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Radical Cyclizations on Sugar Templates: Stereoselective Synthesis of Fused γ-Butyrolactones of Carbohydrates

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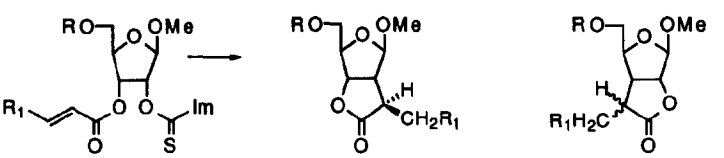
Abstract: A stereoselective method is described for the synthesis of [3.3.0] fused lactones (γ-butyrolactones) of carbohydrates at the 2 and 3 positions of the furanose ring, by intramolecular addition of radicals onto the α-position of α,β-unsaturated esters. A new stereogenic center is formed at an off-template site of the ribofuranose ring, with good diastereoselectivity. Stereocontrol is discussed on the basis of conformational preference in the transition state. These γ-butyrolactones of carbohydrates are useful chiral synthons for the preparation of branched-chain sugars. Opening of the lactone ring afforded homochiral branched-chain sugars having a highly functionalized C-branch at C-2 or C-3.

INTRODUCTION

Free-radical cyclizations are widely used for stereo- and regio-controlled C-C bond formation, and their utility is well recognized in natural product synthesis.[1,2] In the last years radical cyclizations on sugar templates have attracted considerable interest.[3-5] These studies have not only opened new ways for the synthesis of C-branched sugars but also provided a lot of mechanistic information. γ-Butyrolactones are present in a wide range of natural products, many of them having biological activity.[6] γ-Butyrolactones of carbohydrates are considered good candidates for a solution of the "off-template" problem.[7,8]

In a preliminary communication[9] we reported a facile and highly stereoselective method for the synthesis of fused 3,2-γ-butyrolactones of sugars (**2**) by intramolecular addition of alkyl radicals onto the α-position of α,β-unsaturated esters (Scheme 1).



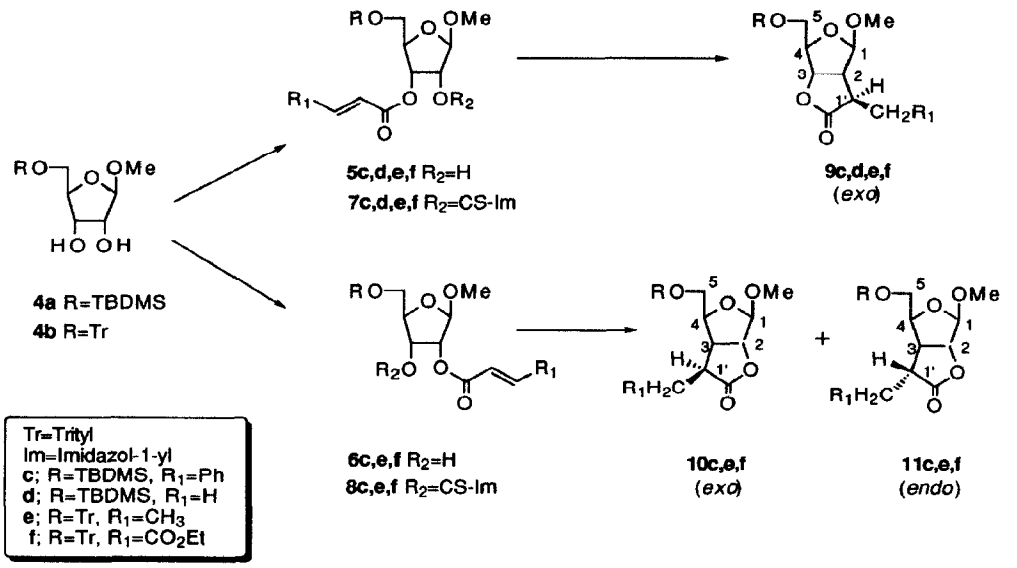
1 **2** **3**

Scheme 1

In these cyclizations a new stereocenter is formed with excellent diastereoselectivity at the "off-template" site of the ribofuranose ring. Here we describe this reaction in detail and extend our studies to the synthesis of fused 2,3-γ-butyrolactones of carbohydrates (**3**). These γ-butyrolactones are potentially useful chiral synthons for preparation of branched-chain sugars. Therefore, we report herein the synthesis of highly functionalized chiral C-2 and C-3 branched-chain sugars through ring opening of the γ-lactone moiety.

RESULTS AND DISCUSSION

Radical precursors **7c-f** and **8c,e,f** were prepared by a two-step reaction sequence as outlined in scheme 2. Thus, reaction of the 5'-*O*-protected sugar derivative **4a** with cinnamoyl chloride in dichloromethane/DMAP gave an isomeric mixture (1:1) of the respective 3- and 2-cinnamoyl derivatives **5c** and **6c** (70% yield). A similar acylation of compounds **4a** and **4b**[10] with crotonyl or acryloyl chloride, gave poor yields of the desired products. However, reaction of **4a** or **4b** with dibutyltin oxide and subsequent treatment of the stannylene intermediates with acryloyl or crotonyl chloride[11] afforded the 3-acryloyl derivative **5d** (60% yield) and a mixture (1:1) of the 3- and 2-crotonyl derivatives **5e** and **6e** (55% yield). Finally, reaction of **4b** with ethylfumaric acid according to the Mukaiyama's procedure[12] gave a mixture (2:1) of the 3- and 2-acyl derivatives **5f** and **6f** (50% yield).



Scheme 2

Treatment of the mixture of 3- and 2-acyl derivatives **5c-f** and **6c,e,f** with thiocarbonyldiimidazole[13] afforded the corresponding radical precursors **7c-f** and **8c,e,f** in good yields (75-90%), which were separated by column chromatography. Slow addition (8 h) of a 0.08 M solution of Bu_3SnH in benzene and a catalytic

amount of AIBN to a 0.02 M refluxing benzene solution of the radical precursors **7cf** and **8c,e,f,** gave the γ-lactones **9c-f, 10c,e,f** and **11c,e,f** in moderate yields (see Table 1), together with the reduction byproducts **12c-f** and **15c,e,f.** In some reactions the byproducts resulting from the addition of $Bu_3Sn^{\cdot}$ or $H^{\cdot}$ radicals onto the double bond of the α,β-unsaturated ester **13d, 14f** and **16f** (Figure 1) were isolated. Slower addition of Bu_3SnH (10-24 h) did not improve the yields of the cyclization products with respect to those of the products resulting from the competing reduction process.

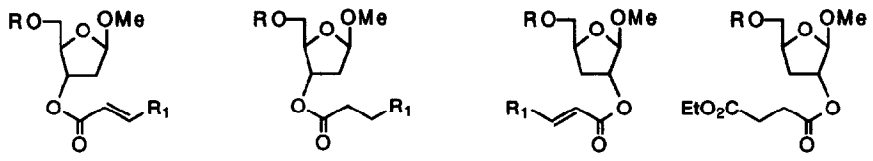


Figure 1

Structures of all new compounds were assigned on the basis of the corresponding analytical and spectroscopic data. The absolute configurarion of the newly formed stereocenter (C-1')[14] in the cyclized products was unequivocally determined, as *R* for **9c,d,e,f** and **11c,e,f** and as *S* for **10c,e,f,** by NOE difference experiments.[15,16]

Table 1. *Cyclization and Reduction Products from Radical Precursors 7c-f and 8c,e,f*

Radical precursor	Product (yield %)[a] γ-butyrolactones[b]	Product[c] ratio *exo*/*endo*	Reduced
7c	**9c** (50)	only *exo*	**12c** (16)
7d	**9d** (26)	only *exo*	**13d** (20)
7e	**9e** (36)	only *exo*	**12e** (24)
7f	**9f** (25)	only *exo*	**14f** (20)
8c	**10c** + **11c** (56)	68/32	**15c** (8)
8e	**10e** + **11e** (42)	57/43	**15e** (24)
8f	**10f** + **11f** (32)	56/44	**16f** (17)

[a] *Yields after purification.* [b] *Total yield of cyclized products.* [c] *Product ratios after purification.*

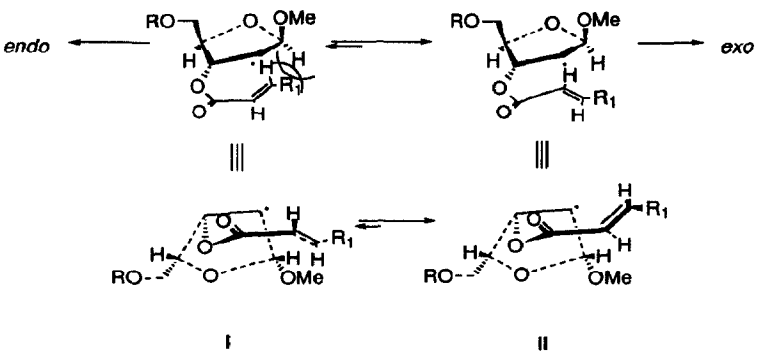
The ratios of the cyclized to the reduced products could be explained by differences in acceptor character of the double bond[17] (R_1=CO_2Et > R_1=Ph > R_1=H, CH_3). As shown in Table 1, the higher acceptor character of the double bond, the higher yields of the cyclized products and the lower yields of the reduced products. The poor yields observed in the cyclization of precursors **7f** and **8f** (R_1=COOEt) could be explained by the high rate

of addition of radicals to the alkene that lead to complex reaction mixtures of the γ-lactones **9f, 10f** and **11f** and the reduced products **14f** and **16f**, together with uncyclized products, which could not be identified.

In the cyclization of radical precursors **7c-f** and **8c,e,f** the γ-butyrolactones formed were *cis*-fused and exclusively the 5-*exo* isomers were obtained.[18] These results indicate that the addition process is kinetically controled[19] and that the radicals add to the "anti-Michael" α-position of the double bond.[20]

The stereoselectivity of these 5-*exo* radical cyclizations is strongly influenced by the position of the prochiral radical (C-2 versus C-3). Thus, when the prochiral radical is generated at carbon C-2 (radical precursors **7c-f**) the cyclization proceeds with excellent diastereoselectivity affording exclusively the *exo* isomers (**9c-f**). However, almost no stereoselectivity was observed when the prochiral radical is generated at carbon C-3 (radical precursors **8c,e,f**) yielding mixtures of the *exo* (**10c,e,f,**) and *endo* (**11c,e,f**) diastereoisomers. Polar and steric effects of the substituents attached to the double bond seem to have no influence on the stereochemical outcome of the reaction.

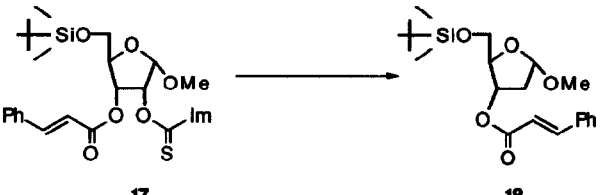
A possible rationale for the stereochemical results obtained in the cyclization of radical precursors **7c-f** is shown in Scheme 3. Beckwith has proposed, for the addition of a radical to a double bond and hence for the cyclization, a transition state in which the radical adopts a trajectory perpendicular to the nodal plane of the π system[18a,21]. The precursors **7c-f** are able to form such a transition state if the α,β-unsaturated ester moiety adopts either the S-*cis* (rotamer II) or S-*trans* (rotamer I) conformation. The unfavourable steric interactions between the anomeric proton and the double bond in the rotamer I drives the equilibrium to the right to rotamer II, thus yielding, exclusively, the *exo* γ-butyrolactones (**9c-f**).



Transition states leading to exo and endo products

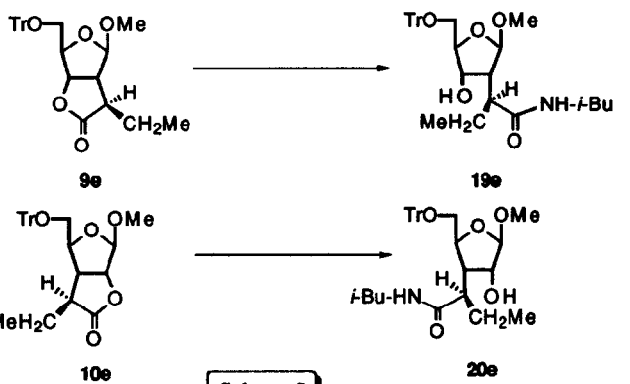
Scheme 3

The importance of the steric effects is supported by the fact that the reaction of the radical precursor **17** (Scheme 4) with Bu_3SnH yielded, exclusively, the reduction product **18**. This seems to indicate that the sterically bulkier OMe group does not allow the radical to adopt the adequate trajectory for the cyclization in the transition state. The reduced selectivity *exo:endo* observed in the cyclization of the radical precursors **8c,e,f** (Scheme 3) points, in this case, to an almost equal participation of both conformers (S-*cis* and S-*trans*) in the transition state.



Scheme 4

Initial attempts to open the γ-lactone moiety of compound **9e** by aminolysis with different amines following standard conditions[22] were unsuccessful. The starting material was recovered unchanged. However, γ-lactones **9e** and **10e** were readily opened by a recently described method which promoted aminolysis of lactones in the presence of aluminun chloride.[23] Thus, treatment of **9e** and **10e** (Scheme 5) with 2 equivalents of iso-butylamine and 1 equivalent of aluminun chloride gave the corresponding 2-*C*- and 3-*C*-branched sugars **19e** and **20e** in 69% and 60% yield, respectively.



Scheme 5

In summary, a stereoselective method for the preparation of fused γ-butyrolactones of carbohydrates at positions 2,3 of the ribofuranose ring has been achieved. In the cyclizations, a higher "off-template" stereoselectivity has been observed when the radical is generated at C-2, where enantiomerically pure γ-butyrolactones were isolated. Aminolysis of the lactone moiety afforded highly functionalized chiral C(2) and C(3) branched chain sugars. The overall result of the process described in this paper is the transformation of a 2(3)-*O*-acyl group to a highly functionalized 3(2)-*C*-branch through a free-radical cyclization and subsequent ring opening methodology.

EXPERIMENTAL SECTION

Chemical Procedures. Microanalyses were obtained with a Heraeus CHN-O-RAPID instrument. ^1H NMR spectra were recorded with a Varian EM-390, a Varian XL-300 and a Bruker AM-200 spectrometer operating at 300 and 200 MHz, and ^{13}C NMR spectra with a Bruker AM-200 spectrometer operating at 50 MHz with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrometer.

Analytical TLC was performed on silica gel 60 F_{254} (Merck). Separations on silica gel were performed by preparative centrifugal circular thin layer chromatography (CCTLC) on a Chromatotron^R (Kiesegel 60 PF 254 gipshaltig (Merck)), layer thickness (1mm), flow rate (5 mL/min), or by flash column chromatography performed with silica gel 60 (230-400 mesh) (Merck). Proximities were established conventionally on the basis of using NOE. For the NOE difference spectra the signals were irradiated during 3 s with γB_2=20 Hz of decoupling power.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-β-D-ribofuranoside (4a).

To a solution of methyl D-ribofuranoside[24] (10.00 g, 6.09 mmol) in dry pyridine (150 mL) *t*-butyldimethylsilylchloride (9.18 g, 6.09 mmol) was added. The mixture was stirred at room temperature for 5 h and the solvent was evaporated to dryness. The residue was taken up in dichloromethane (50 mL), washed with cold 1N HCl (2 x 25 mL) and finally with water (2 x 25 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography (dichloromethane/methanol, 50:1). The faster moving fractions afforded 2.00 g (12 %) of **methyl 5-*O*-(*t*-butyldimethylsilyl)-α-D-ribofuranoside** as a syrup. $[\alpha]_D$ +18.5 (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.88 (s, 9H, *t*-Bu), 3.50 (s, 3H, OCH_3), 3.40 (m, 1H, $J_{5a,5b}$=10, $J_{4,5a}$=6 Hz, H-5a), 3.70 (m, 1H, H-5b), 3.90-4.20 (m, 3H, H-2, H-3, H-4), 5.00 (d, 1H, $J_{1,2}$=4 Hz, H-1). Anal. Calcd. for $C_{12}H_{26}O_5Si$: C, 51.76; H, 9.41. Found: C, 51.91; H, 9.60.

The slower moving fractions afforded 12.50 g (75%) of **4a** as a syrup. $[\alpha]_D$ -57.6 (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.88 (s, 9H, *t*-Bu), 3.30 (s, 3H, OCH_3), 3.45 (m, 1H, $J_{5a,5b}$=10, $J_{4,5a}$=6 Hz, H-5a), 3.70 (m, 1H, H-5b), 3.90-4.30 (m, 3H, H-2, H-3, H-4), 4.80 (s, 1H, H-1). Anal. Calcd. for $C_{12}H_{26}O_5Si$: C, 51.76; H, 9.41. Found: C, 52.01; H, 9.65.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cynnamoyl-β-D-ribofuranoside and Methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*O*-cynnamoyl-β-D-ribofuranoside (5c and 6c).

To an ice cooled solution of **4a** (1.97 g, 7.07 mmol) in dry dichloromethane (50 mL) containing 4-dimethylaminopyridine (1 g, 8.18 mmol), a solution of cynnamoyl chloride (1.20 g, 7.20 mmol) in dichloromethane (4 mL) was slowly added and the mixture was stirred at room temperature for 3 h. The solvent was evaporated to dryness. The residue was purified by flash-column chromatography (hexane/ethyl acetate, 5:1) to afford 1.96 g (70% yield) of a (1:1) mixture of **5c** and **6c** as a syrup. IR (film) 3450 (OH), 3500 (OH), 1710 (CO ester), 1640 (C=C); ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.90 (s, 18H, 2*t*-Bu), 2.30, 2.50 (2 bs, 2H, 2OH), 3.40 (s, 6H, $2OCH_3$), 3.70-3.80 (m, 4H, 4H-5), 4.00-4.50 (m, 4H, H-2_{5c}, H-3_{6c}, 2H-4), 4.87, 4.90 (2s, 2H,2H-1), 5.10-5.40 (m, 2H, H-2_{6c}, H-3_{5c}), 6.50 (d, 2H, J=4 Hz, 2C*H*=CHPh), 7.30-7.50 (m, 10H, 2Ph), 7.70 (d, 2H, 2CH=C*H*Ph). Anal. Calcd. for $C_{21}H_{32}O_6Si$: C, 61.73; H, 7.90. Found: C, 61.95; H, 8.11.

Methyl 3-*O*-acryloyl-5-*O*-(*t*-butyldimethylsilyl)-β-D-ribofuranoside (5d).

Compound **4a** (2.00 g, 7.18 mmol) was dissolved in dry methanol (60 mL) containing dibutyltin oxide (1.78 g, 7.18 mmol). The mixture was heated to reflux, under an stream of argon, until it became clear. The solvent was removed at reduced pressure. The residue (the stannylene derivative) was suspended in dry dioxane (100 mL) containing NEt_3 (1.18 mL), and then, a solution of freshly distilled acryloyl chloride (0.73 mL, 7.89 mmol) in dry dioxane (2 mL) was added dropwise. The reaction was stirred at room temperature for 3 h and then evaporated to dryness. The residue was taken up in chloroform (25 mL), washed with water (2 x 15 mL) dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The residue was purified by column chromatography (hexane/ethyl acetate, 5:1) to give compound **5d** (1.4 g, 60%) as a syrup. IR (film) 3440 (OH), 1720 (CO), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.90 (s, 9H, *t*-Bu), 2.40 (bs, 1H, OH), 3.40 (s, 3H, OCH_3), 3.67-3.80 (m, 2H, 2H-5), 4.35-4.10 (m, 2H, H-2, H-4), 4.87 (d, 1H, $J_{1,2}$=3 Hz, H-1), 5.22 (t, 1H, $J_{2,3}$=$J_{3,4}$=4.5 Hz, H-3), 5.80-6.60 (m, 3H, C*H*=CH_2). Anal. Calcd. for $C_{15}H_{28}O_6Si$: C, 54.19; H, 8.49. Found: C, 54.43; H, 8.58.

Methyl 3-*O*-crotonyl-5-*O*-trityl-β-D-ribofuranoside and Methyl 2-*O*-crotonyl-5-*O*-trityl-β-D-ribofuranoside (5e and 6e).

Following the method described for the synthesis of **5d**, compound **4b** (1.60 g, 3.93 mmol) was treated with dibutyltin oxide (1.00 g, 3.93 mmol) and crotonyl chloride (0.39 mL, 4.32 mmol). The oily residue, obtained after the work-up, was purified by column chromatography (chloroform/acetone, 20:1) to give 1.69 g (92% yield) of a (1:1) mixture of **5e** and **6e** as a syrup. IR (film) 3450 (OH), 1720 (CO), 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.80 (dd, 6H, 2C*H*$_3$-CH=), 3.00-3.30 (m, 10H, 2OCH_3, 4H-5), 4.10-4.30 (m, 4H, 2H-4, H-2$_{5e}$, H-3$_{6e}$), 4.80-5.20 (m, 4H, 2H-1, H-3$_{5e}$, H-2$_{6e}$), 5.80 (m, 2H, J=15 Hz, 2C*H*=CH-CH_3), 6.80-7.10 (m, 2H, 2CH=C*H*-CH_3), 7.10-7.47 (m, 30H, 6Ph). Anal. Calcd. for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.65; H, 6.53.

Methyl 3-*O*-ethylfumaroyl-5-*O*-trityl-β-D-ribofuranoside and Methyl 2-*O*-ethylfumaroyl-5-*O*-trityl-β-D-ribofuranoside (5f and 6f).

To a suspension of 2-choro-1-methylpyridinium iodide (1.50 g, 5.88 mmol) in dry dichloromethane (12 mL) was added a solution of **4b** (2.00 g, 4.9 mmol), ethylfumaric acid (0.70 g, 4.9 mmol) and Bu_3N (2.16 g, 11.76 mmol) under an argon atmosphere. The reaction was heated to 70°C for 4 h. After evaporation of the solvent, the residue was purified by column chromatography (hexane/ethyl acetate, 3:1) to give 1.20 g (50%) of a (2:1) mixture of **5f** and **6f** as a syrup. IR (film) 3500 (OH), 1710 (CO), 1635 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.30 (t, 6H, J=7 Hz, 2C*H*$_3$-CH_2-O), 1.92, 2.12 (2bs, 2H, 2OH), 3.20-3.40 (m, 10H, 2OCH_3, 4H-5), 4.22 (m, 8H, 2CH_2, 2H-4, H-2$_{5f}$, H-3$_{6f}$), 4.87, 4.92 (2s, 2H, 2H-1), 5.17 (d, 1H, H-2$_{6f}$), 5.30 (t, 1H, H-3$_{5f}$), 6.90 (d, 2H, C*H*=C*H*), 7.20-7.47 (m, 30H, 6Ph). Anal. Calcd. for $C_{31}H_{32}O_8$: C, 69.91; H, 6.06. Found: C, 70.04; H, 6.23.

General Procedure for the Synthesis of the Radical Precusors 7c-f and 8c,e,f.

To a solution of the 2(3)-*O*-acyl-5-*O*-protected-carbohydrate **5c-f, 6c,e,f** (1 mmol) in dry DMF (15 mL), 1,1'-thiocarbonyldiimidazole (3 mmol) was added, and the reaction was stirred at room temperature overnight. The reaction mixture was treated with a (2:1) mixture of ethyl acetate:water (150 mL). The organic phase was separated, washed with water (2 x 50 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography. Due to the instability of the compounds they were immediately used in the next step.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cynnamoyl-2-*O*-(imidazol-1-yl)thiocarbonyl-β-D-ribofuranoside and Methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*O*-cynnamoyl-3-*O*-(imidazol-1-yl)thiocarbonyl-β-D-ribofuranoside (7c and 8c).

The general procedure was followed with a (1:1) mixture of **5c** and **6c** (1.70 g, 4.16 mmol). The residue was chromatographed (chloroform/acetone, 100:1). The faster moving fractions afforded 0.71 g (33%) of **8c** as a syrup. IR (film) 1710 (CO), 1635 (C=C), 1170 cm^{-1} (C=S); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.03 (s, 9H, *t*-Bu), 3.43 (s, 3H, OCH_3), 3.83 (m, 2H, 2H-5), 4.44 (m, 1H, H-4), 5.08 (d, 1H, $J_{1,2}$=2 Hz, H-1), 5.52 (dd, 1H, $J_{2,3}$=5.1 Hz, H-2), 6.11 (t, 1H, $J_{3,4}$=5 Hz, H-3), 6.38 (d, 1H, J=16 Hz C*H*=CHPh), 6.98, 7.60, 8.27 (3s, 3H, imidazole), 7.37, 7.43 (2m, 5H, Ph), 7.63 (d, 1H, CH=C*H*Ph).

The slower moving fractions afforded 1.12 g (52%) of **7c** as a syrup. IR (film) 1710 (CO), 1640 (C=C), 1170 cm^{-1} (C=S); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.01 (s, 9H, *t*-Bu), 3.43 (s, 3H, OCH_3), 3.81 (m, 2H, 2H-5), 4.32 (m, 1H, H-4), 5.17 (d, 1H, $J_{1,2}$=1.3 Hz, H-1), 5.64 (dd, 1H, $J_{2,3}$=5.0, $J_{3,4}$=6 Hz, H-3), 5.91 (dd, 1H, H-2), 6.33 (d, 1H, J=16 Hz, C*H*=CHPh), 7.01, 7.61, 8.32 (3s, 3H, imidazole), 7.37, 7.43 (2m, 5H, Ph), 7.61 (d, 1H, CH=C*H*Ph).

Methyl 3-*O*-acryloyl-5-*O*-(*t*-butyldimethylsilyl)-2-*O*-(imidazol-1-yl)thiocarbonyl-β-D-ribofuranoside (7d).

The general procedure was followed with **5d** (0.96 g, 2.88 mmol) and after column chromatography (hexane/ethyl acetate, 5:1) 0.70 g (80%) of **7d** was obtained as a syrup. IR (film) 1720 (CO), 1635 (C=C), 1170 cm^{-1} (C=S); ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.85 (s, 9H, *t*-Bu), 3.40 (s, 3H, OCH_3), 3.77 (d, 2H, $J_{5a,5b}$=4.0 Hz 2H-5), 4.27 (d, 1H, H-4), 5.22 (s, 1H, H-1), 5.60 (t, 1H, $J_{2,3}=J_{3,4}$=6.0 Hz, H-3), 5.80-6.50 (m, 4H, H-2, $CH=CH_2$), 7.00, 7.60, 8.30 (s, 3H, imidazole).

Methyl 3-*O*-crotonyl-2-*O*-(imidazol-1-yl)thiocarbonyl-5-*O*-trityl-β-D-ribofuranoside and Methyl 2-*O*-crotonyl-3-*O*-(imidazol-1-yl)thiocarbonyl-5-*O*-trityl-β-D-ribofuranoside (7e and 8e).

The general procedure was followed with a (1:1) mixture of **5e** and **6e** (2.09 g, 4.39 mmol). The residue was chromatographed (hexane/ethyl acetate, 3:1). The faster moving fractions afforded 1.51 g (45%) of **8e** as a syrup. IR (film) 1720 (CO), 1640 (C=C), 1175 (C=S); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1,80 (dd, 3H, CH_3-CH=), 3,30 (m, 5H, OCH_3, 2H-5), 4.40 (m, 1H, H-4), 5.00 (s, 1H, H-1), 5.30-6.20 (m, 3H, H-2, H-3, CH=CH-CH_3), 6.80-7.10 (m, 2H, imidazole, CH=CH-CH_3), 7.20-7.60 (m, 16H, Tr, imidazole), 8.20 (s, 1H, imidazole).
The slower moving fractions gave 1.50 g (45%) of **7e** as a syrup. IR (film) 1720 (CO), 1640 (C=C), 1180 (C=S); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.80 (dd, 3H, CH_3-CH=), 3.30 (m, 5H, OCH_3, 2H-5), 4.25 (m, 1H, H-4), 5.16 (s, 1H, H-1), 5.40-6.20 (m, 3H, H-2, H-3, CH=CH-CH_3), 6.80-7.10 (m, 2H, imidazole, CH=CH-CH_3), 7.20-7.60 (m, 16H, 3Ph, imidazole), 8.25 (s, 1H, imidazole).

Methyl 3-*O*-ethylfumaroyl-2-*O*-(imidazol-1-yl)thiocarbonyl-5-*O*-trityl-β-D-ribofuranoside and Methyl 2-*O*-ethylfumaroyl-3-*O*-(imidazol-1-yl)thiocarbonyl-5-*O*-trityl-β-D-ribofuranoside (7f and 8f).

The general procedure was followed with a (2:1) mixture of **5f** and **6f** (1.10 g, 2.06 mmol). The residue was chromatographed (hexane/ethyl acetate, 2:1). The faster moving fractions afforded 0.32 g (25%) of **8f** as a syrup. IR (film) 1710 (CO), 1635 (C=C), 1175 (C=S); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1,30 (t, 3H, J=7 Hz, O-CH_2-CH_3), 3.20-3.40 (m, 5H, OCH_3, 2H-5), 4.22 (q, 2H, O-CH_2-CH_3), 4.47 (m, 1H, H-4), 5.25 (d, 1H, $J_{1,2}$=1.5 Hz, H-1), 5.57 (dd, 1H, $J_{2,3}$=4,5 Hz, H-2), 6.15 (t, 1H, H-3), 6.80 (s, 2H, CH=CH), 7.03 (s, 1H, imidazole), 7.10-7.50 (m, 16H, 3Ph, imidazole), 8.20 (s, 1H, imidazole).
The slower moving fractions afforded 0.66 g (50%) of **7f** as a syrup. IR (film) 1710 (CO), 1635 (C=C), 1175 (C=S); ^1H NMR ($CDCl_3$, 90 MHz) δ: 1.27 (t, 3H, J=7 Hz, O-CH_2-CH_3), 3.20-3.40 (m, 5H, OCH_3, 2H-5), 4.10-4.40 (m, 3H, O-CH_2-CH_3, H-4), 5.12 (s, 1H, H-1), 5.62 (t, 1H, $J_{2,3}=J_{3,4}$=4.5 Hz, H-3), 5.97 (d, 1H, H-2), 6.67 (s, 2H, CH=CH), 7.03 (s, 1H, imidazole), 7.10-7.50 (m, 16H, 3Ph, imidazole), 8.27 (s, 1H, imidazole).

Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cinnamoyl-2-*O*-(imidazol-1-yl)thiocarbonyl-α-D-ribofuranoside (17).

a) Following the method described for the synthesis of **5c** and **6c**, **methyl 5-*O*-(*t*-butyldimethylsilyl)-α-D-ribofuranoside** (1.00 g, 3.59 mmol) was treated with 4-dimethylaminopyridine and cinnamoyl chloride. The oily residue, obtained after the work-up, was purified by column chromatography (hexane/ethyl acetate, 5:1) to give 0.89 g (64% yield) of a (4:1) mixture of **methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cynnamoyl-α-D-ribofuranoside and methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*O*-cinnamoyl-α-D-ribofuranoside** as a syrup. IR (film) 3450 (OH), 1710 (CO ester), 1640 (C=C); ^1H NMR ($CDCl_3$, 90 MHz) δ: 0.88 (s, 18H, 2*t*-Bu), 2.00, 2.60 (2 bs, 2H, 2OH), 3.50 (s, 6H, $2OCH_3$), 3.45-3.75 (m, 4H, 4H-5), 4.10-4.50 (m, 4H, H-2, H-3, 2H-4), 4.90-5.50 (m, 4H, 2H-1, H-2, H-3), 6.50 (d, 2H, J=4.0 Hz, 2CH=CHPh), 7.30-7.50 (m, 10H, 2Ph), 7.70 (d, 2H, 2CH=CHPh). Anal. Calcd. for $C_{21}H_{32}O_6Si$: C, 61.73; H, 7.90. Found: C, 61.87; H, 8.00.
b) According to the general procedure, described for the synthesis of the radical precusors, the above obtained mixture (0.80 g, 1.96 mmol) was treated with 1,1'-thiocarbonyldiimidazole. The residue was chromatographed (chloroform/acetone, 100:1). The faster moving fractions afforded 0.15 g (15%) of a syrup which was

identified as **methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*O*-cynnamoyl-3-*O*-(imidazol-1-yl)thiocarbonyl-α-D-ribofuranoside.** IR (film) 1710 (CO), 1635 (C=C), 1170 (C=S); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.90 (s, 9H, *t*-Bu), 3.50 (s, 3H, OCH_3), 3.90-4.15 (m, 2H, 2H-5), 4.25 (m, 1H, H-4), 5.21 (d, 1H, $J_{1,2}$=4,0 Hz, H-1), 5.50 (dd, 1H, $J_{2,3}$=4,8 Hz, H-2), 6.10 (t, 1H, $J_{3,4}$=5.5 Hz, H-3), 6.41 (d, 1H, J=16.0 Hz C*H*=CHPh), 6.98, 7.55, 8.21 (3s, 3H, imidazole), 7.35, 7.41 (2m, 5H, Ph), 7.61 (d, 1H, CH=C*H*Ph).
The slower moving fractions afforded 0.61 g (60%) of a syrup which was identified as **17.** IR (film) 1710 (CO), 1635 (C=C), 1170 (C=S); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0,91 (s, 9H, *t*-Bu), 3.44 (s, 3H, OCH_3), 3.81 (m, 1H, H-5a), 3.91 (m, 1H, $J_{5a,5b}$=11.2 Hz, H-5b), 4.31 (m, 1H, $J_{4,5a}$=$J_{4,5b}$=2,4 Hz, H-4), 5.34 (d, 1H, $J_{1,2}$=4,3 Hz, H-1), 5.57 (dd, 1H, $J_{3,4}$=2.3 Hz, H-3), 5.64 (dd, 1H, $J_{2,3}$=6.9 Hz, H-2), 6.49 (d, 1H, J=16 Hz, C*H*=CHPh), 6.95, 7.57, 8.28 (3s, 3H, imidazole), 7.38, 7.49 (2m, 5H, Ph), 7.70 (d, 1H, CH=C*H*Ph).

General Procedure for Free Radical Cyclization of the Radical Precusors 7c-f, 8c,e,f and 17. A 0.8 M solution of Bu_3SnH (1.5 equiv.) and AIBN (cat.) in dry benzene was injected during 8 h (syringe pump), under argon, to a stirred 0.02 M solution of the radical precursor **7c-f, 8c,d,f** or **17** in refluxing benzene, previously degassed with argon for 30 min. At the end of the addition refluxing was continued for additional 2 h. The mixture was cooled to room temperature, treated with a 10% aqueous solution of KF (20 mL) and stirred overnight. The two layers were separated, the aqueous phase extracted with ethyl ether (2 x 10 mL), and the combined organic extracts were dried with Na_2SO_4 and evaporated. Repeated chromatography of the residue, first by flash column chromatography and then by preparative CCTLC on the chromatotron, is required to give pure the γ-lactones.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*C*-[(*R*)carboxybenzylmethyl]-2-deoxy-3,2-γ-lactone-β-D-ribofuranoside (9c).
According to the general procedure compound **7c** (0.73 g, 1.41 mmol) was treated with Bu_3SnH/AIBN for 8 h. The residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1). The faster moving fractions afforded 0.09 g (16%) of a white foam which was identified as **methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cinnamoyl-2-deoxy-β-D-ribofuranoside (12c).** IR (KBr) 1710 (CO), 1640 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.88 (s, 9H, *t*-Bu), 2.17 (ddd, 1H, $J_{2a,2b}$=9.6, $J_{2a,3}$=4.2, $J_{1,2a}$=5.4 Hz, H-2a), 2.38 (ddd, 1H, $J_{2b,3}$=6.8, $J_{1,2b}$=3.1 Hz, H-2b), 3.35 (s, 3H, OCH_3), 3.66 (m, 1H, $J_{4,5a}$=6.7, $J_{5a,5b}$=10.5 Hz, H-5a), 3.74 (m, $J_{4,5b}$=5,7 Hz, 1H, H-5b), 4.16 (m, 1H, $J_{3,4}$=2.7 Hz, H-4), 5.15 (dd, 1H, H-1), 5.37 (m, 1H, H-3), 6.40 (d, 1H, J=16 Hz, C*H*=CHPh), 7.30, 7.50 (2 m, 5H, Ph), 7.66 (d, 1H, CH=C*H*Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 36.84 (CH_2Ph), 45.17, 51.32 (*C*HCH_2Ph, C-2), 55.00 (OCH_3), 63.45 (C-5), 83.18, 85.53 (C-3, C-4), 110.3 (C-1), 177.52 (CO). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.35; H, 8.11.
The slower moving fractions afforded a syrup that was purified by preparative CCTLC (dichloromethane/methanol, 100:1) to give **9c** (0.33 g, 50%) as a white foam. $[\alpha]_D$ -2 (c 1, $CHCl_3$). IR (KBr) 1770 cm^{-1} (CO lactone); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (s, 9H, *t*-Bu), 2.86 (m, 3H, CH_2-1', H-2), 3.12 (s, 3H, OCH_3), 3.18 (m, 1H, $J_{1',2}$=10.8 Hz, H-1'), 3.45 (m, 1H, $J_{5a,5b}$=10.2, $J_{4,5a}$=9.0 Hz, H-5a), 3.60 (m, 1H, $J_{4,5b}$=5.6 Hz, H-5b), 4.10 (m, 1H, H-4), 4.44 (s, 1H, H-1), 4.64 (dd, 1H, $J_{2,3}$=7.2, $J_{3,4}$=1.6 Hz, H-3), 7.34 (m, 5H, Ph). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.01; H, 8.00.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*C*-[(*R*)carboxymethylmethyl]-2-deoxy-3,2-γ-lactone-β-D-ribofuranoside (9d). The general procedure was followed with **7d** (0.45 g, 1.02 mmol). The residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1). The faster moving fractions afforded 0.11 g (20%) of a syrup which was identified as **methyl 5-*O*-(*t*-butyldimethylsilyl)-2-deoxy-3-*O*-[3-(tributylstannyl)propionyl]-β-D-ribofuranoside (13d).** IR (KBr) 1735 cm^{-1} (CO aliphatic ester); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.80-1.50 (m, 38H, *t*-Bu, Bu_3Sn, CH_2-CH_2SnBu_3), 2.07 (dt, 1H, $J_{1,2a}$=$J_{2a,3}$=5.0, $J_{2a,2b}$=9.9 Hz, H-2a), 2.28 (ddd, 1H, $J_{1,2b}$=3,2, $J_{2b,3}$=6.8 Hz, H-2b), 2.41 (dd, 2H, J_2=6.9, 8.6 Hz, CO-CH_2-

CH_2), 3.27 (s, 3H, OCH_3), 3.68 (m, 1H, $J_{4,5a}$=6.6, $J_{5a,5b}$=10.0 Hz, H-5a), 3.70 (m, 1H, $J_{4,5b}$=5.5 Hz, H-5b), 4.16 (m, 1H, $J_{3,4}$=2.8 Hz, H-4), 5.11 (dd, 1H, H-1), 5,20 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 3.15 (CH_2SnBu_3), 8.93, 13.68, 27.37, 29.14 (Bu_3Sn), 31.50 ($COCH_2CH_2SnBu_3$), 39.03 (C-2), 55.32 (OCH_3), 64.88 (C-5), 75.43, 83.06 (C-3, C-4), 105.63 (C-1), 174.86 (CO). Anal. Calcd. for $C_{27}H_{56}O_5SiSn$: C, 53.37; H, 9.29. Found: C, 53.0; H, 9.00.

The slower moving fractions afforded a syrup which was purified by preparative CCTLC (dichloromethane/methanol, 100:1) to give **9d** (0.08 g, 26%) as an amorphous solid. $[\alpha]_D$ -30.0 (c 1, $CHCl_3$). IR (KBr) 1780 cm^{-1} (CO lactone); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (s, 9H, *t*-Bu), 1.35 (d, 1H, $J_{CH_3,H-1'}$=7.7, Hz, CH_3-1'), 2.60 (m, 1H, H-1'), 2.73 (m, 1H, $J_{1',2}$=$J_{2,3}$=6.5 Hz, H-2), 3.28 (s, 3H, OCH_3), 3.57 (m, 1H, $J_{5a,5b}$=10.2, $J_{4,5a}$=6.9 Hz, H-5a), 3.70 (m, 1H, $J_{4,5b}$=5.6 Hz, H-5b), 4.21 (m, 1H, H-4), 4.87 (d, 1H, $J_{1,2}$=0.5 Hz, H-1), 5.00 (dd, 1H, $J_{2,3}$=7.5, $J_{3,4}$=1.7 Hz, H-3). Anal. Calcd. for $C_{15}H_{28}O_5Si$: C, 56.93; H, 8.92. Found: C, 57.02; H, 8.98.

Methyl 2-*C*-[(*R*)carboxyethylmethyl]-2-deoxy-5-*O*-trityl-3,2-γ-lactone-β-D-ribofuranoside (9e).

The general procedure was followed with **7e** (1.20 g, 2.05 mmol). The residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1). The faster moving fractions afforded 0.20 g (24%) of a syrup which was identified as **methyl 3-*O*-crotonyl-2-deoxy-5-*O*-trityl-β-D-ribofuranoside (12e).** IR (film) 1720 (CO), 1635 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.86 (dd, 3H, CH_3-CH=), 2.09 (dt, 1H, $J_{1,2a}$=$J_{2a,3}$=5.1, $J_{2a,2b}$=9.9 Hz, H-2a), 2.31 (ddd, 1H, $J_{1,2b}$=3.2, $J_{2b,3}$=6.7 Hz, H-2b), 3.20 (m, 2H, 2H-5), 3.28 (s, 3H, OCH_3), 4.19 (m, 1H, $J_{3,4}$=3.1, $J_{4,5a}$=$J_{4,5b}$=5.5 Hz, H-4), 5.11 (dd, 1H, H-1), 5.26 (m, 1H, H-3), 5.77-5.85 (m, 1H, CH=CH-CH_3), 6.90-7.10 (m, 1H, CH=CH-CH_3), 7.20-7.50 (m, 15H, 3Ph). Anal. Calcd. for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.76; H, 6.40.

The next moving fractions gave **9e** (0.32 g, 36%) as an amorphous solid. $[\alpha]_D$ -11.8 (c 1, $CHCl_3$). IR (KBr) 1770 cm^{-1} (CO lactone); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.01 (t, 3H, CH_3-CH_2), 1.62, 1.87 (2m, 2H, CH_2-1'), 2.49 (m, 1H, H-1'), 2.68 (m, 1H, $J_{1',2}$=$J_{2,3}$=6.5 Hz, H-2), 3.15 (s, 3H, OCH_3), 3.24 (m, 2H, H-5), 4,37 (m, 1H, H-4), 4.82 (s, 1H, H-1), 4.87 (dd, 1H, $J_{3,4}$=1.7 Hz, H-3), 7.20-7.50 (m, 15H, 3 Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.07 (CH_2CH_3), 24.36 (CH_2CH_3), 44.48, 51.59 ($CHCH_2CH_3$, C-2), 54.90 (OCH_3), 64.03 (C-5), 83.13, 84.26 (C-3, C-4), 110.37 (C-1), 177.94 (CO). Anal. Calcd. for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.73; H, 6.29.

Methyl 2-*C*-[(*R*)carboxy(etoxycarbonylmethyl)methyl]-2-deoxy-5-*O*-trityl-3,2-γ-lactone-β-D-ribofuranoside (9f).

According to the general procedure compound **7f** (0.30 g, 0.47 mmol) was treated with Bu_3SnH/AIBN. The residue was purified by flash column chromatography (hexane/ethyl acetate, 5:1). The faster moving fractions afforded 0.06 g (20%) of a syrup which was characterized as **methyl 2-*O*-deoxy-3-*O*-ethylsuccinyl-5-*O*-trityl-β-D-ribofuranoside (14f).** IR (film) 1735 cm^{-1} (CO aliphatic esther); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, 3H, J=7.0 Hz, CH_2-CH_3), 2.06 (dt, 1H, $J_{2a,2b}$=10.0, $J_{1,2a}$=$J_{2a,3}$=5.0 Hz, H-2a), 2.28 (ddd, 1H, $J_{1,2b}$=3.2, $J_{2b,3}$=6.7 Hz, H-2b), 2.58 (s, 4H, CO-CH_2-CH_2-CO), 3.19 (m, 2H, 2H-5), 3.27 (s, 3H, OCH_3), 4.14 (m, 3H, H-4, CH_2-CH_3), 5.10 (dd, 1H, H-1), 5.23 (m, 1H, H-3), 7.20-7.40 (m, 15H, Tr); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.17 (CH_2-CH_3), 29.14, 29.25 (CO-CH_2-CH_2-CO), 38.97 (C-2), 55.33 (OCH_3), 60.71 (CH_2-CH_3), 64.79 (C-5), 75.91, 82.95 (C-3, C-4), 105.62 (C-1), 171.64, 172.08 (2CO). Anal. Calcd. for $C_{31}H_{34}O_7$: C, 71.79; H, 6.61. Found: C, 71.56; H, 6.45.

The slower moving fractions afforded a syrup that was purified by preparative CCTLC (dichloromethane/methanol, 50:1) to give **9f** (0.06 g, 25%) as a syrup. $[\alpha]_D$ -1.4 (c 1, $CHCl_3$). IR (KBr) 1780 (CO lactone), 1735 cm^{-1} (CO aliphatic ester); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.28 (t, 3H, CH_2-CH_3) 2.75 (m, 4H, CH_2-1', H-1', H-2), 3.10 (s, 3H, OCH_3), 3.19 (m 1H, $J_{5a,5b}$=9.4, $J_{4,5a}$=8.2 Hz, H-5a), 3.30 (m, 1H, $J_{4,5b}$=6.2 Hz, H-5b), 4.15 (q, 2H, CH_2-CH_3), 4.94 (s, 1H, H-1), 4.98 (dd, 1H, $J_{2,3}$=7.1, $J_{3,4}$=1.8 Hz, H-3), 7.20-

7.50 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.08 (CH_2-CH_3), 35.14 (CH_2-CO), 39.39 (CH-CH_2-CO), 52.17 (C-2), 54.64 (OCH_3), 61.50 (CH_2-CH_3), 64.24 (C-5), 83.35, 84.30 (C-3, C-4), 109.83 (C-1), 170.75 (COOEt), 177.13 (CO lactone). Anal. Calcd. for $C_{31}H_{32}O_7$: C, 72.07; H, 6.24. Found: C, 72.30; H, 6.42.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*C*-[(*S*)carboxybenzylmethyl]-3-deoxy-2,3-γ-lactone-β-D-ribofuranoside and Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*C*-[(*R*)carboxybenzylmethyl]-3-deoxy-2,3-γ-lactone-β-D-ribofuranoside (10c and 11c).

Following the general procedure compound **8c** (0.50 g, 0.97 mmol) was treated with Bu_3SnH/AIBN. The residue was purified by flash column chromatography (hexane/ethyl acetate, 10:1). The faster moving fractions gave 0.03 g (8%) of a white foam which was identified as **methyl 5-*O*-(*t*-butyldimethylsilyl)-2-*O*-cynnamoyl-3-deoxy-β-D-ribofuranoside (15c).** IR (KBr) 1715 (CO), 1630 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.90 (s, 9H, *t*-Bu), 2.05 (m, 1H, H-3a), 2.40 (m, 1H, H-3b), 3.20 (s, 3H, OCH_3), 3.70 (m, 1H, $J_{4,5a}$=2.0, $J_{5a,5b}$=10.0 Hz, H-5a), 4.20 (m, 1H, $J_{4,5b}$=2,0 Hz, H-5b,), 4.40 (m, 1H, H-4), 4.90 (s, 1H, H-1), 5.20 (t, 1H, $J_{2,3a}$=$J_{2,3b}$=2.5 Hz, H-2), 6.44 (d, 1H, J=16 Hz, C*H*=CHPh), 7.40, 7.55 (2 m, 5H, Ph), 7.70 (d, 1H, CH=C*H*Ph). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.11; H, 8.06.

The next moving fractions afforded a foam which was purified by preparative CCTLC (dichloromethane/methanol, 50:1). The faster moving fractions afforded **10c** (0.14 g, 38%) as an amorphous solid. $[\alpha]_D$ -85.2 (c 1, $CHCl_3$). IR (KBr) 1770 (CO lactone); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (s, 9H, *t*-Bu), 2.79 (m, 1H, $J_{1',3}$=$J_{3,4}$=3.5 Hz, H-3), 2.87 (m, 1H, H-1'), 2.97, 3.05 (2m, 2H, CH_2-1'), 3.27 (s, 3H, OCH_3), 3.37 (m, 1H, $J_{5a,5b}$=9.9, $J_{4,5a}$=7.8 Hz, H-5a), 3.59 (m, 1H, $J_{4,5b}$=5.4 Hz, H-5b), 3.93 (m, 1H, H-4), 4.28 (d, 1H, $J_{2,3}$=6.6 Hz, H-2), 4.95 (s, 1H, H-1), 7.23 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 36.90 (CH_2Ph), 45.23, 47.90 (*C*HCH$_2$Ph, C-3), 54.86 (OCH_3), 65.51 (C-5), 85.95, 87.54 (C-2, C-4), 107.32 (C-1), 177.81 (CO). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 63.89; H, 7.98.

The slowest moving fractions afforded **11c** (0.07 g, 18%) as an amorphous solid. $[\alpha]_D$ -105.6 (c 1, $CHCl_3$). IR (KBr) 1775 cm^{-1} (CO lactone); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.87 (s, 9H, *t*-Bu), 2.80 (m, 1H, CH_{2a}-1'), 2.97 (m, 1H, $J_{1',3}$=8.1 Hz, H-3), 3.26 (m, 3H, H-1', CH_{2b}-1', H-5a), 3.30 (s, 3H, OCH_3), 3.47 (m, 1H, $J_{5a,5b}$=10.3, $J_{4,5b}$=6.4 Hz, H-5b), 4.28 (m, 1H, H-4), 4.70 (d, 1H, $J_{2,3}$=5.3 Hz, H-2), 5.06 (s, 1H, H-1), 7.20 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 38.08 (CH_2Ph), 48.37, 49.17 (*C*HCH$_2$Ph, C-3), 60.10 (OCH_3), 71.95 (C-5), 86.90, 90.41 (C-2, C-4), 111.73 (C-1), 181.88 (CO). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 63.93; H, 8.00.

Methyl 3-*C*-[(*S*)carboxyethylmethyl]-3-deoxy-5-*O*-trityl-2,3-γ-lactone-β-D-ribofuranoside and Methyl 3-*C*-[(*R*)carboxyethylmethyl]-3-deoxy-5-*O*-trityl-2,3-γ-lactone-β-D-ribofuranoside (10e and 11e).

The general procedure was followed with **8e** (1.20 g, 2.05 mmol). The residue was purified by column chromatography (hexane/ethyl acetate, 10:1). The fastest moving fractions afforded 0.20 g (24%) of a syrup which was identified as **methyl 2-*O*-crotonyl-3-deoxy-5-*O*-trityl-β-D-ribofuranoside (15e).** IR (film) 1720 (CO), 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.86 (dd, 3H, C*H*$_3$-CH=), 2.02 (m, 2H, H-2a, H-2b), 3.09 (m, 1H, $J_{5a,5b}$=9.6, $J_{4,5a}$=4,3 Hz, H-5a), 3.20 (m, 1H, $J_{4,5b}$=6,1 Hz, H-5b), 3.27 (s, 3H, OCH_3), 4.52 (m, 1H, H-4), 4.90 (s, 1H, H-1), 5.10 (t, 1H, $J_{2,3a}$=$J_{2,3b}$=2,4 Hz, H-2), 5.7-5.8 (m, 1H, C*H*=CH-CH$_3$), 6.90-7.20 (m, 1H, CH=C*H*-CH$_3$), 7.20-7.50 (m, 15H, 3Ph). Anal. Calcd. for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.76; H, 6.45.

The slower moving fractions afforded a syrup that was purified by preparative CCTLC (chloroform/methanol, 100:1). The faster moving fractions afforded **10e** (0.25 g, 25%) as a white foam. $[\alpha]_D$ -49.4 (c 1, $CHCl_3$). IR (KBr) 1780 cm^{-1} (CO lactone); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.02 (t, 3H, C*H*$_3$-CH$_2$), 1.62, 1.80 (2m, 2H, CH_2-1'), 2.47 (m, 1H, H-1'), 2.68 (m, 1H, $J_{1',3}$=2.7, $J_{3,4}$=4.0 Hz, H-3), 3.16 (m, 1H, $J_{5a,5b}$=9.5, $J_{4,5a}$=7.5 Hz, H-5a), 3.22 (s, 3H, OCH_3), 3.37 (m, 1H, $J_{4,5b}$=5.4 Hz, H-5b), 4.07 (m, 1H, H-4), 4,68 (d, 1H, $J_{2,3}$=5.3 Hz, H-2), 5.00 (s, 1H, H-1), 7.20-7.50 (m, 15H, 3 Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 11.52 (CH_2CH_3), 24.89

(CH_2CH_3), 46.16, 47.69 ($CHCH_2CH_3$, C-3), 54.80 (OCH_3), 66.09 (C-5), 85.96, 86.14 (C-2, C-4), 107.28 (C-1), 178.07 (CO). Anal. Calcd. for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.74; H, 6.31.
The slower moving fractions afforded **11e** (0.14 g, 18%) as an amorphous solid. $[\alpha]_D$ -40.4 (c 1, $CHCl_3$). IR (KBr) 1780 cm^{-1} (CO lactone); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (t, 3H, CH_3-CH_2), 1.32, 1.87 (2m, 2H, CH_2-1'), 2.59 (m, 1H, H-1'), 2.98 (m, 1H, $J_{1',3}$=7.8 Hz, H-3), 3.15 (m, 1H, H-5a), 3.24 (m, 1H, H-5b), 3.26 (s, 3H, OCH_3), 4.28 (m, 1H, $J_{3,4}$=$J_{4,5a}$=$J_{4,5b}$=5.9 Hz, H-4), 4.64 (d, 1H, $J_{2,3}$=5.4 Hz, H-2), 5.05 (s, 1H, H-1), 7.20-7.50 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.53 (CH_2CH_3), 19.97 (CH_2CH_3), 42.52, 44.44 ($CHCH_2CH_3$, C-3), 54.69 (OCH_3), 66.71 (C-5), 79.98, 84.93 (C-2, C-4), 106.26 (C-1), 176.65 (CO). Anal. Calcd. for $C_{29}H_{30}O_5$: C, 75.96; H, 6.59. Found: C, 75.64; H, 6.30.

Methyl 3-*C*-[(*S*)carboxy(etoxycarbonylmethyl)methyl]-3-deoxy-5-*O*-trityl-2,3-γ-lactone-β-D-ribofuranoside and Methyl 3-*C*-[(*R*)carboxy (etoxycarbonylmethyl) methyl]-3-deoxy-5-*O*-trityl-2,3-γ-lactone-β-D-ribofuranoside (10f and 11f).
According to the general procedure, compound **8f** (0.37 g, 0.57 mmol) was treated with Bu_3SnH/AIBN. The residue was purified by flash column chromatography (hexane/ethyl acetate, 5:1) to afford 0.10 g (34%) of a syrup which was characterized as an inseparable mixture (4:3) of **methyl 3-*O*-deoxy-2-*O*-ethylsuccinyl-5-*O*-trityl-β-D-ribofuranoside (16f)** and **11f**. The ratio was determined from ^1H NMR (**16f**: $\delta_{H\text{-}2}$ 5.06, dd; **11f**: $\delta_{H\text{-}2}$ 4.75, d). In the following, the signals assigned to both compounds are identified whenever they are distinct. IR (film) 1780 (CO lactone), 1730 cm^{-1} (CO aliphatic esther); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.20, 1.25 (2t, 6H, $2CH_3$-CH_2O), 2.00 (m, 2H, 2H-3_{16f}), 2.60 (m, 5H, CH_2-$CH2_{16f}$, CH_{2a}-$1'_{11f}$), 2.69 (m, 1H, $J_{3,4}$=4.4, $J_{1',3}$=3.7 Hz, H-3_{11f}), 2.75 (m, 1H, CH_{2b}-$1'_{11f}$), 2.78 (m, 1H, H-$1'_{11f}$), 3.19 (m, 10H, 4H-5, $2OCH_3$), 4.12 (m, 5H, H-4_{11f}, $2OCH_3$-CH_2O), 4.50 (m, 1H, H-4_{16f}), 4.75 (d, 1H, $J_{2,3}$=7.2 Hz, H-2_{11f}), 4.87 (s, 1H, H-1_{16f}), 4.99 (s, 1H, H-1_{11f}), 5.06 (dd, 1H, $J_{2,3a}$=1,7, $J_{2,3b}$=4.2 Hz, H-2_{16f}).
The slower moving fractions afforded a syrup which was purified by preparative CCTLC (dichloromethane/methanol, 50:1) to give **10f** (0.045 g, 15%) as a syrup. $[\alpha]_D$ -54.5 (c 1, $CHCl_3$). IR (film) 1780 (CO lactone), 1730 cm^{-1} (CO aliphatic esther); ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.26 (t, 3H, CH_3-CH_2-O), 2.43, 2.84 (2m, 2H, CH_2-1'), 3.15 (m, 3H, H-3, 2H-5), 3.19 (s, 3H OCH_3), 3.33 (m, 1H, $J_{1',3}$=8.3, H-1'), 4.00 (m, 2H, CH_3-CH_2O), 4.16 (m, 1H, $J_{3,4}$=5.6, H-4), 4.70 (d, 1H, $J_{2,3}$=5.4 Hz, H-2), 5.02 (s, 1H, H-1), 7.20-7.50 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.05 (CH_2-CH_3), 31.56 (CH_2-CO), 39.16, 43.34 (CH-CH_2-CO, C-3), 54.72 (OCH_3), 61.12 (CH_2-CH_3), 67.05 (C-5), 85.13, 86.97 (C-2, C-4), 106.22 (C-1), 170.77 (COOEt), 175.62 (CO lactone). Anal. Calcd. for $C_{31}H_{32}O_7$: C, 72.07; H, 6.24. Found: C, 72.41; H, 6.50.

Methyl 5-*O*-(*t*-butyldimethylsilyl)-3-*O*-cynnamoyl-2-deoxy-α-D-ribofuranoside (18).
According to the general procedure, radical precursor **17** (0.40 g, 0.77 mmol) was reacted with Bu_3SnH/AIBN. The residue was purified by flash column chromatography (hexane/ethyl acetate, 5:1) to give 0.17 g (59%) of **18** as a syrup. IR (film) 1720 (CO ester), 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.85 (s, 9H, *t*-Bu), 2.23 (m, 1H, $J_{2a,2b}$=10.1, $J_{2a,3}$=4.5, $J_{1,2a}$=3.9 Hz, H-2a), 2.39 (m, 1H, $J_{1,2b}$=5.9, $J_{2b,3}$=6.5 Hz, H-2b), 3.50 (s, 3H, OCH_3), 3.65-3.80 (m, 2H, $J_{4,5b}$=5.7 Hz, 2H-5), 4.23 (m, 1H, H-4), 5.28 (dd, 1H, H-1), 5.64 (m, 1H, H-3), 6.51 (d, 1H, J=16 Hz, CH=CHPh), 7.30, 7.59 (2m, 5H, Ph), 7.71 (d, 1H, CH=CHPh). Anal. Calcd. for $C_{21}H_{32}O_5Si$: C, 64.25; H, 8.22. Found: C, 64.49; H, 8.13.

Methyl 2-deoxy-2-*C*-[1'-(*N*-isobutyl)carbamoyl-1'(*R*)propyl]-5-*O*-trityl-β-D-ribofuranoside (19e).
To an ice bath cooled suspension of $AlCl_3$ (0.017 g, 0.13 mmol) in dry 1,2-dichloroethane (0.5 mL) was added, drop by drop, a solution of isobutylamine (0.02 g, 0.25 mmol) in dry 1,2-dichloroethane (0.25 mL). The reaction mixture was allowed to reach room temperature and then, a solution of **9e** (0.055 g, 0.1 mmol) in 1,2-dichloroethane (0.25 mL) was added. The resulting mixture was stirred at room temperature for 1 h and then (10 mL) of ice-water, was added, and the reaction was stirred for 1 h additional, and filtered through celite. The

organic phase was separated and the aqueous phase was extracted with 1,2-dichloroethane (2 x 5 mL), the organic extracts were combined, washed with water (2 x 5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by preparative CCTLC (hexane/ethyl acetate, 2:1) to give **19e** (0.043 g, 69%) as a white foam. $[\alpha]_D$ -17.2 (c 1, $CHCl_3$). IR (KBr) 3350 (OH, NH), 1640 cm^{-1} (C=O amide); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.85 (m, 9H, 3 CH_3), 1.52-1.78 (m, 3H, $CH(CH_3)_2$, CH_2CH_3), 2.25 (m, 1H, $J_{1',2}$=8.9 Hz, H-2), 2.36 (m, 1H, H-1'), 3.02-3.07 (m, 4H, 2H-5, $NHCH_2CH$), 3.23 (s, 3H, OCH_3), 4.07 (m, 1H, $J_{3,4}$=1.3, $J_{4,5a}$=$J_{4,5b}$=5.5 Hz, H-4), 4.15 (dd, 1H, $J_{2,3}$=5.2, H-3), 4.80 (d, 1H, $J_{1,2}$=5.9 Hz, H-1), 5.87 (t, 1H, $NHCH_2CH$), 5.99 (bs, 1H, OH), 7.11-7.47 (m, 15H, 3 Ph). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 12.21 (CH_2CH_3), 20.06 (2 CH_3), 24.06 (CH_2CH_3), 28.41 ($CH(CH_3)_2$), 47.05, 51.18 (C-2, $CHCH_2CH_3$, $CH_2CH(CH_3)_2$), 55.99 (OCH_3), 64.74 (C-5), 73.68 (C-3), 86.04 (C-4), 108.37 (C-1), 126.93, 127.72, 128.75, 143.92 (3 Ph), 175,19 (CONH). Anal. Calcd. for $C_{33}H_{41}NO_5$: C, 74.54; H, 7.77; N, 2.63. Found: C, 74.23; H, 7.65; N, 2.56.

Methyl 3-deoxy-3-*C*-[1'-(*N*-isobutyl)carbamoyl-1'(*S*)-propyl]-5-*O*-trityl-β-D-ribofuranoside (20e). Following the procedure described for the synthesis of **19e**, the γ-lactone nucleoside **10e** (0.04 g, 0.09 mmol) was treated with isobutylamine (0.018 g, 0.22 mmol). The reaction mixture was stirred at room temperature for 1 h. After the work-up the residue was purified by preparative CCTLC (hexane:ethyl acetate, 2:1) to give **20e** (0.025 g, 60%) as a white foam. $[\alpha]_D$ -0.4 (c 1, $CHCl_3$). IR (KBr) 3350 (OH, NH), 1640 cm^{-1} (CO amide); ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.70, 0.71 (2d, 6H, J=6.6, J=6.7 Hz, $CH(CH_3)_2$), 0.80 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.41-1.72 (m, 3H, $CH(CH_3)_2$, CH_2CH_3), 2.00-2.08 (m, 1H, H-1'), 2.35 (m, 1H, $J_{1',3}$=6.8, $J_{2,3}$=3.7, $J_{3,4}$=4.6 Hz, H-3), 2.75 (m, 1H, J=6.7, J=13.3 Hz, NCH_{2a}), 2.98 (m, 1H, J=6.8 Hz, NCH_{2b}), 3.18 (m, 1H, $J_{4,5a}$=4.8, $J_{5a,5b}$=10.2 Hz, H-5a), 3.25 (s, 3H, OCH_3), 3.33 (m, 1H, $J_{4,5b}$=4.8, H-5b), 3.96 (m, 1H, H-4), 4.03 (d, 1H, H-2), 4.71 (s, 1H, H-1), 5.31 (t, 1H, NH), 5.74 (bs, 1H, OH), 7.17-7.40 (m, 15H, 3 Ph). Anal. Calcd. for $C_{33}H_{41}NO_5$: C, 74.54; H, 7.77; N, 2.63. Found: C, 74.35; H, 7.66; N, 2.58.

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16. γ-Butyrolactones **9c-f**: NOES observed upon irradiation of the anomeric proton signal (H-1): **9c**: H-1' (5%); **9d**: H-1' (8%); **9e**: H-1' (8%); and **9f**: H-1' (8%). NOES observed upon irradiation of the signal of H-2: **9c**: H-3 (7%); **9d**: H-3 (10%); **9e**: H-3 (10%); and **9f**: H-3 (9%).
Compounds **10c,e,f** and **11c,e,**: NOES observed upon irradiation of the signal of H-4: **10c**: H-1' (9%); **10e**: H-1' (8%); **10f**: H-1' (5%); **11c**: CH_2-1' (3%); **11e**: CH_2-1' (6%). NOES observed upon irradiation of the signal of H-2: **10c**: H-3 (8%); **10e**: H-3 (9%); **10f**: H-3 (10%); **11c**: H-3 (6%) and **11f**: H-3 (9%).
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