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Heteroannelated (+)-muricatacin mimics: synthesis, antiproliferative properties and structure–activity relationships

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ABSTRACT

Six new (+)-muricatacin mimics bearing a furano-furanone core have been synthesized and their in vitro antiproliferative activity was evaluated against a panel of human tumour cell lines. A straightforward total synthesis of (+)-muricatacin (**1**) from D-xylose is disclosed providing a sample of **1** that served as a positive control in antitumour assays. All new compounds showed diverse antiproliferative effects against human malignant cell lines, but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). Additionally, the most of (+)-muricatacin analogues show selective cytotoxicities towards certain cancer cell lines, whereas only two of six analogues are broadly toxic against all cell lines under evaluation. A SAR study reveals the structural features that may be beneficial for the antiproliferative activity of these lactones. These include the absolute stereochemistry, introduction of a THF ring, interchange of the O_8 ether functionality and the C_8 methylene group in the side chain of muricatacin oxa analogues, as well as the one- or two-carbon homologation of the side chain in both **3** and **6**.

1. Introduction

Muricatacin, a naturally occurring acetogenin derivative has been isolated by McLaughlin and co-workers from the seeds of *Annona muricata*.[1] The isolated material was found to be a mixture of (+)-(4*S*,5*S*)-5-hydroxyheptadecan-4-olide (**1**, Fig. 1) and its (−)-(4*R*,5*R*)-enantiomer (*ent*-**1**), with a slight predominance of the later. Both (+)- and (−)-muricatacin have demonstrated a remarkable antiproliferative activity towards several human tumour cell lines. These findings have stimulated a significant interest in the synthesis of this type of compounds. Accordingly, many syntheses of (+)- and (−)-muricatacin and congeners from various precursors have been reported.[2–4] In addition, these molecules have been used as starting materials for the synthesis of other complex biologically relevant natural products.[5] A number of muricatacin analogues and stereoisomers have also been synthesized,[6] and some of them were evaluated for their antitumour activity.[6h,7,8]

Previous studies in our laboratory revealed that a mimic of (−)-muricatacin in which a methylene group from the side chain

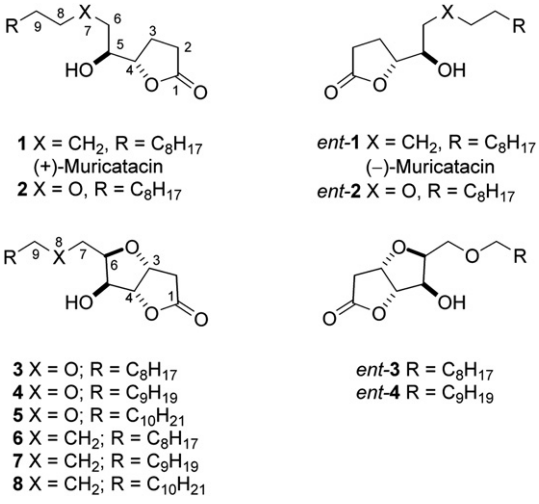

Fig. 1. Structures of (+)-muricatacin (**1**), (−)-muricatacin (*ent*-**1**) and the related analogues.

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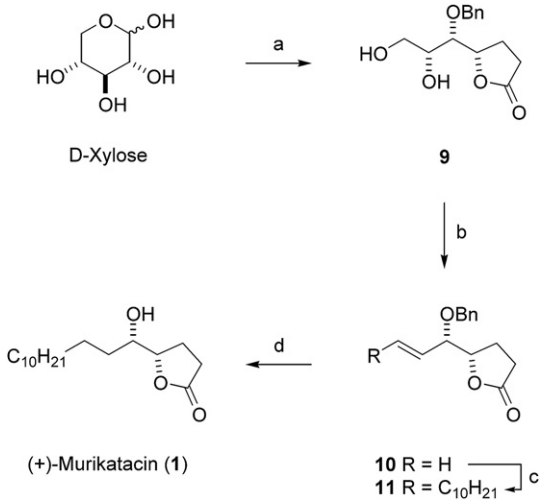
has been replaced by an ether function (compound *ent*-**2**) exhibited in vitro antitumour activity against several human cancer cell lines.[9] We have also found that introduction of a THF ring increases the activity of heteroannelated (−)-muricatacin mimic *ent*-**3** against the HeLa malignant cells, and that one-carbon homologation of the side chain in *ent*-**3** increases the activity of resulting homologue *ent*-**4** against the K562, HL-60 and HeLa cell lines.[10]

As part of our continuing efforts to further optimize the antitumour potency of leads of type *ent*-**1**, *ent*-**2**, *ent*-**3** and *ent*-**4**, we have investigated the corresponding opposite enantiomers, as conformationally constrained analogues of (+)-muricatacin (**1**). The target compounds **3**–**8** were designed to restrict the rotation around the C_4–C_5 and C_5–C_6 bonds through incorporation of a condensed THF ring as shown in Fig. 1, providing a number of heteroannelated (+)-muricatacin mimics. Thus, compounds **3** and **4** are the opposite enantiomers of *ent*-**3** and *ent*-**4**, while the molecule **5** represents a one-carbon higher homologue of **4**. Analogues **6**–**8** represent classical isosteres of **3**–**5** designed by replacement of an ether function from the side chain with a methylene group. Analogues **3** and **6** represent one-carbon lower homologues of **4** and **7**, while lactones **5** and **8** represent one-carbon higher homologues of **4** and **7**. In addition to the synthesis of analogues **3**–**8**, a novel route to (+)-muricatacin (**1**) was developed in order to provide a sample of the lead that would serve as a positive control in antitumour assays.

2. Results and discussion

2.1. Chemical synthesis

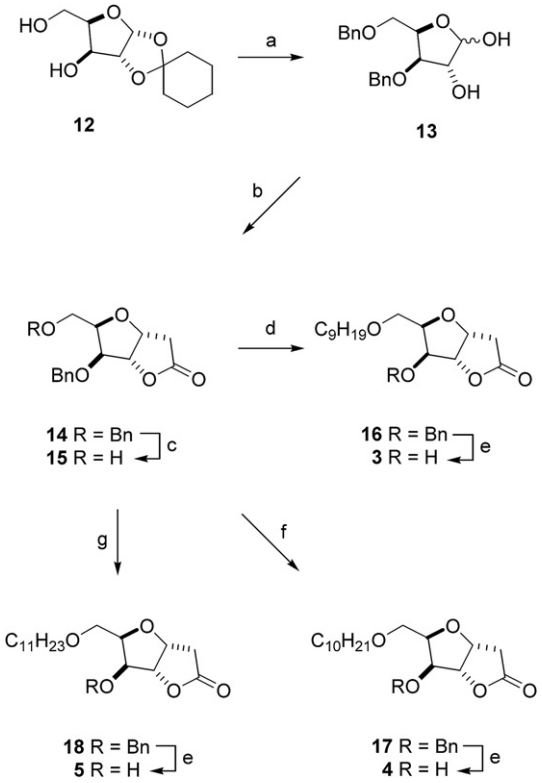
The synthesis of (+)-muricatacin (**1**) is shown in Scheme 1. The starting hydroxy lactone **9** was prepared from D-xylose in eight steps as reported earlier by us.[9]



Scheme 1. Reagents and conditions: (a) eight steps, 23.6%, Ref. 9; (b) I_2, ImdH, Ph_3P, MeCN, N_2, 90 °C, 1.5 h, 96%; (c) dodec-1-ene, Grubbs catalyst II generation, CH_2Cl_2, rt, 27.5 h, 61%; (d) H_2, 10% Pd/C, MeOH, rt, 4 h, 90%.

Reaction of **9** with iodine, triphenylphosphine and imidazole, according to the methodology developed by Garegg and Samuelsson,[11] gave the corresponding terminal alkene **10** in 96% yield. The cross metathesis reaction of **10** with dodec-1-ene (5 mol equiv) in the presence of Grubbs second generation catalyst (10 mol %) afforded the corresponding disubstituted olefin **11** in 61% yield with exclusively *E*-selectivity ($J_{6,7}$=15.5 Hz). Catalytic hydrogenation of **11** over 10% Pd/C in methanol gave (+)-muricatacin (**1**) in 90% yield. The physical data of thus obtained product **1** {mp 68–69 °C, $[\alpha]_D$ +22.3 (*c* 0.43, $CHCl_3$)}, were found to be in reasonable agreement with those previously reported {lit.[3] mp 68–70 °C, $[\alpha]_D$ +22.4 (*c* 0.42, $CHCl_3$); lit.[4] mp 68–70 °C, $[\alpha]_D$ +19.6 (*c* 1.0, $CHCl_3$)}.

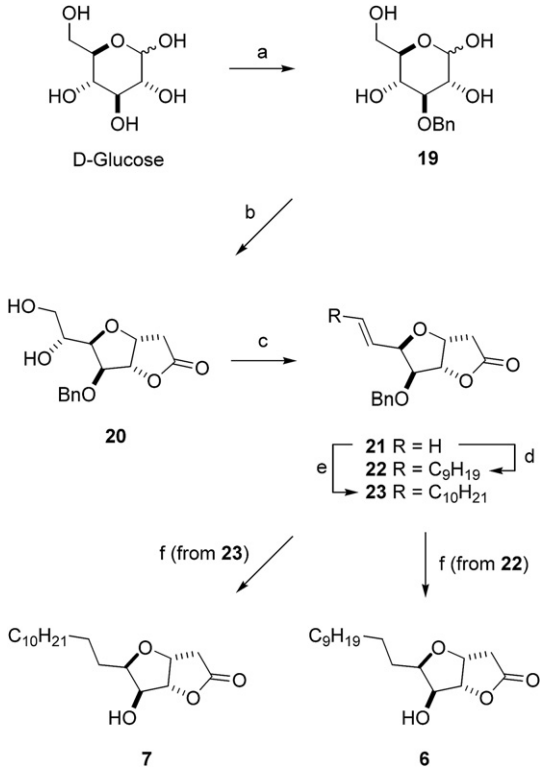
Syntheses of conformationally restricted (+)-muricatacin oxa analogues **3**–**5** are outlined in Scheme 2.



Scheme 2. Reagents and conditions: (a) two steps, 50%, Ref. 12; (b) Meldrum's acid, Et_3N, DMF, 46–48 °C, 48 h, 82%; (c) H_2, 10% Pd/C (0.1 equiv of Pd), abs EtOH, rt, 105 min, 87%; (d) $C_9H_{19}Br$, Ag_2O, AgOTf, Et_2O, reflux, 30 h, 61%; (e) H_2, 10% Pd/C, EtOH, rt, 18 h for **16**, 96% of **3**, 20 h for **17**, 86% of **4**, 3.5 h for **18**, 83% of **5**; (f) $C_{10}H_{21}Br$, Ag_2O, AgOTf, Et_2O, reflux, 31 h, 51%; (g) $C_{11}H_{23}Br$, Ag_2O, AgOTf, Et_2O, reflux, 48 h, 56%.

The sequence started with the preparation of the protected primary alcohol **15** from the known[12] D-xylose derivative **13**. Compound **13** was treated with Meldrum's acid in DMF, in the presence of Et_3N, whereupon the protected lactone **14** was obtained in 82% yield. Compound **14** was previously prepared in our laboratory by *Z*-selective Wittig olefination of lactol **13** with $Ph_3P{=}CHCO_2Me$ but only in 61% yield. Catalytic reduction of **14** over 10% Pd/C (0.1 mol equiv of Pd) for 105 min at room temperature effected selective removal of the benzyl group from the primary position to afford the alcohol **15** in 87% yield.[13] Alcohol **15** readily reacted with an excess of nonyl bromide and silver oxide in ether, in the presence of a catalytic amount of silver triflate, to give the corresponding 7-*O*-nonyl derivative **16** in 61% yield. The 5-*O*-benzyl protecting group from **16** was removed by catalytic hydrogenolysis over 10% Pd/C in methanol, to give a 96% yield of **3**. Treatment of **15** with decyl bromide, under the reaction conditions similar to those applied for the preparation of **16**, gave the expected 7-*O*-decyl derivative **17** in 51% yield. Intermediate **17** was earlier synthesized in our laboratory in 18% overall yield from starting compound **12**.[14] This new synthesis of **4** proceeds in five steps with 24% overall yield based on the same starting compound. Hydrogenolytic removal of the benzyl ether protective group in **17** under the same reaction conditions as reported earlier by us,[14] afforded **4** in 86% yield. Moreover, by using the undecyl bromide as an alkylation agent, compound **15** was first converted to the protected lactone **18** (56%) and finally to target **5** (83%), after removal of the benzyl protecting group.

Syntheses of (+)-muricatacin mimics **6** and **7** are presented in Scheme 3.

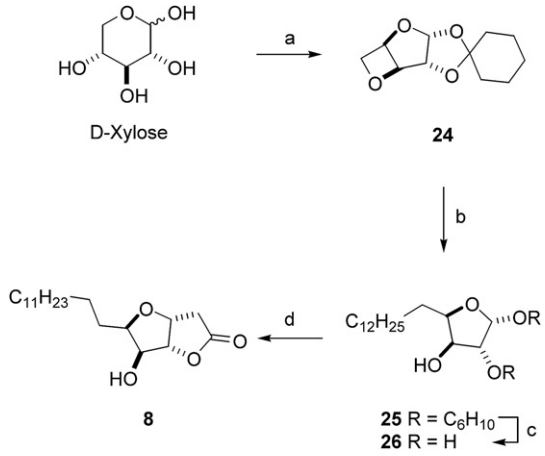


Scheme 3. Reagents and conditions: (a) three steps, 56%, Ref. 15a; (b) Meldrum's acid, Et_3N, DMF, 46–48 °C, 70 h, 43%; (c) I_2, ImdH, Ph_3P, MeCN, N_2, 90 °C, 1.5 h, 93%; (d) undec-1-ene, Grubbs catalyst II generation, CH_2Cl_2, rt, 24 h, 68%; (e) dodec-1-ene, Grubbs catalyst II generation, CH_2Cl_2, Ar, rt, 68 h, 69%; (f) H_2, 10% Pd/C, MeOH, rt, 3 h for **22**, 82% of **6**, 4.5 h for **23**, 57% of **7**.

3-*O*-Benzyl-D-glucose (**19**), readily available from D-glucose,[15] was used as a convenient starting compound in this part of the work. Thus, compound **19** was allowed to react with Meldrum's acid in DMF, in the presence of Et_3N, to afford the expected lactone **20** in 43% yield. Reaction of **20** with iodine, imidazole and triphenylphosphine gave the corresponding terminal olefin **21** in 93% yield. Preparation of (±)-**21** has been recently disclosed by Kapitán and Gracza.[16] The authors have described this product as a colourless oil, but we have isolated it in the form of colourless needles, mp 62–63 °C. However, the ^1H and ^{13}C NMR data of thus obtained furanolactone **21** were in full agreement with reported values. The cross metathesis between **21** and undec-1-ene or dodec-1-ene, in presence of Grubbs second generation catalyst (10 mol %) produced the desired long-chain olefins **22** (68%) and **23** (69%), respectively, both with exclusively *E*-selectivity ($J_{7,8}$=15.5 Hz). In the final step, the hydrogenation of double bond simultaneously with the removal of the benzyl ether protection in **22** and **23** were carried out smoothly by hydrogenation over 10% Pd/C in MeOH, to afford the target molecules **6** (82%) and **7** (57%) as white solids.

The 3,5-anhydro-D-xylose derivative **24**, readily available from D-xylose,[17] was used as a convenient starting material for the synthesis of target **8** (Scheme 4).

Treatment of **24** with dodecylmagnesium bromide produced the expected alcohol **25** in 56% yield. Hydrolytic removal of the cyclohexylidene protective group (7:3 H_2O/AcOH) gave the expected lactol **26** (57%), which was finally converted to the furanolactone **8** (66%) after treatment with Meldrum's acid and Et_3N in DMF.



Scheme 4. Reagents and conditions: (a) four steps, 40%, Ref. 17; (b) $C_{12}H_{25}MgBr$, THF, reflux, 4 h, 56%; (c) 70% aq AcOH, reflux, 3.5 h, 57%; (d) Meldrum's acid, Et_3N, DMF, 46 °C, 48 h, 66%.

2.2. X-ray analysis

The complete structure and relative stereochemistry of **7** and **8** were established by X-ray diffraction analysis.[18] The absolute configuration was determined by the use of D-xylose or D-glucose as the enantiomerically pure starting materials. A view of the molecular structures is provided in Fig. 2a and b. Additional details of crystallographic data are given in Supplementary data.

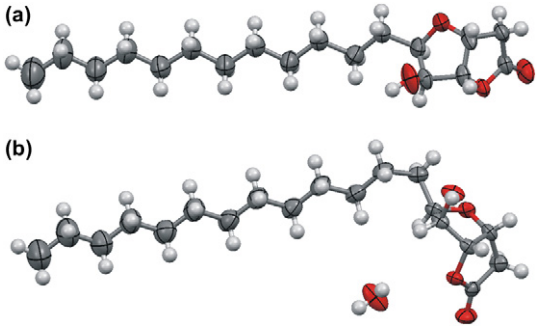


Fig. 2. ORTEP drawing of (a) analogue **7** and (b) analogue **8**.

2.3. In vitro antitumour activity

The human cancer cell lines used in this study represent several common types of solid cancer and leukaemia. These include the myelogenous leukaemia (K562), promyelocytic leukaemia (HL-60), Jurkat T cell leukaemia, Burkitt's lymphoma (Raji), colon carcinoma (HT-29), oestrogen receptor negative breast carcinoma (MDA-MB-231), and cervix carcinoma (HeLa) cells. The use of human foetal lung fibroblasts (MRC-5) serves to evaluate the toxicity of the analogues towards normal cells. Cytotoxic activity was evaluated by using the standard MTT assay, after exposure of cells to the tested compounds for 72 h. (+)-Muricatacin (**1**), the corresponding 7-oxa analogue **2**,[19] and the commercial antitumour agent doxorubicin (DOX) were used as reference compounds.

According to the resulting IC_{50} values of the cytotoxic assay (Table 1), all synthesized compounds demonstrated diverse antiproliferative effects against human malignant cell lines but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). Additionally, the most of (+)-muricatacin analogues show selective cytotoxicities towards certain cancer cell

Table 1
In vitro cytotoxicity of (+)-muricatacin (**1**), analogues **3**–**8** and DOX

Compd	IC_{50}[a] (μM)							
	K562	HL-60	Jurkat	Raji	HT-29	MDA-MB-231	HeLa	MRC-5
1	0.03	0.06	0.14	1.32	>100	>100	1.09	>100
2	1.01	17.36	1.16	>100	0.02	>100	>100	>100
3	1.95	>100	25.46	13.25	1.69	>100	9.17	>100
4	3.91	0.06	>100	0.99	>100	45.32	>100	>100
5	7.71	1.64	2.03	5.33	35.71	5.58	10.19	>100
6	1.55	5.31	2.54	0.95	>100	>100	1.01	>100
7	2.02	4.44	3.87	1.01	>100	>100	0.22	>100
8	0.36	0.89	0.05	1.23	15.45	3.56	2.24	>100
DOX	0.25	0.92	0.03	2.98	0.15	0.09	0.07	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control. Values are means of three independent experiments. Coefficients of variation were less than 10%.

lines, whereas only **5** and **8** are broadly toxic against all cell lines under evaluation.

Remarkably all analogues **3**–**8**, as well as both parent compounds **1** and **2** exhibit potent in vitro anticancer activity towards the K562 cell line, with IC_{50} values in the low-micromolar range. The most active compound against this cell line was lead **1** (IC_{50}=0.03 μM), being 8-fold more potent than the commercial antitumour agent doxorubicin. Only analogue **8** exhibited a submicromolar antiproliferative activity (IC_{50}=0.36 μM) against the K562 cells, being essentially as potent as the commercial antitumour agent doxorubicin.

Most of synthesized analogues demonstrated potent cytotoxicities against HL-60 cell line. The only exception is the analogue **3**, which was inactive towards HL-60 cells, as well as **2** that showed a moderate cytotoxicity (IC_{50}=17.36 μM) in the same cell line. The 7-*O*-decyl derivative **4** is the most potent cytotoxic agent in this cell line, showing exactly the same antiproliferative activity as the natural product **1** (IC_{50}=0.06 μM).

Analogues **5**–**8** including parent compounds **1** and **2** exhibited strong antiproliferative activities against the Jurkat cells with IC_{50} values in the range of 0.05–3.87 μM. Compound **4** was inactive towards these cells, while analogue **3** showed a moderate cytotoxicity (IC_{50}=25.46 μM) in the same cell line. The most active molecule in the culture of Jurkat cells is analogue **8** that exhibited over 2- and 20-fold higher potency than both control compounds **1** and **2**, respectively. In the same time, this molecule showed a similar activity as DOX in the same cell line.

Parent compound **2** was inactive against Raji cells. However, analogues **4**, **6**, **7** and **8** exhibited notable cytotoxic effects towards this cell line with IC_{50} values in the range of 0.95–1.23 μM. These molecules are the most active compounds against the Raji cells, being essentially 2–3-fold more active than the commercial antitumour agent doxorubicin.

HT-29 cell line appears to be much less sensitive to the synthesized (+)-muricatacin analogues, including the parent compound **1** that was inactive against these cells. However, 7-oxa analogue **2** demonstrated the most potent activity against the HT-29 cells (IC_{50}=0.02 μM) being 7.5-fold more cytotoxic than the standard antitumour agent doxorubicin.

MDA-MB-231 cells are even less sensitive to the synthesized (+)-muricatacin analogues. Both parent molecules **1** and **2**, as well as analogues **3**, **6** and **8** were inactive towards this cell line, while analogue **4** showed a weak cytotoxicity (IC_{50}=45.32 μM) in the same cell line. The most active molecule in the culture of MDA-MB-231 cells is analogue **8** (IC_{50}=3.56 μM).

The majority of synthesized analogues exhibited notable antiproliferative effects on HeLa cells, with IC_{50} values in the range of 0.22–10.19 μM. The most active compound against this cell line was **8** (IC_{50}=0.22 μM), being approximately 5-fold more potent than the control compound **1**. Lead **2** and analogue **4** were inactive against these cells.

2.4. SAR studies

In an early attempt to correlate the structures of muricatacin and congeners with their cytotoxic activities against KB and VERO cell lines, Figadère and co-workers[7] have found that cytotoxicity was dependent on the length of the alkyl chain. A shorter chain dramatically decreased the activity, whereas a longer chain did not influence to the activity. Introduction of unsaturation in the lactone ring improved the activity of the analogues with a short chain but had no effect on muricatacin itself. When other functionalities were present, such as an oxo function, the activity was about the same as for the parent compound. Addition of a tetrahydrofuran ring did not change the activity of the analogues as long as the length of the alkyl chain was not changed. In the cases of the pyrrolidones (azamuricatacins), the activity was either identical to that of muricatacin or even better, independent of the relative or absolute stereochemistry of the analogues.

Our previous findings[9] observed with (−)-muricatacin derivatives have prompted us to execute a more comprehensive SAR investigation of the analogues of both (+)- and (−)-muricatacin series. The first structural element considered was the absolute stereochemistry of analogues. The importance of this structural feature for the cytotoxic activities of these compounds was studied by comparing the IC_{50} values of (+)- (**1**) and (−)-muricatacin (*ent*-**1**), as well as of 3 pairs of analogues (**2** and *ent*-**2**, **3** and *ent*-**3**, **4** and *ent*-**4**), each of which contains exactly the same substituents and differs only in their absolute stereochemistry. As shown in Fig. 3a, the results indicate that, in most cases, the (−)-muricatacin mimics show a more potent cytotoxicity than the opposite enantiomers of (+)-muricatacin series. A comparison of biological data of **1** with **6**, **7**, and **8** (Fig. 3b), revealed that introduction of a THF ring may only slightly affect the cytotoxic activities of the corresponding (+)-muricatacin mimics (**6**–**8**). Interestingly, the effect is significantly more pronounced if the side chain of (+)-muricatacin is extended for two carbon atoms. However, it is difficult to evaluate any trend conclusively in this case, as only three pairs of analogues were available for comparison. As shown in Fig. 3c, heteroannelation of lead **1** followed by replacement of the C_7 atom with an ether group significantly decreases the activities of (+)-muricatacin mimics (**3**–**5**). However, the same structural changes in lead *ent*-**1** increases the cytotoxicities of the resulting (−)-muricatacin mimics (*ent*-**3** and *ent*-**4**). As observed in (+)-muricatacin series the effect is significantly more pronounced in the analogue with the extended side chain for one carbon atom (*ent*-**4**). As shown in Fig. 3d, interchange of the O_8 ether functionality and C_8 methylene groups in the side chain of muricatacin oxa analogues results

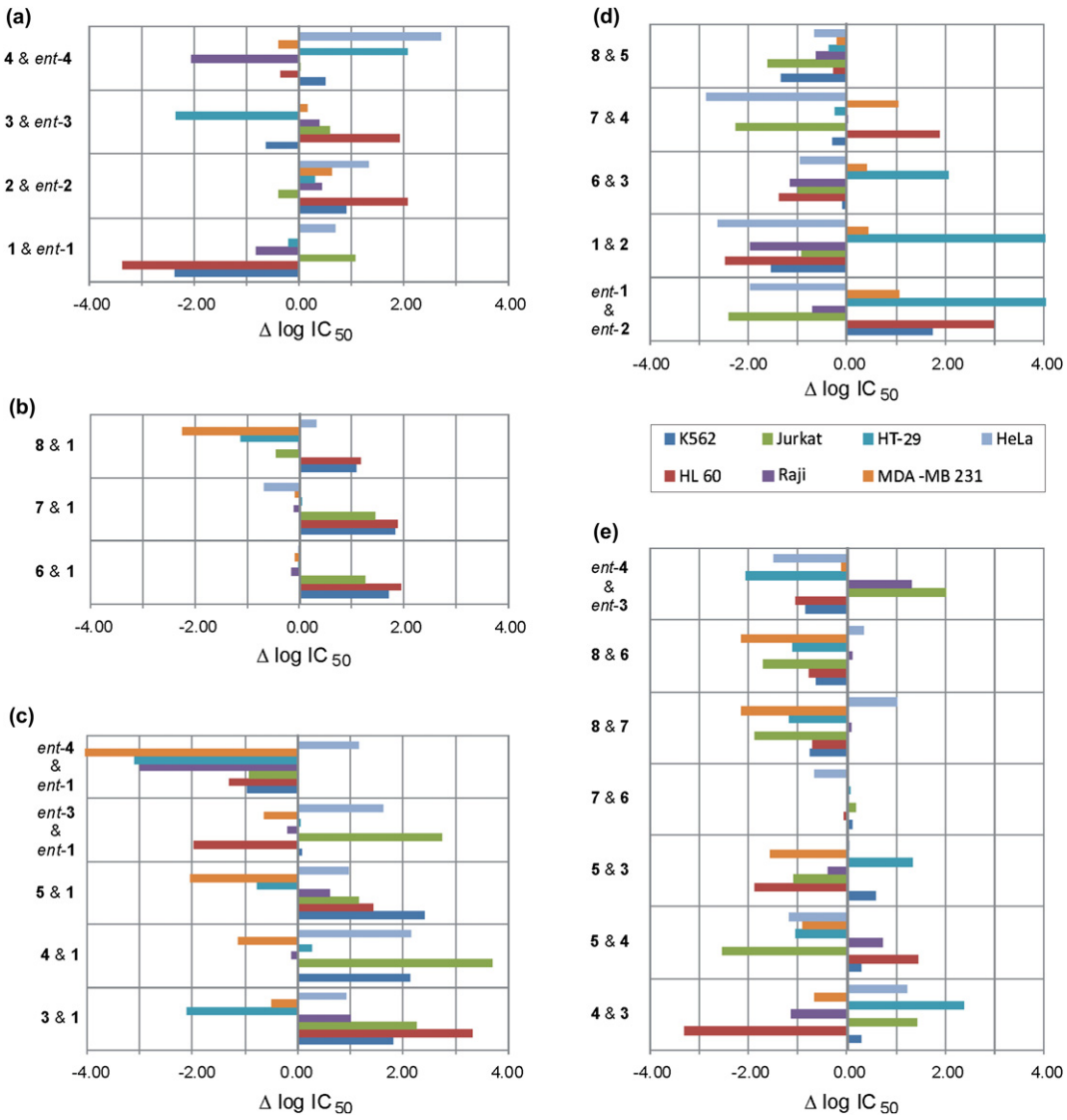


Fig. 3. Contributions of selected structural features to the cytotoxic activities: (a) influence of absolute stereochemistry, (b) influence of an additional THF ring, (c) influence of introduction of a THF ring followed by $CH_2 \rightarrow O$ isosteric replacement, (d) influence of $O \rightarrow CH_2$ interchange, (e) influence of one- or two-carbon homologation of the side chain. The IC_{50} values of two structures differing in one given position were compared, and the $\Delta\log IC_{50}$ was subsequently calculated ($\Delta\log IC_{50}$ is a difference between the IC_{50} values of an analogue and the corresponding control compound). Positive $\Delta\log IC_{50}$ values indicate a decrease of cytotoxic activity, whereas negative values show an increase in the activity upon the structural modification being considered.

in a substantial increase in cytotoxic activity against most of the cell lines tested in this study. The most pronounced activities were observed with analogues **2**, **3** and **5**. These findings indicated that-introduction of an oxygen atom in the side chain increases the antiproliferative activity of the analogues against most tumour cell lines under evaluation. The final structural element considered was the length of the alkyl chain (Fig. 3e). Thus, one-or two-carbon homologation of the side chain in **3** (to give analogues **4** and **5**), as well as in **6** (to afford analogues **7** and **8**) increases the activity of the resulting homologues against most of the cell lines tested. These results are in good agreement with previous findings that the length of the side chain is crucial for antitumour activity of muricatacin analogues.[7] However, the mechanism of action is still not understood. Since it has been proposed that acetogenins of Annonaceae act as an inhibitor of complex I in the mitochondrial respiratory system,[20] it is possible that muricatacin and analogues act via an identical mechanism. The observed differences in the antiproliferative potencies in respect to the cancer cell lines used may then be explained by a specificity difference in the hosts' mitochondrial complex I (NADH-ubiquinone oxidoreductase), but more work is needed before any conclusion can be made.

3. Conclusion

In conclusion, we have developed a straightforward synthesis of antitumour acetogenin derivative (+)-muricatacin, as well as a divergent route to several new (+)-muricatacin mimics (**3**–**8**) and evaluated them for in vitro cytotoxic activities against seven human tumour cell lines. All synthesized compounds demonstrated diverse antiproliferative effects against human malignant cell lines but were devoid of any significant cytotoxicity towards the normal foetal lung fibroblasts (MRC-5). Additionally, the most of (+)-muricatacin analogues show selective cytotoxicities towards certain cancer cell lines, whereas only two of six are broadly toxic against all cell lines under evaluation. A SAR study reveals that the following structural features are beneficial for the antiproliferative activity of these lactones: the absolute stereochemistry, presence of an additional tetrahydrofuran ring, interchange of the O_8 ether

functionality and C_8 methylene groups in the side chain of muricatacin oxa analogues, as well as the one- and two-carbon homologation of the side chain in both **3** and **6**. It was found that cytotoxicity is dependent on the length of the alkyl chain, whereby the C_2 homologation has the most pronounced effects on inhibition of cells growth. The results of MTT assay along with the SAR analysis enabled us to identify the (+)-muricatacin mimic **8** as the most promising antitumour agent, since it exhibited a potent antiproliferative activity against all malignant cell lines under evaluation, but was completely inactive against the normal human cells (MRC-5). Hence, we believe that this approach may be of use in the search for new, more potent and selective anticancer agents derived from the natural product **1**.

4. Experimental section

4.1. Chemistry

4.1.1. General methods. Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on P 3002 (Krüss) and Autopol IV (Rudolph Research) polarimeters at 24 °C. NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in parts per million downfield from TMS. IR spectra were recorded with an FTIR Nexus 670 spectrophotometer (Thermo-Nicolet). Low resolution mass spectra (CI) were recorded on Finnigan-MAT 8230 and on an Agilent Technologies HPLC/MS 3Q system (ESI), series 1200/6410. High resolution mass spectra (ESI) of synthesized compounds were acquired on an Agilent Technologies 1200 series instrument equipped with Zorbax Eclipse Plus C18 (100 mm×2.1 mm i.d. 1.8 μm) column and DAD detector (190–450 nm) in combination with a 6210 time-of-flight LC/MS instrument (ESI) in the positive ion mode. Flash column chromatography was performed using Kieselgel 60 (0.040–0.063, E. Merck). All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under reduced pressure at a bath temperature below 35 °C.

*4.1.2. 5-O-Benzyl-2,3,6,7-tetradeoxy-L-threo-hept-6-enono-1,4-lactone (**10**).* To a mixture of iodine (0.98 g, 3.84 mmol), imidazole (1.08 g, 15.94 mmol) and triphenylphosphine (1 g, 3.79 mmol) in dry MeCN (6 mL) was added a solution of **9** (0.25 g, 0.95 mmol) in dry MeCN (6 mL). The mixture was vigorously stirred at 90 °C (bath temperature) for 1.5 h, in an atmosphere of N_2, then evaporated and purified by flash column chromatography (9:1→4:1→1:1 light petroleum/EtOAc), to yield unsaturated lactone **10** (0.21 g, 96%) as a pale yellow oil, $[\alpha]_D$ +51.5 (*c* 2.04, $CHCl_3$), R_f=0.63 (1:1 light petroleum/EtOAc). IR (neat): ν_{max} 1777 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.96–2.26 (m, 2H, H-3), 2.33–2.64 (m, 2H, H-2), 3.84 (dd, 1H, $J_{4,5}$=4.5 Hz, $J_{5,6}$=7.8 Hz, H-5), 4.39 (d, 1H, J_{gem}=12.0 Hz, PhCH_2), 4.53 (ddd, 1H, $J_{3,4}$=6.1 Hz, $J_{3,4}$=7.9 Hz, $J_{4,5}$=4.5 Hz, H-4), 4.66 (d, 1H, J_{gem}=12.0 Hz, PhCH_2), 5.38 (d, 1H, $J_{6,7a}$=18.5 Hz, H-7a), 5.40 (d, 1H, $J_{6,7b}$=10.5 Hz, H-7b), 5.82 (m, 1H, H-6), 7.22–7.41 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 23.6 (C-2), 28.0 (C-3), 70.2 (PhCH_2), 81.2 and 81.24 (C-4 and C-5), 120.4 (C-7), 127.5, 128.2, 137.6 (Ph), 133.4 (C-6), 177.2 (C-1). HRMS (ESI): *m*/*z* 233.1165 (M^++H), calcd for $C_{14}H_{17}O_3$: 233.1172.

*4.1.3. (E)-5-O-Benzyl-7-C-decyl-2,3,6,7-tetradeoxy-L-threo-hept-6-enono-1,4-lactone (**11**).* To a stirred solution of olefin **10** (0.12 g, 0.50 mmol) and dodec-1-ene (1.1 mL, 5.0 mmol) in dry CH_2Cl_2 (2.3 mL) was added the second generation Grubbs catalyst (42 mg, 0.05 mmol). The reaction mixture was stirred in an argon atmosphere for 27.5 h at room temperature. The solvent was evaporated and the remaining crude product was purified by flash column chromatography (19:1→9:1→4:1 light petroleum/EtOAc), to give **11** (0.12 g, 61%) as a bright yellow syrup, $[\alpha]_D$ +58.2 (*c* 1.03, $CHCl_3$), R_f=0.19 (19:1 light petroleum/EtOAc). IR (neat): ν_{max} 1779 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J*=6.8 Hz, Me), 1.13–1.48 (m, 16H, 8×CH_2), 1.97–2.28 (m, 4H, CH_2–3, CH_2–8), 2.35–2.66 (m, 2H, CH_2–2), 3.81 (dd, 1H, $J_{4,5}$=4.6 Hz, $J_{5,6}$=8.4 Hz, H-5), 4.38 and 4.66 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.54 (m, 1H, $J_{3,4}$=7.8 Hz, $J_{3,4}$=5.8 Hz, $J_{4,5}$=4.6 Hz, H-4), 5.44 (m, 1H, $J_{5,6}$=8.4 Hz, $J_{6,7}$=15.5 Hz, $J_{6,8}$=1.3 Hz, H-6), 5.78 (dt, 1H, $J_{6,7}$=15.5 Hz, $J_{7,8}$=6.6 Hz, H-7), 7.28–7.40 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 22.6, 23.8, 23.9, 28.3, 29.0, 29.1, 29.3, 29.4, 29.6, 31.9, 32.3, (9×CH_2, C-2 and C-3), 69.9 (PhCH_2), 81.2, 81.8 (C-4 and C-5), 125.0 (C-6), 127.6, 127.7, 128.4 (Ph), 138.1 (C-7), 177.4 (C-1). HRMS (ESI): *m*/*z* 373.2728 (M^++H), calcd for $C_{24}H_{37}O_3$: 373.2737.

*4.1.4. (+)-Muricatacin (**1**).* To a stirred solution of **11** (59 mg, 0.2 mmol) in MeOH (1.2 mL) was added 10% Pd/C (83 mg, 0.08 mmol). The suspension was hydrogenated at room temperature and normal pressure of H_2 for 4 h, then filtered through a Celite pad, washed with 1:1 CH_2Cl_2/EtOAc and evaporated. Silica gel flash column chromatography (7:3 light petroleum/EtOAc) of the residue gave pure **1** (39 mg, 90%) as a white solid that was recrystallized from a mixture of Et_2O/pentane to afford colourless needles, mp 68–69 °C, $[\alpha]_D$ +22.3 (*c* 0.43, $CHCl_3$), R_f=0.21 (7:3 light petroleum/EtOAc); lit.[3] mp 68–70 °C, $[\alpha]_D$ +22.4 (*c* 0.42, $CHCl_3$); lit.[4] mp 68–70 °C, $[\alpha]_D$ +19.6 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3360 and 2447 (OH), 1742 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J*=6.7 Hz, Me), 1.13–1.64 (m, 22H, 11×CH_2), 1.90 (d, 1H, $J_{5,OH}$=5.9 Hz, OH), 2.01–2.33 (m, 2H, 2×H-3), 2.50 (dd, 1H, $J_{2a,2b}$=17.8 Hz, $J_{2a,3}$=9.0 Hz, H-2a), 2.63 (ddd, 1H, $J_{2a,2b}$=17.8 Hz, $J_{3,2b}$=9.5 Hz, $J_{3,2b}$=5.2 Hz, H-2b), 3.56 (m, 1H, $J_{4,5}$=4.6 Hz, H-5), 4.41 (td, 1H, $J_{3,4}$=7.4 Hz, $J_{4,5}$=4.6 Hz, H-4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 24.1 (C-3), 28.7 (C-2), 22.7, 25.4, 29.3, 29.5, 29.6, 29.63, 29.65, 31.9 and 33.0 (9×CH_2), 73.7 (C-5), 82.9 (C-4), 177.1 (C-1). HRMS (ESI): *m*/*z* 285.2420 (M^++H), calcd for $C_{17}H_{33}O_3$: 285.2424.

*4.1.5. 3,6-Anhydro-5,7-di-O-benzyl-2-deoxy-D-ido-heptono-1,4-lactone (**14**).* To a solution of **13** (0.95 g, 2.89 mmol) in dry DMF (9.4 mL), was added anhydrous Et_3N (0.81 mL, 5.81 mmol) and Meldrum's acid (0.83 g, 5.78 mmol). The mixture was stirred for 48 h at 46–48 °C and then evaporated. The residue was purified by flash column chromatography on silica gel (49:1 CH_2Cl_2/EtOAc) to afford pure **14** (0.84 g, 82%), as a colourless solid. Recrystallization from a mixture of CH_2Cl_2/Et_2O/light petroleum gave colourless needles, mp 90–91 °C, R_f=0.50 (3:2 Et_2O/toluene); lit.[21] mp 90 °C. Spectroscopic data of thus prepared sample **14** matched those previously reported by us.[21]

*4.1.6. 3,6-Anhydro-5-O-benzyl-2-deoxy-D-ido-heptono-1,4-lactone (**15**).* A solution of **14** (0.56 g, 1.58 mmol) in a mixture of EtOAc (4 mL) and abs EtOH (4 mL) was added to a stirred suspension of 10% Pd/C (0.17 g, 0.16 mmol, 0.1 equiv Pd) in abs EtOH (8 mL), which was pre-saturated with H_2 for 1 h. The suspension was hydrogenated at room temperature and normal pressure of H_2 for 105 min, then filtered through a Celite pad, washed with EtOH, and evaporated. Flash column chromatography (9:1 Et_2O/light petroleum) of the residue gave pure **15** (0.36 g, 87%), as a colourless syrup, $[\alpha]_D$ +4.3 (*c* 1.0, $CHCl_3$), R_f=0.31 (Et_2O). IR ($CHCl_3$): ν_{max} 3467 (OH), 1789 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.52 (br s, 1H, OH), 2.58–2.78 (m, 2H, 2×H-2), 3.76 (dd, 1H, $J_{6,7a}$=4.3 Hz, $J_{7a,7b}$=12.0 Hz, H-7a), 3.84 (dd, 1H, $J_{6,7b}$=5.1 Hz, $J_{7a,7b}$=12.0 Hz, H-7b), 4.17 (m, 1H, $J_{5,6}$=4.9 Hz, H-6), 4.25 (d, 1H, $J_{5,6}$=4.9 Hz, H-5), 4.56 and 4.71 (2×d, J_{gem}=11.9 Hz, CH_2Ph), 4.91–5.01 (m, 2H, H-3 and H-4), 7.26–7.42 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.8 (C-2), 61.1 (C-7), 72.7 (CH_2Ph), 76.7 (C-3), 80.7 (C-6), 82.1 (C-5), 85.7 (C-4), 127.6, 128.2, 128.6, 136.7 (Ph), 175.2 (C-1). LRMS (ESI): *m*/*e* 265 (M^++H), 529 (2 M^++H). HRMS (ESI): *m*/*z* 265.1066 (M^++H), calcd for $C_{14}H_{17}O_5$:

265.1070; *m/z* 287.0885 (M^++Na), calcd for $C_{14}H_{16}NaO_5$: 287.0890; *m/z* 303.0625 (M^++K), calcd for $C_{14}H_{16}KO_5$: 303.0629.

*4.1.7. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-O-nonyl-D-ido-heptono-1,4-lactone (**16**).* To a solution of **15** (0.25 g, 0.95 mmol) in dry Et_2O (5 mL) were added successively Ag_2O (0.55 g, 2.36 mmol), AgOTf (61 mg, 0.24 mmol) and $C_9H_{19}Br$ (0.45 mL, 2.35 mmol). The mixture was stirred under reflux for 30 h, then diluted with CH_2Cl_2 (10 mL), filtered, and evaporated. The residue was purified on a column of flash silica (3:2 light petroleum/Et_2O) to give pure **16** (0.23 g, 61%), a colourless oil that crystallized from cooled (−10 °C) CH_2Cl_2/hexane as colourless needles, mp 31–32 °C, $[\alpha]_D$ +11.6 (*c* 1.8, $CHCl_3$), R_f=0.33 (1:1 Et_2O/light petroleum). IR (neat): ν_{max} 1790 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.7 Hz, Me), 1.18–1.49 (m, 12H, 6×CH_2), 1.58 (m, 2H, CH_2), 2.72 (d, 2H, 2×H-2), 3.46 (m, 2H, O*C*$H_2$$CH_2$), 3.65 (d, 2H, $J_{6,7}$=5.4 Hz, H-7), 4.20 (d, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.25 (m, 1H, H-6), 4.60 and 4.70 (2×d, 2H, J_{gem}=11.9 Hz, C*H*$_2$Ph), 4.93 (d, 1H, $J_{3,4}$=4.8 Hz, H-4), 4.99 (m, 1H, H-3), 7.29–7.46 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (Me), 22.6, 26.0, 29.2, 29.4, 29.45, 29.5, 31.8 (7×CH_2) 35.9 (C-2), 68.5 (2×H-7), 71.7 (O*C*$H_2$$CH_2$), 72.6 (Ph*C*$H_2$), 76.7 (C-3), 79.5 (C-6), 81.3 (C-5), 85.3 (C-4), 127.6, 128.1, 128.5, 137.0 (Ph), 175.3 (C-1). LRMS (ESI): *m/z* 391 (M^++H). Anal. Found: C, 70.47; H, 8.70. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78.

*4.1.8. 3,6-Anhydro-2-deoxy-7-O-nonyl-D-ido-heptono-1,4-lactone (**3**).* A solution of **16** (0.11 g, 0.28 mmol) in MeOH (4 mL) was hydrogenated over 10% Pd/C (21 mg, 0.02 mmol) at room temperature and normal pressure of H_2 for 18 h, then filtered through a Celite pad, washed with MeOH, and evaporated. The residue was purified by flash column chromatography (7:3 CH_2Cl_2/EtOAc), to afford pure **3** (81 mg, 96%) as a colourless syrup oil that crystallized from CH_2Cl_2/hexane, as transparent needles, mp 51–52 °C, $[\alpha]_D$ +29.7 (*c* 1.9, $CHCl_3$), R_f=0.40 (7:3 CH_2Cl_2/EtOAc). IR (neat): ν_{max} 3286 (OH), 1776 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J*=6.8 Hz, Me), 1.11–1.39 (m, 12H, 6×CH_2), 1.57 (m, 2H, CH_2), 2.65 (dd, 1H, $J_{2a,2b}$=18.7 Hz, $J_{2a,3}$=1.0 Hz, H-2a), 2.76 (dd, 1H, $J_{2a,2b}$=18.7 Hz, $J_{2b,3}$=5.4 Hz, H-2b), 3.49 (m, 2H, O*C*$H_2$$CH_2$), 3.85 (m, 2H, 2×H-7), 4.10 (m, 1H, H-6), 4.28 (d, 1H, $J_{5,OH}$=3.8 Hz, OH), 4.50 (dd, 1H, $J_{5,6}$=3.1 Hz, $J_{5,OH}$=3.8 Hz, H-5), 4.86 (d, 1H, $J_{3,4}$=4.2 Hz, H-4), 5.01 (ddd, 1H, $J_{2a,3}$=1.0 Hz, $J_{2b,3}$=5.4 Hz, $J_{3,4}$=4.2 Hz, H-3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (Me), 22.6, 25.8, 29.1, 29.26, 29.3, 29.4, 31.7 (7×CH_2) 36.0 (C-2), 69.4 (C-7), 72.5 (O*C*$H_2$$CH_2$), 75.8 (C-5), 76.8 (C-3), 78.5 (C-6), 88.2 (C-4), 175.5 (C-1). LRMS (ESI): *m/z* 301 (M^++H), 601 (2 M^++H).

*4.1.9. 3,6-Anhydro-5-O-benzyl-7-O-decyl-2-deoxy-D-ido-heptono-1,4-lactone (**17**).* To a solution of **15** (0.18 g, 0.66 mmol) in dry Et_2O (3.5 mL) were added successively Ag_2O (0.39 g, 1.66 mmol), AgOTf (43 mg, 0.17 mmol) and $C_{10}H_{21}Br$ (0.35 mL, 1.66 mmol). The mixture was heated under reflux for 31 h, then cooled to room temperature, diluted with CH_2Cl_2 (5 mL), filtered, and evaporated. Flash column chromatography (4:1→7:3 hexane/Et_2O) of the residue gave pure **17** (0.14 g, 51%) as a colourless oil, $[\alpha]_D$ +13.1 (*c* 1.0, $CHCl_3$), R_f=0.25 (1:1 hexane/Et_2O). Anal. Found: C, 71.14; H, 8.72. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Spectroscopic data of thus prepared sample **17** matched those previously reported by us.[14]

*4.1.10. 3,6-Anhydro-7-O-decyl-2-deoxy-D-ido-heptono-1,4-lactone (**4**).* A solution of **17** (0.15 g, 0.37 mmol) in EtOH (3 mL) was hydrogenated over 10% Pd/C (76 mg, 0.07 mmol) at room temperature and normal pressure of H_2 for 20 h. The suspension was filtered through a Celite pad and washed with ether. The combined filtrates were evaporated and the residue purified by flash column chromatography (4:1 Et_2O/hexane→Et_2O), to afford pure **4** (0.1 g, 86%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave an analytical sample **4**, as colourless needles, mp 59–60 °C, $[\alpha]_D$ +35.4 (*c* 0.45, $CHCl_3$), R_f=0.24 (4:1 Et_2O/hexane). Anal. Found: C, 64.66; H, 9.86. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Spectroscopic data of thus prepared sample **4** matched those previously reported by us.[14]

*4.1.11. 3,6-Anhydro-5-O-benzyl-2-deoxy-7-O-undecyl-D-ido-heptono-1,4-lactone (**18**).* A mixture of **15** (84 mg, 0.32 mmol), Ag_2O (0.2 g, 0.85 mmol), AgOTf (17 mg, 0.07 mmol) and $C_{11}H_{23}Br$ (0.18 mL, 0.81 mmol) in anhydrous Et_2O (2 mL) was heated under reflux for 48 h. After the mixture cooled to room temperature it was diluted with CH_2Cl_2 (5 mL), filtered, and evaporated. Flash column chromatography (3:2 light petroleum/Et_2O) of the residue gave pure lactone **18** (74 mg, 56%) as a colourless oil, $[\alpha]_D$ +10.9 (*c* 0.19, $CHCl_3$), R_f=0.23 (3:2 light petroleum/Et_2O). IR (neat): ν_{max} 1790 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J*=6.8 Hz, Me), 1.12–1.41 (m, 16H, 8×CH_2), 1.58 (m, 2H, $OCH_2CH_2CH_2CH_2$), 2.70 (m, 2H, 2×H-2), 3.46 (m, 2H, O*C*$H_2$$CH_2$), 3.64 (d, 2H, $J_{6,7}$=5.3 Hz, H-7), 4.20 (d, 1H, $J_{5,6}$=4.0 Hz, H-5), 4.24 (m, 1H, H-6), 4.59 and 4.70 (2×d, 2H, J_{gem}=11.9 Hz, C*H*$_2$Ph), 4.92 (d, 1H, $J_{3,4}$=4.7 Hz, H-4), 4.97 (m, 1H, H-3), 7.29–7.40 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 22.7, 26.1, 29.3, 29.4, 29.6, 31.9 (9×CH_2), 36.0 (C-2), 68.5 (C-7), 71.8 ($OCH_2CH_2CH_2CH_2$), 72.7 (*C*H_2Ph), 76.8 (C-3), 79.6 (C-6), 81.4 (C-5), 85.5 (C-4), 127.7, 128.1, 128.6, 137.2 (Ph), 175.4 (C-1). HRMS (ESI): *m/z* 441.2625 (M^++Na), calcd for $C_{25}H_{38}NaO_5$: 441.2612; *m/z* 457.2370 (M^++K), calcd for $C_{25}H_{38}KO_5$: 457.2351.

*4.1.12. 3,6-Anhydro-2-deoxy-7-O-undecyl-D-ido-heptono-1,4-lactone (**5**).* A solution of benzyl ether **18** (59 mg, 0.14 mmol) in MeOH (1.5 mL) was hydrogenated over 10% Pd/C (30 mg, 0.03 mmol) at room temperature and normal pressure of H_2 for 3.5 h. The suspension was filtered through a Celite pad and washed with MeOH. The combined filtrates were evaporated and the residue purified by flash column chromatography (24:1 CH_2Cl_2/MeOH) to afford pure **5** (38 mg, 83%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane gave transparent needles, mp 60 °C, $[\alpha]_D$ +27.3 (*c* 0.98, $CHCl_3$), R_f=0.49 (19:1 CH_2Cl_2/MeOH). IR (neat): ν_{max} 3484–3275 (OH), 1790 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J*=6.7 Hz, Me), 1.12–1.39 (m, 16H, 8×CH_2), 1.57 (m, 2H, CH_2), 2.65 (dd, 1H, $J_{2a,3}$=1.2 Hz, $J_{2a,2b}$=18.6 Hz, H-2a), 2.76 (dd, 1H, $J_{2b,3}$=5.3 Hz, $J_{2a,2b}$=18.7 Hz, H-2b), 3.51 (m, 2H, O*C*$H_2$$CH_2$), 3.84 (dd, 1H, $J_{6,7a}$=3.2 Hz, $J_{7a,7b}$=11.0 Hz, H-7a), 3.90 (dd, 1H, $J_{6,7b}$=3.3 Hz, $J_{7a,7b}$=11.2 Hz, H-7b), 4.11 (m, 1H, H-6), 4.52 (d, 1H, $J_{5,6}$=3.2 Hz, H-5), 4.86 (d, 1H, $J_{3,4}$=4.2 Hz, H-4), 5.02 (m, 1H, H-3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (Me), 22.6, 25.9, 29.2, 29.3, 29.36, 29.4, 29.5, 31.8 (9×CH_2), 36.0 (C-2), 69.5 (C-7), 72.6 (O*C*$H_2$$CH_2$), 76.0 (C-5), 76.8 (C-3), 78.6 (C-6), 88.2 (C-4), 175.4 (C-1). HRMS (ESI): *m/z* 329.2317 (M^++H), calcd for $C_{18}H_{33}O_5$: 329.2322; *m/z* 351.2146 (M^++Na), calcd for $C_{18}H_{32}NaO_5$: 351.2142.

*4.1.13. 3,6-Anhydro-5-O-benzyl-2-deoxy-D-glycero-D-ido-octono-1,4-lactone (**20**).* To a solution of **19** (0.25 g, 0.94 mmol) in dry DMF (2.5 mL) were added anhydrous Et_3N (0.52 mL, 3.73 mmol) and Meldrum's acid (0.55 g, 3.85 mmol). The resulting reaction mixture was stirred at 46–48 °C for 70 h, and then evaporated. Purification by flash column chromatography (4:1 EtOAc/light petroleum) gave **20** (0.12 g, 43%) as a white solid. Recrystallization from a mixture of CH_2Cl_2/hexane gave pure **20** as a colourless powder, mp 104–105 °C, $[\alpha]_D$ +32.2 (*c* 0.5, EtOH); R_f=0.2 (Et_2O). IR (KBr): ν_{max} 3444 (OH), 1784 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.64 (d, 1H, $J_{2a,2b}$=18.5 Hz, H-2a), 2.74 (dd, 1H, $J_{2a,2b}$=18.5 Hz, $J_{3,2b}$=4.5 Hz, H-2b), 3.66 (dd, 1H, $J_{7,8a}$=4.7 Hz, $J_{8a,8b}$=12.7 Hz, H-8a), 3.79 (dd, 1H, $J_{7,8b}$=2.7 Hz, $J_{8a,8b}$=12.7 Hz, H-8b), 3.94–4.04 (m, 2H, H-5 and H-7), 4.35 (d, 1H, *J*=2.5 Hz, H-6), 4.65 and 4.75 (2×d, 2H, J_{gem}=11.7 Hz, Ph*C*H_2), 4.91–4.98 (m, 2H, H-3 and H-4), 7.31–7.43 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.0 (C-2), 64.2 (C-8), 69.2 (C-7), 72.9 (Ph*C*H_2), 77.1 (C-3), 80.2 (C-5), 81.4 (C-6), 85.0 (C-4), 128.0, 128.5,

128.8, 136.8 (Ph), 175.4 (C-1). HRMS (ESI): *m/z* 317.0999 (M^++Na), calcd for $C_{15}H_{18}NaO_6$: 317.0996.

*4.1.14. 3,6-Anhydro-5-O-benzyl-2,7,8-trideoxy-D-ido-oct-7-enono-1,4-lactone (**21**).* To a mixture of iodine (0.55 g, 2.18 mmol), imidazole (0.26 g, 4.40 mmol) and Ph_3P (0.56 g, 2.14 mmol) in dry MeCN (4.0 mL) was added a solution of **20** (0.16 g, 0.53 mmol) in dry MeCN (4 mL). The mixture was stirred at 90 °C (bath temperature) for 1.5 h, in an atmosphere of N_2, and then evaporated. Flash column chromatography (1:1 Et_2O/light petroleum) of the residue yielded pure **21** (0.13 g, 93%) as a white solid. Recrystallization from CH_2Cl_2/hexane/Et_2O afforded colourless needles, mp 62–63 °C, $[\alpha]_D$ +11.2 (*c* 1.0, $CHCl_3$), R_f=0.29 (1:1 Et_2O/light petroleum). IR ($CHCl_3$): ν_{max} 1789 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.66 (dd, 1H, $J_{2a,2b}$=18.9 Hz, $J_{2a,3}$=1.7 Hz, H-2a), 2.76 (dd, 1H, $J_{2b,3}$=4.8 Hz, $J_{2a,2b}$=18.9 Hz, H-2b), 4.14 (d, 1H, $J_{5,6}$=3.6 Hz, H-5), 4.51 (dd, 1H, $J_{5,6}$=3.7 Hz, $J_{6,7}$=7.0 Hz, H-6), 4.62 and 4.68 (2×d, 2H, J_{gem}=12.1 Hz, CH_2Ph), 4.80–5.00 (m, 2H, H-3 and H-4), 5.35 (dd, 1H, $J_{7,8a}$=10.4 Hz, $J_{8a,8b}$=1.0 Hz, H-8a), 5.42 (dd, 1H, $J_{7,8b}$=17.3 Hz, $J_{8a,8b}$=1.0 Hz, H-8b), 6.01 (ddd, 1H, $J_{6,7}$=7.0 Hz, $J_{7,8a}$=10.4 Hz, $J_{7,8b}$=17.3 Hz, H-7), 7.27–7.42 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 35.9 (C-2), 72.7 (CH_2Ph), 76.4 (C-3), 81.9 (C-6), 82.6 (C-5), 85.8 (C-4), 119.4 (C-8), 127.6, 128.0, 128.5, 137.0 (Ph), 132.0 (C-7), 175.3 (C-1). HRMS (ESI): *m/z* 261.1112 (M^++H), calcd for $C_{15}H_{17}O_4$: 261.1121.

*4.1.15. (E)-3,6-Anhydro-5-O-benzyl-2,7,8-trideoxy-8-C-nonyl-D-ido-oct-7-enono-1,4-lactone (**22**).* To a solution of **21** (79 mg, 0.30 mmol) in dry CH_2Cl_2 (1.6 mL) were added undec-1-ene (0.5 mL, 2.43 mmol) and the second generation Grubbs catalyst (25 mg, 0.03 mmol). The mixture was stirred in an argon atmosphere for 24 h at room temperature. The solvent was removed under vacuum and the mixture purified by flash column chromatography (CH_2Cl_2). Eluted first was pure **22** (80 mg, 68%), isolated as a colourless oil, $[\alpha]_D$ +7.5 (*c* 0.99, $CHCl_3$), R_f=0.35 (CH_2Cl_2). IR (neat): ν_{max} 1790 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.9 (t, 3H, *J*=7.0 Hz, Me), 1.06–1.49 (m, 14H, 7×CH_2), 2.10 (m, 2H, 2×H-9), 2.63 (d, 1H, $J_{2a,2b}$=17.8 Hz, H-2a), 2.75 (dd, 1H, $J_{2a,2b}$=17.8 Hz, $J_{2b,3}$=4.7 Hz, H-2b), 4.07 (d, 1H, $J_{5,6}$=3.4 Hz, H-5), 4.46 (dd, 1H, $J_{5,6}$=3.4 Hz, $J_{6,7}$=7.7 Hz, H-6), 4.61 and 4.67 (2×d, 2H, J_{gem}=12.1 Hz, CH_2Ph), 4.90–4.98 (m, 2H, H-3 and H-4), 5.66 (dd, 1H, $J_{6,7}$=7.8 Hz, $J_{7,8}$=15.5 Hz, H-7), 5.85 (dt, 1H, $J_{7,8}$=15.5 Hz, $J_{8,9}$=6.5 Hz, H-8), 7.29–7.42 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (Me), 22.6, 28.8, 29.1, 29.2, 29.4, 29.6, 31.8, 32.3 (8×CH_2), 36.0 (C-2), 72.6 (CH_2Ph), 76.1 (C-3), 81.8 (C-5), 82.5 (C-6), 85.9 (C-4), 123.2 (C-7), 127.5, 127.9, 128.4 (Ph), 137.2 (C-8), 175.4 (C-1). HRMS (ESI): *m/z* 387.2517 (M^++H), calcd for $C_{24}H_{35}O_4$: 387.2530; *m/z* 425.2077 (M^++K), calcd for $C_{24}H_{34}KO_4$: 425.2089. Eluted second was unchanged starting compound **21** (0.019 g, 25%).

*4.1.16. 3,6-Anhydro-2-deoxy-6-C-undecyl-D-ido-hexono-1,4-lactone (**6**).* To a stirred solution of **22** (57 mg, 0.15 mmol) in dry MeOH (1.13 mL) was added 10% Pd/C (78 mg, 0.07 mmol). The suspension was hydrogenated at room temperature and normal pressure of H_2 for 3 h, then filtered through a Celite pad, washed with 1:1 CH_2Cl_2/EtOAc, and evaporated. Flash chromatography (7:3 Et_2O/light petroleum) of the residue gave pure **6** (36 mg, 82%) as a white solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 74–75 °C, $[\alpha]_D$ +23.9 (*c* 0.51, $CHCl_3$), R_f=0.18 (7:3 Et_2O/light petroleum). IR ($CHCl_3$): ν_{max} 1779 (C=O), 3389 (OH). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J*=6.9 Hz, Me), 1.16–1.72 (m, 20H, 10×CH_2), 2.32 (br s, 1H, OH), 2.62 (d, 1H, $J_{2a,2b}$=18.9 Hz, H-2a), 2.77 (dd, 1H, $J_{2a,2b}$=18.9 Hz, $J_{2b,3}$=5.9 Hz, H-2b), 3.91 (td, 1H, $J_{5,6}$=2.6 Hz, $J_{6,7}$=6.7 Hz, H-6), 4.27 (d, 1H, $J_{5,6}$=2.6 Hz, H-5), 4.87–4.98 (m, 2H, H-3 and H-4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 22.6, 26.1, 27.8, 29.4, 29.5, 29.6, 29.62, 31.8 (10×CH_2), 35.9 (C-2), 74.4 (C-5), 75.6 (C-3), 80.5 (C-6), 87.8 (C-4), 175.9 (C-1). HRMS (ESI): *m/z* 299.2213 (M^++H), calcd for $C_{17}H_{31}O_4$: 299.2217; *m/z* 316.2475 (M^++NH_4), calcd for $C_{17}H_{34}NO_4$: 316.2482; *m/z* 337.1772 (M^++K), calcd for $C_{17}H_{30}KO_4$: 337.1776.

*4.1.17. (E)-3,6-Anhydro-5-O-benzyl-8-C-decyl-2,7,8-trideoxy-D-ido-oct-7-enono-1,4-lactone (**23**).* To a solution of **21** (32 mg, 0.12 mmol) in dry CH_2Cl_2 (0.65 mL) was added dodec-1-ene (0.27 mL, 1.22 mmol) and the second generation Grubbs catalyst (8 mg, 0.01 mmol). The mixture was stirred in an argon atmosphere for 68 h at room temperature. The solvent was removed in vacuum and the mixture purified by flash column chromatography (CH_2Cl_2) to afford pure **23** (34 mg, 69%) as a pale yellow oil, $[\alpha]_D$ +11.2 (*c* 0.52, $CHCl_3$), R_f=0.38 (1:1 Et_2O/light petroleum). IR (neat): ν_{max} 1790 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J*=6.8 Hz, Me), 1.02–1.49 (m, 16H, 8×CH_2), 2.09 (m, 2H, 2×H-9), 2.64 (d, 1H, $J_{2a,2b}$=17.6 Hz, H-2a), 2.74 (dd, 1H, $J_{2b,3}$=4.6 Hz, $J_{2a,2b}$=17.6 Hz, H-2b), 4.01 (d, 1H, $J_{5,6}$=3.4 Hz, H-5), 4.45 (dd, 1H, $J_{5,6}$=3.4 Hz, $J_{6,7}$=7.7 Hz, H-6), 4.61 and 4.67 (2×d, 2H, J_{gem}=12.1 Hz, CH_2Ph), 4.89–4.99 (m, 2H, H-3 and H-4), 5.65 (dd, 1H, $J_{6,7}$=7.8 Hz, $J_{7,8}$=15.5 Hz, H-7), 5.84 (dt, 1H, $J_{7,8}$=15.5 Hz, $J_{8,9}$=6.6 Hz, H-8), 7.29–7.43 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (Me), 22.6, 28.8, 29.1, 29.2, 29.4, 29.5, 31.8, 32.8 (9×CH_2), 36.0 (C-2), 72.7 (CH_2Ph), 76.2 (C-3), 81.9 (C-5), 82.6 (C-6), 85.9 (C-4), 123.3 (C-7), 127.6, 128.0, 128.4, 136.6 (Ph), 137.2 (C-8), 175.5 (C-1). HRMS (ESI): *m/z* 383.2572 (M^++H−H_2O), calcd for $C_{25}H_{35}O_3$: 383.2581; *m/z* 423.2486 (M^++Na), calcd for $C_{25}H_{36}NaO_4$: 423.2506.

*4.1.18. 3,6-Anhydro-2-deoxy-6-C-dodecyl-D-ido-hexono-1,4-lactone (**7**).* To a stirred solution of **23** (54 mg, 0.13 mmol) in dry MeOH (1 mL) was added 10% Pd/C (61 mg, 0.06 mmol). The suspension was hydrogenated at room temperature and normal pressure of H_2 for 4.5 h, then filtered through a Celite pad, washed with 1:1 CH_2Cl_2/EtOAc, and evaporated. Flash chromatography (3:2 Et_2O/light petroleum) of the residue gave pure **7** (24 mg, 57%) as a white solid. Recrystallization from CH_2Cl_2/hexane gave colourless needles, mp 88–89 °C, $[\alpha]_D$ +19.3 (*c* 0.52, $CHCl_3$), R_f=0.32 (1:1 Et_2O/light petroleum). IR (neat): ν_{max} 1779 (C=O), 3394 (OH). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J*=6.7 Hz, Me), 1.12–1.73 (m, 22H, 11×CH_2), 2.34 (br s, 1H, OH), 2.62 (d, 1H, $J_{2a,2b}$=18.9 Hz, H-2a), 2.78 (dd, 1H, $J_{2a,2b}$=18.9 Hz, $J_{2b,3}$=5.9 Hz, H-2b), 3.91 (td, 1H, $J_{5,6}$=2.6 Hz, $J_{6,7}$=6.8 Hz, H-6), 4.27 (d, 1H, $J_{5,6}$=2.5 Hz, H-5), 4.87–4.99 (m, 2H, H-3 and H-4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 22.6, 26.1, 27.8, 29.3, 29.4, 29.5, 29.6, 29.62, 31.9 (11×CH_2), 35.8 (C-2), 74.4 (C-5), 75.6 (C-3), 80.5 (C-6), 87.8 (C-4), 175.8 (C-1). HRMS (ESI): *m/z* 313.2373 (M^++H), calcd for $C_{18}H_{33}O_4$: 313.2373; *m/z* 330.2634 (M^++NH_4), calcd for $C_{18}H_{36}NO_4$: 330.2639.

*4.1.19. 1,2-O-Cyclohexylidene-5-deoxy-5-C-dodecyl-α-D-xylo-pentofuranose (**25**).* A crystal of iodine was added to a suspension of magnesium turnings (0.75 g, 30 mmol) in dry THF (15 mL) and then dodecylbromide (7.5 g, 30 mmol) was added while stirring, in one portion at room temperature. The reaction started spontaneously and was completed after 1 h at reflux, whereupon the complete dissolution of magnesium was observed. To this mixture was added a solution of **24** (6.3 g, 30 mmol) in dry THF (15 mL) and the stirring under reflux was continued for the next 4 h. The mixture was quenched by the addition of 10% aq hydrochloric acid (100 mL) and products were extracted with light petroleum (3×50 mL). The combined organic layers were washed with 20% aq $NaHCO_3$ (50 mL), dried, discoloured with activated carbon and evaporated. Flash column chromatography (C_6H_6) of the residue (9.6 g) gave pure **25** (6.4 g, 56%) as a white waxy solid, $[\alpha]_D$ −9.5 (*c* 1.1, $CHCl_3$), R_f=0.69 (1:1 Et_2O/light petroleum). IR (neat): ν_{max} 3409 (OH). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, 3H, *J*=6.8 Hz, Me), 1.18–1.77 (m, 34H, 17×CH_2), 2.54 (br s, 1H, OH), 4.00 (d, 1H, $J_{3,4}$=2.4 Hz, H-3), 4.07 (dt, 1H, $J_{3,4}$=2.2 Hz, $J_{4,5}$=6.7 Hz, H-4), 4.46 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 5.86 (d, 1H, $J_{1,2}$=3.8 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 14.0 (Me), 22.6, 23.4, 23.8, 24.8, 26.0, 27.5, 29.3, 29.46, 29.5, 29.6, 29.7, 31.8, 35.5,

36.1 (17×CH_2), 60.7 (C-7), 75.2 (C-3), 80.3 (C-4), 84.7 (C-2), 103.6 (C-1), 111.9 (qC). LRMS (ESI): *m/z* 383 (M^++H), 382 (M^+). HRMS (ESI): *m/z* 421.2711 (M^++K), calcd for $C_{23}H_{42}KO_4$: 421.2715.

*4.1.20. 5-Deoxy-5-C-dodecyl-D-xylo-pentofuranose (**26**).* A solution of **25** (0.26 g, 0.68 mmol) in 70% aq AcOH (10 mL) was stirred for 3.5 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 (EtOAc), to afford pure **26** (0.12 g, 57%) as a colourless solid. Recrystallization from a mixture of MeOH/H_2O gave an analytical sample **26**, as transparent needles, mp 115–117 °C, $[\alpha]_D$ +12.4 (*c* 0.50, MeOH) the initial $[\alpha]_D$ value that mutarotated to +4.2 after equilibration for 71 h, R_f=0.32 (EtOAc). IR (KBr): ν_{max} 3381 (OH). ^{1}H NMR (250 MHz, acetone-d_6): δ 0.81 (t, 6H, *J*=6.8 Hz, Me α and β), 1.11–1.67 (m, 48H, 12×CH_2 α and β), 3.82–4.21 (m, 6H, H-2, H-3, H-4 α and β), 4.97 (s, 1H, H-1β), 5.30 (d, 1H, $J_{1,2}$=3.7 Hz, H-1α). ^{13}C NMR (62.9 MHz, methanol-d_4): δ 14.5 (Me), 23.8, 27.1, 27.3, 30.0, 30.5, 30.76, 30.8, 30.9, 33.1 (13×CH_2 α and β), 77.2, 77.9, 78.4, 80.3, 82.6 and 83.4 (C-2, C-3 and C-4, α and β), 97.3 (C-1α), 104.0 (C-1β). HRMS (ESI): *m/z* 347.2444 (M+$HCOO^-$), calcd for $C_{18}H_{35}O_6$: 347.2439.

*4.1.21. 3,6-Anhydro-2-deoxy-6-C-tridecyl-D-ido-hexono-1,4-lactone (**8**).* To a solution of **26** (76 mg, 0.25 mmol) in dry DMF (1 mL) were added Meldrum's acid (80 mg, 0.56 mmol) and dry Et_3N (0.07 mL, 0.51 mmol). The mixture was stirred for 48 h at 46 °C and then evaporated. The residue was purified by flash chromatography (4:1 Et_2O/light petroleum) to afford pure **8** (54 mg, 66%) as a colourless solid. Recrystallization from CH_2Cl_2/hexane, gave colourless needles, mp 92 °C, $[\alpha]_D$ +16.2 (*c* 1.09, $CHCl_3$), R_f=0.30 (4:1 CH_2Cl_2/EtOAc). IR ($CHCl_3$): ν_{max} 3384 (OH), 1777 (C=O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.83 (t, 3H, *J*=6.7 Hz, Me), 1.12–1.71 (m, 24H, 12×CH_2), 2.20 (br s, 1H, OH), 2.62 (d, 1H, $J_{2a,2b}$=18.9 Hz, H-2a), 2.77 (dd, 1H, $J_{2a,2b}$=18.9 Hz, $J_{2b,3}$=5.8 Hz, H-2b), 3.91 (td, 1H, $J_{5,6}$=2.7 Hz, $J_{6,7}$=6.8 Hz, H-6), 4.27 (d, 1H, $J_{5,6}$=2.7 Hz, H-5), 4.88–4.98 (m, 2H, H-3 and H-4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.1 (Me), 22.6, 26.1, 27.8, 29.3, 29.4, 29.5, 29.6, 31.9 (12×CH_2), 35.9 (C-2), 74.3 (C-5), 75.6 (C-3), 80.5 (C-6), 87.8 (C-4), 175.9 (C-1). HRMS (ESI): *m/z* 327.2525 (M^++H), calcd for $C_{19}H_{35}O_4$: 327.2530; *m/z* 349.2347 (M^++Na), calcd for $C_{19}H_{34}NaO_4$: 349.2349; *m/z* 365.2084 (M^++K), calcd for $C_{19}H_{34}KO_4$: 365.2089.

4.2. X-ray crystal structure determination

Single colourless crystals of compounds **7** and **8** were selected and glued on glass fibres. 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 MoKα (λ=0.71073 Å) X-radiation was employed in both measurements. The frame width of 1° in ω, with 40 and 154 s were used to acquire each frame for both **7** and **8**. More than one hemisphere of three-dimensional data was collected in the measurement. The data were reduced using the Oxford Diffraction program CrysAlisPro.[22] A semi empirical absorption-correction based upon the intensities of equivalent reflections was applied, and the data were corrected for Lorentz, polarization, and background effects. The structure was solved by direct methods[23] and the figures were drawn using Mercury v. 2.4.[24] Refinements were based on F^2 values and done by full-matrix least-squares[25] 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. At the final stage of the refinement H atoms were positioned geometrically (O–H=0.82 and C–H=0.96–0.98 Å) and refined using a riding model with fixed isotropic displacement parameters. The crystal data and refinement parameters are listed in Table S1 in Supplementary data.

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) or 5×10^3 (HT-29, MDA-MB-231, HeLa, and MRC-5) cells per well to assure logarithmic growth rate throughout the assay period. Antiproliferative activity was evaluated by the tetrazolium colorimetric MTT assay, after exposure of cells to the tested compounds for 72 h, following the recently reported procedure.[14]

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Supplementary data

More detailed description of the crystallographic results. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.132.

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Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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