 (d, \( J_{d,3} = 3.1 \) Hz, 1H, –H-4 (mi)), 5.27 (dd, \( J_{d,3} = 2.7 \) Hz, 1H, –H-4 (ma)); 4.99 (dd, \( J_{d,3} = 3.1 \) Hz, \( J_{2,3} = 9.8 \) Hz, 1H, –H-3 (mi)); 4.92 (dd, \( J_{d,3} = 3.1 \) Hz, \( J_{2,3} = 9.8 \) Hz, 1H, –H-3 (ma)); 4.32 (d, \( J_{d,1} = 9.4 \) Hz, 1H, –H-1 (mi)); 4.16 (m, \( J_{d,1} = 9.4 \) Hz, 1H, –H-1 (ma), H-6 (ma, mi)); 3.94 (m, 1H, –CH\(_2\)-N (ma, mi)); 3.90 (m, 2H, –CH (ma) H-6’ (ma)); 3.81 (m, 2H, –CH (ma) H-6’ (ma)); 3.57 (m, 1H, –H-5 (ma)); 2.92 (m, 1H, –CH\(_2\)-N- (ma, mi)); 2.78 (m, 1H, –CH\(_2\)-N- (ma, mi)); 1.42 (d, \( J = 6.7 \) Hz, 3H, \( \beta \)-CH\(_3\) (mi)); 1.38 (d, \( J = 6.7 \) Hz, 3H, \( \beta \)-CH\(_3\) (mi)) 1.24–0.97 (m, 39H, Piv–CH\(_2\)+CH\(_3\)). – \(^{13}C\) NMR (100.6 MHz, CDCl\(_3\)); \( \delta = 177.78, 178.80, 176.28, 176.84, 176.80, 176.77 \) (Piv–C=O); 144.16, 143.97 (arom. C\textsubscript{quat}); 128.17, 128.02, 127.79, 127.75, 127.04, 126.74 (arom. C); 89.89, 88.98 (C-1); 72.97, 72.85, 71.52, 71.33, (C-3, C-5); 67.62, 67.42, 66.18, 65.69 (C\textsubscript{2}, C-4); 62.07 (C-6); 58.06, 56.50 (\( \alpha \)-C); 39.27 (–CH\(_2\)-N); 39.02, 38.39, 38.69 (Piv–C\textsubscript{quat}); 27.24, 27.19, 27.08 (Piv–CH\(_3\)); 26.79 (–CH\(_2\)-); 21.20, 17.98, 14.82, 14.21 (–CH\(_3\)).

N-Ethyl-N-(2,3,4,6-tetra-O-pivaloyl-\( \beta \)-D-galactopyranosyl)-(1-phenyl)-propylamine (7)

According to the general procedure 0.1 g of \( N \)-benzyldiene-ethylaniline (1) was glycosylated and reacted with 5 mL of a solution of diethylzinc (1M in n-heptane, 5 mmol). The diastereomeric ratio was recorded by \(^{1}H\) NMR spectroscopy of 7 (dd (93 %). The product 7 was purified by preparative HPLC in MeCN-H\(_2\)O = 93 : 7 to 100 : 0 within 30 min on a Knauer Kromasil C18 column; the diastereomeric excess (dd (91 %) and purified by preparative HPLC in MeCN-H\(_2\)O = 93 : 7 to 100.0 min on a Knauer Kromasil C18 column. Yield: 19 mg (R)-10 (3.6 %).}

- \( R \)-diastereomer, (R)-10: \( [\alpha]^{D}_{D} = +71.7 \) (c = 1, CHCl\(_3\)); \( R \)-10: \( [\alpha]^{D}_{D} = +71.7 \) (c = 1, CHCl\(_3\)); \( R \)-10: \( [\alpha]^{D}_{D} = +71.7 \) (c = 1, CHCl\(_3\)); \( R \)-10: \( [\alpha]^{D}_{D} = +71.7 \) (c = 1, CHCl\(_3\)).

- \( S \)-diastereomer, (S)-10: \( [\alpha]^{D}_{D} = +60.2 \) (c = 1, CHCl\(_3\)); \( S \)-10: \( [\alpha]^{D}_{D} = +60.2 \) (c = 1, CHCl\(_3\)); \( S \)-10: \( [\alpha]^{D}_{D} = +60.2 \) (c = 1, CHCl\(_3\)); \( S \)-10: \( [\alpha]^{D}_{D} = +60.2 \) (c = 1, CHCl\(_3\)).

In this case, 0.16 g (0.75 mmole) \( N \)-benzylidene-(4-methoxyphenyl)amine [19] (8) was glycosylated with 2 and the intermediate glycosyl iminin salt 9 reacted with 5 mL of a diethylzinc solution (1M in n-heptane) according to the general procedure. The diastereomers 10 were separated by analytical HPLC in MeCN-H\(_2\)O = 93 : 7 to 100.0 min on a Knauer Kromasil C18 column; the diastereomeric excess (dd (91 %) and purified by preparative HPLC in MeCN-H\(_2\)O = 93 : 7 to 100.0 min on a Knauer Kromasil C18 column. Yield: 19 mg (R)-10 (3.6 %) and 419 mg (S)-10 (79 %); mixture of diastereomers 10: colorless solid, m. p. 69–72 °C, \( R_{f} = 0.66 \) (light petroleum-ethyl acetate 4:1). – C\textsubscript{67}H\textsubscript{86}N\textsubscript{10}O\textsubscript{9} (740.0): calcld. C 68.17, H 8.31, N 1.89; found C 67.84, H 8.26, N 1.79.
(Piv-C\textsubscript{quant}); 28.19 (-CH\textsubscript{2}); 27.23, 27.07, 26.94 (Piv-CH\textsubscript{3}); 10.83 (-CH\textsubscript{3}).

1-Phenyl-propylamine hydrochloride (12)

(S)-N-(4-Methoxyphenyl)-N-(2,3,4,6-tetra-O-pivaloyl-β-d-galactopyranosyl)-(1-phenyl)-propylamine (10) (370 g, 0.5 mmol) was dissolved in 50 mL of MeCN. To this solution, 1N HCl (5 mL) was added, and the mixture was stirred at r.t. for 10 h. This solution containing tetra-O-pivaloyl-β-d-galactopyranose and N-(4-methoxy-phenyl)-(1-phenyl)-propylamine (11) was neutralized with 1N NaOH. To the neutral solution 0.825 g (1.5 mmol) of ceric ammonium nitrate was added. After stirring for 1 h, the black solution was filtered, the solvents were evaporated from the filtrate in vacuo, and the remainder was dissolved in 1N HCl (10 mL). This solution was extracted three times with CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The aqueous solution was made alkaline by addition of K\textsubscript{2}CO\textsubscript{3} and extracted three times with CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The organic solution was extracted three times with 1N HCl (10 mL), and the combined acidic aqueous solutions were evaporated to dryness to give the amine hydrochloride 12. Yield: 80 mg (94%); colorless solid, m.p. 194 °C. \([\alpha\text{D}\text{22}^\circ] = +5.82 (c = 2, EtOH)\) lit. \([22]: [\alpha\text{D}\text{22}^\circ] = +5.1 (c = 2.0, EtOH), m.p. 191 – 194 °C. – 1H NMR (200 MHz, D\textsubscript{2}O): \(\delta\) = 7.35 (m, 5H, arom.); 4.15 (t, J = 7.3 Hz; 1H, α-CH); 1.95 – 1.86 (m, 2H, –CH\textsubscript{2}); 0.75 (t, J = 7.3 Hz; 3H, -CH\textsubscript{3}).