Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 9901–9908

Synthesis of unexpected six-membered imides by free-radical carbocyclisation on carbohydrate templates

Renata B. de Oliveira,[a] José D. de Souza Filho,[a] Maria Auxiliadora F. Prado,[b] Marcos N. Eberlin,[c] Eduardo C. Meurer,[c] Leonardo S. Santos[c] and Ricardo J. Alves[b,*]

[a]*Departamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais (UFMG), Avenida Antônio Carlos 6627, Belo Horizonte, MG 31.270-901, Brazil*
[b]*Departamento de Produtos Farmacêuticos, Faculdade de Farmácia, Universidade Federal de Minas Gerais (UFMG), Avenida Antônio Carlos, 6627, Belo Horizonte, MG 31.270-901, Brazil*
[c]*Laboratório Thomson de Espectrometria de Massas, Instituto de Química, Universidade Estadual de Campinas (UNICAMP), Campinas, SP 13083-970, Brazil*

Received 9 April 2004; revised 13 August 2004; accepted 16 August 2004

Available online 11 September 2004

Abstract—Free-radical reactions of amido-esters anchored to a carbohydrate derived from methyl α-D-glucopyranoside afforded unexpected six-membered cyclic imides. Their structures were elucidated by ESI-MS/MS and NMR spectral analyses, and a mechanism for the formation of these imides is proposed.

1. Introduction

The use of carbohydrate derivatives in the synthesis of carbocycles via free-radical cyclisation reaction has been a theme of interest in our laboratory.[1–5] Encouraged by our previous studies on tri-*n*-butyltin-mediated radical carbocyclisation reaction of *o*-iodobenzamides, we decided to test this methodology for the synthesis of chiral polysubstituted macrocycles exploring the stereocontrolling properties of carbohydrates to create chirality at a 'site' outside the carbohydrate ring.

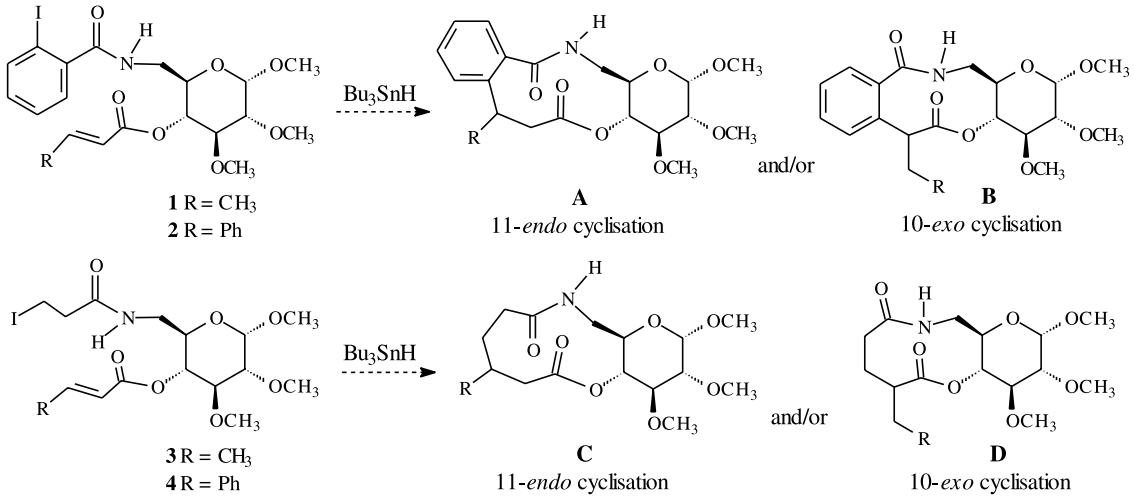
Thus, we report herein the results of our recent studies on free-radical cyclisation reactions of the amido-esters (**1**–**4**) anchored to a carbohydrate derived from methyl α-D-glucopyranoside. We expected that free-radical cyclisations of these precursors could lead to the macrocycles **A/C** and/or **B/D** by 11-*endo* or 10-*exo* cyclisations, respectively. Although the construction of ten- and eleven-membered ring carbocycles are very difficult,[6,7] we expected that cyclisation could be favored by the conformational restraints imposed by the sugar unit (Scheme 1).

Precursors **1**–**4** were prepared from readily available methyl α-D-glucopyranoside in seven steps using classical carbohydrate chemistry. The C-6 and C-4 hydroxy groups of the starting material were protected as a benzylidene acetal and the C-2 and C-3 hydroxyl groups were *O*-methylated.[8] Hannesian reaction followed by treatment of the 6-bromo derivative[9] with sodium azide gave the 6-azido derivative, which was treated with MeONa in MeOH to give methyl 6-azido-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside **5**.[10] Compound **5** was treated with either crotonic or cinnamic acid, *N*,*N*′-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP), furnishing the ester derivatives **6** or **7**, respectively. The amido-esters **1**–**4** were finally prepared from the corresponding azido-esters through a two-step one-pot reaction sequence: selective reduction of the azido group with PPh_3 in THF or ethyl ether and subsequent treatment of the resulting 6-amino derivative with 2-iodobenzoic acid, DCC and DMAP or with 3-iodopropanoyl chloride (Scheme 2).

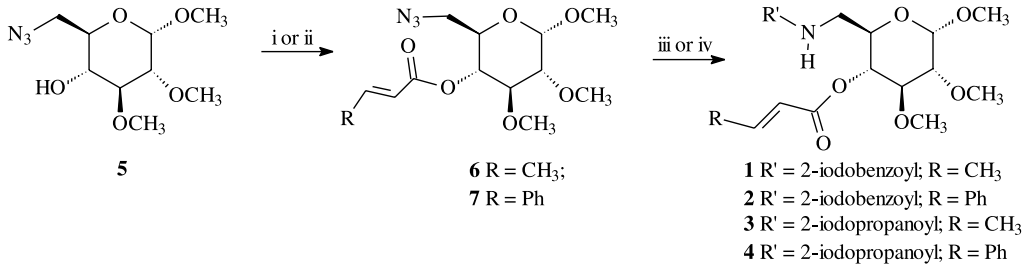
Free-radical reaction of **1** and **3** in boiling benzene (0.01 mol L^{-1}) with Bu_3SnH (1.1 equiv) in the presence of AIBN (catalytic amount) afforded only the hydrogenolysed products **8** (72%) and **11** (62%), respectively. When compounds **2** and **4** were treated under the same conditions, the unexpected six-membered imides **10** and **13** were obtained in 11 and 22% yield, respectively, with none of the anticipates macrocycles **A/C** and/or **B/D**. The

Keywords: Radical cyclisation; Carbohydrate; Imides.
* Corresponding author. Tel.: +55-31-3339-7676; fax: +55-31-3339-7663; e-mail: rickydylan@ig.com.br

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.08.039



Scheme 1.



Scheme 2. Reagents, conditions and yields i = crotonic acid, DCC, DMAP, CH_2Cl_2 (44%); ii = cinnamic acid, DCC, DMAP, CH_2Cl_2 (85%); iii = (a) PPh_3, THF; (b) 2-iodobenzoic acid, DCC [54% (**1**), 44% (**2**)]; iv = (a) PPh_3, $(C_2H_5)_2O$; (b) HCl, H_2O, (c) Na_2CO_3, 3-iodopropanoyl chloride, acetone [43% (**3**), 71% (**4**)].

corresponding hydrogenolysed products (**9**) and (**12**) were also isolated in 35 and 15% yield, respectively (Scheme 3).

The structures of imides **10** and **13** were determined by ESI-MS/MS analysis, IR, ^1H and ^{13}C NMR spectral data, DEPT experiment, and ^1H–^1H COSY, ^1H–^{13}C HMQC and HMBC experiments.

The ESI-MS spectra of **10** in the positive ion mode show major ions of *m/z* 472.228, (*m/z* 472.197 calculated for $C_{25}H_{29}NO_8+H^+$), *m/z* 494.180 (*m/z* 494.179 calculated for $C_{25}H_{29}NO_8+Na^+$) and *m/z* 510.165 (*m/z* 510.153 calculated for $C_{25}H_{29}NO_8+K^+$). In the negative ion mode, an abundant ion of *m/z* 470.465 corresponding to the deprotonated molecule (*m/z* 470.181 for $C_{25}H_{29}NO_8–H^+$) is detected, as well as its water adduct of *m/z* 488.489. The ESI-MS spectra indicate therefore that a structure with additional 17 u in mass has been formed. This mass shift likely corresponds to the incorporation of a new hydroxyl group. The ESI-MS/MS spectra of the protonated molecule of *m/z* 472 is also in agreement with structure **10** as it shows major dissociation by loss of neutral molecules of methanol (*m/z* 440), water plus methanol (*m/z* 422), two neutral molecules of methanol (*m/z* 408) and two methanol molecules plus a water molecule (*m/z* 390).

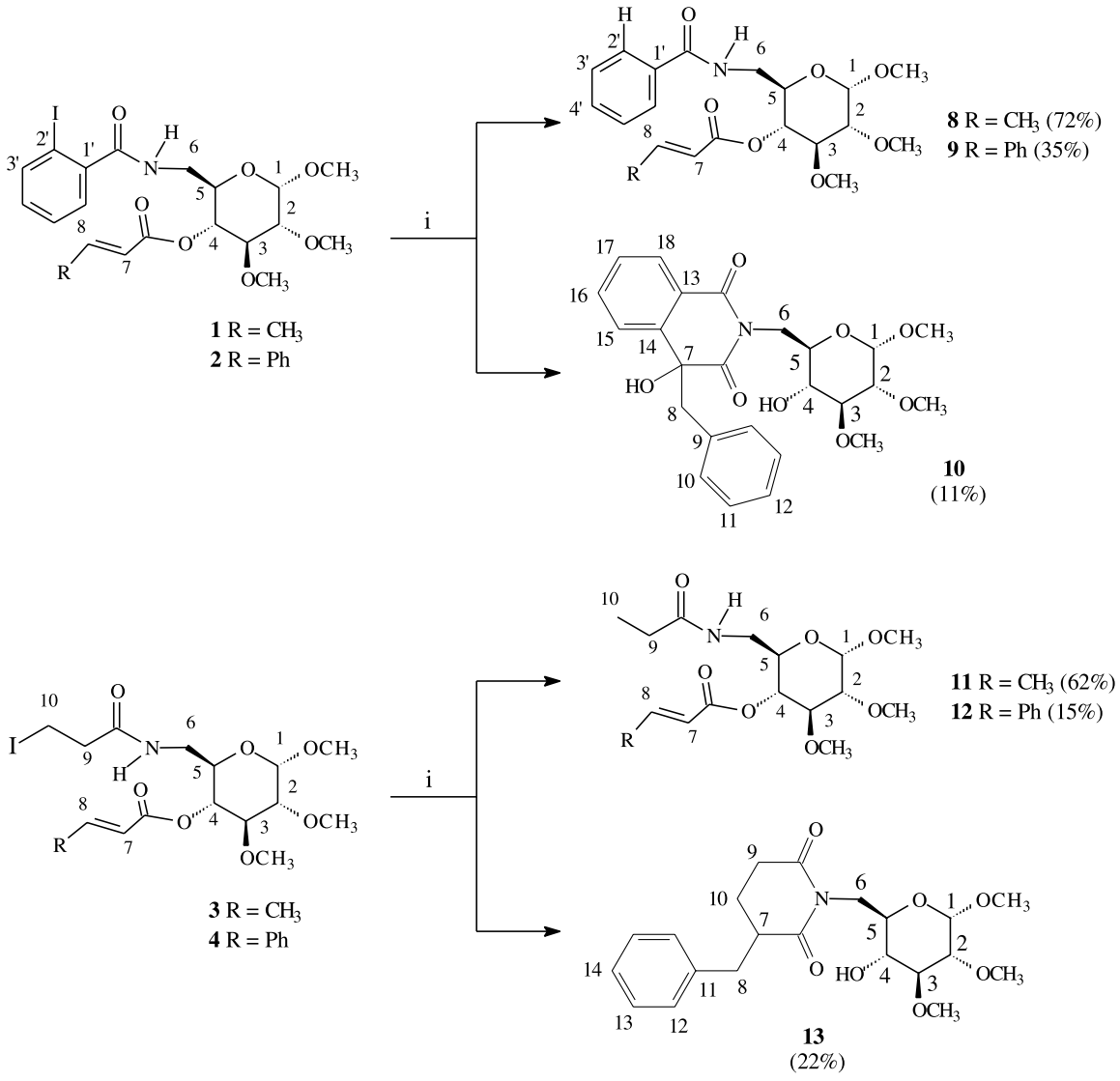
Similarly, the ESI-MS spectra of **13** in the positive ion mode show ions of *m/z* 408.217 (*m/z* 408.202 calculated for $C_{21}H_{29}NO_7+H^+$), *m/z* 430.191 (*m/z* 430.184 calculated for $C_{21}H_{29}NO_7+Na^+$) and *m/z* 446.167 (*m/z* 446.158 calculated for $C_{21}H_{29}NO_7+K^+$) whereas the ESI-MS/MS spectra shows the same dissociation sequence displayed by **10**, that is: losses of methanol (*m/z* 376), methanol plus water (*m/z* 358), two methanol molecules (*m/z* 344) and two methanol molecules plus a water molecule (*m/z* 326). For **13**, the additional 17 u in mass has therefore not been observed.

The comparison of **10** and **13** spectral data with those of their precursors **2** and **4**, respectively, are shown in Table 1.

The IR spectrum of **10** and **13** showed the characteristic absorption bands at 3450 (O–H stretching), 1710 and 1680 cm^{-1} (C=O stretching of cyclic imide-six-membered ring).

The ^1H and ^{13}C NMR data of **10** and **13** reveal the presence of a nearly 1:1 mixture of diastereoisomers. The presence of the hydroxyl group attached to C-4 was deduced on the basis of the chemical shift of H-4 (δ 3.3 ppm) compared to the downfield signal at δ 5.0 and 4.9 ppm for the amido-esters **2** and **4**, respectively.

The conversion of amido-esters into the imides was confirmed by ^1H–^{13}C HMBC correlation. The signals assigned to H-6a and H-6b showed coupling to the carbonyl carbons (Fig. 1). The regioselectivity of the reaction (*exo*-cyclisation mode) was also deduced by ^1H–^{13}C HMBC



Scheme 3. Reagents, conditions and yields i = Bu_3SnH, AIBN (cat.), benzene, reflux.

Table 1. Selected spectroscopic data for compounds **2**, **4**, **10** and **13**

Compound	IR (cm^{-1})			^1H NMR[a] δ (ppm) m, J (Hz)	^{13}C NMR[a] (DEPT) δ (ppm)	
	νN–H	νO–H	νC=O	H-4	C-7	C-8
(**2**)	3300	—	1710 (ester), 1640 (amide)	5.0, t, 9.4	117.00 (CH)	146.27 (CH)
(**4**)	3350	—	1700 (ester), 1650 (amide)	4.9, t, 9.4	116.89 (CH)	146.32 (CH)
(**10**)	—	3450	1710 and 1680 (imide)	3.3, t, 9.4	75.91, 75.82(C)	53.58, 53.49 (CH_2)
(**13**)	—	3450	1710 and 1680 (imide)	3.3, t, 9.2	44.01 (CH)	36.36 (CH_2)

[a] Samples were dissolved in $CDCl_3$.

cross peak, which showed coupling between the multiplet at δ 3.12–3.16 ppm, assigned to benzylic hydrogen, and the *ortho* carbons at δ 130.09 and 130.22 ppm (Fig. 1). The additional hydroxyl group in imide **10** revealed by MS analysis was deduced to be at C-7 on the basis of the chemical shift (δ 75.9 ppm) typical of a hydroxylated tetrasubstituted carbon.

The unexpected formation of six-membered imides **10** and **13** was rationalised as being the result of a 10-*exo* radical cyclisation as initially proposed followed by ring contraction of the unstable ten-membered macrocycles **B** and **D**. The ring strain in macrocycles **B** and **D** associated to proximity between the amide nitrogen atom and the ester carbonyl group might favour the ring contraction. The

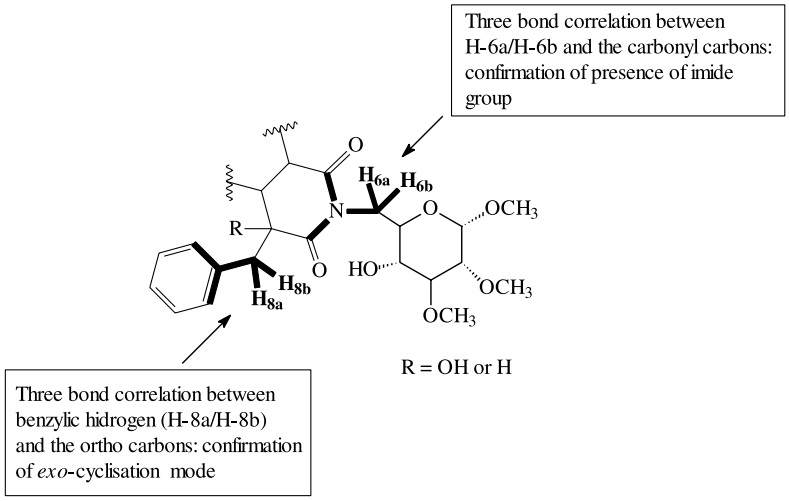


Figure 1.

proposed pathways leading to the formation of imides **10** and **13** are outlined in Figure 2.

In contrast with the guideline that '*endo*-cyclisation modes are favoured in radical macrocyclisation',[11] we have found that cinnamoyl precursors provide exclusively macrocycles resulting from *exo* radical cyclisation. These results can be attributed to the stability of the intermediate benzyl radical from cinnamoyl precursors and to the steric retardation of *endo*-cyclisation.

We have been intrigued by the presence of the additional

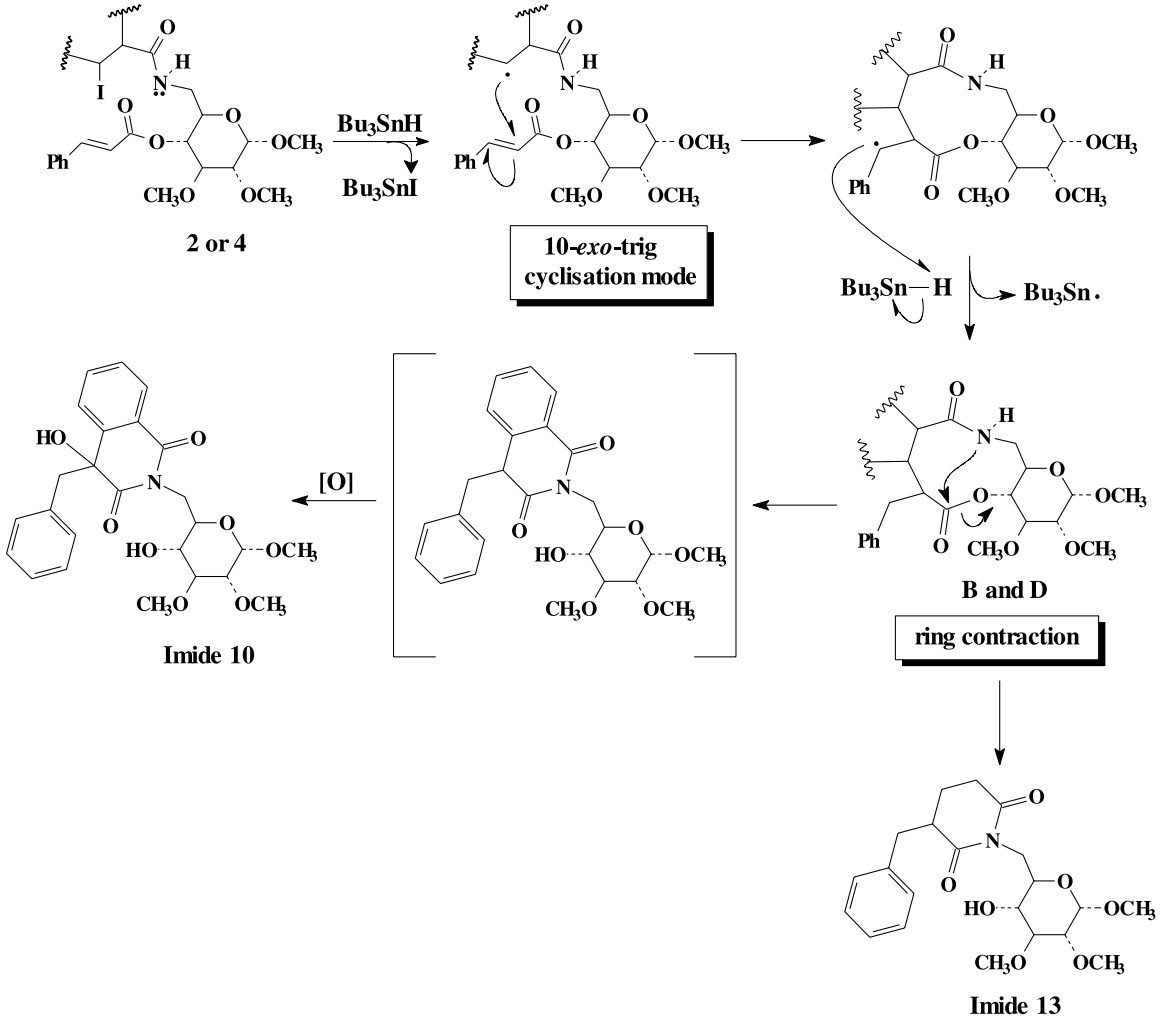


Figure 2.

hydroxyl group in the imide **10**. It is not so straightforward to rationalise how this oxidation occurred. However, the aromatic ring of benzoyl group is likely to play an important role in the oxidation step, since no such reaction was observed for **4**. The ease of oxidation of a given substrate depends markedly on the strength of its weakest C–H bond.[12] In this case, the hydrogen abstraction in C-7 forms a stabilised radical (tertiary, α-carbonyl and benzylic radical), which could account for the observed autoxidation.

In conclusion, we have described the synthesis of six-membered cyclic imides bearing a new stereogenic center via 10-*exo*-trig radical carbocyclisation followed by ring contraction on carbohydrate template. This cyclisation, though regioselective, proved to be nonstereoselective, affording inseparable mixture of diastereoisomers.

2. Experimental

2.1. General information

All melting points were determined on a Kofler Sybron apparatus and are uncorrected. Optical rotations were determined at 25 °C with a Bellingham and Stanley P20 Polarimeter. The IR spectra were recorded on a Shimadsu IR-408 spectrometer. The NMR spectra were recorded on a Bruker *AVANCE* DRX400 or a Bruker *AVANCE* DPX400 instruments. Samples were dissolved in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in δ (ppm) scale and *J* values are given in Hz. ESI-MS and ESI-MS/MS data were obtained using a Micromass QTOF hybrid quadrupole orthogonal time-of-flight mass spectrometer operating at 7.000 mass resolution and 5 ppm mass accuracy using typical analytical conditions as described elsewhere.[13] ESI-MS spectra for mass measurements were taken using both positive- and negative-ion electronspray ionization from 1:1 H_2O–MeOH solutions with the addition of either a few microliters of formic acid or ammonium hydroxide. Column chromatography was performed with silica gel 60, 70–230 mesh (Merck).

2.2. General procedure for the synthesis of the azido-esters (6) and (7)

To a 0.2 mol L^{-1} solution of **5**[10] in methylene chloride were added carboxylic acid (crotonic or cinnamic acid) (1.6 equiv), *N*,*N*′-dicyclohexylcarbodiimide (1.6 equiv) and 4-dimethylaminopyridine (0.16 equiv). The solution was allowed to stand at room temperature for 12 h. The dicyclohexylurea, which precipitates, was removed by filtration. The filtrate was concentrated to give crude azido-ester, which was submitted to chromatography (hexane–EtOAc). The azido-esters **6** and **7** were unstable if stored for a few hours and, thus, they were reacted soon after their purification.

2.2.1. Methyl 6-azido-4-*O*-crotonyl-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (6). Oil; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.05 (dq, 1H, $J_{8,7}=15.5$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 5.85 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.93–4.83 (m, 2H, H-1 and H-4), 3.85 (ddd, 1H, $J_{5,4}=10$ Hz, $J_{5,6a}=7.2$ Hz, $J_{5,6b}=2.8$ Hz, H-5), 3.6 (t, 1H, $J_{3,2}=J_{3,4}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.49 (s, 6H, 2×OMe), 3.40–3.27 (m, 2H, H-2 and H-6a), 3.20 (dd, 1H, $J_{6b,6a}=13.2$ Hz, $J_{6b,5}=2.8$ Hz, H-6b), 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,9}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 165.19 (C=O), 146.41 (C-8), 121.72 (C-7), 97.42 (C-1), 81.14 (C-2 or C-3), 80.53 (C-3 or C-2), 70.98 (C-4), 69.10 (C-5), 60.76, 59.19, 55.40 (3×OMe), 51.27 (C-6), 18.03 (Me).

2.2.2. Methyl 6-azido-4-*O*-cinnamoyl-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (7). Oil; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.74 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.57–7.38 (m, 5H, Ph), 6.44 (d, 1H, $J_{7,8}=16$ Hz, H-7), 4.98 (dd, 1H, $J_{4,5}=10.1$ Hz, $J_{4,3}=9.4$ Hz, H-4), 4.90 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 3.92 (ddd, 1H, $J_{5,4}=10.1$ Hz, $J_{5,6a}=7$ Hz, $J_{5,6b}=3$ Hz, H-5), 3.67 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.55 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.42–3.31 (m, 2H, H-6a and H-2), 3.25 (dd, 1H, $J_{6b,6a}=13.2$ Hz, $J_{6b,5}=3$ Hz, H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 165.63 (C=O), 146.08 (C-8), 133.91–128.08 (Ph), 116.84 (C-7), 97.40 (C-1), 81.14 (C-2 or C-3), 80.51 (C-3 or C-2), 71.24 (C-4), 69.04 (C-5), 60.74, 59.11, 55.37 (3×OMe), 51.23 (C-6).

2.3. General procedure for the synthesis of the amido-esters (1) and (2)

To a 0.08 mol L^{-1} solution of azido-esters **6** or **7** in THF was added triphenylphosphine (1.5 equiv). After 6 h at room temperature, TLC showed complete conversion of the substrate. Then, *N*,*N*′-dicyclohexylcarbodiimide (2.0 equiv) was added, followed by 2-iodobenzoic acid (2.0 equiv), and the stirring was continued for 24 h. The dicyclohexylurea was removed by filtration. The filtrate was concentrated to give crude amido-ester, which was submitted to chromatography (hexane–EtOAc).

2.3.1. Methyl 4-*O*-crotonyl-6-deoxy-6-(2-iodobenzoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (1). White solid; mp 149.6–151.2 °C; $[\alpha]_D=+105.7$ (*c* 1.4 in $CHCl_3$); ν_{max}/cm^{-1} 3300 (NH), 1710 (C=O), 1640 (C=O), 1620 (C=C), 1050 (C–O); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.85 (d, 1H, $J_{3',4'}=7.8$ Hz, H-3′), 7.45–7.33 (m, 2H, H-5′ and H-6′), 7.16–7.01 (m, 2H, H-4′ and H-8), 6.31 (t, 1H, $J_{NH,6a}=J_{NH,6b}=6.8$ Hz, NH), 5.90 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.90 (t, 1H, $J_{4,3}=J_{4,5}=9.6$ Hz, H-4), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.02–3.84 (m, 2H, H-5 and H-6a), 3.64 (t, 1H, $J_{3,4}=J_{3,2}=9.6$ Hz, H-3) 3.53 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.27–3.17 (m, 2H, H-2 and H-6b); 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,9}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 169.13, 165.64 (2×C=O), 146.50 (C-8), 142.08-128.09 (Ar), 121.80 (C-7), 97.51 (C-1), 92.22 (C-2′), 81.33 (C-2), 80.58 (C-3), 71.15 (C-4), 67.94 (C-5), 60.85, 59.21, 55.61 (3×OMe), 39.78 (C-6), 18.07 (Me); Anal. Calc. for $C_{20}H_{26}INO_7$: C, 46.24; H, 5.01; N, 2.70; Found: C, 46.06; H, 4.64; N, 2.68.

2.3.2. Methyl 4-*O*-cinnamoyl-6-deoxy-6-(2-iodobenzoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (2). White solid; mp 164.2–165.9 °C; $[\alpha]_D=+211$ (*c* 0.5 in $CHCl_3$); ν_{max}/cm^{-1} 3300 (NH), 1710 (C=O), 1640 (C=O), 1625 (C=C), 1050 (C–O); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)

7.85 (d, 1H, $J_{3',4'}=7.8$ Hz, H-3′), 7.76 (d, 1H, $J_{8,7}=16$ Hz, H-7) 7.58–7.33 (m, 7H, Ar-H), 7.10 (td, 1H, $J_{4',3'}=J_{4',5'}=7.8$ Hz, $J_{4',6'}=1.2$ Hz, H-4′), 6.49 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.31 [s (broad), 1H, NH], 4.99 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 4.86 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.06–3.91 (m, 2H, H-5 and H-6a), 3.71 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.48 (s, 3H, OMe), 3.38–3.26 (m, 2H, H-2 and H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 169.16, 166.25 (2×C═O), 146.27 (C-8), 142.11–128.13 (Ar), 117.00 (C-7), 97.58 (C-1), 92.26 (C-2′), 81.42 (C-2), 80.67 (C-3), 71.54 (C-4), 67.97 (C-5), 60.96, 59.26, 55.69 (3×OMe), 39.88 (C-6); Anal. Calc. for $C_{25}H_{28}INO_7$: C, 51.64; H, 4.82; N, 2.41; Found: C, 51.44; H, 4.57; N, 2.40.

2.4. General procedure for the synthesis of the amido-esters (3) and (4)

To a 0.13 mol L^{-1} solution of azido-esters **6** or **7** in diethyl ether was added triphenylphosphine (1.5 equiv). After completion of the reduction (~4 h) the reaction mixture was extracted with cold diluted hydrochloric acid (0.2 mol L^{-1}, 15 mL) to separate the triphenylphosphine oxide from the amine. The aqueous layer was transferred to a round-bottom flask immersed in an ice bath and then were added acetone (20 mL), saturated aqueous sodium carbonate (ca. 10 mL), followed by a dropwise solution of the 3-iodopropanoyl chloride (2.5 equiv) in anhydrous acetone (5 mL). After 1 h at room temperature, TLC showed complete conversion of the substrate. For workup, acetone was removed under reduced pressure, water (50 mL) was added and the aqueous layer was washed with $CHCl_3$ (3×50 mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (hexane–EtOAc).

2.4.1. Methyl 4-*O*-crotonyl-6-deoxy-6-(3-iodopropanoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (3). White solid; mp 87.9–88.6 °C; $[\alpha]_D=+106.2$ (*c* 2.0 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (NH), 1700 (C═O), 1650 (C═O), 1625 (C═C), 1050 (C–O); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.06 (dq, 1H, $J_{8,7}=15.5$ Hz, $J_{8,Me}=6.9$ Hz, H-8), 6.19 [s (broad), 1H, NH], 5.88 (dd, 1H, $J_{7,8}=15.5$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.80 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 3.90–3.71 (m, 2H, H-5 and H-6a), 3.61 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.53 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.44–3.33 (m, 4H, OMe and H-6b), 3.27 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.08–2.59 (m, 4H, H-9a, H-9b, H-10a and H-10b), 1.92 (dd, 3H, $J_{Me,8}=6.9$ Hz, $J_{Me,7}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 170.19, 165.81 (2×C═O), 146.59 (C-8), 121.77 (C-7), 97.45 (C-1), 81.30 (C-3), 80.50 (C-2), 71.15 (C-4), 67.90 (C-5), 60.83, 59.17, 55.45 (3×OMe), 40.63 (C-9), 39.23 (C-6), 18.07 (Me), -1,92 (C-10); Anal. Calc. for $C_{16}H_{26}INO_7$: C, 40.76; H, 5.52; N, 2.97; Found: C, 41.44; H, 5.13; N, 2.89.

2.4.2. Methyl 4-*O*-cinnamoyl-6-deoxy-6-(3-iodopropanoylamino)-2,3-di-*O*-methyl-α-D-glucopyranoside (4). White solid; mp 101.7–102.8 °C; $[\alpha]_D=+101.2$ (*c* 1.2 in $CHCl_3$); ν_{max}/cm^{-1} 3350 (NH), 1700 (C═O), 1650 (C═O), 1625 (C═C); 1050 (C–O); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.75 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.58–7.38 (m, 5H, Ph), 6.47 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.16 [s (broad), 1H, NH], 4.90 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4),4.86 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 3.95–3.78 (m, 2H, H-5 and H-6a), 3.68 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.46–3.36 (m, 4H, OMe and H-6b), 3.30 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.18–2.96 (m, 2H, H-9a, H-9b), 2.94–2.71 (m, 2H, H-10a and H-10b); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 170.20, 166.39 (2×C═O), 146.32 (C-8), 133.95–128.20 (Ph), 116.89 (C-7), 97.48 (C-1), 81.36 (C-3), 80.55 (C-2), 71.48 (C-4), 67.91 (C-5), 60.92, 59.21, 55.50 (3×OMe), 40.66 (C-9), 39.28 (C-6), −1,87 (C-10); Anal. Calc. for $C_{21}H_{28}INO_7$: C, 47.28; H, 5.25; N, 2.67; Found: C, 47.63; H, 5.31; N, 2.55.

2.5. General procedure for free radical cyclisation

To a stirring and boiling solution of amido-esters in nitrogen-saturated benzene (0.01 mol L^{-1}) was added a solution of Bu_3SnH (1.1 equiv) and AIBN (cat.) in nitrogen-saturated benzene (0.2 mol L^{-1}) via an addition funnel during 3 h. The reaction mixture was heated under reflux in nitrogen atmosphere for a further 1 h. After solvent removal the residue was dissolved in acetonitrile (50 mL). The solution was extracted three times with hexane (30 mL) to remove tin compounds. After evaporation of the acetonitrile the residue was chromatographed (hexane–EtOAc).

2.5.1. Free radical cyclisation of amido-ester (1). The uncyclized product (**8**) was obtained as a white solid; mp 129.3–130.2; $[\alpha]_D=+113$ (*c* 1.0 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.83 (dd, 2H, $J_{2',3'}=7.8$ Hz, $J_{2',4'}=1.8$ Hz, 2×H-2′), 7.54–7.34 (m, 3H, Ar-H), 7.10 (dq, 1H, $J_{8,7}=15.6$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 7.01–6.94 (m, 1H, NH), 5.91 (dd, 1H, $J_{7,8}=15.6$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.87 (t, 1H, $J_{4,3}=J_{4,5}=9.4$ Hz, H-4), 4.84 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.13 (ddd, 1H, $J_{6a,6b}=14.3$ Hz, $J_{6a,NH}=8.5$ Hz, $J_{6a,5}=2.8$ Hz, H-6a), 3.85 (ddd, 1H, $J_{5,4}=9.4$ Hz, $J_{5,6b}=5.6$ Hz, $J_{5,6a}=2.8$ Hz, H-5), 3.65 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.51 (s, 6H, 2×OMe), 3.42 (s, 3H, OMe), 3.26 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.09 (ddd, 1H, $J_{6b,6a}=14.3$ Hz, $J_{6b,NH}=4.2$ Hz, $J_{6b,5}=5.6$ Hz, H-6b), 1.92 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,7}=1.6$ Hz, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 167.11, 166.09 (2×C═O), 146.75 (C-8), 134.20-126.89 (Ph), 121.76 (C-7), 97.40 (C-1), 81.31 (C-3), 80.51 (C-2), 71.51 (C-4), 67.93 (C-5), 60.86, 59.12, 55.28 (3×OMe), 39.47 (C-6), 18.06 (Me); ESI-MS $[M+H]^+$ 394.195 $C_{20}H_{27}NO_7$ requires for $[M+H]^+$ 394.187).

2.5.2. Free radical cyclisation of amido-ester (2). The uncyclized product **9** was obtained as a white solid; mp 80.9–81.5; $[\alpha]_D=+126.9$ (*c* 0.75 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.84 (dd, 2H, $J_{2',3'}=7.8$ Hz, $J_{2',4'}=1.4$ Hz, 2×H-2′), 7.79 (q, 1H, $J_{8,7}=15.8$ Hz, H-8), 7.59–7.39 (m, 8H, Ar-H), 6.96 (dd, 1H, $J_{NH,6a}=8.4$ Hz, $J_{NH,6b}=4.2$ Hz, NH), 6.50 (d, 1H, $J_{7,8}=15.8$ Hz, H-7), 4.96 (dd, 1H, $J_{4,5}=10.0$ Hz, $J_{4,3}=9.4$ Hz, H-4), 4.87 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.18 (ddd, 1H, $J_{6a,6b}=14.3$ Hz, $J_{6a,NH}=8.4$ Hz, $J_{6a,5}=2.8$ Hz, H-6a), 3.92 (ddd, 1H, $J_{5,4}=10.0$ Hz, $J_{5,6b}=5.4$ Hz, $J_{5,6a}=2.8$ Hz, H-5), 3.72 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.55 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.30 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz H-2), 3.24–3.09 (m, 1H, H-6b); ^{13}C NMR (50 MHz, $CDCl_3$) δ

(ppm) 167.20, 166.75 (2×C=O), 146.54 (C-8), 134.24–126.95 (Ar-C), 116.91 (C-7), 97.50 (C-1), 81.43 (C-2), 80.61 (C-3), 71.96 (C-4), 67.99 (C-5), 61.02, 59.22, 55.40 (3×OMe), 39.59 (C-6); ESI-MS $[M+H]^+$ 456.200 $C_{25}H_{29}NO_7$ requires for $[M+H]^+$ 456.202).

The six-membered cyclic imide **10** was obtained as an oil; ν_{max}/cm^{-1} 3450 (OH), 1710 (C=O), 1680 (C=O), 1050 (C–O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07–8.02 (m, 2H, H-18 and H-18′), 7.66–7.59 (m, 2H, H-16 and H-16′), 7.56–7.52 (m, 2H, H-15 and H-15′), 7.50–7.45 (m, 2H, H-17 and H-17′), 7.23–7.19 (m, 2H, H-12 and H-12′), 7.16-7.11 (m, 4H, 2×H-11 and 2×H-11′), 6.70–6.65 (m, 4H, 2×H-10 and 2×H-10′), 4.76 (d, 1H, $J_{1',2'}=3.6$ Hz, H-1′), 4.75 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.30 (dd, 1H, $J_{6a,6b}=14.0$ Hz, $J_{6a,5}=4.8$ Hz, H-6a), 4.15–4.13 (m, 2H, H-6b and H-6b′), 4.08 (dd, 1H, $J_{6a',6b'}=14.0$ Hz, $J_{6a',5'}=4.8$ Hz, H-6a′), 3.92 (dt, 1H, $J_{5',4'}=9.4$ Hz, $J_{5',6a'}=J_{5',6b'}=6.0$ Hz, H-5′), 3.84 (dt, 1H, $J_{5,4}=9.4$ Hz, $J_{5,6a}=J_{5,6b}=4.8$ Hz, H-5), 3.62 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.44–3.39 (m, 5H, OMe, H-3 and H-3′), 3.33 (t, 1H, $J_{4',5'}=J_{4',3'}=9.4$ Hz, H-4′), 3.31 (s, 3H, OMe), 3.27 (t, 1H, $J_{4,5}=J_{4,3}=9.4$ Hz, H-4), 3.24 (s, 3H, OMe), 3.19 (dd, 1H, $J_{2',3'}=9.4$ Hz, $J_{2',1'}=3.6$ Hz, H-2′), 3.16–3.13 (m, 5H, H-2 and H-8a, H-8a′, H-8b and H-8b′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.12, 176.60, 164.12, 163.96 (4×C=O), 139.66, 139.53 (C-14 and C-14′), 133.93 (C-16 and C-16′), 133.24, 133.13 (C-9 and C-9′), 130.22, 130.09 (2×C-10 and 2×C-10′), 128.58, 128.54 (C-17 and C-17′), 128.30, 128.15 (C-18 and C-18′), 128.06, 127.99 (2×C-11 and 2×C-11′), 127.64 (C-12 and C-12′), 125.64, 125.50 (C-15 and C-15′), 124.43 (C-14 and C-14′), 97.40, 97.31 (C-1 and C-1′), 82.52, 82.28 (C-3 and C-3′), 81.66, 81.60 (C-2 and C-2′), 75.91, 75.82 (C-7 and C-7′), 73.33 (C-4), 73.50 (C-4′), 68.92 (C-5), 68.28 (C-5′), 61.24, 58.66, 58.55, 55.18, 55.10 (6×OMe), 53.58, 53.49 (C-8 and C-8′), 42.22 (C-6), 41.33 (C-6′); ESI-MS $[M+H]^+$ 472.228 $C_{25}H_{29}NO_8$ requires for $[M+H]^+$ 472.197).

2.5.3. Free radical cyclisation of amido-ester (3). The uncyclized product **11** was obtained as a white solid; mp 85.5–87.0; $[\alpha]_D=+118$ (*c* 0.8 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.06 (qd, 1H, $J_{8,7}=15.6$ Hz, $J_{8,Me}=6.8$ Hz, H-8), 6.07 [s (broad), 1H, NH), 5.88 (dd, 1H, $J_{7,8}=15.6$ Hz, $J_{7,Me}=1.6$ Hz, H-7), 4.83 (d, 1H, $J_{1,2}=3.6$ Hz, H-1), 4.79 (t, 1H, $J_{4,5}=J_{4,3}=9.4$ Hz, H-4), 3.89–3.70 (m, 2H, H-6a and H-5), 3.61 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.53 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.42 (s, 3H, OMe), 3.27 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.6$ Hz, H-2), 3.01–2.88 (m, 1H, H-6b) 2.23 (q, 2H, $J_{9,10}=7.6$ Hz, H-9a and H9b), 1.91 (dd, 3H, $J_{Me,8}=6.8$ Hz, $J_{Me,7}=1.6$ Hz, Me), 1.16 (t, 3H, $J_{10,9a}=J_{10,9b}=7.6$ Hz, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 173.74, 165.77 (2×C=O), 146.47 (C-8), 121.83 (C-7), 97.43 (C-1), 81.34 (C-3), 80.61 (C-2), 71.25 (C-4), 67.94 (C-5), 60.84, 59.17, 55.23 (3×OMe), 39.14 (C-6), 29.65 (C-9), 18.06 (Me), 9.70 (C-10); ESI-MS $[M+H]^+$ 346.193 $C_{16}H_{27}NO_7$ requires for $[M+H]^+$ 346.187).

2.5.4. Free radical cyclisation of amido-ester (4). The uncyclized product **12** was obtained as a white solid; mp 112.0–113.5; $[\alpha]_D=+79.2$ (*c* 1.0 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.76 (d, 1H, $J_{8,7}=16$ Hz, H-8), 7.57–7.27 (m, 5H, Ar-H), 6.47 (d, 1H, $J_{7,8}=16$ Hz, H-7), 6.06 [s (broad), 1H, NH), 4.93–4.80 (m, 2H, H-1, H-4), 3.95–3.77 (m, 2H, H-6a and H-5), 3.67 (t, 1H, $J_{3,4}=J_{3,2}=9.4$ Hz, H-3), 3.54 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.28 (dd, 1H, $J_{2,3}=9.4$ Hz, $J_{2,1}=3.4$ Hz, H-2), 3.05–2.97 (m, 1H, H-6b), 2.24 (q, 2H, $J_{9,10}=7.6$ Hz, H-9a and H9b), 1.17 (t, 3H, $J_{10,9a}=J_{10,9b}=7.6$ Hz, H-10); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 173.76, 166.35 (2×C=O), 146.29 (C-8), 134.05–128.24 (Ar-C), 117.03 (C-7), 97.51 (C-1), 81.45 (C-3), 80.71 (C-2), 71.63 (C-4), 67.98 (C-5), 60.99, 59.26, 55.34 (3×OMe), 39.23 (C-6), 29.76 (C-9), 9.78 (C-10); ESI-MS $[M+H]^+$ 408.204 $C_{21}H_{29}NO_7$ requires for $[M+H]^+$ 408.202).

The six-membered cyclic imide **13** was obtained as an oil; ν_{max}/cm^{-1} 3450 (OH), 1710 (C=O), 1680 (C=O), 1050 (C–O); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36–7.18 (m, 10H, Ar-H), 4.79–4.77 (m, 2H, H-1 and H-1′), 4.23 (dd, 2H, $J_{6a,6b}=J_{6a',6b'}=13.6$ Hz, $J_{6a,5}=J_{6a',5'}=4.8$ Hz, H-6a and H-6a′), 4.08 (dd, 2H, $J_{6b,6a}=J_{6b',6a'}=13.6$ Hz, $J_{6b,5}=J_{6b',5'}=5.6$ Hz, H-6b and H-6b′), 3.79–3.73 (m, 2H, H-5 and H-5′), 3.63 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.48 (s, 6H, 2×OMe), 3.47–3.41 (m, 2H, H-8a and H-8a′), 3.41 (t, 2H, $J_{3,4}=J_{3,2}=J_{3',4'}=J_{3',2'}=9.2$ Hz, H-3 and H-3′), 3.35 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.27 (t, 2H, $J_{4,5}=J_{4,3}=J_{4',5'}=J_{4',3'}=9.2$ Hz, H-4 and H-4′), 3.19 (dd, 2H, $J_{2,3}=J_{2',3'}=9.2$ Hz, $J_{2,1}=J_{2',1'}=3.6$ Hz, H-2 and H-2′), 2.80–2.69 (m, 6H, H-7, H-7′, H-8b, H-8b′, H-10a and H-10a′) 2.58–2.47 (m, 2H, H-10b and H-b′), 1.91–1.83 (m, 2H, 2×H-9a and H-9$^{a\prime}$), 1.66–1.55 (m, 2H, H-9b and H-9b′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.72, 174.52, 172.80, 172.67 (4×C=O), 138.33, 138.28 (C-11 and C-11′), 129.22, 129.17 (2×C-12 and 2×C-12′), 128.57, 128.54 (2×C-13 and 2×C-13′), 126.62 (C-14 and C-14′), 97.21 (C-1 and C-1′), 82.39 (C-3 and C-3′), 81.55 (C-2 and C-2′), 72.96, 72.90 (C-4 and C-4′), 68.49, 68.40 (C-5 and C-5′), 61.14, 58.51, 54.90 (6×OMe), 44.01 (C-7 and C-7′), 40.69, 40.64 (C-6 and C-6′), 36.36 (C-8 and C-8′), 32.08, 32.02 (C-10 and C-10′), 21.70 (C-9 and C-9′); ESI-MS $[M+H]^+$ 408.217 $C_{21}H_{29}NO_7$ requires for $[M+H]^+$ 408.202).

Acknowledgements

The authors are grateful to Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), for financial support. The authors thank the referees for their suggestions.

References and notes

1. Prado, M. A. F.; Alves, R. J.; Souza Filho, J. D.; Alves, R. B.; Pedrosa, M. T. C.; Prado, R. F.; Faraco, A. A. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1853–1857.
2. Binatti, I.; Prado, M. A. F.; Alves, R. J.; Souza Filho, J. D. *J. Braz. Chem. Soc.* **2002**, *13*, 570–575.
3. Faraco, A. A. G.; Prado, M. A. F.; Alves, R. J.; Souza Filho,

J. D.; Alves, R. B.; Faraco, R. F. P. *Synth. Commun.* **2003**, *33*, 463–474.
4. Oliveira, R. B.; Alves, R. J.; Souza Filho, J. D.; Prado, M. A. F. *J. Braz. Chem. Soc.* **2003**, *14*, 442–448.
5. Faraco, A. A. G.; Prado, M. A. F.; Alves, R. A.; Faraco, R. F. P.; Alves, R. J.; Souza-Filho, J. D.; Meurer, E. C.; Eberlin, M. N. *Tetrahedron Lett.* **2004**, *45*, 3317–3320.
6. Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48*, 3413–3428.
7. Lamas, C.; Saá, L.; Castedo, L.; Domínguez, D. *Tetrahedron Lett.* **1992**, *33*, 5653–5654.
8. Vogel, A. *Vogel's Textbook of Practical Organic Chemistry*; Longman Scientific and Technical: New York, 1978; pp 118–119.
9. (a) Sato, K. I.; Yoshimura, J. *Carbohydr. Res.* **1982**, *103*, 221. (b) Hanessian, S. *Org. Synth.* **1987**, *65*, 243.
10. Fürstner, A.; Baumgartner, J.; Jumbam, D. N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 131–138.
11. Porter, N. A.; Chang, V. H. T. *J. Am. Chem. Soc.* **1987**, *109*, 4976–4981.
12. Perkins, M. J. *Radical Chemistry: the Fundamentals*; Oxford University Press: New York, 2000.
13. Rioli, V.; Gozzo, F. C.; Shida, C. S.; Krieger, J. E.; Heimann, A. S.; Linardi, A.; Almeida, P. C.; Hyslop, S.; Eberlin, M. N.; Ferro, E. S. *J. Biol. Chem.* **2003**, *278*, 8547.