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Article

tri-*n*-Butyltin Hydride-Mediated Radical Reaction of a 2-Iodobenzamide: Formation of an Unexpected Carbon-Tin Bond

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A reação radicalar mediada por hidreto de tri-*n*-butilestanho de 2,3-di-*O*-benzil-4-*O*-*trans*-cinamil-6-desoxi-6-(2-iodobenzoilamino)-α-D-galactopyranosídeo de metila levou à formação de um produto inesperado, o 2,3-di-*O*-benzil-4-*O*-*trans*-cinamil-6-desoxi-6-(2-tri-*n*-butilestanhobenzoilamino)-α-D-galactopyranosídeo de metila. A estrutura do produto foi elucidada por meio das espectrometrias de RMN unidimensionais (^{1}H, ^{13}C e DEPT) e bidimensionais (COSY e HMQC) e confirmada por espectrometria de massas. Foram apresentadas propostas de mecanismos para explicar a formação do derivado organoestanho.

The tri-*n*-butyltin hydride-mediated reaction of methyl 2,3-di-*O*-benzyl-4-*O*-*trans*-cinnamyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside afforded an unexpected aryltributyltin compound. The structure of this new tetraorganotin(IV) product has been elucidated by ^{1}H, ^{13}C NMR spectroscopy, COSY and HMQC experiments and electrospray ionization mass spectrometry (ESI-MS). The formation of this new compound *via* a radical coupling reaction and a radical addition-elimination process is discussed.

Keywords: tetraorganotin, arylstannane, aryl radical cyclization, 2-iodobenzamide

Introduction

In our studies of Bu_3SnH-mediated radical cyclizations, we have applied unsaturated organohalides to synthesize large- and medium-size heterocycles.[1-8] Most particularly, *ortho*-iodobenzamides bearing a side allyloxy group have been used to form benzomacrolactams with 11-, 12- and 20-membered ring *via* regioselective *endo* aryl radical cyclization.[1-5] In this context, the benzamide methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside (**1**) was found to give the benzomacrolactam **2** owing to 11-*endo* cyclization in 32% yield.[2]

To continue these studies, we applied the Bu_3SnH-mediated radical reaction in an attempt to form the benzomacrolactams **3** and/or **4** from methyl 2,3-di-*O*-benzyl-4-*O*-*trans*-cinnamyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside (**5**), a cinnamylated analogue of **1**. Despite our knowledge of preferential *endo* cyclization mode over the *exo*-mode in macrocyclization reactions,[1-5,9-16] we expected that 10-*exo* cyclization could also occur due to the higher stability of the benzyl radical. This hypothesis was supported by the observation that precursors with cinnamyl group provided macrocycle intermediates resulting from 10-*exo* carbocyclization.[6] Moreover, the cinnamyl moiety of **5** would generate a new stereogenic center upon 10-*exo* or 11-*endo* cyclization, hence the stereoselectivity of the reaction could be evaluated. In fact, the tri-*n*-butyltin hydride-mediated reaction of **5** afforded an unexpected aryltributyltin compound.

Results and Discussion

To prepare the iodobenzamide **5**, the C-4 and C-6 hydroxyl groups of methyl α-D-galactopyranoside were protected as benzylidene acetal[17] and the C-2 and C-3 hydroxyl groups were *O*-benzylated.[18] Removal of the benzylidene group[19] following by regioselective replacement of the hydroxyl group at C-6 by iodine atom,[2,20] substitution

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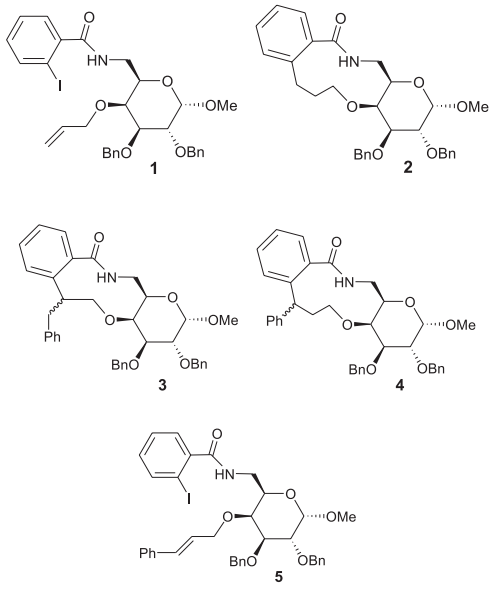


of iodine atom by azido group[2,21] and *O*-cinnamylation of C-4 hydroxyl group[22] gave the methyl 6-azido-2,3-di-*O*-benzyl-4-*O*-*trans*-cinnamyl-6-deoxy-α-D-galactopyranoside (**6**). Selective reduction of the azido group[23] gave the expected amine **7**, which upon treatment with 2-iodobenzoyl chloride[24] furnished the desired iodobenzamide **5** (Scheme 1).

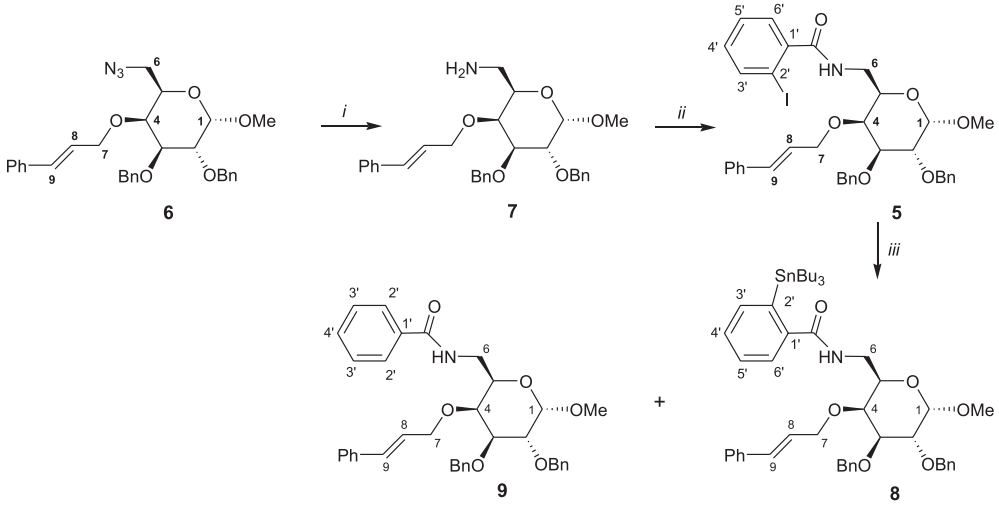
The radical reaction was carried out with slow addition of Bu_3SnH/AIBN to a benzene solution of **5** and very low concentrations of both **5** and Bu_3SnH (0.013 mol L^{-1}). These reaction conditions are recommended to improve the formation of cyclized products and to decrease the intermolecular reactions and the rate of hydrogen atom transfer to uncyclized radicals.[25-28] Two main products were formed in the radical reaction: the unexpected tetraorganotin(IV) compound **8** in 29% yield and the uncyclized reduced product **9** in 27% yield (Scheme 1).

The hydrogenolysis product **9** was readily identified from its ^1H and ^{13}C NMR data. The structure of **8** required a detailed analysis of the NMR spectra (^1H, ^{13}C and DEPT) and connectivity studies by COSY and HMQC experiments. The NMR spectra indicated the presence of a single aromatic hydrogen (δ 7.63) more deshielded than the others eighteen aromatic hydrogens and five *ipso* carbons. Two of these *ipso* carbon atoms show chemical shifts compatibles with aryl carbons bound to tin and *ortho* to tin[29,30] (δ 139.8 and 145.7). Signals of 3 *n*-butyl moieties bound to Sn,[29-31] cinnamyloxy group, methyl galactopyranoside moiety and benzamide were also observed. Table 1 lists selected data of ^1H and ^{13}C spectra for iodobenzamide **5**, tetraorganotin compound **8** and hydrogenolysis product **9**.

The ESI(+)-MS spectrum was also found to be fully compatible with the structure of the organotin product **8**. It shows major ions due to cationized forms of **8**, that is, of *m/z* 906.3898 (*m/z* 906.3743 calculated for $[C_{49}H_{65}NO_6Sn + Na]^+$) and *m/z* 922.3260 (*m/z* 922.3481 calculated for $[C_{49}H_{65}NO_6Sn + K]^+$) with a cluster of isotopologue ions characteristic for the presence of Sn multi-isotope element.

Only two articles that describe the isolation of aryltri-*n*-butyltin compounds, as by-products, from Bu_3SnH-mediated aryl radical cyclization were found in the literature.[32,33] Moreover, the formation of this kind of stannylated compound was not observed in our previous studies.[1-5] The formation of aryltributyltin compounds is described using other methods.[34,35]

One possible rationalization for the formation of the tri-*n*-butylaryltin compound **8** is *via* the coupling of the aryl and tri-*n*-butyltin radicals, since chain termination steps can occur in radical reactions.[27,36] Other plausible proposals can not be ruled out. For instance, the formation



Scheme 1. Reagents, conditions and yields. *i*: $LiAlH_4$, THF, rt; *ii*: 2-iodobenzoyl chloride, 10% $NaOH_{(aq.)}$, CH_2Cl_2, rt, 44% (over the steps *i* and ii); *iii*: Bu_3SnH, AIBN, benzene, reflux, **8** 29%, **9** 27%.

Table 1. Selected ^{1}H and ^{13}C NMR data for compounds **5**, **8** and **9**

Compound	^{1}H NMR δ		^{13}C NMR δ		
	aromatic H	*n*-butyl H[a]	C=O	*ipso* C	*n*-butyl C[a]
5	7.80, 1 H, d, 7.9 Hz (3')	–	169.5	142.0 (1') 138.6, 138.5 (benzyl) 136.4 (cinnamyl) 92.4 (2')	–
9	7.68, 2 H, d, 7.4 Hz (2')	–	167.7	138.8, 138.6 (benzyl) 136.6 (cinnamyl) 134.4 (1')	–
8	7.63, 1 H, d, 6.5 Hz (3' or 6')	1.62-1.40, 6 H, m (β) 1.34-1.19, 12 H (α, γ) 0.84, 9 H, 7.1 Hz (δ)	169.7	145.7, 139.8 (1', 2')* 138.8, 138.7 (benzyl) 136.6 (cinnamyl)	29.5 (β) 27.7 (γ) 13.9 (δ) 11.6 (α)

*Respectively or not. [a] $\overset{\delta}{CH_3}\overset{\gamma}{CH_2}\overset{\beta}{CH_2}\overset{\alpha}{CH_2}-Sn$

of **8** could be also attributed to the aromatic substitution by reaction of the reduced product **9** and the tri-*n*-butyltin radical in an addition-elimination process.[37]

The formation of **8**, as the main product, by intermolecular reaction(s) was unexpected for us, since the reaction was carried out at low concentration of radicals, either by working at high dilution and by slow addition of Bu_3SnH. Additionally, the benzamide **1,** which differs from **5** by the lack of the phenyl group, at the same reaction conditions gave the benzomacrolactam **2**.[2]

To favour the desired cyclization reaction at the expense of reduction at the aryl radical to give **9** and formation of organotin compound **8**, the reaction of **5** and Bu_3SnH was carried out under two different conditions that were expected to disfavour intermolecular and reduction reactions.[25-28] When the addition of Bu_3SnH/AIBN solution was made over a longer period (2.5 hours instead of 1 h) the yields of **8** and **9** reduced to 20% and 21%, respectively. When the concentration of Bu_3SnH was reduced to 0.0065 mol L^{-1} and the addition of the reagents was maintained to 2.5 hours none of **8** was formed and the hydrogenolysis product **9** was obtained in 25% yield. In both experiments none of the cyclized product was isolated.

The absence of cyclization product from **5**, in contrast with the radical reaction of **1**, can be attributed to the steric hindrance between the phenyl ring of the cinnamyl group and the attacking aryl radical in the preferential *endo*-mode. Other possible explanation for this would be the generation of aryl radical followed by intramolecular hydrogen-atom transfer from the allyl group to the aryl group with the formation of a stable cinnamyl radical, which undergoes reduction to give **9**.

In conclusion, Bu_3SnH-induced aryl radical cyclization of methyl 2,3-di-*O*-benzyl-4-*O*-*trans*-cinnamyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside (**5**) fails to proceed through the expected 10-*exo* and 11-*endo* modes that would afford the 10- and 11-membered lactams **3** and **4**, respectively. Instead, **5** gives the hydrogenolysis product **9** and the aryltributyltin compound **8**, as indicated by MS and NMR data.

Experimental

General procedures

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 a Mattson Instruments Galaxy 3000 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 spectra for mass measurements were taken using both positive- and negative-ion mode from 1:1 H_2O-MeOH solutions with addition of either a few microlitres of formic acid or ammonium hydroxide. 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 new carbohydrate derivatives **5**, **6** and **7** were prepared according to published procedures.[22-24] The radical reaction was carried out using standard procedure.[1,2,25,26]

*Methyl 6-azido-2,3-di-O-benzyl-4-O-trans-cinnamyl-6-deoxy-α-D-galactopyranoside (**6**)*

To a solution of methyl 6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-galactopyranoside (0.40 g, 1.0 mmol) in CH_2Cl_2 (8 mL) were added, under magnetic stirring, 50% (m/v) aqueous NaOH (3 mL) and Bu_4NBr (0.48 g, 1.5 mmol), as phase transfer catalyst. The mixture was stirred for 15 minutes. Cinnamyl bromide (0.51 g, 2.6 mmol) was added and the mixture was stirred for 18 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Standard work-up gave a residue, which was submitted to column chromatography. The compound **6** (0.45 g, 0.87 mmol, 87%), eluted with hexane-ethyl acetate 8:2 (v/v), was obtained as a syrup; $[\alpha]_D$ +22.5 (*c* 2.00, $CHCl_3$); IR ν_{max}/ cm^{-1}: 2100 (N_3); ^{1}H NMR (200 MHz, $CDCl_3$, δ, *J* Hz) 7.73-7.24 (15 H, m, Ar); 6.52 (1 H, d, $J_{9,8}$ 15.9, 9-H); 6.32-6.18 (1 H, m, 8-H); 4.87 (1 H, d, J_{gem} 11.8, one of PhCH_2); 4.85 (1 H, d, J_{gem} 11.8, one of PhCH_2); 4.54-4.75 (4 H, m, two of PhCH_2,1-H, one of 7-H); 4.26 (1 H, dd, J_{gem} 12.4 $J_{7,8}$ 6.9, one of 7-H); 4.00 (1 H, dd, $J_{2,3}$ 9.9 $J_{2,1}$ 3.4, 2-H); 3.92-3.91 (1 H, m, sugar H), 3.87-3.77 (2 H, sugar H); 3.60 (1 H, dd, J_{gem} 12.4, $J_{6,5}$ 7.9, one of 6-H); 3.40 (3 H, s, MeO); 3.19 (1 H, dd, $J_{6,5}$ 4.8, one of 6-H); ^{13}C NMR (50 MHz, $CDCl_3$, δ) 138.8, 138.6 (2 *ipso* C of benzyl groups); 136.7 (*ipso* C of cinnamyl group); 128.8, 128.6, 128.2, 128.0, 127.8, 127.7 (Ar); 126.2 (8-C); 99.0 (1-C); 78.8, 76.6, 75.5 (sugar C); 73.8, 73.7, 73.3 (2× Ph*C*H_2 and 7-C); 79.9 (sugar C); 55.4 (MeO); 51.5 (6-C).

*Methyl 6-amino-2,3-di-O-benzyl-4-O-trans-cinnamyl-6-deoxy-α-D-galactopyranoside (**7**)*

To a suspension of lithium aluminum hydride (48 mg, 1.3 mmol) in THF (5 mL) was added a solution of methyl 6-azido-2,3-di-*O*-benzyl-4-*O-trans*-cinnamyl-6-deoxy-α-D-galactopyranoside **6** (0.30 g, 0.58 mmol) in THF (4 mL). The solution was stirred for 24 h at room temperature. Water (2 mL), 5% (m/v) aqueous NaOH (1 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Standard work-up gave a residue which was not purified.

*Methyl 2,3-di-O-benzyl-4-O-trans-cinnamyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-galactopyranoside (**5**)*

To a solution of 2-iodobenzoyl chloride (0.40 g, 1.5 mmol) in CH_2Cl_2 (5 mL) were added 10% (m/v) aqueous NaOH (2 mL) and a solution of methyl 6-amino-2,3-di-*O*-benzyl-4-*O-trans*-cinnamyl-6-deoxy-α-D-galactopyranoside **7**, obtained as described above, in CH_2Cl_2 (5 mL). The mixture was stirred for 16 h at room temperature. 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 iodobenzamide **5** (0.18 g, 0.26 mmol, 44% from **6**), eluted with hexane-ethyl acetate 6:4 (v/v), was obtained as a white solid; mp 144.8-150.2 °C; $[\alpha]_D$ +20.4 (*c* 2.70, $CHCl_3$); IR ν_{max}/ cm^{-1}: 3250 (NH), 1650 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, δ, *J* Hz) 7.80 (1 H, d, $J_{3',4'}$ 7.9, 3'-H); 7.40-7.22 (17 H, m, Ar); 7.02-7.08 (1 H, m, Ar); 6.52 (1 H, d, $J_{9,8}$ 15.9, 9-H); 6.27 (1 H, dt, $J_{8,7}$= $J_{8,7'}$ 6.9, 8-H); 6.18 (1 H, dd, $J_{NH,6}$ 5.2, $J_{NH,6'}$ 3.6, N-*H*); 4.86 (1 H, d, J_{gem} 11.8, one of PhCH_2); 4.85 (1 H, d, J_{gem} 11.9, one of PhCH_2); 4.73 (1 H, d, J_{gem} 11.9, one of PhCH_2); 4.68 (1 H, d, J_{gem} 11.8, one of PhCH_2); 4.67 (1 H, d, $J_{1,2}$ 3.5, 1-H); 4.31 (1 H, dd, J_{gem} 12.4 $J_{7,8}$ 7.0, one of 7-H); 4.00 (1 H, dd, $J_{2,3}$ 9.7, $J_{2,1}$ or $J_{3,4}$ 3.5, 2-H or 3-H); 3.97-3.91 (4 H, m, sugar H, one of 7-H); 3.46-3.39 (2 H, m, sugar H); 3.37 (3 H, s, MeO); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 169.5 (C=O); 142.0 (1'-C); 140.0 (3'-C); 138.6, 138.5 (2 *ipso* C of benzyl groups); 136.4 (*ipso* C of cinnamyl group); 133.5 (9-C); 131.1, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.9, 127.7, 127.6 (Ar); 126.6 (8-C); 99.0 (1-C); 92.4 (2'-C); 78.6, 76.4, 76.3 (sugar C); 73.7, 73.6, 73.5 (2× Ph*C*H_2 and 7-C); 68.7 (sugar C); 55.8 (MeO); 40.9 (6-C); ESI(+)-MS *m/z* found: 720.1552, *m/z* calculated for $[C_{37}H_{38}INO_6 + H]^+$: 720.1822; *m/z* found: 742.1527, *m/z* calculated for $[C_{37}H_{38}INO_6 + Na]^+$: 742.1642.

*Radical reaction of compound **5***

To a stirring and boiling solution of compound **5** (0.20 g, 0.28 mmol) in nitrogen-saturated benzene (27 mL) was added a solution of Bu_3SnH (0.13 mL, 0.14 g, 0.49 mmol) and AIBN (18 mg) in nitrogen-saturated benzene (10 mL) *via* an addition funnel during 1 h. The reaction mixture was heated under reflux and nitrogen atmosphere for a further 1 h. Subsequent solvent removal and column chromatography gave, successively, the organotin compound **8** (72 mg, 0.082 mmol, 29%), eluted with hexane-ethyl acetate 8:2 (v/v), and the hydrogenolysis product **9** (45 mg, 0.076 mmol, 27%), eluted with hexane-ethyl acetate 6:4 (v/v). The organotin compound **8** was

obtained as a white solid; mp 47.5-50.0 °C; $[\alpha]_D$ + 9.9 (*c* 0.93, $CHCl_3$); IR ν_{max}/ cm^{-1}: 3350 (NH), 1610 (C=O); ^1H NMR (200 MHz, $CDCl_3$, δ, *J* Hz) 7.63 (1 H, d, J_{orto} 6.5, 3'-H or 6'-H); 7.41-7.13 (18 H, m, Ar, N-*H*); 6.54 (1 H, d, $J_{8,9}$ 16.2, 9-H); 6.36-6.31 (1 H, m, 8-H); 4.87 (1 H, d, J_{gem} 10.5, one of PhCH_2); 4.76-4.56 (4 H, m, 3 of PhCH_2, one of 7-H); 4.70 (1 H, d, $J_{1,2}$ 3.6, 1-H); 4.29 (1 H, dd, J_{gem} 11.9, $J_{7,8}$ 6.3, one of 7-H); 4.02 (1 H, dd, $J_{2,3}$ 9.5, 2-H); 3.94-3.88 (4 H, m, 5-H, 4-H, 3-H, one of 6-H); 3.50-3.35 (1 H, m, one of 6-H); 3.31 (3 H, s, MeO); 1.62-1.40 (6 H, m, $SnCH_2CH_2CH_2CH_3$); 1.34-1.19 (12 H, m, $SnCH_2CH_2CH_2CH_3$); 0,84 (9 H, t, *J* 7.1, CH_3 of *n*-butyl group); ^{13}C NMR (50 MHz, $CDCl_3$, δ) 169.7 (C=O); 145.7, 139.8 (1'-C, 2'-C); 138.8, 138.7 (2 *ipso* C of benzyl groups); 137.7 (3'-C); 136.6 (*ipso* C of cinnamyl group); 133.4 (9-C); 130.5, 128.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 126.8, 126.2 (Ar); 125.2 (8-C); 99.1 (1-C); 79.0, 76.7, 76.6 (2-C, 3-C, 4-C); 73.9, 73.7 (2× PhCH_2, 7-C); 68.8 (5-C); 55.6 (MeO); 41.2 (6-C); 29.5 ($SnCH_2CH_2CH_2CH_3$), 27.7 ($SnCH_2CH_2CH_2CH_3$); 13.9 (CH_3 of *n*-butyl group); 11.6 ($SnCH_2CH_2CH_2CH_3$); [ESI(+)-MS] *m/z* found: 906.3898, *m/z* calculated for $[C_{49}H_{65}NO_6Sn + Na]^+$: 906.3743; *m/z* found: 922.3260, *m/z* calculated for $[C_{49}H_{65}NO_6Sn + K]^+$: 922.3481. The uncyclized product **9** was obtained as a white solid; mp 49.1-51.7 °C; $[\alpha]_D$ +20.3 (*c* 0.45, $CHCl_3$); IR ν_{max}/ cm^{-1}: 3360 (NH), 1610 (C=O); ^1H NMR (200 MHz, $CDCl_3$, δ, *J* Hz) 7.68 (2 H, d, $J_{2',3'}$ 7.4, 2'-H); 7.39-7.25 (18 H, m, Ar); 6.69 (1 H, dd, $J_{NH,6}$ 7.1, $J_{NH,6'}$ 3.7, N-*H*); 6.53 (1 H, d, $J_{9,8}$ 15.9, 9-H); 6.29 (1 H, ddd, $J_{8,7}$ 6.8, $J_{8,7'}$ 5.8, 8-H); 4.87 (1 H, d, J_{gem} 11.7, one of PhCH_2); 4.86 (1 H, d, J_{gem} 12.0, one of PhCH_2); 4.76-4.64 (4 H, two of PhCH_2, 1-H, 7-H); 4.29 (1 H, dd, J_{gem} 12.5, $J_{7,8}$ 6.8, one of 7-H); 4.02 (1 H, dd, $J_{2,3}$ 9.7, $J_{2,1}$ 3.4, 2-H); 3.97-3.88 (4 H, m, 3-H, 4-H, 5-H, one of 6-H); 3.45(1 H, m, one of 6-H); 3.30 (3 H, s, MeO); ^{13}C NMR (50 MHz, $CDCl_3$, δ) 167.7 (C=O); 138.8, 138.6 (2 *ipso* C of benzyl group); 136.6 (*ipso* C of cinnamyl group); 134.4 (1'-C); 131.6, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 126.9 (Ar); 126.1 (8-C); 99.0 (1-C); 79.0, 76.6 (2-C, 3-C, 4-C); 73.8, 73.7 (2 x PhCH_2, 7-C); 68.6 (5-C); 55.5 (MeO); 41.2 (6-C); ESI(+)-MS *m/z* found: 594.2607, *m/z* calculated for $[C_{37}H_{39}NO_6 + H]^+$: 594.2856; *m/z* found: 616.2512, calculated for $[C_{37}H_{39}NO_6 + Na]^+$: 616.2675; *m/z* found: 632.2560, calculated for $[C_{37}H_{39}NO_6 + K]^+$: 632.2415.

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