Synthesis of a Polymer-Bound Galactosylamine and Its Application as an Immobilized Chiral Auxiliary in Stereoselective Syntheses of Piperidine and Amino Acid Derivatives

Gernot Zech and Horst Kunz*[a]

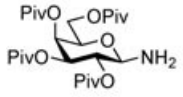
Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday

Abstract: A 2,3,4-tri-*O*-pivaloylated β-D-galactopyranosyl azide bearing a hydroxy-functionalized spacer unit at the C-6 position of the galactose was synthesized and immobilized on the solid phase by using a polymer-bound chlorosilane. The azide was reduced to the corresponding galactopyranosylamine, which served as a versatile chiral auxiliary in highly diastereoselective Ugi four-component condensation reactions at ambient temperature. Fluoride-induced cleavage from the polymeric support furnished *N*-glycosylated *N*-acylated α-amino acid amides. The reaction of the immobilized galactosylamine with aldehydes gave rise to the corresponding aldimines, which underwent a domino Mannich–Michael condensation reaction with Danishefsky's diene at ambient temperature to yield 2-substituted 5,6-didehydropiperidin-4-ones on the solid phase. Subsequent cleavage with tetra-*n*-butylammonium fluoride delivered the *N*-glycosylated products in high yields, purities, and diastereoselectivities. A chemoselective 1,4-hydride addition to the polymer-bound dehydropiperidinones was achieved in the presence of the bulky oxygenophilic Lewis acid methylaluminum [bis(2,6-di-*tert*-butyl-4-methylphenoxide)]. The conjugate addition of cyano-modified Gilman reagents to the immobilized dehydropiperidinones furnished 2,6-*cis*-substituted piperidine derivatives as the major diastereomers that were isolated after cleavage from the support.

Keywords: carbohydrates · chiral auxiliaries · chiral piperidines · combinatorial chemistry · solid-phase synthesis

Introduction

Combinatorial solid-phase chemistry[1] has proven to be an essential tool for rapid and efficient drug development. Although the synthesis of enantiomerically pure compounds is of significant importance for the medicinal industry, generally applicable asymmetric solid-phase strategies are still rare.[2] While polymer-bound chiral catalysts usually suffer from limited applicability, several immobilized chiral auxiliaries have been described in the literature.[3] Auxiliaries bound to the solid phase so far include enantiomerically pure 1,3-oxazolidine-2-ones,[4] prolinols,[5] pseudoephedrins,[6] or different carbohydrates;[7] these auxiliaries allow asymmetric enolate reactions,[4] Diels–Alder reactions,[8] 1,3-dipolar cycloadditions,[9] conjugate additions,[4e,10] and other types of reaction.[11]



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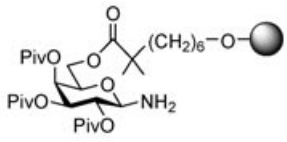

2a

2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**)[12] was shown to be a versatile chiral auxiliary enabling, for example, diastereoselective Strecker[13] and Ugi reactions,[14] hetero-Diels–Alder[15] and domino Mannich–Michael reactions.[16] Recently, we reported an immobilized version (**2a**) of this chiral galactosylamine, which allows diastereoselective syntheses of piperidine derivatives on the solid phase.[7e]

Herein, we describe the preparation of this polymer-bound galactosylamine and its employment in diastereoselective syntheses of piperidine and amino acid derivatives, which are generally obtained in excellent overall yields and high chemical and optical purities after cleavage from the polymeric support.

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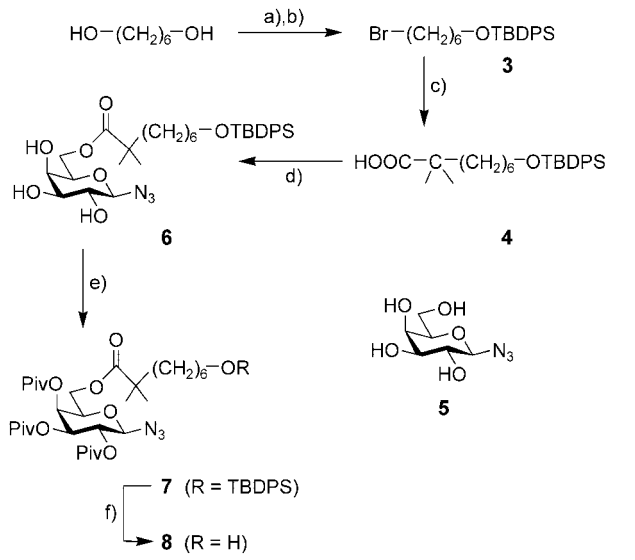
DOI: 10.1002/chem.200400253

Results and Discussion

Preparation of the immobilized galactosylamine: Polymer-bound silyl ethers, especially those substituted with bulky groups, have been investigated extensively as reaction surfaces due to the facile detachment of the reaction products by mild fluoridolysis. Resin-bound aryl dialkylsilyl ethers have been used in numerous syntheses of oligosaccharides,[17] glycopeptides,[18] polyketides,[19] and prostaglandins[20] and have been found to be stable towards a variety of organometallic reagents. For these reasons, we employed a sterically encumbered diisopropylchlorosilane as the anchor for the immobilization of the galactosylamine. Coupling with a suitable hydroxy-functionalized galactosyl azide should furnish a precursor of the auxiliary from which the desired galactosylamine can be obtained by on-bead reduction.

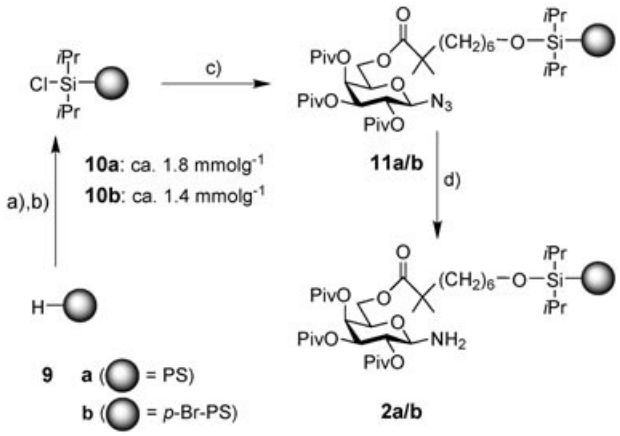
According to preceding studies,[7c] glycosyl azide **8** (Scheme 1) bearing an ω-hydroxy carboxylic acid spacer unit at C-6 of the carbohydrate was envisioned as a suitable



Scheme 1. Solution-phase synthesis of **8**. a) TBDPSCl, imidazole, DMF, 20 °C, 88 %; b) CBr_4, PPh_3, CH_2Cl_2, 0→20 °C, 97 %; c) $Me_2C{=}C(OLi)_2$, THF, −20→40 °C, 78 %; d) 1. $C_2O_2Cl_2$, CH_2Cl_2, 20 °C; 2. β-D-galactopyranosyl azide **5**, pyridine, DMAP, 60 °C, 59 %; e) PivCl, pyridine, 60 °C, 85 %; f) TBAF·3 H_2O, THF, 20 °C, 86 %. TBDPS = *tert*-butyldiphenylsilyl, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, Piv = pivaloyl (*t*BuCO), TBAF = tetra-*n*-butylammonium fluoride.

precursor. Galactosyl azide **8** was readily synthesized on a multigram scale from 1,6-hexanediol and β-D-galactopyranosyl azide **5** by a six-step protocol. Monoprotection of 1,6-hexanediol with *tert*-butyldiphenylchlorosilane, transformation of the remaining hydroxy function to form bromide **3**, and treatment with isobutyric acid dianion delivered the chain-extended pivalic acid derivative **4** (Scheme 1). This was treated with oxalyl chloride and coupled to β-D-galactopyranosyl azide **5**[21] to give selectively 6-*O*-acylated galactosyl azide **6**. The remaining carbohydrate hydroxy functions were pivaloylated and the silyl protecting group was finally removed by using tetra-*n*-butylammonium fluoride (TBAF) in THF, thereby furnishing the desired galactosyl azide **8** bearing a hydroxy-terminated spacer unit.

Polymer-bound chlorosilane **10a** was obtained with a relatively high loading of approximately 1.8 mmol g^{-1} (corresponding to a substitution of every fourth arene unit) by direct lithiation of polystyrene **9a** (cross-linked with 1 % divinylbenzene) and subsequent treatment with dichlorodiisopropylsilane according to a general procedure given by Farrall and Fréchet (Scheme 2).[22] *O*-Silylation of glycosyl azide



Scheme 2. Synthesis of the immobilized galactosylamine. a) For **9a**: *n*BuLi, TMEDA, C_6H_{12}, 60 °C; for **9b**: *n*BuLi, toluene, 60 °C (2 cycles); b) iPr_2SiCl_2, THF, 20 °C; c) 1. imidazole, **8** (0.23 equiv), CH_2Cl_2, 20 °C, 12 h; 2. addition of MeOH, 24 h; d) 1,3-propanedithiol (10 equiv), NEt_3 (10 equiv), DMF, 20 °C, 12 h. PS = polystyrene, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

8 with chlorosilane **10a** led to the immobilized auxiliary precursor **11a** with a loading of approximately 0.4 mmol g^{-1}.[23] It should be noted that due to the high loading of **10a**, 0.2 of an equivalent of **8** was sufficient to allow complete coupling onto the solid phase and that there was no need to reisolate any potentially remaining alcohol **8** from the washing solutions. If more than 0.2 of an equivalent of **8** was employed, the loading of **11a** only slightly increased to a maximum value of 0.484 mmol g^{-1} (with 1.0 equivalent of **8**), a result indicating that the polymeric support is saturated with the bulky auxiliary, probably due to steric reasons.[24] Substituted polystyrene resins obtained by the lithiation procedure described above and subsequent reaction with electrophiles mainly show a *para* substitution pattern.[25] Selectively *para*-substituted chlorosilane **10b** was obtained when commercially available *para*-bromopolystyrene **9b** was lithiated instead of polystyrene and was subsequently treated with dichlorodiisopropylsilane according to the procedures of Farrall and Fréchet[22] and Heinze et al.,[26] respectively (loading: approximately 1.437 mmol g^{-1}). Chlorosilane **10b** has been described to be advantageous with respect to reproducibility, control of the degree of functionalization, and homogeneity of the resin. However, in our hands, resin **10b** and resins **11b** and **2b**, obtained thereof, did not show any noticable difference in reactivity compared to resins **11a** and **2a**. Therefore, due to the lower costs of preparation, the following transformations on the solid phase have all been performed with silyl resins based on chlorosilane **10a**.

On-bead reduction of the azide moiety was accomplished by using 10 equivalents each of 1,3-propanedithiol and triethylamine in DMF at room temperature to give galactosylamines **2** (Scheme 2). This method of reduction[27] has already been employed for the reduction of β-D-glycosyl azides[28] on the solid phase and resulted in retention of the β configuration at the anomeric center. Both the coupling and the reduction reaction are favorably monitored by FT-IR spectroscopy of KBr pellets prepared from the resins. The spectrum obtained from resin **11a** showed strong absorption for the azide ($\tilde{\nu}_{azide} = 2116\ cm^{-1}$) and the ester carbonyl groups ($\tilde{\nu}_{C=O} = 1745\ cm^{-1}$), while in the spectrum of resin **2a** the azide absorption almost disappeared, thereby indicating complete reduction after 22 h of vigorous shaking (Figure 1). Galactosylamine resin **2a** can be prepared on a

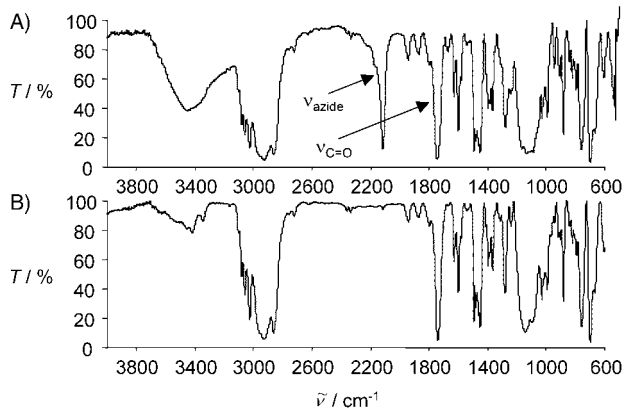
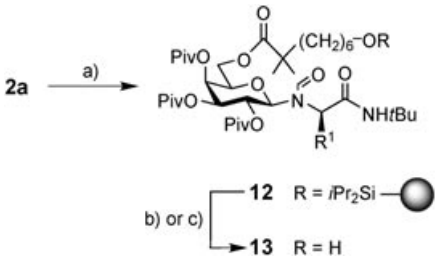


Figure 1. IR spectra of resin-bound glycosyl azide **11a** (A) and amine **2a** (B).

multigram scale and stored without any loss of reactivity for several months. Its loading was determined by elemental analysis to be 0.414 mmol g^{-1} (corresponding to a substitution of every eighteenth arene unit with the galactose moiety).[29]

With the immobilized amine **2a** in hand, we first set out to explore the use of this auxiliary in asymmetric Ugi four-component condensation reactions on solid phase to give *N*-formyl-*N*-galactosyl-α-amino acid derivatives. Reaction conditions of the corresponding solution-phase process include stirring of the galactosylamine **1** with a small excess of aldehyde, isocyanide, formic acid, and the activating Lewis acid zinc chloride at low temperature.[14] Preliminary investigations with a similar polymer-bound galactosylamine bearing a different spacer unit have shown that asymmetric Ugi reactions can be performed on the solid phase by using reaction conditions similar to those reported for the solution-phase process. In these previous studies, the *N*-formyl-*N*-galactosyl-α-amino acid derivatives were obtained after cleavage from the support with diastereoselectivities (d.r. 86:14–94:6)[7c] comparable to those reported for the solution-phase process (d.r. 91:9–97:3).[14] However, to obtain sufficiently pure reaction products purification by preparative HPLC was necessary.

During the present work, we reinvestigated the reaction and found that the condensation could be performed at ambient temperature without any decrease in diastereoselectivity. Shaking of the galactosylamine **2a** with five equivalents each of aldehyde, *tert*-butyl isocyanide, formic acid, and zinc chloride gave rise to *N*-formylated *N*-galactosylated amino acid derivatives **12** on the solid phase; the products were subsequently released from the support by treatment with fluoride (Scheme 3). Standard cleavage conditions include



Scheme 3. Diastereoselective Ugi synthesis on the solid phase. a) R^1–CHO (5 equiv), HCO_2H (5 equiv), *t*BuNC (5 equiv), $ZnCl_2$ (3 equiv), THF, 20 °C; b) cleavage method A: TBAF·3H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h; c) cleavage method B: 1. HF-pyridine complex (10 equiv based on silyl units), THF, 20 °C, 2. addition of $MeOSiMe_3$.

stirring with five equivalents of tetra-*n*-butylammonium fluoride (TBAF) in THF buffered with acetic acid (molar ratio TBAF/AcOH 3:1). The crude products were generally obtained with high yield, purity, and diastereoselectivity (according to LC-MS analysis with UV and ELS detection) and did not require any further purification.[30] In cases with electron-deficient phenylglycine derivatives as the reaction products **13** (see **13a**, **13b**, and **13d** in Table 1), cleavage of the silyl anchor with the nonbasic HF-pyridine complex is recommended instead of cleavage with TBAF. Although buffered with acetic acid, treatment with TBAF led to partial epimerization of the amino acid derivatives (Table 1). As expected from the corresponding reactions in solution, the major diastereomers belong to the D series of α-amino acids.[31]

Table 1. Analysis of Ugi condensation products **13** after cleavage from the polymeric support.

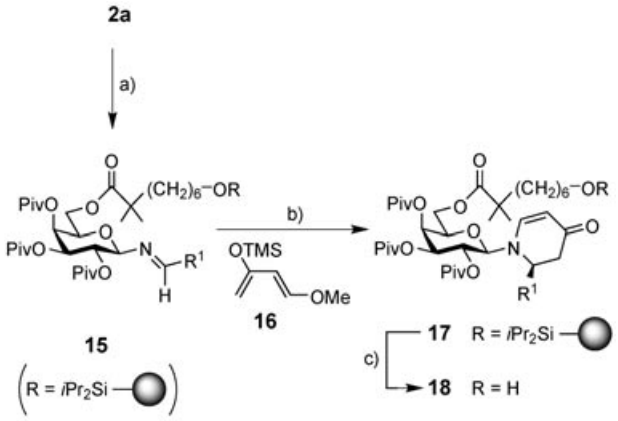
Compound	R^1	Yield [%][a]	Purity [%][b]	d.r.[b]
13a	*p*-O_2N–C_6H_4	66 (56)	92 (99)	76:24 (95:5)
13b	*p*-F_3C-C_6H_4	65	99	74:26
13c	Ph	58	98	96:4
13d	*p*-Cl-C_6H_4	84	96	80:20
13e	*p*-MeO-C_6H_4	67	98	94:6
13f	*i*Pr	68 (96)	99 (95)	91:9 (93:7)
13g	*n*Pr	70	95	91:9
13h	*i*Bu	64	96	90:10

[a] Overall yield of crude product (3 steps, based on loading of galactosyl azide **11a**). [b] Determined by LC-MS (ELSD) of crude products; results obtained from cleavage with HF-pyridine are given in parentheses (for **13a** and **13f**).

Galactosyl imines prepared from **1** and aldehydes undergo a Lewis acid promoted domino Mannich–Michael reaction with Danishefsky's diene **16** and yield *N*-galactosyl-5,6-dide-

hydropiperidin-4-ones, which represent versatile synthons for the diastereoselective synthesis of highly functionalized piperidine derivatives.[16,32] In a preliminary communication, we reported on the application of galactosylamine **2a** as a highly efficient chiral matrix for the asymmetric solid-phase synthesis of dehydropiperidinones. As all solid-phase methodologies leading to dehydropiperidinones described in the literature so far[33] only gave racemic products, this approach, to the best of our knowledge, represents the only asymmetric route towards a combinatorial solid-phase synthesis of piperidinones.

According to this approach the primary reaction step was the condensation of amine **2a** with 5 equivalents of an aromatic or an aliphatic aldehyde; this was successfully achieved under optimized reaction conditions at room temperature in the presence of 10 equivalents of acetic acid (Scheme 4). It should be noted that under these conditions



Scheme 4. Solid-phase synthesis of dehydropiperidinones. a) R^1–CHO (5 equiv), AcOH (10 equiv), toluene, 20 °C, 6 h; b) Danishefsky's diene **16** (10 equiv), $ZnCl_2$ (5 equiv), THF, 20 °C, 48 h; c) TBAF·3 H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h.

anomerization was not a problem, as could be anticipated from preceding studies on reactions of the galactosylamine **1** in solution.[13] Moreover, undesired cleavage from the support during the condensation did not occur, as was proven by gravimetric control and analysis of the combined washing solutions. Interestingly, imine formation cannot be performed with trimethylorthoformate as the dehydrating agent.[34] However, the imine purity and the completeness of imine formation could only be estimated by analysis of the products derived from polymer-bound galactosyl imines.

Subsequent Mannich–Michael reactions of aldimines **15** with Danishefsky's diene **16** to give resin-bound dehydropiperidinones **17** were preferably performed at room temperature as well (Scheme 4). The diastereoselectivities determined for the crude products **18** after fluoride-induced cleavage compared well with those reported for the corresponding solution-phase process,[16a,b] especially in cases of dehydropiperidinones bearing an aromatic substituent at C-2 (Table 2). It has to be emphasized that lowering of the reaction temperature did not improve the diastereomeric ratio

Table 2. Diastereoselective synthesis of dehydropiperidinones on the solid phase (after cleavage from polymeric support with TBAF).

Compound	R^1	Yield [%][a]	Purity [%][b]	d.r.[b]
18a	C_6H_5	81	98	95:5
18b	4-F-C_6H_4	77	97	99:1
18c	3-F-C_6H_4	n.d.	91	>99:1
18d[c]	4-Br-C_6H_4	n.d.	97	98:2
18e	3-Br-C_6H_4	57 (90[c])	95 (88[c])	99:1 (95:5[c])
18f	4-Cl-C_6H_4	77	n.d.	97:3
18g	2-Cl-6-F-C_6H_3	49	89	97:3
18h	4-CN-C_6H_4	76	93	>99:1
18i	4-CF_3-C_6H_4	81	97	98:2
18j	4-NO_2-C_6H_4	42	80	93:7
18k	4-Me-C_6H_4	n.d.	66	91:9
18l	4-MeO-C_6H_4	84	98	98:2
18m[d]	4-pyridyl	13	<45	n.d.
18n	CH_2CH_2-C_6H_5	50	83	90:10
18o	CH_3	50	90	78:22
18p[c][e]	CH_3CH_2	78	92	85:15
18q[c][e]	*n*-Pr	90	n.d.	81:19
18r	*i*Pr	73	92	98:2
18s	*i*Bu	61	88	82:18
18t	*t*Bu	–	–	–
18u[c][e]	*n*-pentyl	87	95	84:16
18v	*n*-heptyl	57	74	89:11

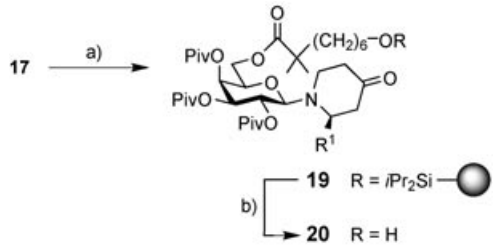
[a] Overall yield of crude product (4 steps, based on loading of galactosyl azide **11a**). [b] Determined by LC-MS (ELSD). [c] Cleavage with HF-pyridine. [d] 15 equivalents of $ZnCl_2$ were used. [e] Domino reaction at −10 °C. n.d. = not determined.

in cases with aromatic-substituted dehydropiperidinones, whereas an increase of reaction temperature to 60 °C resulted in significantly diminished purity of crude products after cleavage. Obviously aliphatic dehydropiperidinones (except for **18r** where R is the bulky isopropyl group; see Table 2) were formed with lower diastereoselectivity than their aromatic counterparts. As this difference was not observed in the corresponding solution-phase reaction, it has to be ascribed to either reaction or cleavage conditions on the solid phase. However, for aliphatic-substituted enaminones **17** and **18**, respectively, the diastereomeric ratio could be shifted towards the major diastereomer by lowering the reaction temperature (for **18q**, for example, the following diastereomeric ratios at different reaction temperatures have been determined: 68:32 at 20 °C, 81:19 at −10 °C, and 81:19 at −25 °C). Moreover, in contrast to the α-amino acid derivatives mentioned above, the nature of the fluoride source did not influence the chemical or optical purity of crude products **18** (Table 2, **18e** and **18q**).[35]

After elaborating efficient reaction conditions for the synthesis of polymer-bound dehydropiperidinones, we were next interested in achieving transformations leading to higher-functionalized piperidine derivatives on the solid phase.

The first transformation envisioned by us was the chemoselective reduction of the C–C double bond, to give finally chiral 2-substituted piperidines. In solution chemistry, sterically demanding borohydride reagents (for example, L-selectride) have been found to be the reagents of choice for this hydride addition. However, if polymer-bound dehydropiperidinones **17** were treated with varying quantities of L-selectride, mixtures of the desired 1,4 and concurring 1,2 ad-

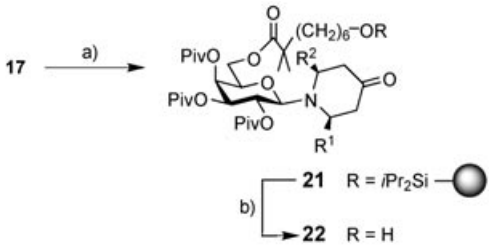
dition products were isolated in all cases. In addition, the corresponding tetrahydropyridines resulting from reduction of both the C–C double bond and the carbonyl group and subsequent elimination of water, probably under the conditions of the fluoride-induced cleavage from the polymeric support, have been detected as by-products. Reaction conditions, as well as stoichiometry, could not be optimized in favor of the chemoselective conjugate C=C bond reduction of the enone moiety. Improved purities of the products were only observed when the sterically demanding Lewis acid methyl aluminum-bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) was added to the reaction mixture. Beside some other interesting synthetic applications,[36] this oxygenophilic aluminum complex has been shown to allow chemoselective conjugate addition of Li organyls to α,β-unsaturated ketones.[37] In the present case, the carbonyl function of dehydropiperidinones **17** is activated and simultaneously effectively blocked, thereby allowing selective attack of the hydride at the β position (Scheme 5). Piperidinones **20** were



Scheme 5. Conjugate hydride addition to polymer-bound enones **17**. a) L-Selectride (10 equiv), MAD (20 equiv), THF/toluene, −20 °C, 4 h; b) TBAF·3 H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h. MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide).

obtained after fluoridolytic detachment from the resins **19** in satisfactory yields and purities. The major impurities either arose from unreduced dehydropiperidinones **18** or from piperidin-4-ols formed by double reduction (Scheme 5, Table 3). It has to be noted that product purity could not be enhanced by employing the sterically more demanding methyl aluminum-bis(2,4,6-tri-*tert*-butylphenoxide) (MAT; Table 3, **20r**).[36a]

The conjugate addition of soft nucleophiles (for example, organocuprates) to dehydropiperidinones generates the 2,6-disubstitution pattern of piperidines that is a common structure motif in natural products.[38] Therefore, we were interested in the stereoselective solid-phase synthesis of 2,6-disubstituted piperidine derivatives, which are readily available by using the glycosyl imine strategy in solution. Due to the vinylogous amide structure of the enone the conjugate addition requires soft nucleophiles in combination with hard electrophiles for activation (for example, Yamamoto-type[39] mono-organocuprates $RCu{\cdot}BF_3{\cdot}OEt_2$ or Gilman reagents activated with trimethylsilylchloride (TMSCl)[40]). However, all attempts to apply these cuprate reagents to the corresponding reaction on the solid phase failed to give selectively 2,6-disubstituted piperidines. In most cases either no reaction or an unselective cuprate addition took place. The reasons for this unexpected outcome probably lie in processes that occur upon slowly warming up the reaction mixtures. Therefore, it was necessary to investigate other cuprate reagents which show sufficient reactivity and especially stability—even at the higher temperatures that are obviously needed for cuprate addition on the solid phase to occur. After several attempts with different donor-stabilized cuprate reagents and β-silyl cuprates,[41] cyano-modified Gilman cuprates[42] proved to be the reagents of choice for this transformation on the solid phase. When resin-bound dehydropiperidinones were subjected to an excess of cuprate reagent $R_2Cu(CN)Li_2$ in the presence of $BF_3{\cdot}OEt_2$, conjugate addition took place and furnished piperidine derivatives **21** (Scheme 6, Table 4). Crude 2,6-disubstituted piperidinones



Scheme 6. Conjugate cuprate addition to polymer-bound enones **17**. a) $(R^2)_2Cu(CN)Li_2$ (30 equiv), $BF_3{\cdot}OEt_2$ (30 equiv), THF, −60→−15 °C, 14 h, then washing with ammonium pyrrolidine dithiocarbamate solution; b) TBAF·3 H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h.

Table 3. Conjugate hydride addition on the solid phase in the presence of MAD (after cleavage from the polymeric support).

Compound	R^1	Yield [%][a]	Purity [%][b]
20c	3-F-C_6H_4	53	99
20d	4-Br-C_6H_4	34	82[f]
20e	3-Br-C_6H_4	n.d.	51
20f	4-Cl-C_6H_4	50	65[f]
20g	2-Cl-6-F-C_6H_3	n.d.	47
20i[c]	4-F_3C-C_6H_4	n.d.	83
20l[d]	4-MeO-C_6H_4	n.d.	21
20r[e]	*i*Pr	28 (32)	74 (77)

[a] Overall yield of crude product (5 steps, based on loading of galactosyl azide **11a**). [b] Determined by LC-MS (ELS detection unless otherwise stated). [c] 40 equivalents of MAD and 15 equivalents of L-selectride were used. [d] 10 equivalents of MAD and 5 equivalents of L-selectride were used at −40 °C. [e] Numbers in parentheses show results when MAT was used instead of MAD. [f] UV detection at $\lambda = 215$ nm. n.d. = not determined.

22 were obtained in satisfactory yields and purities after release from the polymeric support. However, it has to be noted that there was a distinct relationship between the reaction temperature and the purity and diastereomeric ratio of crude products **22**. The lower the temperature chosen for the cuprate addition and the longer this temperature was kept, the higher was the diastereomeric ratio observed for the piperidinones in most cases. As anticipated from preceding studies carried out on reactions in solution, the major diastereomer was the *cis*-configured form (Scheme 6, Table 4).

Table 4. Addition of cyano-modified Gilman reagents to polymer-bound enones **17** (after cleavage from the polymeric support).

Compound	R^1	R^2	Temp. grad.[a]	Yield [%][b]	Purity [%][c]	d.r.[d]
22ac	Ph	*n*Bu	A	38	33 (61)	n.d.
22ca	3-F-C_6H_4	*n*Bu	B	75	49 (40)	98:2
22ca	3-F-C_6H_4	*n*Bu	C	47	99	90:10
22ca	3-F-C_6H_4	*n*Bu[e]	D	n.d.	52 (47)	67:33
22ea	3-Br-C_6H_4	*n*Bu	B	71	78 (22)	95:5
22ea	3-Br-C_6H_4	*n*Bu	E	44	90	74:26
22gc	2-Cl-6-F-C_6H_3	Ph	D	48	68	78:22
22gb	2-Cl-6-F-C_6H_3	Me	D	67	81 (12)	96:4
22ia	4-F_3C-C_6H_4	*n*Bu	B	76	61 (27)	93:7
22ia	4-F_3C-C_6H_4	*n*Bu	C	47	85 (15)	72:28
22ia	4-F_3C-C_6H_4	*n*Bu	E	62	99	84:16
22rc	*i*Pr	Ph	A	39	30 (30)	n.d.

[a] Temperature gradients used: A: −40 °C for 18 h; B: −78 °C→−60 °C over 2 h, then −60 °C→−15 °C over 12 h; C: −60 °C for 2 h, then −55 °C for 12 h; D: −20 °C for 16 h; E: −40 °C for 2 h, then −40 °C→−15 °C over 14 h. [b] Overall yield of crude product (5 steps, based on loading of galactosyl azide **11a**). [c] Determined by LC-MS (ELSD), percentage of reisolated dehydropiperidinone is given in parentheses. [d] Determined by LC-MS (ELSD). [e] TMSCl was used instead of $BF_3{\cdot}OEt_2$. n.d = not determined.

Conclusion

Herein, we have described the fluoride-labile linking strategy of a galactosylamine as a polymer-bound chiral auxiliary and its employment in Ugi four-component and domino Mannich–Michael condensation reactions. In both types of transformations stereodifferentiation was readily and efficiently achieved at room temperature. The reaction products were usually obtained in high yield and good chemical and optical purity. It has to be emphasized that the analogous solution-phase reactions leading to the corresponding products with comparable diastereoselectivities had to be conducted at −25 °C or even at lower temperatures. Dehydropiperidinones arising from the domino Mannich–Michael condensation reaction were further functionalized by conjugate addition reactions, thereby enabling an efficient access to piperidine derivatives of higher structural diversity. As the presented methodology delivered the glycosylated diastereomeric reaction products and allowed a direct analysis of the diastereomeric ratio, the optimization of reaction sequences was achieved in a time-efficient manner. However, to obtain enantiomerically pure amino acid and piperidine derivatives, respectively, the *N*-glycosidic bond has to be cleaved. Strategies towards the selective cleavage of the *N*-glycosidic bond of immobilized reaction products with the chiral auxiliary left on the polymeric support will be reported in due course.

Experimental Section

General procedures: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200, AC-300, AM-400, or DRX-600 spectrometers. LC-MS spectra were measured with an assembly consisting of a Knauer Maxi-Star K-1001 gradient pump, a Phenomenex Luna C-18 (2) column (3 μ, 75×4.6 mm), an LKB 2140 diode array detector, a PL-ELS 1000 ELS detector (Polymer Laboratories), and a Navigator-1 ESI mass spectrometer (ThermoQuest). Unless otherwise noted, all analytical HPLC runs were performed with a flow rate of 0.75 mL min^{-1} and a gradient of MeCN/H_2O (80:20→100:0 (v/v) within 10 min). Preparative and semi-preparative HPLC was performed with Luna C-18 (2) columns (10 μ, 250×50 mm and 250×21.2 mm, respectively), 2 Knauer Mini-Star K-500 gradient pumps, and a variable wavelength detector (Knauer). Flow rates were 20 mL min^{-1} for preparative and 10 mL min^{-1} for semi-preparative separations. IR spectra were measured on a Perkin–Elmer FT-1760X apparatus by using KBr pellets (5 mg of resin with 120 mg of KBr).

Solid-phase reactions were either run in standard glassware or in fritted glass cylinders being shaken in a Miniblock apparatus (Bohdan). All reactions involving organometallic species were carried out under an argon atmosphere with oven-dried glassware.

Materials: TLC was performed on Merck silica gel 60 F_{254} aluminum sheets. Silica gel was used for flash chromatography (40–63 μm) and for filtrations (63–200 μm). The resins were purchased from Acros and Nova-Biochem, washed successively with water, ethanol, THF, CH_2Cl_2, and diethyl ether, dried under high vacuum at 60 °C for 12 h, and stored in a desiccator over P_2O_5. THF was distilled over potassium benzophenone ketyl, toluene over sodium benzophenone ketyl, and CH_2Cl_2 over calcium hydride immediately prior to use. Aldehydes used for imine formation were distilled und stored under argon at 4 °C. A solution of zinc chloride in THF was prepared by melting $ZnCl_2$ (3.41 g, 25 mmol) with 3 drops of conc. HCl under high vacuum and dissolving it in dry THF (25 mL) after recooling. Diene **16** was prepared from 4-methoxybut-3-ene-2-one by the silylation procedure given by Danishefsky and Kitahara followed by repeated careful distillation at moderate temperature (oil bath temperature has to be kept below 70 °C).[43]

6-(*tert*-Butyldiphenylsilyloxy)hexylbromide (3): *tert*-Butyldiphenylchlorosilane (36.3 mL, 0.140 mol) was added to a solution of 1,6-hexanediol (50.0 g, 0.423 mol) and imidazole (15.3 g, 0.224 mol) in DMF (700 mL) at room temperature. After 36 h the solvent was removed and the residue was dissolved in dichloromethane (400 mL) and washed twice with 1 N HCl and water. The organic layer was dried with $MgSO_4$. Silica gel flash chromatography (petroleum ether/ethyl acetate (4:1)) enabled separation of excess 1,6-hexanediol and of bissilylated by-product from the monosilylated product 6-(*tert*-butyldiphenylsilyloxy)hexanol (44.2 g, 88 %), which was obtained as a colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate (2:1)); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.68–7.63 (m, 4H, aryl); 7.41–7.32 (m, 6H, aryl); 3.61 (pq, 4H, ^3J = 6.6 Hz, CH_2OH, CH_2OSi); 1.56–1.50 (m, 4H, 2×CH_2); 1.38–1.24 (m, 4H, 2×CH_2); 1.04 (s, 9H, *t*Bu) ppm; MS (FD): *m*/*z*: 356.4 $[M]^+$; elemental analysis: calcd (%) for $C_{22}H_{32}O_2Si$ (356.57): C 74.10, H 9.05; found: C 73.83, H 9.26.

Transformation into bromide **3**: A solution of tetrabromomethane (43.11 g, 0.130 mol) in dry dichloromethane (150 mL) was added to a solution of the silyl ether prepared as described above (36.64 g, 0.103 mol) in dichloromethane (700 mL). At 0 °C, a solution of triphenylphosphine (39.34 g, 0.150 mol) in dichloromethane (100 mL) was added dropwise. The reaction mixture was stirred for 3 h at 0 °C and for 12 h at room temperature. After evaporation of the solvent, the residue was suspended in diethyl ether (700 mL) and filtered. The filter cake was washed several times with diethyl ether. The combined filtrates were concentrated in vacuo und the remaining yellowish oil was purified by silica gel flash chromatography (petroleum ether/ethyl acetate (15:1)) to give **3** (41.86 g, 97 %) as colorless oil; R_f = 0.84 (petroleum ether/ethyl acetate (15:1)); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.67–7.63 (m, 4H, aryl); 7.41–7.36 (m, 6H, aryl); 3.64 (t, 2H, ^3J = 6.1 Hz, CH_2OSi); 3.37 (t, 2H, ^3J = 6.8 Hz, CH_2Br); 1.86–1.79 (m, 2H, 1×CH_2); 1.58–1.53 (m, 2H, 1×CH_2); 1.39–1.36 (m, 4H, 2×CH_2); 1.03 (s, 9H, *t*Bu) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 135.6, 129.5, 127.6 (phenyl); 134.1 (*ipso*-phenyl); 63.7 (CH_2O); 33.9 (CH_2Br); 32.8, 32.3, 27.9, 25.0 (4×CH_2); 26.9 (3×Me); 19.3 (CMe_3) ppm; MS (FD): *m*/*z*: 418.2 $[M]^+$, 340.3 $[M-Br]^+$; elemental anal-

ysis: calcd (%) for $C_{22}H_{31}BrOSi$ (419.47): C 62.99, H 7.45; found: C 62.25, H 7.35.

2,2-Dimethyl-8-(*tert*-butyldiphenylsilyloxy)-octanoic acid (4): Lithium diisopropylamide was prepared by adding *n*BuLi (1.6 M in *n*-hexane; 235.1 mL, 0.376 mol) dropwise to a solution of diisopropylamine (52.7 mL, 0.376 mol) in dry THF (400 mL) at −20 °C. The solution was stirred for an additional 20 min and subsequently treated with isobutanoic acid (15.9 mL, 0.171 mol). The mixture was slowly warmed to 50 °C (2 h) and recooled to −20 °C. A solution of hexylbromide **3** (35.86 g, 0.086 mol) in THF (50 mL) was added dropwise to the solution of the dianion at −20 °C, then the mixture was warmed to 40 °C and kept at this temperature for 1 h. The reaction mixture was hydrolyzed with cold 2 N HCl (220 mL) and the organic solvents were removed to a great extent. The aqueous layer was extracted twice with dichloromethane (each 500 mL) and the organic solutions were washed with 1 N HCl and water and dried over $MgSO_4$. Purification of the crude product by silica gel flash chromatography (petroleum ether/ethyl acetate (8:1)) gave **4** (38.78 g, 78 %) as colorless oil; $R_f = 0.65$ (petroleum ether/ethyl acetate (6:1)); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.67$–7.62 (m, 4H, aryl); 7.38–7.35 (m, 6H, aryl); 3.63 (t, 2H, $^3J = 6.3$ Hz, CH_2OSi); 1.53–1.46 (m, 4H, $2\times CH_2$); 1.32–1.20 (m, 6H, $3\times CH_2$); 1.17 (s, 6H, $2\times$Me); 1.03 (s, 9H, *t*Bu) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 184.9$ (COOH); 135.6, 129.5, 127.6 (phenyl); 134.2 (*ipso*-phenyl); 64.0 (CH_2O); 42.1 (CMe_2COOH); 40.5, 32.5, 29.9, 25.7, 24.8 ($5\times CH_2$); 26.9 ($3\times$Me); 25.0 ($2\times$Me); 19.3 (CMe_3) ppm; MS (ES^-): m/z: 425.4 $[M-H]^-$; 255.2 $[OTBDPS]^-$; elemental analysis: calcd (%) for $C_{26}H_{38}O_3Si$ (426.66): C 73.19, H 8.98; found: C 73.17, H 8.73.

6-*O*-[2,2-Dimethyl-8-(*tert*-butyldiphenylsilyloxy)-octanoyl]-β-D-galactopyranosyl azide (6): α,α-Branched carboxylic acid **4** (28.24 g, 66.2 mmol) was dissolved in dry dichloromethane (200 mL) and treated with oxalyl chloride (7.2 mL, 86.1 mmol). When gas evolution had ceased, the solvent was evaporated and the crude acid chloride was dried under high vacuum. The acid chloride was taken up in dry pyridine (150 mL) and added dropwise to a solution of β-D-galactopyranosyl azide **5**[21] (9.05 g, 44.1 mmol) in pyridine (60 mL). After addition of catalytic amounts of DMAP, the mixture was stirred for 20 h at 70 °C. After concentration in vacuo the residue was dissolved in ethyl acetate (500 mL) and extracted twice with 1 N HCl (300 mL), saturated $NaHCO_3$, and water. The organic solution was dried with $MgSO_4$ and the residue obtained after evaporation of the solvent was purified by silica gel flash chromatography (ethyl acetate) to furnish **6** (15.90 g, 59 %) as a yellowish oil; $R_f = 0.62$ (ethyl acetate); $[\alpha]_D^{25} = 0.43$ ($c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.64$ (dd, 4H, $^3J = 7.8$, $^4J = 1.6$ Hz, $4\times$aryl); 7.41–7.32 (m, 6H, $6\times$aryl); 4.51 (br d, 1H, H-1); 4.36–4.27 (m, 2H, H-6a, H-6b); 3.88 (br s, 1H, H-4); 3.74 (t, 1H, $^3J = 6.3$ Hz, H-5); 3.63–3.58 (m, 4H, CH_2OSi, H-2, H-3); 3.52 (br s, 3H, $3\times$OH); 1.53–1.45 (m, 4H, $2\times CH_2$); 1.33–1.27 (m, 2H, $1\times CH_2$); 1.26–1.18 (m, 4H, $2\times CH_2$); 1.14 (s, 6H, $2\times$Me); 1.02 (s, 9H, *t*Bu) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 178.5$ (C=O); 134.1 (*ipso*-aryl); 135.6, 129.5, 127.6 (aryl); 90.6 (C-1); 74.6, 73.4, 70.9, 68.5 (C-2, C-3, C-4, C-5); 64.0, 62.5 (C-6, CH_2OR); 42.4 (CMe_2); 40.4, 32.5, 29.8, 25.6, 24.8 ($5\times CH_2$); 26.9 (Me); 25.0 (CMe_2); 19.2 (CMe_3) ppm; MS (ES^+): m/z: 608.0 $[M+Na-N_2]^+$; 636.0 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{32}H_{47}N_3O_7Si$ (613.82): C 62.62, H 7.72, N 6.85; found: C 63.41, H 7.65, N 6.95.

2,3,4-Tri-*O*-pivaloyl-6-*O*-[2,2-dimethyl-8-(*tert*-butyldiphenylsilyloxy)-octanoyl]-β-D-galactopyranosyl azide (7): A solution of linker-conjugated galactosyl azide **6** (5.25 g, 8.6 mmol) in dry pyridine (100 mL) was treated with pivaloyl chloride (5.3 mL, 42.8 mmol) and stirred at 60 °C for 6 days. After filtration of precipitated pyridine hydrochloride and washing, the solution was concentrated in vacuo and the residue was taken up with ethyl acetate (500 mL) and extracted twice with 1 N HCl (300 mL), saturated $NaHCO_3$, and water. The organic layer was dried with $MgSO_4$ and evaporated and the residue was purified by silica gel flash chromatography (petroleum ether/ethyl acetate (12:1)) to give **7** (6.33 g, 85 %) as a colorless oil; $R_f = 0.56$ (petroleum ether/ethyl acetate (10:1)); $[\alpha]_D^{25} = -6.34$ ($c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.67$–7.62 (m, 4H, aryl); 7.40–7.32 (m, 6H, aryl); 5.41 (d, 1H, $^3J = 2.9$ Hz, H-4); 5.19 (dd, 1H, $^3J = 10.2$, $^3J = 8.3$ Hz, H-2); 5.09 (dd, 1H, $^3J = 10.3$, $^3J = 2.9$ Hz, H-3); 4.59 (d, 1H, $^3J = 8.3$ Hz, H-1); 4.24–3.95 (m, 3H, H-5, H-6a, H-6b); 3.62 (t, 2H, $^3J = 6.6$ Hz, CH_2OR); 1.56–1.40 (m, 4H, $2\times CH_2$); 1.36–1.25 (m, 13H, $2\times CH_2$, $1\times$Piv *t*Bu); 1.16, 1.09 (2 s, 18H, Piv *t*Bu); 1.12 (s, 6H, $2\times$Me); 1.02 (s, 9H, *t*Bu) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 177.4$, 177.1, 176.7 (C=O); 135.5, 134.2, 129.5, 127.6 (aryl); 88.5 (C-1); 73.2, 70.8, 67.8, 66.6 (C-2, C-3, C-4, C-5); 64.0, 61.0 (C-6, CH_2OR); 42.3 (CMe_2); 40.5 (CH_2); 39.1, 38.8, 38.8 (Piv CMe_3); 32.6, 29.8 ($2\times CH_2$); 27.2, 27.0, 26.9 (Piv Me, *t*Bu Me); 25.7 (CH_2); 25.1, 25.1, 24.9 (CH_2, $2\times$Me); 19.2 (*t*Bu CMe_3) ppm; MS (FD): m/z: 809.1 $[M-t\text{Bu}]^+$; MS (ES^+): m/z: 888.7 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{47}H_{71}N_3O_{10}Si$ (866.17): C 65.17, H 8.26, N 4.85; found: C 65.16, H 8.11, N 4.96.

2,3,4-Tri-*O*-pivaloyl-6-*O*-(2,2-dimethyl-8-hydroxy-octanoyl)-β-D-galactopyranosyl azide (8): A solution of silyl ether **7** (16.57 g, 18.8 mmol) in THF (250 mL) was treated with TBAF·3 H_2O in THF (1 M, 24.9 mL, 24.9 mmol) and stirred at room temperature until desilylation was complete (24 h). The solvent was evaporated in vacuo and the residue was dissolved in dichloromethane (400 mL), extracted twice with water (200 mL), and dried with $MgSO_4$. The crude product was purified by silica gel flash chromatography (petroleum ether/ethyl acetate (5:1)) to give **8** (10.19 g, 86 %) as colorless needles; $R_f = 0.24$ (petroleum ether/ethyl acetate (4:1)); m.p. 74 °C; $[\alpha]_D^{25} = -9.91$ ($c = 1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.39$ (d, 1H, $^3J = 2.4$ Hz, H-4); 5.17 (dd, 1H, $^3J = 10.2$, $^3J = 7.8$ Hz, H-2); 5.07 (dd, 1H, $^3J = 10.0$, $^3J = 2.7$ Hz, H-3); 4.60 (d, 1H, $^3J = 7.8$ Hz, H-1); 4.21–3.92 (m, 3H, H-5, H-6a, H-6b); 3.59 (t, 2H, $^3J = 6.3$ Hz, CH_2OH); 1.85 (br s, 1H, OH); 1.50–1.39 (m, 4H, $2\times CH_2$); 1.32–1.23 (m, 13H, $2\times CH_2$, $1\times$Piv *t*Bu); 1.14, 1.07 (2 s, 18H, Piv *t*Bu); 1.11 (s, 6H, $2\times$Me) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta = 177.4$, 177.3, 176.7 (C=O); 88.5 (C-1); 73.1, 70.8, 67.9, 66.6 (C-2, C-3, C-4, C-5); 62.8, 61.0 (C-6, CH_2OH); 42.3 (CMe_2); 40.4 (CH_2); 39.1, 38.8 (Piv CMe_3); 32.7, 29.7 ($2\times CH_2$); 27.1, 27.0 (Piv Me); 25.5 (CH_2); 25.1, 25.0, 24.9 (CH_2, $2\times$Me) ppm; MS (ES^+): $m/z = 622.0$ $[M+Na-N_2]^+$; 650.1 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{31}H_{53}N_3O_{10}$ (627.77): C 59.31, H 8.51, N 6.69; found: C 59.44, H 8.64, N 6.70.

Polymer-bound diisopropylchlorosilane (10a): In a solid-phase reaction vessel fitted with frit and heating jacket, washed and dried polystyrene (4.00 g, 38.3 mmol, 100–200 mesh, cross-linked with 1 % divinylbenzene) was suspended in dry cyclohexane (40 mL). After addition of TMEDA (7.52 mL, 49.8 mmol) and *n*-BuLi (1.6 M in *n*-hexane; 31.1 mL, 49.8 mmol) the suspension was shaken at 60 °C for 4 h. After being cooled to room temperature, the deeply red colored resin was washed with dry cyclohexane (2×20 mL) and dry THF (3×20 mL) and swollen in dry THF (60 mL). Upon addition of dichlorodiisopropylsilane (11.8 mL, 65.1 mmol), an instantaneous decolorization was observed. After 1.5 h of shaking the resin was washed successively with dry THF and diethyl ether (3 cycles) and dried under high vacuum for 12 h to furnish **10a** (5.66 g, colorless beads; ($\Delta M = +1.66$ g, which corresponds to 8.73 mmol chlorosilane units or approximately 1.542 mmol g^{-1}): FT-IR (KBr): $\tilde{\nu} = 3025$ (w); 2923 (m); 2850 (w); 1602 (s); 1493 (s); 1452 (s); 1115 (br); 1029 (w); 883 (m); 757 (s); 730 (m); 697 (s) cm^{-1}; elemental analysis: $\{[(C_8H_8)_x(C_{10}H_{10})_y]_1[C_8H_7SiCl(iPr)_2]_{0.32}\}$ with $x = 0.959$ and $y = 0.013$; found: C 80.27, H 8.37, equal to (C+H) = 88.6 %, (Si+Cl) = 11.4 %; the loading (l) was calculated by using Equation 1, where w(Si in SiCl) = 44.2 %.

$$l_{\mathbf{10a}} = \frac{w(\mathrm{Si + Cl}) \times w(\mathrm{Si\ in\ SiCl})}{M(\mathrm{Si})} = 1.794\ \mathrm{mmol\,g^{-1}} \qquad (1)$$

Polymer-bound 2,3,4-tri-*O*-pivaloyl-6-*O*-(2,2-dimethyl-8-hydroxy-octanoyl)-β-D-galactopyranosyl azide (11a)—Immobilization of galactosyl azide: Polymer-bound chlorosilane **10a** (5.59 g, approximately 9.67 mmol) was swollen in dry dichloromethane (40 mL). This was followed by addition of galactosyl azide **8** (1.40 g, 2.23 mmol) and imidazole (1.14 g, 1.81 mmol), each dissolved in dichloromethane (10 mL), and the suspension was shaken at room temperature for 24 h. After addition of dry MeOH (3.6 mL, 89.1 mmol) the suspension was shaken for a further 24 h. After filtration, the resin was washed successively with dichloromethane and diethyl ether (3 cycles), with DMF (4×), and with dichloromethane and diethyl ether (3 cycles). For gravimetric analysis the resin was dried under high vacuum for 12 h. The polymer-bound galactosyl azide was obtained as approximately 7 g of colorless beads: FT-IR (KBr): $\tilde{\nu} =$ 3026 (w); 2925 (br); 2864 (m); 2117 (m); 1745 (s); 1602 (m); 1494 (s); 1453 (s); 1384 (w); 1277 (m); 1111 (br); 883 (m); 759 (s) cm^{-1}; elemental analysis: Calcd. (%) for $(C_8H_8)_{0.959}(C_{10}H_{10})_{0.013}(C_8H_7Si(iPr)_2OX_c)_{0.074}(C_8H_7Si(iPr)_2OMe)_{0.246}$ (wherein $X_c = C_{31}H_{52}N_3O_{10}$): C 78.7, H 8.5, N 1.4; found:

C 80.02, H 9.21, N 1.54; loading based on nitrogen content: $l_{\mathbf{11a}} = 0.366\ \mathrm{mmol\,g^{-1}}$ (calculated from [Eq. (2)], where $\bar{w}(\mathrm{N})$ is the mean value of nitrogen content of a sample of resin **11a**). Coupling was nearly quantitative as only traces of galactosyl azide **8** could be detected in the combined wash solutions.

$$l_{\mathbf{11a}}\ [\mathrm{mmol\,g^{-1}}] = 10\,\bar{w}(\mathrm{N})\ [\%]/[3 \times 14.007\ \mathrm{g\,mmol^{-1}}] \quad (2)$$

Polymer-bound 2,3,4-tri-*O*-pivaloyl-6-*O*-(2,2-dimethyl-8-hydroxy-octanoyl)-β-D-galactopyranosylamine (2a)—Reduction of galactosyl azide: Polymer-bound azide **11a** (approximately 7 g, corresponding to about 2.24 mmol) was swollen in dry DMF (70 mL) and treated with triethylamine (3.10 mL, 22.4 mmol) and 1,3-propanedithiol (2.24 mL, 22.4 mmol). The suspension was shaken at room temperature for 24 h, then filtered. The resin was successively washed with dichloromethane and diethyl ether (3 cycles) and with dichloromethane und methanol (3 cycles). A yield of 6.74 g of colorless beads was obtained: FT-IR (KBr): $\tilde{\nu} = 3027$ (m); 2926 (s); 2864 (s); 1741 (s); 1601 (m); 1494 (s); 1453 (s); 1384 (w); 1280 (m); 1110 (br); 1029 (w); 994 (w); 883 (m); 759 (s) $\mathrm{cm^{-1}}$; elemental analysis: found: C 81.66, H 8.48, N 0.58; loading based on nitrogen content: $l_{\mathbf{2a}} = 0.414\ \mathrm{mmol\,g^{-1}}$ (calculated from [Eq. (3)], where $\bar{w}(\mathrm{N})$ is the mean value of nitrogen content of a sample of resin **2a**).

$$l_{\mathbf{2a}}\ [\mathrm{mmol\,g^{-1}}] = 10\,\bar{w}(\mathrm{N})\ [\%]/14.007\ \mathrm{g\,mmol^{-1}} \quad (3)$$

Polymer-bound, *para*-selective diisopropylchlorosilane (10b): The preparation of resin **10b** from *para*-bromopolystyrene was performed according to the procedure given by Heintze et al.,[26] except that the lithiation procedure was carried out twice before the resin was treated with dichlorodiisopropylsilane. Loading determined by elemental analysis: $l_{\mathbf{10b}} = 1.437\ \mathrm{mmol\,g^{-1}}$.

Polymer-bound 2,3,4-tri-*O*-pivaloyl-6-*O*-(2,2-dimethyl-8-hydroxy-octanoyl)-β-D-galactopyranosyl azide (11b)—Immobilization of galactosyl azide: Coupling of **10b** with **8** was carried out under analogous conditions to those described above for glycosyl azide **11a**; elemental analysis: found: C 78.96, H 10.10, N 1.76; loading based on nitrogen content: $l_{\mathbf{11b}} = 0.414\ \mathrm{mmol\,g^{-1}}$ [Eq. (2)].

Polymer-bound 2,3,4-tri-*O*-pivaloyl-6-*O*-(2,2-dimethyl-8-hydroxy-octanoyl)-β-D-galactopyranosylamine (2b)—Reduction of galactosyl azide: Reduction was carried out as described above for resin **2a**; elemental analysis: found: C 80.23, H 10.71, N 0.61; loading based on nitrogen content: $l_{\mathbf{2b}} = 0.436\ \mathrm{mmol\,g^{-1}}$ [Eq. (3)].

General procedure for TBAF-induced cleavage from the polymeric support (method A): Resin (50 mg; loading: approximately 0.4 $\mathrm{mmol\,g^{-1}}$ carbohydrate, approximately 2 $\mathrm{mmol\,g^{-1}}$ Si units, approximately 0.10 mmol Si units) was swollen in dry THF (2 mL), mixed with acetic acid (10 μL, 0.17 mmol) and tetra-*n*-butylammonium fluoride trihydrate (1 M in dry THF, 0.5 mL, 0.5 mmol) and shaken for 48 h at room temperature. The suspension was filtered and the resin was washed successively with dichloromethane, THF, and methanol (each 2 mL, 6 cycles), then dried under high vacuum. The filtrate was evaporated either under reduced pressure or in a nitrogen stream and the remaining residue was filtered through a short plug of silica (5 cm, Ø1 cm, conditioned with petroleum ether/ethyl acetate (1:1)). Elution with petroleum ether/ethyl acetate (1:1, 15 mL) and evaporation of the solvents delivered the crude reaction products. For LC-MS and gravimetric analysis the crude product was dissolved in CH_3CN and the solution filtered through an Optiflow membrane filter (0.45 μm pore size). The filter was then washed twice with CH_3CN and the solution was evaporated to dryness.

General procedure for the HF-induced cleavage from polymeric support (method B): In a fritted polypropylene syringe the resin (50 mg, loading: approximately 0.4 $\mathrm{mmol\,g^{-1}}$ carbohydrate, approximately 2 $\mathrm{mmol\,g^{-1}}$ Si units, approximately 0.1 mmol Si units) was swollen in dry THF (0.5 mL) and treated with HF-pyridine complex (70%, 26 μL, 1.0 mmol). After 16 h of shaking, methoxytrimethylsilane (414 μL, 3.0 mmol) was added and the suspension was shaken for an additional 5 h. It was filtered, then the resin was washed successively with dichloromethane, THF, and methanol (each 2 mL, 6 cycles) and dried under high vacuum. The residue obtained after thorough evaporation of the wash solutions generally needed no further purification. Both cleavage protocols are viable for resin amounts from 10 mg up to 1 g. For analytical purposes the miniscale cleavage (10 mg) easily allowed quantification of the purity of reaction products. However, due to the small amount of product expected in these cases the corresponding yield is not given (n.d. = not determined).

General procedure for the synthesis of polymer-bound Ugi condensation products (12) by using galactosylamine 2a: A suspension of galactosylamine resin **2a** in dry THF (1 mL per 100 mg resin) was mixed with aldehyde (5 equiv), formic acid (5 equiv), *tert*-butyl isocyanide (5 equiv), and $ZnCl_2$ (3 equiv, 1 M in THF) and shaken for 24 h at room temperature. After filtration the resin was washed with dichloromethane, THF, and diethyl ether and dried under high vacuum. Fluoridolytic cleavage from the support by using either method A or B (see above) gave *N*-formyl-*N*-galactopyranosyl-α-amino acid *tert*-butyl amides **13**. (Due to amide rotamerism partial signal doubling was observed in NMR spectra. This is indicated by the superscript ^{R}.}

***N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4,-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-4-nitrophenylglycine-*tert*-butyl amide (13a)**: *Cleavage A*: Yield: 2.3 mg (66%); colorless oil; LC-MS: $t_R = 4.71$ (minor); 6.20 (major) min; d.r. 24:76 (ELSD), purity 92% (ELSD). *Cleavage B*: LC-MS: $t_R = 4.67$ (minor); 6.17 (major) min; d.r. 5:95 (ELSD), purity 99% (ELSD). Isolation of both stereoisomers by preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min, $\lambda = 215$ nm); *S* isomer: $t_R = 50.0$ min; yield: 14.8 mg (8%); colorless, amorphous solid; $[\alpha]_D^{25} = 5.70$ ($c = 1$, $CDCl_3$); $R_f = 0.30$ (petroleum ether/ethyl acetate (4:1)); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.38^R$, 8.16 (s, 1H, CHO); 8.38, 8.20^R (d, 2H, $^3J = 8.6$ Hz, aryl); 7.52 (d, 2H, $^3J = 7.8$ Hz, aryl); 6.01^R, 5.50 (s, 1H, NH); 6.02, 5.05^R (d, 1H, $^3J = 9.4$ Hz, H-1); 5.48, 5.45^R (d, 1H, $^3J = 2.9$ Hz, H-4); 5.44, 5.35^R (t, 1H, $^3J = 9.6$ Hz, H-2); 5.21, 5.09^R (dd, 1H, $^3J = 9.8$, $^3J = 3.1$ Hz, H-3); 5.11^R, 4.92 (s, 1H, α-CH); 4.17–3.95 (m, 3H, H-5, H-6a, H-6b); 3.62 (t, 2H, $^3J = 6.4$ Hz, CH_2OH); 1.58–1.46, 1.32–1.20, 1.36, 1.31, 1.29, 1.23, 1.10, 1.05, 1.00, 0.91 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; MS (ES$^+$): $C_{44}H_{69}N_3O_{12}$ (864.03): *m*/*z*: 886.7 [*M*+Na]$^+$; *R* isomer: $t_R = 57.9$ min; yield: 84 mg (48%); yellowish, crystalline solid; m.p. 91 °C; $[\alpha]_D^{25} = -32.03$ ($c = 1$, $CDCl_3$); $R_f = 0.47$ (petroleum ether/ethyl acetate (4:1)); elemental analysis: calcd. (%) for $C_{44}H_{69}N_3O_{14}$ (864.03): C 61.16, H 8.05, N 4.86; found: C 60.68, H 7.92, N 4.75; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.31^R$, 8.20 (s, 1H, CHO); 8.13–8.10 (m, 2H, aryl); 7.56^R, 7.50 (d, 2H, $^3J = 8.6$ Hz, aryl); 6.42^R, 5.71 (s, 1H, NH); 5.93, 5.12^R (d, 1H, $^3J = 9.4$ Hz, H-1); 5.49^R, 5.23 (t, 1H, $^3J = 9.2$ Hz, H-2); 5.42, 5.35^R (d, 1H, $^3J = 2.5$ Hz, H-4); 5.33, 5.10^R (s, 1H, α-CH); 5.16–5.12 (m, 1H, H-3); 4.15–4.08, 3.93–3.77 (m, 3H, H-5, H-6a, H-6b); 3.56^R, 3.54 (t, 2H, $^3J = 6.7$ Hz, CH_2OH); 1.49–1.37, 1.28–1.17, 1.36, 1.29, 1.28, 1.22, 1.12, 1.10, 1.08, 1.05 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 177.3$, 177.2, 177.1, 176.7, 176.5, 176.1 (Piv–*C*=O); 165.9^R, 165.6 (*C*ONH*t*Bu); 163.7, 162.9^R (CHO); 147.6, 147.5^R (C–NO_2); 144.9, 142.9^R (*ipso*-aryl); 129.2, 123.9, 123.5 (aryl); 86.3^R, 78.5, 73.6, 73.1^R, 72.0, 71.9^R, 67.2, 66.4^R, 65.8^R, 65.4, 61.3^R, 58.8 (C-1, C-2, C-3, C-4, C-5, α-C); 62.7 (CH_2OH); 61.2, 60.5^R (C-6); 52.6, 51.9^R (*C*Me$_3$); 42.3, 42.2^R (*C*Me$_2$); 40.4, 40.3^R (CH_2); 39.1, 38.8, 38.7 (Piv *C*Me$_3$); 32.6, 29.6 (2×CH_2); 28.6, 28.5^R (*t*Bu Me); 27.3, 27.2, 27.0 (Piv Me); 25.5, 25.5, 24.8 (CH_2); 25.1, 25.0, 24.9 (C*Me*$_2$) ppm; MS (ES$^+$): *m*/*z*: 585.3 [M_{sugar}]$^+$; 864.4 [*M*+H]$^+$; 886.5 [*M*+Na]$^+$.

***N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-(4-trifluoromethyl)phenylglycine-*tert*-butyl amide (13b)**: *Cleavage A*: Yield: 4.6 mg (65%), colorless oil; $R_f = 0.45$ (petroleum ether/ethyl acetate (5:1)); LC-MS: $t_R = 6.23$ (minor); 7.57 (major) min; d.r. 26:74 (ELSD), purity: 99% (ELSD). Separation of diastereomers by semi-preparative HPLC (Luna C-18, MeCN (90%→100%), 40 min): *S* isomer: $t_R = 29.7$ min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.40^R$, 8.16 (s, 1H, CHO); 7.63–7.47 (m, 4H, aryl); 6.21^R, 5.40 (s, 1H, NH); 6.01, 4.99^R (d, 1H, $^3J = 9.4$ Hz, H-1); 5.51–5.42 (m, 2H, H-2, H-4); 5.14^R, 4.87 (s, 1H, α-CH); 5.21, 5.06^R (dd, 1H, $^3J = 10.0$, $^3J = 2.9$ Hz, H-3); 4.14–3.94 (m, 3H, H-5, H-6a, H-6b); 3.62 (t, 2H, $^3J = 6.4$ Hz, CH_2OH); 1.37, 1.31, 1.30, 1.27, 1.12, 1.11, 1.07, 0.99, 0.87 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; MS (ES$^+$): $C_{45}H_{69}F_3N_2O_{12}$ (887.03): *m*/*z*: 909.7 [*M*+Na]$^+$; *R* isomer: $t_R = 34.7$ min; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.35^R$, 8.23 (s, 1H, CHO); 7.61–7.49 (m, 4H, aryl); 6.11^R, 5.37 (s, 1H, NH); 5.95 (d, 1H, $^3J = 9.4$ Hz, H-1); 5.53^R, 5.25 (t, 1H, $^3J = 9.6$ Hz, H-2); 5.45, 5.28^R (d, 1H, $^3J = 2.6$ Hz, H-4); 5.36^R, 5.08 (s, 1H, α-CH); 5.16–5.11 (m, 1H, H-3); 4.20, 3.78^R (dd, 1H, $^2J = 11.0$, $^3J = 7.4$ Hz, H-6a); 4.13, 3.81^R (dd, 1H, $^3J = 7.4$, $^3J = 5.1$ Hz, H-5); 3.93, 3.70^R (dd, 1H, $^2J = 11.0$,

^3J = 4.9 Hz, H-6b); 3.60, 3.57^R (t, 1H, ^3J = 6.6 Hz, CH_2OH); 1.39, 1.30, 1.25, 1.15, 1.13, 1.11, 1.07 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; MS (ES$^+$): *m/z*: 909.7 [*M*+Na]$^+$.

***N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-phenylglycine-*tert*-butyl amide (13c)**: *Cleavage A*: Yield: 3.8 mg (58%), colorless oil; R_f = 0.27 (cyclohexane/ethyl acetate (4:1)); LC-MS: t_R = 5.17 (minor); 6.55 (major) min; d.r. 4:96 (ELSD), purity 98% (ELSD); MS (ES$^+$): *m/z*: 841.6 [*M*+Na]$^+$. On a larger scale (**12c**: 540 mg, approximately 0.216 mmol) cleavage allows the separation of the diastereomers by preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min, λ = 215 nm): *S* isomer: t_R = 54.0 min; yield: 13 mg (7%); colorless, amorphous solid; $[\alpha]_D^{25}$ = 25.14 (*c* = 1, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.44^R, 8.15 (s, 1H, CHO); 7.36–7.34 (m, 5H, aryl); 6.08^R, 5.31 (s, 1H, NH); 6.00, 4.76^R (d, 1H, ^3J = 9.4 Hz, H-1); 5.52, 5.40^R (t, 1H, ^3J = 9.8 Hz, H-2); 5.47, 5.39^R (d, 1H, ^3J = 2.4 Hz, H-4); 5.24^R, 4.84 (s, 1H, α-CH); 5.19, 4.95^R (dd, 1H, ^3J = 9.8, ^3J = 2.8 Hz, H-3); 4.14–3.94 (m, 3H, H-5, H-6a, H-6b); 3.62, 3.61^R (t, 2H, ^3J = 6.4 Hz, CH_2OH); 1.87 (s, 1H, OH); 1.57–1.18 (m, 10H, 5×CH_2); 1.35, 1.30, 1.29, 1.28, 1.12, 1.11, 1.04, 1.00, 0.96 (several singlets, 42H, 3×Piv *t*Bu, *t*Bu, 2×Me) ppm; MS (ES$^+$): $C_{44}H_{70}N_2O_{12}$ (819.03): *m/z*: 838.6 [2*M*+Ca]$^+$/2; 841.6 [*M*+Na]$^+$; 857.6 [*M*+K]$^+$; *R* isomer: t_R = 61.9 min; yield: 85 mg (48%); colorless, amorphous solid; $[\alpha]_D^{25}$ = −28.31 (*c* = 1, $CDCl_3$); elemental analysis: calcd (%): C 64.52, H 8.61, N 3.42; found: C 63.04, H 8.89, N 3.24; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.39^R, 8.15 (s, 1H, CHO); 7.33–7.29 (m, 5H, aryl); 5.87^R, 5.30 (s, 1H, NH); 5.92, 5.10^R (d, 1H, ^3J = 9.4 Hz, H-1); 5.55^R, 5.21 (t, 1H, ^3J = 9.8 Hz, H-2); 5.52^R, 5.07 (s, 1H, α-CH); 5.43, 5.29^R (d, 1H, ^3J = 2.3 Hz, H-4); 5.10 (dd, 1H, ^3J = 10.2, ^3J = 2.7 Hz, H-3); 4.20, 3.58^R (dd, 1H, ^2J = 10.6, ^3J = 7.2 Hz, H-6a); 4.13, 3.58^R (t, 1H, ^3J = 6.3 Hz, H-5); 4.13, 3.58^R (dd, 1H, ^2J = 10.9, ^3J = 5.3 Hz, H-6b); 3.59^R, 3.53 (t, 1H, ^3J = 6.4 Hz, CH_2OH); 2.10 (s, 1H, OH); 1.50–1.20 (m, 10H, 5×CH_2); 1.34, 1.27, 1.20, 1.13, 1.11, 1.08, 1.07, 1.04 (several singlets, 42H, 3×Piv *t*Bu, *t*Bu, 2×Me) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 177.4, 177.3, 177.1^R, 176.8^R, 176.5^R, 176.2, 176.1 (Piv−C=O) ppm; 166.9 (*C*ONH*t*Bu); 164.7, 162.6^R (*C*HO); 137.4, 135.5^R (*ipso*-phenyl); 129.0, 128.8, 128.6, 128.4 (phenyl); 85.7^R, 72.3 (C-3); 78.3 (C-1); 73.2 (C-5); 67.4 (C-4); 65.4 (C-2); 62.7 (CH_2OH); 61.3 (C-6); 58.9 (α-C); 52.3, 51.6^R (*C*Me$_3$); 42.3 (*C*Me$_2$); 40.4 (CH_2); 39.1, 38.9^R, 38.7, 38.6 (Piv *C*Me$_3$); 32.7, 29.7 (2×CH_2); 28.8, 28.6^R (*t*Bu Me); 27.3, 27.2, 27.1 (Piv Me); 25.5, 25.1, 25.0, 24.8 (CH_2, C*Me*$_2$) ppm; MS (ES$^+$): *m/z*: 838.6 [2*M*+Ca]$^+$/2; 841.6 [*M*+Na]$^+$; 857.6 [*M*+K]$^+$.

(2*R*)-*N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galactopyranosyl]-4-chlorophenylglycine-*tert*-butyl amide (13d): *Cleavage A*: Yield: 14.4 mg (84%), colorless oil; R_f = 0.66 (petroleum ether/ethyl acetate (4:1)); LC-MS: t_R = 6.25 (minor); 7.53 (major) min; d.r. 20:80 (ELSD), purity: 96% (ELSD). Isolation of the major diastereomer by semi-preparative HPLC (Spherisorb C-18, MeCN (80%→100%), 120 min): t_R = 20.1 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.35^R, 8.19 (s, 1H, CHO); 7.37–7.21 (m, 4H, 4×aryl); 5.96^R, 5.30 (s, 1H, NH); 5.93, 5.06^R (d, 1H, ^3J = 9.4 Hz, H-1); 5.53^R, 5.22 (t, 1H, ^3J = 9.7 Hz, H-2); 5.44, 5.35^R (d, 1H, ^3J = 2.6 Hz, H-4); 5.31^R, 5.02 (s, 1H, α-CH); 5.14, 5.12^R (dd, 1H, ^3J = 10.1, ^3J = 2.6 Hz, H-3); 4.22 (dd, 1H, ^2J = 11.1, ^3J = 7.4 Hz, H-6a); 4.13 (dd, 1H, ^3J = 7.0, ^3J = 5.6 Hz, H-5); 3.94 (dd, 1H, ^2J = 11.1, ^3J = 5.3 Hz, H-6b); 3.60, 3.57^R (t, 1H, ^3J = 6.4 Hz, CH_2OH); 1.49–1.43, 1.36, 1.29, 1.24, 1.14, 1.12, 1.10 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; MS (ES$^+$): $C_{44}H_{69}ClN_2O_{12}$ (853.48): *m/z*: 875.6 [*M*(^{35}Cl)+Na]$^+$; 877.6 [*M*(^{37}Cl)+Na]$^+$.

(2*R*)-*N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galactopyranosyl]-4-methoxyphenylglycine-*tert*-butyl amide (13e): *Cleavage A:* Yield: 17 mg (67%), colorless oil; R_f = 0.53 (cyclohexane/ethyl acetate (1:1)); $[\alpha]_D^{25}$ = −26.91 (*c* = 0.5, $CDCl_3$); LC-MS: t_R = 4.78 (minor); 6.25 (major) min; d.r. 6:94 (ELSD), purity 98% (ELSD); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.39^R, 8.18 (s, 1H, CHO); 7.34^R, 7.27 (d, 2H, ^3J = 8.8 Hz, 2×aryl); 6.84 (d, 2H, ^3J = 8.6 Hz, 2×aryl); 5.93, 5.01^R (d, 1H, ^3J = 9.4 Hz, H-1); 5.72^R, 5.21 (s, 1H, NH); 5.56^R, 5.22 (t, 1H, ^3J = 9.6 Hz, H-2); 5.45, 5.31^R (d, 1H, ^3J = 2.4 Hz, H-4); 5.42^R, 5.03 (s, 1H, α-CH); 5.11 (dd, 1H, ^3J = 9.8, ^3J = 2.7 Hz, H-3); 4.25 (dd, 1H, ^2J = 11.0, ^3J = 7.4 Hz, H-6a); 4.14 (t, 1H, ^3J = 6.6 Hz, H-5); 3.98 (dd, 1H, ^2J = 11.3, ^3J = 5.7 Hz, H-6b); 3.78 (s, 3H, OMe); 3.61^R, 3.57 (t, 1H, ^3J = 6.6 Hz, CH_2OH); 1.53–1.21, 1.35, 1.29, 1.28^R, 1.23^R, 1.15^R, 1.13, 1.09, 1.06^R (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2) ppm; MS (ES$^+$): $C_{45}H_{72}N_2O_{13}$ (849.06): *m/z*: 871.6 [*M*+Na]$^+$.

(2*R*)-*N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galactopyranosyl]-valine-*tert*-butyl amide (13f): *Cleavage A*: Yield: 2.1 mg (68%), colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate (4:1)); LC-MS: t_R = 5.72 (minor); 6.22 (major) min; d.r. 9:91 (ELSD), purity: 99% (ELSD). *Cleavage B*: Yield: 6 mg (96%), colorless oil; LC-MS: t_R = 5.60; 6.13 min; d.r. 7:93 (ELSD), purity: 95% (ELSD). Separation of diastereomers by semi-preparative HPLC (Luna C-18, MeCN (80%→100%), 30 min): *S* isomer: Yield: <1 mg, t_R = 18.9 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.54, 8.48^R (s, 1H, CHO); 6.16 (s, 1H, NH); 6.01, 4.99^R (d, 1H, ^3J = 9.0 Hz, H-1); 5.59 (t, 1H, ^3J = 10.0 Hz, H-2); 5.41 (d, 1H, ^3J = 2.8 Hz, H-4); 5.32–5.13 (m, 1H, H-3); 4.10–3.83 (m, 3H, H-5, H-6a, H-6b); 3.62 (t, 2H, ^3J = 6.3 Hz, CH_2OH); 3.06 (d, 1H, ^3J = 10.2 Hz, α-CH); 2.25–2.15, 2.03–1.95^R (m, 1H, C*H*Me$_2$); 1.33, 1.30, 1.29, 1.26, 1.12, 1.11, 1.10, 1.09 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2); 1.03, 0.80^R (d, ^3J = 6.3 Hz, Me); 0.96, 0.85^R (d, ^3J = 6.7 Hz, Me) ppm; *R* isomer: Yield: 4 mg, t_R = 20.1 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.66^R, 8.32 (s, 1H, CHO); 6.55 (s, 1H, NH); 5.96 (d, 1H, ^3J = 9.0 Hz, H-1); 5.53 (t, 1H, ^3J = 9.6 Hz, H-2); 5.42 (d, 1H, ^3J = 3.1 Hz, H-4); 5.17 (dd, 1H, ^3J = 9.8, ^3J = 2.8 Hz, H-3); 4.08–3.80 (m, 3H, H-5, H-6a, H-6b); 3.62 (t, 2H, ^3J = 6.3 Hz, CH_2OH); 3.26 (d, 1H, ^3J = 10.1 Hz, α-CH); 2.46–2.35, 2.24–2.16^R (m, 1H, C*H*Me$_2$); 1.35, 1.30, 1.29, 1.11, 1.10, 1.09, 1.06 (m, 52H, 3×Piv *t*Bu, *t*Bu, 2×Me, 5×CH_2); 1.01^R, 0.97, 0.93^R, 0.87 (d, 6H, ^3J = 6.6 Hz, 2×Me) ppm; MS (ES$^+$): $C_{41}H_{72}N_2O_{12}$ (785.02): *m/z*: 807.7 [*M*+Na]$^+$.

(2*R*)-*N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galactopyranosyl]-norvaline-*tert*-butyl amide (13g): *Cleavage A:* Yield: 4.4 mg (70%), colorless oil; R_f = 0.33 (cyclohexane/ethyl acetate (4:1)); LC-MS: t_R = 5.70 (minor); 6.05 (major) min; d.r. 9:91 (ELSD), purity: 95% (ELSD); MS (ES$^+$): $C_{41}H_{72}N_2O_{12}$ (785.02): *m/z*: 807.7 [*M*+Na]$^+$.

(2*R*)-*N*-Formyl-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galactopyranosyl]-leucine-*tert*-butyl amide (13h): *Cleavage A*: Yield: 4.1 mg (64%), colorless oil; R_f = 0.31 (cyclohexane/ethyl acetate (4:1)); LC-MS: t_R = 6.77 (major); 7.13 (minor) min; d.r. 90:10 (ELSD), purity: 96% (ELSD); MS (ES$^+$): $C_{42}H_{74}N_2O_{12}$ (799.04): *m/z*: 821.7 [*M*+Na]$^+$.

General procedure for the formation of *N*-galactosyl aldimines (15) on the solid phase: Galactosylamine resin **2a** (75 mg, 0.03 mmol) was swollen in toluene (0.5 mL), the suspension was combined with the aldehyde (5 equivalents, 0.15 mmol) in toluene (0.3 mL) and acetic acid (10 equivalents, 18 μL, 0.30 mmol), and the mixture was shaken at room temperature for 6 h. After filtration and successive washing with dichloromethane and methanol (6 cycles), the resin was dried in vacuo to constant weight (approximately 2 h).

General procedure for the tandem Mannich–Michael reaction on the solid phase—Synthesis of dehydropiperidinones 18: Galactosyl aldimine resin **15** (75 mg, 0.03 mmol) was swollen in dry THF (1 mL), then zinc chloride (1M in THF; 0.15 mL, 0.15 mmol) and diene **16** (59 μL, 0.30 mmol) were added at room temperature. The suspension was shaken for 48 h, treated with 1N HCl (0.1 mL), shaken for a further 10 minutes, and filtered, then the resin was washed with dichloromethane, THF, and methanol (6 cycles). Subsequent cleavage from the support by using either cleavage method A or B (see above) delivered dehydropiperidinones **18**.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-phenyl-5,6-didehydro-piperidin-4-one (18a): *Cleavage A*: Yield: 19.1 mg (81%); colorless oil; R_f = 0.41 (petroleum ether/ethyl acetate (1:1)); LC-MS: t_R = 3.85 (minor); 4.20 (major) min; d.r. 5:95 (ELSD), purity: 98% (ELSD); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.37–7.28 (m, 6H, 5×aryl, NC*H*=CH); 5.56 (t, 1H, ^3J = 9.8 Hz, H-2); 5.29 (d, 1H, ^3J = 2.9 Hz, H-4); 5.25 (d, 1H, ^3J = 8.4 Hz, NCH=C*H*); 4.93 (dd, 1H, ^3J = 9.8, ^3J = 2.9 Hz, H-3); 4.80 (dd, 1H, ^3J = 9.0, ^3J = 7.1 Hz, NC*H*Ph); 4.27 (d, 1H, ^3J = 9.3 Hz, H-1); 3.97 (dd, 1H, ^3J = 6.8, ^2J = 10.7 Hz, H-6a); 3.81–3.56 (m, 4H, H-5, H-6b, CH_2OH); 2.83–2.70 (m, 2H, CH_2C=O); 1.51–1.20 (m, 10H, 5×CH_2); 1.25, 1.16, 1.08 (3s, 27H, Piv *t*Bu); 1.12 (s, 6H, 2×Me) ppm; MS (ES$^+$): $C_{42}H_{63}NO_{11}$ (757.95): *m/z*: 758.6 [*M*+H]$^+$; 780.6 [*M*+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-fluorophenyl)-5,6-didehydro-piperidin-4-one (18b): *Cleavage A*: Yield: 18.2 mg (77%); colorless oil; R_f = 0.37 (petro-

leum ether/ethyl acetate (1:1)); $[\alpha]_D^{25}=13.64$ ($c=1$, $CHCl_3$); LC-MS: $t_R=$ 3.83 (minor); 4.12 (major) min; d.r. 1:99 (ELSD), purity: 97% (ELSD); MS (ES^+): $C_{42}H_{62}FNO_{11}$ (775.94): m/z: 798.7 $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-fluorophenyl)-5,6-didehydro-piperidin-4-one (18c): *Cleavage A*: Yield: n.d.; colorless oil; $R_f=0.56$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=4.32$ min; d.r. >99:1, purity: 91% (ELSD); MS (ES^+): $C_{42}H_{62}FNO_{11}$ (775.94): m/z: 798.5 $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-bromophenyl)-5,6-didehydro-piperidin-4-one (18d): *Cleavage B*: Yield: n.d.; colorless oil; $R_f=0.58$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=4.42$ (minor); 4.85 (major) min; d.r. 2:98 (ELSD), purity: 97% (ELSD); MS (ES^+): $C_{42}H_{62}BrNO_{11}$ (836.85): m/z: 585.4 $[M_{sugar}]^+$; 836.3 $[M(^{79}Br)+H]^+$; 838.3 $[M(^{81}Br)+H]^+$; 858.3 $[M(^{79}Br)+Na]^+$; 860.3 $[M(^{81}Br)+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-bromophenyl)-5,6-didehydro-piperidin-4-one (18e): *Cleavage A*: Yield: 14.3 mg (57%); colorless oil; $R_f=0.52$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=4.60$ (minor); 5.02 (major) min; d.r. 1:99 (ELSD), purity: 95% (ELSD). *Cleavage B*: Yield: 30 mg (90%); colorless oil; $[\alpha]_D^{25}=13.38$ ($c=1$, $CHCl_3$); LC-MS: d.r. 5:95 (ELSD), 2:98 ($\lambda=215$–218 nm), purity: 88% (ELSD), 99% ($\lambda=215$–218 nm); ^1H NMR ($CDCl_3$, 400 MHz): $\delta=7.44$–7.38, 7.28–7.16 (m, 5H, 4×aryl, NC*H*=CH); 5.56 (t, 1H, $^3J=9.6$ Hz, H-2); 5.32 (d, 1H, $^3J=$ 2.8 Hz, H-4); 5.23 (d, 1H, $^3J=7.8$ Hz, NCH=C*H*); 5.04 (dd, 1H, $^3J=10.0$, $^3J=3.0$ Hz, H-3); 4.80 (t, 1H, $^3J=6.9$ Hz, NC*H*Aryl); 4.41 (d, 1H, $^3J=$ 9.0 Hz, H-1); 3.90 (dd, 1H, $^3J=5.3$, $^2J=10.2$ Hz, H-6a); 3.79–3.71 (m, 2H, H-5, H-6b); 3.60 (t, 2H, $^3J=6.4$ Hz, CH_2OH); 2.83 (dd, 1H, $^3J=6.1$, $^2J=16.6$ Hz, CH_2C=O); 2.64 (dd, 1H, $^3J=7.8$, $^2J=16.8$ Hz, CH_2C=O); 1.74–1.20 (m, 10H, 5×CH_2); 1.24, 1.16, 1.09 (3 s, 27H, Piv *t*Bu); 1.10 (s, 6H, 2×Me) ppm; MS (ES^+): $C_{42}H_{62}BrNO_{11}$ (836.85): m/z: 858.3 $[M(^{79}Br)+Na]^+$; 860.3 $[M(^{81}Br)+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-chlorophenyl)-5,6-didehydro-piperidin-4-one (18f): *Cleavage A*: Yield: 60.9 mg (77%); colorless oil; $R_f=0.48$ (petroleum ether/ethyl acetate (1:1)); $[\alpha]_D^{25}=10.15$ ($c=1$, $CHCl_3$); HPLC (Luna C-18, MeCN (80%→100%), 20 min): $t_R=11.7$ (minor); 12.6 (major) min; d.r. 3:97 ($\lambda=215$ nm); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.33$–7.21 (m, 5H, 4×aryl, NC*H*=CH); 5.55 (t, 1H, $^3J=9.5$ Hz, H-2); 5.31 (d, 1H, $^3J=$ 2.9 Hz, H-4); 5.20 (d, 1H, $^3J=7.8$ Hz, NCH=C*H*); 5.01 (dd, 1H, $^3J=10.0$, $^3J=3.2$ Hz, H-3); 4.80 (dd, 1H, $^3J=6.1$, $^3J=8.6$ Hz, NC*H*Aryl); 4.36 (d, 1H, $^3J=9.3$ Hz, H-1); 3.94 (dd, 1H, $^3J=9.1$, $^2J=12.7$ Hz, H-6a); 3.78–3.69 (m, 2H, H-5, H-6b); 3.60 (t, 2H, $^3J=6.3$ Hz, CH_2OH); 2.78 (dd, 1H, $^3J=5.9$, $^2J=16.1$ Hz, CH_2C=O); 2.62 (dd, 1H, $^3J=8.6$, $^2J=16.4$ Hz, CH_2C=O); 1.87–1.21 (m, 10H, 5×CH_2); 1.23, 1.15, 1.08 (3 s, 27H, Piv *t*Bu); 1.10 (s, 6H, 2×Me) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta=191.3$ (keto C=O); 177.3, 177.2, 177.1, 176.5 (Piv C=O); 149.8 (N*C*H=CH); 137.2, 134.4 (*ipso*-aryl); 129.1, 128.5 (aryl); 103.3 (NCH=*C*H); 88.7 (C-1); 72.7, 71.4, 66.7, 65.2 (C-2, C-3, C-4, C-5); 62.8, 61.0 (C-6, CH_2OH); 59.1 (N*C*HAryl); 43.6 (*C*H_2C=O); 42.3 (*C*Me_2–COOR); 40.5 (CH_2); 39.1, 38.9, 38.8 (Piv *C*Me_3); 32.7, 29.8 (2×CH_2); 27.2, 27.1 (Piv Me); 25.6, 24.9 (2×CH_2); 25.0 (2×Me) ppm; MS (ES^+): $C_{42}H_{62}ClNO_{11}$ (792.39): m/z: 814.7 $[M(^{35}Cl)+Na]^+$; 816.7 $[M(^{37}Cl)+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(2-chloro-6-fluorophenyl)-5,6-didehydro-piperidin-4-one (18g): *Cleavage A*: Yield: 11.9 mg (49%); colorless oil; $R_f=0.48$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=4.90$ (minor); 6.23 (major) min; d.r. 3:97 (ELSD), purity: 89% (ELSD); MS (ES^+): $C_{42}H_{61}ClFNO_{11}$ (810.38): m/z: 832.4 $[M(^{35}Cl)+Na]^+$; 834.4 $[M(^{37}Cl)+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-cyanophenyl)-5,6-didehydro-piperidin-4-one (18h): *Cleavage A*: Yield: 59 mg (76%); colorless oil; $R_f=0.38$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=3.22$ min; d.r. >99:1 (ELSD), purity: 93% (ELSD); MS (ES^+): $C_{43}H_{62}N_2O_{11}$ (782.96): $m/z=805.7$ $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-trifluoromethylphenyl)-5,6-didehydro-piperidin-4-one (18i): *Cleavage A*: Yield: 67 mg (81%); colorless oil; $R_f=0.59$ (petroleum ether/ethyl acetate (1:1)); HPLC (Luna C-18, MeCN (80%→100%), 20 min): $t_R=12.3$ (minor); 13.6 (major) min; d.r. 7:93, purity: 97% (ELSD); MS (ES^+): $C_{43}H_{62}F_3NO_{11}$ (825.95): m/z: 848.6 $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-nitrophenyl)-5,6-didehydro-piperidin-4-one (18j): *Cleavage A*: Yield: 10.1 mg (42%); yellowish oil; $R_f=0.43$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=3.45$ (minor); 3.65 (major) min; d.r. 7:93 (ELSD), purity: 80% (ELSD); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=$ 8.15 (d, H, $^3J=8.8$ Hz, 2×aryl); 7.46 (d, 2H, $^3J=8.8$ Hz, 2×aryl); 7.24 (d, 1H, $^3J=7.4$ Hz, NC*H*=CH); 5.56 (t, 1H, $^3J=9.5$ Hz, H-2); 5.32 (d, 1H, $^3J=2.9$ Hz, H-4); 5.15 (d, 1H, $^3J=7.8$ Hz, NCH=C*H*); 5.11 (dd, 1H, $^3J=$ 9.8, $^3J=2.7$ Hz, H-3); 5.00 (dd, 1H, $^3J=6.1$, $^3J=8.6$ Hz, NC*H*Aryl); 4.36 (d, 1H, $^3J=9.3$ Hz, H-1); 3.94 (dd, 1H, $^3J=9.1$, $^2J=12.7$ Hz, H-6a); 3.78–3.69 (m, 2H, H-5, H-6b); 3.60 (t, 2H, $^3J=6.3$ Hz, CH_2OH); 2.78 (dd, 1H, $^3J=5.9$, $^2J=16.1$ Hz, CH_2C=O); 2.62 (dd, 1H, $^3J=8.6$, $^2J=16.4$ Hz, CH_2C=O); 1.87–1.21 (m, 10H, 5×CH_2); 1.23, 1.15, 1.08 (3 s, 27H, Piv *t*Bu); 1.10 (s, 6H, 2×Me) ppm; MS (ES^+): $C_{42}H_{62}N_2O_{13}$ (802.95): m/z: 825.7 $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-methylphenyl)-5,6-didehydro-piperidin-4-one (18k): *Cleavage A*: Yield: n.d.; colorless oil; $R_f=0.13$ (petroleum ether/ethyl acetate (2:1)); LC-MS: $t_R=4.23$ (minor); 4.76 (major); 8.45 (imine, 30%, m/z: 726.4 $[M_{imine}+Na]^+$) min; d.r. 9:91 (ELSD), purity: 66% (ELSD); MS (ES^+): $C_{43}H_{65}NO_{11}$ (771.98): m/z: 585.4 $[M_{sugar}]^+$; 772.4 $[M+H]^+$; 794.4 $[M+Na]^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-methoxyphenyl)-5,6-didehydro-piperidin-4-one (18l): *Cleavage A*: Yield: 20.9 mg (84%); colorless oil; $R_f=0.27$ (petroleum ether/ethyl acetate (1:1)); LC-MS: $t_R=3.65$ (minor); 3.98 (major) min; d.r. 2:98 (ELSD), purity: 98% (ELSD); ^1H NMR ($CDCl_3$, 200 MHz): $\delta=7.29$ (d, 1H, $^3J=8.3$ Hz, NC*H*=CH); 7.22 (d, 2H, $^3J=$ 8.1 Hz, 2×aryl); 6.89 (d, 2H, $^3J=8.8$ Hz, 2×aryl); 5.54 (t, 1H, $^3J=9.8$ Hz, H-2); 5.28 (d, 1H, $^3J=2.9$ Hz, H-4); 5.27 (d, 1H, $^3J=8.3$ Hz, NCH=C*H*); 4.92 (dd, 1H, $^3J=9.8$, $^3J=2.9$ Hz, H-3); 4.73 (dd, 1H, $^3J=5.4$, $^3J=$ 12.2 Hz, NC*H*Aryl); 4.20 (d, 1H, $^3J=9.8$ Hz, H-1); 4.03 (dd, 1H, $^3J=7.3$, $^2J=11.2$ Hz, H-6a); 3.85–3.76 (m, 4H, OMe, H-6b); 3.66 (m, 3H, CH_2OH, H-5); 2.76 (dd, 1H, $^3J=11.7$, $^2J=16.6$ Hz, CH_2C=O); 2.61 (dd, 1H, $^3J=5.4$, $^2J=16.6$ Hz, CH_2C=O); 1.56–1.22 (m, 10H, 5×CH_2); 1.25, 1.15, 1.07 (3 s, 27H, Piv *t*Bu); 1.13 (s, 6H, 2×Me) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): $\delta=192.5$ (keto C=O); 177.3, 176.9, 176.6 (Piv C=O); 160.0 (MeO*C*); 149.8 (N*C*H=CH); 129.5 (*ipso*-aryl); 128.9, 114.5 (aryl); 104.0 (NCH=*C*H); 86.8 (C-1); 72.6, 71.7, 66.9, 65.9 (C-2, C-3, C-4, C-5); 62.8, 61.3, 60.9 (N*C*HAryl, C-6, *C*H_2OH); 55.3 (OMe); 43.9 (*C*H_2C=O); 42.3 (*C*Me_2–COOR); 40.6 (CH_2); 39.1, 38.9, 38.8 (Piv *C*Me_3); 32.8, 29.8, 29.7 (3×CH_2); 27.2, 27.1 (Piv Me); 25.6 (CH_2); 25.1, 24.9 (2×Me) ppm; MS (ES^+): $C_{43}H_{65}NO_{12}$ (787.98): m/z: 810.7 $[M+Na]^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(2-phenylethyl)-5,6-didehydro-piperidin-4-one (18n): *Cleavage A*: Yield: 11.9 mg (50%); colorless oil; $R_f=0.13$ (petroleum ether/ethyl acetate (2:1)); LC-MS: $t_R=4.55$ (minor); 4.93 (major) min; d.r. 10:90 (ELSD), purity: 83% (ELSD); MS (ES^+): $C_{44}H_{67}NO_{11}$ (786.00): m/z: 786.4 $[M+H]^+$; 808.4 $[M+Na]^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-methyl-5,6-didehydro-piperidin-4-one (18o): *Cleavage A*: Yield: 15.3 mg (73%); colorless oil; $R_f=0.37$ (petroleum ether/ethyl acetate (2:1)); HPLC (Luna C-18, MeCN (80%→100%), 20 min): $t_R=8.63$ (minor); 9.07 (major) min; d.r. 22:78 ($\lambda=320$ nm); purity: 90% (ELSD); MS (ES^+): $C_{37}H_{61}NO_{11}$ (695.88): m/z: 696.5 $[M+H]^+$; 718.5 $[M+Na]^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-ethyl-5,6-didehydro-piperidin-4-one (18p): *Cleavage B:* Yield from tandem condensation at −10°C: 11.1 mg (78%); colorless oil; $R_f=0.37$ (petroleum ether/ethyl acetate (2:1)); HPLC (Luna C-18, MeCN (80%→100%), 20 min): $t_R=9.63$ (major); 10.58 (minor) min; d.r. 85:15 ($\lambda=320$ nm), purity: 87% (ELSD); ^1H NMR (major diastereomer, $CDCl_3$, 400 MHz): $\delta=7.00$ (d, 1H, $^3J=7.4$ Hz, NC*H*=CH); 5.63 (t, 1H, $^3J=9.8$ Hz, H-2); 5.50 (d, 1H, $^3J=2.7$ Hz, H-4); 5.25 (dd, 1H, $^3J=$ 9.8, $^3J=2.9$ Hz, H-3); 5.06 (d, 1H, $^3J=7.8$ Hz, NCH=C*H*); 4.63 (d, 1H, $^3J=9.4$ Hz, H-1); 4.29 (dd, 1H, $^3J=6.6$, $^2J=11.0$ Hz, H-6a); 4.10 (t, 1H, $^3J=6.6$ Hz, H-5); 3.99 (dd, 1H, $^3J=6.6$, $^2J=11.0$ Hz, H-6b); 3.72–3.69 (m, 3H, H-2, CH_2OH); 2.69 (dd, 1H, $^3J=7.3$, $^2J=16.4$ Hz, CH$_2$C=O); 2.48

(br d, 1H, ^2J = 15.6 Hz, CH_2C=O); 1.93–1.27 (m, 12H, 6×CH_2); 1.36, 1.21 (2 s, 27H, Piv *t*Bu); 1.23 (s, 6H, 2×Me); 0.96 (t, 3H, ^3J = 7.6 Hz, Me) ppm; MS (ES$^+$): $C_{38}H_{63}NO_{11}$ (709.91): *m*/*z*: 585.5 [M_{sugar}]$^+$; 710.5 [*M*+H]$^+$; 732.4 [*M*+Na]$^+$.

***N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-*n*-propyl-5,6-didehydro-piperidin-4-one (18q)**: *Cleavage B*: Yield from tandem condensation at −10 °C: 13.0 mg (90 %); colorless oil; R_f = 0.39 (petroleum ether/ethyl acetate (2:1)); HPLC (Luna C-18, MeCN (80 %→100 %), 20 min): t_R = 10.80 (minor); 12.02 (major) min; d.r. 19:81 (λ = 320 nm). Separation of diastereomers by semi-preparative HPLC (Luna C-18, MeCN (80 %→90 %), 30 min): t_R = 15.9 (minor); 17.2 (major) min. Major diastereomer: 8 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.89 (d, 1H, ^3J = 7.8 Hz, NC*H*=CH); 5.52 (t, 1H, ^3J = 9.6 Hz, H-2); 5.41 (d, 1H, ^3J = 2.7 Hz, H-4); 5.16 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.95 (d, 1H, ^3J = 7.8 Hz, NCH=C*H*); 4.55 (d, 1H, ^3J = 9.4 Hz, H-1); 4.22 (dd, 1H, ^3J = 6.7, ^2J = 11.0 Hz, H-6a); 4.01 (t, 1H, ^3J = 6.9 Hz, H-5); 3.90 (dd, 1H, ^3J = 6.6, ^2J = 11.0 Hz, H-6b); 3.76–3.70 (m, 1H, NC*H*Pr); 3.61 (t, 2H, ^3J = 6.5 Hz, CH_2OH); 2.60 (dd, 1H, ^3J = 6.6, ^2J = 16.8 Hz, CH_2C=O); 2.34 (br d, 1H, ^2J = 16.4 Hz, CH_2C=O); 1.92–1.83 (m, 1H, CH_2); 1.64–1.13 (m, 13H, 6.5×CH_2); 1.27, 1.10 (2 s, 27H, Piv *t*Bu); 1.11 (s, 6H, 2×Me); 0.88 (t, 3H, ^3J = 7.2 Hz, Me) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 192.2 (keto C=O); 177.3, 177.0, 176.5 (Piv C=O); 149.8 (NCH=CH); 99.9 (NCH=*C*H); 91.5 (C-1); 72.9, 71.3, 66.6, 65.7 (C-2, C-3, C-4, C-5); 62.8 (*C*H_2OH); 60.8 (C-6); 53.3 (N*C*HPr); 42.3 (*C*Me_2−COOR); 40.3 (CH_2); 39.1, 38.9, 38.8 (*C*H_2C=O, Piv *C*Me_3); 32.7, 29.7 (2×CH_2); 27.2, 27.1, 27.0 (CH_2, Piv Me); 25.5 (CH_2); 25.0, 24.8 (2×Me, CH_2); 18.9 (*C*$H_2$$CH_3$); 13.8 ($CH_2$*C*$H_3$) ppm; MS (ES$^+$): $C_{39}H_{65}NO_{11}$ (723.93): *m*/*z*: 585.5 [M_{sugar}]$^+$; 724.4 [*M*+H]$^+$; 746.6 [*M*+Na]$^+$. Minor diastereomer: 3 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.11 (d, 1H, ^3J = 9.0 Hz, NC*H*=CH); 5.42 (d, 1H, ^3J = 2.8 Hz, H-4); 5.36 (t, 1H, ^3J = 9.6 Hz, H-2); 5.15 (dd, 1H, ^3J = 10.2, ^3J = 3.1 Hz, H-3); 5.12 (d, 1H, ^3J = 8.2 Hz, NCH=C*H*); 4.42 (d, 1H, ^3J = 9.0 Hz, H-1); 4.12 (dd, 1H, ^3J = 6.6, ^2J = 10.6 Hz, H-6a); 4.03 (t, 1H, ^3J = 6.3 Hz, H-5); 3.96 (dd, 1H, ^3J = 5.9, ^2J = 10.6 Hz, H-6b); 3.61 (t, 2H, ^3J = 6.4 Hz, CH_2OH); 3.55–3.49 (m, 1H, NC*H*Pr); 2.64 (dd, 1H, ^3J = 6.6, ^2J = 16.0 Hz, CH_2C=O); 2.39 (br d, 1H, ^2J = 16.0 Hz, CH_2C=O); 1.87–1.77 (m, 1H, CH_2); 1.53–1.18 (m, 13H, 6.5×CH_2); 1.28, 1.14, 1.11 (3 s, 27H, Piv *t*Bu); 1.12 (s, 6H, 2×Me); 0.89 (t, 3H, ^3J = 7.2 Hz, Me) ppm; MS (ES$^+$): *m*/*z*: 585.5 [M_{sugar}]$^+$; 724.4 [*M*+H]$^+$; 746.6 [*M*+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-isopropyl-5,6-didehydro-piperidin-4-one (18r): *Cleavage A*: Yield: 16.2 mg (73 %); colorless oil; R_f = 0.24 (petroleum ether/ethyl acetate (1:1)); LC-MS: t_R = 3.57 (minor); 4.12 (major) min; d.r. 2:98 (ELSD); purity: 92 % (ELSD); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.01 (d, 1H, ^3J = 7.8 Hz, NC*H*=CH); 5.55 (t, 1H, ^3J = 9.5 Hz, H-2); 5.41 (d, 1H, ^3J = 2.9 Hz, H-4); 5.15 (dd, 1H, ^3J = 10.3, ^3J = 3.2 Hz, H-3); 4.96 (d, 1H, ^3J = 7.8 Hz, NCH=C*H*); 4.61 (d, 1H, ^3J = 9.3 Hz, H-1); 4.19 (dd, 1H, ^3J = 5.9, ^2J = 9.8 Hz, H-6a); 4.04–3.87 (m, 3H, H-5, H-6b, NC*H*-*i*Pr); 3.61 (t, 2H, ^3J = 6.3 Hz, CH_2OH); 2.60 (dd, 1H, ^3J = 7.3, ^2J = 17.1 Hz, CH_2C=O); 2.41 (dd, 1H, ^3J = 2.9, ^2J = 17.1 Hz, CH_2C=O); 2.30–2.18 (m, 1H, C*H*Me_2); 1.51–1.22 (m, 10H, 5×CH_2); 1.26, 1.11, 1.10 (3 s, 33H, Piv *t*Bu, 2×Me); 0.91 (2 d, 6H, ^3J = 7.2 Hz, 2×Me) ppm; MS (ES$^+$): $C_{39}H_{65}NO_{11}$ (723.93): *m*/*z*: 746.6 [*M*+Na]$^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-isobutyl-5,6-didehydro-piperidin-4-one (18s): *Cleavage A*: Yield: 13.4 mg (61 %); colorless oil; R_f = 0.37 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 4.42 (minor); 4.93 (major) min; d.r. 18:82 (ELSD); purity: 88 % (ELSD); MS (ES$^+$): $C_{40}H_{67}NO_{11}$ (737.96): *m*/*z*: 760.3 [*M*+Na]$^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-*n*-pentyl-5,6-didehydro-piperidin-4-one (18u): *Cleavage B:* Yield from tandem condensation at −10 °C: 13.1 mg (87 %); colorless oil; R_f = 0.40 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 5.25 (minor); 6.02 (major) min; d.r. 16:84 (ELSD); purity: 95 % (ELSD); MS (ES$^+$): $C_{41}H_{69}NO_{11}$ (751.99): *m*/*z*: 585.5 [M_{sugar}]$^+$; 752.4 [*M*+H]$^+$; 774.4 [*M*+Na]$^+$.

(2*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-*n*-heptyl-5,6-didehydro-piperidin-4-one (18v): *Cleavage A*: Yield: 13.3 mg (57 %); colorless oil; R_f = 0.42 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 7.07 (minor); 8.07 (major) min; d.r. 11:89 (ELSD); purity: 74 % (ELSD); MS (ES$^+$): $C_{43}H_{73}NO_{11}$ (780.04): *m*/*z*: 780.4 [*M*+H]$^+$; 802.5 [*M*+Na]$^+$.

General procedure for conjugate hydride addition on solid phase (50 mg resin scale): a) Preparation of methyl aluminum-bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD):[36a] At room temperature, $AlMe_3$ (2 M in toluene, 0.2 mL, 0.40 mmol) was added dropwise to a solution of 2,6-di-*tert*-butyl-4-methyl-phenol (176 mg, 0.80 mmol) in dry toluene (2 mL). When methane evolution ceased (after approximately 30 min), the clear solution of the methyl alumoxane was ready for use. b) Conjugate hydride addition: A suspension of polymer-bound enone **17** (50 mg, approximately 0.02 mmol) in dry THF (4 mL) was cooled to −20 °C and treated with MAD (approximately 2.2 mL, 0.40 mmol) prepared according to the procedure described above. After 15 min, L-selectride (1 M in THF, 0.2 mL, 0.2 mmol) was added at this temperature and the mixture was shaken for the given time period before being quenched with acetic acid (10 % in THF, 1 mL). The suspension was warmed to room temperature, then the resin was filtered and thoroughly washed with CH_2Cl_2 and MeOH (6 cycles). The following *N*-galactosylpiperidin-4-ones **20** were obtained after treatment with TBAF (yields given are based on loading of galactosyl azide **11a**).

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-fluorophenyl)-piperidin-4-one (20c): Reaction time: 3.5 h; Yield: 8.3 mg (53 %); colorless oil; R_f = 0.63 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 6.73 min; purity: 99 % (ELSD); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (td, 1H, ^3J = 8.0, ^4J(H,F) = 5.5 Hz, aryl-H-5); 7.07–6.99 (m, 3H, aryl); 5.45 (t, 1H, ^3J = 9.8 Hz, H-2); 5.25 (d, 1H, ^3J = 2.7 Hz, H-4); 4.89 (dd, 1H, ^3J = 10.2, ^3J = 3.1 Hz, H-3); 4.10 (dd, 1H, ^3J = 10.6, ^3J = 4.3 Hz, NC*H*Aryl); 4.05 (dd, 1H, ^3J = 7.0, ^2J = 11.3 Hz, H-6a); 3.90 (d, 1H, ^3J = 9.4 Hz, H-1); 3.85 (dd, 1H, ^3J = 6.3, ^2J = 11.4 Hz, H-6b); 3.62–3.58 (m, 3H, NCH_2, CH_2OH); 3.50 (t, 1H, ^3J = 6.5 Hz, H-5); 2.98–2.91 (m, 1H, NCH_2); 2.61–2.45 (m, 4H, CH_2C=O); 1.58–1.22 (m, 10H, 5×CH_2); 1.23, 1.21, 1.07 (3 s, 27H, Piv *t*Bu); 1.14 (s, 6H, 2×Me) ppm; MS (ES$^+$): $C_{42}H_{64}FNO_{11}$ (777.96): *m*/*z*: 698.6 [*M*−PivOH+Na]$^+$; 800.6 [M−Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-bromophenyl)-piperidin-4-one (20d): Reaction time: 7 h; Yield: 15.9 mg (34 %); colorless oil; R_f = 0.32 (petroleum ether/ethyl acetate (2:1)); HPLC (Luna C-18, MeCN (80 %→100 %), 20 min): t_R = 21.50 min; purity: 82 % (λ = 215 nm). Isolation by preparative HPLC (Luna C-18, MeCN (80 %→100 %), 60 min): t_R = 72.2 min; Yield: 7.9 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50 (d, 2H, ^3J = 8.6 Hz, 2×aryl); 7.16 (d, 2H, ^3J = 8.2 Hz, 2×aryl); 5.44 (t, 1H, ^3J = 9.8 Hz, H-2); 5.25 (d, 1H, ^3J = 2.7 Hz, H-4); 4.89 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.08–4.03 (m, 2H, H-6a, NC*H*Aryl); 3.86 (d, 1H, ^3J = 9.4 Hz, H-1); 3.84 (dd, 1H, ^3J = 6.3, ^2J = 11.3 Hz, H-6b); 3.63–3.57 (m, 3H, NCH_2, CH_2OH); 3.48 (t, 1H, ^3J = 6.6 Hz, H-5); 2.93 (td, 1H, ^3J = 7.7, ^2J = 11.8 Hz, NCH_2); 2.60–2.44 (m, 4H, CH_2C=O); 1.53–1.16 (m, 10H, 5×CH_2); 1.23, 1.21, 1.07 (3 s, 27H, Piv *t*Bu); 1.14 (s, 6H, 2×Me) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 207.6 (keto C=O); 177.4, 177.2 (Piv C=O); 138.8, 132.2, 129.5, 122.4 (aryl); 87.9 (C-1); 71.9, 71.7, 67.2, 65.0, 63.4, 62.8, 61.7 (C-2, C-3, C-4, C-5, C-6, NCHAryl, CH_2OH); 48.9, 43.6, 41.6 (NCH_2, *C*H_2C=O); 42.2 (*C*Me_2−COOR); 40.5 (CH_2); 39.0, 38.8, 38.7 (Piv *C*Me_3); 32.7, 29.8 (2×CH_2); 27.4, 27.2, 27.0 (Piv Me); 25.6 (CH_2); 25.1, 25.0, 24.9 (2×Me, CH_2) ppm; MS (ES$^+$): $C_{42}H_{64}BrNO_{11}$ (838.86): *m*/*z*: 758.2 [*M*(^{79}Br)−PivOH+Na]$^+$; 760.2 [*M*(^{81}Br)−PivOH+Na]$^+$; 860.4 [*M*(^{79}Br)+Na]$^+$; 862.4 [*M*(^{81}Br)+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-bromophenyl)-piperidin-4-one (20e): Reaction time: 3.5 h; Yield: n.d.; colorless oil; R_f = 0.35 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 4.97 (37 %, **18e**); 8.12 (51 %, **20e**) min; MS (ES$^+$): $C_{42}H_{64}BrNO_{11}$ (838.86): *m*/*z*: 758.3 [*M*(^{79}Br)−PivOH+Na]$^+$; 760.3 [*M*(^{81}Br)−PivOH+Na]$^+$; 860.5 [*M*(^{79}Br)+Na]$^+$; 862.5 [*M*(^{81}Br)+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-chlorophenyl)-piperidin-4-one (20f): Reaction time: 7 h; Yield: 8.3 mg (50 %); colorless oil; R_f = 0.35 (petroleum ether/ethyl acetate (2:1)); HPLC (Luna C-18, MeCN (80 %→100 %), 20 min): t_R = 28.67 min; purity: 65 % (λ = 215 nm). Isolation by preparative HPLC (Luna C-18, MeCN (80 %→100 %), 60 min): t_R = 72.3 min; yield: 6.2 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, 2H, ^3J = 8.6 Hz, 2×aryl); 7.22 (d, 2H, ^3J = 8.6 Hz, 2×aryl); 5.44 (t, 1H, ^3J = 9.6 Hz, H-2); 5.25 (d, 1H,

^3J = 3.1 Hz, H-4); 4.89 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.09–4.04 (m, 2H, H-6a, NC*H*Aryl); 3.87–3.81 (m, 2H, H-1, H-6b); 3.63–3.59 (m, 3H, NCH_2, CH_2OH); 3.48 (t, 1H, ^3J = 6.5 Hz, H-5); 2.93 (td, 1H, ^3J = 7.8, ^2J = 12.1 Hz, NCH_2); 2.60–2.42 (m, 4H, CH_2C=O); 1.53–1.16 (m, 10H, 5× CH_2); 1.23, 1.20, 1.07 (3 s, 27H, Piv *t*Bu); 1.14 (s, 6H, 2×Me) ppm; MS (ES$^+$): $C_{42}H_{64}ClNO_{11}$ (794.41): *m*/*z*: 816.6 [*M*(^{35}Cl)+Na]$^+$; 818.6 [*M*(^{37}Cl)+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(2-chloro-6-fluorophenyl)-piperidin-4-one (20g): Reaction time: 3.5 h; Yield: n.d.; colorless oil; LC-MS: t_R = 4.92 (32%, **18g**); 7.37 (47%, **20g**) min; MS (ES$^+$): $C_{42}H_{63}ClFNO_{11}$ (812.40): *m*/*z*: 732.4 [*M*(^{35}Cl)−PivOH+Na]$^+$; 734.4 [*M*(^{37}Cl)−PivOH+Na]$^+$; 834.6 [*M*(^{35}Cl)+Na]$^+$; 836.6 [*M*(^{37}Cl)+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-trifluoromethylphenyl)-piperidin-4-one (20i): Reaction time: 4 h (40 equivalents of MAD and 15 equivalents of L-selectride were used); yield: n.d.; colorless oil; LC-MS: t_R = 7.63 (83%, **20i**) min; MS (ES$^+$): $C_{43}H_{64}F_3NO_{11}$ (827.96): *m*/*z*: 748.5 [*M*−PivOH+Na]$^+$; 850.7 [*M*+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-methoxyphenyl)-piperidin-4-one (20l): Reaction time: 4 h at −40°C (40 equivalents of MAD and 15 equivalents of L-selectride were used); yield: n.d.; colorless oil; R_f = 0.42 (petroleum ether/ethyl acetate (2:1)); LC-MS: R_t = 3.93 (64%, **18l**); 6.70 (21%, **20l**) min; MS (ES$^+$): $C_{43}H_{67}NO_{12}$ (789.99): *m*/*z*: 710.4 [*M*−PivOH+Na]$^+$; 812.5 [*M*+Na]$^+$.

(2*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-isopropyl-piperidin-4-one (20r): Reaction time: 7 h; yield: 4.1 mg (28%); colorless oil; R_f = 0.49 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 7.07 (74%, **20r**). Isolation by semi-preparative HPLC (Luna C-18, MeCN (80%→100%), 30 min): t_R = 22.3 min; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 5.50 (t, 1H, ^3J = 9.7 Hz, H-2); 5.36 (d, 1H, ^3J = 2.9 Hz, H-4); 5.15 (dd, 1H, ^3J = 10.0, ^3J = 2.9 Hz, H-3); 4.41 (d, 1H, ^3J = 9.1 Hz, H-1); 4.05 (dd, 1H, ^3J = 7.0, ^2J = 11.2 Hz, H-6a); 3.93 (dd, 1H, ^3J = 6.2, ^2J = 10.9 Hz, H-6b); 3.87 (t, 1H, ^3J = 6.5 Hz, H-5); 3.61 (t, 2H, ^3J = 5.6 Hz, CH_2OH); 3.29 (td, 1H, ^2J = 14.1, ^3J = 5.6 Hz, NCH_2); 3.14 (ddd, 1H, ^2J = 13.8, ^3J = 8.5, ^3J = 5.1 Hz, NCH_2); 2.87 (pq, 1H, ^3J = 6.2 Hz, NC*H*-*i*Pr); 2.65 (dd, 1H, ^2J = 13.7, ^3J = 5.2 Hz, CH*i*PrCH_2); 2.54 (ddd, 1H, ^2J = 14.3, ^3J = 6.8, ^3J = 7.6 Hz, NCH_2CH_2); 2.36 (dd, 1H, ^2J = 14.1, ^3J = 5.6 Hz, CH*i*PrCH_2); 2.21 (td, 1H, ^2J = 14.3, ^3J = 5.3 Hz, NCH_2CH_2); 1.78–1.73 (m, 1H, C*H*(Me)$_2$); 1.53–1.16 (m, 10H, 5×CH_2); 1.25, 1.13, 1.11 (3 s, 27H, Piv *t*Bu); 1.14 (s, 6H, 2×Me); 0.87 (d, 3H, ^3J = 6.7 Hz, Me); 0.86 (d, 3H, ^3J = 6.6 Hz, Me) ppm; MS (ES$^+$): $C_{39}H_{67}NO_{11}$ (725.95): *m*/*z*: 585.3 [M_{sugar}]$^+$; 646.3 [*M*−PivOH+Na]$^+$; 726.3 [*M*+H]$^+$; 748.2 [*M*+Na]$^+$.

General procedure for conjugate cuprate addition to polymer-bound enaminones (17): a) Cuprate preparation: At −78°C a suspension of copper(I) cyanide in dry THF (approximately 1 mL per 50 mg) was treated with organolithium reagent (2 equiv). The suspension was slowly warmed up until cuprate formation was complete and the solution had become clear. Before addition to the enone, the cuprate solution was recooled to −78°C. b) Conjugate addition: $BF_3{\cdot}OEt_2$ (for amounts, see below) and the cooled cuprate solution (for reaction times and temperatures, see below) were added successively to a suspension of resin **17** in THF (1 mL per 50 mg) at −78°C. After the given reaction time the suspension was treated with ammonium pyrrolidine dithiocarbamate solution (0.1% in CH_2Cl_2/MeOH (5:1)), warmed to room temperature, filtered, and vigorously washed with the carbamate solution several times until the resin had reached its initial amber colour. The resin was further washed with CH_2Cl_2, THF, und MeOH (6 cycles) and dried under high vacuum. Cleavage from support was performed by using TBAF.

(2*S*,6*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-fluorophenyl)-6-*n*-butyl-piperidin-4-one (22ca): (nBu)$_2$Cu(CN)Li$_2$ (30 equiv, cuprate formation: −60°C), $BF_3{\cdot}OEt_2$ (30 equiv); reaction time: 2 h at −60°C, then warm to −55°C for 12 h; Yield of crude product: 7.9 mg (47%); yellowish oil; LC-MS: t_R = 9.50 (90%, major); 10.07 (10%, minor) min; purification by semi-preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min): t_R = 48.17 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (td, 1H, ^3J = 7.8, $^4J_{H,F}$ = 5.9 Hz, aryl H-5); 7.09–6.98 (m, 3H, aryl); 5.50 (t, 1H, ^3J = 9.6 Hz, H-2); 5.23 (d, 1H, ^3J = 2.3 Hz, H-4); 4.83 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.48 (dd, 1H, ^3J = 5.1, ^3J = 9.0 Hz, NC*H*Aryl); 4.07 (dd, 1H, ^3J = 7.0, ^2J = 11.3 Hz, H-6a); 3.93 (d, 1H, ^3J = 9.4 Hz, H-1); 3.82–3.78 (m, 2H, H-6b, NC*H*Bu); 3.60 (t, 2H, ^3J = 6.5 Hz, CH_2OH); 3.30 (t, 1H, ^3J = 6.8 Hz, H-5); 2.51–2.46 (m, 4H, CH_2C=O); 1.52–1.42, 1.38–1.20 (m, 16H, 8×CH_2); 1.23, 1.22, 1.07 (3 s, 27H, Piv *t*Bu); 1.13 (s, 6H, 2×Me); 0.88 (t, 3H, ^3J = 6.8 Hz, CH_2CH_3) ppm; MS (ES$^+$): $C_{46}H_{72}FNO_{11}$ (834.06): *m*/*z*: 732.5 [*M*−PivOH+H]$^+$; 754.5 [*M*−PivOH+Na]$^+$; 856.6 [*M*+Na]$^+$.

(2*S*,6*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(3-bromophenyl)-6-*n*-butyl-piperidin-4-one (22ea): (nBu)$_2$Cu(CN)Li$_2$ (30 equiv, cuprate formation: −60°C); $BF_3{\cdot}OEt_2$ (30 equiv); reaction time: 2 h at − 40°C, then warm to −12°C for 14 h; Yield of crude product: 7.9 mg (44%); yellowish oil; LC-MS: t_R = 4.93 (2%, **18e**); 10.60 (71%, major); 11.30 (15%, minor) min. Purification by preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min): t_R = 60.47 (74%, major); 64.50 (26%, minor) min. Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.45 (m, 2H, 2×aryl); 7.28–7.20 (m, 2H, 2×aryl); 5.50 (t, 1H, ^3J = 9.4 Hz, H-2); 5.24 (d, 1H, ^3J = 2.7 Hz, H-4); 4.84 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.45 (dd, 1H, ^3J = 4.7, ^3J = 9.8 Hz, NC*H*Aryl); 4.09 (dd, 1H, ^3J = 6.7, ^2J = 11.0 Hz, H-6a); 3.90 (d, 1H, ^3J = 9.8 Hz, H-1); 3.82–3.77 (m, 2H, H-6b, NC*H*Bu); 3.60 (t, 2H, ^3J = 6.6 Hz, CH_2OH); 3.32 (t, 1H, ^3J = 6.6 Hz, H-5); 2.52–2.46 (m, 4H, CH_2C=O); 1.57–1.16 (m, 16H, 8×CH_2); 1.23, 1.22, 1.07 (3 s, 27H, Piv *t*Bu); 1.13 (s, 6H, 2×Me); 0.88 (t, 3H, ^3J = 6.8 Hz, CH_2CH_3) ppm. Minor diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.49–7.42 (m, 2H, 2×aryl); 7.25–7.18 (m, 2H, 2×aryl); 5.49 (t, 1H, ^3J = 9.8 Hz, H-2); 5.29 (d, 1H, ^3J = 2.7 Hz, H-4); 4.85 (dd, 1H, ^3J = 9.8, ^3J = 2.8 Hz, H-3); 4.55 (dd, 1H, ^3J = 3.5, ^3J = 12.5 Hz, NC*H*Aryl); 4.17 (dd, 1H, ^3J = 7.0, ^2J = 11.0 Hz, H-6a); 4.15 (d, 1H, ^3J = 9.8 Hz, H-1); 3.89 (dd, 1H, ^3J = 6.4, ^2J = 11.4 Hz, H-6b); 3.78 (t, 1H, ^3J = 6.6 Hz, H-5); 3.62–3.57 (m, 3H, CH_2OH, NC*H*Bu); 2.87 (dd, 1H, ^3J = 5.5, ^2J = 16.4 Hz), 2.63–2.44 (m, 3H, CH_2C=O); 1.56–1.46, 1.35–1.23 (m, 16H, 8×CH_2); 1.27, 1.18, 1.08 (3 s, 27H, Piv *t*Bu); 1.14 (s, 6H, 2×Me); 0.87 (t, 3H, ^3J = 7.0 Hz, CH_2CH_3) ppm; MS (ES$^+$): $C_{46}H_{72}BrNO_{11}$ (894.97): *m*/*z*: 814.4 [*M*(^{79}Br)−PivOH+Na]$^+$; 816.4 [*M*(^{81}Br)−PivOH+Na]$^+$; 916.6 [*M*(^{79}Br)+Na]$^+$; 918.6 [*M*(^{81}Br)+Na]$^+$.

(2*S*,6*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(2-chloro-6-fluorophenyl)-6-methyl-piperidin-4-one (22gb): Me_2Cu(CN)Li$_2$ (30 equiv, cuprate formation: −30°C); $BF_3{\cdot}OEt_2$ (30 equiv); reaction time: 16 h at −20°C; Yield of crude product: 11 mg (67%); yellowish oil; R_f = 0.31 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 5.10 (12%, **18g**); 7.95 (3%, minor); 8.32 (78%, major) min. Purification by preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min): t_R = 59.15 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 2H, ^3J = 8.2 Hz, 2×aryl); 7.03 (t, 1H, ^3J = 8.6 Hz, aryl); 5.52 (t, 1H, ^3J = 9.6 Hz, H-2); 5.26–5.23 (m, 2H, H-4, NC*H*Aryl); 4.89 (dd, 1H, ^3J = 9.8, ^3J = 3.1 Hz, H-3); 4.17–4.05 (m, 2H, H-6a, H-6b); 3.96 (d, 1H, ^3J = 9.4 Hz, H-1); 3.80 (t, 1H, ^3J = 10.2 Hz, H-5); 3.60 (t, 2H, ^3J = 6.4 Hz, CH_2OH); 3.35 (br s, 1H), 2.92 (br s, 1H), 2.66 (dd, 1H, ^3J = 5.5, ^2J = 14.1 Hz), 2.52–2.47 (m, 1H), 2.23 (br d, 1H, ^2J = 14.5 Hz, NC*H*Me, CH_2C=O); 1.54–1.24 (m, 10H, 5×CH_2); 1.23, 1.16, 1.08 (3 s, 27H, Piv *t*Bu); 1.08 (s, 6H, 2×Me); 1.32 (d, 3H, ^3J = 6.7 Hz, Me) ppm; MS (ES$^+$): $C_{43}H_{65}ClFNO_{11}$ (826.43): *m*/*z*: 724.4 [*M*−PivOH+H]$^+$; 746.3 [*M*−PivOH+Na]$^+$; 848.5 [*M*+Na]$^+$.

(2*S*,6*R*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(2-chloro-6-fluorophenyl)-6-phenyl-piperidin-4-one (22gc): Ph_2Cu(CN)Li$_2$ (30 equiv, cuprate formation: −30°C); $BF_3{\cdot}OEt_2$ (30 equiv); reaction time: 16 h at −20°C; Yield of crude product: 11 mg (48%); yellowish oil, R_f = 0.28 (petroleum ether/ethyl acetate (2:1)); LC-MS: t_R = 4.92 (27%, **18g**); 7.75 (53%, major); 8.92 (15%, minor) min. Purification by preparative HPLC (Luna C-18, MeCN (80%→100%), 60 min): t_R = 52.40 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43 (d, 2H, ^3J = 7.8 Hz, 2×aryl); 7.32–7.26 (m, 4H, 4×aryl); 7.18 (t, 1H, ^3J = 7.2 Hz, 1×aryl); 7.03–6.98 (m, 1H, 1×aryl); 5.50 (br d, 1H, ^3J = 13.3 Hz, CHN); 5.29 (d, 1H, ^3J = 2.4 Hz, H-4); 5.18 (t, 1H, ^3J = 9.4 Hz, H-2); 5.04 (br d, 1H, ^3J = 4.3 Hz, CHN); 4.87 (dd, 1H, ^3J = 9.8, ^3J = 2.7 Hz, H-3); 4.26 (d, 1H, ^3J = 9.4 Hz, H-1); 4.24 (dd, 1H, ^3J = 5.9, ^2J = 10.6 Hz, H-6a); 3.98 (t, 1H, ^3J = 6.3 Hz, H-5); 3.93 (dd, 1H, ^3J = 6.6, ^2J = 10.2 Hz, H-6b); 3.61 (t, 2H, ^3J = 6.5 Hz, CH_2OH); 3.39 (dd, 1H, ^3J = 6.2, ^2J = 16.4 Hz), 3.27 (dd, 1H, ^3J = 14.9, ^2J = 18.0 Hz), 2.94 (dd, 1H, ^3J = 2.0, ^2J = 16.8 Hz), 2.42 (dd, 1H, ^3J = 2.7, ^2J = 18.0 Hz, CH_2C=O); 1.55–1.48, 1.35–1.23 (m, 10H, 5×CH_2); 1.24, 0.99, 0.98 (3 s, 27H, Piv *t*Bu); 1.15 (s, 6H, 2×

Me) ppm; MS (ES^+): $C_{48}H_{67}ClFNO_{11}$ (888.50): *m/z*: 786.5 $[M-PivOH+H]^+$; 808.5 $[M-PivOH+Na]^+$; 910.5 $[M+Na]^+$.

(2*S*,6*S*)-*N*-[6-*O*-(8-Hydroxy-2,2-dimethyloctanoyl)-2,3,4-tri-*O*-pivaloyl-β-D-galacto-pyranosyl]-2-(4-trifluoromethylphenyl)-6-*n*-butyl-piperidin-4-one (22ia): ($nBu)_2Cu(CN)Li_2$ (30 equiv, cuprate formation: −60 °C); $BF_3{\cdot}OEt_2$ (30 equiv); reaction time: 2 h at −60 °C, then warm to −55 °C for 12 h; Yield of crude product: 8.3 mg (47 %); yellowish oil; LC-MS: t_R = 4.82 (15 %, **18i**); 10.22 (61 %, major); 10.87 (24 %, minor) min. Purification by semi-preparative HPLC (Luna C-18, MeCN (90 %→100 %), 60 min): t_R = approximately 23.3 (diastereomeric mixture) min. Major diastereomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.65 (d, 2H, ^3J = 8.2 Hz, 2× aryl); 7.44 (d, 2H, ^3J = 7.8 Hz, 2× aryl); 5.52 (t, 1H, ^3J = 9.8 Hz, H-2); 5.23 (d, 1H, ^3J = 3.1 Hz, H-4); 4.84 (dd, 1H, ^3J = 9.6, ^3J = 2.9 Hz, H-3); 4.56 (dd, 1H, ^3J = 4.7, ^3J = 9.4 Hz, NC*H*Aryl); 4.08 (dd, 1H, ^3J = 6.6, ^2J = 11.3 Hz, H-6a); 3.90 (d, 1H, ^3J = 9.4 Hz, H-1); 3.81–3.77 (m, 2H, H-6b, NC*H*Bu); 3.60 (t, 2H, ^3J = 6.2 Hz, CH_2OH); 3.27 (t, 1H, ^3J = 6.6 Hz, H-5); 2.55–2.48, 2.14–2.04 (m, 5H, $CH_2C{=}O$, NCH−CH_2−Pr); 1.57–1.17 (m, 15H, 7.5×CH_2); 1.24, 1.22, 1.07 (3 s, 27H, Piv *t*Bu); 1.13 (s, 6H, 2×Me); 0.89 (t, 3H, ^3J = 6.8 Hz, CH_2CH_3) ppm; MS (ES^+): $C_{47}H_{72}F_3NO_{11}$ (884.07): *m/z*: 804.6 $[M-PivOH+Na]^+$; 906.6 $[M+Na]^+$.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (FCI). G.Z. is grateful to the FCI for a Doktorandenstipendium.

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[23] The loading was determined by elemental analysis and found to be reproducible. It should be noted that the loading calculated from the nitrogen content was in good agreement with the loading calculated either from complete fluoridolytic cleavage of **11a** and isolation of **8** or from hypothetical quantitative coupling of **8** with **10a**.

[24] Due to the high nominal mass of the auxiliary such a saturation has to be considered: For a given 50-mg portion of azide resin **11a** with a loading of approximately 0.38 mmol g^{-1}, the resin mass stemming from the carbohydrate unit is 19 mg (corresponding to 38 %).

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[31] The absolute configuration of compounds **13** was assigned according to comparison of ^{1}H NMR data with compounds of known configuration that were synthesized by analogous routes.[14b]

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Received: March 16, 2004
Published online: July 12, 2004

