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Synthesis of anti-proliferative [3.3.0]furofuranone derivatives by lactonization and functionalization of *C*-glycosyl compounds

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Abstract: The [3.3.0]furofuranone structure is found in numerous families of biologically active natural products. We took advantage of the stereodiversity afforded by carbohydrate derivatives to prepare several compounds structurally similar to goniofufurone and crassalactones which are natural cytotoxic agents. We designed and synthesized several stereoisomers of these natural compounds via lactonization of *C*-glycosyl compounds bearing an hydroxyl on position 4 and a methyl ester on the pseudo-anomeric position. The reactivity of this bicyclic moiety was explored through etherification of hydroxyls in position 5 and 7 and various substituents (halogen, phenyl, benzyl, cyanomoyl) were introduced. The anti-proliferative properties of these mimics were then evaluated on various cancer cell lines and two compounds **24** and **35** demonstrated IC₅₀ value of 1.34 μM (U251) and 7.60 μM (U87) respectively.

Keywords: *C*-glycosyl compound, furofuranone, anti-proliferative compound

1. Introduction

Carbohydrate chemistry is a field of major interest for synthetic chemists because these types of compounds play important roles in biological processes. Moreover sugars are often used as starting chiral materials in total synthesis and are useful scaffolds for the construction of bioactive compounds. Indeed, their polyfunctional structure is really attractive to design bioactive compounds by appending substituents at selected positions which requires the development of efficient synthetic strategies. Close analogs of *O*-glycosyl derivatives, *C*-glycosyl compounds display chemical and biological stabilities toward enzymatic hydrolysis and are thus extensively studied.[1–4] In this context, our lab was early involved in the development of *C*-glycosidic derivatives[5–8] to build bioactive compounds,[9,10] peptidomimetic derivatives[11] suitable for imaging applications[12] and also for the design and synthesis of foldamers.[13,14] In the course of the synthesis of glycopeptides based on sugar γ -amino acids, we reported the spontaneous formation of a *C*-glycosyl bicyclic lactone in which the lactone ring is annulated to a furanoid system.[13]

The [3.3.0]furofuranone scaffold obtained this way is found in numerous families of biologically active natural and synthetic products explaining the continual interest nowadays in its chemistry.[15–19] Figure 1a shows some natural molecules with [3.3.0]furofuranone structure. (+)-Goniofufurone was isolated from *Goniothalamus* and the absolute configuration of natural (+)-Goniofufurone was attributed by Shing *et al.*[20] Crassalactones B and C are cinnamoyl esters of Goniofufurone isolated from *Polyalthiacrassa* [21] and their absolute configurations were determined thanks to chemical modification of (+)-Goniofufurone. These natural products and number of their analogues have been the subject of many syntheses. Just to mention some of them, the total synthesis of natural (+)-Goniofufurone was early reported by a non-classical Wittig reaction on furanolactone obtained from D-glucose.[22,23] A great number of total syntheses of (+)-Goniofufurone have been reported [18,24–28] and a photochemical approach has been recently reported.[29] Crassalactone C is also the subject of many investigations and its first total synthesis was reported from D-xylose in a multistep sequence by Popsavin *et al.*[30] An expeditious enantiospecific synthesis involving a ring-closing metathesis reaction was also reported by Prasad *et al.*[31]

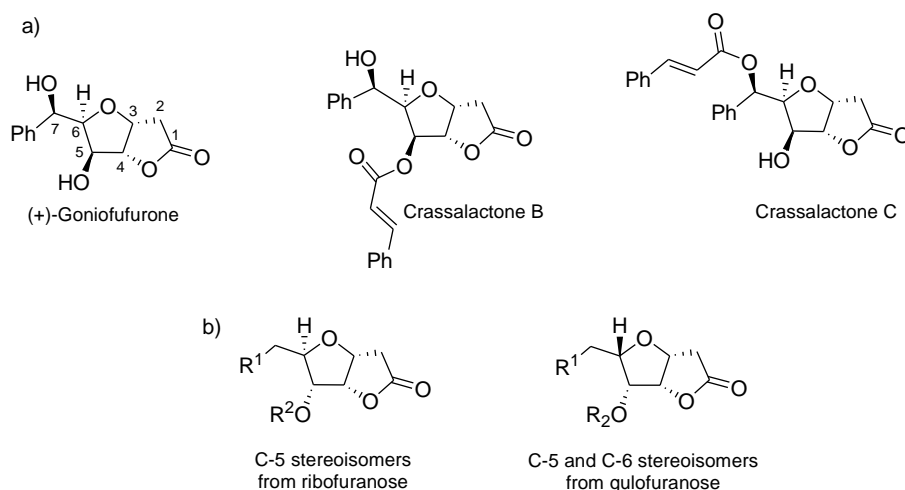


Figure 1. a) Natural compounds with the [3.3.0]furofuranone structure. b) Structures of the envisioned stereoisomers. The representation is chosen in order to clearly visualise C-5 and C-6 configurations.

Together with the development of synthetic approaches, Popsavin's group is fully implicated in the synthesis of many series of lactone derivatives with significant cytotoxic activity against human tumor cell lines.[32–36]. Just to mention few of them, the C7-dephenylated, 7-halogeno and 7-azido-7-deoxy mimics were prepared and showed a potent and selective in vitro cytotoxicity against specific human tumor cell lines.[37–39] Conformationally constrained goniofufurone mimics with 1,3-dioxane heterocyclic ring embedded in 5,7-positions were designed and evaluated[40,41] and a series of conformationally restricted analogs with halogen, azido or benzyloxy groups at the C-7

position were recently described.[42] Mimics bearing a methoxy group at C-5 and C-7 positions[43] and C-7-alkyloxymethyl groups (C6-C13) were recently investigated.[44] Related to Crassalactones B and C, Popsavin *et al.* also designed and evaluated structural features through a 3D-QSAR model for various styryl lactones and the crucial effect of the cinnamic acid ester moiety at C-7 was highlighted.[45,46]

Based on these data and considering our expertise in carbohydrates and more particularly in C-glycosyl compounds chemistry, we planned to design and prepare several compounds featuring a furofuranone moiety. Amongst the stereodiversity afforded by carbohydrates, ribo- and gulofuranose derivatives were chosen as starting compounds since they give access to C-5 and C-5/C-6 stereoisomers of (+)-Goniofufurone (Figure 1b). To the best of our knowledge, these stereoisomers featuring a clear structural similarity with goniofufurone and crassalactones have never been prepared and could potentially display cytotoxic activity. Most of the time, the synthetic pathway for (+)-Goniofufurone synthesis involves 1,2-*O*-isopropylidene-D-glucose or 1,2-*O*-isopropylidene-D-xylofuranose as starting chiral precursors and the most active derivatives described by Popsavin's group are often prepared by *O*-alkylation prior to lactonization. We propose herein the synthesis of mimics based on the lactonization of a C-glycosyl compound involving the hydroxyl on position 4 (carbohydrate numbering) and a methyl ester on the pseudo-anomeric position.

The objective of this work was the synthesis of the targeted lactone moiety based on two furanoses and the insertion of various substituents (halogen, phenyl, benzyl, cyanomoyl) selected according to biological evaluations found in the literature. The introduction of these substituents led us to explore the scope and limitation of etherification of this lactone. The anti-proliferative properties of the targeted analogs were evaluated on various cancer cell lines.

2. Results and Discussion

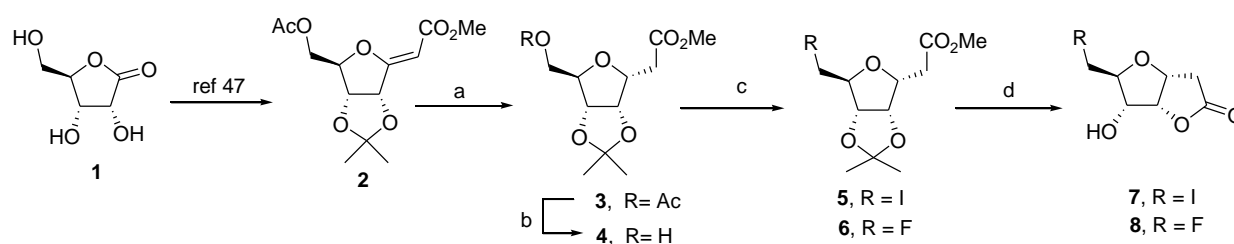
2.1. Chemistry

Our approach for the preparation of the bicyclic furofuranone moiety is based on the intramolecular lactonization of a C-glycosyl compound. Indeed, we previously described a spontaneous concomitant acetal deprotection and lactonization during acid catalyzed removal of isopropylidene leading to a C-glycosyl bicyclic lactone in which the lactone ring is annulated to a furanoid system.[13]

Among the numerous synthetic methods to prepare C-glycosyl derivatives, we developed and used for several years the double bond reduction of C-glycosylidene compounds commonly called *exo*-glycals (compound **2**). Thus, starting from commercially available D-ribonolactone **1** (Scheme 1) and

D-gulonolactone **18** (Scheme 4), we managed to prepare C-5 and C-5/C-6 stereoisomers of the bicyclic furofuranone moiety of (+)-Gogniofufurone respectively. In line with the most active compounds recently described by Popsavin's group, we selected halogens, phenyl, benzyl and cinnamoyl groups to be introduced at positions 5 or 7.

The C-glycosyl compound **3** was obtained by a three steps synthetic sequence involving hydroxyl protection, Wittig reaction and stereoselective hydrogenation, a classical method used in our laboratory (Scheme 1).[47,48]



Scheme 1. Reagents and conditions. a) H₂, Pd/C, EtOAc, 90 %; b) Na(0), MeOH, 80 %; c: R = I, I₂, imidazole, PPh₃, THF, reflux, 3 h, 77 %; R = F, DAST, CH₂Cl₂/ACN, 0 °C-rt, 2 h, 76 %; d: TFA, CH₂Cl₂, 0 °C, 3 h, **7**: 67 %, **8**: 93 %.

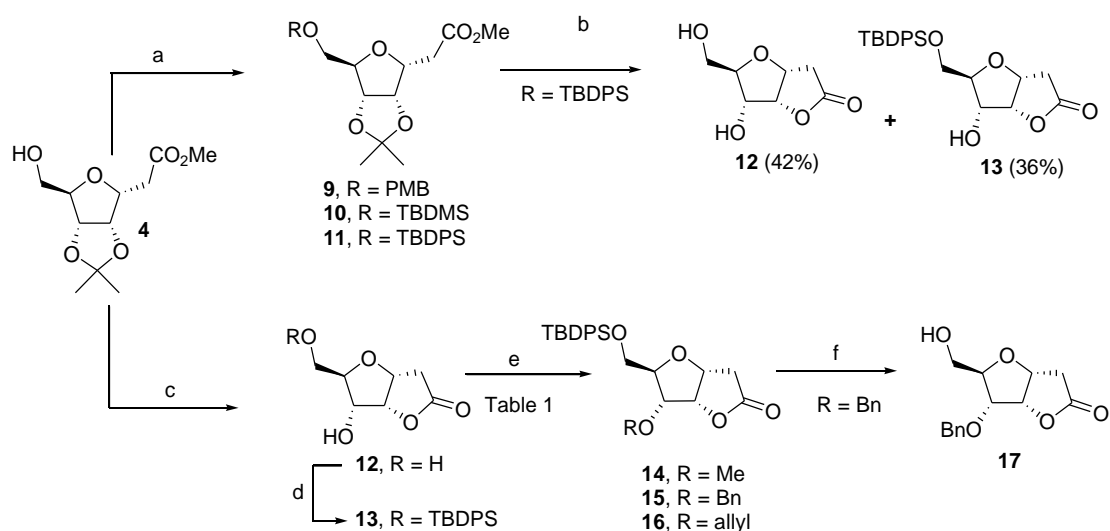
In the first instance, we envisioned the preparation of 7-halogeno derivatives. The C-glycosyl compound **4** obtained by a Zemplen reaction on compound **3** was reacted with iodide and PPh₃ for iodination and diethylaminosulfur trifluoride (DAST) for fluorination. The targeted 7-iodo and 7-fluoro derivatives **7** and **8** were obtained in 67 and 93 % yields respectively after lactonisation during acid catalyzed removal of isopropylidene (Scheme 1).

In order to prepare mimics bearing a benzyl or phenyl group at C-5 and C-7 positions, the reactivity of the corresponding hydroxyl groups was explored. The protection of the primary hydroxyl group on position 7 was first required (Scheme 2). We planned to adopt a *para*-methoxybenzyl as protecting group. The reaction with PMB-Cl in presence of NaH leads to the PMB-ester resulting from a transesterification of the methyl ester together with the protection in position 7. This issue was easily circumvented by the use of PMB-trichloroacetimidate with BF₃.Et₂O, leading to the 7-*O*-PMB derivative **9**.

We next attempted the concomitant acetal deprotection and lactonisation in acidic conditions. 7-*O*-PMB compound **9** was treated by a mixture of trifluoroacetic acid TFA/H₂O (1/1) at 0 °C, which are the conditions used for lactonization of related compounds in our previous work. We only observed the formation of the unprotected bicyclic compound **12** revealing the instability of the PMB protecting group in these acidic conditions. Other carefully controlled acidic conditions were attempted to perform lactonization while avoiding PMB removal (1N HCl in MeOH, TFA in

CH₂Cl₂, Amberlite IR-120, AcOH/H₂O 8/2). Nevertheless, the C-7 unprotected compound **12** was consistently obtained in quantitative yield. We moved on silyl protecting groups and *O*-TBDMS and *O*-TBDPS derivatives **10** and **11** were successfully prepared in good yields by reaction with the corresponding silyl chloride and imidazole in DMF. With PMB and TBDMS, the concomitant acetal deprotection and lactonization occurred but along with the unwanted removal of these protecting groups. The TBDPS group is known to be less acid sensitive than TBDMS and thus the compound **13** was successfully obtained in 36% yield when the reaction was performed in a mixture of AcOH/H₂O (8/2) at 0 °C, which were the best conditions to obtain **13**. The simultaneous formation of compound **12** in 42% could not be avoided.

The lactonization prior to the protection of hydroxyl in position 7 seemed to be a more efficient way in terms of global yield of compound **13**. Compound **4** treated in a mixture of trifluoroacetic acid TFA/H₂O (1/1) for 3 hours led to lactone **12** in 69 % yield and subsequent reaction with TBDPSCl and imidazole in DMF furnished **13** in 48 % yield, even when more equivalents of silylating agent were used.



Scheme 2. Reagents and conditions. a) PMB-trichloroacetimidate, BF₃.OEt₂, CH₂Cl₂, 16 h, **9**: 75 %; TBDMSCl or TBDPSCl, imidazole, DMF, **10**: 78 %, **11**: 95 %; b) AcOH/H₂O (8/2 v/v), 80 °C, 2 h, quantitative yield for R = PMB and TBDMS, 36 % for R = TBDPS; c) TFA/H₂O, (1/1 v/v), 3 h, 69 %; d) TBDPSCl, imidazole, DMF, 48 %; e) see table 1; f) PTSA, MeOH, 30 °C, 3 h, 61 %.

The resulting furofuranone **13** was derivatized in order to prepare a benzylated compound close to the most active one described by Popsavin's group. This prompted us to explore the reactivity of lactone **13** towards etherification, which proved to be challenging. As we suspected that the use of a base could be troublesome given the presence of the lactone moiety, we carefully explored the scope and limitation of this reaction with various commonly used electrophiles and bases (Table 1). Firstly, the reaction was performed with iodomethane and NaH in DMF. The complete degradation of **13** was observed whether the reaction was conducted at 0 °C or -20 °C (entries 1 and 2). The use of

dimethyl sulfate instead of iodomethane did not permit to obtain the targeted methylether and interestingly, no reaction occurred and starting compound **13** was totally recovered when sodium carbonate was used instead of sodium hydride (entry 3), the same result was observed with benzylbromide (entry 4). The reaction conducted at 70 °C did not allow the formation of the benzylated compound and led to complete degradation of compound **13** (entry 5). The reaction with benzyl bromide and KHMDS in THF at -80 °C was also unsuccessful (entry 6). We then turned to silver oxide used for *O*-alkylation of the primary hydroxyl in the preparation of goniofufurone mimics bearing an alkoxymethyl chain.[44] For *O*-alkylation of **13**, the use of silver oxide in dichloromethane has proven to be efficient in a sealed tube at 60 °C during 24 h. In these conditions (entry 7), the attempted 5-*O*-Bn **15** was obtained in 48 % yield. A prolonged reaction time (48 h) afforded 5-*O*-Me **14** and 5-*O*-Bn **15** in high yields (entries 8 and 10). 5-*O*-allyl **16** was obtained with lower yield but the unreacted starting compound **13** was easily recovered (entry 9). These results clearly showed that the *O*-alkylation of the lactone **13** is challenging in basic media required for this type of reaction. 5-*O*-Bn **15** was then treated with PTSA in methanol and afforded compound **17** in 61 % yield.

Table 1. Scope and limitation of *O*-alkylation of **13**

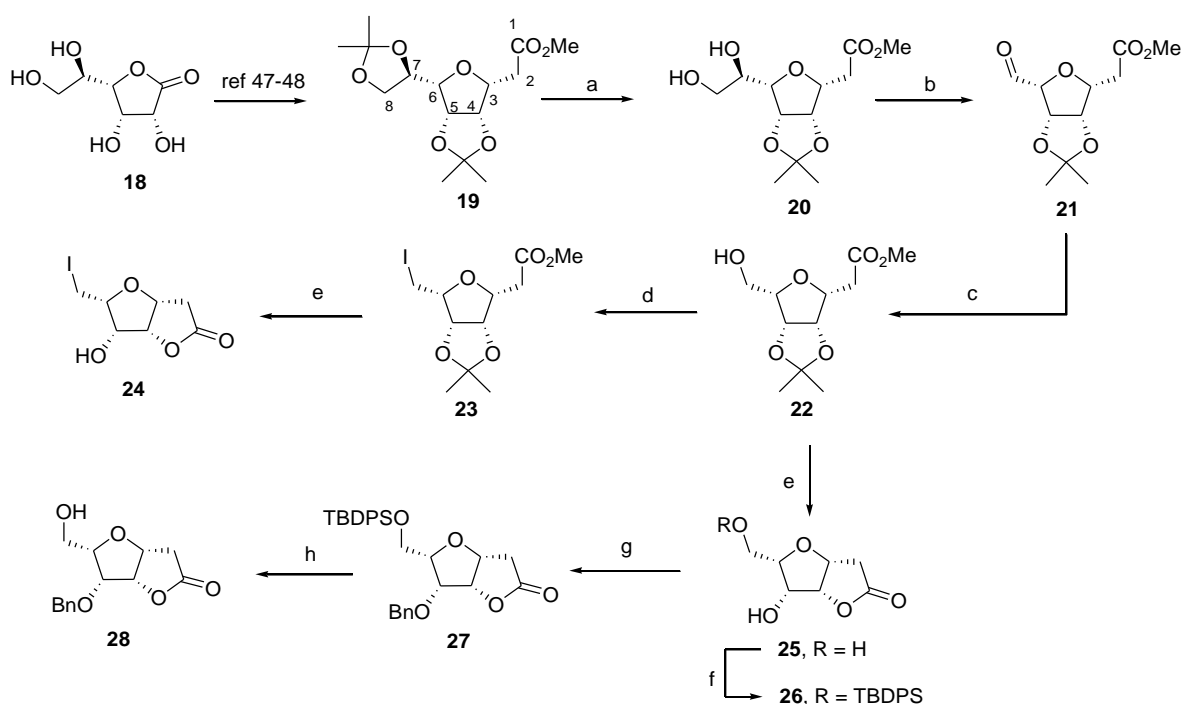
Entry	Reagent (2 eq.)	Base (1 eq.)	Solvent	T (°C)	t (h)	Starting compound 13 (%)	Alkylated compound (%)
1	MeI	NaH	DMF	0	0.5	0	0
2	MeI	NaH	DMF	-20	0.5	0	0
3	Me ₂ SO ₄	K ₂ CO ₃	DMF	20	12	100	0
4	BnBr	K ₂ CO ₃	DMF	20	12	100	0
5	BnBr	K ₂ CO ₃	DMF	70	12	0	0
6	BnBr	KHMDS	THF	-80	1	0	0
7	BnBr	Ag ₂ O ^a	CH ₂ Cl ₂	60 ^b	24	15	48
8	BnBr	Ag ₂ O ^a	CH ₂ Cl ₂	60 ^b	48	0	88
9	allylBr	Ag ₂ O ^a	CH ₂ Cl ₂	60 ^b	48	37	35
10	MeI	Ag ₂ O ^a	CH ₂ Cl ₂	60 ^b	48	0	72

^a: 3eq. of Ag₂O, b: in sealed tube

We next turned to the preparation of C-5/C-6 stereoisomers starting from commercially available D- γ -1,4-gulonolactone **18**. As described above for compound **3**, C-glycosyl compound **19** was obtained by a three steps synthetic sequence involving hydroxyl protection by isopropylidene, Wittig reaction and stereoselective hydrogenation. Selective 7,8-isopropylidene removal was carried out in a 1N HCl methanolic solution and diol **20** was thus obtained in 90 % yield (Scheme 3). The oxydative cleavage

of this diol by NaIO₄ led to aldehyde **21**, used without purification in the subsequent reduction to alcohol **22** or nucleophilic addition of phenyl magnesium bromide (Scheme 4).

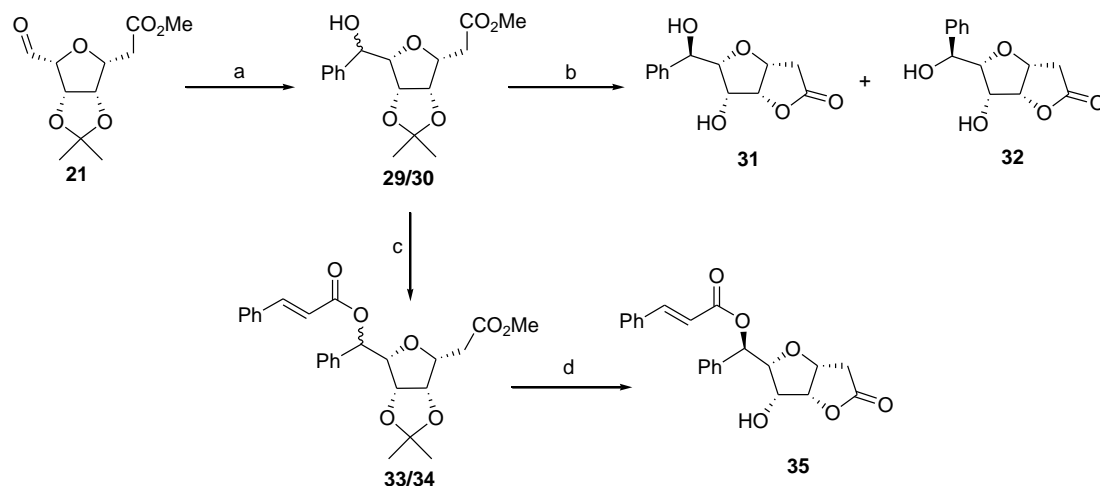
Starting from alcohol **22**, the targeted 7-iodo derivative **24** was prepared by reaction with iodine followed by lactonization performed in a TFA/H₂O (1/1 v/v) mixture. From compound **22**, the lactonization in a TFA/H₂O (1/1 v/v) mixture and the subsequent reaction with TBDPSCl likewise led to compound **26** in 57 % yield. According to conditions established for compound **13**, compound **26** was benzylated in the presence of Ag₂O in CH₂Cl₂. Despite the low yield of this etherification (29 %), the expected 5-*O*-benzyl ether **28** was obtained after TBDPS removal which was carried out in presence of a catalytic amount of PTSA in MeOH.



Scheme 3. Reagents and conditions: a) HCl (1N), MeOH, 3 h, 90 %; b) NaIO₄, MeOH, 91 %; c) NaBH₄, MeOH, 3 h, 64 %; d) I₂, imidazole, PPh₃, THF, 61 %; e) TFA/H₂O (1/1 v/v), 3 h, 44 % for **24**, 62 % for **25**; f) TBDPSCl; imidazole, DMF, 18 h, 57 %; g) Ag₂O, BnBr, CH₂Cl₂, 60 °C, 48 h, 29 %; h) PTSA, MeOH, 30 °C, 18 h, 49 %.

We also prepared C-7-phenylated mimics by nucleophilic addition of phenyl magnesium bromide on aldehyde **21** (Scheme 4).^[49] Two C-7 diastereoisomers **29** and **30** were obtained in 65/35 ratio determined by ¹H NMR on the basis of signal integration of H-6 and methyl ester, but these compounds were not separable by column chromatography. In contrast, the polarities of diols **31** and **32** obtained after lactonisation were sufficiently different to allow their separation by column chromatography. X-ray analysis on **32** (Figure 2) unambiguously confirmed that **32** is a C-5,C-6,C-7 stereoisomer and compound **31** is a C-5,C-6 stereoisomer of (+)-Goniofufurone. Finally, a Crassalactone C mimic was prepared by a cinnamoylation of the diastereomeric mixture of **29/30**.

We were not able to separate the mixture of cinnamoylated diastereoisomers **33/34** but fortunately, the pure major stereoisomer **35** was obtained after lactonization and careful purification by column chromatography.



Scheme 4. Reagents and conditions: a) PhMgBr, Et₂O, 0 °C, ratio **29/30**: 65/35; global yield 35 %; b) TFA/H₂O (1/1 v/v), **31**: 25 % and **32**: 15 %. c) cinnamoyl carboxylic acid, DCC, DMAP, CH₂Cl₂, 53 %, ratio **33/34**: 65/35; d) TFA/CH₂Cl₂ (1/1 v/v), 56 %.

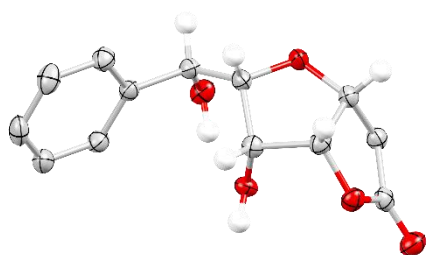


Figure 2. Crystal structure of **32**, showing 50% probability thermal ellipsoids. Some hydrogen atoms are omitted for clarity.

2.2 Biological evaluation and discussion

The 7-halogeno compounds **7**, **8** and **24**, 5-*O*-Bn derivatives **17** and **28**, 7-dephenylated compounds **12** and **25** and goniofufurone and crassalactone stereoisomers **31**, **32** and **35** (Figure 3) were evaluated for their *in vitro* cytotoxicity against a panel of human cancer cells. The main objective is to evaluate stereoisomers which have never been prepared and the main question was to know if these type of stereoisomers and mimics could potentially display cytotoxic activity. The choice of the cancer cells line was oriented regarding the difficulties of therapy notably for brain or triple negative

breast cancers, thus two glioblastoma cell lines U87 and U251, medulloblastoma cell line DAOY and also breast triple negative cancer cell line MDA-MB-231 were selected.

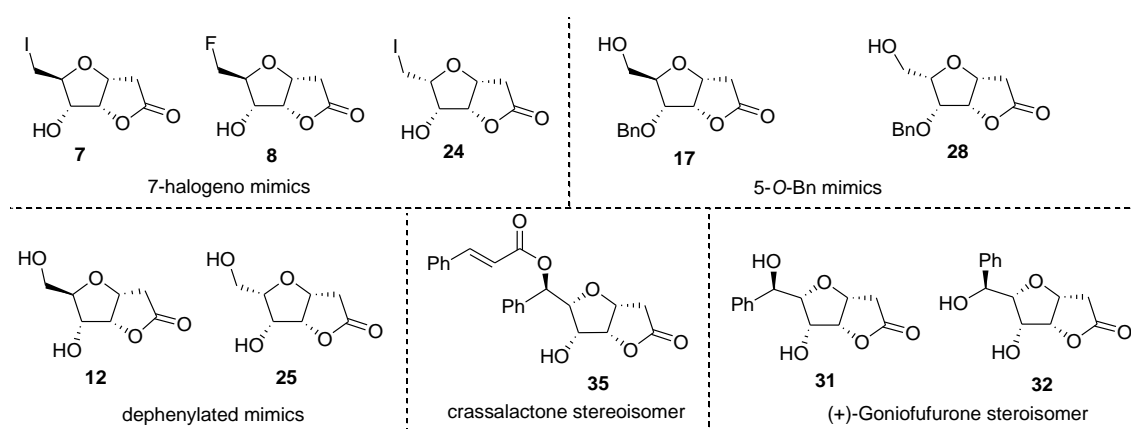


Figure 3. Structure of tested compounds

Cytotoxic activity was evaluated using the standard MTT assay after 72 h exposure of cells to the compounds at different concentrations (0.1, 1, 10, 100, 250 μ M). The commercial antitumour agent Doxorubicin (Dox) was used as reference. As a representative result, the cytotoxic activity of all compounds on U87 cells line is depicted in Figure 4 and other cancer cell lines results can be found in the SI. The compounds showed weak growth inhibitory activity against all tumour cell lines, except compounds **35** and **24** for which IC_{50} values were calculated (Table 2). Remarkably, the styryl lactone **35** exhibited toxicity toward U87 and U251 cell lines with IC_{50} of 32.4 μ M and 1.34 μ M respectively. This compound exhibited a lesser effect against MDA-MB-231 and DAOY cells. The iodo derivative **24** demonstrated a significant cytotoxic activity on U87 cells (IC_{50} of 7.6 μ M). The stereoisomers of goniofufurone **31** and **32** showed no cytotoxic activity. This result revealed that these derivatives did not have the appropriate structural spatial arrangement of the furofuranone segments although they display a clear structural similarity with goniofufurone. The dephenylated analogs **12** and **25**, which are respectively C-5 and C-5/C-6 stereoisomers also demonstrated a total loss of activity, although dephenylated derivatives described by Popsavin's group are cytotoxic compounds towards a large panel of cancer cell lines. In a similar way, 5-O-Bn substituted mimics **17** and **28** did not display a significant biological activity. 7-iodo mimics **24** and **7**, which are C-6 stereoisomers, displayed completely different results. Based on a D-gulo- configured scaffold, the 7-iodinated compound **24** and the crassalactone mimic **35** have the highest potency with $IC_{50} < 10 \mu$ M on U87 and U251 cell lines.

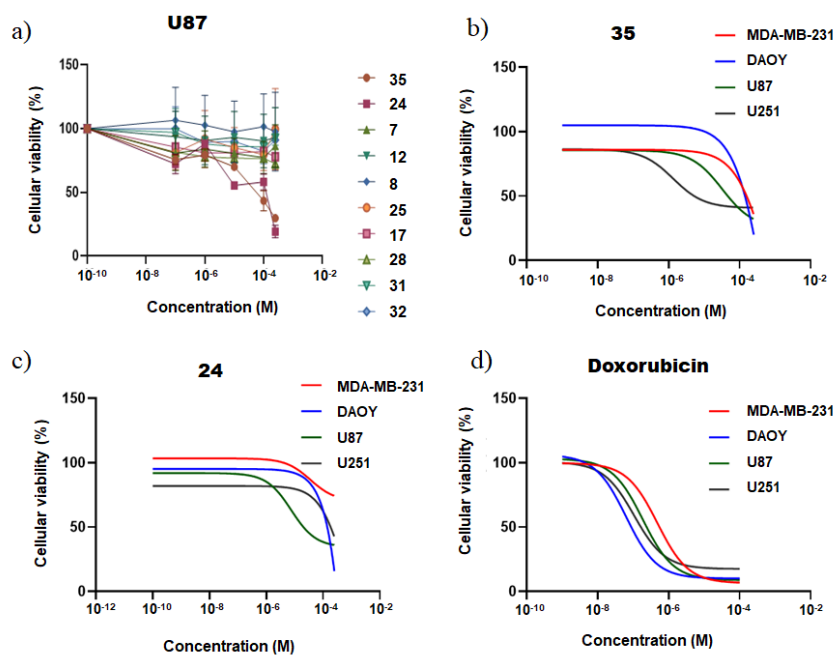


Figure 4. Cytotoxic activity of mimics on U87 cell lines a). Cytotoxic activity on U87, U251, DAOY and MDA-MB-231 cells of compound **35** b), compound **24** c) and Doxorubicin d).

Table 2. IC₅₀ values of compounds **24**, **35** and Doxorubicine

Compounds	IC ₅₀ (μM) ^a			
	MDA-MB-231	DAOY	U87	U251
35	534.6	612.4	32.40	1.341
24	nd	141.07	7.606	528.6
Doxorubicin	0.4817	0.0629	0.1864	0.106

^a: The values are means of three independent experiments done in quadruplicates. Coefficients of variation are <10%.

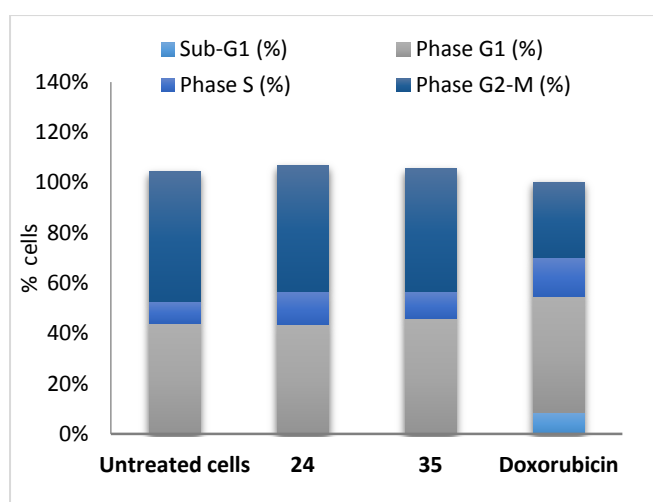


Figure 5. Cell cycle of U251 cells treated (72 h) with compounds **24** and **35** (1 μM) and Doxorubicine (0.1 μM)

Preliminary studies on the cytotoxicity mechanism of compounds **24** and **35** were next investigated. In their studies, Popsavin *et al.* mentioned that their synthesized compounds induced apoptosis.[43,50] The capacity of compounds to induce apoptosis was determined by considering their influence on U251 cell cycle. The detection of the different phases is based on fluorescence emission of propidium iodide which is an ADN intercalant. As Figure 5 indicates, treatment of U251 cells with compounds **24** and **35** (1 μM) induced no change in the percentage of cells in the S, G2-M and G1 phases compared to non treated cells. When cells are treated with doxorubicine (0.1 μM), the percentage in the sub-G1 phase increased, which is suggestive of apoptosis. The percentage of cells in the non proliferative phase G1 also increased. These results do not permit to elucidate the cytotoxic activity mechanism observed for compounds **24** and **35** that is presumably not related to a sudden cell cycle arrest but could be due to a subsequent effect on mitochondrial activity as previously shown by Atabaki *et al.*[51] Indeed, several various cytotoxic activity mechanisms could be postulated with a very late effect such as mitochondrial transmembrane potential disruption or DNA damages. Furthermore, the differential activity of compounds **24** and **35** on specific cell types is not yet understood, but could be exploited to elaborate more selective chemotherapies. This could prevent several side effects observed in conventional chemotherapies, such as cardiotoxicity of doxorubicine.

3. Conclusion

Several compounds featuring a clear structural similarity with goniofufurone and crassalactones which are natural cytotoxic agents were prepared based on the stereodiversity afforded by carbohydrate derivatives. The targeted bicyclic lactone moieties were obtained by intramolecular lactonization between the hydroxyl and a methylcarboxylate of C-glycosyl compounds. The reactivity of the hydroxyl in position 5 was explored and the C-5 and/or C-5/C-6 stereoisomers were etherified with various substituents (phenyl, allyl or methyl) in presence of Ag_2O . The reactivity of the hydroxyl in position 7 was explored in order to obtain the halogenated, benzylated and cinnamoylated C-5 and/or C-5/C-6 stereoisomers. Their anti-proliferative properties were then evaluated on various cancer cell lines. Some mimics showed no significant growth inhibitory activity against all tumour cell lines, highlighting that the stereochemistry of the furofuranone moiety is a crucial point to ensure cellular activity. Interestingly, compounds **24** and **35** demonstrated IC_{50} values of 1.34 μM on U251 and 7.60 μM on U87 cells, respectively. The cell cycle phases were examined but these experiments did not permit to establish that the cytotoxic effect is due to

apoptosis. Nevertheless, the cytotoxic effects observed for these compounds towards distinctive cell lines could be explored in the future in order to consider more specific chemotherapies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge: Copy of NMR spectra of new compounds and biological assays.

Acknowledgments

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4. Experimental Part

General information

Solvents and liquid reagents were purified and dried according to recommended procedures. Thin layer chromatography (TLC) analyses were performed using standard procedures on Kieselgel 60F254 plates (Merck, Kenilworth, NJ, USA). Compounds were visualized using UV light (254 nm) and a methanolic solution of sulfuric acid and charred. Column chromatography was performed on silica gel SI 60 (63–200 μm) (Merck). Melting points were determined with a Tottoli apparatus and are uncorrected. FTIR spectra were recorded on a Shimadzu IRAffinity-1, ATR PIKE Technologies model GladiAT (cm⁻¹). Optical rotations were measured on an Anton-Paar MCP 300 polarimeter. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance III 400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ¹H and ¹³C signals, two-dimensional ¹H, ¹H COSY and ¹H, ¹³C correlation spectra were recorded. Chemical shifts (δ) are given in parts per million relatives to the solvent residual peak. For clarity, the atom numbering used for NMR signals attribution is described in the figure 1. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, b=broad signal and app=apparent multiplicity. The given *J* values refer to apparent multiplicities and do not represent the true coupling

constants. Mass and high-resolution mass spectrometry spectra were recorded on a Bruker microTOFQ apparatus. Compounds **2-4**, **10**, **18-20** and **22** have been prepared according to literature procedures.[11,47,52]

3,6-anhydro-2-deoxy-4,5-O-(1-methylethylidene)-7-fluoro-D-ribo-heptanoic acid methyl ester 6

To a solution of **4** (100 mg, 0.40 mmol) in a mixture of dry acetonitrile/dichloromethane 2/3 (v/v) (8 mL), 110 μ L of DAST (2 eq., 0.81 mmol) were added dropwise at 0 °C under inert atmosphere. The reaction mixture was stirred for 2 h at room temperature. The mixture was neutralized by addition of a saturated solution of NaHCO₃ (10 mL) and the organic solvent was removed under *vacuum*. The aqueous layer was extracted with CH₂Cl₂ (2x20 mL) and the organic layer was dried over MgSO₄. The solvent was removed under *vacuum* and the crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 60/40) to afford compound **6** (86 mg).

Yield: 85 %; colorless oil; R_f = 0.85 (cyclohexane/EtOAc 6/4); $[\alpha]_D = -11.3$ (c = 0.10, CHCl₃); IR (film): ν 2988, 2955, 1734, 1437, 1381, 1307, 1267 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.34 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 2.72 (dd, 1H, $J_{2a,2b} = 16.5$ Hz, $J_{2a,3} = 7.0$ Hz, H-2a), 2.78 (dd, 1H, $J_{2b,3} = 7.0$ Hz, H-2b), 3.71 (s, 3H, OCH₃), 4.19 (app dt, 1H, $J_{6,F} = 33.0$ Hz, $J_{6,7a} = J_{6,7b} = 3.0$ Hz, H-6), 4.40-4.46 (m, 1H, H-3), 4.46 (ddd, 1H, $J_{7a,F} = 47.5$ Hz, $J_{7b,7a} = 10.5$ Hz, $J_{7b,6} = 3.5$ Hz, H-7b), 4.58 (ddd, 1H, $J_{7b,F} = 47.5$ Hz, $J_{7b,7a} = 10.5$ Hz, $J_{7b,6} = 3.0$ Hz, H-7b), 4.80 (dd, 1H, $J_{4,5} = 6.0$ Hz, $J_{4,3} = 4.0$ Hz, H-4), 4.85 (app brd, 1H, H-5); ¹³C NMR (CDCl₃, 100.6 MHz): δ 25.1 (CH₃), 26.3 (CH₃), 36.4 (C-2), 51.9 (OCH₃), 78.6 (d, $J_{C3-F} = 2$ Hz, C-3), 81.6 (C-4), 82.4 (d, $J_{C5-F} = 8$ Hz, C-5), 82.5 (d, $J_{C6-F} = 19$ Hz, C-6), 85.1 (d, $J_{C7-F} = 172$ Hz, C-7), 112.9 (C(CH₃)₂), 171.6 (C=O). HRMS (ESI): calcd for C₁₁H₁₈FN₂O₅ [M+Na]⁺: 271.0958, found: 271.0952.

3,6-anhydro-2-deoxy-5-hydroxy-7-iodo-D-ribo-1,4-lactone 7

To a solution of **4** (200 mg, 0.81 mmol) in dry THF (8 mL), 111 mg of imidazole (2.0 eq., 1.62 mmol) and 425 mg of triphenylphosphine (2.0 eq., 1.62 mmol) were added. The reaction was heated at reflux and 350 mg of I₂ (1.2 eq., 0.97 mmol) solubilized under inert atmosphere in 2 mL of dry THF were added. The reaction was stirred at reflux for 3 h. The solvent was evaporated and the crude intermediate **5** was used without further purification. The intermediate **5** was dissolved in a mixture of TFA/CH₂Cl₂ 4/1 (v/v) (10 mL) at 0 °C. The reaction was stirred at room temperature for 3 h. The mixture was neutralized by addition of solid NaHCO₃ and diluted with water. The aqueous layer was extracted with CH₂Cl₂ (3x20 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 0/100) to afford compound **7** (154 mg).

Yield: 67 %; white solid; $R_f = 0.30$ (cyclohexane/EtOAc 7/3); $[\alpha]_D = 49.9$ ($c = 0.11$, CHCl_3); mp: 143-145°C; IR (film): ν 3335, 2955, 2833, 1774, 1396, 1362, 1292 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 2.17 (d, 1H, $J_{\text{OH},5} = 10.5$ Hz OH), 2.76 (dd, 1H, $J_{2a,2b} = 19.0$ Hz, $J_{2a,3} = 1.0$ Hz, $H-2a$), 2.84 (dd, 1H, $J_{2b,3} = 6.0$ Hz, $H-2b$), 3.35 (dd, 1H, $J_{7a,7b} = 12.0$ Hz, $J_{7a,6} = 6.0$ Hz, $H-7a$), 3.51-3.57 (m, 2H, H-6, $H-7b$), 4.07 (ddd, 1H, $J_{5,6} = 8.0$ Hz, $J_{5,4} = 4.5$ Hz, $H-5$), 4.92 (ddd, 1H, $J_{3,4} = 4.5$ Hz, $H-3$), 5.00 (app t, 1H, $J_{4,3} = J_{4,5} = 4.5$ Hz, $H-4$); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 6.6 ($C-7$), 37.1 ($C-2$), 76.2 ($C-3$), 77.4 ($C-5$), 79.6 ($C-6$), 82.9 ($C-4$), 174.6 ($C=O$); HRMS (ESI): calcd for $\text{C}_7\text{H}_9\text{NaIO}_5$ $[\text{M}+\text{Na}]^+$: 306.98443, found: 306.9438.

3,6-anhydro-2-deoxy-5-hydroxy-7-fluoro-D-ribo-1,4-lactone 8

Product **6** (86 mg, 0.35 mmol) was dissolved in a mixture of TFA/ CH_2Cl_2 4/1 (v/v) (10 mL) at 0 °C. The reaction was stirred at room temperature for 3 h. The mixture was neutralized by addition of solid NaHCO_3 and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 0/100) to afford compound **8** (57 mg). Yield: 93 %; white solid; $R_f = 0.28$ (cyclohexane/EtOAc 6/4); $[\alpha]_D = 103.9$ ($c = 0.11$, CHCl_3); mp: 93-95°C; IR (film): ν 3377, 1737, 1357, 1292, 1200 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 2.26 (d, 1H, $J_{\text{OH},5} = 10.0$ Hz, OH), 2.75 (brd, 1H, $J_{2a,2b} = 19.0$ Hz, $H-2a$), 2.85 (dd, 1H, $J_{2b,3} = 6.0$ Hz, $H-2b$), 3.87-3.95 (brdd, 1H, $J_{6,\text{F}} = 27.0$ Hz, $J_{6,5} = 9.0$ Hz, $H-6$), 4.32 (ddd, 1H, $J_{5,6} = 9.0$ Hz, $J_{5,4} = 4.5$ Hz, $H-5$), 4.55 (ddd, 1H, $J_{7a,\text{F}} = 47.5$ Hz, $J_{7a,7b} = 10.5$ Hz, $J_{7a,6} = 3.5$ Hz, $H-7a$), 4.68 (ddd, 1H, $J_{7b,\text{F}} = 47.5$ Hz, $J_{7b,6} = 1.5$ Hz, $H-7b$), 4.91 (app brt, 1H, $J_{3,4} = 4.5$ Hz, $H-3$), 4.99 (app t, 1H, $J_{4,3} = J_{4,5} = 4.5$ Hz, $H-4$). ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 37.0 ($C-2$), 72.0 (d, $J_{\text{C}5-\text{F}} = 7$ Hz, $C-5$), 76.5 ($C-3$), 80.8 (d, $J_{\text{C}6-\text{F}} = 18$ Hz, $C-6$), 81.8 (d, $J_{\text{C}7-\text{F}} = 175$ Hz, $C-7$), 82.7 ($C-4$), 174.8 ($C=O$); HRMS (ESI): calcd for $\text{C}_7\text{H}_9\text{NaFO}_4$ $[\text{M}+\text{Na}]^+$: 199.0383, found: 199.0424.

3,6-anhydro-2-deoxy-4,5-O-(1-methylethylidene)-7-O-(*p*-methoxybenzyl)-D-ribo-heptanoic acid methyl ester 9

To a solution of **4** (100 mg, 0.40 mmol) in dry dichloromethane (5 mL), 225 mg of 4-methoxybenzyl 2,2,2-trichloroacetimidate (2 eq., 0.80 mmol) were added under inert atmosphere. The reaction mixture was cooled at 0 °C and 2 μL of $\text{BF}_3 \cdot \text{OEt}_2$ (0.04 eq, 0.016 mmol) were added and the mixture was stirred overnight at room temperature. After 16 h, the catalyst was filtered off through a Celite[®] pad and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 60/40) to afford compound **9** (110 mg). Yield: 75 %; colorless gum; $R_f = 0.40$ (cyclohexane/EtOAc 8/2); $[\alpha]_D^{25} = -4.6$ ($c = 0.11$,

CHCl₃); IR (film): ν 3370, 2936, 1732, 1670, 1610, 1512, 1458, 1373, 1301, 1246 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.31 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 2.69 (dd, 2H, $J_{2a,2b} = 16.5$ Hz, $J_{2a,3} = 7.0$ Hz, *H-2a*), 2.74 (dd, 2H, $J_{2b,3} = 6.5$ Hz, *H-2b*), 3.46-3.51 (m, 2H, *H-7*), 3.70 (s, 3H, OCH₃), 3.80 (s, 3H, Ar-OCH₃), 4.16 (app t, 1H, $J_{6,7a} = J_{6,7b} = 4.5$ Hz, *H-6*), 4.40-4.47 (m, 1H, *H-3*), 4.42 (d, 1H, $J = 11.5$ Hz, CH₂Ph), 4.47 (d, 1H, $J = 11.5$ Hz, CH₂Ph), 4.72-4.76 (m, 2H, *H-4*, *H-5*), 6.87 (bd, 2H, $J = 8.5$ Hz, *H-Ar*), 7.22 (bd, 2H, $J = 8.5$ Hz, *H-Ar*); ¹³C NMR (CDCl₃, 100.6 MHz): δ 25.1 (CH₃), 26.3 (CH₃), 34.7 (*C-2*), 51.9 (OCH₃), 55.4 (OCH₃), 70.5 (*C-7*), 73.2 (CH₂Ph), 78.1 (*C-3*), 81.7, 82.8, 83.3 (*C-4*, *C-5*, *C-6*), 112.5 (C(CH₃)₂), 114.0 (2*C*_{Ar}), 129.3 (2*C*_{Ar}), 130.0 (*C*_qAr), 159.4 (*C*_qAr), 172.0 (*C=O*). HRMS (ESI): calcd for C₁₉H₂₆NaO₇ [M+Na]⁺: 389.157, found: 389.1590.

3,6-anhydro-2-deoxy-4,5-*O*-(1-methylethylidene)-7-*O*-(*tert*-butyldiphenylsilyl)-*D*-ribo-heptanoic acid methyl ester **11**

To a solution of **4** (1 g, 4.05 mmol) in dry DMF (10 mL), a solution of 1.58 mL of *tert*-butyldiphenylsilyl chloride (1.5 eq., 6.07 mmol) and 496 mg of imidazole (1.8 eq., 7.29 mmol) in dry DMF (3 mL) was added dropwise at 0 °C under inert atmosphere. The reaction was stirred overnight at room temperature. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3x80 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 90/10) to afford compound **11** (1.86 g). Yield: 95 %; colorless oil; $R_f = 0.47$ (cyclohexane/EtOAc 8/2); $[\alpha]_D^{25} 0.40$ ($c = 0.36$, CHCl₃); IR (film); ν 2928, 1742, 1425, 1351, 1210 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.06 (s, 9H, Si-*tert*-butyl), 1.35 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 2.70 (dd, 1H, $J_{2a,2b} = 16.5$ Hz, $J_{2a,3} = 7.0$ Hz, *H-2a*), 2.76 (dd, 1H, $J_{2b,3} = 7.0$ Hz, *H-2b*), 3.67 (dd, 1H, $J_{7a,7b} = 11.0$ Hz, $J_{7a,6} = 4.0$ Hz, *H-7a*), 3.71 (s, 3H, COOCH₃), 3.77 (dd, 1H, $J_{7b,6} = 4.0$ Hz, *H-7b*), 4.11 (app bt, 1H, *H-6*), 4.59 (app td, 1H, $J_{3,2a} = J_{3,2b} = 7.0$ Hz, $J_{3,4} = 4.0$ Hz, *H-3*), 4.80 (dd, 1H, $J_{4,5} = 6.0$ Hz, *H-4*), 4.86 (br d, 1H, *H-5*), 7.36-7.46 (m, 6H, *H*_{Ar}), 7.64-7.68 (m, 4H, *H*_{Ar}); ¹³C NMR (CDCl₃, 100.6 MHz): δ 19.2 (*C-Si*), 25.2 (CH₃), 26.4 (CH₃), 27.0 (Si-*tert*-butyl), 34.9 (*C-2*), 51.8 (OCH₃), 65.4 (*C-7*), 78.6 (*C-3*), 82.0 (*C-4*), 83.4 (*C-5*), 84.3 (*C-6*), 112.5 (C(CH₃)₂), 128.0 (4*C*_{Ar}), 130.0 (*C*_{Ar}), 130.0 (*C*_{Ar}), 132.9 (*C*_qAr), 133.0 (*C*_qAr), 135.8 (4*C*_{Ar}), 171.8 (*C=O*); HRMS (ESI): calcd for C₂₇H₃₆KO₆Si: [M+K]⁺: 523.1913, found: 523.1877.

3,6-anhydro-2-deoxy-5,7-hydroxy-*D*-ribo-1,4-lactone **12**

A solution of **4** (500 mg, 2.03 mmol) in a mixture of TFA/H₂O 1/1 (v/v) (20 mL) was stirred for 3 h at room temperature. The solvent was removed *in vacuum* and the crude residue was purified by column chromatography on silica gel (eluent: EtOAc/MeOH 100/0 to 90/10) to afford compound **12**

(244 mg). Yield: 69 %; yellowish oil; $R_f = 0.40$ (EtOAc/MeOH 9/1); $[\alpha]_D^{25} 77.4$ ($c = 0.13$, EtOH); IR (film): ν 3389, 2934, 2872, 1770, 1678, 1400, 1356, 1305, 1263, 1193 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 2.73 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 1.0$ Hz, *H-2a*), 2.85 (dd, 1H, $J_{2b,2a} = 18.5$ Hz, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.74 (dd, 1H, $J_{7a,7b} = 12.0$ Hz, $J_{7a,6} = 4.5$ Hz, *H-7a*), 3.78 (ddd, 1H, $J_{6,5} = 8.5$ Hz, $J_{6,7a} = 4.5$ Hz, $J_{6,7b} = 2.5$ Hz, *H-6*), 3.94 (dd, 1H, $J_{7b,7a} = 12.0$ Hz, $J_{7b,6} = 2.5$ Hz, *H-7b*), 4.29 (dd, 1H, $J_{5,6} = 8.5$ Hz, $J_{5,4} = 4.5$ Hz, *H-5*), 4.88 (ddd, 1H, $J_{3,2b} = 6.0$ Hz, $J_{3,4} = 4.5$ Hz, $J_{3,2a} = 1.0$ Hz, *H-3*), 4.98 (app t, 1H, $J_{4,5} = J_{4,3} = 4.5$ Hz, *H-4*); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 37.1 (*C-2*), 61.3 (*C-7*), 72.4 (*C-5*), 76.2 (*C-3*), 81.4 (*C-6*), 83.1 (*C-4*), 174.9 (*C=O*). HRMS (ESI): calcd for $\text{C}_7\text{H}_{10}\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 197.0420, found: 197.0401.

3,6-anhydro-2-deoxy-5-hydroxy-7-*O*-(*tert*-butyldimethylsilyl)-*D*-ribo-1,4-lactone 13

To a solution of **12** (140 mg, 0.80 mmol) in dry DMF (4 mL), a solution of 225 μL of *tert*-butyldiphenylsilyl chloride (1.1 eq., 0.86 mmol) and 120 mg of imidazole (2.2 eq., 1.76 mmol) in dry DMF (2 mL) was added dropwise at 0 $^\circ\text{C}$ under inert atmosphere. The reaction was stirred for 24 h at 40 $^\circ\text{C}$. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3x20 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford compound **13** (158 mg). Yield: 48 %; colorless oil; $R_f = 0.40$ (cyclohexane/EtOAc 7/3); $[\alpha]_D^{25} 22.4$ ($c = 0.06$, CHCl_3); IR (film): ν 3672, 2926, 1782, 1472, 1427, 1394, 1250 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.06 (s, 9H, *Si-tert-butyl*), 2.10 (brs, 1H, *OH*), 2.72 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 1.5$ Hz, *H-2a*), 2.82 (dd, 1H, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.81 (dd, 1H, $J_{7a,7b} = 11.0$ Hz, $J_{7a,6} = 3.5$ Hz, *H-7a*), 3.85 (ddd, 1H, $J_{6,5} = 7.0$ Hz, $J_{6,7a} = 3.5$ Hz, $J_{6,7b} = 2.5$ Hz, *H-6*), 3.91 (dd, 1H, $J_{7b,7a} = 11.0$ Hz, $J_{7b,6} = 2.5$ Hz, *H-7b*), 4.40-4.46 (m, 1H, *H-5*), 4.89 (ddd, 1H, $J_{3,2b} = 6.0$ Hz, $J_{3,4} = 4.5$ Hz, $J_{3,2a} = 1.5$ Hz, *H-3*), 5.01 (app t, 1H, $J_{4,3} = J_{4,5} = 4.5$ Hz, *H-4*), 7.37-7.46 (m, 6H, H_{Ar}), 7.65-7.69 (m, 4H, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 19.4 (*C-Si*), 27.0 (*Si-tert-butyl*), 37.2 (*C-2*), 63.5 (*C-7*), 73.0 (*C-5*), 76.5 (*C-3*), 82.9 (*C-6*), 83.3 (*C-4*), 127.9 (*2CAr*), 128.0 (*2CAr*), 130.0 (*CAr*), 130.0 (*CAr*), 133.1 (*CqAr*), 133.1 (*CqAr*), 135.7 (*2CAr*), 135.7 (*2CAr*), 175.3 (*C=O*); HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{NaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 435.1604, found: 435.1598.

3,6-anhydro-2-deoxy-5-*O*-(methyl)-7-*O*-(*tert*-butyldiphenylsilyl)-*D*-ribo-1,4-lactone 14

To a solution of **13** (100 mg, 0.24 mmol) in dry dichloromethane (5 mL), 185 mg of Ag_2O (3 eq., 0.73 mmol) and methyl iodide (4 eq., 0.96 mmol) were added under inert atmosphere. The reaction was stirred for 48 h at 60 $^\circ\text{C}$ in a sealed tube. The reaction mixture was filtered off through a Celite[®] pad and the solvent was removed under *vacuum*. The crude product was purified by flash

chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford **14** (74 mg). Yield: 72 %; colorless oil; $R_f = 0.72$ (cyclohexane/EtOAc 6/4); $[\alpha]_D^{25} 65.9$ ($c = 2.48$, CHCl_3); IR (film) : ν 2930, 2857, 1782, 1462, 1390 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.06 (s, 9H, *Si-tert-butyl*), 2.69 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 2.0$ Hz, *H-2a*), 2.77 (dd, 1H, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.47 (s, 3H, OCH_3), 3.75 (dd, 1H, $J_{7a,7b} = 11.5$ Hz, $J_{7a,6} = 3.0$ Hz, *H-7a*), 3.91 (dd, 1H, $J_{7b,6} = 2.5$ Hz, *H-7b*), 3.98 (app dt, 1H, $J_{6,5} = 7.0$ Hz, *H-6*), 4.07 (dd, 1H, $J_{5,4} = 4.5$ Hz, *H-5*), 4.89 (ddd, 1H, $J_{3,4} = 4.5$ Hz, *H-3*), 5.07 (app t, 1H, *H-4*), 7.36-7.47 (m, 6H, H_{Ar}), 7.67 (br d, 4H, $J = 6.5$ Hz, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 19.4 (*C-Si*), 27.0 (*Si-tert-butyl*), 37.0 (*C-2*), 58.6 (CH_3), 63.3 (*C-7*), 77.1 (*C-3*), 80.7 (*C-5*), 81.2 (*C-4*), 81.8 (*C-6*), 127.9 (*2CAr*), 127.9 (*2CAr*), 130.0 (*CAr*), 130.0 (*CAr*), 133.2 (*CqAr*), 133.3 (*CqAr*), 135.7 (*2CAr*), 135.7 (*2CAr*), 175.5 (*C=O*); HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{30}\text{NaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 449.1760, found: 449.1818.

3,6-anhydro-2-deoxy-5-*O*-(benzyl)-7-*O*-(*tert*-butyldiphenylsilyl)-*D*-ribo-1,4-lactone **15**

To a solution of **13** (100 mg, 0.24 mmol) in dry dichloromethane (5 mL), 185 mg of Ag_2O (3 eq., 0.73 mmol) and benzyl bromide (4 eq., 0.96 mmol) were added under inert atmosphere. The reaction was stirred for 48 h at 60 °C in a sealed tube. The reaction mixture was filtered off through a Celite[®] pad and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford **15** (106 mg). Yield: 88 %; colorless oil; $R_f = 0.25$ (cyclohexane/EtOAc 7/3); $[\alpha]_D^{25} 84.4$ ($c = 0.10$, CHCl_3); IR (film): ν 3088, 2927, 2856, 1782, 1589, 1454, 1427, 1398, 1360, 1308, 1261 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.03 (s, 9H, *Si-tert-butyl*), 2.71 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 2.5$ Hz, *H-2a*), 2.77 (dd, 1H, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.74 (dd, 1H, $J_{7a,7b} = 11.5$ Hz, $J_{7a,6} = 3.0$ Hz, *H-7a*), 3.90 (dd, 1H, $J_{7b,6} = 2.5$ Hz, *H-7b*), 4.06 (app dt, 1H, $J_{6,5} = 7.0$ Hz, *H-6*), 4.26 (dd, 1H, $J_{5,4} = 4.5$ Hz, *H-5*), 4.56 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.76 (d, 1H, CH_2Ph), 4.86 (ddd, 1H, $J_{3,4} = 4.5$ Hz, *H-3*), 4.98 (app t, 1H, *H-4*), 7.29-7.46 (m, 11H, H_{Ar}), 7.62-7.65 (m, 4H, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 19.4 (*C-Si*), 27.0 (*Si-tert-butyl*), 37.1 (*C-2*), 63.1 (*C-7*), 72.9 (CH_2Ph), 77.1 (*C-3*), 78.2 (*C-5*), 81.4 (*C-4*), 81.9 (*C-6*), 127.9 (*2CAr*), 127.9 (*2CAr*), 128.1 (*2CAr*), 128.2 (*2CAr*), 128.7 (*CAr*), 129.9 (*CAr*), 130.0 (*CAr*), 133.1 (*CqAr*), 133.3 (*CqAr*), 135.7 (*2CAr*), 135.7 (*2CAr*), 137.4 (*CqAr*), 175.6 (*C=O*); HRMS (ESI): calcd for $\text{C}_{30}\text{H}_{34}\text{NaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 525.2068, found: 525.2077.

3,6-anhydro-2-deoxy-5-*O*-(allyl)-7-*O*-(*tert*-butyldiphenylsilyl)-*D*-ribo-1,4-lactone **16**

To a solution of **13** (100 mg, 0.24 mmol) in dry dichloromethane (5 mL), 185 mg of Ag_2O (3 eq., 0.73 mmol) and allyl bromide (4 eq., 0.96 mmol) were added under inert atmosphere. The reaction was stirred for 48 h at 60 °C in a sealed tube. The reaction mixture was filtered off through a Celite[®]

pad and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford **16** (38 mg). Yield: 35 %; colorless oil; $R_f = 0.63$ (cyclohexane/EtOAc 6/4); $[\alpha]_D = 65.1$ ($c = 0.92$, CHCl_3); IR (film): ν 2928, 2857 1782, 1471, 1458, 1427 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.06 (s, 9H, *Si-tert-butyl*), 2.70 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 2.0$ Hz, *H-2a*), 2.77 (dd, 1H, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.75 (dd, 1H, $J_{7a,7b} = 11.5$ Hz, $J_{7a,6} = 3.0$ Hz, *H-7a*), 3.91 (dd, 1H, $J_{7b,6} = 2.5$ Hz, *H-7b*), 4.01 (app dt, 1H, $J_{6,5} = 7.0$ Hz, *H-6*), 4.06 (app ddt, 1H, $J_{8a,8b} = 12.5$ Hz, $J_{8a,9} = 6.0$ Hz, $J_{8a,10a} = J_{8a,10b} = 1.0$ Hz, *H-8a*), 4.21 (app ddt, 1H, $J_{8b,9} = 5.5$ Hz, $J_{8b,10a} = J_{8b,10b} = 1.5$ Hz, *H-8b*), 4.23 (dd, 1H, $J_{5,4} = 4.5$ Hz, *H-5*), 4.88 (ddd, 1H, $J_{3,4} = 4.5$ Hz, *H-3*), 5.03 (app t, 1H, *H-4*), 5.22 (br dd, 1H, $J_{10a,9} = 10.5$ Hz, $J_{10a,10b} = 2.5$ Hz, *H-10a*), 5.31 (br dd, 1H, $J_{10b,9} = 17.0$ Hz, *H-10b*), 5.93 (app ddt, 1H, *H-9*), 7.35-7.47 (m, 6H, H_{Ar}), 7.65-7.68 (m, 4H, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 19.4 (*C-Si*), 27.0 (*Si-tert-butyl*), 37.1 (*C-2*), 63.1 (*C-7*), 71.9 (*C-8*), 77.1 (*C-3*), 78.2 (*C-5*), 81.4 (*C-4*), 81.8 (*C-6*), 118.1 (*C-9*), 127.9 (*2CAr*), 127.9 (*2CAr*), 130.0 (*CAr*), 130.0 (*CAr*), 133.1 (*CqAr*), 133.3 (*CqAr*), 134.3 (*C-10*), 135.7 (*2CAr*), 135.7 (*2CAr*), 175.6 (*C=O*); HRMS (ESI): calcd for $\text{C}_{26}\text{H}_{32}\text{NaO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 475.1911, found: 475.1916.

3,6-anhydro-2-deoxy-5-*O*-(benzyl)-7-hydroxy-*D*-ribo-1,4-lactone **17**

To a solution of the benzylated lactone **15** (30 mg, 0.06 mmol) in methanol (2 mL), 23 mg of PTSA monohydrate (2.0 eq., 0.12 mmol) were added. After stirring at 30 °C (TLC monitoring) the solvent was removed *in vacuum* and the crude product was purified by chromatography on silica gel (eluent: cyclohexane/EtOAc 80/20) to afford **17** (10 mg). Yield: 61 %; white solid; $R_f = 0.25$ (cyclohexane/EtOAc 7/3); $[\alpha]_D^{25} = 172.7$ ($c = 0.28$, CHCl_3); mp: 80-82°C; IR (film): ν 3343, 2920, 2870, 1770, 1452, 1394, 1310, 1259 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 2.69 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 1.0$ Hz, *H-2a*), 2.78 (dd, 1H, $J_{2b,3} = 6.0$ Hz, *H-2b*), 3.65 (br d, 1H, $J_{7a,7b} = 12.0$ Hz, *H-7a*), 3.89 (dd, 1H, $J_{7b,6} = 2.0$ Hz, *H-7b*), 3.93 (app dt, 1H, $J_{6,5} = 8.5$ Hz, *H-6*), 4.08 (dd, 1H, $J_{5,4} = 4.5$ Hz, *H-5*), 4.61 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.77 (d, 1H, CH_2Ph), 4.84 (ddd, 1H, $J_{3,4} = 4.5$ Hz, *H-3*), 4.93 (app t, 1H, *H-4*), 7.29-7.42 (m, 5H, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 37.0 (*C-2*), 61.2 (*C-7*), 72.8 (CH_2Ph), 76.9 (*C-3*), 77.7 (*C-5*), 80.1 (*C-6*), 80.9 (*C-4*), 128.2 (*2CAr*), 128.4 (*CAr*), 128.7 (*2CAr*), 137.3 (*CqAr*), 175.4 (*C=O*); HRMS (ESI): calcd for $\text{C}_{14}\text{H}_{17}\text{O}_5$ $[\text{M}+\text{H}]^+$: 265.1071, found: 265.1057.

3,6-anhydro-2-deoxy-4,5-*O*-(1-methylethylidene)-7-iodo-*D*-galacto-heptanoic acid methyl ester

To a solution of **22** (370 mg, 1.50 mmol) in dry THF (3.5 mL), 215 mg of imidazole (2.1 eq., 3.15 mmol) and 826 mg of PPh₃ (2.1 eq., 3.15 mmol) were added. The mixture was heated at reflux and a solution of I₂ (480 mg, 1.90 mmol, 1.25 eq.) solubilized in dry THF was added (1.5 mL). After stirring at reflux until completion of the reaction, the solvent was removed *in vacuum* and the crude residue was purified by column chromatography (eluent: cyclohexane/EtOAc 100/0 to 20/80) to provide **23** (326 mg). Yield: 61 %; colorless oil; $R_f = 0.60$ (cyclohexane/EtOAc 5/5); $[\alpha]_D = 15.6$ (c = 0.10, CHCl₃); IR (film): ν 3333, 2988, 2939, 1774, 1400, 1362, 1281, 1248 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.33 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 2.74 (dd, 1H, $J_{2a,2b} = 17.0$ Hz, $J_{2,3} = 6.5$ Hz, H-2a), 2.80 (dd, 1H, $J_{2b,3} = 7.0$ Hz, H-2b), 3.25 (dd, 1H, $J_{7a,7b} = 9.5$ Hz, $J_{7a,6} = 6.0$ Hz, H-7a), 3.34 (dd, 1H, $J_{7b,6} = 8.5$ Hz, H-7b), 3.70 (s, 3H, OCH₃), 3.79 (app brt, 1H, H-6), 3.97 (app brt, 1H, H-3), 4.74-4.79 (m, 2H, H-4, H-5); ¹³C NMR (CDCl₃, 100.6 MHz): δ -1.1 (C-7), 25.1 (CH₃), 26.0 (CH₃), 33.5 (C-2), 51.9 (OCH₃), 77.9 (C-3), 80.8, 81.3 (C-4, C-5), 82.1 (C-6), 112.8 (C(CH₃)₂), 171.4 (C=O); HRMS (ESI): calcd for C₁₁H₁₈IO₅ [M+Na]⁺: 357.0193, found: 357.0215.

3,6-anhydro-2-deoxy-5-hydroxy-7-iodo-D-gulo-1,4-lactone **24**

A solution of compound **23** (200 mg, 0.56 mmol) in a mixture of TFA/H₂O 1/1 (v/v) (1 mL) was stirred for 3 h at room temperature. The solvent was removed *in vacuum* and the crude residue was purified by column chromatography on silica gel (eluent: EtOAc/MeOH 100/0 to 90/10) to afford **24** (70 mg). Yield: 44 %; white solid; $R_f = 0.33$ (EtOAc/MeOH 9/1); $[\alpha]_D = 49.6$ (c = 0.10, CHCl₃); mp: 183-185°C; IR (film): ν 3333, 2988, 2939, 1774, 1400, 1362, 1281, 1248 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.76 (dd, 1H, $J_{2a,2b} = 19.0$ Hz, $J_{2a,3} = 3.5$ Hz, H-2a), 2.81 (dd, 1H, $J_{2b,3} = 6.0$ Hz, H-2b), 3.26 (dd, 1H, $J_{7a,7b} = 10.0$ Hz, $J_{7a,6} = 6.5$ Hz, H-7a), 3.42 (dd, 1H, $J_{7b,6} = 7.0$ Hz, H-7b), 4.09 (app td, 1H, $J_{6,5} = 4.0$ Hz, H-6), 4.49 (br dd, 1H, $J_{5,4} = 5.5$ Hz, H-5), 4.73 (app td, 1H, $J_{3,2b} = J_{3,4} = 6.0$ Hz, H-3), 5.04 (app t, 1H, H-4); ¹³C NMR (CDCl₃, 100.6 MHz): δ -0.8 (C-7), 35.9 (C-2), 71.0 (C-5), 76.6 (C-3), 82.6 (C-4), 83.6 (C-6), 174.8 (C=O). HRMS (ESI): calcd for C₇H₉NaIO₅ [M+Na]⁺: 306.9438, found: 306.9448.

3,6-anhydro-2-deoxy-5,7-hydroxy-D-gulo-1,4-lactone **25**

A solution of **22** (402 mg, 1.63 mmol) in a mixture of TFA/H₂O 1/1 (v/v) (20 mL) was stirred for 3 h at room temperature. The solvent was removed *in vacuum* and the crude residue was purified by column chromatography on silica gel (eluent: EtOAc/MeOH 100/0 to 90/10) to afford **25** (176 mg). Yield: 62%; white solid; $R_f = 0.40$ (EtOAc/MeOH 9/1); $[\alpha]_D^{25} = 58.7$ (c = 0.10, EtOH); mp: 97-99°C; IR (film): ν 3395, 2938, 1755, 1678, 1429, 1367, 1312, 1276 cm⁻¹. ¹H NMR (CD₃OD, 400 MHz): δ 2.61 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 2.5$ Hz, H-2a), 2.83 (dd, 1H, $J_{2b,3} = 7.5$ Hz, H-2b), 3.69 (dd, 1H,

$J_{7a,7b} = 12.0$ Hz, $J_{7a,6} = 7.0$ Hz, $H-7a$), 3.81 (dd, 1H, $J_{7b,6} = 4.5$ Hz, $H-7b$), 3.92 (app dt, 1H, $J_{6,5} = J_{6,7b} = 5.0$ Hz, $H-6$), 4.41 (app t, 1H, $J_{5,4} = J_{5,6} = 5.0$ Hz, $H-5$), 4.67 (ddd, 1H, $J_{3,4} = 5.0$ Hz, $H-3$), 5.01 (app t, 1H, $J_{4,5} = J_{4,3} = 5.0$ Hz, $H-4$); ^{13}C NMR (CD_3OD , 100.6 MHz): δ 37.2 ($C-2$), 61.8 ($C-7$), 72.3 ($C-5$), 77.4 ($C-3$), 84.0 ($C-6$), 85.0 ($C-4$), 178.4 ($C=O$); HRMS (ESI): calcd for $\text{C}_7\text{H}_{10}\text{NaO}_5$ $[\text{M}+\text{Na}]^+$: 197.0426, found: 197.0420.

3,6-anhydro-2-deoxy-5-hydroxy-7-*O*-(*tert*-butyldimethylsilyl)-*D*-galacto-1,4-lactone 26

To a solution of **25** (200 mg, 1.14 mmol) in dry DMF (5 mL), a solution of 321 μL of *tert*-Butyldiphenylsilyl chloride (1.1 eq., 1.25 mmol) and 171 mg of imidazole (2.2 eq., 2.51 mmol) in dry DMF (2 mL) was added dropwise at 0 °C under inert atmosphere. The reaction was stirred for 24 h at 40 °C. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3x20 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford compound **26** (187 mg). Yield: 57%; colorless oil; $R_f = 0.32$ (cyclohexane/EtOAc 7/3); $[\alpha]_D = 10.8$ ($c = 0.11$, CHCl_3); IR (film): ν 3447, 2930, 2857, 1774, 1472, 1427 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.06 (s, 9H, *Si-tert-butyl*), 2.71 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 3.0$ Hz, $H-2a$), 2.78 (dd, 1H, $J_{2b,3} = 6.5$ Hz, $H-2b$), 3.09 (d, 1H, $J_{\text{OH},5} = 5.5$ Hz, *OH*), 3.91 (dd, 1H, $J_{7a,7b} = 10.5$ Hz, $J_{7a,6} = 4.5$ Hz, $H-7a$), 3.95 (app q, 1H, $J_{6,7a} = J_{6,7b} = J_{6,5} = 4.5$ Hz, $H-6$), 4.03 (dd, 1H, $H-7b$), 4.51 (app dt, 1H, $J_{5,\text{OH}} = J_{5,4} = 5.5$ Hz, $H-5$), 4.89 (ddd, 1H, $J_{3,4} = 5.5$ Hz, $H-3$), 4.96 (app t, 1H, $H-4$), 7.36-7.47 (m, 6H, H_{Ar}), 7.66-7.70 (m, 4H, H_{Ar}); ^{13}C NMR (CDCl_3 , 100.6 MHz): δ 19.2 ($C\text{-Si}$), 26.9 (*Si-tert-butyl*), 36.3 ($C-2$), 62.6 ($C-7$), 72.2 ($C-5$), 76.1 ($C-3$), 82.2 ($C-6$), 82.9 ($C-4$), 127.9 (2*C*_{Ar}), 127.9 (2*C*_{Ar}), 130.0 (2*C*_{Ar}), 132.8 (*C*_q*Ar*), 133.0 (*C*_q*Ar*), 135.7 (2*C*_{Ar}), 135.8 (2*C*_{Ar}), 175.1 ($C=O$); HRMS (ESI): calcd for $\text{C}_{23}\text{H}_{28}\text{KO}_5\text{Si}$ $[\text{M}+\text{Na}]^+$: 451.1338, found: 451.1339.

3,6-anhydro-2-deoxy-5-*O*-(benzyl)-7-*O*-(*tert*-butyldiphenylsilyl)-*D*-galacto-1,4-lactone 27

To a solution of **26** (100 mg, 0.24 mmol) in dry dichloromethane (5 mL), 185 mg of Ag_2O (3 eq., 0.73 mmol) and benzyl bromide (4 eq., 0.96 mmol) were added under inert atmosphere. The reaction was stirred for 48 h at 60 °C in a sealed tube. The reaction mixture was filtered off through a Celite[®] pad and the solvent was removed under *vacuum*. The crude product was purified by flash chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford **27** (35 mg). Yield: 29%; colorless oil; $R_f = 0.66$ (cyclohexane/EtOAc 7/3); $[\alpha]_D = 30.7$ ($c = 0.11$, CHCl_3); IR (film): ν 2928, 2856, 1780, 1471, 1427 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 1.06 (s, 9H, *Si-tert-butyl*), 2.64 (dd, 1H, $J_{2a,2b} = 18.5$ Hz, $J_{2a,3} = 4.0$ Hz, $H-2a$), 2.72 (dd, 1H, $J_{2b,3} = 7.5$ Hz, $H-2b$), 3.83 (br dd, 1H, $J_{7a,7b} = 12.5$ Hz, $J_{7a,6} = 8.0$ Hz, $H-7a$), 3.97-4.03 (m, 2H, $H-6$ and $H-7b$), 4.15 (dd, 1H, $J_{5,4}$

= 5.0 Hz, $J_{5,6} = 3.5$ Hz, $H-5$), 4.47 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.69 (ddd, 1H, $J_{3,4} = 7.0$ Hz, $H-3$), 4.78 (d, 1H, CH_2Ph), 5.04 (dd, 1H, $H-4$), 7.23-7.45 (m, 11H, H_{Ar}), 7.62-7.66 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 19.3 ($C-Si$), 27.0 ($Si-tert-butyl$), 36.2 ($C-2$), 62.2 ($C-7$), 73.9 (CH_2Ph), 76.0 ($C-3$), 77.2 ($C-5$), 82.4 ($C-4$), 82.8 ($C-6$), 127.9 ($4CAr$), 128.0 (CAr), 128.2 ($2CAr$), 128.5 ($2CAr$), 129.9 (CAr), 129.9 (CAr), 133.4 ($CqAr$), 133.5 ($CqAr$), 135.7 ($2CAr$), 135.7 ($2CAr$), 137.5 ($CqAr$), 175.3 ($C=O$); HRMS (ESI): calcd for $C_{30}H_{35}O_5Si$ $[M+H]^+$: 503.2248, found: 503.2246.

3,6-anhydro-2-deoxy-5-O-(benzyl)-7-hydroxy-D-galacto-1,4-lactone 28

To a solution of compound **27** (35 mg, 0.07 mmol) in methanol (2 mL), 26 mg of PTSA monohydrate (2.0 eq., 0.14 mmol) were added. After stirring at 30 °C overnight, the solvent was removed *in vacuum* and the crude product was purified by chromatography on silica gel (eluent: Cyclohexane/EtOAc 80/20) to afford **28** (9 mg). Yield: 49%; colorless oil; $R_f = 0.34$ (cyclohexane/EtOAc 2/8); $[\alpha]_D = 102.1$ ($c = 0.11$, $CHCl_3$); IR (film): $\nu = 3447, 2924, 2882, 1497, 1454, 1400, 1340, 1311$ cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 2.77 (d, 2H, $J_{2,3} = 4.5$ Hz, $H-2$), 3.77 (dd, 1H, $J_{7a,7b} = 12.0$ Hz, $J_{7a,6} = 5.0$ Hz, $H-7a$), 3.81 (dd, 1H, $J_{7b,6} = 5.0$ Hz, $H-7b$), 4.09 (dt, 1H, $J_{6,5} = 5.5$ Hz, $H-6$), 4.29 (app t, 1H, $J_{5,4} = J_{5,6} = 5.5$ Hz, $H-5$), 4.50 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 4.72 (dt, 1H, $J_{3,4} = 5.5$ Hz, $H-3$), 4.84 (d, 1H, $J = 11.5$ Hz, CH_2Ph), 5.00 (app t, 1H, $H-4$), 7.30-7.39 (m, 5H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 36.7 ($C-2$), 62.0 ($C-7$), 73.4 (CH_2Ph), 76.6 ($C-3$), 78.5 ($C-5$), 81.4 ($C-6$), 81.7 ($C-4$), 128.2 ($2CAr$), 128.5 (CAr), 128.8 ($2CAr$), 136.9 ($CqAr$), 175.3 ($C=O$); HRMS (ESI): calcd for $C_{14}H_{16}NaO_5$ $[M+Na]^+$: 287.0890, found: 287.089.

Compounds 29/30

To a solution of intermediate aldehyde **21** (532 mg, 2.18 mmol) in dry Et_2O (100 mL), were added dropwise at - 20 °C, 2.15 mL of 1M phenyl magnesium bromide in THF (0.95 eq., 2.07 mmol). The mixture was stirred overnight at room temperature. The reaction was quenched by addition of a saturated solution of NH_4Cl (until pH = 6) and the aqueous layer was extracted with Et_2O (2x50 mL) and with CH_2Cl_2 (2x50 mL). The combined organic layer was dried over $MgSO_4$, filtered and evaporated under *vacuum*. The crude residue was purified by column chromatography to provide a mixture of **29** and **30** (246 mg). Yield: 35%; colorless oil; $R_f = 0.32$ (cyclohexane/EtOAc 6/4); 1H NMR of **29/30** (ratio 65/35) ($CDCl_3$, 400 MHz): δ 1.27 (s, 1.95H, CH_3), 1.35 (s, 1.05H, CH_3), 1.43 (s, 1.95H, CH_3), 1.57 (s, 1.05H, CH_3), 2.79-2.91 (m, 2H, $H-2$), 3.57 (dd, 0.65H, $J_{6,7} = 8.0$ Hz, $J_{6,5} = 3.5$ Hz, $H-6$), 3.62 (dd, 0.35H, $J_{6,7} = 6.5$ Hz, $J_{6,5} = 3.5$ Hz, $H-6$), 3.68 (s, 1.05H, OCH_3), 3.72 (s, 1.95H, OCH_3), 3.90-3.99 (m, 1H, $H-3$), 4.38 (dd, 0.65H, $J_{4,5} = 6.0$ Hz, $J_{4,3} = 3.5$ Hz, $H-4$), 4.71 (dd,

0.65H, *H*-5), 4.76 (dd, 0.35H, $J_{4,5} = 6.0$ Hz, $J_{4,3} = 3.5$ Hz, *H*-4), 4.79 (dd, 0.35H, *H*-5), 5.02 (t, 0.35H, $J_{7,OH} = J_{7,6} = 6.5$ Hz, *H*-7), 5.07 (d, 0.65H, $J_{7,6} = 8.0$ Hz, *H*-7), 7.27-7.53 (m, 5H, H_{Ar}).

3,6-anhydro-2-deoxy-5,7-hydroxy-7-phenyl-D-gulo-1,4-lactone **31** and **32**

Mixture **29/30** (180 mg, 0.56 mmol) was dissolved in a solution of TFA/H₂O 6/4 (10 mL) and stirred for 16 h at room temperature. The solvent was removed under *vacuum* and the crude product was purified by chromatography on silica gel (eluent: toluene/acetone 85/15) to afford compounds **31** (35 mg) and **32** (21 mg).

31: Yield: 25%; white solid; $R_f = 0.38$ (toluene/acetone 8/2); $[\alpha]_D = 2.0$ ($c = 0.32$, CHCl₃); mp: 121-123°C; IR (film): ν 3404, 292, 2852, 1772, 1456, 1369, 1163 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.55 (d, 1H, $J_{OH,7} = 3.0$ Hz, *OH*-7), 2.63 (d, 1H, $J_{OH,5} = 6.0$ Hz, *OH*-5), 2.81 (dd, 1H, $J_{2a,2b} = 19.0$ Hz, $J_{2a,3} = 6.0$ Hz, *H*-2a), 2.87 (dd, 1H, $J_{2b,3} = 3.5$ Hz, *H*-7b), 4.02 (app t, 1H, $J_{6,7} = J_{6,5} = 5.0$ Hz, *H*-6), 4.29 (app q, 1H, $J_{5,4} = J_{5,OH} = J_{5,6} = 6.0$ Hz, *H*-5), 4.72 (td, 1H, $J_{3,2a} = J_{3,4} = 6.0$ Hz, $J_{3,2b} = 3.5$ Hz, *H*-3), 4.96 (app t, 1H, $J_{4,5} = J_{4,3} = 6.0$ Hz, *H*-4), 5.11 (dd, 1H, $J_{7,OH} = 3.0$ Hz, *H*-7), 7.30-7.40 (m, 3H, H_{Ar}), 7.47 (d, 2H, $J = 7.5$ Hz, H_{Ar}). ¹³C NMR (CDCl₃, 100.6 MHz): δ 36.2 (*C*-2), 71.8 (*C*-5), 72.3 (*C*-7), 76.2 (*C*-3), 82.5 (*C*-4), 86.1 (*C*-6), 126.9 (2*C*_{Ar}), 128.4 (*C*_{Ar}), 128.7 (2*C*_{Ar}), 140.2 (*C*_q*Ar*), 175.2 (*C*=O); HRMS (ESI): calcd for C₁₃H₁₄NaO₅ [M+Na]⁺: 273.0733, found: 273.0733.

32: Yield: 15%; white solid; $R_f = 0.33$ (toluene/acetone 8/2); $[\alpha]_D = 23.1$ ($c = 0.16$, CHCl₃); mp: 152-154°C; IR (film): ν 3390, 2924, 2853, 1770, 1454, 1363, 1248, 1363, 1248 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.77 (d, 2H, $J_{2,3} = 5.0$ Hz, *H*-2), 3.07-3.11 (m, 2H, *OH*-5 and *OH*-7), 3.94 (dd, 1H, $J_{6,7} = 7.5$ Hz, $J_{6,5} = 5.0$ Hz, *H*-6), 4.58 (app t, 1H, $J_{5,6} = J_{5,4} = 5.0$ Hz, *H*-5), 4.64 (app q, 1H, $J_{3,2} = J_{3,4} = 5.0$ Hz, *H*-3), 4.99 (app t, 1H, *H*-4), 5.02 (d, 1H, *H*-7), 7.33 (br d, 1H, $J = 7.0$ Hz, H_{Ar}), 7.38 (br t, 2H, $J = 7.0$ Hz, H_{Ar}), 7.43 (br d, 2H, $J = 7.0$ Hz, H_{Ar}); ¹³C NMR (CDCl₃, 100.6 MHz): δ 36.1 (*C*-2), 71.7 (*C*-5), 72.8 (*C*-7), 76.5 (*C*-3), 82.5 (*C*-4), 85.3 (*C*-6), 126.7 (2*C*_{Ar}), 128.4 (*C*_{Ar}), 128.7 (2*C*_{Ar}), 140.6 (*C*_q*Ar*), 174.9 (*C*=O); HRMS (ESI): calcd for C₁₃H₁₄NaO₅ [M+Na]⁺: 273.0733, found: 273.0724.

3,6-anhydro-2-deoxy-5-hydroxy-7-(*trans*-cynamate)-7-phenyl-D-gulo-1,4-lactone **35**

To a solution of **29/30** (360 mg, 1.12 mmol) in CH₂Cl₂ (15 mL), 183 mg of *trans*-cinnamic acid (1.1 eq., 1.23 mmol), 164 mg of DMAP (1.2 eq., 1.34 mmol) and 277 mg of DCC (1.2 eq., 1.34 mmol) were added. The solution was stirred for 48 h at 25 °C. The solution was washed with an aqueous solution of 1 M HCl (2x10 mL), a saturated solution of NaHCO₃ (2x10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed under *vacuum*. The crude

was purified by chromatography on silica gel (eluent: cyclohexane/EtOAc 100/0 to 70/30) to afford 265 mg of esterified compounds **33/34** (53 % yield). A solution of **33/34** (80 mg, 0.18 mmol) in a mixture of TFA/CH₂Cl₂ 1/1 (v/v) (5 mL) was stirred under inert atmosphere for 24 h at room temperature. The solvent was removed under *vacuum* and the crude was purified by chromatography on silica gel (eluent: Et₂O/petroleum ether 50/50 to 80/20) to afford compound **35** (125 mg).

Yield: 56%; yellowish solid; $R_f = 0.22$ (Et₂O/petroleum ether 8/2); $[\alpha]_D = 17.5$ (c = 0.10, CHCl₃); mp: 157-159°C; IR (film): ν 3416, 2920, 1770, 1697, 1634, 1450, 1371, 1269 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.82 (dd, 1H, $J_{2a,2b} = 19.0$ Hz, $J_{2a,3} = 7.0$ Hz, *H*-2a), 2.90 (dd, 1H, $J_{2b,3} = 3.0$ Hz, *H*-2b), 4.14 (app t, 1H, $J_{5,4} = J_{5,6} = 6.0$ Hz, *H*-5), 4.27 (dd, 1H, $J_{6,7} = 7.5$ Hz, *H*-6), 4.78 (app td, 1H, $J_{3,2a} = J_{3,4} = 6.0$ Hz, *H*-3), 4.97 (app t, 1H, $J_{4,5} = J_{4,3} = 6.0$ Hz, *H*-4), 6.22 (d, 1H, *H*-7), 6.55 (d, 1H, $J = 16.0$ Hz, *H*-styryl), 7.29-7.43 (m, 6H, *H*_{Ar}), 7.48-7.56 (m, 4H, *H*_{Ar}), 7.70 (d, 1H, *H*-styryl). ¹³C NMR (CDCl₃, 100.6 MHz): δ 36.3 (*C*-2), 71.3 (*C*-5), 74.3 (*C*-7), 76.5 (*C*-3), 82.3 (*C*-4), 84.8 (*C*-6), 117.9 (*C*-styryl), 127.6 (2*C*_{Ar}), 128.4 (2*C*_{Ar}), 128.7 (2*C*_{Ar}), 128.8 (*C*_{Ar}), 129.0 (2*C*_{Ar}), 130.5 (*C*_{Ar}), 134.5 (*C*_{qAr}), 137.4 (*C*_{qAr}), 145.9 (*C*-styryl), 166.1 (*C*=O), 175.2 (*C*=O). HRMS (ESI): calcd for C₂₂H₂₀KO₆ [M+K]⁺: 419.0891, found: 419.0877.

Biological evaluation

Cytotoxic activity: MDA-MB231 Breast cancer cells, U87 and U251 glioblastoma cells and DAOY medulloblastoma cells were seeded in P96 plate at 5.10⁴ cells per mL. 24 h post-incubation, cells were treated with different concentrations of lactone products (0.1; 1; 10; 100; 250 μ M). Doxorubicin was used as reference. Then, MTT test was performed after 72 h of treatment adding 2.5 mg/ml MTT solution on cells. Formazan crystals have been dissolved in DMSO and results were obtained by an absorbance lecture at 540 nm. IC₅₀ was then calculated from fitting curves by linear regression with graphpad prism 8.

Cells cycle: The detection of the different phases of the cell cycle is based on the fluorescence emission of propidium iodide. Propidium iodide is a fluorochrome ($\lambda_{ex} = 488$ nm, $\lambda_{em} = 617$ nm) that intercalates between the bases of the DNA double helix. Thanks to this property, the fluorescence intensity is dependent on its DNA content. Two peaks of fluorescence can then be observed: cells in G1 phase with 2N chromosomes, cells in G2-M phase with 4N chromosomes and cells in S phase whose DNA content is between 2N and 4N. Experimentally, after three days of culture, U251 cells are treated with 1 μ M lactones or 0.1 μ M doxorubicin (positive control). After 72 h of contact with the compounds, the cells are recovered by trypsination and 1.10⁶ cells of each condition are fixed in cold 70% ethanol. Then, half of this suspension (5.10⁵ cells) is centrifuged for 10 minutes at 500 g and the pellet is resuspended in 500 μ l of labelling buffer: PBS containing

0.5 mg/mL RNase A and 2.5 µg/ml propidium iodide. After 10 min of incubation in the dark in the labelling buffer, the cells are passed to the BD Accuri C6 Plus flow cytometer (BD biosciences) to measure the different phases of the cell cycle.

Crystallographic data for the structure reported in this article have been deposited at the Cambridge Crystallographic Data Center and allocated with the deposition number CCDC 2083324 for compound **32**.

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