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$InCl_3$-catalyzed asymmetric aza-Friedel–Crafts reaction of indoles with imines generated from O-pivaloylated β-D-galactosylamine

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ABSTRACT

The highly diastereoselective $InCl_3$-catalyzed aza-Friedel–Crafts reaction of substituted indoles with aldimines generated from Kunz's amine was studied. The reaction afforded the desired product in good to high yields with up to >19:1 diastereoselective ratios. The O-pivaloylated β-D-galactosyl moiety could not be cleaved under the traditional acidic conditions. It was removed successfully after unmasking of the *O*-pivaloyl groups using MeOH/NaOMe and treatment with $HOAc/H_2O$ subsequently, to yield the 3-indolyl aryl methanamine derivatives in high optical purity.

1. Introduction

Carbohydrate derivatives are effective chiral auxiliaries in many asymmetric syntheses.[1–3] In particular, O-pivaloylated β-D-galactosylamine, which was developed by Kunz et al., has been used in a series of reactions, such as Strecker reaction,[4–6] Ugi reaction,[7–12] Mannich reaction,[13–15] and hetero-Diels–Alder reaction.[16] Chiral homoallyl amines,[17–19] α-aminophosphonic acid derivatives,[15,20] and α-amino (phenyl)methyl(phenyl)phosphinic acids[21] were also synthesized with this chiral amine. In recent years, some examples of alkaloid synthesis[22–25] were reported using Domino Mannich–Michael reactions,[26–30] in which O-pivaloylated β-D-galactosylamine was utilized to generate the crucial chiral center. The use of O-pivaloylated β-galactosylamine as a chiral auxiliary to induce high enantioselectivity has been well defined.

Indole-containing compounds have attracted much attention due to their widely recognized unique properties in drug design. These structures exist in numerous alkaloids as well as other synthesized bioactive agents that show significant biological activities.[31,32] Among those, the 3-indolyl methanamine derivatives are of particular interest to us. Direct asymmetric aza-Friedel–Crafts reaction of indoles with aldimines is a convenient approach to the synthesis of these 3-indolyl methanamine derivatives. Initially, the imines were limited to the highly active N-protected α-imino esters.[33–35] Later, it was extended to aryl aldimines. Several new methods have been developed recently, in which $Cu(OTf)_2$/bisoxazoline complexes,[36] 9-thiourea cinchona alkaloids,[37] chiral phosphoric acid,[38–40] and axially chiral cyclometalated bidentate N-heterocyclic carbene palladium(II) complexes[41] have been used as the catalysts. In the reactions reported with a variety of aldimines and indoles with different electronic properties, the steric hindrance of the indole derivatives has been a problem.[40] In addition, the removals of the N-protecting groups remain unsolved.[33–41] In this note, we present an $InCl_3$-catalyzed aza-Friedel–Crafts reaction of indoles, including the 2-substituted indoles, with aldimines prepared from O-pivaloylated β-D-galactosylamine. The reaction proceeds in good to high yields with high diastereoselectivity.

2. Results and discussion

It is well known that the acid-triggered aza-Friedel–Crafts reaction of indoles is often associated with the side reaction to form bisindole compounds. The extent of the side reaction is largely dependent on the catalyst and the N-protection group of the aldimine. Since a specific N-protection group as the chiral auxiliary was used in our method, we then investigated different Lewis acid catalysts to find one that can catalyze the reaction efficiently and has limited side reaction. The reaction of 4-nitro-*N*-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl) benzylideneamine (**1a**) and indole (**2a**) was used to screen the Lewis acid catalysts (Scheme 1). At −30 °C with 4 equiv of indole and 0.2 equiv of catalyst in dichloromethane, the reaction proceeded smoothly with all Lewis acids tested. Good yields were obtained when $MgBr_2{\cdot}Et_2O$ and $ZnCl_2$ were used, but the diastereoselectivity was moderate (Table 1, entries 1–2). When $SnCl_4$ and $FeCl_3$[42] were used, on the contrary,

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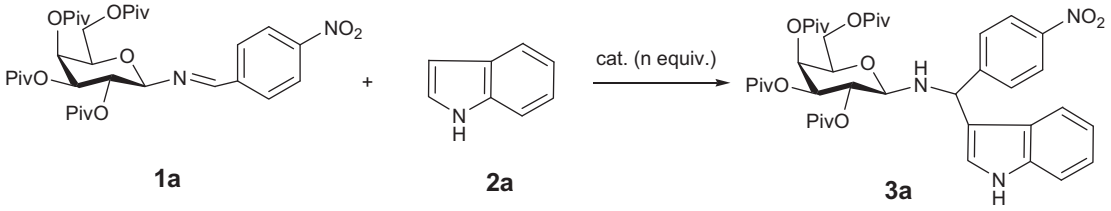


Scheme 1. Aza-Friedel–Crafts reaction of indole with imine.

Table 1
Catalysts screened for aza-Friedel–Crafts reaction

Entry[a]	T (°C)	Time (h)	Indole (equiv)	Catalyst	n (equiv)	Yield[b] (%)	Ratio[c]
1	−30	1	4	$MgBr_2{\cdot}Et_2O$	0.2	85	6:1
2	−30	15	4	$ZnCl_2$	0.2	70	5:1
3	−30	3	4	$SnCl_4$	0.2	18	10:1
4	−30	3	4	$FeCl_3$	0.2	47	13:1
5	−30	15	4	$InCl_3$	0.2	80	>19:1
6	−30	15	4	$InCl_3$	0.5	73	15:1
7	−40	15	4	$InCl_3$	0.2	82	>19:1
8	−50	42	4	$InCl_3$	0.2	25	>19:1
9	−40	15	2	$InCl_3$	0.2	64	>19:1
10	−40	15	1.1	$InCl_3$	0.2	42	12:1

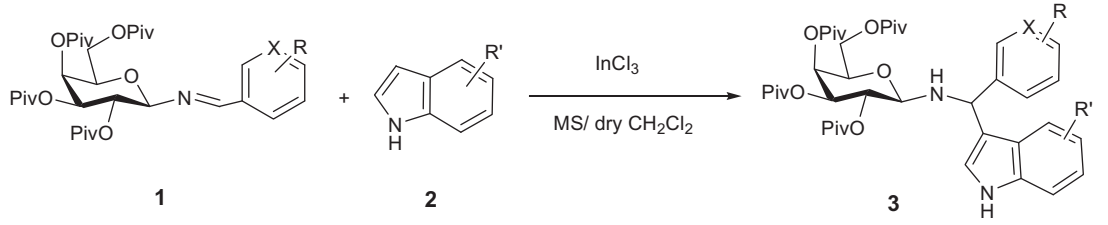
[a] All reactions were carried out with 0.5 g 4 Å molecular sieves in dry CH_2Cl_2.
[b] Isolated yield after column chromatography.
[c] Ratio of diastereomers was determined by 400 MHz ^1H NMR.

the reaction product was obtained with high diastereoselectivity but in low yield, due to the formation of the bisindole side product (entries 3–4). $InCl_3$[43–47] turned out to be the most efficient catalyst. The aza-Friedel–Crafts reaction catalyzed by $InCl_3$ afforded the product in 80% yield and the ratio of diastereomers was >19:1 (entry 5).

We then optimized the ratio of the catalyst and indole as well as the reaction temperature. We found that when the catalyst ratio was increased to 0.5 equiv, both the yield and the diastereoselectivity decreased slightly (entry 6). Lowering the temperature to −40 °C resulted in a slight increase in yield with the same diastereoselectivity (entry 7). However, at −50 °C, the reaction proceeded so slowly that even after 42 h, only a small portion of the reactant **1a** was consumed and the product was obtained in 25% yield (entry 8). Decreasing the amount of indole proved to be unsuccessful (entries 9–10), with a dramatic drop in yield due to the formation of the bisindole by-product. It was probably because the amount of indole greatly affected the aza-Friedel–Crafts reaction rate, but had little effect on the formation of the side product.

Under the optimized reaction conditions, which were at −40 °C with 0.2 equiv of $InCl_3$ as the catalyst and 4 equiv of indole in dry dichloromethane, the scope of this method was tested with a variety of aldimines and indoles. The reactions of various aldimines formed from different aldehydes with the unsubstituted indole and the reactions of the aldimine **1a** with various substituted indoles were investigated (Scheme 2). The results are summarized in Table 2. For aldimines, when electron-withdrawing groups such as the nitro- and cyano- groups were present, the reaction proceeded smoothly and gave the product in moderate to good yields (65–80%), and the diastereoselectivity ratio was up to >19:1 (entries 1–3). The 2-nitro-substituted benzaldimine did not affect the diastereoselectivity (entry 2, ratio >19:1), which indicated that the reaction was tolerant for the steric hindrance of aldimine, although the yield was moderate. Moreover, the basic 3-pyridinyl aldimine yielded the product in 70% yield with good diastereoselectivity, although more catalyst and indole were needed (entry 6). Aldimines formed from the 4-trifluoromethyl, or 4-fluoro benzaldehyde afforded no desired product but the bisindole by-product (entries 4–5).

For substituted indoles, most of the reactions proceeded smoothly to afford the final product **3** except that in entries 8 and 9 of Table 2. It was expected that the 3-Me indole would fail to react to form product **3i** (entry 9) due to the weaker nucleophilicity of the 2-position of indole comparing with the 3-position. And the *N*-Boc-protected indole also afforded no product as a result of the electron-withdrawing property of the Boc group (entry 8). Indoles bearing electron-donating groups generally provided better yields (entries 7 and 10, yields were >90%, respectively, compared to entry 11, with yield of 60%). The electronic property of substituted indole did not affect the diastereoselectivity significantly, since 5-methoxyindole provided product in 8:1 dr (entry 10), and the reaction of 6-cloroindole proceeded with slightly higher diastereoselectivity (entry 11). We found that the reaction with 2-methylindole proceeded with



Scheme 2. Aza-Friedel–Crafts reaction of indole derivatives with aldimines.

Table 2
Aza-Friedel–Crafts reaction of indole derivatives with various aldimines

Entry[a]	X	R	R′	*T* (°C)	Time (h)	Yield[b] (%)	Ratio[c]
1	1a: C	*p*-NO_2	2a: H	−40	15	80	>19:1
2	1b: C	*o*-NO_2	H	−40	15	65	>19:1
3	1c: C	*p*-CN	H	−40	15	73	10:1
4	1d: C	*p*-CF_3	H	−40	15	—	—
5	1e: C	*p*-F	H	−40	15	—	—
6	1f: N	H	H	−30	15	70	10:1[d]
7	1a: C	*p*-NO_2	2g: 2-Me	−40	15	92	>19:1
8	C	*p*-NO_2	2h: 1-Boc	−20	15	—	—
9	C	*p*-NO_2	2i: 3-Me	−40	15	—	—
10	C	*p*-NO_2	2j: 5-MeO	−40	15	90	8:1
11	C	*p*-NO_2	2k: 6-Cl	−40	15	60	19:1

[a] Without specific indication, all reactions were carried out with 0.2 equiv $InCl_3$, 4 equiv indole, and 0.5 g 4 Å MS at the shown temperature in dry CH_2Cl_2.
[b] Isolated yield by column chromatography.
[c] Ratio of diastereomers was determined by 400 MHz ^1H NMR.
[d] The reaction was carried out with 1.2 equiv $InCl_3$ and 10 equiv indole.

good yield (90%) and excellent diastereoselectivity (>19:1), indicating that 2-substituted indole did not affect the diastereoselectivity as previously reported.[40]

To prepare the final product 3-indolyl methanamine derivatives, we tested different methods to remove the auxiliary. The typical method with HCl[4–19,21–30] in methanol was not successful since the 3-indolyl methane was the only product. We later found that a new method using HOAc–H_2O after treatment with NaOMe in methanol[20] (Scheme 3) generated the desired 3-indolyl methanamine derivatives **4g** and **4k** with high yields and without racemization, as representative examples.

In summary, we have developed a method to synthesize 3-indolyl methanamine derivatives with $InCl_3$ as the catalyst and using O-pivaloylated β-D-galactosylamine as a chiral auxiliary. Excellent yield and diastereoselectivity were obtained (yield up to 92% and dr up to >19:1). Even the 2-substituted indole reacted to generate the desired product in high yield and diastereoselectivity, which was difficult to obtain under previously reported conditions. Moreover, a new method to remove the sugar moiety using aqueous HOAc after treatment with NaOMe in methanol was developed. This deprotection method may be useful for the removal of the protecting group of other N-glycoside substrates with high acid sensitivity.

3. Experimental

3.1. General methods

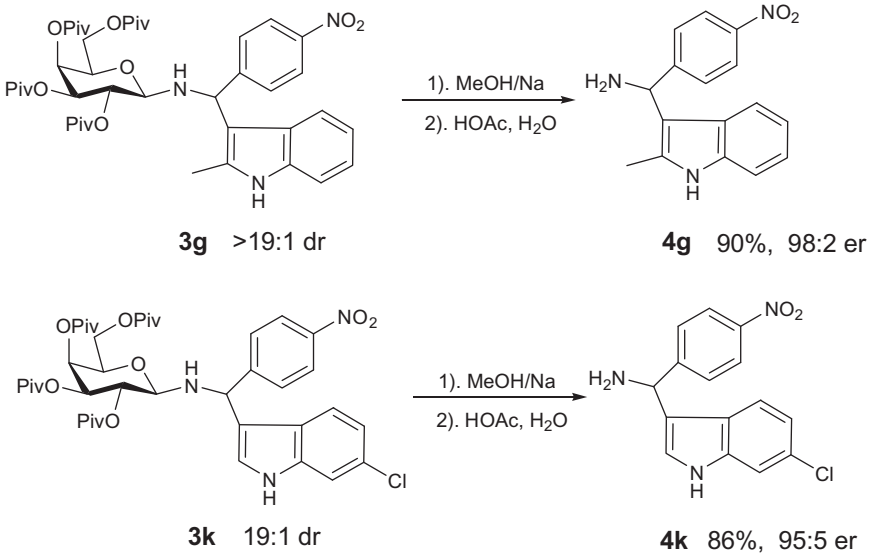
All reagents were obtained from commercial suppliers and were used without further purification. CH_2Cl_2 was distilled over CaH_2. Reactions were monitored by thin-layer chromatography (TLC) using commercial silica gel HSGF254 plates. Column chromatography was performed on Silica Gel 60 (E. Merck, 0.063–0.200 mm). The ^1H (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with Bruker AM-400 spectrometer in DMSO-d_6 solution. Chemical shifts were referenced to the residual solvent signals (2.50 ppm for ^1H and 39.43 ppm for ^{13}C). The HR-ESI-MS data were measured on a Bruker Apex IV FTMS. Enantiomeric ratio (er) was determined using a Hitachi HPLC system with a Hitachi L6200 pump and an ABI 783A UV detector with Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID, *n*-hexane/*i*-PrOH = 30:70, 0.5 mL/min, 254 nm).

3.2. General procedure for the aza-Friedel–Crafts reaction to form the compounds 3a–k

An oven-dried 10 mL vial was charged with O-pivaloylated β-galactosylaldimine (0.30 mmol), $InCl_3$ (0.06 mmol, 0.2 equiv) and 0.5 g 4 Å molecular sieves. After the vessel was flushed with alternating vacuum and nitrogen purge cycles, 4 mL of dry CH_2Cl_2 was added to the vessel via a syringe, and the mixture was stirred under N_2 at −40 °C for 15 min before indole or substituted indole (1.2 mmol, 4 equiv) was added. The resulting mixture was stirred for the indicated time until the reaction was completed as shown by TLC (usually 15 h). Then three drops of triethylamine were added and the mixture was gradually warmed to room temperature. After removal of the molecular sieves by filtration, the mixture was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1), yielding the corresponding compounds **3a**–**k** as mixed diastereomers. The diastereomers could not be separated by flash chromatography.

3.2.1. *N*-[Indol-3-yl-(4-nitrophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3a)

^1H NMR: δ 11.00 (s, 1H, indole N*H*), 8.16 (d, *J* 8.8 Hz, 2H, *ph*), 7.74 (d, *J* 8.8 Hz, 2H, *ph*), 7.57 (d, *J* 8.0 Hz, 1H, *indole*), 7.34 (d, *J* 8.0 Hz,



Scheme 3. Cleavage of chiral auxiliary under basic conditions.

1H, *indole*), 7.15 (s, 1H, *indole*), 7.05 (t, *J* 7.6 Hz, 1H, *indole*), 6.91 (t, *J* 7.6 Hz, 1H, *indole*), 5.68 (s, 1H, C*H*), 5.26–5.23 (m, 2H, 3-*H*,4-*H*), 5.10 (t, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 8.8 Hz, 1H, 2-*H*), 4.16–4.06 (m, 3H, 1-*H*, 5-*H*, 6a-*H*), 3.92 (dd, $J_{6a,6b}$ 9.2 Hz, $J_{6b,5}$ 4.8 Hz, 1H, 6b-*H*), 1.21 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ176.83, 176.30, 176.18, 176.11, 151.42, 146.34, 136.33, 128.65, 124.98, 123.26, 122.41, 121.30, 118.61, 118.50, 116.78, 111.61, 85.31, 71.20, 70.35, 68.92, 67.40, 61.15, 53.47, 26.95, 26.72, 26.68, 26.65, 26.60. HR-ESI-MS: Calcd for $C_{41}H_{55}N_3O_{11}$ [M+Na]$^+$: 788.3729, found: 788.3713.

3.2.2. *N*-[Indol-3-yl-(2-nitrophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3b)

^{1}H NMR: δ 11.01 (s, 1H, indole N*H*), 8.18 (d, *J* 8.0 Hz, 1H, *ph*), 7.84 (d, *J* 8.0 Hz, 1H, *ph*), 7.65 (t, *J* 8.0, 7.2 Hz, 1H, *ph*), 7.60 (d, *J* 8.0 Hz, 1H, *indole*), 7.49 (t, *J* 7.6 Hz, 1H, *ph*), 7.34 (d, *J* 8.0 Hz, 1H, *indole*), 7.06 (t, *J* 7.6 Hz, 1H, *indole*), 6.93–6.89 (m, 2H, *indole*), 6.10 (s, 1H, C*H*), 5.26–5.24 (m, 2H, 3-*H*, 4-*H*), 5.06 (t, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 9.6 Hz, 1H, 2-*H*), 4.22–4.18 (m, 2H, 1-*H*, 5-*H*), 4.04 (dd, $J_{6a,6b}$ 10.8 Hz, $J_{6a,5}$ 7.6 Hz, 1H, 6a-*H*), 3.92 (dd, $J_{6a,6b}$ 10.8 Hz, $J_{6b,5}$ 7.2 Hz, 1H, 6b-*H*), 1.18 (s, 9H, C(CH_3)$_3$), 1.17 (s, 9H, C(CH_3)$_3$), 1.13 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 177.00, 176.25, 176.19, 176.10, 149.61, 146.34, 137.14, 136.26, 132.30, 129.70, 128.08, 125.19, 123.68, 122.97, 121.33, 118.67, 118.53, 116.22, 111.58, 85.81, 71.24, 70.40, 68.87, 67.42, 61.20, 54.82, 26.93, 26.70, 26.68, 26.61. HR-ESI-MS: Calcd for $C_{41}H_{55}N_3O_{11}$ [M+Na]$^+$: 788.3729, found: 788.3723.

3.2.3. *N*-[Indol-3-yl-(4-cyanophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3c)

^{1}H NMR: δ 10.99 (s, 1H, indole N*H*), 7.77 (d, *J* 8.0 Hz, 2H, *ph*), 7.66 (d, *J* 8.0 Hz, 2H, *ph*), 7.55 (d, *J* 8.0 Hz, 1H, *indole*), 7.33 (d, *J* 8.0 Hz, 1H, *indole*), 7.12 (s, 1H, *indole*), 7.05 (t, *J* 8.0 Hz, 1H, *indole*), 6.90 (t, *J* 7.6 Hz, 1H, *indole*), 5.61 (s, 1H, C*H*), 5.26–5.23 (m, 2H, 3-*H*,4-*H*), 5.09 (t, $J_{2,3}$ 9.2 Hz, $J_{1,2}$ 9.2 Hz, 1H, 2-*H*), 4.13–4.06 (m, 3H, 1-*H*, 5-*H*, 6a-*H*), 3.92 (dd, $J_{6a,6b}$ 9.6 Hz, $J_{6b,5}$ 6.0 Hz, 1H, 6b-*H*), 1.20 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 176.83, 176.30, 176.18, 176.09, 149.24, 136.30, 132.04, 128.49, 124.98, 122.28, 121.26, 118.76, 118.45, 116.98, 111.60, 109.49, 85.28, 71.17, 70.31, 68.94, 67.41, 61.17, 53.69, 26.95, 26.72, 26.68, 26.60. HR ESI MS: Calcd for $C_{42}H_{55}N_3O_9$ [M+Na]$^+$: 768.3830, found: 768.3813.

3.2.4. *N*-[Indol-3-yl-(pyridine-3-yl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3f)

^{1}H NMR: δ 10.98 (s, 1H, indole N*H*), 8.68 (s, 1H, *py*), 8.42 (br, 1H, *py*), 7.79 (d, *J* 8.0 Hz, 1H, *indole*), 7.55 (d, *J* 8.0 Hz, 1H, *indole*), 7.35–7.31 (m, 2H, *py*), 7.13 (s, 1H, *indole*), 7.05 (t, *J* 7.6 Hz, 1H, *indole*), 6.91 (t, *J* 7.6 Hz, 1H, *indole*), 5.58 (s, 1H, C*H*), 5.27–5.24 (m, 2H, 3-*H*, 4-*H*), 5.09 (t, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 9.2 Hz, 1H, 2-*H*), 4.16–4.07 (m, 3H, 1-*H*, 5-*H*, 6a-*H*), 3.94 (dd, $J_{6a,6b}$ 10.4 Hz, $J_{6b,5}$ 6.0 Hz, 1H, 6b-*H*), 1.19 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.17 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 176.87, 176.31, 176.21, 176.07, 149.10, 148.07, 138.49, 136.20, 135.15, 134.42, 124.98, 123.28, 121.95, 121.28, 118.44, 117.30, 111.55, 85.17, 71.14, 70.39, 68.96, 67.50, 61.33, 51.71, 26.91, 26.74, 26.69, 26.64, 26.61. HR-ESI-MS: Calcd for $C_{40}H_{55}N_3O_9$ [M+Na]$^+$: 744.3830, found: 744.3819.

3.2.5. *N*-[2-Metyl-Indol-3-yl-(4-nitrophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3g)

^{1}H NMR: δ 10.92 (s, 1H, indole N*H*), 8.14 (d, *J* 8.8 Hz, 2H, *ph*), 7.74 (d, *J* 8.8 Hz, 2H, *ph*), 7.54 (d, *J* 8.0 Hz, 1H, *indole*), 7.21 (d, *J* 8.0 Hz, 1H, *indole*), 6.95 (t, *J* 7.6 Hz, 1H, *indole*), 6.84 (t, *J* 7.6 Hz, 1H, *indole*), 5.69 (s, 1H, C*H*), 5.27 (dd, $J_{3,4}$ 3.2 Hz, $J_{2,3}$ 10.0 Hz, 1H, 3-*H*), 5.23 (d, $J_{3,4}$ 3.2 Hz, 1H, 4-*H*), 5.12 (t, $J_{2,3}$ 10.0 Hz, $J_{1,2}$ 8.8 Hz, 1H, 2-*H*), 4.24 (d, $J_{1,2}$ 8.8 Hz, 1H, 1-*H*), 4.13 (t, $J_{5,6a}$ 6.4 Hz, $J_{5,6b}$ 6.8 Hz, 1H, 5-*H*), 4.06 (dd, $J_{6a,6b}$ 10.4 Hz, $J_{5,6b}$ 6.8 Hz, 1H, 6b-*H*), 3.92 (dd, $J_{6a,6b}$ 10.4 Hz, $J_{5,6a}$ 6.4 Hz, 1H, 6a-*H*), 2.40 (s, 3H, CH_3), 1.26 (s, 9H, C(CH_3)$_3$), 1.17 (s, 9H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$), 1.04 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 176.86, 176.26, 176.23, 176.17, 151.94, 146.06, 134.91, 131.94, 127.93, 126.08, 123.29, 120.19, 118.57, 118.26, 111.55, 110.52, 85.54, 71.36, 70.49, 69.02, 67.49, 61.37, 52.90, 27.04, 26.74, 26.70, 26.64, 11.96. HR-ESI-MS: Calcd for $C_{42}H_{57}N_3O_{11}$ [M+Na]$^+$: 802.3885, found: 802.3867.

3.2.6. *N*-[5-Methoxy-Indol-3-yl-(4-nitrophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3j)

^{1}H NMR: δ 10.86 (s, 1H, indole N*H*), 8.18 (d, *J* 8.4 Hz, 2H, *ph*), 7.74 (d, *J* 8.4 Hz, 2H, *ph*), 7.24 (d, *J* 8.8 Hz, 1H, *indole*), 7.04 (d, *J* 2.0 Hz, 1H, *indole*), 6.96 (s, 1H, *indole*), 6.72 (dd, J_1 2.0 Hz, J_2 8.8 Hz, 1H, *indole*), 5.64 (s, 1H, C*H*), 5.25–5.23 (m, 2H, 3-*H*,4-*H*), 5.09 (t, $J_{2,3}$ 10.0 Hz, $J_{1,2}$ 9.6 Hz, 1H, 2-*H*), 4.16–4.08 (m, 3H, 1-*H*, 5-*H*, 6a-*H*), 3.94 (dd, $J_{6a,6b}$ 10.0 Hz, $J_{6b,5}$ 6.0 Hz, 1H, 6b-*H*), 3.72 (s, 3H, OCH_3), 1.19–1.16 (m, 27H, three C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 176.86, 176.32, 176.22, 176.13, 153.08, 151.91, 151.40, 146.40, 131.27, 128.70, 125.36, 123.26, 116.45, 112.29, 111.46, 100.31, 99.50, 85.55, 71.24, 70.37, 68.89, 67.41, 61.22, 55.20, 53.30, 26.96, 26.75, 26.68, 26.62. HR-ESI-MS: Calcd for $C_{42}H_{58}N_3O_{12}$ [M+Na]$^+$: 818.3834, found: 818.3822.

3.2.7. *N*-[6-Chloro-Indol-3-yl-(4-nitrophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (3k)

^{1}H NMR: δ 11.15 (s, 1H, indole N*H*), 8.16 (d, *J* 8.8 Hz, 2H, *ph*), 7.71 (d, *J* 8.8 Hz, 2H, *ph*), 7.54 (d, *J* 8.4 Hz, 1H, *indole*), 7.38 (d, *J* 1.6 Hz, 1H, *indole*), 7.22 (s, 1H, *indole*), 6.91 (dd, J_1 8.4 Hz, J_2 1.6 Hz, 1H, *indole*), 5.64 (s, 1H, C*H*), 5.24–5.21 (m, 2H, 3-*H*,4-*H*), 5.10 (t, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 9.2 Hz, 1H, 2-*H*), 4.14–4.06 (m, 3H, 1-*H*, 5-*H*, 6a-*H*), 3.90 (dd, $J_{6a,6b}$ 9.6 Hz, $J_{6b,5}$ 6.4 Hz, 1H, 6b-*H*), 1.20 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.14 (s, 9H, C(CH_3)$_3$), 1.03 (s, 9H, C(CH_3)$_3$). ^{13}C NMR: δ 176.84, 176.26, 176.20, 176.12, 151.20, 146.39, 136.52, 128.65, 128.03, 123.79, 123.32, 120.01, 118.78, 117.08, 111.18, 99.49, 85.34, 71.24, 70.29, 68.86, 67.34, 61.07, 54.82, 53.41, 26.96, 26.90, 26.72, 26.69. HR-ESI-MS: Calcd for $C_{41}H_{54}ClN_3O_{11}$ [M+Na]$^+$: 822.3339, found: 822.3320.

3.3. General procedure for the removal of the auxiliary to form compounds 4g and 4k

A solution of compound **3g** or **3k** (0.4 mmol) in dry methanol (2 mL) was treated with a freshly prepared (0.5 M) solution of sodium methoxide (2 mL), which was prepared from sodium and dry methanol. The solution was stirred until the reactant was consumed (TLC control). To the mixture were added a few drops of water, and the mixture was neutralized with acetic acid, after which the mixture was stirred for another 4 h. Then the mixture was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and filtered, and the volatiles were removed under vacuum. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 30/1, with 0.1% Et_3N), yielding the corresponding compounds **4g** or **4k**.

3.3.1. *N*-[2-Metyl-Indol-3-yl-(4-nitrophenyl)methyl]amine (4g)

98:2 er, t_{major} = 16.39 min and t_{minor} = 19.74 min. ^{1}H NMR: δ 10.84 (s, 1H, indole N*H*), 8.14 (d, *J* 8.8 Hz, 2H, *ph*), 7.74 (d, *J* 8.8 Hz, 2H, *ph*), 7.42 (d, *J* 8.0 Hz, 1H, *indole*), 7.21 (d, *J* 8.0 Hz, 1H, *indole*), 6.93 (t, *J* 7.2 Hz, 1H, *indole*), 6.81 (t, *J* 7.2 Hz, 1H, *indole*), 5.52 (s, 1H, C*H*), 2.43 (s, 3H, CH_3). ^{13}C NMR: δ 154.92, 145.62, 135.04, 131.73, 127.54, 126.22, 123.00, 119.96, 118.66, 118.16, 113.81, 110.36, 50.75, 11.75. HR-ESI-MS: Calcd for $C_{16}H_{15}N_3O_2$ [M−H]$^+$: 280.1080, found: 280.1078.

3.3.2. *N*-[6-Chloro-indol-3-yl-(4-nitrophenyl)methyl]amine (4k)

90:5 er, t_{major} = 11.66 min and t_{minor} = 14.66 min. ^{1}H NMR: δ 8.15 (d, *J* 8.4 Hz, 2H, *ph*), 7.73 (d, *J* 8.4 Hz, 2H, *ph*), 7.47 (d, *J* 8.4 Hz, 1H, *indole*), 7.37 (s, 1H, *indole*), 7.31 (s, 1H, *indole*), 6.92 (d, *J* 8.4 Hz, 1 H, *indole*), 5.47 (s, 1H, C*H*). ^{13}C NMR: δ154.84, 145.93, 136.67, 127.95, 125.81, 124.13, 123.43, 123.22, 120.42, 119.45, 118.68, 110.98, 51.84. HR-ESI-MS: Calcd for $C_{15}H_{12}ClN_3O_2$ $[M-NH_2]^+$: 285.0425, found: 285.0422.

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