Tetrahedron 66 (2010) 5244–5249

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formal synthesis of (+)-varitriol. Application of Pd(II)/Cu(II)-catalysed bicyclisation of unsaturated polyols

Miroslav Palík, Oľga Karlubíková, Daniela Lackovičová, Angelika Lásiková, Tibor Gracza *

Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

ARTICLE INFO

Article history:
Received 27 January 2010
Received in revised form 31 March 2010
Accepted 19 April 2010
Available online 24 April 2010

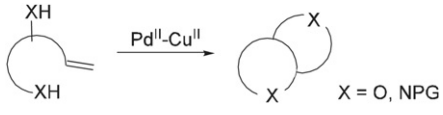
Keywords:
Palladium(II)-catalysis
Bicyclisation
Diastereoselectivity
Natural products
Varitriol

ABSTRACT

A formal and improved synthesis of natural (+)-varitriol from D-glucose and dimethyl L-tartrate, respectively, are reported. The key steps are the Pd(II)/Cu(II)-catalysed bicyclisation of *O*-benzyl protected triols L-*xylo*-**15** and L-*xylo*-**15**/L-*lyxo*-**15**, respectively, followed by ring opening of intermediate dianhydro-L-gulitol **16**. The syntheses of key intermediate of the furanoside portion **17** proceed in 13 steps with 5% (from bisacetone-D-glucose), and in 12 steps with 7.6% over-all yield from dimethyl L-tartrate, respectively.

1. Introduction

The direct oxidative bisfunctionalisation of alkenes represents a powerful transformation in the field of chemical synthesis. Considering the accessibility of alkenes and their robust nature, there is clearly an increased interest to develop new catalytic difunctionalisation reactions that add two functional groups across alkenes in a regio- and stereocontrolled manner.[1] Over the past few decades, several protocols for transition metal mediated direct diamination,[2] amino-acetoxylation,[3] diacetoxylation[4] and dioxygenation,[4] have been developed. In the course of our program directed towards the application of palladium(II)-catalysed bicyclisation of unsaturated polyols[5] in natural product synthesis, we have developed a novel type of $PdCl_2/CuCl_2$-catalysed dialkoxylation/aminoalkoxylation reaction of alkenes.[6] The terminal carbon–carbon double bond is bis-*O*/*N*,*O*-functionalised with two hydroxyl/amino-hydroxyl groups by sequential intramolecular/intramolecular process, which allows selective formation of two distinct carbon–heteroatom bonds by employing substrates containing nucleophiles tethered to the alkene (Scheme 1).



Scheme 1. $PdCl_2/CuCl_2$-catalysed bicyclisation of unsaturated polyols and amino polyols.

The tandem of diastereoselective bicyclisation reaction followed by a regioselective ring opening of the bicyclic skeleton represents a new synthetic access to heterocyclic compounds with defined stereochemistry. In our previous paper,[7] we described application of this method for the construction of 2,3-*trans*-tetrahydrofuran derivative en route to natural varitriol (+)-**1** (Fig. 1).

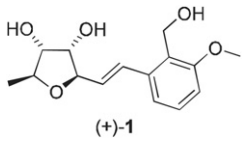


Figure 1. (+)-Varitriol.

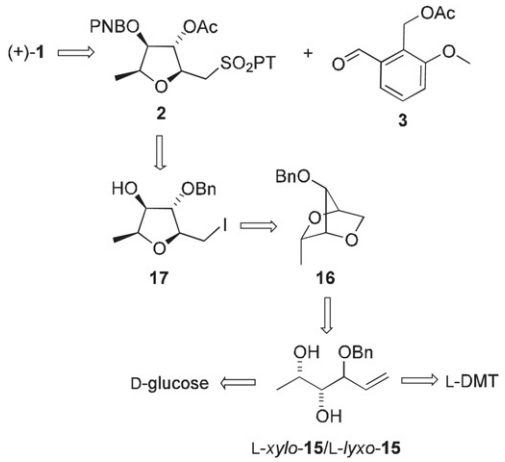
Varitriol was isolated from a marine-derived strain of fungus *Emericella variecolor* and shown to exhibit considerable cytotoxic activity against several human tumour cell lines.[8] Strikingly, (+)-**1** demonstrated increased potency towards selected renal, CNS and breast cancer cell lines.[8,9] The structure and relative stereochemistry of **1** was assigned on the basis of NMR spectroscopy and the absolute configuration was determined in the course of the synthesis of its unnatural enantiomer (−)-**1**.[10]

Meanwhile, growing attention is given to this cytotoxic compound, as demonstrated by development of total synthesis of varitriol (+)-**1**,[11] its unnatural enantiomer (−)-**1**[10,12] and structural analogues.[13,14] Jennings[10] and Taylor[12] reported the total syntheses of (−)-**1** from D-ribose utilising the alkene metathesis and the HWE/conjugate addition/Ramberg–Bäcklund rearrangement sequence, respectively. The synthesis of natural (+)-**1** is based on a cross

* Corresponding author. Tel.: +421 2 593 25 160; fax: +421 2 529 68 560; e-mail address: tibor.gracza@stuba.sk (T. Gracza).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.074

metathesis of the corresponding styrene and tetrahydrofuran subunit, the latter obtained from methyl α-D-mannopyranoside.[11] Recently, we described the synthesis of (+)-**1** starting with dimethyl L-tartrate using intramolecular Pd(II)/Cu(II)-catalysed bisalkoxylation of corresponding alkene triol as the key step.[7] We report herein details of the optimised synthesis of the key tetrahydrofuran intermediate **17** from dimethyl L-tartrate and a new synthesis starting from D-glucose, respectively (Scheme 2).



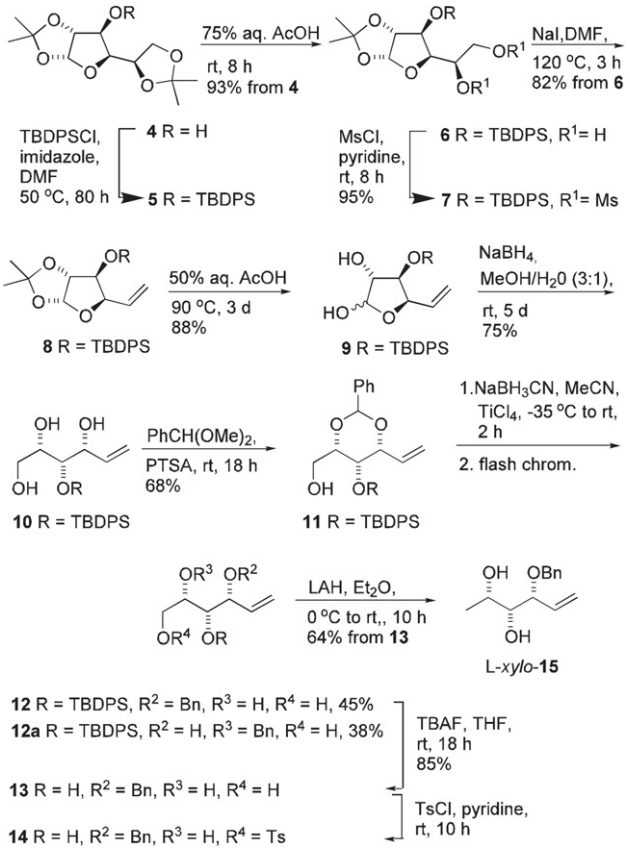
Scheme 2. Retrosynthetic analysis of (+)-**1**.

2. Results and discussion

Our synthetic approach to (+)-**1** was based on the coupling of furanoside subunit **2** with 2-acetoxymethyl-3-benzaldehyde **3** via Kocienski–Julia olefination.[15] The key reactions: (i) olefination, (ii) Pd(II)-catalysed bicyclisation and (iii) regioselective ring opening worked well, as expected.[7] The approach took advantage of our preliminary work, showing that unsaturated polyols undergo palladium(II)-catalysed bicyclisation with high *xylo*-substrate preference and excellent *threo*-selectivity.[6a] Thus, the mixture of diastereomeric triols L-*xylo*-**15**/L-*lyxo*-**15** in a ratio 3/7, subjected to standard bicyclisation reaction conditions, provided the bicyclic dianhydro-alditol **16** solely from L-*xylo*-diastereomer of the starting alkenol. Unfortunately, at the same time its major L-*lyxo* counterpart was transformed to a set of undesired products, complicating the purification of **16**. Undesirable ratio of triols L-*xylo*-**15**/L-*lyxo*-**15** (3:7) and impossibility to isolate the bicycle **16** in pure form decreased the total yield of target (+)-**1**. In connection with the above-mentioned, we were interested in obtaining a reliable access to pure L-*xylo*-**15**.

Optically pure triol L-*xylo*-**15** was finally synthesised from commercially available bisacetone-D-glucose in 11 steps, adopting a standard carbohydrate chemistry (Scheme 3). Silylation of bisacetone-D-glucose **4** followed by selective hydrolysis of the terminal acetonide, *O*-mesylation of both unprotected hydroxyl groups, reductive elimination with sodium iodide[16] and subsequent hydrolysis of the second acetonide with 50% aq acetic acid furnished D-*xylo*-5-hexenose **9** that subsequently underwent sodium borohydride reduction to provide alkene **10**.

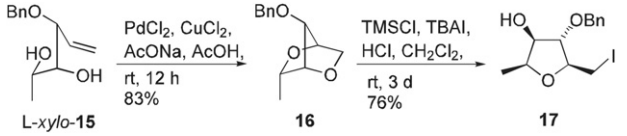
Introduction of an α-*O*-benzyl protecting group,[6a] required for Pd/Cu-bicyclisation was accomplished in two steps; acetalisation of **10** with benzaldehyde dimetyl acetal in the presence of *p*-toluenesulfonic acid followed by reduction of benzylidene ring with $NaBH_3CN/TiCl_4$ system, furnishing the α-*O*Bn-protected tetraol **12** (45%) along with its regioisomer **12a** (38%). The synthesis continued with desilylation of **12** using TBAF in THF affording triol **13** in good yield (85%). The first key intermediate, 1-deoxy-L-*xylo*-5-hexenitol L-*xylo*-**15**, was obtained in two-steps sequence to convert



Scheme 3. Synthesis of L-*xylo*-**15**.

hydroxymethyl to methyl group. Selective tosylation of primary hydroxyl group in pyridine, followed by hydride displacement afforded L-*xylo*-**15** in 64% yield over two steps. The protected hexenitols **10**, **12** and **12a**, respectively, have, to the best of our knowledge not been reported in the literature yet and we expect these to be highly interesting, versatile building blocks in other areas as well.

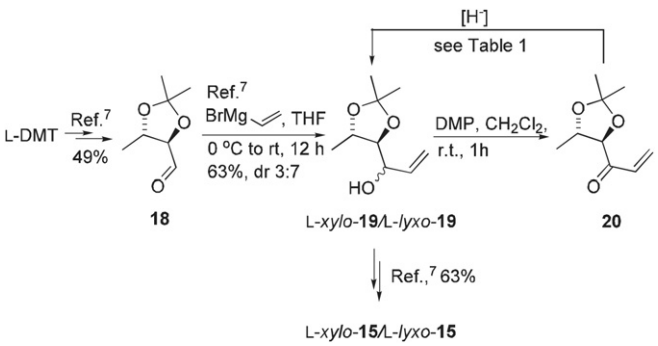
With diastereomerically pure triol L-*xylo*-**15** in our hands the synthesis was set up for the first key reaction of the sequence—intramolecular Pd(II)/Cu(II)-catalysed bisalkoxylation (Scheme 4). The reaction, performed under standard reaction conditions[6a,7] with $PdCl_2$ as catalyst (0.1 equiv), $CuCl_2$ (3 equiv), NaOAc (3 equiv) in AcOH as buffer at room temperature, proceeded very cleanly, providing bicyclic dianhydro-alditol **16** in good yield (83%) and with excellent *threo*-diastereoselectivity. The second crucial step of the synthesis is the opening of less substituted ring of bicyclic skeleton **16**. This was accomplished by treatment of dianhydro-alditol **16** with TBAI/TMSCl/HCl in dichloromethane at room temperature for 3 days. The required furan derivative **17** was formed with high *exo*-regioselectivity and in good yield (76%).



Scheme 4. Pd/Cu-catalysed bicyclisation of L-*xylo*-**15** and ring-opening of bicyclic dianhydro-alditol **16**.

Next, we decided to improve the efficiency of our previous varitriol synthesis[7] from dimethyl L-tartrate. The weak spot of this approach is the unfavourable stereochemical outcome of vinylmagnesium bromide addition to aldose **18**, providing the required diastereomer L-*xylo*-**19** only as a minor product along with L-*lyxo*-**19**

in the ratio of 3:7 and in 63% yield (Scheme 5). In order to reverse the diastereomeric triols distribution a stereoselective reduction of ketone **20** was examined. Thus, Dess–Martin oxidation of the mixture of alcohols L-*xylo*-**19**/L-*lyxo*-**19** afforded ketone **20**, which was subjected without purification to the reduction under various reaction conditions.



Scheme 5. Synthesis of L-*xylo*-**19**/L-*lyxo*-**19**.

Table 1 summarises results of a series of micro scale experiments with several metal hydrides in the presence of different Lewis acids. General *syn*-diastereoselectivity, observed in this set of reactions is in agreement with literature references describing additions of *C*-nucleophiles to analogous isopropylidene-threose derivatives.[5j,17] The best result was noted with $NaBH_4$ (1 equiv) in the presence of $CeCl_3 \cdot 7H_2O$ (1.1 equiv) in methanol at −78 °C (entry 4), affording the requisite L-*xylo*-diastereomer in dr 4:1 and 74% yield.

Table 1
Diastereoselective reduction of ketone **20**

Entry	Reagent (equiv)	Lewis acid	Solvent/ Temp °C	L-*xylo*-**19**/L-*lyxo*-**19**[a]	Yield[b] %
1	LAH (0.5)	—	Et_2O/−78	75:25	16
2	LAH (1)	$MgBr_2$	Et_2O/−78	76:24	32
3	$NaBH_4$ (1)	$CeCl_3$[c]	MeOH/0	75:25	43
4	$NaBH_4$ (1)	$CeCl_3$[c]	MeOH/−78	80:20	74
5	DIBAL (1)	—	CH_2Cl_2/−40	74:26	13
6	DIBAL (2)	$MgBr_2$	THF/−78	55:45	60
7	L-Selectride (3)	—	THF/−50	60:40	35
8	L-Selectride (3)	$MgBr_2$	THF/−78	64:26	70
9	Red-Al (4)	$MgBr_2$	THF/−78	70:30	33

[a] Relative ratios were determined from crude reaction mixture by ^1H and ^{13}C NMR spectroscopy.
[b] Total isolated yield of both diastereomers.
[c] $CeCl_3 \cdot 7H_2O$ was used.

3. Conclusions

In summary, a new formal and improved synthesis of natural (+)-varitriol has been developed from bisacetone-D-glucose and dimethyl L-tartrate, respectively. The key intermediate of the furanoside part of varitriol—iodide **17** was constructed using two key reactions, namely *threo*-diastereoselective Pd(II)/Cu(II)-catalysed intramolecular bisalkoxylation of L-*xylo*-**15** unsaturated triol followed by *exo*-regioselective ring opening of bicyclic dianhydroalditol **16**. Facility and effects of the two-reaction sequence performed with pure L-*xylo*-**15** demonstrates the applicability of the bicyclisation strategy in the synthesis of 2,3-*trans*-substituted tetrahydrofurans, the latter being hardly accessible by other means.

The total yield of **17** from dimethyl L-tartrate was doubled[7] utilising stereoselective reduction of the ketone **20**.

4. Experimental section

4.1. General methods

Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refer to the fraction boiling at 60–65 °C. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminium plates pre-coated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV_{254}, Macherey/Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat-gun. Optical rotations were measured with a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10,000 cm cell at the wavelength of sodium line D (λ=589 nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL. Elemental analyses were run on FISONS EA1108 instrument. FTIR spectra were obtained on a Nicolet 5700 spectrometer (Thermo Electron) equipped with a Smart Orbit (diamond crystal ATR) accessory, using the reflectance technique (4000–400 cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on either 300 (75) MHz MercuryPlus or 600 (150) MHz Unity Inova spectrometers from Varian. Chemical shifts (δ) are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as internal standard. Compounds are numbered according to carbohydrate naming scheme.

*4.1.1. 3-O-[(tert-Butyl)-diphenylsilyl]-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**5**).* To the solution of bisacetone-D-glucose **4** (20 g, 76.8 mmol) and imidazole (23 g, 307.2 mmol, 4.4 equiv) in dry dimethylformamide (200 mL) a solution of (*tert*-butyl)-diphenylsilylchloride (46.46 g, 169 mmol, 2.2 equiv) in dry dimethylformamide (100 mL) was added dropwise at room temperature over 30 min. After 80 h stirring at 50 °C the mixture was concentrated in vacuo (rotary evaporator, 50 °C, 5 mbar). The residue was dissolved in ethyl acetate (200 mL) and washed with water (50 mL) and brine (50 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (38.76 g, colourless oil, R_f 0.2, 5% AcOEt/hexanes) was used without further purification in the next step.

*4.1.2. 3-O-[(tert-Butyl)-diphenylsilyl]-1,2-O-isopropylidene-α-D-glucofuranose (**6**).* Crude bisacetonide **5** (38.76 g), dissolved in aq acetic acid (75%, 30 mL), was stirred at 40 °C for 50 h (TLC-monitoring). Removal of solvents in vacuo (20 mbar) furnished a yellow oil, which was purified by flash chromatography (silica gel, 30% AcOEt/hexanes). The furanose monoacetonide **6** was obtained as a colourless oil; yield 32.76 g (93% after two steps); [found: C, 65.72; H, 7.51. $C_{25}H_{34}O_6Si$ requires C, 65.47; H, 7.47%]; R_f (30% AcOEt/hexanes) 0.2; $[\alpha]_D^{25}$ −7.4 (*c* 0.325, MeOH); ν_{max} (ATR) 3514, 3396 (br), 2939, 2856, 1429, 1375, 1100, 1075, 1014, 969, 823, 739, 701 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.09 (s, 9H, $C(CH_3)_3$), 1.12, 1.38 (2×s, 6H, $C(CH_3)_2$), 1.98, 2.16 (2×br s, 2H, OH), 3.70–3.83 (m, 2H, H-6), 3.99, 4.46 (2×br s, 3H, H-3, H-4, H-5), 4.26 (d, 1H, $J_{1,2}$ 3.6 Hz, H-2) 5.82 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 7.37–7.49, 7.65–7.70 (2×m, 10H, Ph); δ_C (75 MHz $CDCl_3$) 19.4 (s, $C(CH_3)_3$), 26.0, 26.7 (all q, $C(CH_3)_2$), 26.9 (q, $C(CH_3)_3$), 64.6 (t, C-6), 68.5, 76.6, 81.2, 84.4 (all d, C-2, C-3, C-4, C-5), 104.8 (d, C-1), 111.6 (s, $C(CH_3)_2$), 127.9, 128.0, 130.1, 130.2 (all d, Ph), 132.3, 133.6 (all s, *i*-Ph), 135.6, 135.7 (all d, Ph).

*4.1.3. 3-O-[(tert-Butyl)-diphenylsilyl]-1,2-O-isopropylidene-5,6-di-O-mesyl-α-D-glucofuranose (**7**).* To the cooled (0 °C) solution of diol **6** (12 g, 26.1 mmol) in pyridine (150 mL) a solution of methanesulfonyl chloride (6.58 g, 57.5 mmol, 2.2 equiv) in pyridine (50 mL)

was added dropwise under vigorous stirring, keeping the reaction temperature below 10 °C. After 10 h stirring at rt the mixture was concentrated under reduced pressure and the remainder distributed between AcOEt (200 mL) and water (150 mL). Organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide product **7** as a yellow oil [15.23 g, 95%, R_f 0.2, 20%AcOEt in hexanes, $[\alpha]_D^{25}$ +6.1 (*c* 0.314, MeOH)], which was used without further purification in the next reaction; ν_{max} (ATR) 2947, 2851, 1428, 1356, 1174, 1075, 916, 821, 740, 701 cm^{-1}; δ_H (600 MHz $CDCl_3$) 1.06 (s, 3H, CH_3), 1.10 (s, 9H, C(CH_3)$_3$), 1.37 (s, 3H, CH_3), 2.97, 3.04 (2×s, 6H, SO_2CH_3), 4.22 (d, 1H, $J_{1,2}$ 3.5 Hz, H-2), 4.36 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 4.6 Hz, H-4), 4.53–4.58 (m, 2H, $J_{3,4}$ 2.6, $J_{5,6A}$ 6.8 Hz, H-3, H-6A), 4.69 (dd, 1H, $J_{5,6B}$ 2.0, $J_{6A,6B}$ 11.8 Hz, H-6B) 5.11–5.16 (m, 1H, $J_{5,6B}$ 2.0, $J_{5,6A}$ 6.8 Hz, H-5), 5.68 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 7.42–7.47, 7.65–7.72 (2×m, 10H, Ph); δ_C (150 MHz $CDCl_3$) 19.4 (s, C(CH_3)$_3$), 25.9, 26.6 (all q, C(CH_3)$_2$), 26.9 (q, C(CH_3)$_3$), 37.4, 39.0 (all q, SO_2CH_3), 68.7 (t, C-6), 75.9, 76.8, 80.3, 83.7 (all d, C-2, C-3, C-4, C-5), 104.4 (d, C-1), 112.1 (s, C(CH_3)$_2$), 128.0, 128.2, 130.3, 130.4 (all d, Ph), 131.9, 133.3 (all s, *i*-Ph), 135.6, 135.7 (all d, Ph).

*4.1.4. 3-O-[(tert-Butyl)-diphenylsilyl]-1,2-O-isopropylidene-α-D-xylo-5-hexenofuranose (**8**).* Varying the procedure given by Bladon and Owen,[16] a solution of crude dimesylate **7** (15.23 g) and NaI (31.24 g, 209 mmol, 8 equiv) in DMF (150 mL) was heated at 120 °C for 3 h. The solvent was removed on a rotavapor (45 °C, 5 mbar), the residue was distributed between $Na_2S_2O_3$ solution (10% in H_2O, 100 mL) and AcOEt (100 mL). Inorganic phase was extracted with AcOEt (3×50 mL) and combined organic phases were dried over Na_2SO_4. Concentrated crude mixture was purified by chromatography (silica gel, 2.5% AcOEt in hexanes). Yield of **8** as a colourless oil: 9.1 g (82% calculated from **6**); [found: C, 70.56; H, 7.71. $C_{25}H_{32}O_4Si$ requires C, 70.72; H, 7.60]; R_f (2.5% AcOEt/hexanes) 0.1; $[\alpha]_D^{26}$ −14.7 (*c* 0.375, MeOH); ν_{max} (ATR) 2931, 2858, 1427, 1373, 1164, 1112, 1075, 1018, 990, 823, 730, 701 cm^{-1}; δ_H (600 MHz $CDCl_3$) 1.07 (s, 9H, C(CH_3)$_3$), 1.16, 1.42 (2×s, 6H, C(CH_3)$_2$), 4.24–4.26 (m, 2H, H-2, H-3), 4.52 (dd, 1H, $J_{3,4}$ 2.6, $J_{4,5}$ 7.4 Hz, H-4), 5.24 (d, 1H, ddd, $J_{4,6E}$ 0.8, $J_{6E,6Z}$ 1.7, $J_{5,6E}$ 10.4 Hz, H-6E) 5.33 (ddd, 1H, $J_{4,6Z}$ 1.0, $J_{6E,6Z}$ 1.7, $J_{5,6Z}$ 17.4 Hz, H-6Z), 5.91 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.96 (ddd, 1H, $J_{4,5}$ 7.4, $J_{5,6E}$ 10.4, $J_{5,6Z}$ 17.5 Hz, H-5), 7.34–7.47, 7.62–7.67 (2×m, 10H, Ph); δ_C (150 MHz $CDCl_3$) 19.4 (s, C(CH_3)$_3$), 26.1, 26.7 (all q, C(CH_3)$_2$), 26.9 (q, C(CH_3)$_3$), 78.4, 82.6, 85.1 (all d, C-2, C-3, C-4), 104.6 (d, C-1), 111.4 (s, C(CH_3)$_2$), 119.3 (t, C-6), 127.6, 127.7, 129.9, 130.0 (all d, Ph), 132.7 (s, *i*-Ph), 132.8 (d, C-5), 133.6 (s, *i*-Ph), 135.8, 135.9 (all d, Ph).

*4.1.5. 3-O-[(tert-Butyl)-diphenylsilyl]-α/β-D-xylo-5-hexenofuranose (**9**).* The silyl-furanose **8** (8 g, 18.75 mmol) was dissolved in 50% aqueous AcOH (100 mL) and heated to 90 °C for 3 days (TLC control). Removal of solvents in vacuo (20 mbar) left a yellow oil, which was purified by chromatography on silica gel (eluent 5% AcOEt/CH_2Cl_2). The furanose **9** was obtained as a yellow, but analytically pure oil; yield 6.34 g (88%); [found: C, 68.56; H, 7.30. $C_{22}H_{28}O_4Si$ requires C, 68.71; H, 7.34]; $[\alpha]_D^{25}$ +22.7 (*c* 0.22, MeOH); ν_{max} (ATR) 3384 (br), 2929, 2856, 1471, 1427, 1104, 1021, 989, 820, 699 cm^{-1}; δ_H (600 MHz $CDCl_3$) mixture of α/β-anomers (2:1); α-anomer: 1.08 (s, 9H, C(CH_3)$_3$), 2.30 (d, 1H, *J* 4.6 Hz, OH), 3.68 (m, 1H, H-2), 3.87 (m, 1H, OH), 4.23–4.26 (m, 1H, H-3), 4.52–4.58 (m, 1H, H-4), 5.22–5.32 (m, 2H, H-6), 5.51 (dd, 1H, $J_{1,OH}$ 4.5, $J_{1,2}$ 5.4 Hz, H-1), 5.98 (ddd, 1H, $J_{4,5}$ 7.5, $J_{5,6E}$ 10.3, $J_{5,6Z}$ 17.7 Hz, H-5), 7.34–7.47, 7.61–7.69 (2×m, 10H, Ph); β-anomer: 1.09 (s, 9H, C(CH_3)$_3$), 1.71 (d, 1H, *J* 4.3 Hz OH), 3.58 (d, 1H, $J_{1,2}$ 11.3 Hz H-2), 3.91–3.94 (m, 1H, OH), 4.19–4.23 (m, 1H, H-3), 4.52–4.58 (m, 1H, H-4), 5.06 (d, 1H, $J_{1,2}$ 11.2 Hz, H-1), 5.26–5.41 (m, 2H, H-6) 6.04 (ddd, 1H, $J_{4,5}$ 7.3, $J_{5,6E}$ 10.2, $J_{5,6Z}$ 17.6 Hz, H-5), 7.34–7.47, 7.61–7.69 (2×m, 10H, Ph); δ_C (150 MHz $CDCl_3$) mixture of anomers (α/β, 2:1): 19.2, 19.3 (s, C(CH_3)$_3$), 26.9, 27.0 (q, C(CH_3)$_2$), 76.9, 77.2, 78.6, 79.6, 80.3, 81.4, 83.8, 83.9 (all d, C-2, C-3, C-4), 96.2, 103.6 (d, C-1), 118.7, 118.9 (t, C-6), 127.7, 127.8, 127.8, 127.9, 129.9, 130.0, 130.2, 130.3, 131.8, 132.8, 132.9, 133.6, 135.8, 135.8, 135.9, 136.0 (all d, Ph), 134.0, 134.3 (d, C-5).

*4.1.6. 3-O-[(tert-Butyl)-diphenylsilyl]-L-xylo-5-hexenitol (**10**).* To the solution of aldofuranose **9** (5.5 g, 14.30 mmol) in a mixture of MeOH/H_2O (3:1, 700 mL) solid $NaBH_4$ (3.727 g, 100 mmol, 7 equiv) was portionwise added. After 5 days stirring at rt the solution was concentrated to a third of original volume (rotary evaporator, 30 mbar) and acidified by addition of concd H_2SO_4 (several drops) to attain pH 5–6. The residue was distributed between AcOEt (200 mL) and water (50 mL) and separated water layer was extracted with AcOEt (6×50 mL). Combined organic extracts were dried over Na_2SO_4 and after solvent removal separated by flash column chromatography on silica (20% AcOEt/hexanes). Yield of **10** as a colourless oil: 4.147 g (75%); [found: C, 68.72; H, 7.51. $C_{22}H_{30}O_4Si$ requires C, 68.36; H, 7.82]; R_f (20% AcOEt/CH_2Cl_2) 0.21; $[\alpha]_D^{25}$ +15.7 (*c* 0.28, MeOH); ν_{max} (ATR) 3384 (br), 2930, 2856, 1471, 1427, 1110, 997, 823, 700 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.09 (s, 9H, C(CH_3)$_3$), 2.83, 2.90 (2×br s, 3H, 3×OH), 3.56, 3.76–3.81 (2×m, 4H, H-1, H-2, H-3), 4.22–4.25 (m, 1H, H-4), 5.25 (ddd, 1H, $J_{4,6E}$=$J_{6Z,6E}$ 1.2, $J_{5,6E}$ 10.5 Hz, H-6E), 5.38 (ddd, 1H, $J_{4,6Z}$ 1.2, $J_{6Z,6E}$ 1.3, $J_{5,6Z}$ 17.2 Hz, H-6Z), 5.87 (ddd, 1H, $J_{4,5}$ 6.2, $J_{5,6E}$ 10.5, $J_{5,6Z}$ 17.1 Hz, H-5), 7.36–7.47, 7.63–7.68 (2×m, 10H, Ph); δ_C (75 MHz $CDCl_3$) 19.2, (s, C(CH_3)$_3$), 26.8, (q, C(CH_3)$_2$), 65.6 (t, C-1), 71.7, 73.1, 74.2 (all d, C-2, C-3, C-4), 117.6 (t, C-6), 127.8, 127.8, 129.9, 129.9 (all d, Ph), 132.6, 132.7 (all s, *i*-Ph), 135.4, 135.5 (all d, Ph), 136.8 (d, C-5).

*4.1.7. 2,4-O-Benzylidene-3-O-[(tert-butyl)-diphenylsilyl]-L-xylo-5-hexenitol (**11**).* To a solution of hexenitol **10** (4 g, 10.34 mmol) in toluene (150 mL) was added benzaldehyde dimethyl acetal (3.1 g, 20.68 mmol, 2 equiv) and PTSA (98 mg, 0.517 mmol, 0.05 equiv). The resulting solution was stirred at room temperature for 18 h (TLC-monitoring). After concentration (rotavapor) the residue was purified by flash column chromatography (silica gel, 5% AcOEt/hexanes) to provide 3.3 g (68%) of benzylidene acetal **11** as a colourless oil; [found: C, 73.12; H, 7.31. $C_{29}H_{34}O_4Si$ requires C, 73.38; H, 7.22]; R_f (5% AcOEt/hexanes) 0.3; $[\alpha]_D^{27}$ +17.4 (*c* 0.219, MeOH); ν_{max} (ATR) 3469 (br), 2929, 2856, 1471, 1427, 1105, 1025, 823, 688 cm^{-1}; δ_H (600 MHz $CDCl_3$) 1.06 (s, 9H, C(CH_3)$_3$), 3.75 (br s, 1H, H-3), 3.85 (A of ABX, dd, 1H, $J_{1A,2}$ 5.4, $J_{1A,1B}$ 10 Hz, H-1A), 3.98 (B of ABX, ddd, 1H, $J_{1B,2}$ 6.6, $J_{1A,1B}$ 10 Hz, H-1B), 4.05 (X of ABX, ddd, 1H, $J_{2,3}$ 1.2, $J_{1A,2}$ 5.4, $J_{1B,2}$ 6.6 Hz, H-2), 4.44 (dddd, 1H, $J_{3,4}$ 1.4, $J_{4,6E}$=$J_{4,6E}$ 1.5, $J_{4,5}$ 5.2 Hz, H-4), 5.34 (ddd, 1H, $J_{4,6E}$=$J_{6Z,6E}$ 1.5, $J_{5,6E}$ 10.7 Hz, H-6E), 5.47 (ddd, 1H, $J_{4,6Z}$=$J_{6Z,6E}$ 1.5, $J_{5,6Z}$ 17.4 Hz, H-6Z), 5.66 (s, 1H, C*H*Ph), 6.03 (ddd, 1H, $J_{4,5}$ 5.2, $J_{5,6E}$ 10.7, $J_{5,6Z}$ 17.4 Hz, H-5), 7.34–7.42 (m, 9H, Ph), 7.49–7.50 (m, 2H, Ph), 7.68–7.72 (m, 4H, Ph); δ_C (150 MHz $CDCl_3$) 19.2, (s, C(CH_3)$_3$), 26.8, (q, C(CH_3)$_2$), 63.0 (t, C-1), 65.9 (d, C-3), 80.3, 80.9 (all d, C-2, C-4), 100.9 (s, *C*HPh), 117.6 (t, C-6), 126.1, 127.7, 127.9, 128.2, 128.9 (all d, Ph), 133.1, 133.3 (all s, *i*-Ph), 134.4 (d, C-5), 135.6, 135.5 (all d, Ph), 137.7 (s, *i*-Ph).

*4.1.8. 4-O-Benzyl-3-O-[(tert-butyl)-diphenylsilyl]-L-xylo-5-hexenitol (**12**).* To a solution of acetal **11** (1780 mg, 3.75 mmol) and $NaBH_3CN$ (307 mg, 4.875 mmol, 1.3 equiv) in dry MeCN (80 mL) $TiCl_4$ (925 mg, 0.536 mL, 4.875 mmol, 1.3 equiv) was added dropwise through septum at −35 °C over 5 min under Ar. The reaction mixture was stirred for 2 h, while the temperature reached rt. After hydrolysis with satd aq K_2CO_3 soln (20 mL), the mixture was evaporated in vacuo. The residue was extracted with AcOEt (3×20 mL), combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. Separation of the crude reaction mixture by FLC (silica gel, 20% AcOEt/hexanes) provided fraction one containing 4-*O*-benzylated hexenitol **12**, 804 mg (45%), colourless oil; [found: C, 73.22; H, 7.56. $C_{29}H_{36}O_4Si$ requires C, 73.07; H, 7.61]; R_f (25% AcOEt/hexanes) 0.25; $[\alpha]_D^{25}$ −7.2 (*c* 0.415, MeOH); fraction two after evaporation and drying (P_2O_5, 0.1 mbar) gave analytically pure

regioisomer 2-*O*-benzyl-3-*O*-[(*tert*-butyl)-diphenylsilyl]-L-*xylo*-5-hexenitol **12a**, 679 mg, (38%), colourless oil; [found: C, 72.89; H, 7.73. $C_{29}H_{36}O_4Si$ requires C, 73.07; H, 7.61]; R_f (25% AcOEt/hexanes) 0.15; $[\alpha]_D^{25}$+19.6 (*c* 0.458, MeOH).

Compound **12**: ν_{max} (ATR) 3469 (br), 2929, 2856, 1722, 1471, 1427, 1110, 1051, 823, 700 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.04 (s, 9H, C(CH_3)$_3$), 2.68, 2.89 (2×br s, 2H, 2×OH), 3.69–3.72 (m, 4H, H-1, H-2, H-3), 3.96 (dd, 1H, $J_{3,4}$=$J_{4,5}$ 7.4 Hz, H-4), 4.35 (d, 1H, *J* 11.4 Hz, CH_2Ph), 4.65 (d, 1H, *J* 11.4 Hz, CH_2Ph), 5.37–5.43 (m, 2H, H-6), 5.77 (m, 1H, $J_{5,6E}$ 10.7, $J_{5,6Z}$ 17.1 Hz, H-5), 7.30–7.39 (m, 11H, Ph), 7.64–7.65 (m, 4H, Ph); δ_C (75 MHz $CDCl_3$) 19.2, (s, $C(CH_3)_3$), 26.8, (q, C(CH_3)$_2$), 65.0 (t, C-1), 70.5 (t, CH_2Ph), 70.8, 72.3 (all d, C-2, C-3), 81.9, (d, C-4), 120.7 (t, C-6), 127.6, 127.7, 127.8, 127.9, 128.5, 129.7, 129.8 (all d, Ph), 133.1, 133.2 (all s, *i*-Ph), 134.7 (d, C-5), 135.6, 135.5 (all d, Ph), 137.7 (s, *i*-Ph).

Compound **12a**: ν_{max} (ATR) 3400 (br), 2929, 2856, 1724, 1471, 1427, 1110, 1070, 823, 700 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.06 (s, 9H, C(CH_3)$_3$), 2.69, 2.96 (2×br s, 2H, 2×OH), 3.55 (ddd, 1H, $J_{2,3}$ 3.2, $J_{1A,2}$ 4.9, $J_{1B,2}$ 5.6 Hz, H-2), 3.63–3.69 (m, 1H, H-3), 3.84 (dd, 1H, $J_{1A,2}$ 4.8, $J_{1A,1B}$ 10.9 Hz, H-1A), 3.91 (dd, 1H, $J_{1B,2}$ 5.6, $J_{1A,1B}$ 10.9 Hz, H-1B), 4.16 (dd, 1H, $J_{3,4}$ 5.9, $J_{4,5}$ 6.1 Hz, H-4), 4.39 (d, 1H, *J* 11.5 Hz, CH_2Ph), 4.63 (d, 1H, *J* 11.5 Hz, CH_2Ph), 5.20 (ddd, 1H, $J_{4,6Z}$ 1.2, $J_{6E,6Z}$ 1.6, $J_{5,6E}$ 10.4 Hz, H-6E), 5.22 (ddd, 1H, $J_{4,6E}$ 1.4, $J_{6E,6Z}$ 1.6, $J_{5,6Z}$ 17.3 Hz, H-6E), 5.79 (ddd, 1H, $J_{4,5}$ 6.3, $J_{5,6E}$ 10.5, $J_{5,6Z}$ 17.2 Hz, H-5), 7.22–7.45 (m, 11H, Ph), 7.66–7.70 (m, 4H, Ph); δ_C (75 MHz $CDCl_3$) 19.1, (s, $C(CH_3)_3$), 26.8, (q, C(CH_3)$_2$), 62.8 (t, C-1), 72.5 (t, CH_2Ph), 73.3, 73.4 (all d, C-2, C-3), 78.4, (d, C-4), 117.4 (t, C-6), 127.7, 127.8, 127.9, 128.0, 128.5, 129.8, 129.9 (all d, Ph), 132.8, 133.0 (all s, *i*-Ph), 135.5, 135.6 (all d, Ph), 137.1 (d, C-5), 137.6 (s, *i*-Ph).

*4.1.9. 4-O-Benzyl-L-xylo-5-hexenitol (**13**).* A mixture of silylated hexenitol **12** (461 mg, 0.967 mmol) and TBAF×3H_2O (671 mg, 2.127 mmol, 2.2 equiv) in THF (20 mL) was stirred at room temperature for 18 h. Removal of solvents in vacuo (20 mbar) gave a yellow oil, which was purified by flash chromatography (silica gel, 50% AcOEt/CH_2Cl_2). The benzyl-hexenitol **13** was obtained as a colourless oil; yield 195 mg (85%); [found: C, 65.72; H, 7.34. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61]; R_f (50% AcOEt/CH_2Cl_2) 0.15; $[\alpha]_D^{26}$ −16.1 (*c* 0.223, MeOH); ν_{max} (ATR) 3363 (br), 2927, 2871, 1720, 1496, 1454, 1421, 1392, 1054, 735, 698 cm^{-1}; δ_H (300 MHz $CDCl_3$) 2.76–2.81 (m, 3H, 3×OH), 3.59 (d, 1H, *J* 6.7 Hz, H-2), 3.64–3.72 (m, 3H, H-1, H-3), 3.98 (dd, 1H, $J_{3,4}$=$J_{4,5}$ 7.2 Hz, H-4), 4.35 (d, 1H, *J* 11.5 Hz, CH_2Ph), 4.65 (d, 1H, *J* 11.5 Hz, CH_2Ph), 5.42–5.44 (m, 2H, H-6), 5.80 (ddd, 1H, $J_{4,5}$ 8.0, $J_{5,6E}$ 10.0, $J_{5,6Z}$ 17.8 Hz, H-5), 7.29–7.36 (m, 5H, Ph); δ_C (75 MHz $CDCl_3$) 65.0 (t, C-1), 70.5 (t, CH_2Ph), 70.5, 74.4, 81.7 (all d, C-2, C-3, C-4), 120.9 (t, C-6), 127.9 (d, *p*-Ph), 128.0 (d, *o*-Ph), 128.6 (d, *m*-Ph), 134.4 (d, C-5), 137.6 (s, *i*-Ph).

*4.1.10. 4-O-Benzyl-1-deoxy-L-xylo-5-hexenitol (**15**).* To the solution of hexenitol **13** (176 mg, 0.738 mmol) in pyridine (15 mL) *p*-toluenesulfonyl chloride (148 mg, 0,775 mmol, 1.05 equiv) was added at room temperature. After 10 h stirring at rt the mixture was concentrated in vacuo (rotary evaporator, 50 °C, 5 mbar). The residue was dissolved in ethyl acetate (50 mL) and washed with water (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4 a concentrated under reduced pressure. The crude tosylated product **14** (295 mg, yellow oil, R_f 0.7, 50% AcOEt/CH_2Cl_2) was dissolved in Et_2O (5 mL) and added dropwise to a stirred suspension of LAH (56 mg, 1.476 mmol, 2 equiv) in Et_2O (10 mL) at 0 °C. The reaction mixture was then warmed to room temperature, and stirring continued for another 10 h. Glauber salt (300 mg) was added until the colour of the mixture changed from grey to white to quench the excess reducing agent. The mixture was diluted with ether (50 mL) and filtered through a Celite bed. The filtrate and washings were combined and concentrated under reduced pressure. Purification of the crude product by FLC (silica gel, 10% AcOEt in CH_2Cl_2) provided **15**, 105 mg (64%), colourless oil; [found: C, 69.97; H, 8.22. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16]; R_f (10% AcOEt/CH_2Cl_2) 0.15; $[\alpha]_D^{25}$ −26.8 (*c* 0.190, MeOH); ν_{max} (ATR) 3417 (br), 2927, 2871, 1496, 1454, 1047, 1027, 991, 735, 697 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.19 (d, 3H, H-1), 2.57 (d, 1H, $J_{2,OH}$ 5.5 Hz, OH-2), 2.80 (d, 1H, $J_{3,OH}$ 5.1 Hz, OH-3), 3.31–3.35 (m, 1H, $J_{2,3}$ 2.8, $J_{3,OH}$ 5.1 Hz, H-3), 3.81–3.86 (m, 1H, H-2), 3.91 (dd, 1H, $J_{3,4}$ 5.6, $J_{4,5}$ 8.0 Hz, H-4), 4.34 (d, 1H, *J* 11.6 Hz, CH_2Ph), 4.65 (d, 1H, *J* 11.6 Hz, CH_2Ph), 5.36–5.43 (m, 2H, $J_{4,6E}$=$J_{4,6Z}$ 0.8, $J_{6Z,6E}$ 1.6, $J_{5,6E}$ 10.6, $J_{5,6Z}$ 17.0 Hz, H-6), 5.86 (ddd, 1H, $J_{4,5}$ 8.0, $J_{5,6E}$ 10.6, $J_{5,6Z}$ 17.0 Hz, H-5), 7.30–7.36 (m, 5H, Ph); δ_C (75 MHz $CDCl_3$) 20.0 (q, C-1), 70.3 (t, CH_2Ph), 67.5, 76.6, 81.9 (all d, C-2, C-3, C-4), 120.4 (t, C-6), 127.9 (d, *p*-Ph), 128.0 (d, *o*-Ph), 128.5 (d, *m*-Ph), 134.9 (d, C-5), 137.6 (s, *i*-Ph).

*4.1.11. 6-Deoxy-1,4:2,5-di-anhydro-3-O-benzyl-L-gulitol (**16**).* The mixture of alkenitol **15** (87 mg, 0.391 mmol), $PdCl_2$ (7 mg, 0.039 mmol, 0.1 equiv), anhydrous $CuCl_2$ (159 mg, 1.174 mmol, 3 equiv) and anhydrous AcONa (96 mg, 1.174 mmol, 3 equiv) in glacial AcOH (10 mL) was stirred at room temperature for 12 h. Solvent was evaporated in vacuo and the residue distributed between an aq soln of ammonia (10%, 25 mL) and AcOEt (20 mL). Water phase was extracted with AcOEt (5×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the resultant residue by FLC (30 g of silica gel, 15% AcOEt in hexanes) yielded 71 mg (83%) of bicycle **16** as a colourless oil; [found: C, 70.07; H, 7.43. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32]; R_f (20% AcOEt/hexanes) 0.2; $[\alpha]_D^{25}$ +33.3 (*c* 0.03, MeOH); ν_{max} (ATR) 2924, 2852, 1724, 1452, 1270, 1091, 1028, 699 cm^{-1}; δ_H (300 MHz $CDCl_3$) 1.33 (d, 3H, $J_{5,6}$ 6.5 Hz, H-6), 3.87 (s, 2H, H-1), 3.94–3.95 (m, 1H, $J_{4,5}$ 0.8, $J_{3,4}$ 2.2 Hz, H-4), 4.21–4.22 (m, 2H, $J_{3,4}$ 2.2 Hz, H-2, H-3), 4.43 (dq, 1H, $J_{4,5}$ 0.8, $J_{5,6}$ 6.5 Hz, H-5), 4.43 (d, 1H, *J* 11.8 Hz, CH_2Ph), 4.68 (d, 1H, *J* 11.8 Hz, CH_2Ph), 7.36–7.38 (m, 5H, Ph); δ_C (75 MHz $CDCl_3$) 15.3 (q, C-6), 72.3, 73.6 (2×t, CH_2Ph, C-1), 76.6, 77.6, 77.8, 81.9 (all d, C-2, C-3, C-4, C-5), 127.9 (d, *o*-Ph), 128.0 (d, *p*-Ph), 128.5 (d, *m*-Ph), 137.5 (s, *i*-Ph).

*4.1.12. 3-O-Benzyl-1,6-dideoxy-1-iodo-2,5-anhydro-L-gulitol (**17**).* In accord with the described procedure;[7] dianhydro-gulitol **16** (45 mg, 0.204 mmol), trimethylsilyl chloride (33 mg, 0.306 mmol, 1.5 equiv), tetrabutylammonium iodide (150 mg, 0.449 mmol, 2.2 equiv) and concd HCl (0.08 mL) were stirred in CH_2Cl_2 (5 mL) at room temperature for 3 days. The crude product, a yellowish oil, was purified by flash chromatography (silica gel, 30% AcOEt in toluene), and a colourless, analytically pure oil of **17** was obtained; yield 53 mg (76%); R_f (30% AcOEt/toluene) 0.4; $[\alpha]_D^{25}$ +12.5 (*c* 0.126, MeOH){lit., $[\alpha]_D^{20}$ +14.2 (*c* 0.6, $CHCl_3$). The spectral data were in good agreement with that reported.[7]

*4.1.13. 4-O-Benzyl-1-deoxy-2,3-O-isopropylidene-L-xylo-5-hexenitol (L-xylo-**19**) and 4-O-benzyl-1-deoxy-2,3-O-isopropylidene-L-lyxo-5-hexenitol (L-lyxo-**19**). 4.1.13.1. Preparative procedure with $NaBH_4$, $CeCl_3 \cdot 7H_2O$.* Dess–Martin periodinane (364 mg, 0.87 mmol, 1.5 equiv) was added to a solution of triols[7] L-*lyxo*-**19**/L-*xylo*-**19** (100 mg, 0.58 mmol, ratio 69:31 by GC) in dry CH_2Cl_2 (15 mL) at 0 °C. After stirring for 2 h, saturated solution of $NaHCO_3$ (15 mL) and aqueous $Na_2S_2O_3$ (20 mL) were added successively and stirring was continued for another 1 h. The mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine and dried (Na_2SO_4). The combined organic layer was concentrated under reduced pressure to give clear oil (98 mg). To the mixture of crude ketone **20** (98 mg) and $CeCl_3 \cdot 7H_2O$ (216 mg, 0.58 mmol, 1 equiv) in MeOH (5 mL) at −78 °C was added $NaBH_4$ (22 mg, 0.58 mmol, 1 equiv) and the reaction mixture was stirred at the same temperature for 3 h. An aqueous solution of NH_4Cl (5 mL) was added and resulting mixture was extracted with Et_2O (3×10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, to give **19** after column chromatography (silica gel, 50% AcOEt/hexanes, 74 mg, 74% over two steps) as a mixture of diastereomers

L-*lyxo*-**19**/L-*xylo*-**19** (25:75, ^{1}H NMR). The spectral data were in good agreement with those reported.[7]

*4.1.13.2. Typical procedure for reduction of ketone **20** (see Table 1).* Reducing agent (0.5–4 equiv) was added to the solution of crude ketone **20** (50 mg, 0.29 mmol) in 10 mL of corresponding solvent at chosen temperature and the mixture kept at initial temperature for additional 3 h, then left to reach rt. Reaction was left until no **20** was observed, but no longer than 24 h. Reactions were quenched with satd NH_4Cl (10 mL), extracted with Et_2O and dried over Na_2SO_4. Crude oils were analysed by ^{1}H and ^{13}C NMR spectroscopy.

*4.1.13.3. Typical procedure for reduction of ketone **20** in the presence of Lewis acid.* Lewis acid (1.1 mmol) was dissolved or suspended in corresponding solvent (10 mL) and cooled to chosen temperature. Freshly prepared ketone **20** (50 mg, 0.29 mmol) in solvent (5 mL) was added and mixture was left to stir for 30 min. Reducing agent (0.5–4 equiv) was added within 10 min, and the mixture stirred at initial temperature for 3 h, then left to reach rt; until no **20** was observed, but no longer than 24 h. Workup as described above.

Acknowledgements

This work was supported by Slovak Grant Agencies (VEGA, Slovak Academy of Sciences and Ministry of Education, Bratislava, projects No. 1/0115/10, No. 1/0236/09 and APVV, Bratislava, project No. APVV-20-000305, project No. LPP-0071-09).

References and notes

1. For reviews see: (a) Kolb, H. C.; VanNiuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083–4088; (c) Bäckvall, J.-E In. *Metal-Catalyzed Cross-Coupling Reactions*; 2004; Vol. 2, pp 479–529.
2. (a) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309; (b) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762–763; (c) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689; (d) Xu, L.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 749–751; (e) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496–7497; (f) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590–8591; (g) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587; (h) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542–14543; (i) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773.
3. (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691; (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181; (c) Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737–5740; (d) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. *Tetrahedron* **2009**, *65*, 5118–5124.
4. (a) Chevrin, C.; Le Bras, J.; Henin, F.; Muzart, J. *Synthesis* **2005**, 2615–2618; (b) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460–1461; (c) Thiery, E.; Chevrin, C.; Le Bras, J.; Harakat, D.; Muzart, J. *J. Org. Chem.* **2007**, *72*, 1859–1862; (d) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076–3077; (e) Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962–2964; Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074–17075.
5. (a) Gracza, T.; Hasenohrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108–1118; (b) Jäger, V.; Gracza, T.; Dubois, E.; Hasenohrl, T.; Hümmer, W.; Kautz, U.; Kirschbaum, B.; Lieberknecht, A.; Remen, L.; Shaw, D.; Stahl, U.; Stephan, O. Pd(II)-catalyzed carbonylation of unsaturated polyols and aminopolyols In *Organic Synthesis via Organometallics OSM 5*; Helmchen, G., Dibo, J., Flubacher, D., Wiese, B., Eds.; Vieweg: Braunschweig, 1997; pp 331–360; (c) Hümmer, W.; Dubois, E.; Gracza, T.; Jäger, V. *Synthesis* **1997**, *6*, 634–642; (d) Gracza, T.; Jäger, V. *Synlett* **1992**, 191–193; (e) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359–1368; (f) Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolcsányi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 839–841; (g) Szolcsányi, P.; Gracza, T.; Koman, M.; Pronayová, N.; Liptaj, T. *Chem. Commun.* **2000**, 471–472; (h) Szolcsányi, P.; Gracza, T.; Koman, M.; Pronayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2579–2597; (i) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983–6985; (j) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471–2479.
6. (a) Babjak, M.; Remen, L.; Szolcsányi, P.; Zalupsky, P.; Miklos, D.; Gracza, T. *J. Organomet. Chem.* **2006**, *691*, 928–940; (b) Babjak, M.; Remen, L.; Karlubíková, O.; Gracza, T. *Synlett* **2005**, 1609–1611; (c) Szolcsányi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948–3950.
7. Palík, M.; Karlubíková, O.; Lásiková, A.; Kožíšek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709–715.
8. Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364–367.
9. Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, *40*, 2676–2704.
10. Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720–2721.
11. Kumar, V.; Shaw, A. K. *J. Org. Chem.* **2008**, *73*, 7526–7531.
12. McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 12123–12130.
13. Nagarapu, L.; Paparaju, V.; Satyender, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2351–2354.
14. Senthilmurugan, A.; Aidhen, I. S. *Eur. J. Org. Chem.* **2010**, 555–564.
15. (a) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26–28; (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836; (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.
16. Bladon, P.; Owen, L. N. *J. Chem. Soc.* **1950**, *591*, 598–603.
17. For diastereoselectivity of organometallic reagents additions to 2,3-*O*-isopropylidene-D-threose derivatives see: (a) Akita, H.; Uchida, K.; Kato, K. *Heterocycles* **1998**, *47*, 157–162; (b) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045–7048; (c) Wu, W.-L.; Yao, Z.-J.; Li, Y. L.; Li, J.-C.; Xia, Y.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 3257–3259; (d) Marco-Contelles, J.; Bernabe, M.; Ayala, D.; Sanchez, B. *J. Org. Chem.* **1994**, *59*, 1234–1235; (e) Kanger, T.; Liiv, M.; Pehk, T.; Lopp, M. *Synthesis* **1993**, 91–93; (f) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265–276; (g) Lee, W. W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473–4476.