Stereoselective Synthesis of [3.3.0] Fused Lactones (γ-Butyrolactones) of Sugars and Nucleosides by Free Radical Intramolecular Cyclization

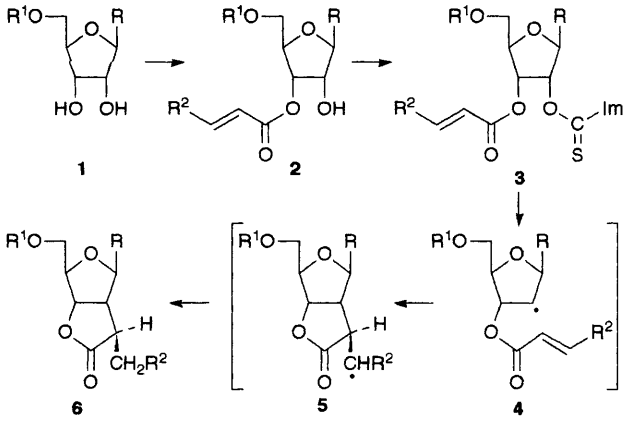
Sonsoles Velázquez, Sophie Huss and María-José Camarasa*

Instituto de Química Médica, Juan de la Cierva 3, 28006 Madrid, Spain

Enantiomerically pure [3.3.0] fused lactones of ribofuranosyl sugars and nucleosides at positions 2, 3 of the ribofuranose ring have been prepared by intramolecular addition of radicals onto the α-position of α,β-unsaturated esters.

γ-Butyrolactones are present in a wide range of natural products, some of them having biological activity.[1] γ-Butyrolactones of carbohydrates are considered good candidates for a solution of the 'off-template' problem.[2,3] 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.[4] Because of the high chemoselectivity of alkyl radicals (with which carbonyl, hydroxy and halogen substituents do not interfere) free radical reactions are particularly suitable for the synthesis of polyfunctional molecules such as carbohydrates.[5,6] The formation of fused rings by cyclization of the hex-5-enyl radical is a particularly useful process; substrates can be cyclized without difficulty by the tin hydride method.[7] *cis*-Ring fusion invariably predominates when fused 6,5- or 5,5-rings are constructed.[8] The factors affecting the rate of cyclization and the stereo- and regiochemical outcome of reactions of hex-5-enyl radicals are well understood and excellent detailed summaries are available.[4,9,10]

In this communication we report a facile and stereoselective synthesis of fused [3.3.0] lactones (γ-butyrolactones) of sugars and nucleosides, using intramolecular addition of radicals onto the α-position of α,β-unsaturated esters by exclusive 5-*exo* cyclization.[11] In these cyclizations a new stereocentre is formed with excellent diastereoselectivity at the off template site. The general strategy is shown in Scheme 1.



Scheme 1 Im = imidazol-1-yl

Table 1 Cyclization and reduction of sugars **3a–3c** and nucleosides **3d–3f** and **8**[a]

	Radical precursor	Product (yield, %)[b]	
Sugars, R = OMe			
R^2 = Ph	**3a**	**6a** (50)	**7a** (16)
R^2 = Me[c]	**3b**	**6b** (35)	**7b** (20)
R^2 = H	**3c**	**6c** (25)	**7c** (—)
Nucleosides, R = Uracyl			
R^2 = Ph	**3d**	**6d** (35)	**7d** (35)
R^2 = Me[c]	**3e**	**6e** (20)	**7e** (50)
R^2 = H	**3f**	**6f** (10)	**7f** (—)
	8	**9** (35)	**10** (35)

[a] R^1 = Me_2Bu^tSi unless otherwise noted. [b] Yields after purification. [c] R^1 = trityl.

The protected sugar or nucleoside derivative undergoes acylation by reaction with the corresponding α,β-unsaturated acid or acid chloride, to give the α,β-unsaturated ester **2** which by reaction with 1,1′-thiocarbonyldiimidazole affords the intermediate **3** ready for free radical cyclization mediated by tributyltin hydride.

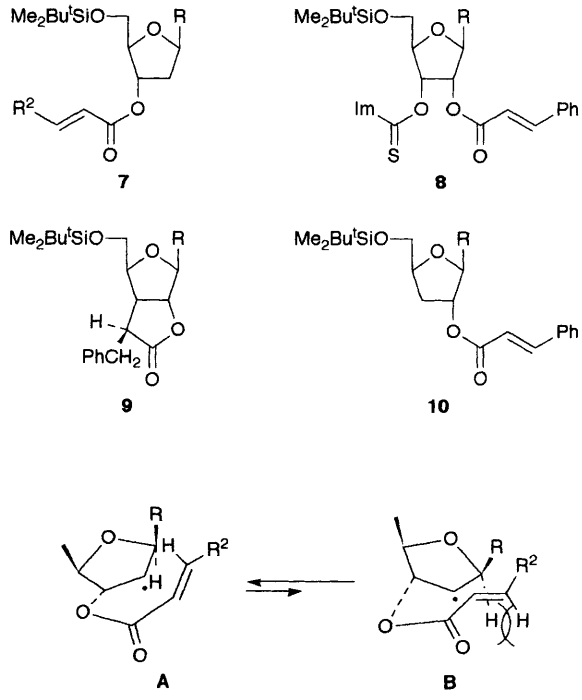
In a typical experiment, a solution of tri-n-butyltin hydride (1.5 equiv.) and azobisisobutyronitrile (AIBN; cat.) in benzene (0.8 mol dm^{-3}) was injected (syringe pump), under argon, to a stirred solution of the radical precursor **3** in refluxing benzene (0.02 mol dm^{-3}) during 8 (for **3a–3d**) or 24 (for **3e–3g** and **8**) h. At the end of the addition refluxing was continued for 2 h. Repeated chromatography is required to give the γ-lactones in the yields shown in Table 1.

The radical precursors **3a–3f** and **8**,[12] on free radical cyclization, gave the γ-lactones **6a–6f** and **9**† together with the corresponding reduction products **7a–7f** and **10**. The ratios of the cyclized to the reduced products could be explained by differences in acceptor character of the double bond.[9b]

The cyclization of the radical precursors **3a–3f** and **8** proceeds with excellent diastereoselectivity; the γ-butyrolactones formed were *cis*-fused and exclusively the 5-*exo* isomers were obtained,[13] which indicates that the addition process is kinetically controlled[14] and that the radicals added to the 'anti-Michael' α-position of the double bond.[15] The absolute stereochemistry at the new stereocentre formed in the cyclized products **6a–6f** was established as *R*, and for the cyclized derivative **9** as *S*, by NOE difference experiments.

In Scheme 2 we show a possible rationale for the stereochemical results obtained in the cyclizations: assuming that in the transition state the radical cyclizes in a chair-like conformation[4,16] slightly distorted by the carbonyl C=O of the ester moiety, the unfavourable steric interactions between the anomeric proton and the proton in the β-position of the double bond in **B** (found if the ester adopts the s-*cis* conformation) drives the equilibrium to the **A** rotamer (the ester adopts the s-*trans* conformation), thus giving the *R* isomers exclusively. A similar rationale can be used for the cyclized product **9** (interactions between the double bond β-proton and H-4′ in the intermediate) giving exclusively the *S* isomer.

In summary, a stereoselective method for the preparation of enantiomerically pure fused γ-lactones of sugars and nucleosides at positions 2,3 of the ribofuranose ring has been achieved.‡ A new chiral centre is formed at an off-template site of the ribofuranose ring. The moderate yield in the cyclization is counterbalanced by the excellent stereoselectivity and the ready availability of the radical precursors. These lactones are potentially useful chiral synthons for preparation of branched-chain sugars and nucleosides. Our preliminary



Scheme 2

† All new compounds gave satisfactory analytical and spectroscopic data consistent with the assigned structures. *Selected spectroscopic data*: **6a** IR (KBr): ν_{max}/cm^{-1}: (C=O) 1770, (C–O) 1170; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.82 (m, 2H, 2-H, CH_2Ph), 2.90 (dd, 1H, J_{gem} 6,3, J_{CH,CH_2} 1.9 Hz, CH_2Ph), 3.18 (dt, 1H, $J_{CH,2}$ 10.8 Hz, CH–CH_2Ph), 4.10 (m, 1H, $J_{3,4}$ 1.6, $J_{4,5a}$ 8.9, $J_{4,5b}$ 5.5 Hz, 4-H), 4.44 (s, 1H, 1-H), 4.65 (dd, 1H, $J_{2,3}$ 7.1 Hz, 3-H) and 7.30 (m, 5H, Ph); **6d**: 2.60 (td, 1H, $J_{2',3'}$, = *ca.* $J_{2',1'}$ = 6.0, $J_{2',CH}$ 2.2 Hz, 2′-H), 2.93 (dd, 1H, J_{gem} 13.7, $J_{CH_2,CH}$ 7.5 Hz, CH_2Ph), 3.10 (dd, 1H, $J_{CH_2,CH}$ 5.2 Hz, CH_2Ph), 3.29 (m, 1H, CH–CH_2Ph), 4.31 (m, 2H, 3′-H, 4′-H), 5.80 (d, 1H, 1′-H), 7.09 (m, 2H, Ph) and 7.19 (m, 3H, Ph); **9**: 2.84 (m, 2H, CH–CH_2Ph, CH–CH_2Ph), 3.01 (td, 1H, $J_{3',CH}$ 2.3, $J_{2',3'}$ = *ca.* $J_{3',4'}$ = 7.2 Hz, 3′-H), 3.18 (d, 1H, J_{gem} 8.8 Hz, CH–CH_2Ph), 3.85 (m, 1H, $J_{4',5'a}$ 3.1, $J_{4',5'b}$ 3.1 Hz, 4′-H), 4.59 (dd, 1H, 2′-H), 5.88 (d, 1H, $J_{1',2'}$ 1.8 Hz, 1′-H) and 7.20 (m, 5H, Ph).

‡ Reports on radical cyclizations of sugars and nucleosides at positions 2 and 3 of the sugar moiety are scarce; see ref. 2. Since the submission of this communication, the cyclization of allyl-type nucleoside derivatives appeared: J. C. Wu, Z. Xi, C. Goeli and J. Chattopadhyaya, *Tetrahedron*, 1991, **47**, 2237.

results indicate that opening of the lactone ring affords 2- or 3-branched chain sugars with a highly functionalized C-branch, very difficult to achieve by more 'classical' chemical reactions.

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