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Enantiodivergent synthesis of cytotoxic styryl lactones from D-xylose. The first total synthesis of (+)- and (−)-crassalactone C

Velimir Popsavin [a,*], Goran Benedeković [a], Bojana Srećo [a], Jovana Francuz [a], Mirjana Popsavin [a], Vesna Kojić [b], Gordana Bogdanović [b], Vladimir Divjaković [c]

[a] Department of Chemistry, Faculty of Sciences, University of Novi Sad, Trg D. Obradovića 3, 21000 Novi Sad, Serbia
[b] Oncology Institute of Vojvodina, Institutski put 4, 21204 Sremska Kamenica, Serbia
[c] Department of Physics, Faculty of Sciences, University of Novi Sad, Trg D. Obradovića 4, 21000 Novi Sad, Serbia

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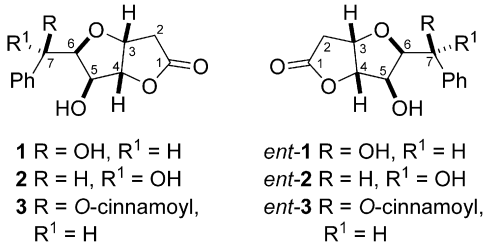
ABSTRACT

Enantiodivergent total syntheses of both (+)- and (−)-enantiomers of goniofufurone, 7-*epi*-goniofufurone and crassalactone C have been accomplished starting from D-xylose. The key steps of the synthesis of 7-*epi*-(+)-goniofufurone were a stereo-selective addition of phenyl magnesium bromide to a protected dialdose, and a stereospecific furano–lactone ring formation by reaction of a related hemiacetal derivative with Meldrum's acid. Synthesis of both (+)-goniofufurone and (+)-crassalactone C required a configurational inversion at C-5 in the common intermediate that was efficiently achieved under the standard Mitsunobu conditions, or alternatively through a sequential oxidation of the benzylic hydroxyl group followed by a stereo-selective reduction with borohydride. A similar approach was then applied to the synthesis of the unnatural (−)-enantiomers of goniofufurone, 7-*epi*-goniofufurone and crassalactone C, as well as two novel, conformationally constrained analogues of both (+)- and (−)-goniofufurone. Their in vitro antiproliferative activities against a number of human tumour cell lines were recorded and compared with those observed for the parent natural products.

1. Introduction

The styryl lactones are a group of secondary metabolites mainly isolated from the genus *Goniothalamus* of the plant family Annonaceae.[1] A number styryl lactones that have been isolated from *Goniothalamus* species or synthesized exhibited a notable cytotoxic activity against certain human tumour cell lines.[2] The cytotoxicity of styryl lactones appears to be specific on neoplastic cells since negligible effects of these compounds on normal cells are reported. (+)-Goniofufurone (**1**; Fig. 1) and 7-*epi*-(+)-goniofufurone[3] (**2**) are naturally occurring styryl lactones that have attracted considerable attention since their isolation from the stem bark of *Goniothalamus giganteus* (Annonaceae).[4,5] Their structures were elucidated by spectroscopic methods, and the relative configurations were determined by X-ray crystallography. The absolute stereochemistry of both natural products was established by Shing et al.[6] through the total synthesis of their opposite enantiomers (*ent*-**1**, and *ent*-**2**) starting from D-*glycero*-D-*gulo*-heptano-1,4-lactone as a chiral source. Due to their unique structural features and promising antitumour activities, both natural products **1** and **2**, along with a number of their analogues been the targets of many total syntheses.[7,8] (+)-Crassalactone C (**3**) is a natural 7-*O*-cinnamoyl derivative of (+)-goniofufurone that was recently isolated from the leaves and twigs of *Polyalthia crassa*.[9] Its structure was determined on the basis of standard spectroscopic methods. The absolute stereochemistry of **3** was established by treatment of the isolated (+)-**1** with cinnamoyl chloride. Apart from this non-selective and low-yielding single step route, no total synthesis of **3** has been hitherto reported. As a part of our continuing interest in the synthesis of biologically active natural products from abundant monosaccharides, we have planned to develop a new approach to



1 R = OH, R^1 = H
2 R = H, R^1 = OH
3 R = *O*-cinnamoyl, R^1 = H

ent-**1** R = OH, R^1 = H
ent-**2** R = H, R^1 = OH
ent-**3** R = *O*-cinnamoyl, R^1 = H

Figure 1. Structures of (+)-goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**) and (+)-crassalactone C (**3**), and the corresponding unnatural enantiomers *ent*-**1**, *ent*-**2** and *ent*-**2**.

* Corresponding author. Tel.: +381 21 485 27 68; fax: +381 21 454 065.
E-mail address: velimir.popsavin@dh.uns.ac.rs (V. Popsavin).

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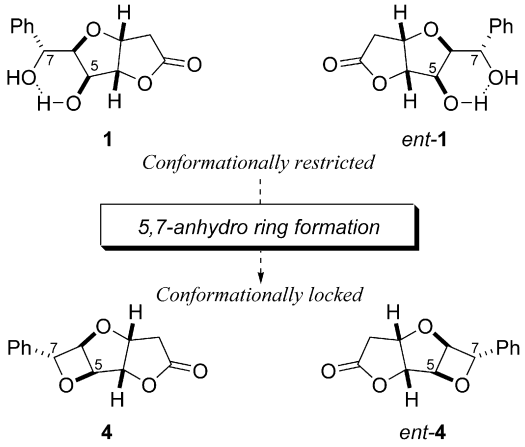
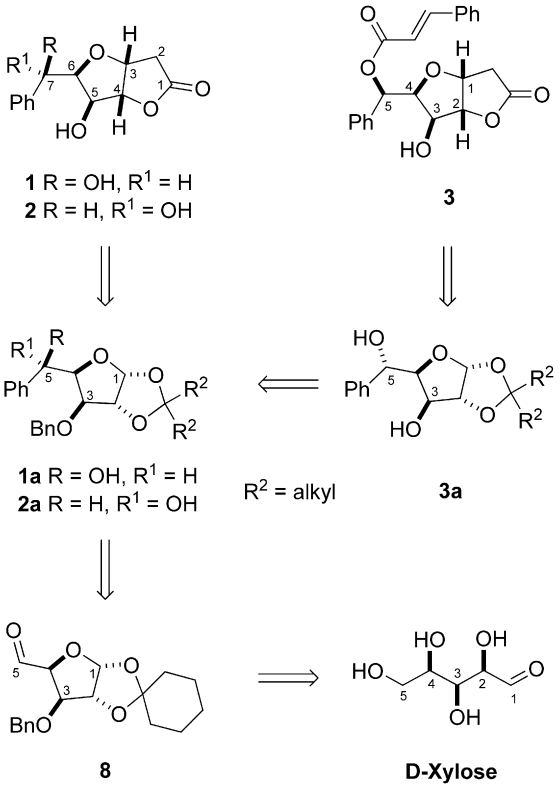
1–**3** by chirality transfer from D-xylose. Apart from these natural products, we were especially keen to prepare and evaluate their opposite enantiomers (*ent*-**1**, *ent*-**2** and *ent*-**3**), since it is well known that enantiomers of certain bioactive compounds may exhibit improved potencies[10] or completely different biological activities altogether.[11] Several syntheses of *ent*-**1** and *ent*-**2** were reported,[6,12] but there was no record in the literature about their antiproliferative activities. Neither the synthesis nor biological activity of *ent*-**3** was reported in the literature. Herein, we disclose a new enantiodivergent synthesis of both enantiomeric forms of **1**, **2** and **3** starting from D-xylose. We also disclose the preparation of novel styryl lactones **4** and *ent*-**4** that are designed as conformationally locked analogues of **1** and *ent*-**1**, respectively. The rationale underlying the preparation of **4** and *ent*-**4** arises from fact that both parent compounds **1** and *ent*-**1** (Scheme 1) have a restricted geometry of the C_5–C_7 segment, due to an intramolecular H-bond formed between the 5-OH and the 7-OH, as established by X-ray analysis.[4] Comparison of antiproliferative activities of synthesized styryl lactones **1**–**4** from both (+)- and (−)-series against a panel of human tumour cells is also provided.[13]



Scheme 1. Design of structurally constrained goniofufurone analogues **4** and *ent*-**4**.

2. Results and discussion

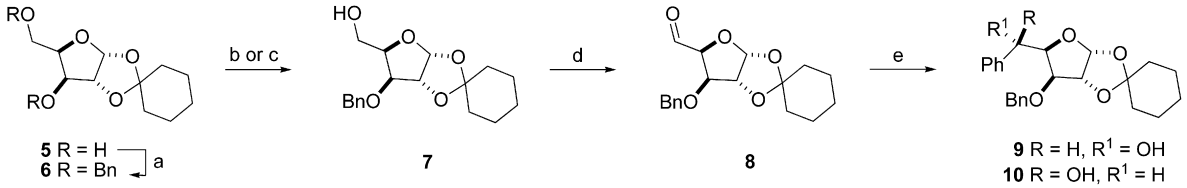
All three target compounds **1**–**3** contain five contiguous stereocenters and display a clear structural similarity. We thus wanted to design a unified synthesis for all three compounds from a common intermediate. Among other methods, the required [3.3.0] bicyclic lactone core could be formed through condensation of Meldrum's acid with a protected sugar lactol derivative.[14] Accordingly, we envisaged the retrosynthetic concept depicted in Scheme 2. For both **1** and **2**, lactone ring-removal would give rise to the epimeric alcohols **1a** and **2a** (R^2,R^2=alkylidene), respectively. It was assumed that intermediate of type **2a** can be prepared from the aldehyde **8** by stereo-selective addition of phenyl magnesium bromide under the 1,2-chelation control.[15] The intermediate **1a** however could be prepared after epimerization of **2a** at C-5. Synthesis of **8** itself is visualized from D-xylose by established chemical reactions.[16] Disconnection of **3** shows that it can be derived from the diol of type **3a** by a number of successive transformations that involve regioselective Mitsunobu reaction in the presence of cinnamic acid and hydrolytic removal of the 1,2-*O*-alkylidene protective group, followed by γ-lactone formation. Intermediate **3a** in turn, should be accessible from **2a** by removal of benzyl protective group from C-3. Accordingly, the protected benzylic alcohol of type **2a** was selected as a convenient common intermediate in the divergent synthesis of all three targets **1**–**3**.



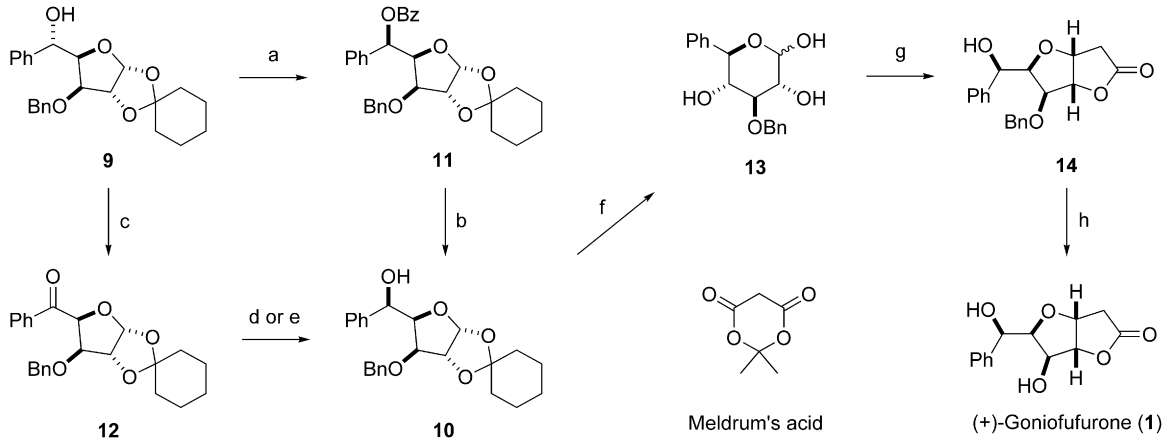
Scheme 2. Retrosynthetic analysis of (+)-goniofufurone (**1**), 7-*epi*-(+)-goniofufurone (**2**) and (+)-crassalactone C (**3**).

In order to synthesize natural products **1**–**3**, we first focused on the preparation of the key building block **9** from D-xylose (Scheme 3). In terms of its stereochemical and topological features, molecule **9** completely corresponds to the intermediate **2a** designed by retrosynthetic analysis. The synthetic sequence commenced with the formation of the protected dialdose **8** from D-xylose derivative **5**[18] by a slight modification of a literature method.[16] Thus, compound **5** was first di-*O*-benzylated under standard conditions (BnBr, NaH, DMF) to give **6** that was converted to the corresponding primary alcohol **7** (72% from **5**) by using $KBrO_3/Na_2S_2O_5$ reagent system.[19] A slightly more efficient regioselective C-5 deprotection of **6** was achieved under the hydrogenolytic conditions in the presence of 0.05 M equiv of Pd. This method provided the desired intermediate **7** in 80% yield (from two steps). Oxidation of **9** was carried out under the conditions similar to that previously reported,[16] to give the protected dialdose **8** in 71% overall yield (from three steps). The preceding preparation of **8** was accomplished in 62% overall yield over four linear steps.[16] Addition of phenyl magnesium bromide to **8** preferentially gave the key divergent intermediate **9** (69%) as a result of 1,2-chelation control. A minor amount of D-*gluco* stereoisomer **10** (13%) was also obtained from this reaction. The key building block **9** was thus successfully synthesized in a facile stereo-selective route from the partially protected D-xylose derivative **5**.

With the requisite intermediate **9** in hand, we next focused on its further transformations to (+)-goniofufurone (**1**). For the synthesis of target **1**, it was necessary first to invert the stereochemistry at C-5 of the major isomer **9** from the Grignard reaction. To prepare compound **10**, an efficient two-step route was developed that involved configurational inversion at C-5 in **9** under the standard Mitsunobu conditions[20] (Scheme 4). Accordingly, treatment of **9** with diethyl azodicarboxylate, triphenyl phosphine, and benzoic acid gave the expected 5-*O*-benzoyl derivative **11**, which



Scheme 3. Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C for 0.5 h, then rt for 1 h; (b) $KBrO_3$, $Na_2S_2O_5$, CH_2Cl_2, H_2O, 12 °C for 15 min, then rt for 3 h, 72% from **5**; (c) H_2-Pd/C (0.05 equiv of Pd), 2:1 EtOH/EtOAc, rt, 1.5 h, 80% from **5**; (d) DCC, anh. H_3PO_4, Py, DMSO, rt, 3.5 h, 89%; (e) PhMgBr, Et_2O, 0 °C, 3.5 h, 69% of **9**, 13% of **10**.



Scheme 4. Reagents and conditions: (a) $PhCO_2H$, Ph_3P, DEAD, THF, 0 °C for 1 h, then rt for 2 h, 82%; (b) NaOMe/MeOH, CH_2Cl_2, 0 °C for 1 h, then rt for 23 h, 99%; (c) PCC, CH_2Cl_2, reflux, 2 h, 98%; (d) $NaBH_4$, MeOH, rt, 2 h, 87% of **10**, 12% of **9**; (e) $NaBH_4$, L-tartaric acid, THF, −7 °C for 1 h, then 0 °C for 2 h, 97% of **10**, (f) 70% aq AcOH, reflux, 4 h, 87%; (g) Meldrum's acid, Et_3N, DMF, 46 °C, 76 h, 52%; (h) H_2-Pd/C, MeOH, rt, 46 h, 97%.

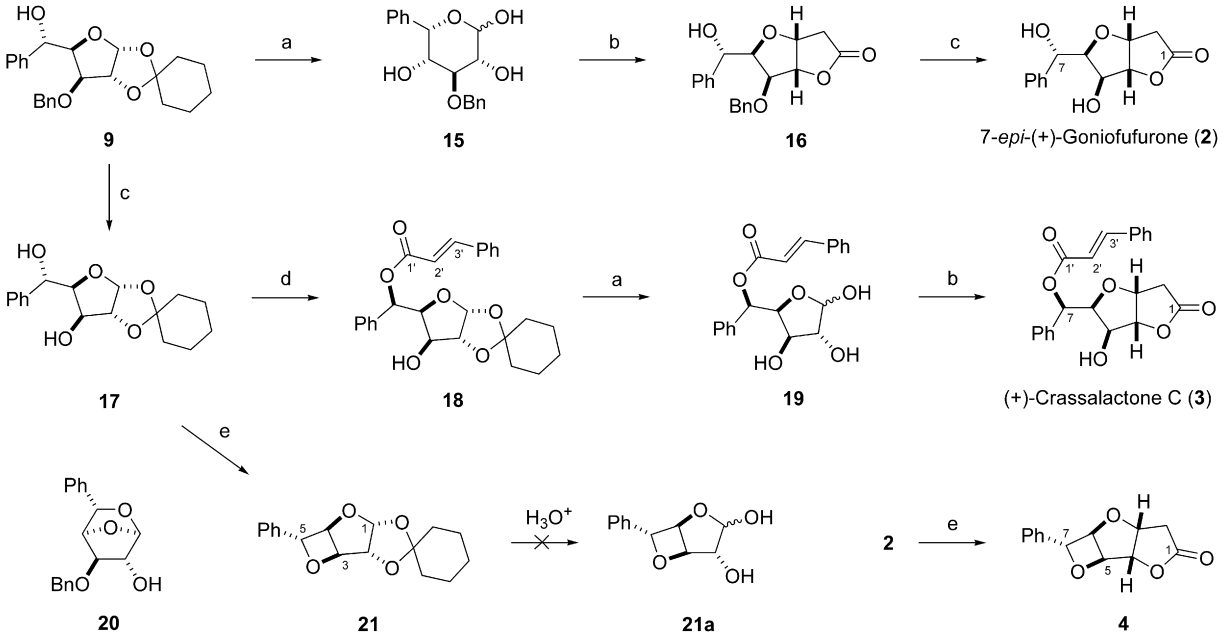
upon deprotection with methanolic sodium methoxide formed **10**. Compound **10** was also prepared by using an alternative two-step sequence that involved oxidation of **9** with PCC whereupon the corresponding ketone **12** was obtained in an almost quantitative yield. Reduction of the keto group in **12** with $NaBH_4$ afforded a 7:1 mixture of diastereomers, which after chromatographic separation furnished the alcohol **10** as the major product in 87% yield. However, when the reduction with $NaBH_4$ was carried out in the presence of L-tartaric acid[21] alcohol **10** was obtained as the only stereoisomer in 97% yield. The last two-step sequence appeared to be a more convenient route to the intermediate **10**, since it provided a considerably higher overall yield (95% from **9**) compared to the former route via the 5-*O*-benzoyl derivative **11** (81% from **9**). Hydrolytic removal of the cyclohexylidene protective group in **10** with aqueous acetic acid gave an 87% yield of the corresponding lactol **13**. Attempted condensation of **13** with Meldrum's acid in the presence of *tert*-butylamine[22] failed to give the expected γ-lactone **14**. However, when the last reaction was carried out in the presence of triethylamine as a catalyst,[23] the desired γ-lactone **14** was obtained in 52% yield. Final cleavage of benzyl protecting group in **14** gave (+)-goniofufurone (**1**). The physical and spectroscopic data of thus obtained sample **1** were identical to those reported in the literature.[8h]

According to our retrosynthetic plan, the L-*ido* isomer **9** also represents a divergent intermediate for the preparation of both 7-*epi*-(+)-goniofufurone (**2**) and (+)-Crassalactone C (**3**). It was also assumed that **9** might serve as an intermediate in the synthesis of conformationally locked (+)-goniofufurone analogue **4** (Scheme 2). The synthesis of targets **2**–**4** is presented in Scheme 5.

The stereoisomer **9** was converted to 7-*epi*-(+)-goniofufurone (**2**) by using the same methodology as that already applied for the conversion of **10**–**1** (Scheme 4). Treatment of **9** with aqueous acetic acid gave **15** (73%) along with a minor amount of 1,5-anhydride **20** (5%).[24] Subsequent treatment of **15** with Meldrum's acid, followed by final hydrogenolytic 5-O-deprotection furnished the target **2**. This synthetic sequence produced 7-*epi*-(+)-goniofufurone (**2**) in 15% overall yield in seven steps from **5**. All physical constants and spectroscopic data of thus prepared natural product **2** were in good agreement with those reported.[22,25]

The synthesis of (+)-crassalactone C (**3**) also started from the L-*ido* stereoisomer **9**. Thus, removal of the benzyl protective group in **9** gave the corresponding diol **17** (70%), that was further allowed to react with cinnamic acid under the standard Mitsunobu conditions. The corresponding cinnamic ester **18** was thus obtained (63%) accompanied by a minor amount of 3,5-anhydro derivative **21** (16%). Hydrolytic removal of the cyclohexylidene protective group in **18** gave the expected lactol **19** (67%), which upon treatment with Meldrum's acid in the presence of triethylamine gave (+)-crassalactone C (**3**), with physical and spectroscopic properties in reasonable agreement with those reported in the literature.[9]

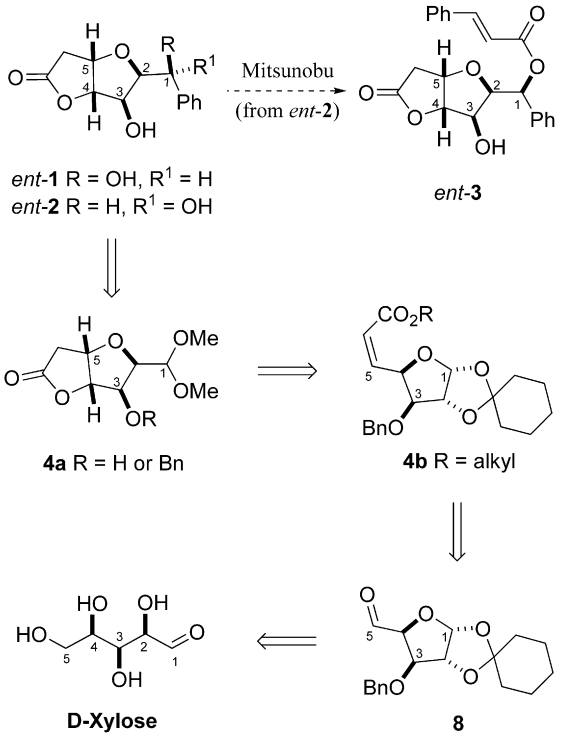
Our initial plan was to utilize oxetane **21** for the preparation of analogue **4** (5,7-anhydro-goniofufurone). In order to increase the yield of **21**, the Mitsunobu reaction of **17** was carried out in absence of cinnamic acid (Ph_3P, DEAD, refluxing toluene, 1.5 h). Under these reaction conditions, the oxetane **21** was isolated as a main reaction product in 77% yield. The assignment of stereochemistry at the C-5 in product **21** was confirmed by an NOE interaction between H-1 and H-5, indicating that these protons are in close proximity on the same side of the ring. It was assumed that the synthesis of **4** can be accomplished by a two-step sequence consisting of hydrolytic removal of the cyclohexylidene protective group in **21**, followed by subsequent lactonisation. However, attempted selective removal of the cyclohexylidene moiety under a variety of hydrolytic conditions failed to afford the desired lactol **21a**. The products of oxetane ring opening always dominated in reaction mixtures. We have therefore decided to prepare the target **4** directly from 7-*epi*-(+)-goniofufurone (**2**). Thus,



Scheme 5. Reagents and conditions: (a) 70% aq AcOH, reflux, 6.5 h for 9, 73% of 15, 5% of 20, 4 h for 18, 67% of 19; (b) Meldrum's acid, Et_3N, DMF, 46 °C, 70 h for 15, 48% of 16, 72 h for 19, 62% of 3; (c) H_2-Pd/C, MeOH, rt, 72 h for 16, 87% of 2, 4 h for 9, 70% of 17; (d) PhCH:$CHCO_2H$, Ph_3P, DEAD, THF, 0 °C for 1 h, then rt for 2 h, 63% of 18, 16% of 21; (e) Ph_3P, DEAD, toluene, reflux, 1.5 h for 17, 77% of 21, 3 h for 2, 35% of 4.

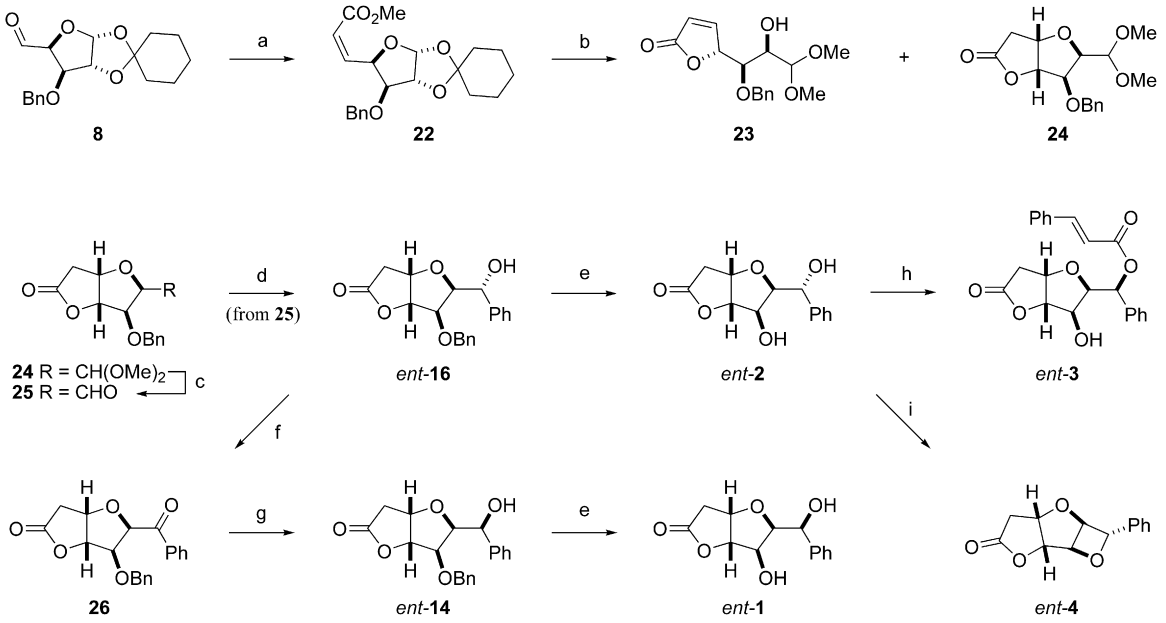
compound **2** was subjected to the intramolecular Mitsunobu reaction, under reaction conditions similar to that already applied for the conversion of **17**–**21** (Ph_3P, DEAD, toluene, reflux). Target **4** was thus obtained as a main reaction product in 35% yield.

Retrosynthetic analysis of *ent*-**1**, *ent*-**2** and *ent*-**3** is outlined in Scheme 6. As their natural counterparts, the opposite enantiomers *ent*-**1**, *ent*-**2** and *ent*-**3** contain five contiguous stereocentres but differ in stereochemistry and functionality at C-7. The presence of the cinnamoyl moiety in *ent*-**3** implies that this molecule could be obtained from *ent*-**2** through a regioselective Mitsunobu reaction with cinnamic acid. Further disconnection of *ent*-**1** and *ent*-**2** shows that they can be derived from the protected aldehyde **4a** by several successive transformations that involve a hydrolysis of the acetal functionality, stereo-selective addition of phenyl magnesium bromide to the liberated aldehyde group, followed by removal of benzyl protective group. The intermediate **4a** should be accessible through an adopted literature procedure,[17] which involves a *Z*-selective Wittig olefination of **8**, followed by an acid-catalyzed methanolysis of the intermediate **4b**. In such a way we identified the protected aldehydo lactone **24** (Scheme 7) as a possible common building block for the synthesis of all three targets (*ent*-**1**, *ent*-**2**, and *ent*-**3**). In the light of its stereochemical features compound **24** fully corresponds to the intermediate **4a** from the retrosynthetic analysis.



Scheme 6. Retrosynthetic analysis of (−)-goniofufurone (*ent*-**1**), 7-*epi*-(−)-goniofufurone (*ent*-**2**) and (−)-crassalactone C (*ent*-**3**).

The synthesis of enantiomers *ent*-**1**, *ent*-**2**, *ent*-**3** and *ent*-**4** is outlined in Scheme 7. The sequence started with the *Z*-selective Wittig olefination[26] of aldehyde **8** with methyl (triphenylphosphoranylidene)-acetate, whereupon the *Z*-unsaturated ester **22** was obtained as a dominant reaction product, in 83% yield. A minor amount (12%) of the corresponding *E*-isomer (not shown in the reaction scheme) was also isolated from the reaction mixture. It was expected that the key intermediate **24** could be obtained by an acid-catalyzed methanolysis of **22**. The procedure followed here is analogous to that previously developed by Prakash and Rao[17] for the conversion of the isopropylidene analogue of **22** into the lactone **24**. Accordingly, compound **22** was refluxed in dry methanol in the presence of a catalytic amount of sulfuric acid (2%). Although complete conversion of starting compound was observed after 4.5 h, only traces of the desired lactone **24** were detected in the reaction mixture. The unsaturated lactone **23** was formed as a major reaction product under these reaction conditions. However, when the reaction solution was alkalized to pH 9 ($NaHCO_3$) and stirred for 1 h at 35 °C, the bicyclic lactone **24** was predominantly formed as a result of the stereospecific Michael ring closure in **23**. The key building block **24** was isolated in 74% yield, along with a minor amount of **23** (4%). These results are in accord with Prakash and Rao's assumption that lactonisation precedes Michael attack in



Scheme 7. Reagents and conditions: (a) Ph_3P:$CHCO_2Me$, MeOH, 0 °C for 0.5 h, then rt for 1.5 h, 83%; (b) (*i*) H_2SO_4 (cat.), MeOH, reflux, 4.5 h, (*ii*) $NaHCO_3$ (pH=9), 35 °C, 1 h, 74% of 24, 4% of 23; (c) 9:1 TFA/H_2O, 0 ° for 0.5 h, then rt for 0.5 h; (d) PhMgBr/THF, Et_2O, −7 °C, 3h, 3% of *ent*-14, 56% of *ent*-16 (from 24); (e) H_2-Pd/C, MeOH, rt, 46 h, 70% of *ent*-1, 64% of *ent*-2; (f) PCC, CH_2Cl_2, reflux, 2 h, 84%; (g) $NaBH_4$, MeOH, rt, 3.5 h, 54% of *ent*-14, 26% of *ent*-16; (h) PhCH:$CHCO_2H$, Ph_3P, DEAD, THF, 0 °C for 1 h, then rt for 2 h, 53% of *ent*-3, 16% of *ent*-4; (i) Ph_3P, DEAD, toluene, reflux, 3 h, 40%.

this process, but contradicts their hypothesis that the tetrahydrofuran ring closure in **23** occurs under the acidic conditions.[17]

Hydrolytic removal of the dimethyl acetal protection in **24** afforded the corresponding aldehyde **25**, which was subsequently treated with phenyl magnesium bromide to give two diastereomeric alcohols *ent*-**16** and *ent*-**14** in a 19:1 ratio and 59% combined yield (calculated to **24**). Major isomer *ent*-**16** was converted to target *ent*-**2** after removal of the benzyl protecting group. The physical and spectroscopic data of thus obtained sample *ent*-**2** were identical to those previously reported.[12a] This new synthesis of *ent*-**2** proceeds in seven steps with 16% overall yield calculated to starting compound **5**. Along with the Gracza and Jäger approach,[12b] it appears to be one of the most efficient routes to this molecule yet disclosed.[27]

The minor stereoisomer from the Grignard reaction of **25** (*ent*-**14**) has the correct stereochemistry for the synthesis of (−)-goniofufurone (*ent*-**1**). The reaction proceeds under chelation control and efforts to change the ratio in favour of *ent*-**14** were unsuccessful. However access to *ent*-**14** was possible by oxidation of *ent*-**16** followed by reduction of the intermediary ketone **26** to give a separable 2:1 mixture of *ent*-**14** and *ent*-**16** in 67% overall yield. Stereoisomer *ent*-**14** was converted to (−)-goniofufurone (*ent*-**1**) after removal of benzyl protecting group. All physical constants and spectroscopic data of thus prepared product *ent*-**1** were in good agreement with those already reported.[12a]

Compound *ent*-**2** was converted to (−)-crassalactone C (*ent*-**3**) upon treatment with cinnamic acid, under the standard Mitsunobu conditions[20] (PhCH:$CHCO_2H$, Ph_3P, DEAD, THF, 0 °C→rt, 3.5 h). The target *ent*-**3** that was isolated in 53% yield, displayed physical and spectroscopic properties in reasonable agreement with those previously reported for the natural (+)-crassalactone C.[9]

A minor amount of oxetane *ent*-**4** (16%) was also obtained from the last Mitsunobu reaction. However, compound *ent*-**2** was more efficiently converted to *ent*-**4** (40%) under the reaction conditions similar to those already used for the conversion of **2**–**4**. Spectroscopic data and physical constants of *ent*-**4** thus obtained were in full agreement with values recorded for the opposite enantiomer **4**. Additionally, an NOE interaction between H-3 and H-7 was consistent with L-*glycero*-L-*ido* stereochemistry of *ent*-**4**. Finally, the above structural elucidation of *ent*-**4** was confirmed by X-ray crystallographic analysis (Fig. 2). The distance between H-3 and H-7 (2.56 Å) is consistent with NOE results.

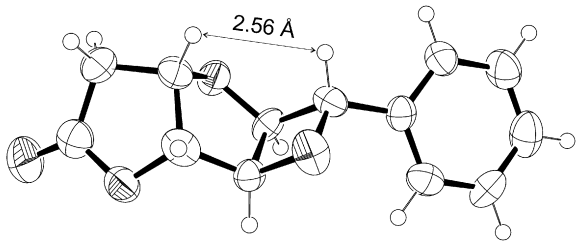


Figure 2. ORTEP presentation of compound *ent*-**4**.

2.1. Evaluation of antiproliferative activity

A side-by-side comparison of the synthesized (+)- and (−)-enantiomers in a range of cytotoxic assays[28] is presented in Table 1. The commercial antitumour agent doxorubicin (DOX) served as a reference compound.

In general, all synthesized styryl lactones showed diverse antiproliferative activities against human malignant cell lines

Table 1
Antiproliferative activities of synthesized compounds and DOX

Compound	IC_{50}, μM[a]				
	K562	HL-60	Jurkat	Raji	MRC-5
1	0.41	>100	32.45	18.45	>100
ent-**1**	2.96	>100	2.49	23.42	>100
2	0.028	22.02	18.64	1.25	>100
ent-**2**	3.35	13.93	0.054	>100	>100
3	3.56	>100	25.45	15.46	>100
ent-**3**	3.67	1.87	15.67	0.57	>100
4	0.39	0.11	0.03	3.65	>100
ent-**4**	2.05	0.025	28.45	0.45	>100
DOX	0.25	0.92	0.03	2.98	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control.

(myelogenous leukaemia K562, promyelocytic leukaemia HL-60, T cells leukaemia Jurkat, and Burkitt's lymphoma Raji cell line), but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). The natural product **2** and the unnatural enantiomer of crassalactone C (*ent*-**3**), as well as both structurally constrained analogues (**4** and *ent*-**4**) exhibited antiproliferative activities towards the all tested cell lines, while compounds **1**, *ent*-**1** and **3** showed potent to moderate activities against K562, Jurkat and Raji cells, but were completely inactive against the HL-60 cell line. The unnatural enantiomer of 7-*epi*-(+)-goniofufurone (*ent*-**2**) however, was completely inactive against Raji cells, but demonstrated a notable antiproliferative activity against K562, HL-60 and Jurkat cell lines. It is noteworthy that both 5,7-anhydrogoniofufurone enantiomers (**4** and *ent*-**4**) displayed higher potency against HL-60 cell line than the commercial cytotoxic agent doxorubicin (DOX).

A comparison of IC_{50} values for (+)- and (−)- enantiomers reveals that both unnatural enantiomers *ent*-**1** and *ent*-**2** had more profound effect only against Jurkat cells being 13- and 345-fold more potent than the natural products **1** and **2**, respectively. At the same time, the growth inhibitory effect of *ent*-**2** on the Jurkat cell line was of the same order of magnitude as that recorded for the standard antitumour agent doxorubicin (DOX). Remarkably, the unnatural enantiomer of crassalactone C (*ent*-**3**) showed a potent antiproliferative activity towards HL-60 cells, while the corresponding natural enantiomer **3** was completely inactive against this cell line. This molecule demonstrated a 27- and 5-fold greater cytotoxicity in Raji cells, when compared to the natural product **3** and DOX, respectively. These results indicate that the unnatural 3*S*, 4*R*, 5*R* and 6*S* absolute configurations may be beneficial for the activity of these styryl lactones.

The results obtained from the treatment of cancer cells with **4** and *ent*-**4** demonstrated that the introduction of a new 5,7-anhydro ring increases the potency originally displayed by **1** and *ent*-**1**. Analogue **4** exhibited a submicromolar antiproliferative activity towards HL-60 cells, while the corresponding parent compound **1** was completely inactive against this cell line. At the same time, molecule **4** showed over 8-fold stronger cytotoxicity in the same cell line when compared to the reference compound (DOX). Remarkably, this analogue demonstrated a 1082- and 5-fold greater cytotoxicity in Jurkat and Raji cells, respectively, when compared to the natural product **1**. Along with DOX, analogue **4** was the most active compound towards Jurkat cell line. On the contrary to **4**, its opposite enantiomer *ent*-**4** exhibited a lower activity against Jurkat cells than the corresponding parent compound *ent*-**1**. However, this analogue demonstrated powerful cytotoxicity in HL-60 cells, on the contrary to the parent compound *ent*-**1** that was completely inactive against this cell line. At the same time, analogue *ent*-**4** exhibited the highest activity against the HL-60 cell line, being approximately 37-fold more potent than DOX. Finally, *ent*-**4** demonstrated over 50- and 6-fold stronger cytotoxicity in Raji cell line when compared to the parent compound *ent*-**1** and DOX, respectively.

3. Conclusions

In conclusion, we have completed a new enantiodivergent synthesis of both (+)- and (−)-enantiomers of styryl lactones goniofufurone (**1** and *ent*-**1**), 7-*epi*-goniofufurone (**2** and *ent*-**2**), crassalactone C (**3** and *ent*-**3**), and novel conformationally constrained goniofufurone analogues (**4** and *ent*-**4**) starting from D-xylose. In addition to providing access to both enantiomers of **1**–**4** this enantiodivergent approach is flexible and straightforward. It uses non-expensive reagents and a readily available starting material. These advantages make the synthetic methodology suitable for easy preparation of a variety of styryl lactone analogues in both enantiomeric series for biological evaluation. In a preliminary bioassay, doxorubicin (DOX, a standard anticancer drug used as a positive control) displayed lower activity against Raji malignant cells (IC_{50}=2.98 μM) than lactones **2** (IC_{50}=1.25 μM), *ent*-**3** (IC_{50}=0.57 μM), and *ent*-**4** (IC_{50}=0.45 μM). Additionally, DOX exhibited one order of magnitude lower antiproliferative effect against the K562 cells (IC_{50}=0.25 μM) when compared with the natural product **2** (IC_{50}=0.028 μM). On HL-60 cells, the analogues **4** (IC_{50}=0.11 μM) and *ent*-**4** (IC_{50}=0.025 μM) were more potent than DOX (IC_{50}=0.92 μM), while approximately the same values were observed for DOX (IC_{50}=0.03 μM), *ent*-**2** (IC_{50}=0.054 μM) and **4** (IC_{50}=0.03 μM) in Jurkat cell line. Based upon the potent antitumour activities of **2**, *ent*-**2**, *ent*-**3**, **4** and *ent*-**4**, as well as upon their non-toxicity against normal MRC-5 cells, we believe that these compounds may serve as convenient leads in the synthesis of more potent and selective antitumour agents. Finally, from a synthetic perspective, the fact that both enantiomers efficiently inhibit tumour cells growth also means that both are equally valuable synthetic targets. In this sense, an additional advantage of this new enantiodivergent approach is that it provides the opportunity to access the cytotoxic properties of not only the natural products, but also (for the first time) their unnatural enantiomers.

4. Experimental

4.1. General methods

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on a KRÜSS P3002 polarimeter at room temperature. IR spectra were recorded with an FTIR/NIR Nexus 670 spectrophotometer (Thermo-Nicolet). NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from TMS. Low resolution mass spectra were recorded on Finnigan-MAT 8230 (CI) and on an Agilent Technologies HPLC/MS 3Q system, series 1200/6410 (ESI). High resolution mass spectra were taken on a 6210 Time-of-Flight LC/MS Agilent Technologies instrument (ESI). Flash column chromatography was performed using ICN silica 32–63. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under diminished pressure at a bath temperature below 30 °C.

*4.1.1. 3-O-Benzyl-1,2-O-cyclohexylidene-α-D-xylofuranose (**7**). 4.1.1.1. Procedure A.* To a cooled (0 °C) and stirred solution of **5** (1.0 g, 4.34 mmol) in dry DMF (20 mL), were added successively NaH (0.625 g, 26.06 mmol) and BnBr (1.5 mL, 12.64 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. Methanol (7 mL) was then added, and the mixture was stirred at room temperature for the next 20 min. The mixture was neutralised with glacial AcOH and evaporated. The residue was suspended in water (200 mL) and extracted with CH_2Cl_2 (2×40 mL). The combined organic solutions were dried and evaporated. The remaining crude **6** (1.97 g) was dissolved in CH_2Cl_2 (50 mL) and the solution was cooled to +12 °C. To the mixture was added dropwise a solution of $KBrO_3$ (1.46 g, 8.68 mmol) in water (30 mL) followed by a solution of $Na_2S_2O_5$ (1.65 g, 8.68 mmol) in water (20 mL) and the temperature maintained at +12 °C for 15 min and then at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 (30 mL) and poured into 5% aq $NaHCO_3$ (100 mL), washed with EtOH. Organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3×60 mL). The combined organic solutions were dried and evaporated. Flash column chromatography of the residue (3:2 hexane/Et_2O) gave pure **7** (1.01 g, 72%), isolated as a colourless syrup, $[\alpha]_D^{20}=-57.7$ (*c* 0.99, $CHCl_3$); R_f=0.37 (2:3 hexane/Et_2O).

4.1.1.2. Procedure B. To a cooled (0 °C) and stirred solution of **5** (1.0 g, 4.34 mmol) in dry DMF (20 mL), were added successively NaH (0.5 g, 16.67 mmol) and BnBr (1.34 mL, 11.29 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The mixture was quenched as described above to give crude **6** as a yellow oil. Crude product **6** was dissolved in a 2:1 mixture EtOH/EtOAc (30 mL) and the solution was added to a suspension of 10% Pd/C (0.46 g, 0.43 mmol) in aps. EtOH (30 mL), which was previously saturated with hydrogen (at room temperature for 1 h). The mixture hydrogenated for 1.5 h at room temperature. The catalyst was filtered off and washed with EtOH. The combined organic solutions were evaporated and the residue was purified by flash column chromatography (3:2 hexane/Et_2O). Eluted first was unreacted intermediate **6** (0.25 g, 14%). Eluted second was pure **7** (1.11 g, 80%), isolated as a colourless syrup, $[\alpha]_D^{20}=-57.7$ (*c* 0.99, $CHCl_3$); R_f=0.37 (2:3 hexane/Et_2O). Spectroscopic data of thus prepared sample **7** matched those previously reported by us.[16]

*4.1.2. 3-O-Benzyl-1,2-O-cyclohexylidene-α-D-xylo-pentodialdo-1,4-furanose (**8**).* To a stirred solution of **7** (2.20 g, 6.87 mmol) and DCC (4.250 g, 20.60 mmol) in anhydrous DMSO (11 mL), was added dry pyridine (0.28 mL, 3.43 mmol) and 1 M solution of anhydrous H_3PO_4 in DMSO (3.4 mL). The resulting reaction mixture was stirred at room temperature for 3.5 h, then diluted with Et_2O (20 mL) and cooled to 0 °C. A solution of oxalic acid (1.73 g, 13.7 mmol) in MeOH (6 mL) was added in two portions every 5 min. The mixture was stirred at room temperature for 10 min, then poured into 10% aq NaCl (100 mL) and extracted with EtOAc (2×40 mL). The combined extracts were washed with 10% aq $NaHCO_3$ (100 mL), dried and evaporated. Flash column chromatography (4:1 hexane/EtOAc) of the residue (2.70 g) gave pure **8** (1.94 g, 89%) as an unstable pale yellow syrup, $[\alpha]_D^{20}=-41.4$ (*c* 0.95, $CHCl_3$); R_f=0.27 (9:1 toluene/EtOAc). Spectroscopic data of thus prepared sample **8** matched those previously reported by us.[16]

*4.1.3. 3-O-Benzyl-1,2-O-cyclohexylidene-5-C-phenyl-α-L-ido-pentofuranose (**9**).* To a cooled (0 °C) and stirred solution of freshly prepared **8** (1.34 g, 4.20 mmol) in dry Et_2O (42 mL) was added 1 M solution of PhMgBr in Et_2O (1.70 mL, 5.10 mmol). The mixture was stirred at 0 °C under atmosphere of nitrogen for 3.5 h, then neutralised with 10% aq NH_4Cl (105 mL) and extracted with CH_2Cl_2 (2×60 mL). The combined extracts were washed with aq 10% NaCl (90 mL), dried and evaporated, and the residue purified by flash column chromatography (9:1 light petroleum/EtOAc). The minor stereoisomer **10** (0.22 g, 13%) was first eluted, followed by the major product **9** (1.15 g, 69%). Pure **9** was isolated as a colourless oil, $[\alpha]_D^{20}=-21.6$ (*c* 0.88, $CHCl_3$), R_f=0.26 (3:2 hexane/Et_2O). IR (neat): ν_{max} 3477 (OH). ^{1}H NMR ($CDCl_3$): δ 1.20–1.80 (m, 10H, C_6H_{10}), 3.01 (br s, 1H, exchangeable with D_2O, OH), 3.65 (d, 1H, $J_{3,4}$=3.0 Hz, H-3), 4.32 and 4.58 (2×d, 1H each, J_{gem}=11.7 Hz, PhCH_2), 4.34 (dd, 1H, $J_{3,4}$=3.0, $J_{4,5}$=7.6 Hz, H-4), 4.62 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 5.08 (d, 1H, $J_{4,5}$=7.6 Hz, H-5), 6.04 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 7.28–7.46 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.6 and 36.3 (5×CH_2), 71.7 (PhCH_2), 72.3 (C-5), 81.6 (C-2), 82.2 (C-3), 84.4 (C-4), 104.6 (C-1), 112.5 (Cq from C_6H_{10}), 127.0, 127.5, 127.87, 127.91, 128.16, 128.22, 128.3, 128.4 and 139.7 (2×Ph). LRMS (CI): *m*/*z* 397 (M^++H), 379 (M^++H–H_2O). Anal. Found: C, 73.00; H, 7.49. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12.

*4.1.4. 5-O-Benzoyl-3-O-benzyl-1,2-O-cyclohexylidene-5-C-phenyl-α-D-gluco-pentofuranose (**11**).* To a cooled (0 °C) and stirred solution of **9** (0.54 g, 1.34 mmol), benzoic acid (0.22 g, 1.76 mmol) and Ph_3P (0.68 g, 2.58 mmol) in dry THF (5 mL), was added dropwise over a period of 5 min a solution of DEAD (0.34 mL, 2.16 mmol) in dry THF (5 mL). The solution was stirred at 0 °C for 1 h, and then at room temperature for additional 2 h. The mixture was quenched with 10% aq $NaHCO_3$ (150 mL), and extracted with CH_2Cl_2 (2×40 mL). The combined extracts were dried and evaporated and the residue purified on a column of flash silica (17:3 light petroleum/Et_2O), to give pure **11** (0.559 g, 82%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 135–138 °C, $[\alpha]_D^{20}=-4.5$ (*c* 1.01, $CHCl_3$); R_f=0.46 (4:1 light petroleum/Et_2O). IR ($CHCl_3$): ν_{max} 1725 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.2–1.86 (m, 10H, C_6H_{10}), 4.19 (d, 1H, $J_{3,4}$=3.0 Hz, H-3), 4.42 (d, 1H, J_{gem}=11.5 Hz, PhCH_a), 4.59–4.74 (m, 3H, H-2, H-4 and PhCH_b), 5.97 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 6.26 (d, 1H, $J_{4,5}$=9.6 Hz, H-5), 7.2–8.11 (m, 15H, 3×Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.6 and 36.4 (5×CH_2), 72.2 (PhCH_2), 72.8 (C-5), 81.1 (C-3), 81.3 (C-2), 81.5 (C-4), 104.8 (C-1), 112.4 (Cq from C_6H_{10}), 127.4, 127.8, 128.0, 128.2, 128.3, 128.4, 129.6, 130.0, 132.9, 136.7 and 138.2 (3×Ph), 164.5 (PhCO). LRMS (CI): *m*/*z* 501 (M^++H). Anal. Found: C, 74.11; H, 6.67. Calcd for $C_{31}H_{32}O_6$: C, 74.38; H, 6.44.

*4.1.5. 3-O-Benzyl-1,2-O-cyclohexylidene-5-C-phenyl-α-D-xylo-pentofurano-5-ulose (**12**).* A solution of **9** (0.42 g, 1.05 mmol) and PCC (0.58 g, 2.67 mmol) in dry CH_2Cl_2 (40 mL) was heated to reflux for 2 h. The mixture was evaporated, and the residue purified by flash column chromatography (17:3 toluene/Et_2O). Pure **12** (0.41 g, 98%) was isolated as colourless syrup, $[\alpha]_D^{20}=-59.3$ (*c* 1.72, $CHCl_3$), R_f=0.38 (3:2 hexane/Et_2O). IR (film): ν_{max} 1704 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.20–1.80 (m, 10H, C_6H_{10}), 4.27 and 4.49 (2×d, 2H, J_{gem}=12.1 Hz, PhCH_2), 4.42 (d, 1H, $J_{3,4}$=3.7 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$=3.6 Hz, H-2), 5.56 (d, 1H, $J_{3,4}$=3.7 Hz, H-4), 6.19 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 6.88–7.96 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.8 and 36.6 (C_6H_{10}), 71.8 (PhCH_2), 81.6 (C-2), 83.4 (C-3), 83.5 (C-4), 105.0 (C-1), 112.9 (Cq from C_6H_{10}), 127.5, 127.7, 128.1, 128.3, 128.4, 133.1, 135.8, 136.3 and 136.8 (2×Ph), 193.9 (C-5). LRMS (CI): *m*/*z* 395 (M^++H). HRMS (ESI): Found: 395.1845 (M^++H), calcd for $C_{24}H_{27}O_5$: 395.1853.

*4.1.6. 3-O-Benzyl-1,2-O-cyclohexylidene-5-C-phenyl-α-D-gluco-pentofuranose (**10**). 4.1.6.1. Procedure A.* To a cooled (0 °C) and stirred solution of **11** (0.31 g, 0.62 mmol) in dry CH_2Cl_2 (1 mL) and MeOH (4 mL), was added 1 M NaOMe in MeOH (1 mL, 1.0 mmol). The solution was stirred at 0 °C for 1 h, and then at room temperature for additional 1 h. An additional amount of 1 M NaOMe in MeOH (1.1 mL, 1.1 mmol) was added to the reaction mixture and stirring was continued for the next 22 h at room temperature. The mixture was neutralised with glac. AcOH and the volatiles were removed by co-distillation with toluene. Flash column chromatography of the residue (4:1 hexane/Et_2O), gave pure **10** (0.24 g, 99%) as a colourless oil, $[\alpha]_D^{20}=-57.0$ (*c* 1.0, $CHCl_3$); R_f=0.46 (3:2 hexane/Et_2O).

4.1.6.2. Procedure B. To a solution of **12** (0.41 g, 1.03 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.08 g, 2.26 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was evaporated, and the residue purified by flash column chromatography (9:1 toluene/Et_2O). The major stereoisomer **10** (0.35 g, 87%) was first isolated as a colourless oil, $[\alpha]_D^{20}=-57.0$ (*c* 1.0, $CHCl_3$), R_f=0.46 (3:2 hexane/Et_2O). Eluted second was pure **9** (0.050 g, 12%), isolated as a colourless syrup, $[\alpha]_D^{20}=-21.6$ (*c* 0.88, $CHCl_3$), R_f=0.26 (3:2 hexane/Et_2O). For spectroscopic data of **9** see Section 4.1.3.

4.1.6.3. Procedure C. To a suspension of L-tartaric acid (0.51 g, 3.41 mmol) in dry THF (5 mL) was added $NaBH_4$ (0.13 g, 3.41 mmol) portionwise and the suspension was heated at reflux for 2 h before being cooled to −7 °C. A solution of **12** (0.22 g, 0.57 mmol) in dry THF (5 mL) was added dropwise and the temperature maintained at −7 °C for 1 h and then at 0 °C for the next 2 h. The mixture was evaporated with silica gel (1 g) and the residue was purified on a column of flash silica (7:3 light petroleum/Et_2O). Pure **10** (0.219 g, 97%) was isolated as a colourless syrup, $[\alpha]_D^{20}=-57.0$ (*c* 1.0, $CHCl_3$);

R_f=0.46 (3:2 hexane/Et_2O). IR (neat): ν_{max} 3480 (OH). ^1H NMR ($CDCl_3$): δ 1.17–1.85 (m, 10H, C_6H_{10}), 3.39 (d, 1H, exchangeable with D_2O, J=6.1 Hz, OH), 4.03 (d, 1H, $J_{3,4}$=3.2 Hz, H-3), 4.34 (dd, 1H, $J_{3,4}$=3.2, $J_{4,5}$=6.1 Hz, H-4), 4.48 and 4.71 (2×d, 1H each, J_{gem}=11.4 Hz, PhCH_2), 4.63 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 5.11 (t, 1H, $J_{5,OH}$=$J_{4,5}$=6.1 Hz, H-5), 6.05 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 7.12–7.60 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.6 and 36.3 (5×CH_2), 72.0 (C-5), 72.2 (PhCH_2), 81.2 (C-2), 82.4 (C-4), 82.9 (C-3), 104.7 (C-1), 112.3 (Cq from C_6H_{10}), 126.0, 127.5, 127.9, 128.3, 128.34, 128.4, 128.7, 136.7, 141.3 (2×Ph). LRMS (CI): m/z 397 (M^++H). Anal. Found: C, 73.05; H, 7.52. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12.

*4.1.7. 3-O-Benzyl-5-C-phenyl-D-gluco-pentopyranose (**13**).* A solution of **10** (0.24 g, 0.61 mmol) in 70% aq AcOH (12 mL) was stirred for 4 h at reflux. After the mixture cooled to room temperature it was concentrated by co-distillation with toluene and the residue purified by flash chromatography (7:3 CH_2Cl_2/EtOAc), to afford pure **13** (0.17 g, 87%) as a colourless solid. Recrystallization from MeOH/CH_2Cl_2 gave an analytical sample **13**, as colourless needles, mp 153–155 °C, $[\alpha]_D^{20}$=+23.7 (c 0.94, Py), after 77 h mutarotated to +39.6; R_f=0.34 (7:3 CH_2Cl_2/EtOAc). IR (KBr): ν_{max} 3396 (OH). ^1H NMR (methanol-d_4): δ 3.39–3.62 (m, 2.4H), 3.68 (dd, 0.3H, J=3.6, 9.5 Hz), 3.81 (t, 0.3H, J=9.5 Hz), 4.22 (d, 0.7H, J=9.0 Hz), 4.66 (d, 0.7H, J=7.3 Hz), 4.76 (d, 0.3H, J=9.8 Hz), 4.90–5.00 (m, 2H), 5.20 (d, 0.3H, J=3.6 Hz), 7.20–7.52 (m, 10H, 2×Ph). ^{13}C NMR (methanol-d_4): δ 74.1, 75.0, 76.1, 76.4, 76.5, 76.8, 79.9, 83.6, 86.2, 94.4, 98.6, 128.5, 128.9, 129.1, 140.4, 140.9. MS (CI): m/z 317 (M^++H), 299 (M^++H−H_2O). Anal. Found: C, 68.11; H, 6.57. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37.

*4.1.8. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-C-phenyl-D-glycero-D-ido-heptono-1,4-lactone (**14**).* To a solution of **13** (0.37 g, 1.17 mmol) in dry DMF (4 mL) was added Meldrum's acid (0.49 g, 3.39 mmol) and dry Et_3N (0.48 mL, 3.44 mmol). The mixture was stirred for 76 h at 46 °C and then evaporated. The residue was purified by flash column chromatography (1:1→3:2 Et_2O/light petroleum) to afford pure **14** (0.165 g, 52% calculated to reacted starting compound **13**) as a colourless solid. Recrystallization from Et_2O/EtOAc/hexane gave colourless crystals, mp 40–42 °C, $[\alpha]_D^{20}$=−4.34 (c 1.06, $CHCl_3$), R_f=0.30 (3:2 Et_2O/light petroleum). IR ($CHCl_3$): ν_{max} 3476 (OH), 1785 (C=O). ^1H NMR ($CDCl_3$+D_2O): δ 2.61 (dd, 1H, $J_{2a,2b}$=18.8, $J_{2a,3}$=1.5 Hz, H-2a), 2.71 (dd, 1H, $J_{2a,2b}$=18.8, $J_{2b,3}$=5.4 Hz, H-2b), 2.87 (d, 1H, exchangeable with D_2O, J=5.7 Hz, OH), 4.21 (dd, 1H, $J_{5,6}$=3.6, $J_{6,7}$=7.2 Hz, H-6), 4.30 (d, 1H, $J_{5,6}$=3.6 Hz, H-5), 4.61 and 4.71 (2×d, 1H each, J_{gem}=11.6 Hz, PhCH_2), 4.92 (d, 1H, $J_{3,4}$=4.4 Hz, H-4), 5.01 (m, 2H, H-3 and H-7), 7.30–7.47 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 35.9 (C-2), 71.7 (C-7), 73.1 (PhCH_2), 77.2 (C-3), 81.7 (C-5), 83.2 (C-6), 84.7 (C-4), 126.2, 127.9, 128.1, 128.5, 128.6, 128.8, 136.4 and 140.9 (2×Ph), 175.3 (C-1). LRMS (CI): m/z 341 (M^++H). Anal. Found: C, 70.19; H, 6.11. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Eluted second was unchanged **13** (0.077 g, 21%).

*4.1.9. (+)-Goniofufurone (**1**).* A solution of **14** (0.082 g, 0.24 mmol) in MeOH (4 mL) was hydrogenated over 10% Pd/C (0.02 g) for 46 h at room temperature. The mixture was filtered and the catalyst washed with EtOAc. The combined organic solutions were evaporated and the residue was purified by flash chromatography (7:3 CH_2Cl_2/EtOAc), to afford pure **1** (0.058 g, 97%) as a colourless solid. Recrystallization from EtOAc/hexane gave colourless prisms, mp 154–155 °C, $[\alpha]_D^{20}$=+39.2 (c 0.94, $CHCl_3$), R_f=0.19 (7:3 CH_2Cl_2/EtOAc); lit.[8h] mp 154–156 °C, $[\alpha]_D^{20}$=+39.5 (c 1.0, $CHCl_3$). IR (KBr): ν_{max} 3410 (OH), 1755 (C=O). ^1H NMR ($CDCl_3$): δ 2.61 (d, 1H, $J_{2a,2b}$=18.7 Hz, H-2a), 2.74 (dd, 1H, $J_{2a,2b}$=18.7, $J_{2b,3}$=5.6 Hz, H-2b), 4.05 (dd, 1H, $J_{5,6}$=2.7, $J_{6,7}$=5.3 Hz, H-6), 4.43 (d, 1H, $J_{5,6}$=2.7 Hz, H-5), 4.87 (d, 1H, Hz $J_{3,4}$=4.2 Hz, H-4), 5.08 (dd, 1H, $J_{2b,3}$=5.6, $J_{3,4}$=4.2 Hz, H-3), 5.12 (d, 1H, $J_{6,7}$=5.3 Hz, H-7), 7.30–7.44 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 36.1 (C-2), 73.5 (C-7), 74.4 (C-5), 77.3 (C-3), 82.9 (C-6), 87.4 (C-4), 125.8, 128.5, 128.8 and 138.8 (Ph), 175.4 (C-1). LRMS (CI): m/z 501 (2 M^++H), 251 (M^++H), 233 (M^++H−H_2O). HRMS (ESI): Found: 251.0912 (M^++H), calcd for $C_{13}H_{15}O_5$: 251.0914.

*4.1.10. 3-O-Benzyl-5-C-phenyl-L-ido-pentopyranose (**15**).* A solution of **9** (0.87 g, 2.2 mmol) in 70% aq AcOH (26 mL) was stirred for 4.5 h at reflux. After the mixture cooled to room temperature it was concentrated by co-distillation with toluene and the residue (0.79 g) purified by flash column chromatography (7:3 light petroleum/Et_2O). The minor product **20** (0.06 g, 9%) was first isolated as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 116 °C, $[\alpha]_D^{20}$=−3.2 (c 1.15, $CHCl_3$), R_f=0.33 (7:3 light petroleum/Et_2O). IR (film): ν_{max} 3285 (OH). ^1H NMR ($CDCl_3$): δ 2.10 (d, 1H, exchangeable with D_2O, J=7.8 Hz, OH), 3.82 (ddd, 1H, $J_{2,3}$=1.4, $J_{1,3}$=0.9, $J_{3,4}$=4.8 Hz, H-3), 3.97 (ddd, 1H, $J_{1,2}$=1.1, $J_{2,3}$=1.4, $J_{2,OH}$=7.8 Hz, H-2), 4.53 (d, 1H, $J_{3,4}$=4.8 Hz, H-4), 4.63 and 4.76 (2×d, 1H each, J_{gem}=11.8 Hz, PhCH_2), 5.23 (s, 1H, H-5), 5.56 (d, 1H, $J_{1,2}$=1.1 Hz, H-1), 7.28–7.55 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 73.2 (PhCH_2), 73.5 (C-5), 77.9 (C-2), 81.4 (C-4), 86.1 (C-3), 104.9 (C-1), 126.4, 127.8, 128.0, 128.2, 128.6, 137.3 and 140.0 (2×Ph). LRMS (CI): m/z 338 (M^++C_4H_{10}−H_2O), 301 (M^++H). Anal. Found: C, 72.47; H, 6.08. Calcd for $C_{18}H_{18}O_4$: C, 72.28; H, 6.19. Eluted second was the major product **15** slightly contaminated with unreacted starting material **9**. Repeated purification on a column of flash silica (3:1 toluene/Et_2O) gave pure **15** (0.443 g, 64%) as a colourless syrup, $[\alpha]_D^{20}$=+15.7 (c 1.65, $CHCl_3$), R_f=0.19 (3:1 toluene/Et_2O). IR ($CHCl_3$): ν_{max} 3396 (OH). ^1H NMR ($CDCl_3$+D_2O): δ 3.78 (m, 2H), 4.02 (t, 1H, J=3.0 Hz), 4.61 and 4.69 (2×d, 1H each, J_{gem}=11.5 Hz, PhCH_2), 4.99 (br s, 1H), 5.11 (br s, 1H), 7.22–7.47 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): β-anomer: δ 67.9, 69.6, 72.4, 75.1, 76.0, 93.0, 126.1, 127.4, 127.6, 127.7, 127.9, 128.0, 128.5, 137.3; α-anomer: δ 65.9, 67.6, 69.4, 73.3, 75.6, 96.0. LRMS (ESI): m/z 598 (2 M^++H−2H_2O), 300 (M^++H−H_2O). Anal. Found: C, 67.98; H, 6.52. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37.

*4.1.11. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-C-phenyl-L-glicero-D-ido-heptono-1,4-lactone (**16**).* To a solution of **15** (0.89 g, 2.82 mmol) in dry DMF (12 mL) was added Meldrum's acid (1.28 g, 8.88 mmol) and dry Et_3N (1.2 mL, 8.61 mmol). The mixture was stirred for 70 h at 46 °C and then evaporated. The residue was purified by flash column chromatography (4:1 Et_2O/light petroleum) to afford slightly impure **16** (0.55 g) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles of pure **16** (0.29 g). Mother liquor was purified by flash column chromatography (9:1 CH_2Cl_2/EtOAc) to give an additional amount of pure **16** (0.16 g). Total yield of pure **16** was 0.45 g (47%). Mp 146–147 °C, $[\alpha]_D^{20}$=+40.0 (c 0.67, $CHCl_3$), R_f=0.26 (1:1 toluene/Et_2O); lit.[8a] mp 146–148 °C, $[\alpha]_D$=+25.5 (c 0.67, $CHCl_3$). IR (KBr): ν_{max} 3469 (OH), 1754 (C=O). ^1H NMR ($CDCl_3$): δ 2.75 (m, 3H, 2×H-2 and OH), 3.93 (d, 1H, $J_{5,6}$=3.9 Hz, H-5), 4.26 (dd, 1H, $J_{5,6}$=3.9, $J_{6,7}$=6.6 Hz, H-6), 4.45 and 4.55 (2×d, 1H each, J_{gem}=11.5 Hz, PhCH_2), 4.92 (d, 1H, $J_{3,4}$=4.7 Hz, H-4), 5.09 (d, 1H, $J_{6,7}$=6.6 Hz, H-7), 5.11 (m, 1H, H-3), 7.28–7.45 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 36.0 (C-2), 72.7 (C-7), 72.8 (PhCH_2), 77.4 (C-3), 81.8 (C-5), 84.6 (C-6), 85.1 (C-4), 126.9, 127.8, 128.3, 128.4, 128.5, 128.7, 136.5 and 139.5 (2×Ph), 175.2 (C-1). LRMS (ESI): m/z 341 (M^++H).

*4.1.12. 7-epi-(+)-Goniofufurone (**2**).* A solution of **16** (0.08 g, 0.24 mmol) in MeOH (3.6 mL) was hydrogenated over 10% Pd/C (0.02 g, 0.015 mmol) for 72 h at room temperature. The mixture was filtered and the catalyst washed with MeOH. The combined organic solutions were evaporated and the residue (0.074 g) was purified by flash chromatography (49:1→24:1→19:1 CH_2Cl_2/MeOH), to afford pure **2** (0.051 g, 87%) as a colourless crystalline mass. Recrystallization from Me_2CO/light petroleum gave colourless needles, mp 197–200 °C, $[\alpha]_D^{20}$=+108.5 (c 0.75, EtOH), R_f=0.40 (7:3 hexane/EtOAc); lit.[8a] mp

200–203 °C, $[\alpha]^{15}_{D}$=+102.0 (*c* 0.5, EtOH); IR (KBr): ν_{max} 3368 and 3283 (OH), 1755 (C=O). ^{1}H NMR (DMSO-d_6+D_2O): δ 2.50 (d, 1H, $J_{2a,2b}$=18.6 Hz, H-2a), 2.85 (dd, 1H, $J_{2a,2b}$=18.6, $J_{2b,3}$=6.4 Hz, H-2b), 3.59 (d, 1H, $J_{5,6}$=2.8 Hz, H-5), 3.82 (dd, 1H, $J_{5,6}$=2.8, $J_{6,7}$=7.9 Hz, H-6), 4.73 (d, 1H, $J_{6,7}$=7.9 Hz, H-7), 4.78 (d, 1H, $J_{3,4}$=4.6 Hz, H-4), 4.93 (dd, 1H, $J_{3,4}$=4.6, $J_{2b,3}$=6.4 Hz, H-3), 7.20–7.38 (m, 5H, Ph). ^{13}C NMR (DMSO-d_6): δ 36.7 (C-2), 72.6 (C-7), 73.6 (C-5), 77.8 (C-3), 85.5 (C-6), 88.8 (C-4), 127.9, 129.0, 129.4 and 142.3 (Ph), 178.3 (C-1). LRMS (CI): *m*/*z* 501 (2 M^++H), 251 (M^++H), 233 (M^++H–H_2O).

*4.1.13. 1,2-O-Cyclohexylidene-5-C-phenyl-β-L-ido-pentofuranose (**17**).* A solution of **9** (0.45 g, 1.13 mmol) in MeOH (11 mL), was hydrogenated over 10% Pd/C (0.09 g, 0.09 mmol) for 4 h at room temperature. The mixture was filtered and the catalyst washed with MeOH. The combined organic solutions were evaporated and the residue was purified by flash chromatography (3:7 hexane/Et_2O) to afford pure **17** (0.24 g, 70%) as colourless solid. Recrystallization from CH_2Cl_2/hexane, gave colourless needles, mp 178–179 °C, $[\alpha]^{20}_{D}$=+20.3 (*c* 1.0, $CHCl_3$), R_f=0.25 (7:3 Et_2O/hexane). IR (KBr): ν_{max} 3427 (OH). ^{1}H NMR ($CDCl_3$): δ 1.16–1.80 (m, 10H, C_6H_{10}), 3.00 (d, 1H, exchangeable with D_2O, $J_{5,OH}$=5.1 Hz, OH-5), 3.27 (d, 1H, exchangeable with D_2O, $J_{3,OH}$=4.9 Hz, OH-3), 4.10 (dd, 1H, $J_{3,OH}$=4.9, $J_{3,4}$=2.8 Hz, H-3), 4.32 (dd, 1H, $J_{3,4}$=2.8, $J_{4,5}$=4.9 Hz, H-4), 4.49 (d, 1H, $J_{1,2}$=3.6 Hz, H-2), 5.06 (t, 1H, $J_{4,5}$=4.9, $J_{5,OH}$=5.1 Hz, H-5), 6.03 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 7.29–7.56 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.6 and 36.3 (5×CH_2), 72.6 (C-5), 76.0 (C-3), 82.6 (C-4), 84.9 (C-2), 104.5 (C-1), 112.6 (Cq from C_6H_{10}), 126.7, 128.2, 128.6 and 140.0 (Ph). LRMS (ESI): *m*/*z* 329 (M^++Na), 307 (M^++H). Anal. Found: C, 66.25; H, 7.44. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24.

*4.1.14. 1,2-O-Cyclohexylidene-5-O-cinnamoyl-5-C-phenyl-α-D-gluco-pentofuranose (**18**).* To a cooled (0 °C) and stirred solution of **17** (0.16 g, 0.52 mmol), cinnamic acid (0.1 g, 0.68 mmol) and Ph_3P (0.29 g, 1.1 mmol) in dry THF (5 mL), was added DEAD (0.15 mL, 0.94 mmol) dropwise over a period of 5 min. The solution was stirred at 0 °C for 1 h, and then at room temperature for additional 2 h. The mixture was quenched with 10% aq $NaHCO_3$ (50 mL), and extracted with EtOAc (2×20 mL). The combined extracts were dried and evaporated and the residue purified on a column of flash silica (4:1 → 1:1 hexane/Et_2O). The minor product **21** (0.037 g, 16%) was first eluted, followed by the major product **18** (0.144 g, 63%). Recrystallization from CH_2Cl_2/hexane gave pure **18** as colourless needles, mp 127 °C, $[\alpha]^{20}_{D}$=+52.5 (*c* 1.0, $CHCl_3$), R_f=0.25 (1:1 hexane/Et_2O). IR (KBr): ν_{max} 3463 (OH), 1715 (C=O), 1636 (C=C). ^{1}H NMR ($CDCl_3$): δ 1.20–1.80 (m, 10H, C_6H_{10}), 3.89 (d, 1H, exchangeable with D_2O, $J_{3,OH}$=2.9 Hz, OH-3), 4.23 (br s, 1H, H-3), 4.42 (dd, 1H, $J_{3,4}$=2.1, $J_{4,5}$=9.2 Hz, H-4), 4.60 (d, 1H, $J_{1,2}$=3.6 Hz, H-2), 5.94 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 6.07 (d, 1H, $J_{4,5}$=9.2 Hz, H-5), 6.48 (d, 1H, $J_{2',3'}$=16.0 Hz, H-2′), 7.31–7.59 (m, 10H, 2×Ph), 7.76 (d, 1H, $J_{2',3'}$=16.0 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.5 and 36.4 (5×CH_2), 72.9 (C-5), 74.0 (C-3), 81.6 (C-4), 84.0 (C-2), 104.4 (C-1), 112.3 (Cq from C_6H_{10}), 116.8 (C-2′), 127.7, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 130.8, 133.8 and 136.9 (2×Ph), 146.9 (C-3′), 167.2 (C-1′). LRMS (ESI): *m*/*z* 459 (M^++Na), 437 (M^++H). Anal. Found: C, 69.26; H, 6.39. Calcd for $C_{26}H_{28}O_6$×H_2O: C, 68.71; H, 6.65.

*4.1.15. 5-O-Cinnamoyl-5-C-phenyl-D-gluco-pentofuranose (**19**).* A solution of **18** (0.21 g, 0.48 mmol) in 70% aq AcOH (7 mL) was stirred for 4 h at reflux. After the mixture cooled to room temperature it was concentrated by co-distillation with toluene and the residue (0.19 g) purified by flash chromatography (7:3 EtOAc/hexane). A minor amount of starting compound **19** (0.02 g, 15%) was first eluted, followed by slightly contaminated diol **19**. Repeated chromatographic purification (4:1 hexane/EtOAc) gave pure **19** (0.10 g, 59%; 67% calculated to reacted **18**) as a colourless syrup. Crystallization from EtOAc/hexane gave colourless needles, mp 171 °C, $[\alpha]^{20}_{D}$=+68.8 (*c* 0.5, EtOAc), R_f=0.26 (7:3 EtOAc/hexane). IR (KBr): ν_{max} 3403 (OH), 1702 (C=O), 1629 (C=C). ^{1}H NMR (acetone-d_6): δ 3.92 (dd, 0.3H, *J*=3.8, 2.4 Hz), 4.10–4.40 (m, 1.7H), 4.40–4.56 (m, 1H), 4.99 (s, 0.7H), 5.35 (d, 0.3H, *J*=3.8 Hz), 5.87 (d, 0.3H, *J*=9.0 Hz), 6.00 (d, 0.7H, *J*=9.8 Hz), 6.52 (d, 0.3H, *J*=16 Hz), 6.52 (d, 0.7H, *J*=16.0 Hz), 7.31–7.59 (m, 11H). ^{13}C NMR (acetone-d_6): δ 73.79, 74.26, 75.98, 76.49, 77.12, 81.10, 81.31, 84.08, 98.04, 104.33, 119.01, 128.52, 128.75, 128.96, 129.72, 131.16, 135.20, 140.43, 140.51, 145.46, 165.79, 165.86. LRMS (ESI): *m*/*z* 379 (M^++Na), 339 (M^++H–H_2O). HRMS (ESI): Found: 379.1150 (M^++Na), calcd for $C_{13}H_{13}NaO_4$: 379.1152.

*4.1.16. 3,5-Anhydro-1,2-O-cyclohexylidene-5-C-phenyl-α-D-gluco-pentofuranose (**21**).* To a cooled (0 °C) and stirred solution of **17** (0.184 g, 0.60 mmol) and Ph_3P (0.392 g, 1.50 mmol) in dry toluene (5 mL), was added DEAD (0.24 mL, 1.5 mmol) dropwise over a period of 2–3 min. The solution was stirred at reflux temperature for 1.5 h and then evaporated. Flash column chromatography of the residue gave pure **21** (0.133 g, 77%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane afforded colourless needles, mp 88–89 °C, $[\alpha]^{20}_{D}$=−43.6 (*c* 1.0, $CHCl_3$), R_f=0.71 (1:1 hexane/Et_2O). ^{1}H NMR ($CDCl_3$): δ 1.32–1.76 (m, 10H, C_6H_{10}), 4.85 (dd, 1H, $J_{3,4}$=4.1, $J_{4,5}$=2.1 Hz, H-4), 4.89 (d, 1H, $J_{1,2}$=3.6 Hz, H-2), 5.31 (d, 1H, $J_{3,4}$=4.1 Hz, H-3), 5.34 (d, 1H, $J_{4,5}$=2.1 Hz, H-5), 6.39 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 7.29–7.50 (m, 5H, Ph); NOE contact: H-1 and H-5. ^{13}C NMR ($CDCl_3$): δ 23.7, 23.8, 24.8, 36.6 and 37.5 (5×CH_2), 84.0 (C-4), 84.1 (C-2), 85.0 (C-3), 90.0 (C-5), 108.0 (C-1), 114.8 (Cq from C_6H_{10}), 125.0, 128.2, 128.7 and 138.9 (Ph). LRMS (ESI): *m*/*z* 311 (M^++Na), 289 (M^++H). Anal. Found: C, 70.56; H, 7.12. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99.

*4.1.17. (+)-Crassalactone C (**3**).* To a solution of **19** (0.034 g, 0.095 mmol) in dry DMF (1 mL) was added Meldrum's acid (0.03 g, 0.19 mmol) and dry Et_3N (0.03 mL, 0.19 mmol). The mixture was stirred for 72 h at 46 °C and then evaporated. The residue was purified by flash column chromatography (17:3 Et_2O/hexane) to afford pure **3** (0.022 g, 62%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 147–150 °C, $[\alpha]^{20}_{D}$=+111.6 (*c* 0.5, EtOH), R_f=0.46 (1:1 light petroleum/EtOAc); lit.[9] mp 147–150 °C, $[\alpha]^{30}_{D}$=+98.4 (*c* 0.5, EtOH). IR (KBr): ν_{max} 3459 (OH), 1784 (C=O, lactone), 1695 (C=O, cinnamoyl), 1635 (C=C, cinnamoyl). ^{1}H NMR ($CDCl_3$): δ 2.56 (d, 1H, $J_{2a,2b}$=18.6 Hz, H-2a), 2.70 (dd, 1H, $J_{2a,2b}$=18.6, $J_{2b,3}$=5.8 Hz, H-2b), 4.19 (br s, 1H, exchangeable with D_2O, OH), 4.26 (dd, 1H, $J_{6,7}$=9.2, $J_{5,6}$=2.4 Hz, H-6), 4.43 (br s, 1H, H-5), 5.00 (m, 2H, H-3 and H-4), 6.00 (d, 1H, $J_{6,7}$=9.2 Hz, H-7), 6.47 (d, 1H, $J_{2',3'}$=15.9 Hz, H-2′), 7.36–7.59 (m, 10H, 2×Ph), 7.78 (d, 1H, $J_{2',3'}$=15.9 Hz, H-3′). ^{13}C NMR ($CDCl_3$): δ 35.8 (C-2), 72.8 (C-7), 73.1 (C-5), 77.1 (C-3), 82.4 (C-6), 87.0 (C-4), 116.4 (C-2′), 127.6, 128.3, 128.6, 128.9, 130.9, 133.6 and 136.6 (2×Ph), 147.5 (C-3′), 167.5 (C-1′), 175.5 (C-1). LRMS (ESI): *m*/*z* 403 (M^++Na), 363 (M^++H–H_2O).

*4.1.18. 3,6:5,7-Dianhydro-2-deoxy-7-C-phenyl-D-glycero-D-ido-heptono-1,4-lactone (**4**).* A solution of **2** (0.036 g, 0.14 mmol) in dry toluene (1 mL), was reacted with Ph_3P (0.098 g, 0.37 mmol) and DEAD (0.06 mL, 0.38 mmol) following the same methodology as described above (procedure in Section 4.1.15). The mixture was refluxed for 3 h and then evaporated. Flash column chromatography (4:1 Et_2O/light petroleum) of the residue gave slightly contaminated **4**. Repeated purification on a column of flash silica (CH_2Cl_2) gave pure **4** (0.012 g, 35%), as white solid. Recrystallization from CH_2Cl_2/hexane afforded colourless needles, mp 145–147 °C, $[\alpha]^{20}_{D}$=+46.0 (*c* 0.5, $CHCl_3$), R_f=0.39 CH_2Cl_2. IR (KBr): ν_{max} 1730 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.83 (d, 1H, $J_{2a,2b}$=18.0 Hz, H-2a), 2.92 (dd, 1H, $J_{2a,2b}$=18.0, $J_{2b,3}$=4.1 Hz, H-2b), 4.83 (dd, 1H, $J_{5,6}$=4.2, $J_{6,7}$=2.5 Hz, H-6), 5.08 (d, 1H, $J_{3,4}$=3.6 Hz, H-4), 5.37 (dd, 1H, $J_{2b,3}$=4.1, $J_{3,4}$=3.6 Hz, H-3), 5.49 (d, 1H, $J_{5,6}$=4.2 Hz, H-5), 5.52 (d, 1H,

$J_{6,7}$=2.5 Hz, H-7), 7.30–7.49 (m, 5H, Ph); NOE contact: H-3 and H-7. ^{13}C NMR ($CDCl_3$): δ 36.0 (C-2), 79.2 (C-3), 84.9 (C-4), 85.1 (C-6), 85.3 (C-5), 89.1 (C-7), 125.0, 128.5, 128.8 and 138.6 (Ph), 174.1 (C-1). HRMS (ESI): Found: 233.0813 (M^++H), calcd for $C_{13}H_{13}O_4$: 233.0808.

*4.1.19. Methyl (Z)-3-O-benzyl-5,6-dideoxy-1,2-O-cyclohexylidene-α-D-xylo-hept-5-enofuranuronate (**22**).* To a cooled (0 °C) and stirred solution of aldehyde **8** (1.38 g, 4.33 mmol) in dry MeOH (35 mL) was added Ph_3P=$CHCO_2Me$ (1.812 g, 5.42 mmol). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1.5 h. The solvent was evaporated and the residue purified by flash column chromatography (4:1 light petroleum/Et_2O), to give pure (*Z*)-isomer **22** (1.35 g, 83%) as a colourless syrup, $[\alpha]_D^{20}$=−262.1 (*c* 1.04, $CHCl_3$); R_f=0.28 (17:3 light petroleum/Et_2O). IR (neat): ν_{max} 1721 (C=O), 1652 (C=C). ^{1}H NMR ($CDCl_3$): δ 1.33–1.81 (m, 10H, C_6H_{10}), 3.68 (s, 3H, CO_2CH_3), 4.31 (d, 1H, $J_{3,4}$=3.3 Hz, H-3), 4.57 and 4.62 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.64 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 5.65 (ddd, 1H, $J_{3,4}$=3.3, $J_{4,5}$=6.7, $J_{4,6}$=1.7 Hz, H-4), 5.93 (dd, 1H, $J_{4,6}$=1.7, $J_{5,6}$=11.7 Hz, H-6), 6.02 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 6.41 (dd, 1H, $J_{4,5}$=6.7, $J_{5,6}$=11.7 Hz, H-5), 7.22–7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 23.6, 23.9, 24.9, 35.9 and 36.6 (5×CH_2), 51.3 (CO_2CH_3), 72.2 (PhCH_2), 78.0 (C-4), 82.7 (C-2), 84.0 (C-3), 104.7 (C-1), 112.5 (Cq from C_6H_{10}), 120.5 (C-6), 127.6, 127.8, 128.3 and 137.5 (Ph), 145.8 (C-5), 165.9 (C-7). LRMS (CI): *m*/*z* 375 (M^++H). Anal. Found: C, 67.10; H, 7.17. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Further elution of the column gave pure (*E*)-isomer **22a** (0.193 g, 12%) as a colourless syrup, $[\alpha]_D^{20}$=−45.0 (*c* 1.09, $CHCl_3$); R_f=0.22 (17:3 light petroleum/Et_2O). IR (neat): ν_{max} 1724 (C=O), 1665 (C=C). ^{1}H NMR ($CDCl_3$): δ 1.30–1.79 (m, 10H, C_6H_{10}), 3.76 (s, 3H, CO_2CH_3), 4.00 (d, 1H, $J_{3,4}$=3.3 Hz, H-3), 4.50 and 4.63 (2×d, 2H, J_{gem}=12.1 Hz, PhCH_2), 4.64 (d, 1H, $J_{1,2}$=3.7 Hz, H-2), 4.80 (ddd, 1H, $J_{3,4}$=3.3, $J_{4,5}$=4.9, $J_{4,6}$=1.7 Hz, H-4), 6.00 (d, 1H, $J_{1,2}$=3.7 Hz, H-1), 6.19 (dd, 1H, $J_{4,6}$=1.7, $J_{5,6}$=15.8 Hz, H-6), 6.98 (dd, 1H, $J_{4,5}$=4.9, $J_{5,6}$=15.8 Hz, H-5), 7.24–7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 23.5, 23.8, 24.8, 35.7 and 36.5 (5×CH_2), 51.5 (CO_2CH_3), 72.2 (PhCH_2), 79.4 (C-4), 82.4 (C-2), 83.1 (C-3), 104.6 (C-1), 112.6 (Cq from C_6H_{10}), 122.7 (C-6), 127.7, 127.9, 128.4 and 137.1 (Ph), 141.8 (C-5), 166.4 (C-7). LRMS (CI): *m*/*z* 375 (M^++H). Anal. Found: C, 66.97; H, 7.00. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00.

*4.1.20. 2,5-Anhydro-3-O-benzyl-6-deoxy-L-ido-hepturono-4,7-lactone dimethyl acetal (**24**).* A solution containing 2.5% H_2SO_4 in dry MeOH (60 mL) and **22** (1.7 g, 4.54 mmol) was stirred under reflux for 4.5 h. The mixture was cooled to 35 °C, then rendered alkaline (to pH=9) by addition of $NaHCO_3$ (5.5 g, 65.48 mmol) in portions (1.0 g) every 5 min. The resulting suspension was stirred at 35 °C for 1 h, then filtered and evaporated. The residue was purified by flash column chromatography (1:3 light petroleum/EtOAc). Eluted first was pure **24** (1.04 g, 74%), isolated as a colourless solid. Recrystallization from EtOAc/light petroleum gave an analytical sample **24** as colourless needles, mp 90 °C, $[\alpha]_D^{20}$=−20.7 (*c* 1.04, $CHCl_3$); R_f=0.44 (7:3 light petroleum/Et_2O). IR (KBr): ν_{max} 1790 (C=O). ^{1}H NMR (acetone-d_6): δ 2.50 (d, 1H, $J_{6a,6b}$=18.8 Hz, H-6a), 2.87 (dd, 1H, $J_{6a,6b}$=18.8, $J_{5,6b}$=6.5 Hz, H-6b), 3.35 and 3.36 (2×s, 3H each, 2×OCH_3), 4.01 (dd, 1H, $J_{1,2}$=7.5, $J_{2,3}$=3.5 Hz, H-2), 4.19 (d, 1H, $J_{2,3}$=3.5 Hz, H-3), 4.59 (d, 1H, $J_{1,2}$=7.5 Hz, H-1), 4.63 and 4.76 (2×d, 2H, J_{gem}=11.6 Hz, PhCH_2), 4.97 (dd, 1H, $J_{4,5}$=4.4, $J_{5,6b}$=6.5 Hz, H-5), 5.09 (d, 1H, $J_{4,5}$=4.4 Hz, H-4), 7.26–7.45 (m, 5H, Ph). ^{13}C NMR (acetone-d_6): δ 36.4 (C-6), 53.1 and 55.1 (2×OCH_3), 73.0 (PhCH_2), 78.4 (C-5), 80.4 (C-2), 82.4 (C-3), 85.4 (C-4), 102.9 (C-1), 128.6, 128.7, 129.1 and 138.8 (Ph), 176.0 (C-7). LRMS (CI): *m*/*z* 309 (M^++H). HRMS (ESI): Found: 347.0891 (M^++K), calcd for $C_{16}H_{20}KO_6$: 347.0891. Eluted second was pure **23** (0.056 g, 4%) as a colourless syrup, $[\alpha]_D^{20}$=+63.0 (*c* 1.85, $CHCl_3$); R_f=0.25 (3:2 toluene/EtOAc). IR (neat): ν_{max} 3465 (OH), 1785 and 1755 (C=O), 1600 (C=C). ^{1}H NMR ($CDCl_3$): δ 2.64 (d, 1H, exchangeable with D_2O, $J_{2,OH}$=5.1 Hz, OH), 3.30 and 3.43 (2×s, 3H each, 2×OCH_3), 3.56 (br s, after treatment with D_2O, dd, 1H, $J_{1,2}$=6.4, $J_{2,3}$=2.2 Hz, H-2), 3.75 (dd, 1H, $J_{2,3}$=2.2, $J_{3,4}$=6.2 Hz, H-3), 4.40 (d, 1H, $J_{1,2}$=6.4 Hz, H-1), 4.63 and 4.86 (2×d, 2H, J_{gem}=11.3 Hz, PhCH_2), 5.29 (dd, 1H, $J_{3,4}$=6.2, $J_{4,5}$=1.6, $J_{4,6}$=2.1 Hz, H-4), 6.16 (dd, 1H, $J_{5,6}$=5.8, $J_{4,6}$=2.1, Hz, H-6), 7.31–7.37 (m, 5H, Ph), 7.57 (dd, 1H, $J_{4,5}$=1.6, $J_{5,6}$=5.8 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ 54.5 and 55.4 (2×OCH_3), 70.4 (C-2), 74.2 (PhCH_2), 78.3 (C-3), 84.6 (C-4), 103.8 (C-1), 122.0 (C-6), 128.1, 128.3, 128.4 and 137.3 (Ph), 153.9 (C-5), 172.8 (C=O). LRMS (CI): *m*/*z* 584 (2 M^+–MeOH), 309 (M^++H), 277 (MH^+–MeOH).

*4.1.21. 2,5-Anhydro-3-O-benzyl-6-deoxy-L-ido-hepturono-4,7-lactone (**25**).* A solution of **24** (0.66 g, 2.16 mmol) in a mixture of TFA/H_2O (9:1, 4.2 mL) was first stirred at 0 °C for 0.5 h and then at room temperature for 0.5 h. The volatiles were removed by co-distillation with toluene and the residue purified by flash column chromatography (1:1 light petroleum/EtOAc). Eluted first was pure **25** (0.508 g, 90%) as a colourless syrup, $[\alpha]_D^{20}$=−21.3 (*c* 1.05, $CHCl_3$); R_f=0.20 (1:1 light petroleum/EtOAc). Eluted second was the mixture of **24** and **25** (0.07 g), which was again subjected to hydrolysis and chromatographic purification by using the same procedure as described above, to afford an additional amount of pure **25** (0.025 g). Total yield of pure **25** was 0.533 g (94%). IR (neat): ν_{max} 1788 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.75 (d, 2H, $J_{5,6}$=3.4 Hz, 2×H-6), 4.49–4.69 (m, 4H, H-2, H-3 and PhCH_2), 4.91 (d, 1H, $J_{4,5}$=4.0 Hz, H-4), 5.14 (dd, 1H, $J_{4,5}$=4.0, $J_{5,6}$=3.4 Hz, H-5), 7.23–7.40 (m, 5H, Ph), 9.61 (d, 1H, $J_{1,2}$=1.2 Hz, CHO). ^{13}C NMR ($CDCl_3$): δ 35.9 (C-6), 73.0 (PhCH_2), 78.8 (C-5), 82.9 (C-3), 84.7 (C-4), 84.9 (C-2), 127.8, 128.4, 128.6 and 136.1 (Ph), 174.3 (C-7), 198.6 (C-1). LRMS (CI): *m*/*z* 263 (M^++H). HRMS (ESI): Found: 263.0917 (M^++H), calcd for $C_{14}H_{15}O_5$: 263.0914.

*4.1.22. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-C-phenyl-D-glicero-L-ido-heptono-1,4-lactone (ent-**16**).* A solution of **24** (0.66 g, 2.16 mmol) in a mixture of 9:1 TFA/H_2O (4.2 mL) was first stirred at 0 °C for 0.5 h and then at room temperature for 0.5 h. The volatiles were removed by co-distillation with toluene, and the remaining crude **25** (0.19 g) was dissolved in dry THF (10 mL) and cooled to −7 °C. To this solution was added a 3 M solution of PhMgBr in Et_2O (0.26 mL, 0.78 mmol). The mixture was stirred at −7 °C, under an atmosphere of nitrogen for 3 h, and then neutralised with 5% AcOH in THF (to pH 7). The mixture was poured to 10% aq NaCl (100 mL) and extracted with CH_2Cl_2 (2×40 mL). The combined extracts were washed with 10% aq NaCl (100 mL), dried and evaporated, and the residue purified by flash column chromatography (5:1 Et_2O/light petroleum). The pure minor stereoisomer *ent*-**14** (0.008 g, 3%) was first eluted that crystallized from a mixture Me_2CO/hexane as colourless needles, mp 43–44 °C, $[\alpha]_D^{20}$=+6.1 (*c* 0.5, $CHCl_3$); R_f=0.63 (1:1 EtOAc/light petroleum). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**14** were consistent with those recorded for the opposite enantiomer **14** (Section 4.1.8). HRMS (ESI): Found: 363.1191 (M^++Na), calcd for $C_{22}H_{20}NaO_6$: 363.1203. Eluted second was the major stereoisomer *ent*-**16** (0.15 g, 56%) that crystallized from CH_2Cl_2/hexane as colourless needles, mp 145–147 °C, $[\alpha]_D^{20}$=−34.0 (*c* 0.95, $CHCl_3$); R_f=0.25 (9:11 EtOAc/light petroleum). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**16** were consistent with those recorded for the opposite enantiomer **16** (Section 4.1.11). HRMS (ESI): Found: 363.1193 (M^++Na), calcd for $C_{22}H_{20}NaO_6$: 363.1203.

*4.1.23. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-C-phenyl-L-ido-hept-7-ulosono-1,4-lactone (**26**).* A solution of *ent*-**17** (0.06 g, 0.18 mmol) and PCC (0.1 g, 0.44 mmol) in dry CH_2Cl_2 (10 mL) was heated to reflux for 2 h. The mixture was evaporated and the residue was purified by flash column chromatography (3:2 cyclohexane/EtOAc),

to give pure **26** (0.05 g, 84%) as a colourless syrup. Crystallization from CH_2Cl_2/hexane gave colourless needles, mp 119–121 °C, $[\alpha]_D^{20}=-3.8$ (*c* 0.5, $CHCl_3$); R_f=0.33 (3:2 cyclohexane/EtOAc). IR ($CHCl_3$): ν_{max} 1788 (C_1=O), 1701 (C_7=O). ^{1}H NMR ($CDCl_3$): δ 2.79 (d, 2H, $J_{2,3}$=3.2 Hz, 2×H-2), 4.27 and 4.45 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.66 (d, 1H, $J_{5,6}$=5.1 Hz, H-5), 4.95 (d, 1H, $J_{3,4}$=4.1 Hz, H-4), 5.26 (m, 1H, H-3), 5.61 (d, 1H, $J_{5,6}$=5.1 Hz, H-6), 6.80–7.93 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 35.9 (C-2), 72.4 (PhCH_2), 78.3 (C-3), 82.4 (C-5), 83.2 (C-6), 84.9 (C-4), 127.7, 127.8, 128.0, 128.3, 128.6, 133.3, 135.5, and 135.6 (2×Ph), 174.8 (C-1), 194.1 (C-7). HRMS (ESI): Found: 339.1238 (M^++H), calcd for $C_{20}H_{19}O_5$: 339.1233.

*4.1.24. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-C-phenyl-L-glycero-L-ido-heptono-1,4-lactone (ent-**14**).* To a solution of **26** (0.05 g, 0.15 mmol) in MeOH (10 mL) was added $NaBH_4$ (0.006 g, 0.16 mmol) in six equal portions and the mixture was stirred at −7 °C for 3.5 h. The mixture was neutralised with glac AcOH and evaporated. The residue was purified by flash column chromatography (3:2 cyclohexane/EtOAc). Pure *ent*-**14** (0.023 g, 54%) was first eluted that crystallized from a mixture Me_2CO/hexane as colourless needles, mp 43–44 °C, $[\alpha]_D^{20}=+6.1$ (*c* 0.5, $CHCl_3$); R_f=0.63 (1:1 EtOAc/light petroleum). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**14** were consistent with those recorded for the opposite enantiomer **14** (Section 4.1.8). HRMS (ESI): Found: 363.1191 (M^++Na), calcd for $C_{22}H_{20}NaO_6$: 363.1203. Eluted second was the minor stereoisomer *ent*-**16** (0.013 g, 26%). For physical and spectroscopic data of *ent*-**16** see Section 4.1.23.

*4.1.25. (−)-Goniofufurone (ent-**1**).* A solution of *ent*-**14** (0.04 g, 0.13 mmol) in MeOH (3 mL) was hydrogenated over 10% Pd/C (0.02 g) following the same methodology as described above (procedure in Section 4.1.9), to afford pure *ent*-**1** (0.02 g, 70% calculated to reacted *ent*-**14**), mp 155 °C, $[\alpha]_D^{20}=-10.2$ (*c* 0.44, EtOH); lit.[6] mp 152–154 °C, $[\alpha]^{30}{}_D=-8.0$ (*c* 0.79, EtOH). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**1** were consistent with those recorded for (+)-enantiomer **1** (Section 4.1.9).

*4.1.26. 7-epi-(−)-Goniofufurone (ent-**2**).* A solution of *ent*-**16** (0.03 g, 0.1 mmol) in MeOH (2 mL), was hydrogenated over 10% Pd/C (0.01 g) following the same methodology as described above (procedure in Section 4.1.12) to afford pure *ent*-**2** (0.02 g, 64%) as a colourless solid. Recrystallization from EtOAc/hexane gave colourless plates, mp 205–206 °C, $[\alpha]_D^{20}=-98.3$ (*c* 0.47, Me_2CO); lit.[6] mp 208–209 °C, $[\alpha]_D^{20}=-92.5$ (*c* 1.1, Me_2CO). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**2** were consistent with those recorded for (+)-enantiomer **2** (Section 4.1.12).

*4.1.27. (−)-Crassalactone C (ent-**3**).* A cooled (0 °C) and stirred solution of *ent*-**2** (0.05 g, 0.20 mmol), cinnamic acid (0.04 g, 0.27 mmol) and Ph_3P (0.11 g, 0.42 mmol) in dry THF (5 mL), was treated with DEAD (0.06 mL, 0.38 mmol) following the same methodology as described above (procedure in Section 4.1.14) to afford pure *ent*-**3** (0.04 g, 53%), which crystallized from Et_2O as colourless needles, mp 147–150 °C, $[\alpha]_D^{20}=-110.1$ (*c* 0.5, EtOH), R_f=0.5 (Et_2O); (+)-enantiomer: lit.[9] mp 147–150 °C, $[\alpha]^{30}{}_D=+98.4$ (*c* 0.5, EtOH). IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**3** were consistent with those recorded for (+)-enantiomer **3** (Section 4.1.17). HRMS (ESI): Found: 403.1133 (M^++Na), calcd for $C_{22}H_{20}NaO_6$: 403.1152.

*4.1.28. 3,6:5,7-Dianhydro-2-deoxy-7-C-phenyl-L-glycero-L-ido-heptono-1,4-lactone (ent-**4**).* A cooled (0 °C) and stirred solution of *ent*-**2** (0.05 g, 0.20 mmol) in dry toluene (3 mL) was treated with Ph_3P (0.13 g, 0.49 mmol) and DEAD (0.08 mL, 0.51 mmol) following the same methodology as described above (procedure in Section 4.1.18) to afford pure *ent*-**4** (0.02 g, 40%) as colourless needles, mp 146 °C; $[\alpha]_D=-48.1$ (*c* 0.5, $CHCl_3$); R_f=0.17 (CH_2Cl_2). Absolute value of optical rotation, mp, IR, ^{1}H and ^{13}C NMR spectroscopic data of *ent*-**4** were consistent with those recorded for (+)-enantiomer **4** (Section 4.1.18). HRMS (ESI): Found: 233.0805 (M^++H), calcd for $C_{13}H_{13}O_4$: 233.0808.

4.2. X-ray crystal structure determination[29]

A single colourless crystal of *ent*-**4** was selected and glued on glass fibber. Diffraction data were collected on an Oxford Diffraction KM4 four-circle goniometer equipped with Sapphire CCD detector. The crystal to detector distance was 45.0 mm and a graphite monochromated MoK_α (λ=0.71073 Å) X-radiation was employed in the measurement. The frame widths of 0.3° and 2° in ω, with 10 and 200 s were used to acquire each frame. More than a hemisphere of three-dimensional data was collected. The data were reduced using the Oxford Diffraction program CrysAlisPro. A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. Scattering curves for neutral atoms, together with anomalous-dispersion corrections, were taken from International Tables for X-ray Crystallography.[30] The structure was solved by direct methods (SHELXS-97).[31] Refinement was based on F^2 values and done by full-matrix least-squares (SHELXL-97)[32] with all non-H atoms anisotropic. The positions of all non H-atoms were located by direct methods. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. The final refinement included atomic positional and displacement parameters for all non-H atoms. The non-H atoms were refined anisotropically, while H sites were refined with isotropic displacement parameters. However, at the final stage of the refinement, H atoms were positioned geometrically (N–H=0.86, O–H=0.82 and C–H=0.93–0.97 Å) and refined using a riding model with fixed isotropic displacement parameters. The crystal data and refinement parameters are listed in Table 2.

Table 2
Crystallographic data and structure refinement of *ent*-**4**

Crystallographic parameter	
Empirical formula	$C_{13}H_{12}O_4$
Formula weight	232.23
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	*P*1
Unit cell dimensions	*a*=5.7553(3) α=98.611(4) *b*=11.7910(7) β=90.003(4) *c*=16.2110(8) γ=90.004(4)
Volume (Å^3)	1087.7(1)
Z	4
Density (calculated, g/cm^3)	1.418
Absorption coefficient (mm^{-1})	0.11
F(000)	488
Crystal size (mm)	0.16×0.18×0.25
$2\theta_{max}$ for data collection (deg)	29.03
Index ranges	$-14\le h\le 14$, $-7\le k\le 4$, $-20\le l\le 21$
Reflections collected	6539
Independent reflections	4917 [*R*(int)=0.0900]
Refinement method	Full-matrix l.s. on F^2
Data/restraints/parameters	2572/2/615
Goodness-of-fit on F^2	0.807
Final *R* indices [$I>2\sigma(I)$]	R_1=0.0350
R indices (all data)	R_1=0.0965, wR_2=0.0551
Maximum shift/esd	0.05
Extinction coefficient	No
Largest diff. peak and hole (e/Å^3)	0.12 and −0.16

4.3. In vitro antitumour assay

Exponentially growing cells were harvested, counted by trypan blue exclusion and plated into 96-well microtitar plates (Costar) at optimal seeding density of 10^4 (K562, HL-60, Jurkat and Raji) cells per well to assure logarithmic growth rate throughout the assay period.

Antiproliferative activity was evaluated by the tetrazolium colourimetric MTT assay following the recently reported procedure.[16]

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