Lewis Acid Catalyzed Diastereoselective Vinylogous Mannich Reaction Induced by O-Pivaloylated D-Galactosylamine as the Chiral Auxiliary: Stereoselective Synthesis of 6-Arylpiperidin-2-ones

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Abstract: The diastereospecific formation of β-N-glycosidically linked α,β-unsaturated δ-aminocarbonyl derivatives, in the form of (*S*)-δ-amino-δ-arylpent-2-enoic ester, has been achieved in high yield via a vinylogous Mannich reaction, utilizing poly-O-pivaloylated D-galacosylamine as the chiral auxiliary. (*S*)-6-*p*-Tolylpiperidine-2-one can be stereoselectively synthesized from (*S*)-δ-amino-δ-arylpent-2-enoic ester by sequential hydrogenation of the double bond, cyclic lactam formation, and removal of the N-glycosidic auxiliary under basic conditions.

Key words: vinylogous Mannich reaction, carbohydrate, chiral auxiliary, stereoselective synthesis, 6-arylpiperidin-2-ones

The asymmetric Mannich reaction is a fundamental C–C bond-forming process in organic chemistry, and the reaction products are versatile intermediates in the synthesis of chiral, enantiomerically enriched β-aminocarbonyl systems.[1] The γ-addition of dienolate equivalents to imines, known as vinylogous Mannich reaction, provides rapid access to δ-amino-α,β-unsaturated carbonyl compounds, which often served a role as advanced intermediates prior to their conversion to piperidinones.[2] Piperidinones have been widely used as building blocks in natural product synthesis and are attractive chiral synthons for the preparation of piperidines.[3] The substituted piperidine-2-ones are also substructural units of barbiturates and glutarimides[4] and are key intermediates for the synthesis of aminopentanoic acids.[5] Thus, the development of chiral nonracemic δ-amino-α,β-unsaturated carbonyl building blocks is still challenging and currently the object of intensive synthetic endeavors. Compared with the well established methodologies for the addition of imines with cyclic siloxyfurans,[6] the asymmetric vinylogous Mannich reaction of acyclic silyl dienolates was rarely investigated.[7] In 2008, Schneider reported the first catalytic, enantioselective, vinylogous Mannich reaction of an acyclic silyl dienolate with imines that was catalyzed by the chiral Brønsted acid.[8] Subsequently, Carretero and co-workers successfully developed a copper(I) complex of Fesulphos ligand as catalyst that could be applied both to silyloxy furans as well as acyclic silyl dienolates as nucleophiles in vinylogous Mannich reactions.[9] Several chiral auxiliaries have also been used to achieve good enantioselectivity of this reaction. Kawęcki described the use of optically active sulfinimines in the vinylogous Mannich reaction with silylated dienes as well as with lithium dienolates leading to enantiomerically enriched dihydropyridones and 2,4-piperidinediones.[10] Waldmann applied amino acid esters as chiral auxiliary groups in Lewis acid catalyzed reactions of electron-rich siloxydienes with imines. Appropriate dihydropyridones were obtained with excellent stereoselectivities. The cleavage of the chiral auxiliary group was achieved by means of a Curtius rearrangement.[11]

Carbohydrates have been utilized as enantiomerically pure candidates, which exert their chirality in chiral pool syntheses of many chiral natural products and drugs.[12] The most pre-eminent feature of carbohydrate auxiliaries lies in their differing configurations of the carbohydrate scaffold, which aid in installing diverse template geometries, thus enabling the introduction of a wide variety of coordinative site.[13] The pioneering work of Vasella[14a] and Kunz[14b] exploited carbohydrates as chiral templates in a 1,3-dipolar cycloaddition reaction and in a Diels–Alder reaction, which prompted the application of carbohydrate chiral auxiliary to construct highly stereoselective molecular skeletons.[14c] Among all the carbohydrates, D-galactose and D-glucose have attracted much synthetic attention because of their great contributions to regio- and stereoselective bond construction.[15] We recently developed a convenient and efficient synthetic protocol for preparation of chiral γ-butenolide derivatives in high yields and high enantiostereoselivities, utilizing O-pivaloylated D-galactosylamine as chiral auxiliary via vinylogous Mannich reactions.[16] Herein we report a novel diastereoselective vinylogous Mannich reactions of acyclic silyl dienolates and imines to furnish highly valuable δ-amino-α,β-unsaturated carboxylic esters in high yields and good to excellent diastereoselectivities, and their subsequent transformations.

The synthesis of β-N-glycosidically linked δ-amino-α,β-unsaturated carbonyl derivatives **5** started with the condensation of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyrano-

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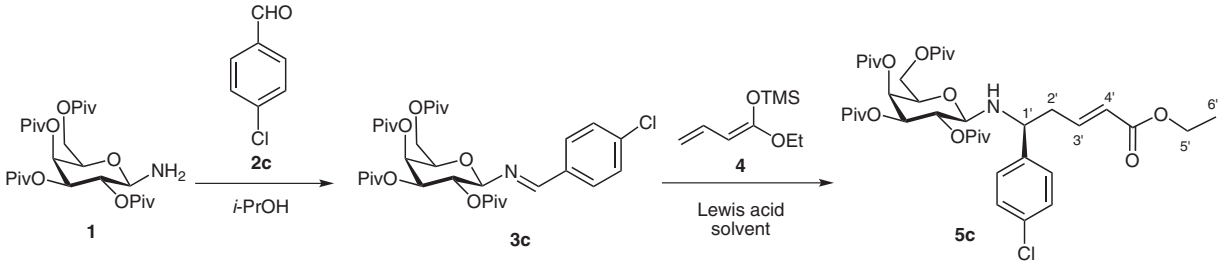
sylamine (**1**) and arylaldehyde **2**. In order to prepare *N*-(2,3,4,6-tetra-*O*-pivaloyl-D-galacopyranosyl)aldimines **3**, *N*-(2,3,4,6-tetra-O-pivaloylated-D-galacopyranosyl)amine **1** was reacted with aldehydes in the presence of acetic acid in propan-2-ol. The reactions proceeded smoothly within a short period of time at room temperature under dehydrating conditions.[17]

We initially investigated the reaction of O-pivaloylated *N*-galactosylimine **3c** (R = 4-ClC_6H_4) with silyl dienolate **4** in tetrahydrofuran without the aid of Lewis acid – no product **5c** was detected (Table 1, entry 1). Since the nucleophilicity of silyl dienolate is low and the electrophilicity of imines **3** is only moderate, the reaction between these compounds requires activation by a Lewis acid to proceed. For this purpose, various Lewis acids were tested in the reaction of the O-pivaloylated *N*-galactosylimine **3c** with silyl dienolate **4** in THF at –78 °C. The results revealed that CuCl, CuBr, and CuI only caused anomerization of the Schiff base **3c**, and no product of **5c** was observed (Table 1, entries 2–4). Other Lewis acids tested (e.g., $BF_3{\cdot}OEt_2$, $SnCl_4$, $AlCl_3$, $ZnCl_2{\cdot}OEt_2$, and $FeCl_3$) were able to promote the addition and gave moderate yields and good diastereoselectivities (Table 1, entries 5–9).

Since $FeCl_3$ gave the higher diastereoselectivity (dr = 19:1:0:0) and higher yield (82%) compared with other Lewis acids, it was used in further investigations. The ratio of diastereomers **5c** was determined by ^{1}H NMR spectroscopy. Particularly, when increasing the reaction temperature to –50 °C and decreasing the loading amount of catalyst, $FeCl_3$ (20 mol%) was able to catalyze the reaction to give the product in 90% yield with a diastereoselectivity ratio of 19:1:0:0 (Table 1, entries 10, 11). Higher diastereoselectivity may be maintained at catalyst load-

Table 1 Survey of the Conditions for the Formation of **5c**[a]



Entry	Lewis acid (equiv)	Solvent	Time	Temp (°C)	Yield (%)[b]	dr[c]
1	–	THF	2 d	–78	n.r.[d]	–
2	CuCl (1)	THF	1 d	–78	trace	–
3	CuBr (1)	THF	1 d	–50	trace	–
4	CuI (1)	THF	2 d	–50	trace	–
5	$BF_3{\cdot}OEt_2$ (1)	THF	2 d	–78	63	5:1:0:0
6	$SnCl_4$ (1)	THF	1 d	–78	74	7:1:0:0
7	$AlCl_3$ (1)	THF	2 d	–50	57	7:1:0:0
8	$ZnCl_2{\cdot}OEt_2$ (1)	THF	2 d	–78	72	19:1:0:0
9	$FeCl_3$ (1)	THF	1 d	–78	82	19:1:0:0
10	$FeCl_3$ (0.5)	THF	8 h	–50	88	19:1:0:0
11	$FeCl_3$ (0.2)	THF	10 h	–50	90	19:1:0:0
12	$FeCl_3$ (0.1)	THF	15 h	–50	83	19:1:0:0
13	$BF_3{\cdot}OEt_2$ (0.5)	THF	8 h	–50	93	5:1:0:0
14	$FeCl_3$ (0.2)	CH_2Cl_2	2 d	–50	n.r.	–
15	$FeCl_3$ (0.2)	Et_2O	2 d	–50	n.r.	–
16	$FeCl_3$ (0.2)	toluene	2 d	–50	90	7:1:0:0

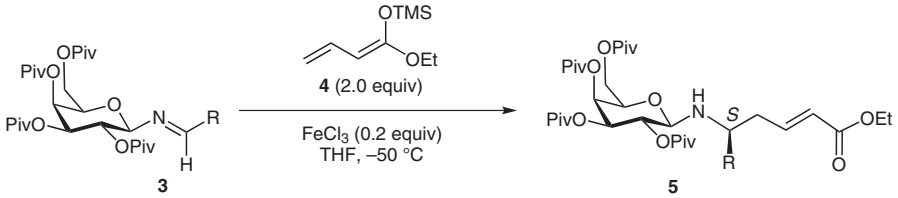
[a] Unless otherwise noted all the reactions were performed with 0.3 mmol of **3**, 0.6 mmol silyl dienolate in 3 mL of solvent.
[b] After purification by chromatography.
[c] Diastereomeric ratio (dr) values were determined from the crude product by ^{1}H NMR spectroscopy.
[d] No reaction.

ings as low as 10 mol% but the yield is decreased (19:1:0:0 dr, 83% yield, Table 1, entry 12). Compared with $FeCl_3$, $BF_3{\cdot}OEt_2$ applied in THF at –50 °C can catalyze this reaction in high yield, but with lower diastereoselectivities (Table 1, entry 13).

Following this evaluation of Lewis acids, a solvent screening was undertaken. The reaction could not proceed in CH_2Cl_2 and Et_2O to afford the desired product (Table 1, entries 14, 15). Toluene gave a high conversion rate, but with a decrease in the diastereomeric excess (Table 1, entry 16). Among the solvents tested, THF was found to be the best with respect to catalytic activity and asymmetric induction.

The optimized procedure was broadly applicable to reactions with various aldimines **3** with silyl dienolate **4**, which were converted into the corresponding vinylogous Mannich products **5** in good to excellent diastereoselectivities (up to dr 99:1:0:0) and typically high yields (Table 2). It was found that O-pivaloylated *N*-galactosylimine **3**, bearing both electron-rich and electron-poor aromatic groups, gave the corresponding asymmetric vinylogous Mannich products **5a**–**p** in good to high yields and diastereoselectivities (Table 2). As for the aldimine in which R was a phenyl group, relatively lower yield and diastereoselectivity was realized under identical conditions (Table 2, **5a**). Particularly, this process was efficient for cinnamaldehyde and afforded the desired product with 90% diastereoselectivity in 75% yield (Table 2, **5p**). Notably, the aldimine derived from heteroaromatic aldehyde gave the adduct in good yield but with poor diastereoselectivity (Table 2, **5o**). Furthermore, the reaction of Schiff base **3** of aliphatic aldehyde with silyl dienolate **4** led to the product in very poor yield, only anomerization and decomposition occurred. The reaction of 1-trimethylsiloxybuta-1,3-diene with aldimine **3m** in the presence of 0.3 equivalent $AlCl_3$ as catalyst in THF at –50 °C, led to the

Table 2 Vinylogous Mannich Reaction of *N*-(2,3,4,6-Tetra-O-pivaloylated D-galactosyl)aldimines **5a**–**p**



Product	R	Time (h)	Yield (%)[a]	dr[b]
5a	Ph	24	81	94:6:0:0
5b	4-$O_2NC_6H_4$	10	90	99:1:0:0
5c	4-ClC_6H_4	16	91	94:6:0:0
5d	4-FC_6H_4	19	78	99:1:0:0
5e	4-BrC_6H_4	18	83	94:6:0:0
5f	4-$F_3CC_6H_4$	14	81	95:5:0:0
5g	4-MeC_6H_4	22	80	99:1:0:0
5h	4-$MeOC_6H_4$	22	97	98:2:0:0
5i	2-ClC_6H_4	17	97	99:1:0:0
5j	2-BrC_6H_4	17	96	98:2:0:0
5k	2-MeC_6H_4	10	93	94:6:0:0
5l	3-FC_6H_4	24	88	99:1:0:0
5m	3-ClC_6H_4	17	88	93:7:0:0
5n	3-MeC_6H_4	16	79	97:3:0:0
5o	furan-2-yl	24	65	59:1:39:1
5p	(*E*)-PhCH=CH	24	75	95:5:0:0
5q[c]	3-ClC_6H_4	54	98	99:1:0:0

[a] After purification by chromatography.
[b] Diastereomeric ratio determined from the crude product by HPLC.
[c] The reaction was performed with **3m** (0.3 mmol), 1-trimethylsiloxybuta-1,3-diene (0.6 mmol), and $AlCl_3$ (0.09 mmol) in THF (5 mL) at –50 °C.

formation of product **5q** in good yield and excellent enantioselectivity (Table 2, **5q**), The products **5** contained exclusively *E*-double bonds, and accordingly no cyclization to the corresponding 5,6-dihydro-2-pyridones was observed.

The ratio of the obtained diastereomers **5** was determined by HPLC from the crude mixture of the reaction. It should be noted that because of the anomeric carbon and one stereogenic center created at the α-position of ethyl acrylate, the four anomeric diastereomers have the β*S*, β*R*, α*R* and α*S* configurations. The experiment results showed that the corresponding α-anomer could be restricted in this reaction. A synthetically relevant advantage of using O-pivaloylated D-galactosylamine as the chiral auxiliary is the facile deprotection of the vinylogous Mannich products **5** by simple treatment with MeONa in MeOH. Adduct **5g** was converted to the δ-lactam **8g** by hydrogenation of the double bond catalyzed by Pd/C and subsequent cyclized to (*S*)-6-*p*-tolylpiperidine-2-one (**8g**) in quantitative yield (Scheme 1). In order to determine the absolute configuration of the main isomer of silyl dienolate addition to *N*-galactosylaldimines **3**, a single crystal X-ray diffraction study of **5b** was performed.[18] The molecular structure of **5b** is shown in Figure 1, and the structure shows that the relative configuration of β-*N*-glycoside-α,β-unsaturated δ-amino carbonylate main product can be assigned as β*S*.

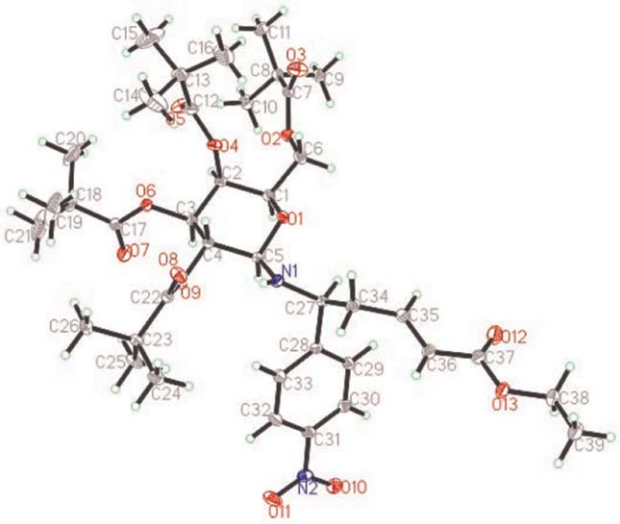


Figure 1 The ORTEP drawing of **5b**

The possible mechanism for the reactions is shown in Figure 2. The preferred formation of the configured diastereomer of **5** can be rationalized by an attack of silyl dienolate from *Si* side of *N*-galactosylaldimines **3**. In the transition state, the iron atom has hexacoordination, the sites of which are occupied by the imine nitrogen and carbonyl oxygens (C-2 and C-6) of the pivaloyloxy group, respectively; and one of the three chlorines may be removed when silyl dienolate was introduced. According to this rationalization, the S_N2'-type attack of silyl dienolate from the back side of the plane of C=N is initiated. Based on these results, this hypothesis would explain the course of the main isomer synthesis. The mechanism indicates that the pivaloyl group in the aldimines **3** plays a significant role in controlling the diastereoselective addition of silyl dienolate to *N*-galactosylaldimines **3**.

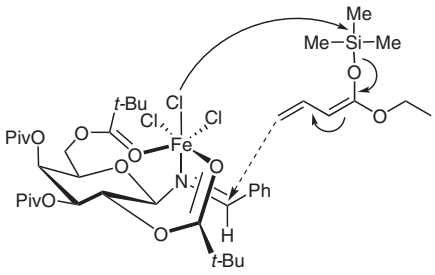
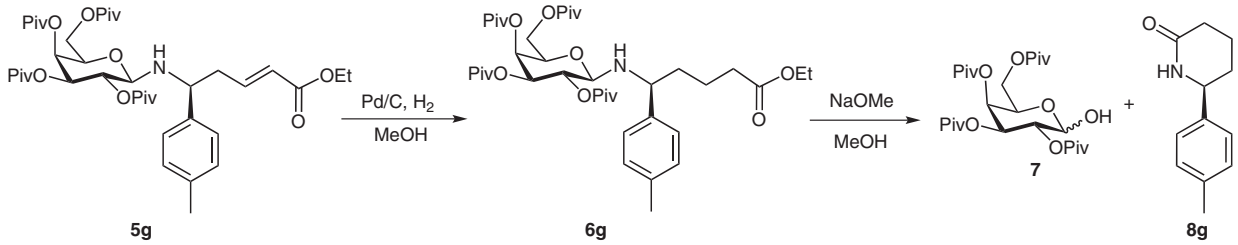


Figure 2 Plausible reaction mechanism

In conclusion, we have developed a new efficient synthetic protocol for the preparation of chiral δ-lactam derivatives in high yields and high enantiostereoselectivity, utilizing $FeCl_3$ as the promoter and O-pivaloylated D-galactosylamine **1** as chiral auxiliary via vinylogous Mannich reactions. The O-pivaloylated galactosylamine **1** is an effective chiral template in the synthesis of chiral *N*-galactosyl δ-amino α,β-unsaturated carbonyl derivatives **5**. $FeCl_3$ can form the hexacoordinated intermediate inducing the *S*-configuration at the Cα center by attack at the *Si*-side of the C=N plane of the imine carbon atom. The mild carbohydrate deprotection allows the resulting products to be readily transformed into optically active δ-lactam derivatives. Further studies are being conducted with regard to scope of this reaction and related vinylogous Mannich reaction induced by carbohydrate as chiral auxiliary.

All reactions were carried out under an inert atmosphere and in heat-dried glassware. Anhyd THF was obtained by distillation from Na silk. Flash column chromatography was performed on silica gel



Scheme 1 Synthesis of (*S*)-6-*p*-tolylpiperidine-2-one (**8g**)

(particle size 10–40 μm, Ocean Chemical Factory of Qingdao, P. R. of China). N_2 (99.999%) was purchased from Boc Gas Inc. ^{1}H, and ^{13}C spectra were recorded on Bruker-400 (400 MHz for ^{1}H, 101 MHz for ^{13}C) spectrometers. Chemical shifts were reported in ppm downfield from internal $SiMe_4$. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were recorded on a LCQ advantage spectrometer with ESI resource. HRMS were recorded on APEXII and ZAB-HS spectrometer. Melting points were determined on a T-4 melting point apparatus (uncorrected).

O-Pivaloylated *N*-Galactosylimines of Aromatic Aldehydes 3; General Procedure

To a solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**; 0.515 g, 1 mmol) and aldehyde **2** (1.3 mmol) in propan-2-ol (2.5 mL) was added AcOH (2–3 drops) and the mixture was stirred at r.t. for about 0.5 h. The appearance of a precipitate from the solution indicated the formation of **3**. The precipitate was collected by filtration, washed with ice-cold propan-2-ol (15 mL), and dried in vacuum to afford *N*-galactosylaldimines **3** as colorless solids.

Formation of β-N-Glycosidic Linkages; δ-Amino-α,β-unsaturated Carbonyl Derivatives 5; General Procedure

A solution of *N*-galactosylaldimine **3** (0.2 mmol) and $FeCl_3$ (6.44 mg, 0.04 mmol) in THF (3 mL) was cooled to –50 °C under N_2 protection, and 1-trimethylsilyloxy-1-ethoxybuta-1,3-diene (**4**; 74.4 mg, 0.4 mmol) was added. The mixture was stirred at this temperature until no starting material was monitored by TLC (ca. 10–24 h). The mixture was hydrolyzed with sat. aq $NaHCO_3$ (5 mL) and then stirred at r.t. for 15 min. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. After purification by flash column chromatography on silica gel [petroleum ether (bp 60–90 °C)–EtOAc, 15:1 (v/v)], pure products **5** were obtained (Table 2).

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-phenylpent-2-enoate (5a)

Yield: 117 mg (81%); white solid; mp 56–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.32 (m, 5 H, C_6H_5), 6.77 (dt, $^3J_{3',4'}$ = 15.6 Hz, $^3J_{2',3'}$ = 7.4 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.6 Hz, 1 H, CH=C*H*), 5.33 (d, $^3J_{3,4}$ = 3.0 Hz, 1 H, 4-H), 5.06 (dd, $^3J_{1,2}$ = 8.7 Hz, $^3J_{2,3}$ = 10.3 Hz, 1 H, 2-H), 5.00 (dd, $^3J_{3,4}$ = 3.0 Hz, $^3J_{2,3}$ = 10.3 Hz, 1 H, 3-H), 4.27 (t, $^3J_{1',2'}$ = 6.1 Hz, 1 H, C*H*NH), 4.15 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^3J_{5,6b}$ = 6.7 Hz, $^2J_{6a,6b}$ = 11.1 Hz, 1 H, 6b-H), 3.99 (dd, $^3J_{5,6a}$ = 6.7 Hz, $^2J_{6a,6b}$ = 11.1 Hz, 1 H, 6a-H), 3.80 (dd, $^3J_{1,2}$ = 8.7 Hz, $^3J_{1,NH}$ = 12.4 Hz, 1 H, 1-H), 3.66 (t, $^3J_{5,6}$ = 6.7 Hz, 1 H, 5-H), 2.52 (t, $^3J_{1',2'}$ = 6.1 Hz, 2 H, CH_2CH=CH), 2.12 (d, $^3J_{NH,1}$ = 12.4 Hz, 1 H, NH), 1.26–1.27 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.86, 176.64, 176.08, 175.88, 165.12 (C=O), 143.30, 139.97, 127.46, 126.73, 126.61, 122.94 (Ph, CH=CH), 85.24, 70.61, 70.26, 67.67, 66.36, 60.72, 59.18, 55.29 (C–O, C–N), 40.15, 38.04, 37.79, 37.68, 26.23, 26.20, 26.10, 26.06, 13.20.

MS (ESI): *m*/*z* = 718.27 [M + H]$^+$, 740.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{59}NO_{11}$ + Na$^+$: 740.3980 [M + Na]$^+$; found: 740.3988.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-nitrophenyl)pent-2-enoate (5b)

Yield: 137 mg (90%); light yellow solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.7 Hz, 2 H$_{arom}$), 7.44 (d, *J* = 8.7 Hz, 2 H$_{arom}$), 6.72 (dt, $^3J_{3',4'}$ = 15.6 Hz, $^3J_{2',3'}$ = 7.4 Hz, 1 H, C*H*=CH), 5.80 (d, $^3J_{3',4'}$ = 15.6 Hz, 1 H, CH=C*H*), 5.35 (d, $^3J_{3,4}$ = 2.6 Hz, 1 H, 4-H), 5.08 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{1,2}$ = 8.5 Hz, 1 H, 2-H), 5.02 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{3,4}$ = 2.6 Hz, 1 H, 3-H), 4.42 (t, $^3J_{1',2'}$ = 6.6 Hz, $^3J_{NH,1'}$ = 12.8 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.11 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{6b,5}$ = 6.8 Hz, 1 H, 6b-H), 3.98 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{6a,5}$ = 6.8 Hz, 1 H, 6a-H), 3.78 (dd, $^3J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 3.69 (t, $^3J_{5,6}$ = 6.8 Hz, 1 H, 5-H), 2.55 (t, $^3J_{2',1'}$ = 6.6 Hz, 2 H, CH_2CH=CH), 2.23 (d, $^3J_{NH,1'}$ = 12.8 Hz, 1 H, NH), 1.26–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.82, 176.62, 176.06, 175.80, 164.79 (C=O), 147.94, 146.57, 141.63, 127.32, 123.81, 122.82 (Arom-C_6H_4, CH=CH), 85.31, 70.81, 70.10, 67.69, 66.14, 60.52, 59.40, 54.85 (C–O, C–N), 39.78, 38.05, 37.84, 37.70, 28.67, 26.25, 26.20, 26.099, 26.07, 13.19.

MS (ESI): *m*/*z* = 785.40 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}N_2O_{13}$ + Na$^+$: 785.3831 [M + Na]$^+$; found: 785.3831.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-chlorophenyl)pent-2-enoate (5c)

Yield: 137 mg (91%); white solid; mp 57–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.4 Hz, 2 H$_{arom}$), 7.19 (d, *J* = 8.4 Hz, 2 H$_{arom}$), 6.73 (dt, $^3J_{3',4'}$ = 15.3 Hz, $^3J_{2',3'}$ = 7.4 Hz, 1 H, C*H*=CH), 5.79 (d, $^3J_{3',4'}$ = 15.3 Hz, 1 H, CH=C*H*), 5.34 (d, $^3J_{3,4}$ = 2.5 Hz, 1 H, 4-H), 4.99–5.08 (m, 2 H, 2-H, 3-H), 4.26 (t, $^3J_{1',2'}$ = 6.4 Hz, $^3J_{1',NH}$ = 13.1 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.3 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6b}$ = 6.7 Hz, 1 H, 6b-H), 3.98 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6a}$ = 6.7 Hz, 1 H, 6a-H), 3.77 (dd, $^3J_{1,2}$ = 7.9 Hz, 1 H, 1-H), 3.67 (t, $^3J_{5,6}$ = 6.7 Hz, 1 H, 5-H), 2.50 (t, $^3J_{1',2'}$ = 6.4 Hz, 2 H, CH_2CH=CH), 2.14 (d, $^3J_{1',NH}$ = 13.1 Hz, 1 H, NH), 1.26–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.87, 176.63, 176.08, 175.86, 165.04 (C=O), 142.68, 138.52, 132.42, 127.92, 127.71, 123.25 (Arom-C_6H_4, CH=CH), 85.14, 70.69, 70.21, 67.67, 66.29, 60.66, 59.29, 54.70 (C–O, C–N), 40.01, 38.05, 37.80, 37.70, 28.67, 26.23, 26.20, 26.11, 26.07, 13.20.

MS (ESI): *m*/*z* = 752.20 [M + H]$^+$, 774.27 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}ClNO_{11}$ + Na$^+$: 774.3591 [M + Na]$^+$; found: 774.3582.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-fluorophenyl)pent-2-enoate (5d)

Yield: 115 mg (78%); light yellow solid; mp 58–59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.6 Hz, 2 H$_{arom}$), 7.02 (t, *J* = 8.6 Hz, 2 H$_{arom}$), 6.75 (dt, $^3J_{3',4'}$ = 15.3 Hz, $^3J_{2',3'}$ = 7.9 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.3 Hz, 1 H, CH=C*H*), 5.35 (d, $^3J_{3,4}$ = 1.8 Hz, 1 H, 4-H), 5.00–5.11 (m, 2 H, 2-H, 3-H), 4.28 (t, $^3J_{1',2'}$ = 6.6 Hz, 1 H, C*H*NH), 4.17 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.11 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6b}$ = 6.5 Hz, 1 H, 6b-H), 4.00 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6a}$ = 6.5 Hz, 1 H, 6a-H), 3.78 (d, $^3J_{1,2}$ = 5.8 Hz, 1 H, 1-H), 3.69 (t, $^3J_{5,6}$ = 6.5 Hz, 1 H, 5-H), 2.51 (t, $^3J_{2',1'}$ = 6.6 Hz, 2 H, CH_2CH=CH), 2.15 (s, 1 H, NH), 1.26–1.29 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.21 [s, 18 H, 2 C(CH$_3$)$_3$], 1.11 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.85, 176.61, 176.08, 175.85, 165.03 (C=O), 161.26 ($^1J_{C,F}$ = 246.1 Hz), 142.85, 135.69 ($^4J_{C,F}$ = 3.0 Hz), 128.10 ($^3J_{C,F}$ = 8.0 Hz), 123.18, 114.40 ($^2J_{C,F}$ = 21.3 Hz), 85.20, 70.73, 70.28, 67.70, 66.35, 60.70, 59.24, 54.69 (C–O, C–N), 40.16, 38.06, 37.81, 37.71, 28.68, 26.23, 26.12, 26.09, 26.05, 13.21.

MS (ESI): *m*/*z* = 758.47 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}FNO_{11}$ + Na^+: 758.3886 [M + Na]$^+$; found: 758.3884.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-bromophenyl)pent-2-enoate (5e)
Yield: 132 mg (83%); white solid; mp 70–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.2 Hz, 2 H_{arom}), 7.13 (d, *J* = 8.2 Hz, 2 H_{arom}), 6.72 (dt, $^3J_{3',4'}$ = 15.6 Hz, $^3J_{2',3'}$ = 7.2 Hz, 1 H, C*H*=CH), 5.79 (d, $^3J_{3',4'}$ = 15.6 Hz, 1 H, CH=C*H*), 5.34 (d, $^3J_{3,4}$ = 2.8 Hz, 1 H, 4-H), 5.00–5.08 (m, 2 H, 2-H, 3-H), 4.24 (t, $^3J_{1',2'}$ = 6.4 Hz, $^3J_{NH,1'}$ = 12.2 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6b}$ = 6.8 Hz, 1 H, 6b-H), 3.98 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6a}$ = 6.8 Hz, 1 H, 6a-H), 3.77 (dd, $^3J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 3.67 (t, $^3J_{6a,6b,5}$ = 6.8 Hz, 1 H, 5-H), 2.49 (t, $^3J_{2',1'}$ = 6.4 Hz, 2 H, CH_2CH=CH), 2.13 (d, $^3J_{NH,1'}$ = 12.2 Hz, 1 H, NH), 1.25–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.17–1.19 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.79, 176.57, 176.01, 175.81, 164.94 (C=O), 142.59, 139.17, 130.66, 128.30, 123.32, 120.53 (Arom-C_6H_4, CH=CH), 85.20, 70.74, 70.25, 67.72, 66.33, 60.68, 59.24, 54.79 (C–O, C–N), 39.95, 38.05, 37.80, 37.69, 26.25, 26.22, 26.12, 26.09, 20.00, 13.22.

MS (ESI): *m*/*z* = 798.20 [M + H]$^+$, 820.20 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}BrNO_{11}$ + Na^+: 818.3085 [M + Na]$^+$; found: 818.3084.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-trifluoromethylphenyl)pent-2-enoate (5f)
Yield: 128 mg (81%); white solid; mp 69–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.1 Hz, 2 H_{arom}), 7.38 (d, *J* = 8.1 Hz, 2 H_{arom}), 6.74 (dt, $^3J_{3',4'}$ = 15.3 Hz, $^3J_{2',3'}$ = 7.4 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.3 Hz, 1 H, CH=C*H*), 5.34 (d, $^3J_{3,4}$ = 2.9 Hz, 1 H, 4-H), 5.00–5.10 (m, 2 H, 2-H, 3-H), 4.36 (t, $^3J_{1',2'}$ = 6.6 Hz, $^3J_{NH,1'}$ = 12.7 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.10 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6b}$ = 6.8 Hz, 1 H, 6b-H), 3.98 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6a}$ = 6.8 Hz, 1 H, 6a-H), 3.78 (dd, $^3J_{1,2}$ = 8.5 Hz, 1 H, 1-H), 3.68 (t, $^3J_{5,6}$ = 6.8 Hz, 1 H, 5-H), 2.53 (t, $^3J_{1',2'}$ = 6.6 Hz, 2 H, CH_2CH=CH), 2.18 (d, $^3J_{NH,1'}$ = 12.7 Hz, 1 H, NH), 1.25–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.84, 176.64, 176.06, 175.84, 164.95 (C=O), 144.35, 142.29, 129.05 ($^2J_{C,F}$ = 32.3 Hz), 126.87, 124.50 ($^4J_{C,F}$ = 3.6 Hz), 124.38, 121.67 ($^1J_{C,F}$ = 272.1 Hz), 123.47 (Arom-C_6H_4, CH=CH), 85.22, 70.72, 70.16, 67.68, 66.23, 60.59, 59.32, 54.92 (C–O, C–N), 39.94, 38.05, 37.82, 37.70, 28.68, 26.23, 26.20, 26.09, 26.07, 13.19.

MS (ESI): *m*/*z* = 786.13 [M + H]$^+$, 808.27 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{40}H_{58}F_3NO_{11}$ + Na^+: 808.3854 [M + Na]$^+$; found: 808.3845.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-methylphenyl)pent-2-enoate (5g)
Yield: 117 mg (80%); white solid; mp 69–71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.16 (m, 4 H_{arom}), 6.77 (dt, $^3J_{3',4'}$ = 15.5 Hz, $^3J_{2',3'}$ = 7.7 Hz, 1 H, C*H*=CH), 5.83 (d, $^3J_{3',4'}$ = 15.5 Hz, 1 H, CH=C*H*), 5.32 (d, $^3J_{3,4}$ = 3.0 Hz, 1 H, 4-H), 5.05 (t, $^3J_{2,3}$ = 10.3 Hz, 1 H, 2-H), 5.01 (dd, $^3J_{2,3}$ = 10.3 Hz, $^3J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 4.23 (t, $^3J_{1',2'}$ = 6.5 Hz, 1 H, C*H*NH), 4.15 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.08 (dd, $^2J_{6a,6b}$ = 11.3 Hz, $^3J_{5,6b}$ = 6.9 Hz, 1 H, 6b-H), 3.99 (dd, $^2J_{6a,6b}$ = 11.3 Hz, $^3J_{5,6a}$ = 6.9 Hz, 1 H, 6a-H), 3.79 (dd, $^3J_{1,2}$ = 8.4 Hz, $^3J_{NH,1}$ = 12.3 Hz, 1 H, 1-H), 3.65 (t, $^3J_{5,6}$ = 6.9 Hz, 1 H, 5-H), 2.50 (t, $^3J_{1',2'}$ = 6.5 Hz, 2 H, CH_2CH=CH), 2.35 (s, 3 H, ArCH_3), 2.09 (d, $^3J_{NH,1}$ = 12.3 Hz, 1 H, NH), 1.24–1.29 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 (m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.90, 176.65, 176.10, 175.91, 165.18 (C=O), 143.51, 136.79, 136.37, 128.16, 126.56, 122.83 (Ar-C_6H_4, CH=CH), 85.17, 70.60, 70.28, 67.66, 66.41, 60.76, 59.19, 54.98 (C–O, C–N), 40.17, 38.05, 37.79, 37.69, 28.67, 26.24, 26.21, 26.12, 26.07, 20.10, 13.21.

MS (ESI): *m*/*z* = 732.27 [M + H]$^+$, 754.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{40}H_{61}NO_{11}$ + Na^+: 754.4137 [M + Na]$^+$; found: 754.4125.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(4-methoxyphenyl)pent-2-enoate (5h)
Yield: 145 mg (97%); white solid; mp 66–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.6 Hz, 2 H_{arom}), 6.84 (d, *J* = 8.6 Hz, 2 H_{arom}), 6.76 (dt, $^3J_{3',4'}$ = 15.6 Hz, $^3J_{2',3'}$ = 7.7 Hz, 1 H, C*H*=CH), 5.80 (d, $^3J_{3',4'}$ = 15.6 Hz, 1 H, CH=C*H*), 5.33 (d, $^3J_{3,4}$ = 2.3 Hz, 1 H, 4-H), 4.97–5.07 (m, 2 H, 2-H, 3-H), 4.21 (t, $^3J_{1',2'}$ = 6.6 Hz, $^3J_{NH,1'}$ = 12.8 Hz, 1 H, C*H*NH), 4.15 (q, $^3J_{5',6'}$ = 7.2 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6b}$ = 7.6 Hz, 1 H, 6b-H), 3.98 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{6a,5}$ = 7.6 Hz, 1 H, 6a-H), 3.82 (s, 3 H, OCH$_3$), 3.77 (dd, $^3J_{1,2}$ = 7.7 Hz, 1 H, 1-H), 3.66 (t, $^3J_{5,6}$ = 7.6 Hz, 1 H, 5-H), 2.49 (t, $^3J_{1',2'}$ = 6.6 Hz, 2 H, CH_2CH=CH), 2.10 (d, $^3J_{NH,1'}$ = 12.8 Hz, 1 H, NH), 1.24–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19–1.20 [m, 18 H, 2 C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.87, 177.63, 177.08, 176.89, 166.17 (C=O), 159.10, 144.51, 132.72, 128.71, 123.84, 113.85 (Ar-C_6H_4, CH=CH), 86.13, 71.60, 71.29, 68.65, 67.40, 61.74, 60.18, 55.69, 55.21 (C–O, C–N), 41.19, 39.04, 38.78, 38.76, 38.69, 27.24, 27.21, 27.12, 27.07, 14.21.

MS (ESI): *m*/*z* = 748.27 [M + H]$^+$, 770.40 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{40}H_{61}NO_{12}$ + Na^+: 770.4086 [M + Na]$^+$; found: 770.4083.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(2-chlorophenyl)pent-2-enoate (5i)
Yield: 146 mg (97%); white solid; mp 60–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.48 (m, 1 H_{arom}), 7.33-7.36 (m, 1 H_{arom}), 7.20–7.22 (m, 2 H_{arom}), 6.81 (dt, $^3J_{3',4'}$ = 15.5 Hz, $^3J_{2',3'}$ = 7.5 Hz, 1 H, C*H*=CH), 5.86 (d, $^3J_{3',4'}$ = 15.5 Hz, 1 H, CH=C*H*), 5.35 (d, $^3J_{3,4}$ = 1.9 Hz, 1 H, 4-H), 5.03–5.10 (m, 2 H, 2-H, 3-H), 4.85 (t, $^3J_{1',2'}$ = 6.5 Hz, $^3J_{NH,1'}$ = 11.9 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6b}$ = 6.9 Hz, 1 H, 6b-H), 4.01 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6a}$ = 6.9 Hz, 1 H, 6a-H), 3.86 (dd, $^3J_{1,2}$ = 8.9 Hz, 1 H, 1-H), 3.77 (t, $^3J_{5,6}$ = 6.9 Hz, 1 H, 5-H), 2.55 (t, $^3J_{1',2'}$ = 6.5 Hz, 2 H, CH_2CH=CH), 2.11 (d, $^3J_{NH,1'}$ = 11.9 Hz, 1 H, NH), 1.26–1.28 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.19 [s, 9 H, C(CH$_3$)$_3$], 1.17 [s, 9 H, C(CH$_3$)$_3$], 1.10 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.90, 176.59, 176.13, 175.84, 165.02 (C=O), 142.88, 137.91, 132.57, 128.70, 127.50, 127.46, 125.78, 123.13 (Ar-C_6H_4, CH=CH), 85.73, 70.69, 70.35, 67.85, 66.28, 60.55, 59.19, 50.96 (C–O, C–N), 38.32, 38.05, 37.81, 37.70, 37.67, 26.24, 26.20, 26.15, 26.09, 13.22.

MS (ESI): *m*/*z* = 752.13 [M + H]$^+$, 774.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}ClNO_{11}$ + Na^+: 774.3591 [M + Na]$^+$; found: 774.3588.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(2-bromophenyl)pent-2-enoate (5j)
Yield: 153 mg (96%); white solid; mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.9 Hz, 1 H_{arom}), 7.46 (d, *J* = 7.9 Hz, 1 H_{arom}), 7.25–7.28 (m, 1 H_{arom}), 7.11–7.15 (m, 1

H_{arom}), 6.83 (dt, $^3J_{3',4'}$ = 15.2 Hz, $^3J_{2',3'}$ = 7.6 Hz, 1 H, C*H*=CH), 5.87 (d, $^3J_{3',4'}$ = 15.2 Hz, 1 H, CH=C*H*), 5.36 (d, $^3J_{3,4}$ = 1.7 Hz, 1 H, 4-H), 5.05 (m, 2 H, 2-H, 3-H), 4.81 (t, $^3J_{1',2'}$ = 5.5 Hz, $^3J_{NH,1'}$ = 12.5 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.11 (dd, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6b}$ = 7.3 Hz, 1 H, 6b-H), 4.01 (d, $^2J_{6a,6b}$ = 11.1 Hz, $^3J_{5,6a}$ = 7.3 Hz, 1 H, 6a-H), 3.85 (dd, $^3J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 3.78 (t, $^3J_{5,6}$ = 7.3 Hz, 1 H, 5-H), 2.54 (t, $^3J_{1',2'}$ = 5.5 Hz, 2 H, CH_2CH=CH), 2.12 (d, $^3J_{NH,1'}$ = 12.5 Hz, 1 H, NH), 1.26–1.29 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.17–1.18 [m, 18 H, 2 C(CH$_3$)$_3$], 1.10 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.85, 176.56, 176.10, 175.79, 164.69 (C=O), 142.83, 139.48, 131.99, 127.91, 127.74, 126.41, 123.16, 122.97 (Ar-C$_6$H$_4$, CH=CH), 85.69, 70.61, 70.35, 67.85, 66.20, 60.41, 59.18, 53.48 (C–O, C–N), 52.43, 38.46, 38.04, 37.80, 37.70, 26.25, 26.20, 26.12, 26.09, 13.23.

MS (ESI): *m*/*z* = 798.07 [M + H]$^+$, 820.20 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}BrNO_{11}$ + Na$^+$: 818.3085 [M + Na]$^+$; found: 818.3082.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(2-methylphenyl)pent-2-enoate (5k)
Yield: 136 mg (93%); white solid; mp 61–62 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.39–7.42 (m, 1 H_{arom}), 7.16–7.20 (m, 3 H_{arom}), 6.81 (dt, $^3J_{2',3'}$ = 8.0 Hz, $^3J_{3',4'}$ = 15.4 Hz, 1 H, C*H*=CH), 5.86 (d, $^3J_{3',4'}$ = 15.4 Hz, 1 H, CH=C*H*), 5.38 (d, *J* = 1.9 Hz, 1 H, 4-H), 4.99–5.11 (m, 2 H, 2-H, 3-H), 4.61 (t, $^3J_{1',2'}$ = 6.6 Hz, 1 H, C*H*NH), 4.18 (q, $^3J_{5',6'}$ = 7.2 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^3J_{5,6b}$ = 7.0 Hz, $^2J_{6a,6b}$ = 11.2 Hz, 1 H, 6b-H), 4.01 (dd, $^3J_{5,6a}$ = 7.0 Hz, $^2J_{6a,6b}$ = 11.2 Hz, 1 H, 6a-H), 3.80 (t, $^3J_{1,2}$ = 4.1 Hz, 1 H, 1-H), 3.71 (t, $^3J_{5,6}$ = 6.6 Hz, 1 H, 5-H), 2.50 (t, $^3J_{2',3'}$ = 8.0 Hz, $^3J_{1',2'}$ = 6.6 Hz, 2 H, CH_2CH=CH), 2.33 (s, 3 H, OCH$_3$), 1.26–1.29 [m, 12 H, C(CH$_3$)$_3$], 1.22 [s, 9 H, C(CH$_3$)$_3$], 1.18 [s, 9 H, C(CH$_3$)$_3$], 1.11 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, CDCl$_3$): δ = 175.49, 175.25, 174.71, 174.43, 163.73 (C=O), 142.04, 136.74, 133.61, 128.07, 124.81, 124.46, 123.80, 121.55 (Ar-C$_6$H$_4$, CH=CH), 84.13, 69.11, 68.98, 66.44, 64.90, 59.13, 57.80, 48.83 (C–O, C–N), 38.03, 36.69, 36.46, 36.33, 36.31, 24.91, 24.86, 24.81, 24.72, 16.92, 11.85.

MS (ESI): *m*/*z* = 732.13 [M + H]$^+$, 754.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{40}H_{61}NO_{11}$ + Na$^+$: 754.4137 [M + Na]$^+$; found: 754.4136.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(3-fluorophenyl)pent-2-enoate (5l)
Yield: 130 mg (88%); light yellow solid; mp 60–61 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.28–7.30 (m, 1 H_{arom}), 7.00–7.02 (m, 3 H_{arom}), 6.75 (dt, $^3J_{3',4'}$ = 15.4 Hz, $^3J_{2',3'}$ = 7.9 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.4 Hz, 1 H, CH=C*H*), 5.34 (d, $^3J_{3,4}$ = 2.3 Hz, 1 H, 4-H), 5.00–5.09 (m, 2 H, 2-H, 3-H), 4.28 (t, $^3J_{1',2'}$ = 6.5 Hz, $^3J_{NH,1'}$ = 12.9 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{5,6b}$ = 6.8 Hz, 1 H, 6b-H), 3.99 (d, $^2J_{6a,6b}$ = 11.2 Hz, $^3J_{6a,5}$ = 6.8 Hz, 1 H, 6a-H), 3.82 (dd, $^3J_{1,2}$ = 8.2 Hz, 1 H, 1-H), 3.69 (t, $^3J_{5,6}$ = 6.8 Hz, 1 H, 5-H), 2.51 (t, $^3J_{1',2'}$ = 6.5 Hz, 2 H, CH_2CH=CH), 2.13 (d, $^3J_{NH,1'}$ = 12.9 Hz, 1 H, NH), 1.25–1.27 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.21 [s, 9 H, C(CH$_3$)$_3$], 1.19 [s, 9 H, C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.87, 176.69, 176.09, 175.86, 165.01 (C=O), 162.06 ($^1J_{C,F}$ = 246.2 Hz), 142.97 ($^3J_{C,F}$ = 6.5 Hz), 142.66, 128.98 ($^3J_{C,F}$ = 8.1 Hz), 123.24, 122.32 ($^4J_{C,F}$ = 3.4 Hz), 113.72 ($^2J_{C,F}$ = 21.3 Hz), 113.18 ($^2J_{C,F}$ = 21.7 Hz), 85.22, 70.72, 70.24, 67.64, 66.30, 60.68, 59.27, 54.85 (C–O, C–N), 40.01, 38.04, 37.89, 37.69, 26.23, 26.20, 26.10, 26.70, 21.65, 13.19.

MS (ESI): *m*/*z* = 736.00 [M + H]$^+$, 758.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}FNO_{11}$ + Na$^+$: 758.3886 [M + Na]$^+$; found: 758.3886.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(3-chlorophenyl)pent-2-enoate (5m)
Yield: 132 mg (88%); white solid; mp 65–67 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.09–7.28 (m, 4 H_{arom}), 6.75 (dt, $^3J_{2',3'}$ = 7.4 Hz, $^3J_{3',4'}$ = 15.4 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.4 Hz, 1 H, CH=C*H*), 5.34 (d, $^3J_{3,4}$ = 2.7 Hz, 1 H, 4-*H*), 5.01–5.09 (m, 2 H, 2-H, 3-H), 4.26 (t, $^3J_{1',2'}$ = 6.3 Hz, 1 H, C*H*NH), 4.16 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^2J_{6a,6b}$ = 11.3 Hz, $^3J_{5,6b}$ = 6.8 Hz, 1 H, 6b-H), 3.99 (dd, $^2J_{6a,6b}$ = 11.3 Hz, $^3J_{5,6a}$ = 6.8 Hz, 1 H, 6a-H), 3.81 (dd, $^3J_{1,2}$ = 7.7 Hz, $^3J_{1,NH}$ = 12.0 Hz, 1 H, 1-H), 3.70 (t, $^3J_{5,6}$ = 6.8 Hz, 1 H, 5-H), 2.50 (t, $^3J_{2',3'}$ = 7.4 Hz, 2 H, CH_2CH=CH), 2.13 (d, $^3J_{1,NH}$ = 12.0 Hz, 1 H, NH), 1.25–1.27 [m, 12 H, C(CH$_3$)$_3$, OCH$_2$CH_3], 1.21 [s, 9 H, C(CH$_3$)$_3$], 1.19 [s, 9 H, C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.84, 176.67, 176.06, 175.84, 164.97 (C=O), 142.57, 142.45, 133.60, 128.74, 126.98, 126.35, 124.94, 123.31 (Ar-C$_6$H$_4$, CH=CH), 85.17, 70.74, 70.25, 67.63, 66.31, 60.70, 59.26, 54.83 (C–O, C–N), 40.01, 38.78, 38.04, 37.82, 37.69, 26.28, 26.20, 26.11, 26.07, 13.20.

MS (ESI): *m*/*z* = 774.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}ClNO_{11}$ + Na$^+$: 774.3591 [M + Na]$^+$; found: 774.3584.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-tetra-*O*-pivaloyl-β-d-galactopyranosyl)amino]-5-(3-methylphenyl)pent-2-enoate (5n)
Yield: 116 mg (79%); white solid; mp 60–61 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.19–7.21 (m, 1 H_{arom}), 7.03–7.10 (m, 3 H_{arom}), 6.77 (dt, $^3J_{2',3'}$ = 14.2 Hz, $^3J_{3',4'}$ = 15.4 Hz, 1 H, C*H*=CH), 5.81 (d, $^3J_{3',4'}$ = 15.4 Hz, 1 H, CH=C*H*), 5.33 (d, $^3J_{3,4}$ = 2.9 Hz, 1 H, 4-H), 5.06 (t, $^3J_{2,3}$ = 10.2 Hz, 1 H, 2-H), 5.01 (dd, $^3J_{3,4}$ = 2.9 Hz, $^3J_{2,3}$ = 10.2 Hz, 1 H, 3-H), 4.23 (t, $^3J_{1',2'}$ = 6.9 Hz, 1 H, C*H*NH), 4.15 (q, $^3J_{5',6'}$ = 7.1 Hz, 2 H, OCH_2CH$_3$), 4.09 (dd, $^3J_{5,6b}$ = 7.0 Hz, $^2J_{6a,6b}$ = 11.2 Hz, 1 H, 6b-H), 3.99 (dd, $^3J_{5,6a}$ = 7.0 Hz, $^2J_{6a,6b}$ = 11.2 Hz, 1 H, 6a-H), 3.82 (d, $^3J_{1,2}$ = 8.4 Hz, 1 H, 1-H), 3.67 (t, $^3J_{5,6}$ = 7.0 Hz, 1 H, 5-H), 2.50 (dd, $^3J_{1',2'}$ = 6.9 Hz, $^3J_{2',3'}$ = 14.2 Hz, 2 H, CH_2CH=CH), 2.33 (s, 3 H, ArCH_3), 2.10 (s, 1 H, NH), 1.26–1.28 [m, 12 H, OCH$_2$CH_3, C(CH$_3$)$_3$], 1.21 [s, 9 H, C(CH$_3$)$_3$], 1.19 [s, 9 H, C(CH$_3$)$_3$], 1.09 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, CDCl$_3$): δ = 176.88, 176.62, 176.10, 175.90, 165.16 (C=O), 143.48, 139.96, 137.03, 127.50, 127.29, 127.06, 123.86, 122.84 (Ar-C$_6$H$_4$, CH=CH), 85.22, 70.62, 70.29, 67.68, 66.42, 60.78, 59.17, 55.22 (C–O, C–N), 40.21, 38.04, 37.79, 37.69, 28.64, 26.25, 26.21, 26.12, 26.07, 20.39, 13.21.

MS (ESI): *m*/*z* = 732.27 [M + H]$^+$, 754.33 [M + Na]$^+$.

HRMS (ESI): *m*/*z* calcd for $C_{40}H_{61}NO_{11}$ + Na$^+$: 754.4137 [M + Na]$^+$; found: 754.4149.

Ethyl (5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(furan-2-yl)pent-2-enoate (5o)
Yield: 92 mg (65%); yellow solid; mp 58–59 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31 (d, ^3J = 1.5 Hz, 1 H, H-furan), 6.83 (dt, $^3J_{2',3'}$ = 8.2 Hz, $^3J_{3',4'}$ = 15.6 Hz, 1 H, C*H*=CH), 6.26–6.33 (m, 1 H, H-furan), 6.15 (t, ^3J = 1.5 Hz, 1 H, H-furan), 5.84 (d, $^3J_{3',4'}$ = 15.6 Hz, 1 H, CH=C*H*), 5.39 (d, $^3J_{3,4}$ = 2.9 Hz, 1 H, 4-H), 5.27–5.28 (m, 1 H, 2-H), 4.98–5.09 (m, 1 H, 3-H), 4.56–4.66 (m, 1 H, C*H*NH), 4.13–4.20 (m, 3 H, OCH_2CH$_3$, NH), 4.08 (d, $^2J_{6a,6b}$ = 6.6 Hz, 1 H, 6b-H), 3.99 (d, $^2J_{6a,6b}$ = 6.6 Hz, 1 H, 6a-H), 3.91 (d, $^3J_{1,2}$ = 3.8 Hz, 1 H, 1-H), 3.83 (s, 1 H, 5-H), 2.58–2.76 (m, 2 H, CH_2CH=CH), 1.26–1.28 (m, 3 H, OCH$_2$CH_3), 1.25 [s, 9 H, C(CH$_3$)$_3$], 1.21 [s, 9 H, C(CH$_3$)$_3$], 1.16 [s, 9 H, C(CH$_3$)$_3$], 1.11 [s, 9 H, C(CH$_3$)$_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.86, 176.66, 176.31, 176.17, 175.95, 175.84, 175.60, 165.05, 164.98 (C = O), 154.26, 152.46, 143.48, 143.32, 141.06, 140.63, 123.05, 122.87, 122.83, 109.13, 106.96,105.40 (CH=CH), 86.45, 80.84, 70.58, 70.36, 67.64, 67.18, 67.10, 66.63, 66.14, 65.05, 61.04, 60.30, 59.20, 51.09, 50.10, 38.05, 37.72, 36.55, 35.89, 26.19, 26.15, 26.09, 26.00, 13.23.

MS (ESI): *m*/*z* = 708.3 $[M + H]^+$, 730.4 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{57}NO_{12}$ + Na^+: 730.3773 $[M + Na]^+$; found: 730.3765.

Ethyl (5*S*,2*E*,6*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-7-phenylhepta-2,6-dienoate (5p)
Yield: 111.5 mg (75%); yellow solid; mp 62–63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.35 (m, 5 H, C_6H_5), 6.89 (dt, $^3J_{2',3'}$ = 6.9 Hz, $^3J_{3',4'}$ = 15.5 Hz, 1 H, C*H*=CH), 6.50 (d, *J* = 15.9 Hz, 1 H, PhC*H*=CH), 5.88 (d, $^3J_{3',4'}$ = 15.5 Hz, 1 H, CH=C*H*), 5.84 (t, *J* = 15.9 Hz, 1 H, PhCH=C*H*), 5.39 (d, $^3J_{3,4}$ = 2.5 Hz, 1 H, 4-H), 5.03–5.14 (m, 2 H, 2-H, 3-H), 4.16–4.20 (m, 3 H, C*H*NH, OCH_2CH_3), 4.10–4.15 (m, 2 H, 6a-H, 6b-H), 4.00–4.03 (m, 1 H, 1-H), 3.86–3.98 (m, 1 H, 5-H), 2.43 (t, $^3J_{2',3'}$ = 6.9 Hz, 2 H, CH_2CH=CH), 1.90 (d, $^3J_{NH,1'}$ = 12.4 Hz, 1 H, NH), 1.24–1.29 [m, 12 H, OCH_2CH_3, $C(CH_3)_3$], 1.21 [s, 9 H, $C(CH_3)_3$], 1.19 [s, 9 H, $C(CH_3)_3$], 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.84, 177.58, 177.06, 176.88, 166.10 (C=O), 144.10, 136.41, 132.58, 130.12, 128.65, 127.82, 126.36, 124.14 (Ar-C_6H_4, CH=CH), 86.86, 71.73, 71.28, 68.63, 67.38, 61.71, 60.33, 60.20, 55.18 (C–O, C–N), 39.35, 39.05, 38.74, 38.72, 38.70, 27.21, 27.14, 27.07, 14.23.

MS (ESI): *m*/*z* = 744.2 $[M + H]^+$, 766.4 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{41}H_{61}NO_{11}$ + Na^+: 766.4137 $[M + Na]^+$; found: 766.4134.

(5*S*,2*E*)-5-[(2,3,4,6-Tetra-*O*-pivaloyl-β-D-galactopyranosyl)amino]-5-(3-chlorophenyl)but-2-enal (5q)
Yield: 139 mg (98%); light yellow solid; mp 56–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (d, $^3J_{4',5'}$ = 7.7 Hz, 1 H, CHO), 7.13–7.32 (m, 4 H_{arom}), 6.62 (dt, $^3J_{3',4'}$ = 15.7 Hz, 1 H, C*H*=CHCHO), 6.12 (dd, $^3J_{3',4'}$ = 15.7 Hz, $^3J_{4',5'}$ = 7.7 Hz, 1 H, CH=C*H*CHO), 5.38 (d, $^3J_{3,4}$ = 3.0 Hz, 1 H, 4-H), 5.06–5.10 (m, 2 H, 2-H, 3-H), 4.34 (t, $^3J_{1',2'}$ = 6.3 Hz, 1 H, C*H*NH), 4.14 (dd, $^3J_{5,6b}$ = 6.7 Hz, $^2J_{6a,6b}$ = 11.1 Hz, 1 H, 6b-H), 4.02 (dd, $^3J_{5,6a}$ = 6.7 Hz, $^2J_{6a,6b}$ = 11.1 Hz, 1 H, 6a-H), 3.86 (dd, $^3J_{1,2}$ = 8.7 Hz, 1 H, 1-H), 3.75 (t, $^3J_{5,6}$ = 6.7 Hz, 1 H, 5-H), 2.68 (t, $^3J_{4',5'}$ = 6.3 Hz, 2 H, CH_2CH=CH), 2.19 (d, $^3J_{NH,1'}$ = 12.4 Hz, 1 H, NH), 1.30 [s, 9 H, $C(CH_3)_3$], 1.23–1.24 [m, 18 H, 2 $C(CH_3)_3$], 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 193.29 (CHO), 177.88, 177.77, 177.11, 176.85 (C=O), 152.45, 142.95, 135.34, 134.79, 129.88, 128.25, 127.34, 125.88 (Ar-C_6H_4, CH=CH), 86.13, 71.83, 71.17, 68.65, 67.29, 61.69, 55.87 (C–O, C–N), 41.42, 41.27, 39.06, 38.86, 38.72, 27.29, 27.20, 27.13, 27.08.

MS (ESI): *m*/*z* = 708.1 $[M + H]^+$, 730.4 $[M + Na]^+$.

(6*S*)-6-(4-Methylphenyl)piperidin-2-one (8g)
A solution of **5g** (295 mg, 0.4 mmol) in anhyd MeOH (5 mL) was reduced with H_2 on Pd/C (5%). The reaction mixture was stirred for 4 h [TLC monitoring, eluent: petroleum ether (bp 60–90 °C)–EtOAc, 15:1 (v/v)] at r.t. The mixture was filtered and concentrated in vacuo to yield the crude product **6g**. Then a solution of **6g** in anhyd MeOH (5 mL) was treated with freshly prepared (0.5 M) solution of NaOMe in MeOH (5 mL). The mixture was stirred at r.t. for 4 h [TLC monitoring, eluent: EtOAc–MeOH, 30:1 (v/v)]. Then a few drops of H_2O were added to the mixture, neutralized with AcOH, and stirred at r.t. for another 4 h. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic phases were washed with sat. aq $NaHCO_3$ (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude product **8g**. The residue was purified by column chromatography on silica gel (EtOAc–MeOH, 30:1, with 0.1% Et_3N] to afford **8g** (70 mg, 93%) as a white solid; mp 115–117 °C; $[\alpha]_D^{25}$ –59.6 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 4 H_{arom}), 5.78 (s, 1 H, NH), 5.13 (dd, $^3J_{H,H}$ = 4.3 Hz, $^3J_{H,H}$ = 9.0 Hz, 1 H, C*H*NH), 2.45–2.49 (m, 1 H, $COCH_2$), 2.35 (s, 3 H, ArCH_3), 2.05–2.14 (m, 1 H, $COCH_2$), 1.67–1.92 (m, 4 H, 2 CH_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.38, 138.56, 136.66, 128.45, 124.98, 56.49, 31.18, 30.25, 20.04, 18.67.

MS (ESI): *m*/*z* = 190.0 $[M + H]^+$, 212.0 $[M + Na]^+$.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{15}NO$ + Na^+: 212.1046 $[M + Na]^+$; found: 212.1052.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(18) Crystallographic data for the structural analysis of compound **5b** has been deposited at the Cambridge Crystallographic Data Centre under No. CCDC 802525. These data can be obtained free of charge by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.