

Stereoselective Synthesis of Carbohydrate-Based Fused Bicyclic δ -Lactones

Renata B. de Oliveira^a, Ricardo J. Alves^{*,b}, José Dias de Souza Filho^a and Maria Auxiliadora F. Prado^b

^aDepartamento de Química, Instituto de Ciências Exatas, Universidade Federal de Minas Gerais, Av. Antônio Carlos 6627, 31270-200 Belo Horizonte - MG, Brazil

^bDepartamento de Produtos Farmacêuticos, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Av. Olegário Maciel 2360, 30180-112 Belo Horizonte - MG, Brazil

Relata-se no presente trabalho a síntese de δ -lactonas quirais derivadas de carboidratos, por meio de reações de ciclização radicalar regio- e estereosseletivas. A configuração do novo centro estereogênico depende da estrutura do carboidrato.

We describe in the present work the synthesis of carbohydrate-based chiral δ -lactones by regio- and stereoselective radical cyclization reactions. The configuration of the newly stereogenic center was found to depend on the structure of the carbohydrate moiety.

Keywords: radical cyclization, carbohydrate and δ -lactones

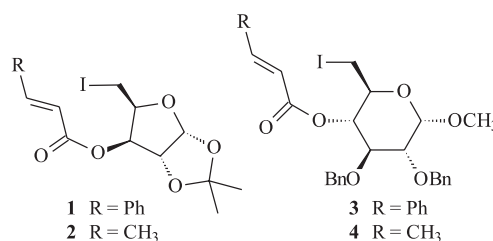
Introduction

Free radical cyclization has been applied extensively in natural product synthesis.¹ A number of biologically active natural products especially pheromones are lactones.² In addition, lactones have assumed importance as building blocks for the synthesis of natural products such as alkaloids, macrocyclic antibiotics and terpenoids. Because of the presence of often numerous chiral centers in natural products, diastereoselectivity is crucial in their synthesis.³

Carbohydrate have been used as "off-templates" for the stereoselective synthesis of chiral γ - and δ -lactones.⁴⁻⁶ In connection with our interest in free radical carbocyclization reactions from carbohydrates,⁷⁻⁹ we report herein our results on the regio- and stereoselective synthesis of chiral δ -lactones by 6-*exo*-trig radical carbocyclization reactions on carbohydrate templates.

The iodo esters **1** to **4** were chosen as radical precursors. They are easily prepared in a few steps using classical carbohydrate chemistry and should allow the comparison of the influence of a pyranose *versus* a furanose template in the outcome of the radical carbocyclization reaction. The cinnamoyl and crotonyl moieties generate a new chiral

center upon cyclization. Hence, the stereoselectivity of the reaction can be evaluated.

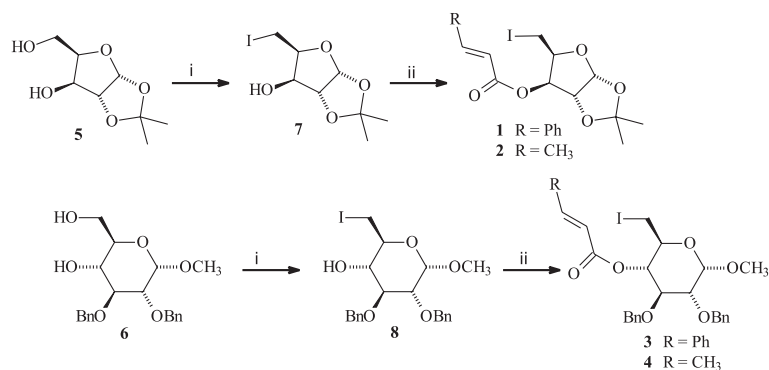


Results and Discussion

Starting with known 1,2-*O*-isopropylidene- α -D-xylofuranose (**5**)¹⁰ and methyl 2,3-di-*O*-benzyl- α -D-glucopyranoside (**6**),¹¹ the radical precursors **1** to **4** were prepared in two steps namely, regioselective replacement of the primary hydroxyl group by iodide,¹² followed by esterification of the remaining hydroxyl group¹³ (Scheme).

The radical carbocyclization reactions of compounds **1** to **4** were then investigated. Thus, a solution of tri-*n*-butyltin hydride (1.2 equivalents) and catalytic amount of azoisobutyronitrile (AIBN) in nitrogen-saturated anhydrous benzene was added slowly (over three hours) to a solution of the radical precursors **1** to **4** in boiling benzene (0.013 mol L⁻¹).

* e-mail: ricky@dedalus.lcc.ufmg.br



Scheme. Reagents and conditions: i) I₂, Ph₃P, imidazole, toluene, reflux [70% (**7**) and 63% (**8**)]; ii) cinnamic acid or crotonic acid, DCC, DMAP, CH₂Cl₂, rt (56-79%).

In all cases, products of completely stereoselective 6-*exo*-trig carbocyclization were formed in 1-30 % yield by addition of the alkyl radical to the α -position of α,β -unsaturated esters. The corresponding hydrogenolysis products were also isolated in 42-70 % yield (Figure 1).

The results are summarised in the Table 1.

Several authors reported failure in attempting 5- and 6-*exo*-trig radical ring closure of ester derivatives due to the geometric constraints associated with the preferred *s*-*Z* conformation of the ester function.¹⁴⁻²⁰ Thus, the successful

Table 1. Cyclization and reduction products from radical precursors **1** to **4**

Radical Precursor	Product (yield %) ^a δ -lactone	reduction	Stereochemistry at α -C ^b
1	9 (30)	13 (42)	<i>S</i>
2	10 (15)	14 (66)	<i>S</i>
3	11 (22)	15 (53)	<i>R</i>
4	12 (1)	16 (70)	<i>R</i>

^a Yields after purification by column chromatography; ^b Deduced by NOESY experiments.

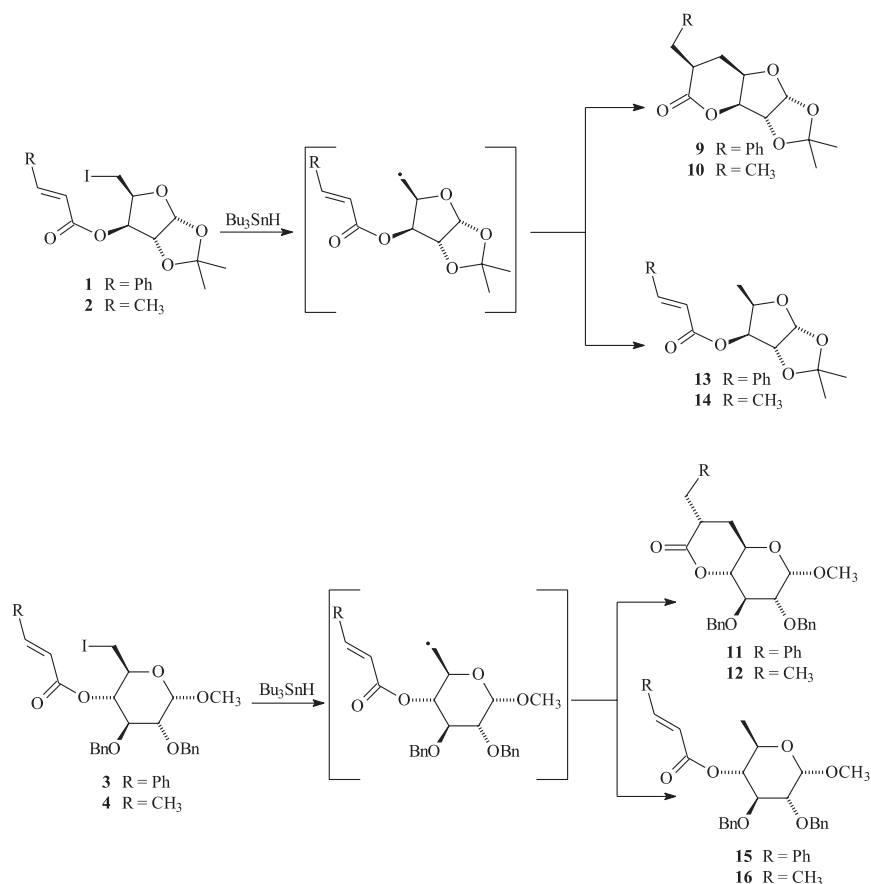


Figure 1. Products of the reactions of precursors **1** to **4** with Bu₃SnH.

outcome of the reactions in our study, despite the low yields of the cyclized products, may be related to the conformational restraints imposed by the carbohydrate moiety. As shown in the Table 1, the cinnamoyl precursors (**1** and **3**) gave better yields of the corresponding δ -lactones. This was attributed to the stability of the intermediate benzyl radical. According to the literature²¹ the formation of fused rings in radical ring closure is predominately or exclusively *cis* for small rings (six or fewer atoms). Thus, the *cis*-relationship between the substituents at C-3 and C-5 of the radical esters in the furanose ring form may account for the better yields of cyclized products in this series.

The regioselectivity of the reaction was deduced by analysis of the NMR spectra. In the case of the crotonyl radical precursors **2** and **4**, the 6-*exo*-trig cyclization mode was indicated by the presence of the ethyl group signals in the ¹H NMR spectra of the respective products **10** and **12**.

For δ -lactones **9** and **11** the analysis of the ¹H NMR spectra was not conclusive. Thus, the connectivity was confirmed by analysis of HMBC contour plots, which showed coupling between H-5, H-5' (lactone **9**) and H-6, H-6' (lactone **11**) and the carbonyl carbon (Figure 2).

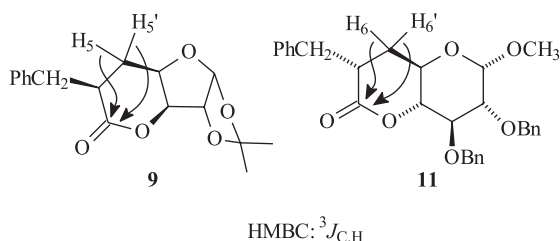


Figure 2. Three-bond correlation between H-5, H-5' (lactone **9**) or H-6, H-6' (lactone **11**) and the carbonyl carbon observed by analysis of the HMBC contour maps.

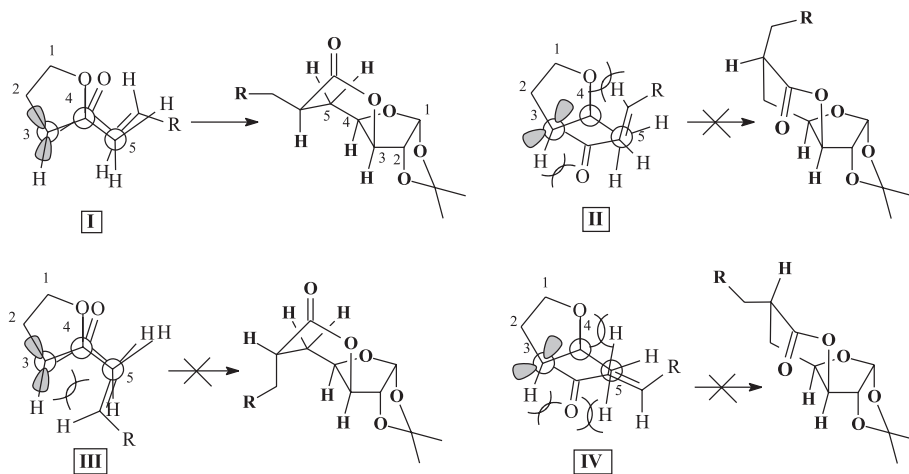


Figure 4. Conformers of the radical esters in the furanose ring forms and the corresponding δ -lactones obtained from the cyclization of the least crowded conformer I.

NOESY experiments allowed the establishment of the configuration of the newly formed stereocenters as *S* for **9** and **10** (correlation between H-3 and H-6) and *R* for **11** and **12** (correlation between H-4 and H-7), as shown in Figure 3.

The stereoselectivity observed in these carbocyclization reactions was rationalized as being the result of the conformational trends of the radical esters in the respective transition states. The conformers of the radical esters in the furanose ring form and the corresponding δ -lactones that should result from their cyclization are shown in Figure 4. Conformer I is less sterically hindered than conformers II, III and IV and, in consequence, the corresponding transition state should be favoured. This explains the formation of δ -lactones **9** and **10**.

Similar arguments were used to rationalize the stereoselectivity observed in the cyclization of the radical esters in the pyranose ring form (Figure 5).

In conclusion, we describe herein the synthesis of carbohydrate-based δ -lactones with complete regio- and stereoselectivity. This is an example of the “off-template” induction by the carbohydrate moiety on the diastereofacial selection. The configuration of the newly

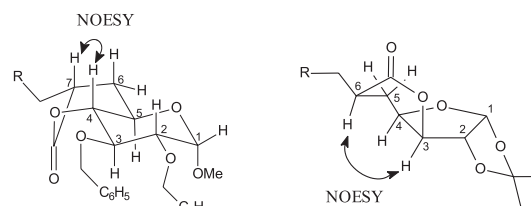


Figure 3. Correlation between H-4 and H-7 (pyranose ring forms) and H-3 and H-6 (furanose ring forms) observed by analysis of the NOESY contour maps.

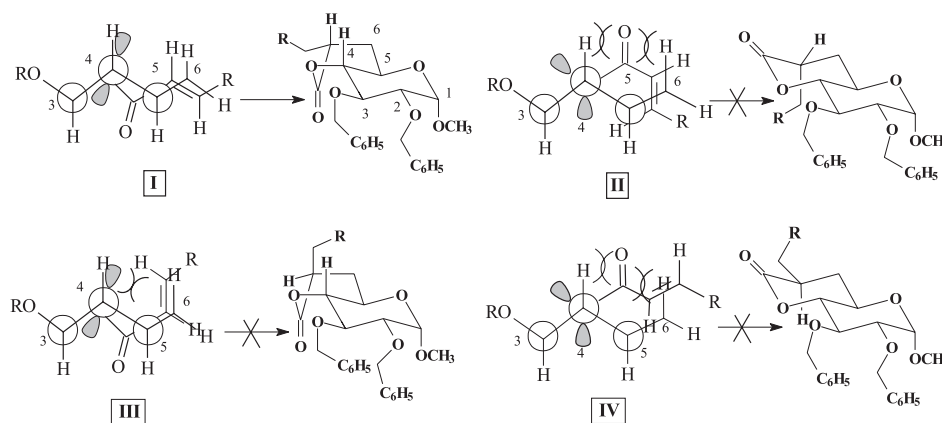


Figure 5. Conformers of the radical esters in the pyranose ring forms and the corresponding δ -lactones obtained from the cyclization of the least crowded conformer I.

formed stereogenic center is dependent on the nature of the carbohydrate. Totally different stereochemical outcome is observed changing from the pyranose to the furanose ring forms.

Experimental

General procedures

All melting points were determined on a Kofler Sybron apparatus and are uncorrected. Optical rotations were determined at 25 °C with a Bellingham & Stanley P20 Polarimeter. The NMR spectra were measured in deuteriochloroform or pyridine 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. Column chromatography was performed with silica gel 60, 70-230 mesh (Merck).

General procedure for the synthesis of the radical precursors

To a 0.05 mol L⁻¹ solution of compound **7**¹⁰ or **8**²² in methylene chloride was added 4-dimethylaminopyridine (0.15 equivalents), carboxylic acid (cinnamic or crotonic acid) (1.5 equivalents) and *N,N'*-dicyclohexylcarbodiimide (1.5 equivalents). The solution was allowed to stand at room temperature for 4 h. The dicyclohexylurea which precipitates was removed by filtration. The filtrate was concentrated to give crude ester which was submitted to chromatography (hexane/EtOAc 8.5:1.5).

3-O-Cinnamoyl-5-deoxy-5-iodo-1,2-O-isopropylidene- α -D-xylofuranose (1). Following the general procedure, compound **7**¹⁰ (0.50 g, 1.7 mmol) was treated with 4-dimethylaminopyridine, cinnamic acid and *N,N'*-

dicyclohexylcarbodiimide. The oily residue was purified by column chromatography to give **1** (0.56 g, 79%) as a white solid: mp 115-116.8 °C; $[\alpha]_D^{25} - 58$ (*c* 2.0, CHCl₃); δ_H (200 MHz, CDCl₃) 7.74 (1 H, d, $J_{7,6}$ 16, 7-H) 7.56-7.40 (5 H, m, Ph), 6.44 (1 H, d, $J_{6,7}$ 16, 6-H), 6.0 (1 H, d, $J_{1,2}$ 3.6, 1-H), 5.46 (1 H, d, $J_{3,4}$ 3.2, 3-H), 4.64 (1 H, d, $J_{2,1}$ 3.6, 2-H), 4.61 (1 H, ddd, $J_{4,3}$ 3.2, $J_{4,5} = J_{4,5}$ 6.0, 4-H), 3.31-3.27 (2 H, m, 5-H and 5'-H), 1.56 (3 H, s, CH₃), 1.33 (3 H, s, CH₃); δ_C (50 MHz, CDCl₃) 165.47 (C=O), 146.45 (7-C), 133.91 (C *ipso*), 130.76-128.24 (Ph), 116.54 (6-C), 112.41 (C(CH₃)₂), 105.24 (1-C), 83.46 (2-C), 79.75 (4-C), 76.24 (3-C), 26.74, 26.22 (2 x CH₃), -2.43 (5-C) (Found: C, 47.71; H, 4.37; Anal. Calc. for C₁₇H₁₉IO₅: C, 47.44; H, 4.42 %).

3-O-Crotonyl-5-deoxy-5-iodo-1,2-O-isopropylidene- α -D-xylofuranose (2). Following the general procedure, compound **7**¹⁰ (0.50 g, 1.7 mmol) was treated with 4-dimethylaminopyridine, crotonic acid and *N,N'*-dicyclohexylcarbodiimide. The oily residue was purified by column chromatography to give **2** (0.47 g, 77%) as a white solid: mp 65.4-65.7 °C; $[\alpha]_D^{25} - 65.3$ (*c* 2.0, CHCl₃); δ_H (200 MHz, CDCl₃) 7.06 (1 H, dq, $J_{7,8}$ 6.9, $J_{7,6}$ 15.5, 7-H), 5.95 (1 H, d, $J_{1,2}$ 3.6, 1-H), 5.87 (1 H, dd, $J_{6,8}$ 1.6, $J_{6,7}$ 15.5, 6-H), 5.37 (1 H, d, $J_{3,4}$ 2.8, 3-H), 4.61-4.52 (2 H, m, 2-H and 4-H), 4.57 (1 H, d, $J_{2,1}$ 3.6, 2-H), 3.27 (1 H, dd, $J_{5,4}$ 6.6, $J_{5,5'}$ 9.7, 5-H), 3.19 (1 H, dd, $J_{5',4}$ 8.3, $J_{5,5'}$ 9.7, 5'-H), 1.92 (3 H, dd, $J_{8,6}$ 1.6, $J_{8,7}$ 6.9, 3 x 8-H), 1.54 (3 H, s, CH₃), 1.31 (3 H, s, CH₃); δ_C (50 MHz, CDCl₃) 164.89 (C=O), 146.74 (7-C), 121.46 (6-C), 112.33 (C(CH₃)₂), 105.19 (1-C), 83.40 (2-C), 79.72 (4-C), 75.89 (3-C), 26.73, 26.19 (2 x CH₃), 18.11 (8-C), -2.41 (5-C); (Found: C, 39.12; H, 4.36; Anal. Calc. for C₁₂H₁₇IO₅: C, 39.13; H, 4.62 %).

Methyl 2,3-di-O-benzyl-4-O-cinnamoyl-6-deoxy-6-iodo- α -D-glucopyranoside (3). Following the general procedure, compound **8**²² (0.52 g, 1.1 mmol) was treated with 4-dimethylaminopyridine, cinnamic acid and *N,N'*-

dicyclohexylcarbodiimide. The oily residue was purified by column chromatography to give **3** (0.37 g, 56%) as a colorless oil: $[\alpha]_D^{25} - 38$ (*c* 2.0, CHCl_3); δ_{H} (200 MHz, CDCl_3) 7.66 (1 H, d, $J_{8,7}$ 16, 8-H), 7.54-7.15 (15 H, m, Ph), 6.29 (1 H, d, $J_{7,8}$ 16, 7-H), 4.92 (1 H, t, $J_{4,3} = J_{4,5}$ 9.4, 4-H), 4.89-4.62 (5 H, m, 4 CH_2Ph and 1-H), 3.99 (1 H, t, $J_{3,4} = J_{3,2}$ 9.4, 3-H), 3.77 (1 H, td, $J_{5,6}$ 2.6, $J_{5,6} = J_{5,4}$ 9.4, 5-H), 3.61 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.4, 2-H), 3.49 (3H, s, OCH_3), 3.27 (1 H, dd, $J_{6,5}$ 2.6, $J_{6,6}$ 10.8, 6'-H), 3.09 (1 H, dd, $J_{6,5}$ 9.4, $J_{6,6}$ 10.8, 6-H); δ_{C} (50 MHz, CDCl_3) 165.7 (C=O), 146.0 (8-C), 138.1 (one of C *ipso*), 137.8 (other of C *ipso*), 134.0 (other of C *ipso*), 130.6-127.5 (Ph), 117.0 (7-C), 98.2 (1-C), 79.6 (2-C), 78.4 (3-C), 75.3, 73.6 (2 x PhCH_2O), 71.9 (4-C), 69.5 (5-C), 55.8 (OCH_3), 4.5 (6-C); (Found: C, 58.36; H, 5.14; Anal. Calc. for $\text{C}_{30}\text{H}_{31}\text{IO}_6$: C, 58.63; H, 5.05 %).

Methyl 2,3-di-O-benzyl-4-O-crotonyl-6-deoxy-6-iodo- α -D-glucopyranoside (4). Following the general procedure, compound **8**²² (0.39 g, 0.8 mmol) was treated with 4-dimethylaminopyridine, crotonic acid and *N,N'*-dicyclohexylcarbodiimide. The oily residue was purified by column chromatography to give **4** (0.25 g, 56%) as a colorless oil: $[\alpha]_D^{25} - 20.2$ (*c* 1.6, CHCl_3); δ_{H} (200 MHz, CDCl_3) 7.36-7.21 (10 H, m, Ph), 6.98 (1 H, dq, $J_{8,9}$ 6.9, $J_{8,7}$ 15.5, 8-H), 5.76 (1 H, dd, $J_{7,9}$ 1.7, $J_{7,8}$ 15.5, 7-H), 4.89-4.60 (5 H, m, 4 x CH_2Ph , 4-H), 4.61 (1 H, d, $J_{1,2}$ 3.6, 1-H), 3.93 (1 H, t, $J_{3,2} = J_{3,4}$ 9.6, 3-H), 3.73 (1 H, td, $J_{5,6}$ 2.4, $J_{5,4} = J_{5,6}$ 9.6, 5-H), 3.57 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.6, 2-H), 3.47 (3 H, s, OCH_3), 3.23 (1 H, dd, $J_{6,5}$ 2.4, $J_{6,6}$ 10.8, 6'-H), 3.05 (1 H, $J_{6,5}$ 9.6, $J_{6,6}$ 10.8, 6-H), 1.88 (3 H, dd, $J_{9,7}$ 1.6, $J_{9,8}$ 6.9, 3 x 9-H); δ_{C} (50 MHz, CDCl_3) 165.20 (C=O), 146.29 (8-C), 138.25, 137.86 (2 x C *ipso*), 128.47-127.49 (Ph); 121.89 (7-C), 98.18 (1-C), 79.49 (2-C), 78.57 (3-C), 75.36, 73.55 (2 x PhCH_2O), 73.37 (4-C), 69.56 (5-C), 55.72 (OCH_3), 18.08 (C-9), 4.48 (6-C); (Found: C, 54.87; H, 5.22; Anal. Calc. for $\text{C}_{25}\text{H}_{29}\text{IO}_6$: C, 54.35; H, 5.25 %).

General procedure for free radical cyclization

To a stirred, boiling solution of radical precursor in nitrogen-saturated benzene (0.01 mol L^{-1}) was added a solution of Bu_3SnH (1.2 equivalents) 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 8:2).

Free radical cyclization of radical precursor 1. Starting from **1** (0.47 g, 1.1 mmol) and following the general

procedure, the δ -lactone **9** (0.10 g, 30%) and the uncyclized product **13** (0.14 g, 42%) were isolated. The δ -lactone **9** was obtained as a white solid; mp 138.5-139.7 °C; $[\alpha]_D^{25} + 218$ (*c* 0.37, CHCl_3); δ_{H} (400 MHz, CDCl_3) 7.33-7.18 (5 H, m, Ph), 5.94 (1 H, d, $J_{1,2}$ 3.6, 1-H), 4.75 (1 H, d, $J_{2,1}$ 3.6, 2-H), 4.60-4.56 (1 H, m, 4-H), 4.55 (1 H, d, $J_{3,4}$ 2.8, 3-H), 3.35 (1 H, dd, $J_{7,6}$ 4.4, $J_{7,7}$ 14.0, 7-H); 2.61 (1 H, dd, $J_{7,6}$ 9.4, $J_{7,7}$ 14.0, 7'-H), 2.54-2.46 (1 H, m, 6-H), 2.36 (1 H, ddd, $J_{5,4}$ 6.4, $J_{5,6}$ 8.2, $J_{5,5}$ 14.2, 5-H), 1.66 (1 H, ddd, $J_{5,4}$ 3.8, $J_{5,6}$ 12.8, $J_{5,5}$ 14.2, 5'-H), 1.46 (3 H, s, CH_3), 1.32 (3 H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 172.92 (C=O), 138.45 (C *ipso*), 129.11, 128.60, 126.66 (Ph), 112.09 ($\text{C}(\text{CH}_3)_2$), 104.86 (1-C), 83.21 (2-C), 81.70 (3-C), 73.65 (4-C), 39.35 (6-C), 36.25 (7-C), 28.10 (5-C), 26.6, 26.2 (2 x CH_3); (Found: C, 67.32; H, 6.64; Anal. Calc. for $\text{C}_{17}\text{H}_{20}\text{O}_5$: C, 67.09; H, 6.62 %).

The uncyclized product **13** was obtained as a white solid; mp 67.9-69.3 °C, lit²³ 73-75 °C; $[\alpha]_D^{25} + 56$ (*c* 1.14, CHCl_3), lit²³ +44 (*c* 4.72, benzene); δ_{H} (200 MHz, CDCl_3) 7.73 (1 H, d, $J_{7,6}$ 16.0, 7-H), 7.56-7.38 (5 H, m, Ph), 6.46 (1 H, d, $J_{6,7}$ 16.0, 6-H), 5.95 (1 H, d, $J_{1,2}$ 3.8, 1-H), 5.25 (1 H, d, $J_{3,4}$ 2.8, 3-H), 4.61 (1 H, d, $J_{2,1}$ 3.8, 2-H), 4.49 (1 H, qd, $J_{4,3}$ 2.8, $J_{4,5}$ 6.4, 4-H), 1.54 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.29 (3 H, d, $J_{5,4}$ 6.4, 3 x 5-H); δ_{C} (50 MHz, CDCl_3) 165.66 (C=O), 145.86 (7-C), 133.94 (C *ipso*), 130.50, 128.83, 128.07 (Ph), 116.89 (6-C), 111.56 ($\text{C}(\text{CH}_3)_2$), 104.41 (1-C), 83.85 (2-C), 77.46 (3-C), 75.13 (4-C), 26.47, 26.04 (2 x CH_3), 13.09 (5-C).

Free radical cyclization of radical precursor 2. Starting from **2** (0.50 g, 1.4 mmol) and following the general procedure, the δ -lactone **10** (0.05 g, 15%) and the uncyclized product **14** (0.22 g, 66%) were isolated. The δ -lactone **10** was obtained as a white solid; mp 91.5-93.4 °C; $[\alpha]_D^{25} + 103$ (*c* 1.3, CHCl_3); δ_{H} (200 MHz, CDCl_3) 5.93 (1 H, d, $J_{1,2}$ 3.8, 1-H), 4.75 (1 H, d, $J_{2,1}$ 3.8, 2-H), 4.72-4.66 (1 H, m, 4-H), 4.57 (1 H, d, $J_{3,4}$ 2.8, 3-H), 2.52 (1 H, ddd, $J_{5,6}$ 6.4, $J_{5,4}$ 8.9, $J_{5,5}$ 14.1, 5'-H), 2.18 (1 H, dq, $J_{6,5} = J_{6,7} = J_{6,7}$ 6.4, $J_{6,5}$ 12.9, 6-H), 1.89 (1 H, tdd, $J_{7,6}$ 6.4, $J_{7,8(\text{CH}_3)}$ 7.6, $J_{7,7}$ 14.1, 7-H), 1.73-1.38 (5 H, m, 5-H, 7'-H and CH_3), 1.33 (3 H, s, CH_3), 1.00 (3 H, t, $J_{8,7} = J_{8,7}$ 7.6 Hz, 8-H (CH_3); δ_{C} (50 MHz, CDCl_3) 173.37 (C=O), 111.98 ($\text{C}(\text{CH}_3)_2$), 104.77 (1-C), 83.06 (2-C), 81.39 (3-C), 72.06 (4-C), 38.73 (6-C), 28.44 (5-C), 26.54, 26.10 (2 x CH_3), 22.88 (7-C), 11.24 (8-C); (Found: C, 59.62, H 7.35; Calc. for $\text{C}_{12}\text{H}_{18}\text{O}_5$: C, 59.49, H, 7.49 %).

The uncyclized product **14** was obtained as an oil; $[\alpha]_D^{25} + 31.9$ (*c* 2.8, benzene), lit²³ +31.0 (*c* 2.8, benzene); δ_{H} (200 MHz, CDCl_3) 7.04 (1 H, dq, $J_{7,8}$ 7.0, $J_{7,6}$ 15.5, 7-H), 5.90 (1 H, d, $J_{1,2}$ 3.8, 1-H), 5.91-5.83 (1 H, m, 6-H), 5.16 (1 H, $J_{3,4}$ 2.8, 3-H), 4.55 (1 H, d, $J_{2,1}$ 3.8, 2-H), 4.47 (1 H, qd, $J_{4,3}$ 2.8, $J_{4,5}$ 6.4, 4-H), 1.90 (3 H, dd, $J_{8,6}$ 1.6, $J_{8,7}$ 7.0, 3 x 8-H), 1.52 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.24 [3 H, d, $J_{5,4}$ 6.4, 5-

H(CH₃); δ_C (50 MHz, CDCl₃) 165.17 (C=O), 146.09 (7-C), 121.72 (6-C), 111.54 (C(CH₃)₂), 104.40 (1-C), 83.86 (2-C), 77.14 (3-C), 75.14 (4-C), 26.49, 26.05 (2 x CH₃), 17.96 (8-C), 13.06 (5-C).

Free radical cyclization of radical precursor 3. Starting from **3** (0.40 g, 0.65 mmol) and following the general procedure, δ -lactone **11** (0.07 g, 22%) and the uncyclized product **15** (0.17 g, 53%) were isolated. The δ -lactone **11** was obtained as a white solid; mp 131.2–132.2 °C; $[\alpha]_D^{25} - 30$ (c 0.8, CHCl₃); δ_H (400 MHz, Py) 7.56–7.24 (15 H, m, Ph), 5.07 (1 H, d, J_{gem} 11.6, one of PhCH₂), 5.02 (1 H, d, J_{gem} 11.6, one of PhCH₂), 4.95 (1 H, d, $J_{1,2}$ 3.6, 1-H), 4.84 (1 H, d, J_{gem} 12.0, one of PhCH₂), 4.79 (1 H, d, J_{gem} 12.0, one of PhCH₂), 4.42 (1 H, t, $J_{4,3} = J_{4,5}$ 9.2, 4-H), 4.24 (1 H, t, $J_{3,4} = J_{3,2}$ 9.2, 3-H), 3.95 (1 H, q, $J_{5,4} = J_{5,6} = J_{5,6'}$ 9.2, 5-H), 3.76 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.2, 2-H), 3.46 (1 H, dd, $J_{8,7}$ 4.8, $J_{8,8'}$ 13.8, 8-H), 3.41–3.33 (4H, m, 7-H and OCH₃), 2.82 (1 H, dd, $J_{8,7}$ 9.2, $J_{8,8'}$ 13.8, 8'-H), 2.02–1.88 (2 H, m, 6-H and 6'-H); δ_C (100 MHz, Py) 173.72 (C=O), 139.51, 139.46, 139.14 (3 x C *ipso*), 129.60–126.89 (Ph), 98.89 (1-C), 79.83 (2-C), 79.15 (4-C), 79.04 (3-C), 75.20, 73.13 (2 x PHCH₂O), 64.07 (5-C), 55.32 (OCH₃), 38.62 (7-C), 37.28 (8-C), 29.63 (6-C).

The uncyclized product **15** was obtained as an oil; $[\alpha]_D^{25} + 12.5$ (c 2.0, CHCl₃); δ_H (400 MHz, CDCl₃) 7.65 (1 H, d, $J_{8,7}$ 16.0, 8-H), 7.52–7.15 (15 H, m, Ph), 6.31 (1 H, d, $J_{7,8}$ 16.0, 7-H), 4.88 (1 H, t, $J_{4,3} = J_{4,5}$ 9.6, 4-H), 4.86 (1 H, d, J_{gem} 11.6, one of PhCH₂), 4.81 (1 H, d, J_{gem} 12.4, one of PhCH₂), 4.69–4.66 (2 H, m, 2 x PhCH₂), 4.56 (1 H, d, $J_{1,2}$ 3.6, 1-H), 3.95 (1 H, t, $J_{3,4} = J_{3,2}$ 9.6, 3-H), 3.82 (1 H, qd, $J_{5,6(CH_3)}$ 6.4, $J_{5,4}$ 9.6, 5-H), 3.61 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.6, 2-H), 3.40 (3 H, s, OCH₃), 1.15 [3 H, d, $J_{6(CH_3),5}$ 6.4, 6-H (CH₃)]; δ_C (100 MHz, CDCl₃) 165.85 (C=O), 145.26 (8-C), 138.57, 138.15, 134.37 (3 x C *ipso*), 128.87–127.38 (Ph), 117.79 (7-C), 98.23 (1-C), 80.04 (2-C), 79.01 (3-C), 75.28 (4-C), 75.23, 75.18 (2 x PhCH₂O), 73.44 (5-C), 55.30 (OCH₃), 17.39 (6-C).

Free radical cyclization of radical precursor 4. Starting from **4** (0.47 g, 0.85 mmol) and following the general procedure, δ -lactone **12** (0.004 g, 1%) and the uncyclized product **16** (0.25 g, 70%) were isolated.

The δ -lactone **12** was obtained as a white solid; δ_H (400 MHz, CDCl₃) 7.30–7.39 (10 H, m, Ph), 4.93 (1 H, d, J_{gem} 10.8, one of PhCH₂), 4.85 (1 H, d, J_{gem} 10.8, one of PhCH₂), 4.83 (1 H, d, J_{gem} 12.0, one of PhCH₂), 4.66 (1 H, d, J_{gem} 12.0, one of PhCH₂), 4.55 (1 H, d, $J_{1,2}$ 3.6, 1-H), 4.04 (1 H, t, $J_{4,3} = J_{4,5}$ 9.2, 4-H), 4.01 (1 H, t, $J_{3,4} = J_{3,2}$ 9.2, 3-H), 3.86 (1 H, q, $J_{5,4} = J_{5,6} = J_{5,6'}$ 9.2, 5-H), 3.51 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.2, 2-H), 3.39 (3 H, s, OCH₃), 2.61–2.52 (1 H, m, 7-H), 2.05 (1 H, ddd, $J_{6,5}$ 9.2, $J_{6,7}$ 10.4, $J_{6,6'}$ 13.5, 6-H), 1.96–1.79 (2 H, m, 6'-H and 8-H), 1.48 (1 H, double quintet, $J_{8,7} = J_{8,9(CH_3)}$ 7.6, $J_{8,8'}$ 14.3, 8'-H), 0.97 [3 H, t, $J_{9(CH_3),8} = J_{9(CH_3),8'}$ 7.6, 9-H (CH₃)]; δ_C (100 MHz, CDCl₃)

173.63 (C=O), 138.43, 138.01 (2 x C *ipso*), 128.45–127.65 (Ph), 98.91 (1-C), 79.13 (4-C), 78.83 (3-C), 78.74 (2-C), 75.55, 73.75 (2 x PHCH₂O), 63.65 (5-C), 55.57 (OCH₃), 38.14 (7-C), 29.25 (6-C), 23.87 (8-C), 11.17 (9-C).

The uncyclized product **16** was obtained as an oil; $[\alpha]_D^{25} + 58.7$ (c 2.0, CHCl₃); δ_H (200 MHz, CDCl₃) 7.36–7.22 (10 H, m, Ph), 6.96 (1 H, dq, $J_{8,9(CH_3)}$ 6.9, $J_{8,7}$ 15.5, 8-H), 5.77 (1 H, dd, $J_{7,9(CH_3)}$ 1.7, $J_{7,8}$ 15.5, 7-H), 4.86–4.61 (5 H, m, 4 x PhCH₂ and 4-H), 4.54 (1 H, d, $J_{1,2}$ 3.6, 1-H), 3.90 (1 H, t, $J_{3,4} = J_{3,2}$ 9.4, 3-H), 3.81–3.70 (1 H, m, 5-H), 3.57 (1 H, dd, $J_{2,1}$ 3.6, $J_{2,3}$ 9.4, 2-H), 3.38 (3 H, s, OCH₃), 1.87 [3 H, dd, $J_{9(CH_3),7}$ 1.7, $J_{9(CH_3),8}$ 6.9, 9-H (CH₃)], 1.12 [3 H, d, $J_{6(CH_3),5}$ 6.2, 6-H (CH₃)]; δ_C (50 MHz, CDCl₃) 165.35 (C=O), 145.36 (8-C), 138.49, 138.02 (2 x C *ipso*), 128.37–127.35 (Ph), 122.30 (7-C), 98.11 (1-C), 79.74 (2-C), 78.99 (3-C), 75.17, 73.40 (2 x PhCH₂O), 74.88 (4-C), 65.37 (5-C), 55.19 (OCH₃), 17.97 [9-C (CH₃)], 17.26 [6-C (CH₃)].

Acknowledgements

We wish to thank Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support.

References

- Jasperse, C. P.; Curran, D. P.; Fevig, T. L.; *Chem. Rev.* **1991**, *91*, 1237.
- Mori, K.; *Tetrahedron* **1989**, *45*, 3233.
- Koch, S. S. C.; Chamberline, A. R.; *J. Org. Chem.* **1993**, *58*, 2725.
- Sharma, G. V. M.; Vepachedu, S. R.; *Tetrahedron Lett.* **1990**, *31*, 4931.
- Xi, Z.; Agback, P.; Sandström, A.; Chattopadhyaya, J.; *Tetrahedron* **1991**, *47*, 9675.
- Velázquez, S.; Camarasa, M. J.; *Tetrahedron Asym.* **1994**, *5*, 2141.
- 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. I.* **2000**, 1853.
- Binatti, I.; Prado, M. A. F.; Alves, R. J.; Souza Filho, J. D.; *J. Braz. Chem. Soc.* **2002**, *13*, 570.
- 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*, in press.
- Levene, P. A.; Raymond, A. L.; *J. Biol. Chem.* **1933**, *102*, 317.
- Bell, D. J.; Lorber, J.; *J. Chem. Soc.* **1940**, 453.
- Garegg, P. J.; Samuelson, B. J.; *J. Chem. Soc., Perkin Trans. I.* **1980**, 2866.
- Hassner, A.; Alexanian, V.; *Tetrahedron Lett.* **1978**, *46*, 4475.

14. Oki, M.; Nakanishi, H.; *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2558.
15. Curran, D. P.; Chang, C. T.; *J. Org. Chem.* **1989**, *54*, 3140.
16. Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B.; Robertson, J.; *J. Chem. Soc., Chem. Commun.* **1990**, 1574.
17. Barth, F.; O-Yang, C.; *Tetrahedron Lett.* **1990**, *31*, 1121.
18. Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O.; *J. Org. Chem.* **1993**, *58*, 3877.
19. Junggebauer, J.; Neumann, W. P.; *Tetrahedron* **1997**, *53*, 1301.
20. Bowman, W. R.; Mann, E.; Parr, J.; *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991.
21. Curran, D. P.; Porter, N. A.; Giese, B.; *Stereochemistry of Radical Reactions*, VHC: Weinheim, 1996, p. 280.
22. Köhn, A.; Schmidt, R. R.; *Liebigs Ann. Chem.* **1987**, 1045.
23. Kawana, M.; Emoto, S.; *Bull. Chem. Soc. Jpn.* **1966**, *39*, 910.

Received: January 3, 2002

Published on the web: February 21, 2003