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Enantiodivergent synthesis of muricatacin related lactones from D-xylose based on the latent symmetry concept: preparation of two novel cytotoxic (+)- and (−)-muricatacin 7-oxa analogs

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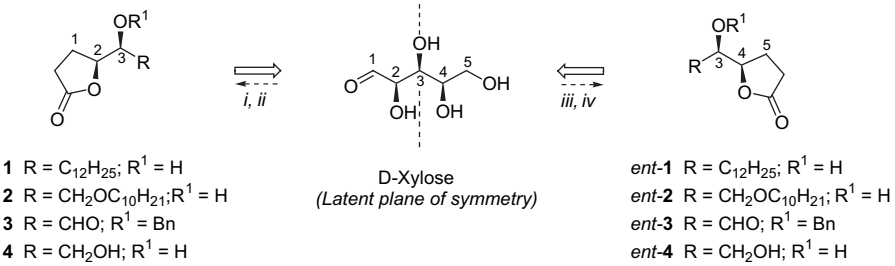
Abstract—Enantiodivergent formal synthesis of (+)- and (−)-muricatacins from D-xylose has been accomplished through utilization of the latent plane of symmetry present in the starting monosaccharide. This approach was extended to the preparation of two novel (+)- and (−)-muricatacin 7-oxa analogs (**2** and *ent*-**2**, respectively), which showed in vitro antitumor activity toward some human malignant cells. The analog *ent*-**2** showed a powerful antiproliferative activity against the K562 cell line, being 36-fold more potent than the standard cytotoxic agent, doxorubicin. Compound **2**, however, showed a powerful cytotoxic activity against HL-60 cells, being more than 17-fold more potent with respect to the reference compound.

1. Introduction

Development of efficient chemical pathways that allow the preparation of both enantiomers of compounds of biomedicinal interest is an important goal in the synthetic organic chemistry. Enantiomers of biologically active natural products often exhibit improved potencies or even novel activities altogether. For example, the unnatural (−)-enantiomer of the antitumor, antibiotic roseophilin is 2–10 times more potent than the natural (+)-isomer in cytotoxicity assays.[1] Numerous nucleoside analogs of natural D-configuration displayed a potent antitumor or antiviral activity, but most of them were found to be too toxic for general clinical applications. On the contrary, the corresponding L-configuration counterparts are not recognized by normal cellular enzymes and are less toxic to normal cells.[2] A number of biologically active natural products comprised of both (+)- and (−)-enantiomers have been described.[3,4] One such molecule that has attracted considerable attention since its isolation from the seeds of the tropical plant *Anona muricata*[4] is muricatacin (5-hydroxy-4-heptadecanolide), an acetogenin derivative that shows strong cytotoxic activity against certain human tumor cell lines. The isolated sample was a mixture of enantiomers **1** and *ent*-**1** (Scheme 1) with the (−)-(*R*,*R*)-isomer



Scheme 1. Enantiodivergent strategy for the preparation of (+)- and (−)-muricatacin related lactones by chirality transfer from D-xylose (sugar numbering). (i) 'CH_2CO_2R'—introduction at C-1 followed by γ-lactonization, (ii) oxidative glycol cleavage of the C_4–C_5 bond, (iii) 'CH_2CO_2R'—elongation at C-5 followed by γ-lactonization, (iv) C_1–C_2 glycol cleavage.

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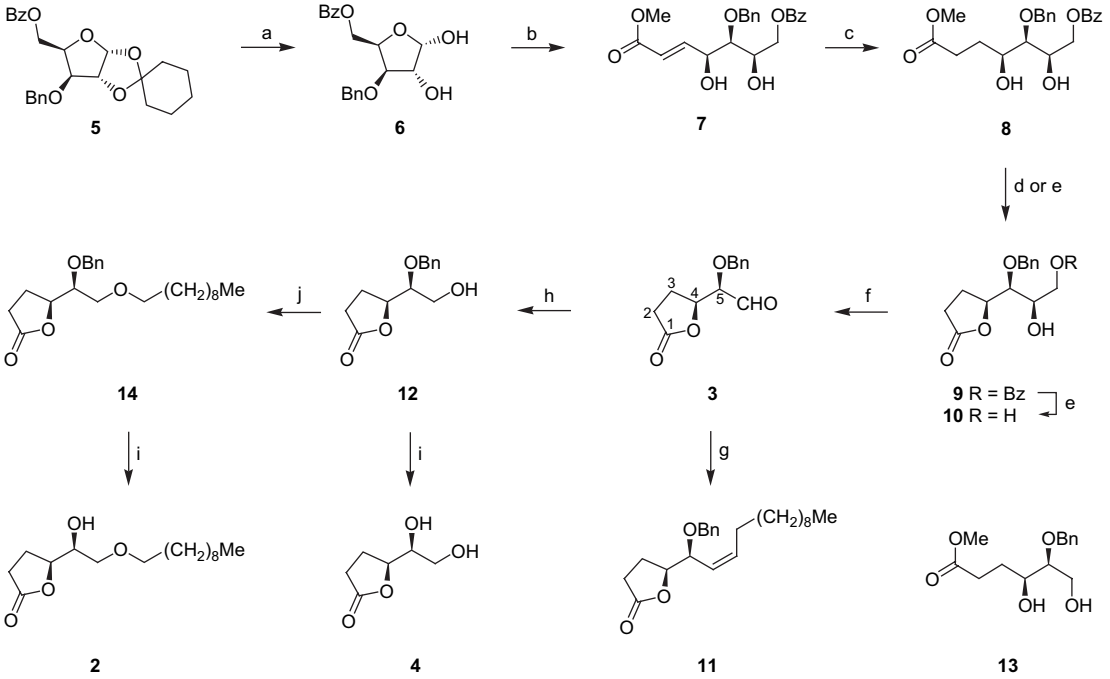
ent-**1** being predominant (ee, ca. 25%). Both (+)- and (−)-muricatacins show similar antitumor potency,[4,5] and not surprisingly were the object of numerous synthetic efforts. Syntheses of (+)- and/or (−)-muricatacin from various non-carbohydrate precursors have been reported,[5,6] along with a number of carbohydrate based approaches,[7,8] most being target oriented. Hence, development of new and flexible strategy that would enable the preparation of not only both enantiomers **1** and *ent*-**1**, but also a variety of their isosteric analogs is still demanded. A number of muricatacin stereoisomers and analogs have also been synthesized,[9,10] but only a few have been evaluated for their antitumor activity.[10] Herein we report a novel general approach to the enantiodivergent formal synthesis of (+)- and (−)-muricatacins from D-xylose[11] based on the latent symmetry concept,[12] as well as the preparation and antitumor screening of two novel (+)- and (−)-muricatacin 7-oxa analogs **2** and *ent*-**2**.

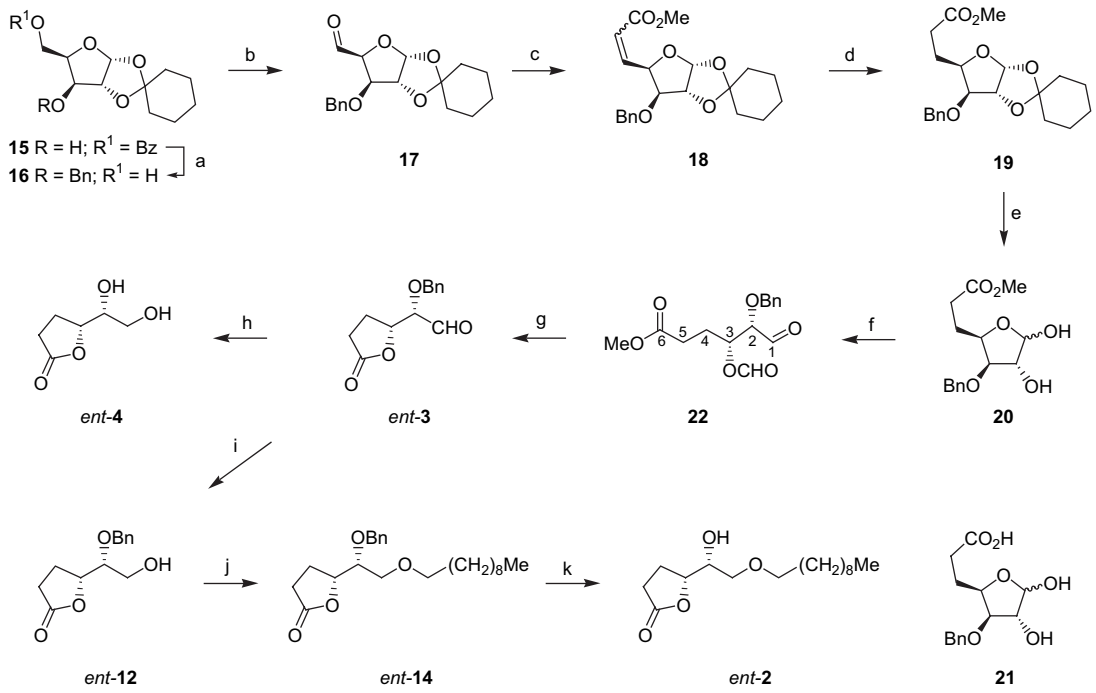
2. Results and discussion

Our enantiodivergent strategy relies on the synthesis of both enantiomeric forms of aldehydo-lactone **3** from D-xylose. As outlined in Scheme 1, (+)-muricatacin (**1**) might be prepared by a sequence that will ensure the introduction of the C-2 and C-3 stereocenters of D-xylose into the target structure **1** via the aldehydo-lactone **3**. It was further assumed that the intermediate **3** should be available from a suitably protected D-xylose derivative through the following several key steps: (i) 'CH_2CO_2R'—introduction at C-1 followed by γ-lactonization and (ii) oxidative glycol cleavage of the C_4–C_5 bond. Due to the latent plane of symmetry present in the starting monosaccharide an alternative sequence, which involves (iii) 'CH_2CO_2R'—elongation at C-5 followed by γ-lactonization and (iv) C_1–C_2 glycol cleavage in a suitably protected D-xylose derivative, should provide access to the aldehydo-lactone *ent*-**3** bearing the C_3–C_4 chiral segment of D-xylose. It was further assumed that both intermediates **3** and *ent*-**3** could be converted to the targets **1** and *ent*-**1** by a Wittig elongation/catalytic reduction process. Alternatively, the chiral synthons **3** and *ent*-**3** may be first converted to the dihydroxylactones **4** and *ent*-**4** and finally to the targets **1** and *ent*-**1** via a known two-step sequence.[8] Moreover, we have also planned to adopt this enantiodivergent strategy for the preparation of both enantiomeric forms of hitherto unknown muricatacin 7-oxa analogs **2** and *ent*-**2** via the hydroxylactones **12** (Scheme 2) and *ent*-**12** (Scheme 3).

The formal synthesis of **1**, along with the preparation of corresponding 7-oxa-analog **2** is summarized in Scheme 2. The sequence started from 5-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-xylofuranose (**5**), which is prepared from D-xylose in four steps.[13] Hydrolytic removal of the cyclohexylidene protective group in **5** with aq acetic acid, gave the corresponding lactol **6**. Wittig olefination of **6** with methyl(triphenylphosphoranylidene)-acetate in DMF took place stereoselectively to afford the (*E*)-unsaturated ester **7** (83%) as the only isolable product. The *E*-selectivity of this step was essential, because it is well known that similar (*Z*)-α,β-unsaturated esters rapidly undergo a sequential lactonization/Michael ring-closure process.[16] Catalytic hydrogenation of **7** over PtO_2 in ethanol yielded the corresponding saturated ester **8**, which upon treatment with aq trifluoroacetic acid gave hydroxylactone **9** in excellent yield. Sodium methoxide O-debenzoylation of **9** furnished a moderate yield of dihydroxylactone **10**. By using the last two-step sequence ester **8** was converted to lactone **10** in 51% overall yield. However, we found that direct treatment of **8** with sodium methoxide in methanol provides the desired intermediate **10** in significantly higher yield (82%).



Scheme 2. (a) 7:3 AcOH/H_2O, reflux, 5.5 h, 85%; (b) $Ph_3P/CHCO_2Me$, DMF, 60–70 °C, 3.5 h, 84%; (c) H_2/PtO_2, EtOH, rt, 16 h, 75%; (d) 2:1 TFA/H_2O, rt, 2.5 h, 92%; (e) NaOMe, MeOH, rt, 1.5 h, 55% from **9**, 82% from **8**; (f) aq $NaIO_4$, silica gel, CH_2Cl_2, rt, 1 h, 89%; (g) $[Ph_3PCH_2(CH_2)_9Me]^+Br^-$, LiHMDS, THF, −78 °C→rt, 72 h, 7%; (h) (i) $NaBH_4$, MeOH, 0 °C→rt, 1.5 h, (ii) TFA, 2 h, 73%; (i) H_2-Pd/C, EtOAc, rt, 19 h, 69% of **4**, 82% of **2**; (j) $C_{10}H_{21}Br$, Ag_2O, AgOTf, Et_2O, reflux, 7.5 h, 80%.



Scheme 3. (a) (i) BnBr, NaH, DMF, 0 °C→rt, 2.5 h, (ii) NaOMe, MeOH, rt, 2 h, 89%; (b) DCC, anhyd H_3PO_4, Py, DMSO, rt, 3.5 h, 83%; (c) $Ph_3P/CHCO_2Me$, CH_2Cl_2, N_2, rt, 2 h, 97%; (d) H_2/PtO_2, EtOH, rt, 19 h, 92%; (e) 1:1 AcOH/H_2O, reflux, 1.5 h, 64% of **20**, 7% of **21**; (f) aq $NaIO_4$, silica gel, CH_2Cl_2, rt, 1.5 h, 98%; (g) 2:1 TFA/H_2O, rt, 1.5 h, 77% from **20**; (h) (i) $NaBH_4$, MeOH, 0 °C→rt, 2.5 h, (ii) TFA, 1 h, (iii) H_2-Pd/C, 19 h, 71%; (i) (i) $NaBH_4$, MeOH, 0 °C→rt, 2 h, (ii) TFA, 1 h, 68% from **20**; (j) $C_{10}H_{21}Br$, Ag_2O, AgOTf, Et_2O, reflux, 5.5 h, 71%; (k) H_2/PtO_2, EtOH, rt, 19 h, 87%.

Oxidative cleavage of the diol functionality in **10** was achieved by treatment with $NaIO_4$-impregnated wet silica in dichloromethane, whereby the aldehydo-lactone **3** was obtained. In the light of its stereochemical features the molecule **3** fully corresponds to the chiral lactone core of (+)-muricatacin (**1**).

With the requisite intermediate **3** in hand, we next focused on its C_{11}-elongation in order to elaborate the muricatacin side chain. According to the initial plan, Wittig olefination of aldehyde **3** with the appropriate C_{11}-ylide should enable us to resolve this problem. However, reaction of **3** with $Ph_3P{=}CH(CH_2)Me$ results in complex mixtures of products under a variety of experimental conditions, possibly because of the electrophilic nature of the lactone moiety. The best experimental protocol, which provides a poor yield (7%) of the desired olefin **11**, involved a reaction of aldehyde **3** with the Wittig reagent generated in situ from undecyltriphenylphosphonium bromide and LiHMDS in THF at −78 °C.[17] Disappointingly, all attempts to improve the outcome of this transformation were unsuccessful. We were therefore forced to find an alternative methodology for elaboration of the muricatacin side chain. According to the plan presented in Scheme 1, conversion of aldehyde **3** to the corresponding diol **4** represents a possible alternative route for completion of the synthesis.

The preparation of **4** began with the synthesis of the primary alcohol **12** from dihydroxylactone **10**. Oxidative cleavage of the terminal diol in **10** provided the aldehydo-lactone **3**, which was isolated in pure form after the usual work-up and used in the next step without further purification. Subsequent reduction of crude **3** with sodium borohydride gave the expected primary alcohol **12** along with an equal amount of ester **13**, as established from ^1H NMR of crude reaction mixture.[18] The mixture was not separated, but was further treated with aq trifluoroacetic acid to complete the lactonization of ester **13** into lactone **12**. The intermediate **12** was thus obtained in a 73% overall yield with respect to the starting compound **10** (based on recovered intermediate **3**). Catalytic hydrogenolysis of **12** (10% Pd/C) furnished the known diol **4**, which was recently used a convenient intermediate for the preparation of conformationally constrained analogs of diacylglycerol.[19] The ^1H and ^{13}C NMR spectral data and the optical rotation of diol **4** thus obtained were in full agreement with reported values.[19] Compound **4** can be converted to (+)-muricatacin according to the reported procedure.[8]

Hydroxylactone **12** also represents a divergent intermediate for the preparation of (+)-muricatacin 7-oxa analog **2**. Thus, O-alkylation of **12** with decyl bromide gave the corresponding 7-*O*-decyl derivative **14** (80%), which was subsequently *O*-debenzylated, under the conditions similar to those already used for the conversion of **12** to **4**. (+)-Muricatacin 7-oxa-analog **2** was thus obtained in 82% yield.

The 5-*O*-benzoyl-1,2-*O*-cyclohexylidene-α-D-xylofuranose (**15**), readily available from D-xylose,[14,15] was used as a starting material for the formal synthesis of (−)-muricatacin (*ent*-**1**), as well as for the preparation of its 7-oxa-analog *ent*-**2** (Scheme 3). Compound **15** was converted to the primary alcohol **16** through a simple one-pot procedure, which involved 3-O-benzylation of **15** (BnBr, NaH, DMF) followed by 5-O-debenzoylation of **5** (NaOMe, MeOH). The intermediate **16** was thus obtained in 89% overall yield with respect to **15**. Oxidation of the primary hydroxyl group in **16** gave the unstable[20] aldehyde **17** (83%), which upon treatment with methyl(triphenylphosphoranylidene)-acetate

in dry dichloromethane afforded the expected unsaturated ester **18** as a 2:1 mixture of the corresponding *Z*- and *E*-isomers. Catalytic hydrogenation of **18**, followed by hydrolytic removal of the cyclohexylidene protective group in **19**, gave a 64% yield of the corresponding lactol **20** (based on recovered **19**), accompanied with a small amount of the carboxylic acid **21** (7%). In an alternative procedure the crude mixture obtained after hydrolysis of **19** was treated with an ethereal solution of diazomethane to convert the carboxylic acid **21** to the ester **20**. In this way, the required intermediate **20** was obtained in 81% yield. Oxidative cleavage of purified diol **20** with sodium periodate on silica gel afforded the formate **22**, which upon treatment with aq trifluoroacetic acid yielded the γ-lactone *ent*-**3**, with absolute configuration of both stereocenters corresponding to (−)-muricatacin (*ent*-**1**). Spectral data (^{1}H and ^{13}C NMR) and physical constants ($[\alpha]_D$ and R_f) of *ent*-**3** thus obtained were in full agreement with values recorded for the opposite enantiomer **3**.

The intermediate *ent*-**3** was converted to dihydroxylactone *ent*-**4** by the newly developed one-pot procedure comprised of previous sodium borohydride reduction of *ent*-**3** to the corresponding primary alcohol (not shown in the reaction scheme), followed by a subsequent hydrogenolytic removal of benzyl ether protective group in the intermediate under the acidic conditions (10% Pd/C, 2:1 TFA/MeOH). This procedure provided the desired intermediate *ent*-**4** in 71% overall yield. The ^{1}H and ^{13}C NMR spectral data, as well as the value of optical rotation for *ent*-**4** were fully consistent with those reported previously.[8] Since the conversion of diol *ent*-**4** to (−)-muricatacin through a three-step sequence has been previously reported by Saniere et al.,[8] the preparation of *ent*-**4** formally represents a novel synthesis of (−)-muricatacin (*ent*-**1**) from D-xylose.

Moreover, the aldehydo-lactone *ent*-**3** was converted to the (−)-muricatacin 7-oxa-analog (*ent*-**2**) through a three-step sequence similar to that already used for the conversion of **3** to **2**. Thus, sodium borohydride reduction of the aldehyde group in *ent*-**3** gave the primary alcohol *ent*-**12**, which was subsequently converted to the 7-*O*-decyl derivative *ent*-**14** after reaction with decyl bromide in refluxing ether, in presence of Ag_2O and AgOTf as catalysts. Hydrogenolytic removal of benzyl ether protective group in *ent*-**14** furnished the target *ent*-**2** to be ready for biological testing.

2.1. Evaluation of cytotoxic activity

Compounds **2** and *ent*-**2** were evaluated for their in vitro cytotoxicity against human myelogenous leukemia K562, promyelocytic leukemia HL-60, human T-cell leukemia (JURKAT), cervix carcinoma HeLa, and estrogen receptor positive breast adenocarcinoma MCF-7 cell line. Cytotoxic activity was evaluated by using MTT assay,[21] after exposure of cells to the tested compounds for 48 h. Standard cytotoxic agent doxorubicin (DOX) was used as a positive control in this assay. The results are presented in Table 1.

Compound **2** showed a powerful antiproliferative activity against the HL-60 cell line, being over 17-fold more potent with respect to doxorubicin. This analog was also active against the K562 and JURKAT cells, but the respective IC_{50} values were more than 5- and 12-fold higher with respect to those observed for the reference compound, DOX. The opposite enantiomer *ent*-**2** showed a powerful cytotoxic activity against K562 cells being 36-fold more potent than doxorubicin. Against the HL-60 cell line, this compound exhibited a significant antiproliferative activity, which was 35% higher than that observed for doxorubicin. This analog was also active against the JURKAT, HeLa, and MCF-7 cells but with respective IC_{50} values being over 2-, 20- and 40-fold higher than those observed for the reference compound.

Table 1. In vitro cytotoxicity of **2**, *ent*-**2**, and DOX

Compds	IC_{50}, μM[a]				
	K562	HL-60	JURKAT	HeLa	MCF-7
2	1.96	0.26	4.89	>100	>100
ent-**2**	0.01	2.96	1.06	23.58	31.55
DOX	0.36	4.62	0.39	1.17	0.75

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

3. Conclusions

In conclusion, a new and general strategy for the synthesis of enantiopure 5-hydroxyalkylbutan-4-olides by chirality transfer from D-xylose has been developed. The synthetic pathway that furnished with the preparation of (+)- and (−)-5,6-dihydroxy-4-hexanolides **4** and *ent*-**4** formally represents a new enantiodivergent synthesis of (+)- and (−)-muricatacins from D-xylose. This approach has been applied for the preparation of hitherto unknown (+)- and (−)-muricatacin 7-oxa analogs **2** and *ent*-**2**, which showed powerful antiproliferative activities against some malignant cells. In addition to providing access to both enantiomers of **1** and **2**, 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 muricatacin analogs in both enantiomeric series for biological evaluation.

4. Experimental

4.1. General methods

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on P 3002 (Krüss) and Polamat A (Zeiss, Jena) polarimeters in chloroform solutions at room temperature. IR spectra were recorded with Specord 75 (Carl–Zeiss) and Nexus 670 (Thermo Nicolet, DTGS-detector) IR spectrophotometers. NMR spectra were recorded on a Bruker AC 250 E instrument and the chemical shifts (δ-scale) are expressed in parts per million values downfield from tetramethylsilane. Chemical ionization mass spectra were recorded on Finnigan-MAT 8230 spectrometer with isobutane as a reagent gas. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Flash column chromatography was performed using Kieselgel 60 (0.040–0.063 mm, 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 35 °C.

4.1.1. 5-*O*-Benzoyl-3-*O*-benzyl-D-xylofuranose (6). A solution of **5** (3.644 g, 8.58 mmol) in 70% aq AcOH was stirred for 5.5 h at reflux. After the mixture cooled to room temperature it was concentrated by co-distillation with toluene and the residue purified by flash column chromatography (3:2 toluene/EtOAc), to afford pure **6** (2.517 g, 85%) as a colorless solid. Recrystallization from CH_2Cl_2/hexane gave an analytical sample **6** as colorless needles, mp 59–60 °C, $[\alpha]_D^{23}$ −18.1→+4.2 (24 h, *c* 1.0, $CHCl_3$), R_f=0.68 (Et_2O), anomeric ratio: α/β=3:1 (from ^1H NMR spectrum recorded immediately after dissolution of the sample). IR (KBr): ν_{max} 3420 (OH), 1720 (C=O), 1600 (Ph). ^1H NMR ($CDCl_3$+D_2O): δ 4.05 (br s, 0.25H, $J_{2,3}$=1.3, $J_{3,4}$=3.5 Hz, H-3β), 4.09 (dd, 0.75H, $J_{2,3}$=2.9, $J_{3,4}$=4.8 Hz, H-3α), 4.24 (dd, 0.75H, $J_{1,2}$=3.8 Hz, H-2α), 4.33 (br s, 0.25H, H-2β), 4.41–4.78 (m, 4H, PhCH_2, H-4β, H-4α, H-5β and H-5α), 5.27 (br s, 0.25H, H-1β), 5.56 (d, 0.75H, $J_{1,2}$=3.8 Hz, H-1α), 7.18–8.09 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 63.61 (C-5α), 64.12 (C-5β), 71.94 (Ph*C*H_2-α), 72.51 (Ph*C*H_2-β), 75.02 (C-2α), 76.35 (C-4α), 77.50 (C-2β), 79.08 (C-4β), 82.07 (C-3β), 82.85 (C-3α), 96.26 (C-1α), 103.36 (C-1β), 127.49, 127.59, 127.73, 127.82, 127.89, 128.19, 128.28, 128.39, 128.46, 128.56, 129.61, 129.72, 129.98, 133.05 and 137.34 (2×Ph), 166.49 (C=O). MS (CI): *m*/*z* 401 (M^+−H+C_4H_{10}), 383 (M^+−OH+C_4H_{10}), 345 (MH^+), 327 (M^+−OH), 237 (M^+−OBn). Anal. Found: C, 66.53; H, 6.06. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85.

4.1.2. Methyl 7-*O*-benzoyl-5-*O*-benzyl-2,3-dideoxy-D-*xylo*-hept-2-enonate (7). To a solution of **6** (1.985 g, 5.76 mmol) in dry DMF (37 mL) was added Ph_3P=$CHCO_2Me$ (2.508 g, 7.5 mmol). The mixture was stirred for 3.5 h at 60–70 °C and then evaporated. The residue was purified by flash column chromatography (Et_2O) to afford pure **7** (1.948 g, 84%) as a colorless syrup, $[\alpha]_D^{23}$ −13.8 (*c* 1.0, $CHCl_3$), R_f=0.5 (4:1 $^iPr_2O$/EtOAc). IR (KBr): ν_{max} 3450 (OH), 1700 (C=O), 1620 (C=C), 1600 (Ph). ^1H NMR ($CDCl_3$): δ 3.33 (br s, 2H, exchangeable with D_2O, 2×OH), 3.63 (t, 1H, $J_{4,5}$=$J_{5,6}$=3.8 Hz, H-5), 3.74 (s, 3H, CO_2Me), 4.15 (m, 1H, H-6), 4.36 (dd, 1H, $J_{6,7a}$=4.8, $J_{7a,7b}$=11.5 Hz, H-7a), 4.46 (dd, 1H, $J_{6,7b}$=6.8, $J_{7a,7b}$=11.5 Hz, H-7b), 4.62 (m, 1H, H-4), 4.64 and 4.72 (2×d, 2H, J_{gem}=11.2 Hz, PhCH_2), 6.20 (dd, 1H, $J_{2,4}$=1.9, $J_{2,3}$=15.6 Hz, H-2), 7.07 (dd, 1H, $J_{3,4}$=4.4, $J_{2,3}$=15.6 Hz, H-3), 7.22–8.06 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 51.68 (CO_2Me), 65.82 (C-7), 70.23 (C-6), 71.19 (C-4), 74.75 (Ph*C*H_2), 79.96 (C-5), 121.25 (C-2), 128.21, 128.29, 128.37, 128.52, 129.49, 129.61, 133.22 and 136.97 (2×Ph), 147.39 (C-3), 166.63 and 166.81 (C-1 and Ph*C*=O). MS (CI): *m*/*z* 401 (MH^+), 369 (M^+−OMe). Anal. Found: C, 66.25; H, 5.88. Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04.

4.1.3. Methyl 7-*O*-benzoyl-5-*O*-benzyl-2,3-dideoxy-D-*xylo*-heptonate (8). A solution of **7** (0.554 g, 1.38 mmol) in EtOH (11 mL) was hydrogenated over PtO_2 (8 mg) for 16 h at room temperature. The mixture was filtered and the catalyst washed with EtOH. The organic solution was evaporated and the residue was purified by flash column chromatography (9:1 $^iPr_2O$/EtOAc) to afford pure **8** (0.419 g, 75%) as a colorless syrup, $[\alpha]_D^{23}$ −12.8 (*c* 1.0, $CHCl_3$), R_f=0.36 (4:1 $^iPr_2O$/EtOAc). IR (film): ν_{max} 3470 (OH), 1720 (C=O), 1600 (Ph). ^1H NMR ($CDCl_3$): δ 1.89 (m, 2H, 2×H-3), 2.49 (m, 2H, 2×H-2), 2.72 (d, 1H, $J_{4,OH}$=6.5 Hz, exchangeable with D_2O, OH-4), 3.06 (d, 1H, $J_{6,OH}$=5.9 Hz, exchangeable with D_2O, OH-6), 3.48 (dd, 1H, $J_{4,5}$=4.0, $J_{5,6}$=3.1 Hz, H-5), 3.67 (s, 3H, CO_2Me), 3.88 (m, 1H, H-4), 4.17 (m, 1H, H-6), 4.41 (dd, 1H, $J_{6,7a}$=5.0, $J_{7a,7b}$=11.5 Hz, H-7a), 4.47 (dd, 1H, $J_{6,7b}$=6.7, $J_{7a,7b}$=11.5 Hz, H-7b), 4.73 (s, 2H, PhCH_2), 7.28–8.09 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 29.0 (C-3), 30.49 (C-2), 51.65 (CO_2Me), 66.12 (C-7), 70.22 (C-6), 71.15 (C-4), 75.11 (Ph*C*H_2), 80.9 (C-5), 128.16, 128.38, 128.42, 128.47, 128.56, 129.63, 133.15 and 137.39 (2×Ph), 166.56 (Ph*C*O), 174.27 (*C*O_2Me). MS (CI): *m*/*z* 403 (MH^+), 371 (M^+−OMe). Anal. Found: C, 66.02; H, 6.21. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51.

4.1.4. 7-*O*-Benzoyl-5-*O*-benzyl-2,3-dideoxy-D-*xylo*-heptono-1,4-lactone (9). A solution of **8** (0.127 g, 0.31 mmol) in a mixture of TFA (2 mL) and water (1 mL) was stirred at room temperature for 2.5 h. The volatiles were removed by co-distillation with toluene and the residue purified by flash column chromatography (4:1 CH_2Cl_2/EtOAc) to give pure **9** (0.106 g, 92%) as a colorless oil, $[\alpha]_D^{23}$ −19.3 (*c* 0.99, $CHCl_3$), R_f=0.46 (4:1 CH_2Cl_2/EtOAc). IR (film): ν_{max} 3450 (OH), 1780 (C=O, lactone), 1710 (C=O, Bz), 1600 (Ph). ^1H NMR ($CDCl_3$): δ 1.82–2.41 (m, 2H, 2×H-3), 2.61 (m, 2H, 2×H-2), 3.15 (s, 1H, exchangeable with D_2O, OH), 3.60 (dd, 1H, $J_{4,5}$=5.8, $J_{5,6}$=3.1 Hz, H-5), 4.11 (m, 1H, H-6), 4.37 (dd, 1H, $J_{6,7a}$=5.2, $J_{7a,7b}$=11.5 Hz, H-7a), 4.49 (dd, 1H, $J_{6,7b}$=6.7, $J_{7a,7b}$=11.5 Hz, H-7b), 4.73 and 4.85 (2×d, 2H, J_{gem}=11.6 Hz, PhCH_2), 4.82 (m, 1H, H-4), 7.29–8.05 (m, 10H, 2×Ph). ^{13}C NMR ($CDCl_3$): δ 24.52 (C-3), 28.24 (C-2), 65.85 (C-7), 69.06 (C-6), 74.18 (Ph*C*H_2), 79.73 (C-5), 80.83 (C-4), 127.91, 128.0, 128.15, 128.25, 128.32, 129.46, 133.08 and 137.21 (2×Ph), 166.4 (Ph*C*O), 176.89 (C-1). MS (CI): *m*/*z* 371 (MH^+).

4.1.5. 5-*O*-Benzyl-2,3-dideoxy-D-*xylo*-heptono-1,4-lactone (10). *Procedure A*: a solution of **9** (0.107 g, 0.29 mmol) in 0.09 M methanolic NaOMe (0.6 mL, 0.06 mmol) was stirred for 1 h at room temperature. An additional amount of 0.09 M NaOMe in MeOH (0.3 mL, 0.03 mmol) was added to the reaction mixture and stirring was continued for the next 1 h at room temperature. The mixture was neutralized with 1 M AcOH in MeOH (0.09 mL, 0.09 mmol) and evaporated. Flash column chromatography (4:1→1:4 CH_2Cl_2/EtOAc) of the residue gave pure **10** (0.043 g, 55%) as a colorless syrup, R_f=0.31 (EtOAc).

Procedure B: a solution of **8** (1.458 g, 3.62 mmol) in 0.09 M methanolic NaOMe (6.9 mL, 0.63 mmol) was stirred for 1.5 h at room temperature, then acidified with 2:1 aq TFA (0.08 mL) and concentrated by co-distillation with toluene. Flash column chromatography (EtOAc) of the residue gave pure **10** (0.7932 g, 82%) as a colorless oil, $[\alpha]_D^{23}$ +3.0 (*c* 1.06, $CHCl_3$), R_f=0.31 (EtOAc). IR (film): ν_{max} 3400 (OH), 1750 (C=O), 1610 (Ph). ^1H NMR ($CDCl_3$+D_2O): δ 1.91 and 2.25 (2×m, 2H, 2×H-3), 2.35 (m, 2H, 2×H-2), 3.49 (t, 1H, $J_{4,5}$=$J_{5,6}$=4.9 Hz, H-5), 3.60 (dd, 1H, $J_{6,7a}$=5.2, $J_{7a,7b}$=11.6 Hz, H-7a), 3.67 (dd, 1H, $J_{6,7b}$=5.2, $J_{7a,7b}$=11.6 Hz, H-7b), 3.81 (m, 1H, H-6), 4.62–4.83 (m, 3H, PhCH_2 and H-4), 7.24–7.4 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 24.49 (C-3), 28.24 (C-2), 63.54 (C-7), 70.98 (C-6), 74.41 (Ph*C*H_2), 80.70 (C-5), 80.73 (C-4), 128.09,

128.17, 128.5 and 137.43 (Ph), 177.32 (C-1). MS (CI): *m/z* 267 (MH^+). Anal. Found: C, 63.43; H, 6.63. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81.

4.1.6. 6-Aldehydo-5-*O*-benzyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (3). To a solution of **10** (0.793 g, 2.98 mmol) in CH_2Cl_2 (11 mL) was added Kieselgel 60 (6.0 g, 0.063–0.2 nm) and 0.65 M aq $NaIO_4$ (6.0 mL, 3.90 mmol). The resulting heterogeneous mixture was vigorously stirred for 1 h at room temperature then filtered and evaporated. Flash column chromatography (2:1 toluene/EtOAc), followed by crystallization from CH_2Cl_2/hexane gave an analytical sample **3** (0.621 g, 89%) as colorless needles, mp 93–94 °C, $[\alpha]_D^{23}$ +135.8 (*c* 1.08, $CHCl_3$), R_f=0.3 (2:1 toluene/EtOAc). IR (film): ν_{max} 1770 (C=O, lactone), 1720 (CH=O). ^{1}H NMR ($CDCl_3$): δ 1.92–2.68 (m, 4H, 2×H-2 and 2×H-3), 3.78 (dd, 1H, $J_{4,5}$=2.7, $J_{5,6}$=1.5 Hz, H-5), 4.58 (d, 1H, J_{gem}=11.9 Hz, PhC*H*a), 4.74–4.85 (m, 2H, H-4 and PhC*H*b), 7.33 (m, 5H, Ph), 9.68 (d, 1H, H-6). ^{13}C NMR ($CDCl_3$): δ 23.38 (C-3), 27.61 (C-2), 73.33 (Ph*C*H_2), 78.69 (C-4), 83.88 (C-5), 128.2, 128.52, 128.69 and 136.76 (Ph), 176.57 (C-1), 201.57 (C-6). MS (CI): *m/z* 469 ($2M^+$+H), 235 (MH^+). Anal. Found: C, 66.30; H, 6.00. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02.

4.1.7. (*Z*)-6-*C*-Decylidene-5-*O*-benzyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (11). To a stirred suspension of undecyltriphenylphosphonium bromide (0.716 g, 1.44 mmol) in dry THF (5 mL) was added a 1 M solution of LiHMDS in dry THF (1.44 mL, 1.44 mmol) dropwise over a period of 5 min at 0 °C under N_2. The bright red solution was stirred for another 15 min, cooled to −78 °C, and a solution of the aldehyde **3** (0.1698 g, 0.72 mmol) in dry THF (1.5 mL) was instantly added. The mixture was stirred for 3 h at −78 °C, while it was allowed to warm to room temperature. The light yellow mixture was stirred at room temperature for 72 h, then quenched with 10% aq NH_4Cl (5 mL), and extracted with Et_2O. The combined organic phases were washed with brine, dried, and evaporated. Flash column chromatography of the residue (2:1 toluene/EtOAc) gave pure (*Z*)-olefin **11** (0.0175 g, 7%) as a colorless oil, $[\alpha]_D^{23}$ +40.2 (*c* 0.74, $CHCl_3$), R_f=0.45 (9:1 toluene/EtOAc). IR (film): ν_{max} 1780 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, *J*=6.4 Hz, Me), 1.07–1.60 (m, 16H, 8×CH_2), 1.95–2.67 (m, 6H, H-2, H-3 and H-8), 4.24 (dd, 1H, $J_{4,5}$=5.4, $J_{5,6}$=9.4 Hz, H-5), 4.38 and 4.66 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.55 (m, 1H, H-4), 5.41 (m, 1H, $J_{5,6}$=9.4, $J_{6,7}$=11.4 Hz, H-6), 5.80 (m, 1H, $J_{6,7}$=11.4, $J_{7,8}$=7.8 Hz, H-7), 7.25–7.43 (m, 5H, Ph). ^{1}H NOE contact: H-6 and H-7. ^{13}C NMR ($CDCl_3$): δ 14.07 (Me), 22.65, 23.80, 28.07, 28.30, 28.31, 29.45, 29.52, 29.58 and 31.88 (9×CH_2, C-2 and C-3), 70.05 (Ph*C*H_2), 75.25 (C-5), 81.77 (C-4), 124.81 (C-6), 127.66, 128.36 and 138.09 (Ph), 137.39 (C-7), 177.20 (C-1). MS (CI): *m/z* 373 (MH^+).

4.1.8. 5-*O*-Benzyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (12). To a cooled (0 °C) and stirred solution of **3** (0.122 g, 0.52 mmol) in MeOH (1.2 mL) was added $NaBH_4$ (0.0197 g, 0.52 mmol) in two portions, and the resulting suspension was stirred at 0 °C for 1.5 h. TFA (2 mL) was then added and the mixture was stirred for additional 2 h while it was allowed to warm to room temperature. The volatiles were removed by co-distillation with toluene and the residue purified by flash column chromatography (4:1 CH_2Cl_2/EtOAc). The unchanged aldehyde **3** (0.015 g, 12%) was first eluted, followed by pure **12** (0.082 g, 73% on the basis of the recovered intermediate **3**) that was isolated as a colorless oil, $[\alpha]_D^{23}$ +22.9 (*c* 1.09, $CHCl_3$), R_f=0.24 (4:1 CH_2Cl_2/EtOAc). IR (film): ν_{max} 3450 (OH), 1770 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.87–2.32 (m, 2H, 2×H-3), 2.36–2.85 (m, 3H, 2×H-2 and OH), 3.50 (m, 1H, H-5), 3.70 (dd, 1H, $J_{5,6a}$=4.9, $J_{6a,6b}$=11.6 Hz, H-6a), 3.79 (dd, 1H, $J_{5,6b}$=5.3, $J_{6a,6b}$=11.6 Hz, H-6b), 4.65 and 4.73 (2×d, 2H, J_{gem}=11.6 Hz, PhCH_2), 4.70 (m, 1H, H-4), 7.28–7.45 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 24.08 (C-3), 28.22 (C-2), 60.93 (C-6), 72.99 (Ph*C*H_2), 80.22 (C-4), 80.51 (C-5), 127.79, 127.86, 128.4 and 137.71 (Ph), 177.36 (C=O). MS (CI): *m/z* 473 ($2M^+$+H), 237 (MH^+).

4.1.9. 2,3-Dideoxy-L-*threo*-hexono-1,4-lactone (4). A solution of **12** (0.082 g, 0.35 mmol) in EtOAc (1.7 mL) was hydrogenated over 10% Pd/C (0.041 g) for 18 h at room temperature. The mixture was filtered and the catalyst washed successively with EtOAc and MeOH. The combined organic solutions were evaporated and the residue was purified by flash column chromatography (EtOAc) to afford pure **4** (0.035 g, 69%) as a colorless syrup, $[\alpha]_D$ +58.0 (*c* 2.01, MeOH), lit.[19] $[\alpha]_D$ +58.18 (*c* 2.03, MeOH), R_f=0.22 (EtOAc). IR (film): ν_{max} 3384 (OH), 1759 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.26 (m, 2H, 2×H-3), 2.57 (m, 2H, 2×H-2), 3.46–3.84 (m, 4H, H-5, 2×H-6 and OH), 4.14 (br s, 1H, OH), 4.59 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 23.9 (C-3), 28.45 (C-2), 63.27 (C-6), 73.56 (C-5), 80.77 (C-4), 178.21 (C-1).

4.1.10. 5-*O*-Benzyl-6-*O*-decyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (14). To a solution of **12** (0.101 g, 0.43 mmol) in dry Et_2O (2 mL) were added successively Ag_2O (0.249 g, 1.07 mmol), AgOTf (0.028 g, 0.11 mmol), and $C_{10}H_{21}Br$ (0.44 mL, 2.13 mmol). The mixture was stirred under reflux for 7.5 h, then diluted with CH_2Cl_2 (10 mL), filtered, and evaporated. The residue was purified by flash column chromatography (CH_2Cl_2) to give pure **14** (0.129 g, 80%) a colorless oil, $[\alpha]_D^{23}$ +30.2 (*c* 1.05, $CHCl_3$), R_f=0.24 (CH_2Cl_2). IR (film): ν_{max} 1779 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 3H, Me), 1.16–1.65 (m, 16H, 8×CH_2), 1.93–2.31 (m, 2H, 2×H-3), 2.32–2.67 (m, 2H, 2×H-2), 3.44 (t, 2H, *J*=6.6 Hz, 2×H-8), 3.60 (m, 3H, H-5 and 2×H-6), 4.60 and 4.77 (2×d, 2H, J_{gem}=11.8 Hz, PhCH_2), 4.70 (m, 1H, H-4), 7.24–7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 13.97 (Me), 22.52, 23.89, 25.98, 28.18, 29.17, 29.29, 29.41, 29.45, 29.49 and 31.74 (8×CH_2, C-2 and C-3), 69.61 (C-6), 71.64 (C-8), 72.77 (Ph*C*H_2), 78.9 (C-5), 79.67 (C-4), 127.65, 127.70, 128.26 and 137.90 (Ph), 177.34 (C-1). MS (CI): *m/z* 377 (MH^+). Anal. Found: C, 73.18; H, 9.50. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64.

4.1.11. 6-*O*-Decyl-2,3-dideoxy-L-*threo*-hexono-1,4-lactone (2). A solution of **14** (0.084 g, 0.22 mmol) in EtOAc (1.7 mL) was hydrogenated over 10% Pd/C (0.042 g) for 19 h at room temperature. The suspension was filtered through a Celite pad and washed with EtOAc. The combined filtrates were evaporated and the residue purified by flash column chromatography (CH_2Cl_2 → 9:1 CH_2Cl_2/EtOAc) to afford pure **2** (0.051 g, 82%) as a colorless solid. Recrystallization from $CHCl_3$/hexane gave an analytical sample **2**, mp

42 °C, $[\alpha]_D^{23}$ +33.0 (*c* 0.83, $CHCl_3$), R_f=0.21 (9:1 CH_2Cl_2/EtOAc). IR (film): ν_{max} 3427 (OH), 1737 (C=O). ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, *J*=6.4 Hz, Me), 1.13–1.63 (m, 16H, 8×CH_2), 2.24 (m, 2H, 2×H-3), 2.39–2.72 (m, 2H, 2×H-2), 2.87 (br s, 1H, exchangeable with D_2O, OH), 3.44 (t, 2H, *J*=6.6 Hz, 2×H-8), 3.51 (d, 2H, $J_{5,6}$=5.8 Hz, 2×H-6), 3.78 (br s, 1H, H-5), 4.56 (td, 1H, $J_{4,5}$=3.4, $J_{3,4}$=7.0 Hz, H-4). ^{13}C NMR ($CDCl_3$): δ 13.99 (Me), 22.56, 23.74, 25.96, 28.27, 29.2, 29.45, 29.47 and 31.78 (8×CH_2, C-2 and C-3), 71.12 (C-6), 71.69 (C-8), 71.94 (C-5), 79.79 (C-4), 177.53 (C-1). MS (CI): *m/z* 573 ($2M^+$+H), 287 (MH^+). Anal. Found: C, 66.99; H, 10.74. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56.

4.1.12. 3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-D-xylofuranose (16). To a cooled (0 °C) and stirred solution of **15** (2.603 g, 7.78 mmol) in anhydrous DMF (39 mL) were added successively NaH (0.403 g, 13.4 mmol) and BnBr (1.4 mL, 11.77 mmol), and the mixture was stirred for 2.5 h at room temperature. The mixture was cooled to 0 °C and treated with 0.1 M NaOMe in MeOH (15.6 mL, 1.56 mmol) while stirring for 2 h at room temperature. The mixture was neutralized with 1 M AcOH in MeOH (1.56 mL, 1.56 mmol), evaporated by co-distillation with toluene, and the residue purified by flash column chromatography (9:1 CH_2Cl_2/EtOAc) to afford pure **16** (2.22 g, 89%) as a colorless oil, $[\alpha]_D^{23}$ −57.7 (*c* 0.99, $CHCl_3$), R_f=0.32 (9:1 CH_2Cl_2/EtOAc). IR (film): ν_{max} 3450 (OH). ^1H NMR ($CDCl_3$): δ 1.32–1.77 (m, 10H, 5×CH_2 from C_6H_{10}), 2.33 (br s, 1H, exchangeable with D_2O, OH), 3.84 (dd, 1H, $J_{4,5a}$=4.6, $J_{5a,5b}$=11.8 Hz, H-5a), 3.96 (dd, 1H, $J_{4,5b}$=5.0 Hz, $J_{5a,5b}$=11.8 Hz, H-5b), 4.03 (d, 1H, $J_{3,4}$=3.4 Hz, H-3), 4.28 (m, 1H, H-4), 4.50 and 4.73 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.65 (d, 1H, $J_{1,2}$=3.8 Hz, H-2), 6.00 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), 7.28–7.44 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 23.53, 23.81, 24.83, 35.78 and 36.42 (5×CH_2 from C_6H_{10}), 60.92 (C-5), 71.86 (PhCH_2), 80.0 (C-4), 81.99 (C-2), 82.86 (C-3), 104.61 (C-1), 112.44 (Cq from C_6H_{10}), 127.63, 128.09, 128.59 and 137.11 (Ph). MS (CI): *m/z* 642 ($2M^+$+H), 321 (MH^+). Anal. Found: C, 65.01; H, 6.61. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63.

4.1.13. 3-*O*-Benzyl-1,2-*O*-cyclohexylidene-α-D-*xylo*-pentadialdo-1,4-furanose (17). To a stirred solution of **16** (2.935 g, 9.16 mmol) and DCC (5.67 g, 27.48 mmol) in anhydrous DMSO (14.6 mL), were added dry pyridine (0.36 mL; 5 mmol) and 0.82 M solution of anhydrous H_3PO_4 in DMSO (5.5 mL, 4.5 mmol). The resulting reaction mixture was stirred at room temperature for 3.5 h and then diluted with EtOAc (50 mL). A solution of oxalic acid (2.31 g, 10.15 mmol) in MeOH (7 mL) was added and the resulting suspension was washed successively with 10% aq NaCl (100 mL) and 10% aq $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous solution extracted with EtOAc (2×30 mL). The combined organic solution was washed with brine, dried, and concentrated by co-distillation with toluene. Flash column chromatography (9:1 toluene/EtOAc) of the residue gave pure **17** (2.429 g, 83%) as an unstable pale yellow syrup, $[\alpha]_D^{23}$ −41.4 (*c* 0.95, $CHCl_3$), R_f=0.27 (9:1 toluene/EtOAc). IR (film): ν_{max} 1720 (CH=O). ^1H NMR ($CDCl_3$): δ 1.34–1.76 (m, 5×CH_2 from C_6H_{10}), 4.37 (d, 1H, $J_{3,4}$=3.7 Hz, H-3), 4.49 and 4.62 (2×d, 2H, J_{gem}=11.9 Hz, PhCH_2), 4.58 (dd, 1H, $J_{3,4}$=3.7, $J_{4,5}$=1.5 Hz, H-4), 4.66 (d, 1H, $J_{1,2}$=3.5 Hz, H-2), 6.14 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 7.27–7.41 (m, 5H, Ph), 9.69 (d, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ 23.53, 23.81, 24.75, 35.85 and 36.67 (5×CH_2 from C_6H_{10}), 72.36 (PhCH_2), 81.76 (C-2), 83.92 (C-3), 84.58 (C-4), 105.8 (C-1), 113.31 (Cq from C_6H_{10}), 127.66, 128.11, 128.51 and 136.69 (Ph), 200.07 (CH=O). MS (CI): *m/z* 637 ($2M^+$+H), 319 (MH^+).

4.1.14. Methyl 3-*O*-benzyl-5,6-dideoxy-1,2-*O*-cyclohexylidene-α-D-*xylo*-heptofuranuronate (19). A mixture of **17** (2.429 g, 7.63 mmol) and Ph_3P=$CHCO_2Me$ (6.412 g, 19.18 mmol) in anhydrous CH_2Cl_2 (92 mL) was stirred under N_2 at room temperature for 2 h and then evaporated. The residue was purified by flash column chromatography (9:1 toluene/EtOAc) to give **18** (2.767 g, 97%) as a 2:1 mixture of corresponding *Z*- and *E*-isomers. A solution of **18** (2.767 g, 7.39 mmol) in EtOH (55 mL) was hydrogenated over PtO_2 (0.029 g) for 19 h at room temperature. The mixture was filtered and the catalyst washed with EtOH. The organic solution was evaporated and the residue was purified by flash column chromatography (15:1 toluene/EtOAc) to afford pure **19** (2.571 g, 92%) as a colorless oil, $[\alpha]_D^{23}$ −38.6 (*c* 1.02, $CHCl_3$), R_f=0.31 (15:1 toluene/EtOAc), IR (film): ν_{max} 1740 (C=O). ^1H NMR ($CDCl_3$): δ 1.33–1.77 (m, 5×CH_2 from C_6H_{10}), 2.04 (m, 2H, 2×H-5), 2.40 (m, 2H, 2×H-6), 3.66 (s, 3H, CO_2Me), 3.82 (d, 1H, $J_{3,4}$=3.1 Hz, H-3), 4.18 (ddd, 1H, $J_{3,4}$=3.1 Hz, $J_{4,5a}$=5.6, $J_{4,5b}$=8.4 Hz, H-4), 4.50 and 4.71 (2×d, 2H, J_{gem}=12.0 Hz, PhCH_2), 4.61 (d, 1H, $J_{1,2}$=3.9 Hz, H-2), 5.91 (d, 1H, $J_{1,2}$=3.9 Hz, H-1), 7.25–7.37 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 23.51 (C-5), 23.81, 23.82, 24.86, 35.68 and 36.29 (5×CH_2 from C_6H_{10}), 30.56 (C-6), 51.41 (CO_2Me), 71.67 (PhCH_2), 79.12 (C-4), 81.82 (C-2), 82.19 (C-3), 104.22 (C-1), 111.97 (Cq from C_6H_{10}), 127.57, 127.80, 128.38 and 137.50 (Ph), 173.57 (C-7). MS (CI): *m/z* 377 (MH^+), 345 (M^+−OMe).

4.1.15. Methyl 3-*O*-benzyl-5,6-dideoxy-D-*xylo*-heptofuranuronate (20) and 3-*O*-benzyl-5,6-dideoxy-D-*xylo*-heptofuranuronic acid (21). *Procedure A*: a solution of **19** (1.322 g, 3.51 mmol) in 50% aq AcOH (38 mL) was heated under reflux for 2 h and then concentrated by co-distillation with toluene. The residue was purified by flash column chromatography (1:1 toluene/EtOAc). Eluted first was the unchanged starting compound **19** (0.142 g, 11%). Eluted second was the pure **20** (0.596 g, 64% on the basis of the recovered starting material **19**) as a colorless syrup, R_f=0.24 (1:1 toluene/EtOAc). Final eluting of the column with EtOAc gave pure **21** (0.074 g, 7%) as a colorless syrup, $[\alpha]_D^{23}$ −4.1 (*c* 0.9, EtOH), R_f=0.44 (999:1 EtOAc/AcOH). IR (film): ν_{max} 3395 (OH), 1713 (C=O). ^1H NMR (acetone-d_6): δ 1.84–2.60 (m, CH_2-5, CH_2-6α and β), 3.87–3.92 (m, H-3α and β), 4.14–4.32 (m, H-2 and H-4α and β), 4.50 and 4.83 (2×d, 2H, PhCH_2), 5.05 (s, H-1β), 5.34 (d, $J_{1,2}$=4.3 Hz, H-1α), 7.21–7.48 (m, 5H, Ph). ^{13}C NMR (acetone-d_6): δ 25.62, 26.39, 30.72 and 30.91 (C-5, C-6α and β), 72.02 and 72.23 (PhCH_2 α and β), 76.23, 77.70, 80.03 and 80.22 (C-2 and C-4α and β), 84.66 (C-3β), 85.01 (C-3α), 96.63 (C-1α), 104.14 (C-1β), 128.22, 128.33, 128.34, 128.46, 129.02, 129.07, 139.28 and 139.51 (Ph), 174.73 and 174.82 (C=O, α and β).

Procedure B: a solution of **19** (1.103 g, 2.9 mmol) in 50% aq AcOH (31 mL) was heated under reflux for 2 h and then

concentrated by co-distillation with toluene. The residue was dissolved in ether (9 mL) and treated for 1.5 h at room temperature with an ethereal solution of diazomethane (9 mL), generated from *N*-methyl-*N*′-nitro-*N*-nitroso guanidine (0.532 g) and 5 M NaOH (2.4 mL). The mixture was evaporated and the residue purified by flash column chromatography (1:1 toluene/EtOAc). Eluted first was the unchanged starting compound **19** (0.149 g, 13%). Eluted second was the pure **20** (0.607 g, 81% on the basis of the recovered starting material **19**) as a colorless syrup, R_f=0.24 (1:1 toluene/EtOAc), $[\alpha]_D^{23}$ +2.0 (*c* 1.08, $CHCl_3$), anomeric ratio: α/β=3:1 (from ^{1}H NMR). IR (film): ν_{max} 3400 (OH), 1720 (C=O). ^{1}H NMR ($CDCl_3$+D_2O): δ 1.96 (m, 2H, 2×H-5α and β), 2.41 (m, 2H, 2×H-6), 3.66 (s, 2.25H, CO_2Me-α), 3.71 (s, 0.75H, CO_2Me-β), 3.84 (dd, 0.25H, $J_{2,3}$=1.2, $J_{3,4}$=4.3 Hz, H-3β), 3.88 (dd, 0.75H, $J_{2,3}$=2.6, $J_{3,4}$=4.6 Hz, H-3α), 4.16–4.32 (m, 2H, H-2 and H-4), 4.54 and 4.71 (2×d, 1.5H, J_{gem}=12.0 Hz, PhCH_2-α), 4.55 and 4.70 (2×d, 0.5H, J_{gem}=11.7 Hz, PhCH_2-β), 5.30 (s, 0.25H, H-1β), 5.44 (d, 0.75H, $J_{1,2}$=4.3 Hz, H-1α), 7.30–7.41 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 24.6 (C-5α), 25.51 (C-5β), 30.53 (C-6α), 30.7 (C-6β), 51.62 (CO_2Me-α), 51.65 (CO_2Me-β), 71.79 (PhCH_2-α), 72.47 (PhCH_2-β), 75.57 (C-2β), 77.63 (C-2α), 77.89 (C-4β), 80.45 (C-4α), 82.56 (C-3β), 83.67 (C-3α), 95.59 (C-1α), 102.9 (C-1β), 127.61, 127.78, 127.87, 128.19, 128.4, 128.59, 136.94 and 137.74 (Ph), 174.06 (C-7). MS (CI): *m*/*z* 557 ($2M^+-OH-H_2O$), 297 (MH^+), 279 (M^+-OH). Anal. Found: C, 61.08; H, 6.66. Calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80.

4.1.16. Methyl 2-*O*-benzyl-4,5-dideoxy-3-*O*-formyl-D-*threo*-hexuronate (22) and 6-aldehydo-5-*O*-benzyl-2,3-dideoxy-D-*threo*-hexono-1,4-lactone (*ent*-3). To a solution of **20** (0.576 g, 1.94 mmol) in CH_2Cl_2 (7.8 mL) were added Kieselgel 60 (3.88 g, 0.063–0.2 nm) and 0.65 M aq $NaIO_4$ (3.9 mL, 2.53 mmol). The resulting heterogeneous mixture was vigorously stirred for 1.5 h at room temperature, then filtered, and evaporated by co-distillation with toluene to afford crude **22** (0.561 g, 98%) as a yellow oil, which was used in the next step without further purification. A minor part of crude **22** was purified by flash column chromatography (49:1 CH_2Cl_2/EtOAc) to afford pure **22** as a colorless syrup, $[\alpha]_D^{23}$ −15.1 (*c* 1.13, $CHCl_3$), R_f=0.28 (49:1 CH_2Cl_2/EtOAc). IR (film): ν_{max} 3460 (OH), 1740–1720 (C=O). ^{1}H NMR ($CDCl_3$): δ 2.06 (m, 2H, 2×H-4), 2.30 (m, 2H, 2×H-5), 3.65 (s, 3H, CO_2Me), 3.90 (dd, 1H, $J_{1,2}$=1.0, $J_{2,3}$=3.7 Hz, H-2), 4.58 and 4.80 (2×d, 2H, J_{gem}=11.8 Hz, PhCH_2), 5.36 (td, 1H, $J_{2,3}$=3.7, $J_{3,4a}$=$J_{3,4b}$=7.0 Hz, H-3), 7.25–7.40 (m, 5H, Ph), 8.03 (s, 1H, OC*H*O), 9.60 (d, 1H, $J_{1,2}$=1.0 Hz, H-1). ^{13}C NMR ($CDCl_3$): δ 25.56 (C-4), 29.58 (C-5), 51.76 (CO_2Me), 71.07 (C-3), 73.42 (PhCH_2), 82.87 (C-2), 128.32, 128.45, 128.64 and 136.34 (Ph), 160.11 (OCHO), 172.67 (C-6), 200.37 (C-1). MS (CI): *m*/*z* 295 (MH^+), 267 (MH^+-CO). A solution of crude ester **22** (0.561 g) in a mixture of TFA (9.1 mL) and water (4.55 mL) was stirred for 1.5 h at room temperature and then concentrated by co-distillation with toluene. The residue was chromatographed on a column of flash silica (2:1 toluene/EtOAc) to give pure *ent*-**3** (0.35 g, 77% from **20**) as a white solid. Recrystallization from CH_2Cl_2/hexane gave an analytical sample as colorless needles, mp 93–94 °C, $[\alpha]_D^{23}$ −129.8 (*c* 1.0, $CHCl_3$), R_f=0.3 (2:1 toluene/EtOAc). IR, NMR, and mass spectral data of thus obtained product *ent*-**3** were consistent with those recorded for the (+)-enantiomer **3** (Section 4.1.6). Anal. Found: C, 66.23; H, 6.03. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02.

4.1.17. 2,3-Dideoxy-D-*threo*-hexono-1,4-lactone (*ent*-4). To a solution of *ent*-**3** (0.111 g; 0.47 mmol) in MeOH (1.1 mL) was added $NaBH_4$ (0.02 g; 0.52 mmol) in portions at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then for 1 h at room temperature. One more equivalent of $NaBH_4$ (0.02 g; 0.52 mmol) was added and stirring was continued for an additional 1 h at room temperature. After cooling to 0 °C, TFA (2 mL) was added and the reaction mixture was stirred for an additional 1 h. To the mixture was finally added 10% Pd/C (0.056 g) and the resulting suspension was hydrogenated for 19 h at room temperature. The mixture was filtered and the catalyst washed with methanol. The organic solution was concentrated by co-distillation with toluene and methanol. The residue was purified by flash column chromatography (4:1 CH_2Cl_2/EtOAc) to afford pure *ent*-**4** (0.048 g; 71%) as a colorless syrup, $[\alpha]_D$ −40.0 (*c* 2.07, MeOH), lit.[8] $[\alpha]_D$ −43.3 (*c* 0.9, MeOH), R_f=0.22 (EtOAc). Spectral data of *ent*-**4** were consistent with those recorded for the opposite enantiomer **4** (Section 4.1.9), as well as with the reported values.[8]

4.1.18. 5-*O*-Benzyl-2,3-dideoxy-D-*threo*-hexono-1,4-lactone (*ent*-12). To a solution of **20** (0.699 g, 2.36 mmol) in CH_2Cl_2 (9.5 mL) were added Kieselgel 60 (4.72 g, 0.063–0.2 nm) and 0.65 M aq $NaIO_4$ (4.7 mL, 3.06 mmol). The mixture was vigorously stirred at room temperature for 45 min, filtered, and the precipitate washed with CH_2Cl_2. The combined organic solutions were dried and evaporated to give chromatographically homogenous sample **22**. A solution of crude **22** (0.665 g) in a mixture of TFA (10.8 mL) and water (5.4 mL) was stirred at room temperature for 1.5 h. The mixture was concentrated by co-distillation with toluene to give chromatographically homogenous lactone *ent*-**3** (0.598 g) as a colorless solid. To a cooled (0 °C) and stirred solution of crude *ent*-**3** (0.598 g) in MeOH (5.6 mL) was added $NaBH_4$ (0.095 g, 2.52 mmol) and the mixture was stirred for 1.5 h at 0 °C. One more equivalent of $NaBH_4$ (0.095 g, 2.52 mmol) was added and stirring was continued for an additional 1 h at room temperature. After cooling to 0 °C, TFA (11.2 mL) was added and the reaction mixture was stirred for an additional 1 h while it was allowed to warm to room temperature. The mixture was concentrated by co-distillation with toluene and the residue was purified by flash column chromatography (4:1 CH_2Cl_2/EtOAc). Eluted first was the unchanged intermediate *ent*-**3** (0.092 g, 17% with respect to **20**). Eluted second was the pure product *ent*-**12** (0.314 g, 68% from **20**, on the basis of the recovered *ent*-**3**), $[\alpha]_D^{23}$ −23.1 (*c* 1.05, $CHCl_3$), R_f=0.24 (4:1 CH_2Cl_2/EtOAc). Spectral data of *ent*-**12** were consistent with those recorded for the opposite enantiomer **12** (Section 4.1.8).

4.1.19. 5-*O*-Benzyl-6-*O*-decyl-2,3-dideoxy-D-*threo*-hexono-1,4-lactone (*ent*-14). A mixture of *ent*-**12** (0.054 g, 0.23 mmol), Ag_2O (0.133 g, 0.57 mmol), AgOTf (0.015 g, 0.06 mmol), and $C_{10}H_{21}Br$ (0.24 mL, 1.15 mmol) in anhydrous Et_2O (0.55 mL) was heated under reflux for 5.5 h. After the mixture cooled to room temperature it was diluted with CH_2Cl_2 (5 mL), filtered, and evaporated. Flash column chromatography (CH_2Cl_2/EtOAc) of the residue gave pure

ent-**14** (0.061 g, 71%) as a colorless oil, $[\alpha]_D^{23}$ −35.1 (*c* 0.92, $CHCl_3$), R_f=0.24 (CH_2Cl_2). Spectral data of *ent*-**14** were consistent with those recorded for (+)-enantiomer **14** (Section 4.1.10). Anal. Found: C, 73.03; H, 9.38. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64.

4.1.20. 6-*O*-Decyl-2,3-dideoxy-D-*threo*-hexono-1,4-lactone (*ent*-2). A solution of *ent*-**14** (0.061 g; 0.16 mmol) in EtOAc (1.25 mL) was hydrogenated over 10% Pd/C (0.031 g) following the same methodology as described above (procedure in Section 4.1.11), to afford pure *ent*-**2** (0.040 g, 87%), mp 42 °C, $[\alpha]_D$ −33.0 (*c* 0.83, $CHCl_3$), R_f=0.21 (9:1 CH_2Cl_2/EtOAc). Spectral data of *ent*-**2** were consistent with those recorded for (+)-enantiomer **2** (Section 4.1.11). Anal. Found: C, 67.01; H, 10.67. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56.

4.2. In vitro antitumor assay

Antitumor activity was evaluated by the tetrazolium colorimetric MTT assay. The assay is based on cleavage of the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) to formazan by mitochondrial dehydrogenases in viable cells. Exponentially growing cells were harvested, counted by trypan blue exclusion, and plated into 96-well microtiter plates (Costar) at optimal seeding density of 10^4 (K562, HL-60, JURKAT) or 5×10^3 (HeLa, MCF-7) cells per well to assure logarithmic growth rate throughout the assay period. Viable cells were plated in a volume of 90 μL per well, and preincubated in complete medium at 37° C for 24 h to allow cell stabilization prior to the addition of substances. Tested compounds, at ten the required final concentration, in growth medium (10 μL/well) were added to all wells except to the control ones and microplates were incubated for 24 h. The wells containing cells without tested compounds were used as control. Three hours before the end of incubation period, 10 μL of MTT solution was added to each well. MTT was dissolved in the medium at 5 mg/mL and filtered to sterilize and remove a small amount of insoluble residue present in some batches of MTT. Acidified 2-propanol (100 μL of 0.04 M HCl in 2-propanol) was added to each well and mixed thoroughly to dissolve the dark blue crystals. After a few minutes at room temperature to ensure that all crystals were dissolved, the plates were read on a spectrophotometer plate reader (Multiscan MCC340, Labsystems) at 540/690 nm. The wells without cells containing complete medium and MTT only acted as blank. The compound cytotoxicity was expressed as the IC_{50} (50% inhibitory concentration).

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References and notes

1. Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515–8519.
2. For recent reviews see: (a) Chen, S. H. *Curr. Med. Chem.* **2002**, *9*, 899–912; (b) Gumina, G.; Song, G. Y.; Chu, C. K. *FEMS Microbiol. Lett.* **2001**, *202*, 9–15; (c) Maury, G. *Antiviral Chem. Chemother.* **2000**, *11*, 165–189; (d) Wang, P.; Hong, J. H.; Cooperwood, J. S.; Chu, C. K. *Antiviral Res.* **1998**, *40*, 19–44.
3. For some recent examples see: (a) Lee, S. T.; Molyneux, R. J.; Panter, K. E.; Chang, C.-W. T.; Gardner, D. R.; Pfister, J. A.; Garrossian, M. *J. Nat. Prod.* **2005**, *68*, 681–685; (b) Heinrich, M. R.; Kashman, Y.; Spiteller, P.; Steglich, W. *Tetrahedron* **2001**, *57*, 9973–9978; (c) Vander Jagt, D. L.; Deck, L. M.; Royer, R. E. *Curr. Med. Chem.* **2000**, *7*, 479–498; (d) Umeyama, A.; Ito, S.; Yuasa, E.; Arihara, S.; Yamada, T. *J. Nat. Prod.* **1998**, *61*, 1433–1434.
4. Reiser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, *32*, 1137–1140.
5. Cavé, A.; Chaboche, C.; Figadère, B.; Haramange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Lafitte, J.; Quero, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617–623.
6. (a) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143–4145; (b) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 7548–7550; (c) Rangavan, S.; Joseph, S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 101–105; (d) Carda, M.; Rodriguez, S.; Gonzalez, F.; Castillo, E.; Villanueva, A.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649–2655; (e) Baylon, C.; Prestat, G.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3833–3835; (f) Couladouros, E. A.; Mihou, A. P. *Tetrahedron Lett.* **1999**, *40*, 4861–4862; (g) Solladie, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071–3074; (h) Szlosek, M.; Franck, X.; Figadère, B.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 5169–5172; (i) Chang, S.-W.; Hung, C.-Y.; Liu, H.-H.; Uang, B. J. *Tetrahedron: Asymmetry* **1998**, *9*, 521–529; (j) Quayle, P.; Rahman, S.; Herbert, J. *Tetrahedron Lett.* **1995**, *36*, 8087–8088; (k) van Aar, M. P. M.; Thijis, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 11223–11234; (l) Bonini, C.; Federici, C.; Rossi, L.; Righi, G. *J. Org. Chem.* **1995**, *60*, 4803–4812; (m) Somfai, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 817–819; (n) Marshall, J. A.; Welmaker, G. S. *J. Org. Chem.* **1994**, *59*, 4122–4125; (o) Makabe, H.; Tanaka, A.; Oritani, T. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1028–1029; (p) Saiah, M.; Bessodes, M.; Antoniakis, K. *Tetrahedron Lett.* **1993**, *34*, 1597–1598; (q) Wang, Z. M.; Zhang, X. L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407–6410; (r) Tochtermann, W.; Scholz, G.; Bunte, G.; Wolff, C.; Peters, E. M.; Peters, K.; Von Schnering, H. G. *Liebigs Ann. Chem.* **1992**, 1069–1080; (s) Marshall, J. A.; Welmaker, G. S. *Synlett* **1992**, 537–538; (t) Figadère, B.; Haramange, J. C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539–7542; (u) Scholz, G.; Tochtermann, W. *Tetrahedron Lett.* **1991**, *32*, 5535–5538.
7. (a) Dhotare, B.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 3103–3105; (b) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *ARKIVOC* **2002**, *7*, 34–45; http://arkat-usa.alfahosting.net/ark/journal/2002/SKessar/SK-387E/387E.asp; (c) Chadrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773–2775; (d) Popsavin, V.; Grabež, S.; Popsavin, M.; Petrović, J. *Carbohydr. Lett.* **2000**, *3*, 411–418; (e) Yoon, S.-H.; Moon, H.-S.; Hwang, S.-K.; Choi, S. R.; Kang, S. K. *Bioorg. Med. Chem.* **1998**, *6*, 1043–1049; (f) Rassu, G.; Pinna, L.; Spanu, P.; Zanardi, F.; Battistini, L.; Casiraghi, G. *J. Org. Chem.* **1997**, *62*, 4513–4517; (g) Gravier-Pelletier, C.; Saniere, M.; Charvet, I.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.*

1994, *35*, 115–118; (h) Kang, S. K.; Cho, H. S.; Sim, H. S.; Kim, B. K. *J. Carbohydr. Chem.* **1992**, *11*, 807–812.
8. Saniere, M.; Charvet, I.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 1653–1662.
9. (a) Konno, H.; Hiura, N.; Yanaru, M. *Heterocycles* **2002**, *57*, 1793–1797; (b) Andres, J. M.; de Elena, N.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1503–1509; (c) Pichon, M.; Jullian, J. C.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1998**, *39*, 1755–1758; (d) See Ref. 6i. (e) See Ref. 7f; (f) Gypser, A.; Peterek, M.; Scharf, H. D. *J. Chem. Soc., Perkin Trans. 1* **1997**, *7*, 1013–1016; (g) Baussanne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1997**, *38*, 2259–2262; (h) See Ref. 6k; (i) See Ref. 6p.
10. (a) Tsai, S. H.; Hsieh, P. C.; Wei, L. L.; Chiu, H. F.; Wu, Y. C.; Wu, M. J. *Tetrahedron Lett.* **1999**, *40*, 1975–1976; (b) Yoon, S. H.; Moon, H. S.; Kang, S. K. *Bull. Korean Chem. Soc.* **1998**, *19*, 1016–1018; (c) See Ref. 7e; (d) See Ref. 5.
11. For a preliminary account of this work see: Popsavin, V.; Krstić, I.; Popsavin, M. *Tetrahedron Lett.* **2003**, *44*, 8897–8900.
12. For recent accounts on application of the latent symmetry concept in enantioselective syntheses see: (a) Kireev, A. S.; Breithaupt, A. T.; Collins, W.; Nadein, O. N.; Kornienko, A. *J. Org. Chem.* **2005**, *70*, 742–745; (b) Ball, M.; Gaunt, M. J.; Hook, D. F.; Jessiman, A. S.; Kawahara, S.; Orsini, P.; Scolaro, A.; Talbot, A. C.; Tanner, H. R.; Yamanoi, S.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5433–5438; (c) Boulineau, F. P.; Wei, A. *Org. Lett.* **2004**, *6*, 119–121; (d) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726–8743; (e) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3–30.
13. Popsavin, V.; Grabež, S.; Krstić, I.; Popsavin, M.; Djoković, D. *J. Serb. Chem. Soc.* **2003**, *68*, 795–804.
14. Popsavin, M.; Popsavin, V.; Vukojević, N.; Miljković, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 1884–1888.
15. Szeja, W. *Pol. J. Chem.* **1980**, *54*, 1323–1325.
16. (a) Popsavin, V.; Grabež, S.; Popsavin, M.; Krstić, I.; Kojić, V.; Bogdanović, G.; Divjaković, V. *Tetrahedron Lett.* **2004**, *45*, 9409–9413; (b) Prakash, K. R. C.; Rao, S. P. *Tetrahedron* **1993**, *49*, 1505–1510.
17. Markidis, T.; Kokotos, G. *J. Org. Chem.* **2001**, *66*, 1919–1923.
18. Selected NMR data for **13**: δ_H 2.88 (br s, 2H, exchangeable with D_2O, 2×OH), 3.65 (s, 3H, CO_2Me); δ_C 51.52 (CO_2Me), 174.31 (CO_2Me).
19. Lee, J.; Lewin, N. E.; Acs, P.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 4912–4919.
20. Although the compound **17** could be stored at −20 °C for weeks without change, it tended to decompose on prolonged standing at room temperature. It should be therefore used in the next synthetic step immediately after its preparation.
21. Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827–4833.