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Article

Tri-*n*-butyltin Hydride-Mediated Radical Reactions of *ortho*- and *meta*-Iodobenzamides to Synthesize Benzomacrolactams. Surprising Formation of Biphenyl Compounds from meta-Regioisomers

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Reações de 4-*O*-alil-2,3-di-*O*-benzil-6-desoxi-6-(3-iodobenzoilamino)-α-D-galactopiranosídeo de metila, seu epímero *glico*, 2,3-di-*O*-benzil-6-desoxi-6-(3-iodobenzoilamino)-4-*O*-(1-pentenil)-α-D-glicopiranosídeo de metila e seu regioisômero *orto*-iodobenzamida com hidreto de tri-*n*-butilestanho foram realizadas em diferentes condições. Dependendo das condições, os três precursores que contêm o átomo de iodo em posição *met*a conduziram a uma surpreendente quantidade de compostos bifenílicos, nos quais o átomo de iodo foi substituído por um grupo fenila. O substrato 2-iodobenzamida levou apenas ao produto de hidrogenólise. Nenhum produto ciclizado foi isolado de nenhuma das reações. As estruturas dos compostos bifenílicos inéditos foram elucidadas utilizando-se as espectrometrias de massa, de RMN ^{1}H e ^{13}C e experimentos DEPT, COSY, HMQC e HMBC. Foram propostos mecanismos de formação dos compostos bifenílicos e hipóteses para explicar os diferentes comportamentos dos isômeros *orto*- e *meta*-iodobenzamidas na reação radicalar.

Reactions of methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-galactopyranoside, its *gluco* epimer, methyl 2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside and its *ortho*-regioisomer with tri-*n*-butyltin hydride were performed in different conditions. Depending on reaction conditions the three *meta*-iodo isomers gave a surprising amount of biphenyl compounds. The 2-iodo isomer led only to the undesired but expected hydrogenolysis product. No cyclized products were isolated in all the reactions. The structures of the new biphenyl products were elucidated by ^{1}H and ^{13}C NMR spectroscopy, DEPT, COSY, HMQC and HMBC experiments and ESI-MS/MS. Mechanisms for the formation of these new biphenyl derivatives and hypotheses to explain the different outcomes for radical reactions of 3- or 2-iodobenzamides were presented.

Keywords: biphenyl compounds, aryl radical cyclization, 3- and 2-iodobenzamides

Introduction

In view of the numerous biological activities of macrolactams[1-4] and the synthetic challenge they present,[3,5] we have studied the Bu_3SnH-mediated radical cyclization reactions using unsaturated iodides as precursors of macrolactams,[6-12] mainly allyloxy-*ortho*-iodobenzamides derived from carbohydrates to give benzomacrolactams.[6-11] These precursors furnished benzomacrolactams with 11-, 12- and 20-membered ring by regioselective *endo* aryl radical carbocyclization.[6-9] The benzamides methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside (**1**) and its *gluco* epimer **2** were found to furnish the benzomacrolactams **3** and **4** owing to 11-*endo* cyclization in 32% and 40% yield, respectively[6,7] (Figure 1).

Considering that (*i*) we have been stimulated to study the Bu_3SnH-mediated radical reactions to construct

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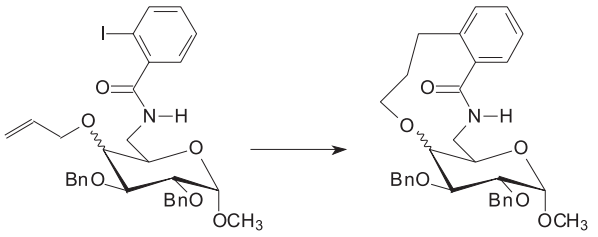


Figure 1. O*rtho*-iodobenzamides and their cyclized products.

macrocycles, since there is a limited number of protocols available for the synthesis of large rings using free radical-mediated macrocyclizations,[13] (*ii*) the *endo*-macrocyclization mode is favoured over the *exo*,[6-9,12,14-20] (*iii*) the carbohydrate moiety impose conformational restriction to favour cyclization,[6-9,12] and (*iv*) although the majority of fused aromatic macrocycles have been obtained from *ortho*-halogenobenzene derivatives bearing an unsaturation in the side chain,[6-9,14-19] 3-halogenobenzene compounds have also been used as precursors of benzomacrolactams,[13] we selected to apply the Bu_3SnH-mediated radical reaction to the methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-galactopyranoside (**5**), methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-glucopyranoside (**6**) (Figure 2), the respective *meta*-isomers of **1** and **2** (Figure 1), in an attempt to form the benzomacrolactams **7** and **8** (Figure 2) by 12-*endo* carbocyclization. In view of the results of these radical reactions, we also carried out the Bu_3SnH-mediated reaction with methyl 2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**9**) and methyl 2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**10**) to synthesize the respectively 14- and 13-membered lactams **11** and **12** (Figure 2).

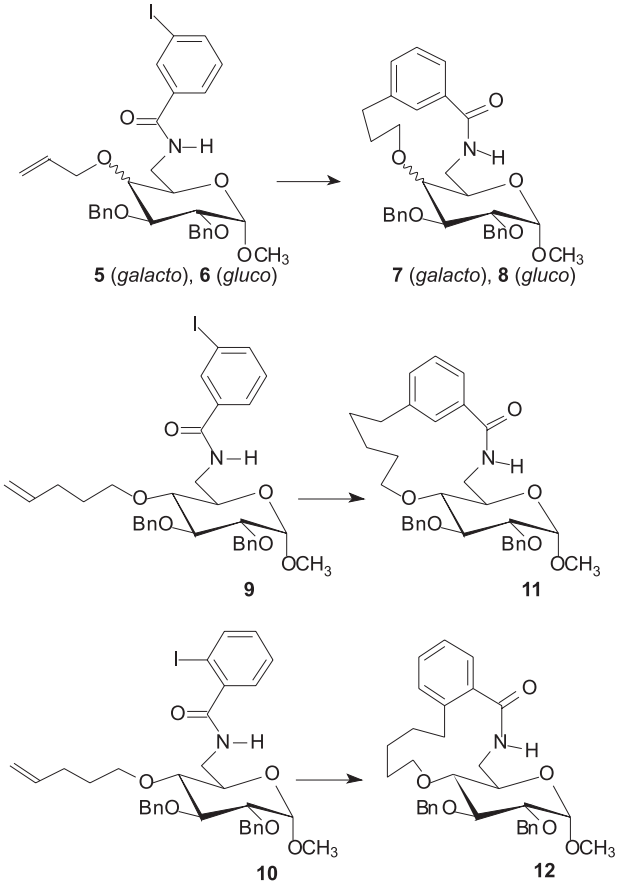


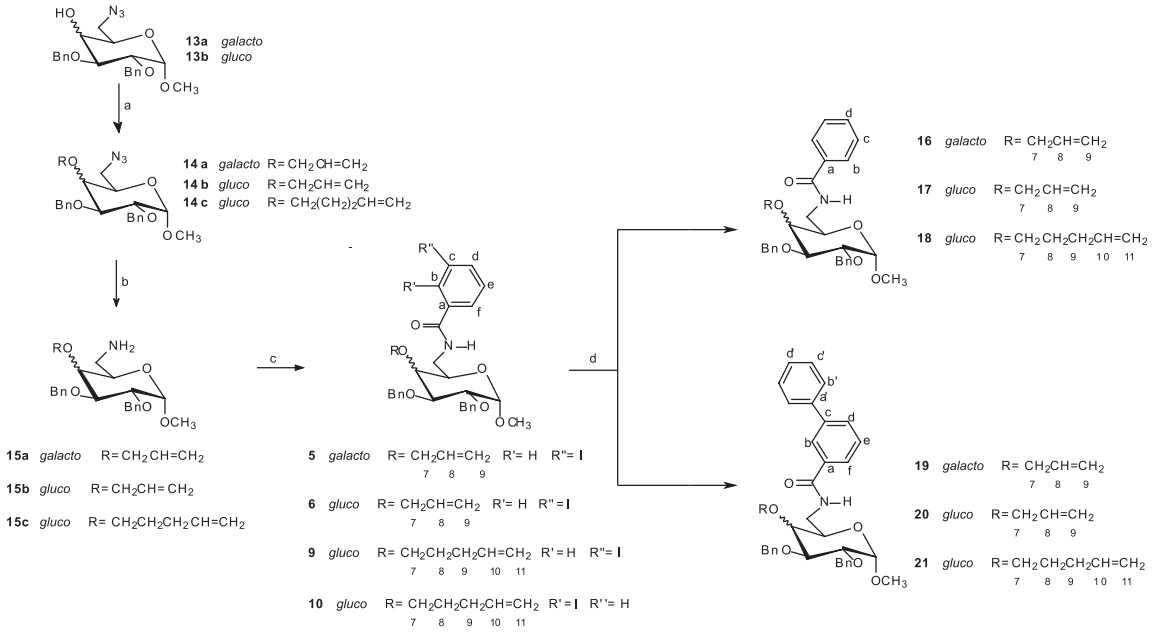
Figure 2. Structures of iodobenzamides and their expected cyclized products.

Results and Discussion

The iodobenzamides **5**, **6**, **9** and **10** were prepared from the adequate methyl α-D-pyranosides (*galact*o for **5**; *gluco* for **6**, **9** and **10**) in eight conventional synthetic steps. The C-4 and C-6 hydroxy groups of starting materials were protected as benzylidene acetal[21] and the C-2 and C-3 hydroxy groups were *O*-benzylated.[22,23] Removal of the benzylidene groups[24,25] followed by regioselective replacement of the hydroxy groups at C-6 by iodine atom[7,26] and substitution of iodine atom by azido group[6,7,27] furnished **13a**[7] and **13b**,[6] known 6-azido-4-hydroxy derivatives. *O*-allylation of C-4 hydroxy groups of **13a** and **13b**[6,7,23] gave **14a**[7] and **14b**,[6] also known compounds. The etherification of free hydroxy group of **13a** with 5-bromo-1-pentene[6,7,23] furnished the new methyl 6-azido-6-deoxy-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**14c**). Selective reduction of the azido groups of **14a**, **14b** and **14c**[7,28] gave the known amines **15a**[7] and **15b**[6] and the new amine **15c**. These amines upon treatment with the suitable iodobenzoyl chloride (3-iodobenzoyl chloride for **5**, **6** and **9**; 2-iodobenzoyl chloride for **10**)[6,7,29] furnished the desired iodobenzamides **5**, **6**, **9** and **10** (Scheme 1).

The radical reactions were performed in the usual way[20,30] with slow addition (1.5 to 5 h) of a solution mixture of Bu_3SnH (1.5 molar equivalents) and catalytic amount of AIBN to a solution of **5**, **6**, **9** and **10** at concentrations ranging from 0.003 to 0.012 mol L^{-1} (Table 1). The products formed (**16**, **17**, **18**, **19**, **20** and **21**) and recovered (**6**) (Scheme 1) were isolated after solvent elimination and column chromatography.

As shown in table 1, different reaction conditions with variable dilution, addition time and solvent were attempted for the synthesis of the macrocycles. Using benzene as solvent, lower dilution (substrate concentration: 0.08 and 0.012) and faster addition of the Bu_3SnH/AIBN mixture (1.5 h) only the uncyclized reduced products (**16** and **18**)



Scheme 1. Reagents and conditions: (a) Bu_4NBr, 50% m/v aqueous NaOH, CH_2Cl_2 or ethyl ether, allyl bromide or 5-bromo-1-pentene, rt; (b) LiAlH4, THF, rt; (c) 3- or 2-iodobenzoyl chloride (2 equivalents), 10% m/v aqueous NaOH, CH_2Cl_2, ice bath; (d) Bu_3SnH (1.5 equivalents), AIBN (catalytic amount), benzene, N_2, reflux.

Table 1. Reactions of benzamides **5**, **6**, **9** and **10** with Bu_3SnH

Entry	Substrate	Solvent	Concentration of substrate / (mol L^{-1})	Addition time of Bu_3SnH/AIBN / h	Product	Yield / (%)
1	**5**	benzene	0.012	1.5	**16**	58
2	**5**	benzene	0.003	5	**19**	35
3	**5**	C_6H_{12}*	0.003	3.5	**16**	71
4	**6**	benzene	0.008	2	**20**	19
					17	61
5	**6**	benzene	0.004	5	**20**	13
					6	42
6	**9**	benzene	0.008	1.5	**18**	58
7	**9**	benzene	0.004	3	**21**	68
8	**9**	C_6H_{12}*	0.004	3	**18**	97
9	**9**	CH_3CN*	0.004	3	**18**	55
10	**10**	benzene	0.008	1.5	**18**	68
11	**10**	benzene	0.004	4	**18**	65

C_6H_{12}*: cyclohexane + small amount of benzene; CH_3CN*: acetonitrile + small amount of benzene.

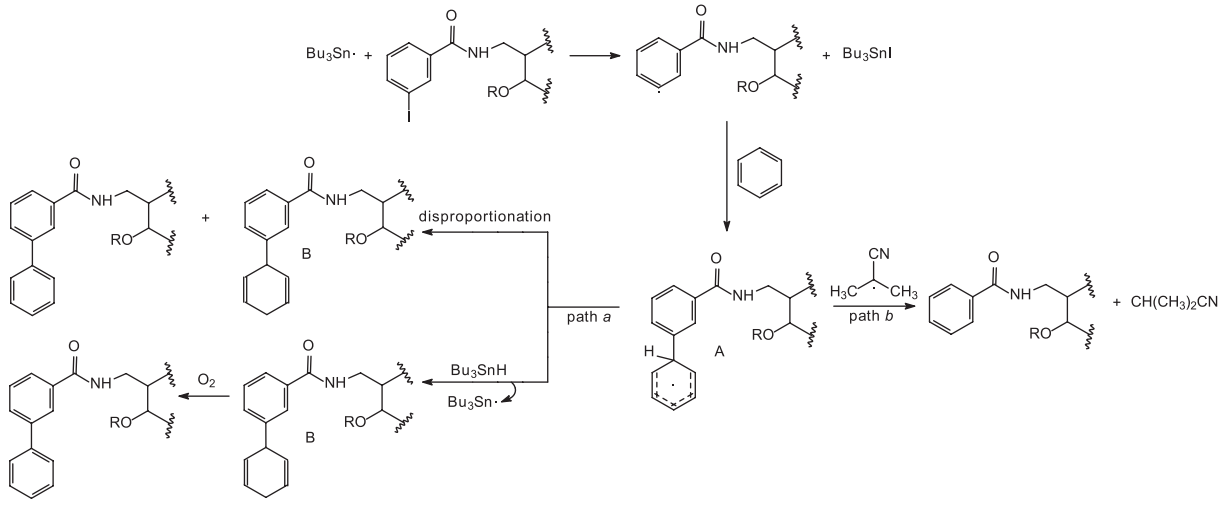
were isolated in the reactions of **5**, **9** and **10** (entries 1, 6 and 10, Table 1). Since higher dilution and longer addition time are recommended to improve the formation of cyclized products and to decrease the rate of hydrogen atom transfer to uncyclized radicals,[20,30] using benzene as solvent, the addition of Bu_3SnH/AIBN solution was made over a longer period (3 to 5 h) and a higher dilution (0.003 mol L^{-1} in **5**; 0.004 mol L^{-1} in **6**, **9** and **10**) (entries 2, 5, 7 and 11, Table 1). Surprisingly, in these conditions, the biphenyl compounds **19**, **20** and **21**, yielded by intermolecular reaction of the aryl radical with bezene, were the only products formed at a sufficient amount for isolation from the three *meta*-iodobenzamides **5**, **6** and **9**. On the other hand, at the same reaction conditions the *ortho*-iodobenzamide **10** only led to the hydrogenolysis product **18**. In an attempt to avoid the formation of the biphenyl products and to favour the desired cyclization, the reactions of **5** and **9** were carried out in cyclohexane[30,31] (entries 3 and 8, Table 1) and the

reaction of **9** was also developed in acetonitrile[32] (entry 9, Table 1). When it was necessary for dissolution of the substrates and Bu_3SnH/AIBN, a small amount of benzene was added and the dilution was made with cyclohexane or acetonitrile to give a reaction mixture of 0.003 and 0.004 mol L^{-1} in *meta*-iodobenzamides **5** and **9** respectively. Only the hydrogenolysis product **16** (71%) and **18** (97% and 55%) were isolated after column chromatography. In contrast with the other substrates, the 3-iodobenzamide **6** also produced the biphenyl product **20** in the reaction carried out in substrate concentration of 0.008 mol L^{-1} and addition time of 2 h (entry 4, Table 1). No cyclized product was isolated in any reaction.

The biphenyl compounds **19**, **20** and **21** are products of homolytic intermolecular aromatic substitution reactions between the radicals of benzamides **5**, **6** and **9** (generated by tri-*n*-butyltin radicals) and benzene, the solvent. The mechanisms of Bu_3SnH-mediated homolytic aromatic substitution presented in the literature[31,33] can be applied to explain the formation of the unexpected biphenyl products. These mechanisms are shown in scheme 2. The first step proceeds by addition of the initial radical of the benzamides **5**, **6** and **9** to the benzene (solvent) to yield the π radical **A**.[31,33] Disproportionation of **A** or hydrogen-atom transfer from Bu_3SnH leads to the intermediate **B** and its isomers, which can undergo oxidation by oxygen on workup (path a).[31] Whilst oxidation during workup may be plausible, dihydro-type systems, such **B**, are not oxidized rapidly in air[31] and the yield of the biphenyl compound **21** was higher than 50% (67%), as occur frequently in this kind of reaction.[31] These facts ruled out the path *a* as the main mechanism. Hydrogen-atom transfer of π radical **A** to other radicals present in the reaction mixture,[31,33] mainly 2-cyanoprop-2-yl radical furnished by the radical initiator AIBN,[31] appears to be the predominant reaction to yield biphenyl compounds (path b).[31,33] Addition of reactive aryl radical to the solvent may compete effectively with the desired chain-transfer processes for reactions involving very low concentrations of substrate.[30,31,34] However, to the best of our knowledge, in the literature there are no biphenyl compounds obtained as main product by the Bu_3SnH method, as described here.

Initially, we were surprised by the total lack of cyclization of benzamides **5** and **6** because there are a number of reports in the literature of successful 12-*endo* cyclization[12,20] and no obvious reason was apparent for the difference between these results and those previously published for their *ortho*-isomers **1** and **2**.[6,7] However, two hypotheses can be presented to explain the difference between the Bu_3SnH-mediated reaction of the *ortho*-iodobenzamides (**1** and **2**) and the *meta*-iodobenzamides (**5** and **6**).

The importance of conformational pre-organization in successful macrocyclization reactions is well known.[1] It is also recognized the role of intramolecular weak forces and structural elements in the pre-organization that facilitates macrocyclization reactions.[5,13] In our previous papers we considered that the cyclization reactions were favoured by the conformational restriction present in the precursors due to the amide bond, the sugar moiety and the presence of a hydrogen bond formed between the hydrogen atom of the amide group and the oxygen atom of the allyloxy group.[6,7,9,35] The lack of cyclization products from radical reactions of **5** and **6** can indicate that the restricted rotation around the aryl-carbonyl bond present in **1** and **2** due to the iodine atom *ortho* to the amide group[36,37] also contributes to give a pre-organization to favour the ring closure. Despite this conformational restriction being absent in the aryl radicals, it is assumed that the relative amounts of



Scheme 2. Mechanisms proposed for the formation of biphenyl compounds.

the aryl radical rotamers is determined by the equilibrium concentrations of the starting rotamers due to the short lifetime of the radicals.[37] Probably, in the benzamides **5** and **6**, and consequently in the aryl radicals formed, there would be a great number of rotamers due to the absence of conformational restriction around the aryl-carbonyl bond. The absence of conformational restriction for pre-organized structure in compounds **5** and **6** could therefore explain the observed results.

Another possible explanation for the absence of cyclization products from **5** and **6**, in contrast with the radical reaction of **1** and **2**, can be attributed to insufficient proximity of the terminal carbon of allyloxy group to the attacking aryl radical. This hypothesis is supported by the fact that no report to date of Bu_3SnH-mediated aryl radical cyclization from *meta*-haloarenes to give products in which the formed rings have smaller than fourteen members. We found only two *meta*-haloarenes as precursors of 14- and 17-membered macrocycles.[13]

In order to verify if this second hypothesis is consistent and considering that a 14-membered lactam was obtained from a *meta*-bromobenzene derivative,[13] we decided to apply the Bu_3SnH-mediated radical reaction to the methyl 2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**9**). The *meta*-iodo derivative **9**, which presents a longer alkenylic chain than **6**, could give the 14-membered benzomacrolactam **11**, formed by *endo* cyclization mode. Aiming at completing the observations in comparing ciclizations of *ortho*- and *meta*-iodo isomers, the *ortho*-iodobenzamide **10** was also synthesized and submitted to the reaction with Bu_3SnH to give the 13-membered lactam **12** (Figure 2).

The reactions with **9** were carried out in four different conditions (entries 6-9, Table 1) but cyclization also failed. Only the uncyclized reduced product **18** and the new biphenyl compound **21** were isolated (Scheme 1). The *ortho*-isomer **10**, with a pentenyl group replacing the allyl group of **1**, was submitted to the reaction with Bu_3SnH in two different conditions (entries 10 and 11, Table 1) and gave only the hydrogenolysis compound **18** (Scheme 1).

The absence of biphenyl compound from **10** can be easily explained taking into account the steric hindrance effect caused by the large substituent in *ortho* position to the aryl radical. The lack of cyclized product in the reactions of **9** can be attributed to the greater conformational freedom of the pentenyl group, which has larger alkyl chain than allyl group present in the C-4 of **1**. Bearing in mind that the *ortho*-iodobenzamide **10** didn't provide the expected macrolactam, we can not judge whether the distance between the aryl radical and the terminal carbon of the allyl group bounded to C-4 of **5** and **6** was the factor that prevented the formation of cyclized products.

The hydrogenolysis products **16**, **17** and **18** were readily identified from their ^1H and ^{13}C NMR data. The structural elucidation of **19**, **20** and **21** required a detailed analysis of the NMR spectra (^1H, ^{13}C and DEPT) and connectivity studies by COSY, HMQC and HMBC experiments. For instance, the ^1H NMR spectrum of **19** indicates the presence of five aromatic hydrogen atoms more deshielded than the other fourteen aromatic hydrogen atoms. These five hydrogen atoms are assigned as the hydrogens *ortho* to the both carbonyl and phenyl groups (δ 7.97, t, 1H), *para* to the carbonyl group (δ 7.71, dt, 1H), *ortho* to the carbonyl group (δ 7.67, dt, 1H) and *ortho* to the benzamide group (δ 7.58, d, 2H). The ^{13}C NMR and DEPT spectra demonstrate the presence of five *ipso* carbons. Two of these *ipso* carbon atoms show chemical shifts compatibles with biphenyl group (δ 141.7 and 140.1). Signals of allyloxy and benzyloxy groups, methyl galactopyranoside moiety and benzamide were also observed. Similar pattern is observed in the spectra of **20** and **21**.

The electrospray ionization mass and tandem mass spectra in the positive ion mode [ESI-MS(/MS)] were also found to be compatible with the formation of **19**, **20** and **21**. For instance, the ESI-MS of **19** shows major ions due to protonated and cationized molecule (Figure 3A), that is, $[M + H]^+$ of *m/z* 594.279 (*m/z* 594.285 calculated for $[C_{37}H_{39}NO_6 + H]^+$), $[C_{37}H_{39}NO_6 + Na]^+$ of *m/z* 616.279 (*m/z* 616.268) and $[C_{37}H_{39}NO_6 + K]^+$ of *m/z* 632.235 (*m/z* 632.241). Fragment ions were also observed: $[M + H - CH_3OH]^+$ of *m/z* 562.3 and $[M + H - CH_3OH–PhCH_2OH]$ of *m/z* 454.2. The ESI(+)-MS/MS of the protonated molecule of *m/z* 594.3 (Figure 3B) is also consistent with the proposed structure **19** since it shows dissociation that can be easily rationalized for the proposed structure (Scheme 3) and occur mainly by the consecutive losses of CH_3OH (*m/z* 562) and $PhCH_2OH$ (*m/z* 454).

In conclusion, no cyclized products were obtained by Bu_3SnH-induced aryl radical reactions of methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-galactopyranoside (**5**), its *gluco* epimer **6**, methyl 2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-galactopyranoside (**9**) and its *ortho*-regioisomer **10**. Instead and unexpectedly, the three *meta*-iodobenzamides **5**, **6** and **9** furnished the biphenyl compounds **19**, **20** and **21** as indicated by MS and NMR data. These studies demonstrated the structural requisites of precursors to give benzomacrolactams: the *ortho*-iodine atom in the aromatic ring and a short side chain bearing the unsaturation, which presents lower conformational freedom.

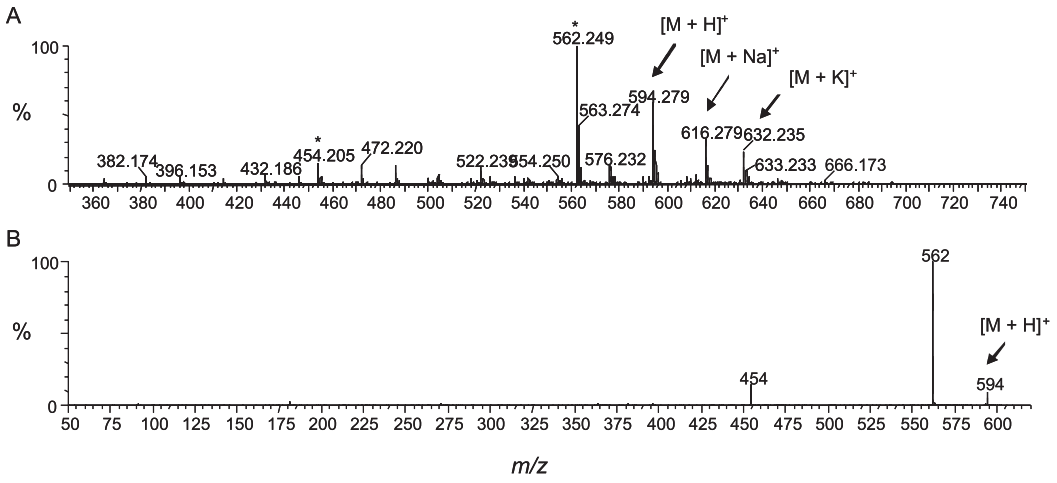
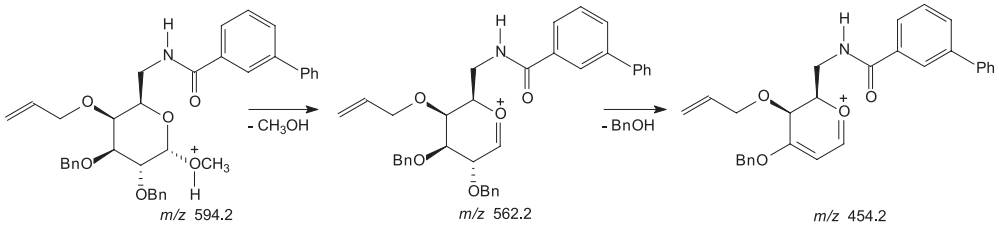


Figure 3. A: ESI-MS of product **19**; B: ESI-MS/MS of the protonated molecules of **19**. Ions marked by an asterisk are fragments due to CH_3OH and $PhCH_2OH$ loss that arise likely from in-source collision-induced dissociation.



Scheme 3. Dissociation mechanism proposed for the protonated molecule of **19** based on its ESI-MS/MS data.

Experimental

General methods

All melting points were determined on a Microquimica MQAPF-301 apparatus and are uncorrected. Optical rotations were determined at 25 °C with a Perkin Elmer 341 Polarimeter. The IR spectra were recorded on an ATR-IR, Spectum One, Perkin Elmer spectrometer. The NMR spectra were measured in deuteriochloroform with TMS as the internal standard with a Bruker Avance DRX-400 or a Bruker Avance-200 instruments. Chemical shifts are given in δ scale and J values are given in Hz. ESI(+)-MS spectra were obtained using a Micromass QTof hybrid quadrupole time-of-flight mass spectrometer operating at 7.000 mass resolution and 5 ppm mass accuracy using typical analytical conditions as described elsewhere.[38] ESI-MS and ESI-MS/MS were acquired in a QTof Waters Micromass mass spectrometer using positive ion mode from 1:1 H_2O-MeOH solutions with addition of a few microlitres of formic acid, and using the following basic operation conditions: capillary and cone voltages were set to 3500 V and 45 V, respectively, with a de-solvation temperature of 100 °C. For the tandem MS experiments, 15 eV collisions with argon were used. The solutions were infused directly into the ESI source by means of syringe pump (Harvard Apparatus) at a flow rate of 10 μL min^{-1}. Column chromatography was performed with silica gel 60, 70-230 mesh (Merck). The term "standard work-up" means that the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The synthesis and characterization of the known derivatives **13a**, **13b**, **14a**, **14b**, **15a** and **15b** from the corresponding methyl α-D-gluco(or galacto)pyranoside were described in previous publications.[6,7]

*Methyl 6-azido-2,3-di-O-benzyl-6-deoxy-4-O-(1-pentenyl)-α-D-glucopyranoside (**14c**)*

To a solution of methyl 6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside (**13b**) (0.26 g, 0.65 mmol) in ethyl ether (6 mL) were added, under magnetic stirring, 50% m/v aqueous NaOH (4 mL) and Bu_4NBr (0.10 g, 0.32 mmol), as phase transfer catalyst. The mixture was stirred for 15 min. The reagent 5-bromo-1-pentene (0.24 mL, 0.29 g, 1.95 mmol) was added and the mixture was stirred for 48 h at room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl ether. Standard work-up gave a residue, which

was submitted to column Chromatography. The compound **14c** (0.22 g, 0.48 mmol, 70%), eluted with hexane-ethyl acetate 8:2 (v/v), was obtained as an oil, $[\alpha]_D$ +61.3 (*c* 1.00; $CHCl_3$).The product was characterized by IR, NMR ^1H and NMR ^{13}C.

*Methyl 6-amino-2,3-di-O-benzyl-6-deoxy-4-O-(1-pentenyl)-α-D-glucopyranoside (**15c**)*

To a suspension of lithium aluminum hydride (36.6 mg, 0.96 mmol) in THF (1.6 mL) was added a solution of **14c** (0.22 g, 0.48 mmol) in THF (4 mL). The solution was stirred for 2.5 h at room temperature. Water (5 mL), 10% m/v aqueous NaOH (1 mL) and CH_2Cl_2 (15 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Standard work-up gave **15c** which was not purified.

*Methyl 4-O-(alkenyl)-2,3-di-O-benzyl-6-deoxy-6-(iodobenzoylamino)-α-D-pyranosides (**5**, **6**, **9**, **10**)*

To a solution of 2- or 3-iodobenzoyl chloride (0.26 g, 0.97 mmol) in CH_2Cl_2 (3.8 mL) under ice bath were added 10% m/v aqueous NaOH (1.2 mL) and a solution of the amine (**15a**, **15b** or **15c**) (0.48 mmol) in CH_2Cl_2 (1.6 mL). The mixture was stirred for 5 min under ice bath. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. Standard work-up gave a residue, which was submitted to column chromatography. The reaction of the amine **15a** with 3-iodobenzoyl chloride gave the methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-galactopyranoside (**5**) (0.19 g, 0.29 mmol, 60% from the azido derivative), eluted with hexane-ethyl acetate, as a white solid; mp 109.0-110.4 °C; $[\alpha]_D$ +45.5 (*c* 1.41, $CHCl_3$); IR ν_{max}/cm^{-1}: 3293 (NH), 1637 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (t, 1H, $J_{b,d}$, $J_{b,f}$ 1.6 Hz, H-b), 7.81 (ddd, 1H, $J_{d,e}$ 7.8, $J_{d,b}$ 1.6, $J_{d,f}$ 1.1 Hz, H-d), 7.67 (ddd, 1H, $J_{f,e}$ 7.8, $J_{f,b}$ 1.6, $J_{f,d}$ 1.1 Hz, H-f), 7.39-7.25 (m, 10H, Ar), 7.15 (t, 1H, $J_{e,d}$, J_{e-f} 7.8 Hz, H-e), 6.62 (dd, 1H, $J_{NH,6}$ 7.0, $J_{NH,6'}$ 4.0 Hz, N-*H*), 5.93 (dddd, 1H, $J_{8,9\ trans}$ 17.3, $J_{8,9'\ cis}$ 10.3, $J_{8,7}$ 6.9, $J_{8,7'}$ 5.2 Hz, H-8), 5.24 (dq, 1H, $J_{9,8\ trans}$ 17.3, $J_{9,9'}$, $J_{9,7}$, $J_{9,7'}$ 1.5 Hz, H-9), 5.20 (dd, 1H, $J_{9',8\ cis}$ 10.3, $J_{9',9}$ or $J_{9',7}$ 1.5 Hz, H-9'), 4.84 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.84 (d, 1H, J_{gem} 11.7 Hz, PhCH_2), 4.71 (d, 1H, J_{gem} 11.7 Hz, PhCH_2), 4.67 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1); 4.66 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.49 (ddt, 1H, $J_{7',7}$ 12.4, $J_{7',8}$ 5.2, $J_{7',9}$, $J_{7',9'}$ 1.5 Hz, H-7'), 4.11 (dd, 1H, $J_{7,7'}$ 12.4, $J_{7,8}$ 6.9 Hz, H-7), 3.98 (dd, 1H, $J_{2,3}$ 10.1, $J_{2,1}$ 3.7 Hz, H-2), 3.94-3.87 (m, 3H, sugar H), 3.80 (broad d, 1H, *J* 2.3 Hz, H-4 or H-5), 3.42-3.38 (m, 1H, sugar H), 3.30 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9 (C=O), 140.4 (C-d), 138.5, 138.4 (*ipso* C of benzyl groups); 136.3 (C-a), 135.9 (C-b), 134.9 (C-8), 130.2 (C-e), 128.4, 128.3, 128.0, 127.7, 127.6, 127.5 (Ar), 125.9 (C-f), 118.0 (C-9), 98.9 (C-1), 94.3 (C-c), 78.7, 76.5, 76.4 (sugar C), 73.9 (C-7), 73.7, 73.5 (Ph*C*H_2), 68.3 (sugar C), 55.3 (*C*H_3O), 41.2 (C-6); ESI(+)-MS *m/z* found: 644.1534, *m/z* calculated for $[C_{31}H_{34}INO_6 + H]^+$: 644.1509, *m/z* found: 666.1451, *m/z* calculated for $[C_{31}H_{34}INO_6 + Na]^+$: 666.1329, *m/z* found: 682.1188, *m/z* calculated for $[C_{31}H_{34}INO_6 + K]^+$: 682.1068. The reaction of the amine **15b** with 3-iodobenzoyl chloride furnished methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-α-D-glucopyranoside (**6**) (0.15 g, 0.24 mmol, 50%) as a white crystal; mp 120.1-121.7 °C; $[\alpha]_D$ +15,1 (*c* 1.58; $CHCl_3$); IR ν_{max}/cm^{-1}: 3290 (NH), 1640 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (t, 1H, $J_{b,d}$, $J_{b,f}$ 1.5 Hz, H-b), 7.82 (ddd, 1H, $J_{d,e}$ 7.8, $J_{d,b}$ 1.5, $J_{d,f}$ 1.1 Hz, H-d), 7.67 (ddd, 1H, $J_{f,e}$ 7.8, $J_{f,b}$ 1.5, $J_{f,d}$ 1.1 Hz, H-f), 7.26-7.37(m, 10H, Ar), 7.16 (t, 1H, $J_{e,d}$ $J_{e,f}$ 7.8 Hz, H-e), 6.40 (dd, 1 H, $J_{NH,6}$ 5.8, $J_{NH,6'}$ 4.4 Hz, N-*H*), 5.89-5.98 (m, 1H, H-8); 5.27 (dq, 1H, $J_{9,8\ trans}$ 17.2, $J_{9,9'}$, $J_{9,7}$, $J_{9,7'}$1.4 Hz, H-9), 5.17 (broad dd, 1H, $J_{9',8\ cis}$ 10.3, $J_{9',7}$ or $J_{9',9}$1.4 Hz; H-9'), 4.94 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.80 (d, 1H, J_{gem} 10.6 Hz, PhCH_2), 4.79 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.65 (d, 1H, J_{gem} 10.6 Hz, PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.34 (ddt, 1H, $J_{7,7'}$ 12.1, $J_{7,8}$ 6.8, $J_{7,9}$, $J_{7,9'}$ 1.4 Hz, H-7), 4.17 (ddt, 1H, $J_{7',7}$ 12.1, $J_{7',8}$ 6.0, $J_{7,9}$, $J_{7,9'}$ 1.4 Hz, H-7'), 3.94 (t, 1H, $J_{3,2}$, $J_{3,4}$ 9.4 Hz, H-3), 3.86 (ddd, 1H, $J_{6,6'}$ 13.7, $J_{6,5}$ 7.1, $J_{6,NH}$ 5.8 Hz, H-6), 3.73-3.77 (m, 1H, H-5), 3.59 (dt, 1H, $J_{6',6}$ 13.7, $J_{6',5}$ $J_{6',NH}$ 4.4 Hz, H-6'), 3.46 (dd, 1H, $J_{2,3}$ 9.4, $J_{2,1}$ 3.5 Hz, H-2), 3.39 (s, 3H, CH_3O), 3.21 (t, 1H, $J_{4,3}$, $J_{4,5}$ 9.4 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=O), 140.4 (C-d); 138.5, 138.1 (*ipso* C of benzyl groups), 136.4 (C-a), 135.9 (C-b), 134.6 (C-8), 130.2 (C-e), 127.7, 127.9, 128.1, 128.4, 128.5 (Ar), 126.0 (C-f), 117.6 (C-9), 98.1 (C-1), 94.3 (C-c), 78.9, 79.8, 81.7 (sugar C), 75.8 (Ph*C*H_2), 74.0 (C-7), 73.4 (Ph*C*H_2), 68.9 (sugar C), 55.4 (*C*H_3O), 40.5 (C-6); ESI(+)-MS *m/z* found: 644,1597, *m/z* calculated for $[C_{31}H_{34}INO_6 + H]^+$: 644.1509, *m/z* found: 666,1329, *m/z* calculated for $[C_{31}H_{34}INO_6 + Na]^+$: 666.1329, *m/z* found: 682.1193, calculated for $[C_{31}H_{34}INO_6 + K]^+$: 682.1068. By treating the amine **15c** with 3-iodobenzoyl chloride was obtained methyl 2,3-di-*O*-benzyl-6-deoxy-6-(3-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**9**) (0.21 g, 0.32 mmol, 66%) as a white crystal; mp 70.3-72.0 °C; $[\alpha]_D$ +12.7 (*c* 1.71; $CHCl_3$); IR ν_{max}/cm^{-1}: 3295 (NH), 1639 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H, H-b), 7.82 (d, 1H, $J_{d,e}$ 7.8 Hz, H-d), 7.67 (d, 1H, $J_{f,e}$ 7.8 Hz, H-f), 7.26-7.36 (m, 10H, Ar), 7.16 (t, 1H, $J_{e,d}$, $J_{e,f}$ 7.8 Hz, H-e), 6.33 (broad t, 1 H, N-*H*), 5.74-5.84 (m, 1H, H-10), 5.00 (dd, 1H, $J_{11',10\ trans}$ 17.1, $J_{11,11'}$ or $J_{11',9}$ 1.5 Hz, H 11'); 4.96 (d, 1H, $J_{11,10\ cis}$ 10.5 Hz, H-11), 4.94 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.79 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.78 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.64 (d, 1H, J_{gem} 12.1 Hz, PhCH_2),

4.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.90 (t, 1H, $J_{3,2}$, $J_{3,4}$ 9.4 Hz, H-3), 3.56-3.86 (m, 5H, 2 H-7, H-5 and 2 H-6), 3.45 (dd, 1H, $J_{2,3}$ 9.4, $J_{2,1}$ 3.5 Hz, H-2), 3.30 (s, 3H, CH_3O), 3.12 (t, 1 H, $J_{4,3}$, $J_{4,5}$ 9.3 Hz, H-4), 2.08-2.14 (m, 2H, H-9), 1.61-1.73 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (C=O), 140.4 (C-d), 138.6, 138.1 (*ipso* C of benzyl groups), 138.20 (C-10), 136.6 (C-a), 136.0 (C-b), 130.3 (C-e), 127.7, 127.9, 128.0, 128.1, 128.4, 128.5 (Ar), 126.0 (C-f), 114.8 (C-11), 98.2 (C-1), 94.3 (C-c), 79.6, 79.8, 81.7 (sugar C), 75.8, 73.5 (Ph*C*H$_2$), 72.9 (C-7), 69.1 (sugar C), 55.4 (*C*H$_3$O), 40.5 (C-6), 30.3 (C-9), 29.6 (C-8); ESI(+)-MS *m/z* found: 672,1500, *m/z* calculated for $[C_{33}H_{38}INO_6 + H]^+$: 672.1821, *m/z* found: 689,1880, calculated for $[C_{33}H_{38}INO_6 + H_2O]^+$: 689.1850. The reaction of the amine **15c** with 2-iodobenzoyl chloride gave the 2-iodobenzamide methyl 2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-4-*O*-(1-pentenyl)-α-D-glucopyranoside (**10**) (0.28 g, 0.41 mmol, 86%) as a white crystal; mp 130.0-132.1 ºC; $[\alpha]_D$ +18,2 (*c* 0.75; $CHCl_3$); IR ν_{max}/cm^{-1}: 3275 (NH), 1648 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H, H-c), 7.26-7.42 (m, 12H, Ar), 7.07-7.11(m, 1H, H-d), 6.03 (broad t, 1 H, N-*H*), 5.75-5.82 (m, 1H, H-10), 5.00 (dd, 1H, $J_{11',10\ trans}$ 17.1, $J_{11',11}$ or $J_{11',9}$1.5 Hz, H 11'), 4.94 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.93 (d, 1H, $J_{10,11\ cis}$ 10.5 Hz, H-11), 4.79 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.78 (d, 1H, J_{gem} 12.2 Hz, PhCH_2), 4.63 (d, 1H, J_{gem} 12.2 Hz, PhCH_2), 4.52 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 3.89 (t, 1H, $J_{3,2}$, $J_{3,4}$ 9.3 Hz, H-3), 3.42-3.87 (m, 5H, 2 H-7, H-5 and 2 H-6), 3.44 (dd, 1H, $J_{2,3}$ 9.3, $J_{2,1}$ 3.4 Hz, H-2), 3.38 (s, 3H, CH_3O), 3.23 (t, 1H, $J_{4,3}$, $J_{4,5}$ 9.3 Hz, H-4), 2.08-2.14 (m, 2H, H-9), 1.63-1.76 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2 (C=O), 142.3 (C-a); 140.0 (C-c), 138.7, 138.1 (*ipso* C of benzyl groups), 138.4 (C-10), 131.1 (C-d), 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5 (Ar), 114.7 (C-11), 98.2 (C-1), 92.3 (C-b), 79.4, 79.7, 81.9 (sugar C), 75.8, 73.4 (Ph*C*H$_2$), 73.1 (C-7), 69.1 (sugar C),. 55.5 (*C*H$_3$O), 40.3 (C-6), 30,3 (C-9), 29.6 (C-8); ESI(+)-MS *m/z* found: 672,1800, *m/z* calculated for $[C_{33}H_{38}INO_6 + H]^+$: 672.1821, *m/z* found: 689,1880, calculated for $[C_{33}H_{38}INO_6 + H_2O]^+$: 689.1850.

*Radical reaction of compounds **5**, **6**, **9** and **10***

To a stirring and boiling solution of 0.31 mmol of benzamide (0.20 g for **5** and **6**; 0,21 g for **9** and **10**) in nitrogen-saturated dry solvent was slowly added a solution of Bu_3SnH (0.13 mL, 0.14 g, 0.47 mmol) and AIBN (*ca.* 20 mg) in nitrogen-saturated dry solvent (from 10 to 15% of the total volume) *via* an addition funnel. The reaction mixture was heated under reflux and nitrogen atmosphere for a further 1 h. Subsequent solvent removal and column chromatography (silica gel and 10% m/m of KF) gave the compounds **6**, **16**, **17**, **18**, **19**, **20** and **21**, that were eluted with a mixture of hexane:ethyl acetate. Details of each reaction are shown in the table 2.

The biphenyl compound **19** was obtained as a white solid; mp 28.1-29.3 ºC; $[\alpha]_D$ +46.6 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (t, 1H, $J_{b,d}$, $J_{b,f}$ 1.5 Hz, H-b), 7.71 (dt, 1H, $J_{d,e}$ 7.3, $J_{d,b}$, $J_{d,f}$ 1.5 Hz, H-d), 7.67 (dt, 1H, $J_{f,e}$ 7.7, $J_{f,b}$, $J_{f,d}$ 1.5 Hz, H-f), 7.58 (d, 2H, $J_{b',c'}$ 7.0 Hz, H-b'), 7.49-7.43 (m, 3H, H-e, Ar); 7.39-7.25 (m, 11H, Ar), 6.69-6,68 (m, 1H, N-*H*), 5.93 (dddd, 1H, $J_{8,9\ trans}$17.2, $J_{8,9'\ cis}$ 10.2, $J_{8,7}$ 6.6, $J_{8,7'}$ 5.1 Hz, H-8), 5.23 (dd, 1H, $J_{9,8\ trans}$ 17.2, $J_{9,9'}$ or $J_{9,7}$ 1.5 Hz, H-9), 5.16 (broad d, 1H, $J_{9',8\ cis}$

Table 2. The Bu_3SnH-mediated reactions of compounds **5**, **6**, **9** and **10**

Substrate	Benzene / mL		Addition time / h	Products
	substrate	AIBN/Bu_3SnH		
5	22	3.7	1.5	**16** (0.18 mmol) 58%
5	87	15	5	**19** (0.11 mmol) 35%
5	1 (+ 86 mL of Ch)	7.5 (+ 7.5 mL of Ch)	3.5	**16** (0.22 mmol) 71%
6	32	7	2	**17** (0.19 mmol) 61% **20** (0.06 mmol) 19%
6	66	11.5	5	**6** (0.13 mmol) 42% **20** (0.04 mmol) 13%
9	31	8	1.5	**18** (0.18 mmol) 58%
9	62	15.5	3	**21** (0.21 mmol) 68%
9	1 (+ 61 mL of Ch)	7.5 (+ 8 mL of Ch)	3	**18** (0.30 mmol) 97%
9	1 (+ 61 mL of CH_3CN)	15.5 mL of CH_3CN	3	**18** (0.17 mmol) 55%
10	31	8	1.5	**18** (0.21 mmol) 68%
10	62	15.5	4	**18** (0.20 mmol) 65%

Ch= cyclohexane.

10.2 Hz, H-9'), 4.84 (d, 1 H, J_{gem} 12.1 Hz, PhCH_2), 4.83 (d, 1H, J_{gem} 12.3 Hz, PhCH_2), 4.71 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.67 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.66 (d, 1H, J_{gem} 12.3 Hz, PhCH_2), 4.48 (broad dd, 1H, $J_{7',7}$ 12.4, $J_{7',8}$ 5.1 Hz, H-7'), 4.13 (broad dd, 1H, $J_{7,7'}$ 12.4, $J_{7,8}$ 6.6 Hz, H-7), 3.99 (dd, 1H, $J_{2,3}$ 10.0, $J_{2,1}$ 3.4 Hz, H-2), 3.95-3.89 (m, 3H, sugar H), 3.82-3.81 (broad d, 1H, *J* 2.6 Hz, sugar H), 3.46-3.37 (m, 1H, sugar H), 3.30 (3H, s, CH_3O); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.5 (C=O), 141.7 (C-c); 140.1 (C-a'), 138.5, 138.4 (*ipso* C of benzyl groups), 134.9 (C-8), 130.2 (C-d), 129.7 (C-a), 129.0, 128.9,128.4, 128.3, 128.0, 127.7, 127.7, 127.6, 127.5, 127.1 (Ar), 125.7 (C-b), 125.4 (C-f), 117.9 (C-9), 98.8 (C-1), 78.7, 76.3, 76.2 (sugar C), 73.9 (C-7), 73.6, 73.4 (Ph*C*H_2), 68.5 (sugar C); 55.2 (*C*H_3O), 41.0 (C-6); ESI(+)-MS *m/z* found: 594.2786, *m/z* calculated for $[C_{37}H_{39}NO_6 + H]^+$: 594.2856, *m/z* found: 616.2792, *m/z* calculated for $[C_{37}H_{39}NO_6 + Na]^+$: 616.2675, *m/z* found: 632.2346, *m/z* calculated for $[C_{37}H_{39}NO_6 + K]^+$: 632.2414. The uncyclized product **16** was obtained as a white solid; mp 101.6-105.5 °C (lit.[7] oil); $[\alpha]_D$ +48.2 (*c* 1.05, $CHCl_3$) (lit.[7] +53.8, *c* 1.30, $CHCl_3$); IR ν_{max}/cm^{-1}: 3315 (NH), 1639 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, 2H, $J_{b,c}$ 6.9, $J_{b,d}$ 1.6 Hz, H-b), 7.48 (tt, 1H, $J_{d,c}$ 7.3, $J_{d,b}$ 1.6 Hz, H-d), 7.43-7.41 (m, 2H, H-c), 7.36-7.25 (m, 10H, Ar), 6.65 (dd, 1H, $J_{NH,6}$ 7.2, $J_{NH,6'}$ 3.4 Hz, N-*H*), 5.92 (dddd, 1H, $J_{8,9\ trans}$ 17.2, $J_{8,9'\ cis}$ 10.2, $J_{8,7}$ 6.9, $J_{8,7'}$ 5.3 Hz, H-8), 5.24 (dq, 1H, $J_{9,8\ trans}$ 17.2, $J_{9,9'}$, $J_{9,7'}$, $J_{9,7'}$ 1.5 Hz, H-9), 5.18 (dd, 1H, $J_{9',8\ cis}$ 10.2, $J_{9',9}$ or $J_{9',7}$ 1.5 Hz, H-9'), 4.84 (d, 1H, J_{gem} 12.0 Hz, PhCH_2), 4.83 (d, 1H, J_{gem} 11.6 Hz, PhCH_2), 4.71 (d, 1H, J_{gem} 11.6 Hz, PhCH_2), 4.67 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.66 (d, 1H, J_{gem} 12.0 Hz, PhCH_2), 4.47 (ddt, 1H, $J_{7',7}$ 12.5, $J_{7',8}$ 5.3, $J_{7',9}$, $J_{7',9'}$ 1.5 Hz, H-7'), 4.12 (dd, 1H, $J_{7,7'}$ 12.5, $J_{7,8}$ 6.9 Hz, H-7), 3.98 (dd, 1H, $J_{2,3}$ 10.1, $J_{2,1}$ 3.5 Hz, H-2), 3.92-3.88 (m, 3H, sugar H), 3.81-3.80 (m, 1H, sugar H), 3.43-3.36 (m, 1H, sugar H), 3.29 (s, 3H, CH_3O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6 (C=O), 138.5, 138.4 (*ipso* C of benzyl groups), 134.9 (C-8), 134.3 (C-a), 131.5 (C-d), 128.6 (C-c), 128.4, 128.3, 128.0, 127.7, 127.6, 127.5 (Ar), 126.8 (C-b), 117.8 (C-9), 98.8 (C-1), 78.7, 76.4, 76.2 (sugar C), 73.9 (C-7), 73.6, 73.4 (Ph*C*H_2), 68.5 (sugar C); 55.2 (*C*H_3O), 41.0 (C-6); ESI(+)-MS *m/z* found: 518.2805, *m/z* calculated for $[C_{31}H_{35}NO_6 + H]^+$: 518.2543, *m/z* found: 540.2753, *m/z* calculated for $[C_{31}H_{35}NO_6 + Na]^+$: 540.2362, *m/z* found: 556.2657, *m/z* calculated for $[C_{31}H_{35}NO_6 + K]^+$: 556.2101. The biphenyl compound **20** was obtained as a white solid; mp 64.7-69.9 °C; $[\alpha]_D$ +17.6 (*c* 1.56, $CHCl_3$); IR ν_{max}/cm^{-1}: 3316 (NH), 1641 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (broad s, 1H, H-b), 7.79-7.67 (m, 2H, Ar), 7.58 (d, 1H, J_{ortho} 7.9 Hz, Ar), 7.51-7.44 (m, 2H, Ar), 7.26-7.39 (m, 11H, Ar), 6.46 (broad s,1H, N-*H*), 5.83-5.97 (m, 1H, H-8), 5.27 (d, 1H, $J_{9,8\ trans}$ 17.3 Hz, H-9), 5.14 (d, 1H, $J_{9',8\ cis}$ 9.6 Hz, H-9'), 4.93 (d, 1H, J_{gem} 10.6 Hz, PhCH_2), 4.77-4.80 (m, 2H, PhCH_2), 4.64 (d, 1H, J_{gem} 12.3 Hz, PhCH_2), 4.35 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.34 (dd, 1H, $J_{7,7'}$ 11.3, $J_{7,8}$ 5.0 Hz, H-7), 4.18 (dd, 1H, $J_{7',7}$ 11.3, $J_{7',8}$ 5.2 Hz, H-7'), 3.95 (t, 1H, $J_{3,2}$, $J_{3,4}$ 9,2 Hz, H-3), 3.85-3.88 (m, 1H, H-6), 3.76-3.79 (m, 1H, H-5), 3.65-3.68 (m, 1H, H-6'), 3.46 (dd, 1H, $J_{2,3}$ 9.2, $J_{2,1}$ 3.4 Hz, H-2), 3.22-3.39 (m, 4H, CH_3O, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C=O), 141.8 (C-c or C-a'), 140.3 (C-a' or C-c), 138.6, 138.1 (*ipso* C of benzyl groups), 135.2 (C-a), 134.7 (C-8), 125.5, 125.9, 127.2, 127.5, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.9, 129.0, 130.2 (Ar), 117.5 (C-9), 98.2 (C-1), 81.7 (C-3), 79.9 (C-2), 79.0 (C-4), 75.8 (Ph*C*H_2), 74.1 (C-7), 73.5 (Ph*C*H_2), 69.1 (C-5), 55.3 (*C*H_3O), 40.4 (C-6); ESI(+)-MS *m/z* found: 594.2786, *m/z* calculated for $[C_{37}H_{39}NO_6 + H]^+$: 594.2856, *m/z* found: 616.2792, *m/z* calculated for $[C_{37}H_{39}NO_6 + Na]^+$: 616.2675. The uncyclized product **17** was obtained as a white solid; mp 146.5-151.4 °C (lit.[6] 148-151 °C); $[\alpha]_D$ +16.5 (*c* 2.66, $CHCl_3$) (lit.[6] +19, *c* 2.70, $CHCl_3$); IR ν_{max}/cm^{-1}: 3269 (NH), 1639 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 2H, $J_{b,c}$ 8.2 Hz, H-b), 7.43 (d, 1H, J_{ortho} 7.6 Hz, Ar), 7.36-7.26 (m, 12H, Ar), 6.35 (broad s,1H, N-*H*), 5.90 (m,1H, H-8), 5.27 (dd, 1H, $J_{9,8\ trans}$ 17,2, $J_{9,9}$ 1.4 Hz, H-9), 5.15 (d, 1H, $J_{9',8\ cis}$ 10.6 Hz, H-9'), 4.94 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.81-4.78 (m, 2H, PhCH_2), 4.65 (d, 1H, J_{gem} 12.1 Hz, PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.33 (dd, 1H, $J_{7,7'}$ 12.0, $J_{7,8}$ 5.6 Hz, H-7), 4.18 (dd, 1 H, $J_{7',7}$ 12,3, $J_{7',8}$ 5.9 Hz, H-7'), 3.94 (t, 1 H, $J_{3,2}$, $J_{3,4}$ 9.3 Hz, H-3), 3.84 (m, 1H, H-6), 3.74-3.78 (m, 1H, H-5), 3.59 (dt, 1H, $J_{6',6}$ 13.2, $J_{6',5}$, $J_{6',NH}$ 3.9 Hz, H-6'), 3.46 (dd, 1 H, $J_{2,3}$ 9.3, $J_{2,1}$ 3.5 Hz, H-2), 3.39 (3H, s, CH_3O), 3.23 (t, 1H, $J_{4,3}$, $J_{4,5}$ 9.3 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 (C=O), 138.6, 138.2 (*ipso* C of benzyl groups), 134,7 (C-8); 134.5 (C-a), 131.5, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 126.9 (Ar), 117.5 (C-9), 98.2 (C-1), 81.7 (C-3), 79.8 (C-2), 78.9 (C-4), 75.9 (Ph*C*H_2), 74.0 (C-7), 73.5 (Ph*C*H_2), 69.1 (C-5), 55.3 (*C*H_3O), 40.4 (C-6); ESI(+)-MS *m/z* found: 518.2445, *m/z* calculated for $[C_{31}H_{35}NO_6 + H]^+$: 518.2543, *m/z* found: 540.2319, *m/z* calculated for $[C_{31}H_{35}NO_6 + Na]^+$: 540.2362, *m/z* found: 556.2130, *m/z* calculated for $[C_{31}H_{35}NO_6 + K]^+$: 556.2101. The biphenyl compound **21** was obtained as a white solid; mp 97.2-98.8 °C; $[\alpha]_D$ +15.2 (*c* 1.71, $CHCl_3$); IR ν_{max}/cm^{-1}: 3324 (NH), 1635 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H, H-b), 7.71 (d, 1H, $J_{d,e}$ 7.6 Hz, H-d), 7.67 (d, 1H, $J_{e,f}$ 7.6 Hz, H-f), 7.60 (broad d, 2H, $J_{b',c'}$ 7.6 Hz, H-b'), 7.49 (t, 1H, $J_{e,d}$, $J_{e,f}$ 7.6 Hz, H-e), 7.46 (t, 2H, $J_{c',d'}$, $J_{c',b'}$ 7.6 Hz, H-c'), 7.25-7.39 (m, 11H, Ar), 6.44 (broad t,1H, N-*H*), 5.73-5.83 (m, 1H, H-10), 5.00 (d, 1H, $J_{11,10\ trans}$ 17.2 Hz, H-11'), 4.94 (d, 1H,

J_{gem} 10.8 Hz, PhCH_2), 4.92 (d, 1H, $J_{11,10\,cis}$ 10.0 Hz, H-11), 4.78 (broad d, 2H, PhCH_2), 4.64 (d, 1H, J_{gem} 12.0 Hz, PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.91 (t, 1H, $J_{3,2}$, $J_{3,4}$ 9,2 Hz, H-3), 3.60-3.85 (m, 5H, 2 H-7, 2 H-6 and H-5), 3.45 (dd, 1H, $J_{2,3}$ 9.2, $J_{2,1}$ 3.5 Hz, H-2), 3.40 (s, 3H, CH_3O), 3.15 (t, 1H, $J_{4,5}$, $J_{3,4}$ 9.2 Hz, H-4), 2.09-2.14 (m, 2H, H-9), 1.64-1.73 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C=O), 141.8 (C-c), 140.3 (C-a'), 138.6, 138.1 (*ipso* C of benzyl groups), 138.2 (C-10), 135.2 (C-a), 130.2 (C-d), 129.0 (C-e ou C-c'), 128.9 (C-e ou C-c'), 127.7, 127.8, 128.0, 128.1, 128.4, 128.5 (Ar), 127.2 (C-b'), 125.9 (C-b), 125.4 (C-f), 114.4 (C-11), 98.2 (C-1), 81.7 (C-3), 80.0 (C-2), 79.6 (C-4), 75.8, 73.5 (Ph*C*H$_2$), 72.9 (C-7), 69.3 (C-5), 55.3 (*C*H$_3$O), 40.5 (C-6), 30.3 (C-9), 29.6 (C-8); ESI(+)-MS *m/z* found: 622.3160, *m/z* calculated for $[C_{39}H_{43}NO_6 + H]^+$: 622.3170, *m/z* found: 644.3070, *m/z* calculated for $[C_{39}H_{43}NO_6 + Na]^+$: 644.2990. The hydrogenolysis product **18** was obtained as a white solid; mp 62.2-67.0 °C; $[\alpha]_D$ +14.1 (*c* 2.10, $CHCl_3$); IR ν_{max}/ cm^{-1}: 3287 (NH), 1638 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (broad d, 2H, J_{b-c} 7.3 Hz, H-b), 7.49 (broad t, 1H, J_{d-c} 7.3 Hz, H-d), 7.42 (broad t, 2H, $J_{c,d}$, $J_{c,b}$ 7.3 Hz, H-c), 7.29-7,36 (m, 10H, Ar), 6.36 (broad t,1H, N-*H*), 5.73-5.82 (m,1H, H-10), 5.00 (dd, 1H, $J_{11,10\,trans}$ 17,1, $J_{11',11}$ or $J_{11',9}$ 1.6 Hz, H-11'), 4.93 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.92 (d, 1H, $J_{11,10\,cis}$ 10.1 Hz, H-11), 4.79 (d, 1H, J_{gem} 12.2 Hz, PhCH_2), 4.78 (d, 1H, J_{gem} 10.7 Hz, PhCH_2), 4.65 (d, 1H, J_{gem} 12.2 Hz, PhCH_2), 4.57 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.91 (t, 1 H, $J_{3,2}$, $J_{3,4}$ 9.2 Hz, H-3), 3.60-3.84 (m, 5H, 2 H-7, 2 H-6 and H-5), 3.46 (dd, 1 H, $J_{2,3}$ 9.3, $J_{2,1}$ 3.5 Hz, H-2), 3.37 (s, 3H, CH_3O), 3.15 (t, 1H, $J_{4,3}$, $J_{4,5}$ 9.2 Hz, H-4), 2.08-2.14 (m, 2H, H-9), 1.58-1.72 (m, 2H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C=O), 138.6, 138.2 (*ipso* C of benzyl groups), 138.3 (C-10); 134.6 (C-a), 131.5 (C-b), 128.6, 128.4, 128.1, 128.0, 127.9, 127.6 (Ar), 126.8 (C-d), 114.7 (C-11), 98.2 (C-1), 81.7 (C-3), 79.8 (C-2), 79.6 (C-4), 75.9, 73.5 (Ph*C*H$_2$), 72.9 (C-7), 69.3 (C-5), 55.3 (*C*H$_3$O), 40.4 (C-6), 30.3 (C-9), 29.6 (C-8); ESI(+)-MS *m/z* found: 546.2940, *m/z* calculated for $[C_{33}H_{39}NO_6 + H]^+$: 546.2940, *m/z* found: 568.3530, *m/z* calculated for $[C_{33}H_{39}NO_6 + Na]^+$: 568.2670, *m/z* found: 584.2400, *m/z* calculated for $[C_{33}H_{39}NO_6 + K]^+$: 556.2410.

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