Pergamon

Tetrahedron 55 (1999) 11819–11832

TETRAHEDRON

An Approach to the Bicyclic Core of the Zaragozic Acids *via* the Aldol Reaction Between Methyl (α-D-xylofuranoside)uronate and D-(R)-Glyceraldehyde Acetonide

Pierre Fraisse,[a] Issam Hanna,[*a] Jean-Yves Lallemand,[a] Thierry Prangé [b] and Louis Ricard.[c]

[a]Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau, France. [b] Laboratoire de Chimie Structurale Biomoléculaire, associé au CNRS, 74 rue M. Cachin, F-93012 Bobigny, France. [c] Laboratoire "Hétéroéléments et Coordination" associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau Cedex, France

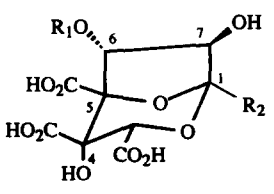
Received 19 May 1999; accepted 22 July 1999

Abstract: *The aldol reaction between methyl (methyl-3-O-benzyl-2-O-methoxymethyl-α-D-xylofurano-side)uronate and D-(R)-glyceraldehyde acetonide, promoted by cerium(III) chloride, led to three diastereoisomers in good yield and high level of stereoselectivity at the newly created quaternary center of the furanoside. Under acidic conditions, the aldol derivatives undergo transketalization to afford different bicyclic ketal isomers. This reaction was used as the key step in the synthesis of a functionalized bicyclic core of the zaragozic acids.*

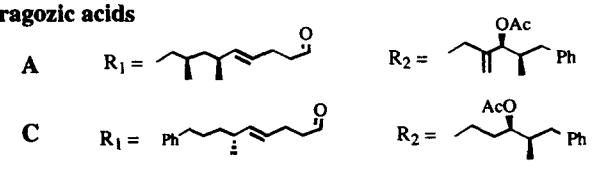
Keywords: *Zaragozic Acids, aldol reaction, (R)-glyceraldehyde acetonide, α-D-xylofuranuronic acid.*

Introduction

The zaragozic acids (squalestatins), a family of naturally occuring fungal metabolites isolated in 1992, have been found to be potent inhibitors of the enzyme squalene synthase. This enzyme is responsible for the first step in the biosynthesis of steroids such as cholesterol. Compounds that inhibit the function of this enzyme have potential as important therapeutic agents, in particular for the treatment of hypercholesterolaemia. Structurally, these compounds share a common densely functionalized 2,8-dioxabicyclo[3.2.1]octane skeleton **1**. The complexity of this structure combined with the biological activity of these natural products has served to stimulate a large amount of synthetic activity in a number of laboratories,[1] and culminated in the total syntheses of zaragozic acids A[2] and C.[3]

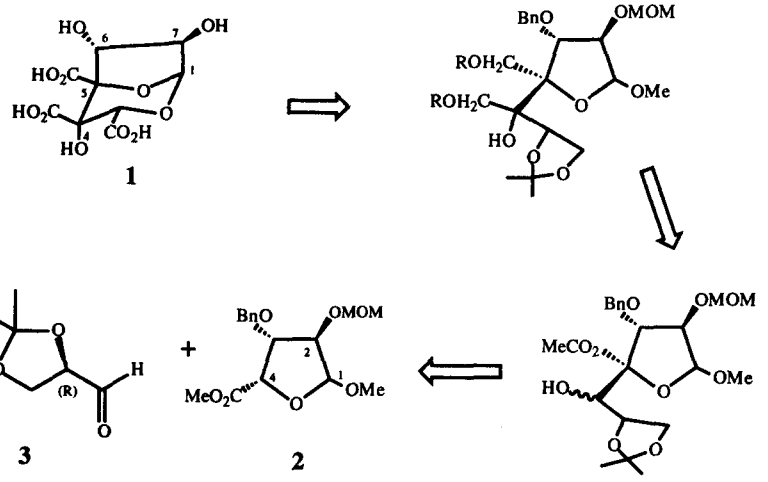


Zaragozic acids



0040-4020/99/$ - see front matter
PII: S0040-4020(99)00637-7

In a new synthetic approach, we envisaged the construction of the bicyclic core of the zaragozic acids starting from the readily available α-D-xylofuranuronic acid derivative **2** and D-(R)-glyceraldehyde acetonide **3**. As shown in the retrosynthetic analysis (Scheme 1), our plan involves the introduction of the three-carbon unit at C-4 by an aldol condensation between the enolate generated from **2** and aldehyde **3**. An attractive feature of this plan is that the entire carbon skeleton of the target can be introduced by the formation of one carbon-carbon bond. The configuration at C-2 and C-3 of ester **2** and the chiral center at C-2 in **3** correlate with the configuration at C-6, C-7 and C-3 respectively of the zaragozic acids. Assessment of the feasibility of quaternization at C-4 as well as internal ketalization would lead to a short alternative synthesis of **1**. The success of such an approach depends on two crucial requirements: (a) The generation of an enolate from **2** and its reaction with a (D)-glyceraldehyde derivative bearing in mind that such a nucleophilic center with an adjacent C-O bond is prone to epimerisation and β-elimination,[4] and (b) the stereoselective introduction at C-4 of the new C-C bond from the β-face of the enolate. Our hope in considering this approach was that the facial selectivity in the attack upon the aldehyde would be induced to a certain extent by the configuration of the benzyloxy group at C-3α.



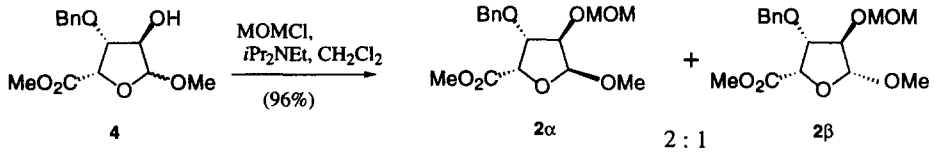
Scheme 1

Few methods for the direct introduction of a C-C bond at C-4 of furanose sugar with a β leaving group leading to a new quaternary carbon center have been reported. Cross aldol condensation between nucleosides 5'-aldehyde and formaldehyde followed by concomitant Cannizzarro reduction, first described by Jones et al.,[5] have been largely used in the synthesis of C-4' ramified nucleotides, and was applied in an approach to the core of zaragozic acids.[6] The second method, introduced by Ireland et al. in the course of the synthesis of polyether-type antibiotics, is based on Claisen rearrangement of silyl ketene acetal (Ireland-Claisen rearrangement),[7] and has been employed in the synthesis of a precursor of zaragozic acids, starting from allyl D-lyxofuranosiduronate.[8] However, as mentioned in a recent study,[9] the formation and reaction of saccharide ketene acetals may be a rather delicate operation. During enolate formation from the ester with a leaving group in the β-position, β-elimination may occur to generate an unstable conjugated product. More recently, Nakai et al. have reported that the [1,2]-Wittig rearrangement of O-glycosides with an additionnal C-substituent at the anomeric center provided a method

for the preparation of a quaternary center.[10] To the best of our knowledge, the aldol reaction has not been used to set up a quaternary center at C-4 of carbohydrates. We describe here the implementation of such a transformation as the key step in a concise synthesis of the core of the zaragozic acids.[11]

Results and Discussion

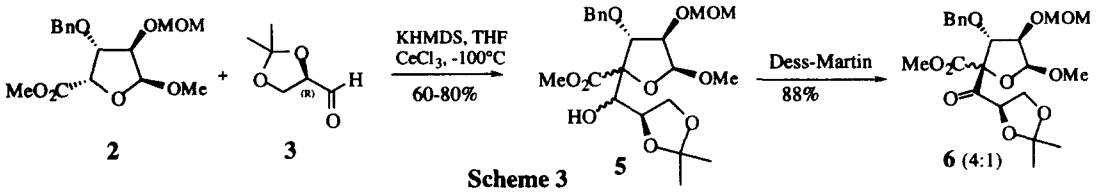
Our study began with the known methyl (methyl-3-O-benzyl-α,β-D-xylofuranoside)-uronate **4**, readily prepared as a α:β (2:1) mixture of epimers at the anomeric center from commercialy available diacetone-D-glucose in five steps and 65% overall yield.[12] Protection of the secondary alcohol as its methoxymethyl ether afforded ester **2** (Scheme 2). Although we experimented with the minor isomer, the present study was carried with the major α-epimer. It is worthy of note that isomerization of the β– to the α-isomer may be accomplished by equilibration under acidic conditions (Dowex 50W resin, in refluxing methanol).



4

Scheme 2

Initial attempts to effect the aldol condensation between ester **2** and D-(R)-glyceraldehyde acetonide **3**[13] *via* lithium, sodium or potassium enolates (using LDA, LiHMDS, NaHMDS or KHMDS) in THF at -100°C were disappointing. Under these conditions, the desired product **5** was isolated in only 0-10% yield along with varying amount of the starting ester. At higher temperature, β-elimination occured, followed by the degradation of the resulting unsaturated ester. In no case was any pure elimination product isolated. We turned next to the corresponding zinc enolate, generated from the potassium enolate by metal exchange ($ZnCl_2$ or $ZnBr_2$) at –100°C.[14] Under these conditions, a higher but still insufficient yield of **5** (20-30%) was obtained. Furthermore, this result turned out to be difficult to reproduce and was therefore considered unreliable for preparative purposes. After considerable experimentation, we found that addition of a precooled 1:1 mixture of cerium(III) chloride[15] and aldehyde **3** in THF to the solution of the potassium enolate in tetrahydrofuran and toluene[16] at -100°C gave **5** reproducibly in 60 to 80% yield. ^{1}H-NMR analysis of the crude product showed that **5** is a mixture of *three* out of the four possible diastereomers in 2.5:1.5:1 ratio (Scheme 3).



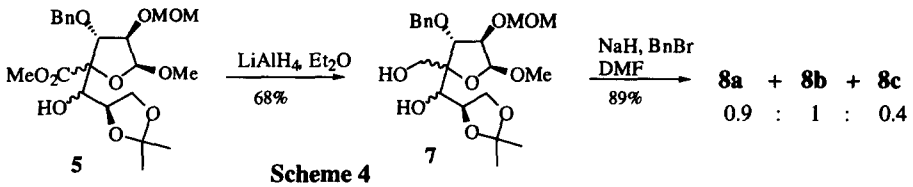
2 3 5

Scheme 3

Dess-Martin oxidation[17] of the mixture afforded *two* readily separable β-ketoesters **6** in a 4:1 ratio and in 88% combined yield (Scheme 3). This result clearly demonstrates that these products are epimers at C-4. Thus the

aldol reaction proceeded with good level of stereoselectivity (80:20) at the newly created quaternary center.[18] However, at this point we were unable to ascertain the stereochemistry of each of these methyl esters, and we were therefore compelled to carry the mixture of aldol diastereomers forward.

Having introduced the C-4 side chain into the furanose ring, we next examined the ketalisation step. To this end, reduction of **5** with lithium aluminum hydride afforded the expected diol **7** which was converted into dibenzyl ether **8** as a mixture of three isomers in 1/ 0.9/ 0.4 ratio (Scheme 4). This mixture was separated by flash chromatography to furnish three isomers denoted as **8a**, **8b** and **8c** which were submitted independently to acid hydrolysis.

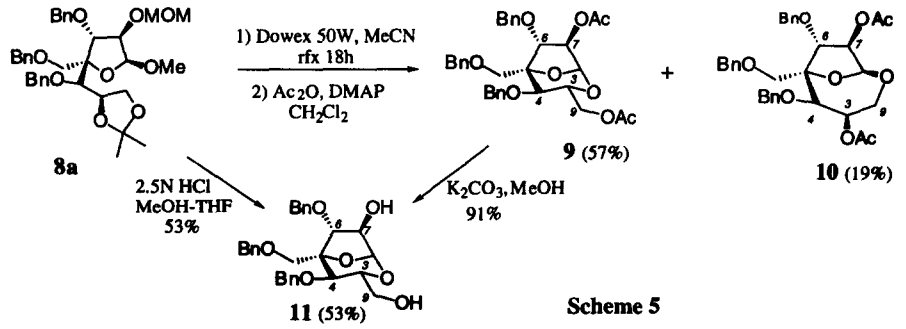


5 **7**

Scheme 4

Whereas acid-promoted cyclization of hemiketal analogues could be achieved under mild conditions, the transketalisation of methyl ketals **8** required more forcing conditions. In all cases, we observed that acid treatment of these compounds rapidly brought about removal of acetonide group followed by the hydrolysis of methoxymethyl ether, and finaly led slowly to the intramolecular cyclization.

Exposure of isomer **8a** to Dowex resin in refluxing acetonitrile for 20 h, followed by treatment of the crude product with acetic anhydride in the presence of dimethylaminopyridine in dichloromethane gave a mixture of the desired 2.8-dioxabicyclo[3.2.1]octane derivative **9** (57%) along with acetal isomer **10** (19%) . These structures were assigned on the basis of an extensive NMR study. In particular, evidence of the configuration of **9** arose from the important cross-peaks in the NOESY spectrum between H-3 and H-6. In addition, the observed coupling constants between H-6 and H-7 (J=2.6 Hz) and H3-H4 (J=10 Hz) are in agreement with the zaragozic acids core structure. On the other hand, treatment of **8a** with 2.5 N HCl in methanol-THF under reflux led to diol **11** in 53% yield (Scheme 5). This compound has been found to be identical in all aspects to the product obtained from the saponification of **9**. The assignment of this structure was confirmed later by comparison of the NMR data with those of compound **13** (Scheme 6). These results clearly indicate that **8a** has the desired absolute configuration at the quaternary stereocenter at C-5.



8a

9 (57%)

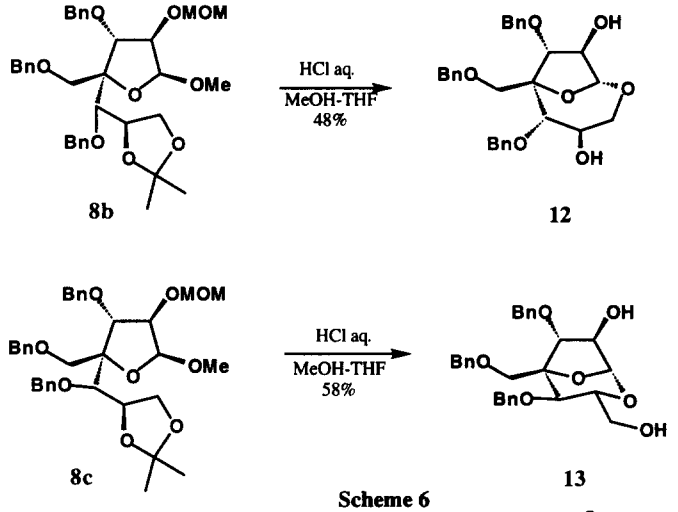
10 (19%)

11 (53%)

Scheme 5

Treatment of **8b** with 2.5N HCl in methanol and tetrahydrofuran (1:1) under reflux led to a mixture in which the major component was isolated as a crystalline compound **12** in 48% yield. Spectral data of this product do not fit the expected bicyclic core of squalestains. Single crystal X-ray analysis[19] (Figure 1) revealed that **12** possesses a 2.9-dioxabicyclo[4.2.1]nonane ring system and is the structural analog of **10**, previously obtained by cyclisation of **8a**, but with the opposite configuration at C-5.

Under the same conditions the third isomer **8c** gave a new crystalline compound **13** in 58% yield (Scheme 6). The spectroscopic data of this compound are in agreement with the 2.8-dioxabicyclo[3.2.1]octane ring system. However, in contrast to **9**, examination of 2D NOESY spectrum of **13** did not rveal any NOE interaction between H-3 and H-6. Since NMR spectroscopic data did not allow unambiguous structural assignement, this compound was submitted to X-ray crystallographic analysis[20] which gave the structure shown in Figure 2. Actually this new ketal isomer has the core of the zaragozic acids, albeit with the wrong stereochemistry of the quaternary center at C-5.



Scheme 6

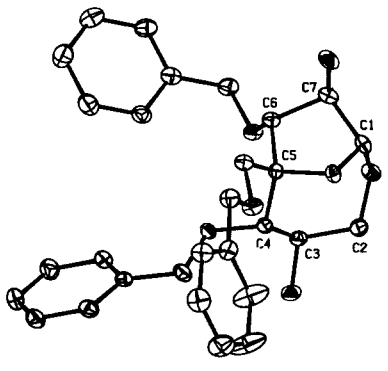


Figure 1. ORTEP drawing of **12**

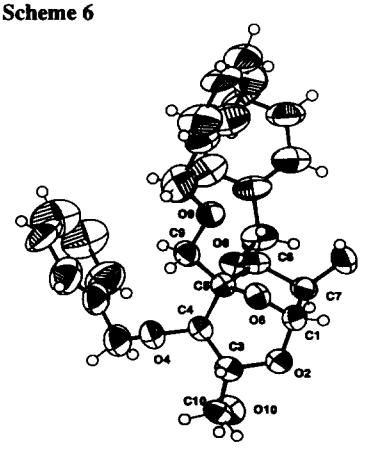
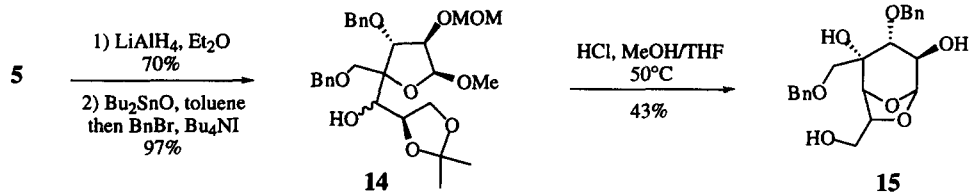


Figure 2. ORTEP drawing of **13**

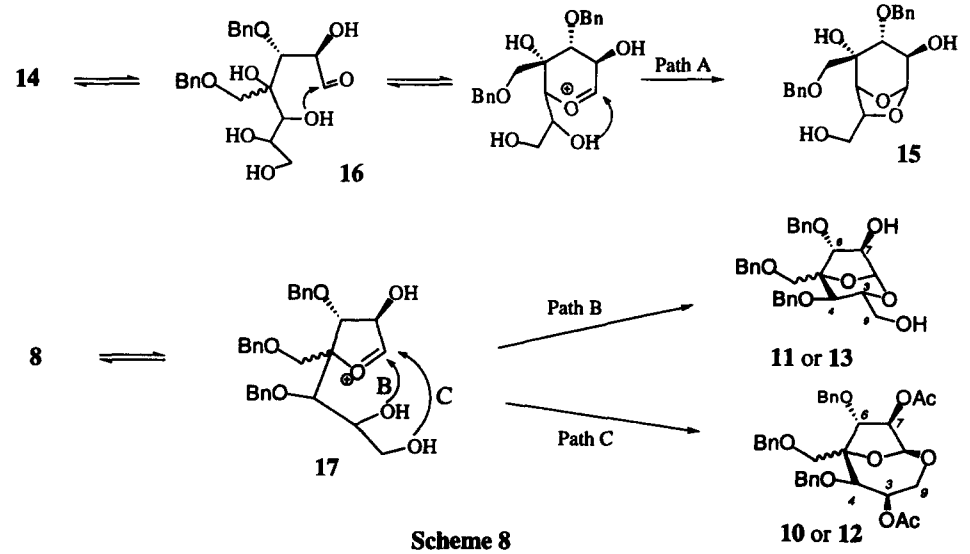
In the light of these results, we deduced that in contrast to **8a**, the aldol isomers **8b** and **8c** possessed the undesired stereochemistry of the quaternary center at C-5. Therefore, and contrary to all expectations, the introduction of the new C-C bond at C-4 of the furanose ring mainly proceeded from the α-face of the enolate.

The ketalization reaction was next attempted on **14** in which the hydroxyl group at C-4 (Squalestatins numbering) is unprotected. This compound was readily prepared by reduction of **5** and subsequent regioselective protection of the primary hydroxyl group using the stannylene procedure.[21] Heating **14** with HCl in MeOH-THF at 50°C for 24 h afforded the undesired ketal **15** in 43% yield and 23% of the starting material was recovered (Scheme 7). The structure of **15** was deduced on the basis of ^{1}H and ^{13}C-NMR experiments.



Scheme 7

As mentioned above, the formation of different ketal isomers proceeded through an intermediate generated from **8** or **14** by removal of the acetonide group followed by hydrolysis of the methyl acetal. As has been already reported for such a system,[22] when the hydroxyl group at C-4 is unprotected, the formation of the 7,8-dioxabicyclo[3.2.1]octane derivative **15** is the result of a thermodynamic equilibration through aldehyde **16** (pathway A). Otherwise the ketalization process occurs *via* the 5-membered oxonium ion **17** according to pathways B or C leading to **11** or **13** and **10** or **12** respectively (Scheme 8).



Scheme 8

In summary, we have shown that the aldol reaction between methyl (methyl-3-O-benzyl-2-O-methoxymethyl-α-D-xylofuranoside)uronate and D-(R)-glyceraldehyde acetonide, promoted by cerium(III) chloride, leads to three diastereoisomers in high yield and proceeds with a good level of stereoselectivity at the newly created quaternary center. Under drastic acidic conditions, the aldol products undergo cyclization to afford different bicyclic ketals isomers. This reaction was used as the key step in the synthesis of a functionalized bicyclic core of the zaragozic acids.

Experimental Section

General: Melting points were determined on a Reichert hot stage apparatus. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer as solutions in CCl_4. NMR spectra were recorded on a Bruker AM 400 MHz (400 MHz and 100.6 MHz, for ^1H and ^{13}C, respectively) spectrometer as solutions in $CDCl_3$, using residual protic solvent $C\underline{H}Cl_3$ (δ_H=7.27 ppm) or $\underline{C}DCl_3$ (δ_C=77.1 ppm) as internal reference. Optical rotations were determined on a Perkin-Elmer 241 polarimeter and reported as follows: $[\alpha]_D$, concentration (g/100mL), and solvent. Mass spectra were determined on a Hewlett Packard HP 5970B/5890A at 70 eV. All reactions were monitored by TLC carried out on 0.2 mm Merck aluminium silica gel (60 F_{254}) pre-coated plates using UV light and 5% ethanolic phosphomolybdic acid and heat as developing agent. Flash chromatography was performed on 40-63 μm (400-230 mesh) silica gel 60 with ethyl acetate (AcOEt)-petroleum ether (b.p. 40-60°C) (PE) as eluent. Commercially available reagents and solvents were purified and dried when necessary by the usual methods.

Methyl (methyl-3-*O*-benzyl-2-*O*-methoxymethyl-α,β-D-xylofuranoside) uronate (2). To a stirred solution of a α:β (2:1) mixture of **4**[12] (3 g, 10.6 mmol) in 20 ml of dry dichloromethane, were added diisopropylethylamine (13 mL, 74,6 mmol, 7 equiv) and dimethylaminopyridine (65 mg, 0.53 mmol, 0.05 equiv). To this solution, cooled in ice-water bath, was added chloromethylmethylether (4 mL, 53 mmol, 5 equiv) dropwise, and the mixture stirred for one week at room temperature. The excess MOMCl was carefully hydrolyzed at 0°C with water (7 mL), and the mixture diluted with 80 ml of dichloromethane. The organic phase was washed with aqueous 0.5 M HCl (3 x 20 mL), and the aqueous layer extracted wih dichloromethane (3 x 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to afford a crude product which was purified by flash chromatography (eluent AcOEt:PE 1/3) to give the minor β-isomer followed by **2α** (3.31 g in 1/2 ratio in 96%, combined yield).

2α : colorless oil, IR ν_{max} 1764, 1743 cm^{-1}. $[\alpha]_D$ = -96° (c 2.11, CH_2Cl_2), ^1H NMR ($CDCl_3$) δ 7.30-7.23 (5 H, m, H-arom), 5.05 (1 H, d, J = 4.3, H-1), 4.75 (1 H, d, J = 7.3, H-4), 4.66 (1 H, d, J = 6.8, H-a CH_2 MOM), 4.63 (1 H, d, J = 6.8, H-b CH_2 MOM), 4.61 (2 H, s, CH_2 Bn), 4.42 (1 H , dd, J = 7.3, 6.4, H-3), 4.17 (1 H , dd, J = 6.4, 4.3, H-2), 3.68 (3 H, s, OMe ester), 3.41 (3 H, s, OMe), 3.35 (3 H, s, OMe) ppm. ^{13}C NMR ($CDCl_3$) δ 169.6 (C, C=O ester), 137.9 (C), 128.2 (CH), 127.6 (CH), 127.3 (CH), 102.0 (CH, C1), 96.8 (CH_2 MOM), 81.4 (CH), 80.7 (CH), 76.2 (CH), 72.9 (CH_2 Bn), 55.6 (CH_3), 55.5 (CH_3), 51.8 (CH_3) ppm. $C_{16}H_{22}O_7$ (326.35) calcd % C 58.89, H 6.79; found: C 59.04, H 6.65.

2β : colorless oil, IR ν_{max} 1773, 1737 cm^{-1}. $[\alpha]_D$ = -41° (c 2.25, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.42-7.30 (5 H, m, H-arom), 5.01 (1 H, s, H-1), 4.87 (1 H, d, J = 7.2, H-4), 4.68 (1 H, d, J = 12.4, H-a CH_2 Bn), 4.61 (1 H, d, J = 6.8, H-a CH_2 MOM), 4.58 (1 H, d, J = 12.4, H-b CH_2 Bn), 4.52 (1 H, d, J = 6.8, H-b CH_2 MOM),

4.22-4.16 (2 H , m, H-2 and H3), 3.78 (3 H, s, OMe ester), 3.53 (3 H, s, OMe), 3.30 (3 H, s) ppm. ^{13}C NMR ($CDCl_3$) δ 169.6 (C, C=O ester), 137.4 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 109.2 (CH, C1), 96.0 (CH_2 MOM), 82.5 (CH), 81.8 (CH), 81.2 (CH), 72.6 (CH_2 Bn), 55.9 (CH_3), 55.7 (CH_3), 52.0 (CH_3) ppm.

Methyl(methyl-3-*O*-benzyl-2-*O*-methoxymethyl-4-*C*-(hydroxy-(2,2-dimethyl[1,3]dioxolan-4-yl)-methyl)-α-D-xylo/β-L-arabinofuranoside) uronate (5). To 0.5 M solution of KHMDS (6.5 mL, 3.25 mmol, 1.23 equiv.) in toluene (2 mL) cooled to -100°C, was added 1 mL THF, followed by a solution of ester **2α** (857 mg, 2.6 mmol) in 1 mL THF. The mixture was stirred at -100°C for 40 min, followed by the addition of a suspension formed by stirring dry $CeCl_3$ (650 mg, 3.25 mmol, 1.0 equiv.) and freshly distilled aldehyde **3** (700 mg, 5.4 mmol, 2.05 equiv) in 3 mL THF at -15°C for 20 min. The cooling bath was slowly warmed to -20°C over 2 h. After being stirred at –20°C for 30 min, the mixture was diluted with 10 ml of ether and quenched by addition 3 ml of saturated aqueous NH_4Cl. The aqueous phase was acidified and extracted with ether (3 x 20 mL). The combined organic extracts were washed with 10 ml of saturated aqueous NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the isolated residue by chromatography on silica gel (gradient elution, 1:3 to 1:1 EtOAc/PE) aforded 800 mg (66%) of **5** (mixture of three isomers) as a colorless oil.

Physical data for one these isomers isolated in a pure form: m.p. 86°C (petroleum ether). $[\alpha]_D$ = +88° (c 1.30, CH_2Cl_2). IR ν_{max} 3458, 1743 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40-7.25 (5 H, m, H-arom), 5.05 (1 H, d, J = 4.7, H-1), 4.80-4.58 (5 H, m, CH_2 MOM, H-7, H-3), 4.23-4.15 (5 H, m, CH_2 Bn, H-2, H-6, H-5), 3.71 (3 H, s), 3.57 and 3.39 (3 H, s), 2.80 (1 H, d, J = 11.3, OH), 1.39 (3 H, s, CH_3 acetonide), 1.33 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 169.6 (C, ester), 137.7 (C, Bn), 128.5 (CH), 128.1 (CH), 127.9 (CH), 109.9 (C, acetonide), 102.0 (CH, C-1), 97.3 (CH_2 MOM), 87.7 (C, C-4), 81.7 (CH, C-2), 81.2 (CH, C-3), 76.1 (CH, C-6), 74.2 (CH, C-5), 74.0 (CH_2, C-7), 67.6 (CH_2 Bn), 57.1 (CH_3), 56.0 (CH_3), 52.6 (CH_3), 26.5 (CH_3), 25.1 (CH_3) ppm. $C_{22}H_{32}O_{10}$ (608.72): calcd C 57.83, H 7.06; found C 57.64, H 7.05.

Methyl(methyl-3-*O*-benzyl-2-*O*-methoxymethyl-4-*C*-(2,2-dimethyl[1,3]dioxolan-4-carbonyl)-methyl)-α-D-xylo/β-L-arabino-furanoside) uronate (6). To a solution of the above mixture of aldols (40 mg, 88 μmol) in 0.8 mL of dichloromethane, was added pyridine (60 μL, 0.74 mmol, 8.5 equiv) followed by Dess-martin periodinane (130 mg, 0.3 mmol, 3.5 equiv.). After stirring for 2 h at room temperature, the mixture was diluted with ether (2 mL) and treated with 1:1 saturated $NaHCO_3$-$Na_2S_2O_3$ (1 mL) for 5 min. Extraction with ether (3 x 3 mL) and usual workup gave 45 mg of a colorless residue. Purification by chromatography on silica gel (gradient elution, 1:6 to 1:4 EtOAc/PE) afforded 32 mg (80%) of **6** (mixture of two isomers in 4:1 ratio) as a colorless oil.

Physical data of the major isomer: $[\alpha]_D$ = 11° (c 1.45, CH_2Cl_2). IR ν_{max} 1757, 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.35-7.26 (5 H, m, H-arom), 5.06 (1 H, d, J = 4.2, H-1), 4.96 (1 H, dd, J = 7.9, 6.2, H-6), 4.91 (1 H, d, J = 6.8, H-3), 4.74 (1 H, d, J = 11.8), 4.66 (1 H, d, J = 6.8), 4.59 (1 H, d, J = 6.8), 4.55 (1 H, d, J = 11.8), 4.30 (1 H, dd, J = 8.8, 7.9, H-7a), 4.14 (1 H, dd, J = 6.8, 4.2, H-2), 4.04 (1 H, dd, J = 8.8, 6.2, H-7b), 3.81 (3 H, s), 3.41 et 3.36 (3 H, s), 1.48 (3 H, s, CH_3 acetonide), 1.39 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 200.6 (C, C=O C-5), 168.8 (C, C=O ester), 137.1 (C, Bn), 128.3 (CH), 128.2 (CH), 127.8 (CH), 111.1 (C, acetonide), 103.0 (CH, C-1), 97.0 (CH_2 MOM), 88.4 (C, C-4), 84.6 (CH, C-6), 82.4 (CH), 78.9 (CH), 73.3 (CH_2, C-7), 66.3 (CH_2, Bn), 55.9 (CH_3), 55.8 (CH_3), 53.1 (CH_3), 25.7 (CH_3), 25.4 (CH_3) ppm.: $C_{22}H_{30}O_{10}$ (454.47): calcd. C: 58.14, H: 6.65.found C 57.91, H 6.77.

Physical data of the minor isomer: $[\alpha]_D$ = -4° (c 0.45, CH_2Cl_2). IR ν_{max} 1741 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33-7.21 (5 H, m, H-arom), 5.09 (1 H, d, J = 4.4, H-1), 4.79 (1 H, dd, J = 7.6, 5.8, H-6), 4.78 (1 H, d, J = 8.2, H-3), 4.73 (1 H, d, J = 5.1), 4.71 (1 H, d, J = 6.8), 4.62 (1 H, d, J = 6.8), 4.60 (1 H, d, J = 5.1), 4.29 (1 H, dd, J = 8.4, 7.6, H-7a), 4.20 (1 H, dd, J = 8.2, 4.4, H-2), 4.18 (1 H, dd, J = 8.4, 5.8, H-7b), 3.69 (3 H, s), 3.45 et 3.36 (3 H, s), 1.42 (3 H, s), 1.39 (3 H, s) ppm. ^{13}C NMR ($CDCl_3$) δ 201.4 (C, C=O C-5), 167.1 (C, C=O ester), 137.8 (C, Bn), 128.3 (CH), 128.0 (CH), 127.8 (CH), 111.2 (C, acetonide), 102.9 (CH, C-1), 97.1 (CH_2 MOM), 88.5 (C, C-4), 82.2 (CH, C-6), 80.3 (CH), 78.1 (CH), 73.4 (CH_2, C-7), 66.8 (CH_2, Bn), 56.7 (CH_3), 55.8 (CH_3), 52.8 (CH_3), 25.5 (CH_3), 25.0 (CH_3) ppm.

(6*R*)-Methyl-2-*O*-methoxymethyl-3-*O*-benzyl-4-*C*-hydroxy-methyl-6,7-*O*-isopropyl-idene-α-D-galacto/α-D-gluco/β-L-altrofuranoside (7). To a stirred suspension of $LiAlH_4$ (65 mg, 2.36 mmol, 2 equiv.) in 1 mL of diethyl ether at 0°C, was added a solution of aldols 5 (mixture of 3 isomers) (390 mg, 0.85 mmol) in 2 mL of diethyl ether dropwise. The mixture was stirred at rt for 2 h, diluted with 5 mL of ether, cooled to 0°C, and treated with water and aqueous 1N HCl. The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (20 mL), saturated NaCl (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on silica gel (gradient elution, 1:2 to 1:1 EtOAc/PE) afforded 100 mg of partially reduced products followed by 248 mg (68%) of 7 as colorless oil.

Two isomers of 7 were isolated in pure form which gave following physical data.

The first one: IR ν_{max} 3504 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.29 (5 H, m, H-arom), 4.88 (1 H, d, J = 4.5, H-1), 4.79 (1 H, d, J = 11.7), 4.72-4.66 (3 H, m), 4.45 (1 H, m, H-6), 4.41 (1 H, d, J = 8.2, H-3), 4.24 (1 H, dd, J = 8.2, 4.5, H-2), 3.97 (1 H, dd, J = 8.2, 6.7, H-7a), 3.89 (1 H, dd, J = 8.2, 7.8, H-7b), 3.81 (1 H, dd, J = 6.7, 3.2, H-5), 3.68 (1 H, dd, J = 11.7, 6.7, H-4'a), 3.68 (1 H, dd, J = 11.7, 6.6, H-4'b), 3.48 (3 H, s), 3.42 (3 H, s), 3.00 (1 H, d, J = 6.7, OH-5), 2.92 (1 H, dd, J = 6.6, 6.7, OH-4'), 1.36 (3 H, s, CH_3 acetonide), 1.30 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 138.1 (C), 128.8 (CH), 128.3 (CH), 128.1 (CH), 109.8 (C, acetonide), 101.3 (CH, C-1), 97.4 (CH_2 MOM), 84.0 (CH), 83.5 (C, C-4), 83.1 (CH), 74.9 (CH), 74.2 (CH_2, C-7), 71.7 (CH), 67.3 (CH_2), 66.2 (CH_2), 56.2 (CH_3), 56.0 (CH_3) , 26.4 (CH_3), 26.0 (CH_3) ppm.

The second isomer: IR ν_{max} 3574 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.34-7.29 (5 H, m, H-arom), 4.88 (1 H, d, J = 4.6, H-1), 4.79-4.65 (4 H, m), 4.58 (1 H, d, J = 8.3, H-3), 4.19 (1 H, dd, J = 8.3, 4.6, H-2), 4.12 (2 H, m, H-6 et H-7a), 3.91 (1 H, dd, J = 6.9, 6.7, H-7b), 3.82 (2 H, m, H-4'), 3.54 (1 H, dd, J = 7.3, 7.2, H-5), 3.49 (3 H, s), 3.40 (3 H, s), 3.08 (1 H, d, J = 7.2, OH-5), 2.83 (1 H, dd, J = 7.3, 6.9, OH-4'), 1.39 (3 H, s, CH_3 acetonide), 1.33 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 138.0 (C, Bn), 128.6 (CH), 128.0 (CH), 127.8 (CH), 109.5 (C, acetonide), 101.4 (CH, C-1), 97.3 (CH_2 MOM), 85.6 (C, C-4), 83.2 (CH), 83.0 (CH), 75.1 (CH), 74.2 (CH), 74.2 (CH_2, C-7), 67.9 (CH_2), 63.4 (CH_2), 56.3 (CH_3,s), 55.9 (CH_3), 26.6 (CH_3) 25.7 (CH_3) ppm.

(6*R*)-Methyl-2-*O*-methoxymethyl-3-*O*-benzyl-4-*C*-benzyloxymethyl-6,7-*O*-isopropyli-dene-α-D-galacto/α-D-gluco/β-L-altro-furanoside (8). To a suspension of sodium hydride, washed three times with dry pentane, (31 mg, 1.29 mmol, 2.44 equiv) in 2 mL of DMF was added a solution of diols 7 (226 mg, 0.53 mmol) in 4 mL of DMF at 0°C dropwise under nitrogen. The solution was stirred at 0° C for 1 h, and benzyl

bromide (157 μL, 1.32 mmol, 2.50 equiv) was added. After stirring the mixture at 0° C for 1h and then 30 min at rt, ether (5 mL), aqueous saturated NH_4Cl (1mL) and water (3 mL) were added. The organic layer was separated and the aqueous layer extracted with ether (3 x 5 mL). The combined organic layers were washed successively with aqueous saturated solution of $CuSO_4$ (4 mL), water, and brine, then dried and concentrated. Purification by chromatography on silica gel (gradient elution, 1:4 to 1:2 EtOAc/PE) afforded **8a**, **8b** and **8c** (286 mg, 89%, combined yield).

8a: colorless oil. $[\alpha]_D$ = +61° (c 1.30, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.31-7.18 (15 H, m, H-arom), 4.90 (1 H, d, J = 4.6, H-1), 4.85 (1 H, d, J = 11.0), 4.74-4.56 (7 H, m,), 4.38 (2 H, m, H-2 et H-6), 4.25 (1 H, d, J = 8.8, H-3), 4.04 (1 H, d, J = 2.9, H-5), 3.99 (2 H, m, H-7), 3.74 (1 H, d, J = 10.2, H-4'a), 3.73 (1 H, d, J = 10.2, H-4'b), 3.49 (3 H, s, OMe), 3.41 (3 H, s, OMe), 1.45 (3 H, s, CH_3 acetonide), 1.31 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 138.7 (C), 138.6 (C), 138.4 (C), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 108.0 (C, acetonide), 100.9 (CH, C-1), 97.1 (CH_2 MOM), 87.3 (C, C-4), 82.0 (CH), 81.8, (CH), 81.7 (CH), 76.0 (CH), 75.7 (CH_2), 73.8 (CH_2), 73.1 (CH_2), 70.3 (CH_2), 65.2 (CH_2), 55.8 (CH_3), 55.7 (CH_3), 26.5 (CH_3), 25.2 (CH_3) ppm.

8b: colorless oil. $[\alpha]_D$ = +81° (c 1.10, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.38-7.25 (15 H, m, H-arom), 4.88 (1 H, d, J = 9.7, CH_2), 4.82 (1 H, d, J = 11.5), 4.79 (1 H, d, J = 4.8, H-1), 4.68-4.53 (7 H, m), 4.35 (1 H, dd, J = 8.4, 4.8, H-2), 4.15 (1 H, d, J = 8.4, H-3), 4.01 (1 H, dd, J = 8.0, 6.4, H-7a), 3.89 (1 H, dd, J = 8.0, 7.9, H-7b), 3.87 (1 H, d, J = 8.4, H-5), 3.54 (1 H, d, J = 9.3, H-4'a), 3.44 (1 H, d, J = 9.3, H-4'b), 3.37 (3 H, s, OMe), 3.36 (3 H, s, OMe), 1.50 (3 H, s, CH_3 acetonide), 1.40 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 138.9 (C), 138.6 (C), 138.4 (C), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 107.9 (C, acetonide), 100.7 (CH, C-1), 97.0 (CH_2 MOM), 87.7 (CH, C-5), 83.7 (C, C-4), 82.2 (CH), 79.8 (CH), 75.9 (CH, C-6), 75.3 (CH_2), 74.6 (CH_2), 74.2 (CH_2), 73.9 (CH_2), 67.6 (CH_2), 55.6 (CH_3, OMe), 55.0 (CH_3, OMe), 26.7 (CH_3), 25.2 (CH_3) ppm.

8c: colorless oil.$[\alpha]_D$ = +71° (c 1.35, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.36-7.23 (15 H, m, H-arom), 5.00 (1 H, d, J = 10.8, CH_2), 4.85 (1 H, d, J = 12.4), 4.75 (1 H, d, J = 4.4, H-1), 4.71-4.61 (6 H, m), 4.53 (1 H, d, J = 11.5, H-4'a), 4.46 (1 H, d, J = 11.5, H-4'b), 4.33 (2 H, m, H-3 et H-5), 4.14 (1 H, dd, J = 8.6, 8.4, H-7a), 3.99 (2 H, m, H-2 et H-6), 3.89 (1 H, dd, J = 8.4, 7.5, H-7b), 3.38 (3 H, s, OMe), 3.36 (3 H, s, OMe), 1.42 (3 H, s, CH_3 acetonide), 1.38 (3 H, s, CH_3 acetonide) ppm. ^{13}C NMR ($CDCl_3$) δ 139.0 (C), 138.4 (C),138.0 (C), 128.3 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 107.1 (C, acetonide), 100.5 (CH, C-1), 97.2 (CH_2 MOM), 86.0 (CH, C-5), 83.9 (C, C-4), 83.3 (CH), 77.9 (CH), 77.8 (CH, C-6), 76.4 (CH_2), 73.7 (CH_2), 73.6 (CH_2), 73.2 (CH_2), 65.1 (CH_2), 55.8 (CH_3), 55.2 (CH_3), 26.5 (CH_3) 25.6 (CH_3) ppm. $C_{35}H_{44}O_9$ (608.72): C 69.06, H 7.29; found C: 69.10, H: 7.22.

(1*S*, 3*R*, 4*R*, 5*S*, 6*R*, 7*R*,)-7-Acetoxy-6-benzyloxy-5-benzyloxymethyl-4-benzyl-oxy-3-acetoxymethyl-2,8-dioxabicyclo[3.2.1]octane (9). To a solution of **8a** (22 mg, 36 μmol) in 1 mL of acetonitrile, was added Dowex 50W (20 mg) and the mixture was heated under reflux for 20 h. After cooling, the resin was removed by filtration through a sintered glass funnel, and the filtrate concentrated *in vacuo*. To the solution of the resulting yellowish residue (17 mg) in 0.5 ml of dichloromethane, were added successively DMAP (150 mg, 1.22 mmol) and acetic anhydride (76 μL, 0.80 mmol) at 0°C. After stirring of the mixture for 1.5 h at rt, dichloromethane (2 mL) and an aqueous solution of NH_4Cl (0.5 mL) were added. The organic layer was

separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by chromatography on silica gel (gradient elution, 5:95 to 1:9 EtOAc/PE) afforded **9** (12 mg, 57%) followed by 4 mg of **10**.

9: Colorless oil. $[\alpha]_D$ = -30° (c 0.81, CH_2Cl_2). IR ν_{max} 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40-7.15 (15 H, m, H-arom), 5.57 (1 H, d, J = 4.5, H-1), 5.10 (1 H, dd, J = 4.5, 2.6, H-7), 4.78 (1 H, d, J = 11.8, H-a CH_2 Bn), 4.65 (1 H, d, J = 6.8, H-a CH_2 Bn), 4.62 (1 H, d, J = 7.6, H-a CH_2 Bn), 4.56 (1 H, d, J = 11.8, H-b CH_2 Bn), 4.50 (1 H, d, J = 7.6, H-b CH_2 Bn), 4.47 (1 H, d, J = 6.8, H-b CH_2 Bn), 4.27 (1 H, d, J = 2.6, H-6), 4.22 (1 H, dd, J = 12.0, 2.2, H-9a), 4.02 (1 H, dd, J = 5.3, 12.0, H-9b), 3.97 (1 H, d, J = 10.0, H-4), 3.92 (1 H, d, J = 11.9, H-11a), 3.87 (1 H, d, J = 11.9, H-11b), 3.78 (1 H, ddd, J = 10.0, 5.3, 2.2, H-3), 2.07 (3 H, s, CH_3 acetate), 2.03 (3 H, s, CH_3 acetate) ppm. ^{13}C NMR ($CDCl_3$) δ 170.9 (C), 169.8 (C), 138.3 (C), 137.6 (C), 137.9 (C), 128.4(CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 96.2 (CH, C-1), 85.7 (C, C-5), 81.0 (CH), 80.7 (CH), 74.0 (CH_2), 73.8 (CH_2), 72.1 (CH), 71.8 (CH_2 Bn), 69.9 (CH), 68.1 (CH_2), 63.7 (CH_2), 20.8 (CH_3), 20.5 (CH_3) ppm.

(1*S*,4*R*,5*R*,6*S*,7*R*,8*R*)-8-Acetoxy-7-benzyloxy-6-benzyloxymethyl-5-benzyloxy-4-acetoxy-2,9-dioxabicyclo[4.2.1]nonane (10). Colorless oil. IR ν_{max} 1740 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.00 (15 H, m, H-arom), 5.42 (2 H, m), 5.00 (1 H, dd, J = 7.0, 3.3, H-8), 4.79 (1 H, d, J = 7.0, H-7), 4.74 (1 H, d, J = 12.0, H-a CH_2 Bn), 4.62 (1 H, d, J = 10.0, H-a CH_2 Bn), 4.54 (1 H, d, J = 12.8, H-a CH_2 Bn), 4.52 (1 H, d, J = 12.0, H-b CH_2 Bn), 4.40 (1 H, d, J = 10.0, H-b CH_2 Bn), 4.36 (1 H, d, J = 12.8, H-b CH_2 Bn), 4.11 (1 H, d, J = 5.6, H-5), 4.02 (1 H, d, J = 13.5, H-3a), 3.89 (1 H, d, J = 10.8, H-11a), 3.80 (1 H, dd, J = 13.5, 3.9, H-3b), 3.75 (1 H, d, J = 10.8, H-11b), 2.09 (3 H, s, CH_3 acetate), 1.80 (3 H, s, CH_3 acetate) ppm. ^{13}C NMR ($CDCl_3$) δ 169.7 (C, C=O), 137.9 (C), 137.8 (C), 137.6 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 95.1 (CH, C-1), 86.9 (C, C-6), 84.4 (CH, C-4), 81.0 (CH), 80.7 (CH), 75.3, 74.0, 73.1, 71.9, 70.1, 69.4, 65.8, 20.8 (CH_3), 15.3 (CH_3) ppm.

(1*S*, 3*R*, 4*R*, 5*S*, 6*R*, 7*R*,)-7-Hydroxy-6-benzyloxy-5-benzyloxymethyl-4-benzyloxy-3-hydoxymethyl-2,8-dioxabicyclo[3.2.1]octane (11). To a solution of the isomer **8a** (72 mg, 0.12 mmol) in THF (1 mL) and MeOH (1 mL), was added aqueous 2.5N HCl (1 mL), and the mixture was heated under reflux for 12 h. After evaporation of the organic solvent, aqueous saturated Na_2CO_3 was added and the product extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by chromatography on silica gel (gradient elution, 1:2 to 2:1 EtOAc/PE) afforded **11** (31 mg, 53%). Colorless crystals, m. p. 101°C (PE / AcOEt). $[\alpha]_D$ = -37° (c 0.52, $CHCl_3$). IR ν_{max} 3559, 3555, 3534, cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38-7.17 (15 H, m, H-arom), 5.30 (1 H, d, J = 4.7, H-1), 4.74-4.51 (6 H, m, CH_2 Bn), 4.33 (1 H, dd, J = 4.7, 2.6, H-7), 4.09 (1 H, d, J = 9.7, H-4), 4.06 (1 H, d, J = 2.6, H-6), 3.90 (1 H, d, J = 11.7, H-10a), 3.83 (1 H, d, J = 11.7, H-10b), 3.72 (2 H, m, H-3 and H-9a), 3.49 (1 H, m, H-9b) ppm. ^{13}C NMR ($CDCl_3$) δ 138.1 (C), 138.0 (C), 137.9 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 97.9 (CH, C-1), 86.3 (C, C-5), 83.7 (CH), 81.1 (CH), 74.5 (CH), 74.1 (CH_2), 73.9 (CH_2), 71.6 (CH_2), 69.7 (CH), 68.2 (CH_2), 62.3 (CH_2) ppm.

(1*S*,4*R*,5*S*,6*R*,7*R*,8*R*)-8-hydroxy-7-benzyloxy-6-benzyloxymethyl-5-benzyloxy-4-hydroxy-2,9-dioxabicyclo[4.2.1]nonane (12). A solution of the isomer **8b** (60 mg, 0.10 mmol), in THF (1 mL) and MeOH (1 mL), was added aqueous 2.5N HCl (1 mL), and the mixture heated under reflux for 12 h. After evaporation of the organic solvent, aqueous saturated Na_2CO_3 was added and the product extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by chromatography on silica gel (gradient elution, 1:2 to 2:1 EtOAc/PE) afforded **12** (23 mg, 48%). Colorless crystals, m. p. 127°C (PE / AcOEt). $[\alpha]_D$ = -43° (c 0.90, $CHCl_3$). IR ν_{max} 3555 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41-7.21 (15 H, m, H-arom), 5.14 (1 H, s, H-1), 4.89 (1 H, d, J = 11.4, H-a CH_2 Bn), 4.66-4.57 (4 H, m, 2 CH_2 Bn), 4.50 (2 H, m, H-b CH_2 Bn and H-3a), 4.07 (1 H, br. s, H-7), 3.97 (1 H, br. s, H-8), 3.82 (1 H, d, J = 9.5, H-5), 3.78 (1 H, dd, J = 11.8, 10.9, H-3a), 4.56-3.49 (3 H, m, H-4 and H-10) ppm. ^{13}C NMR ($CDCl_3$) δ 138.5 (C), 138.2 (C), 136.7 (C), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 104.3 (CH, C-1), 89.3 (C, C-5), 86.6 (CH) 85.8 (CH), 79.6 (CH), 76.1 (CH_2), 74.0 (CH_2), 73.5 (CH_2), 73.4 (CH_2) , 74.4 (CH), 62.6 (CH_2) ppm.

(1*R*, 3*R*, 4*R*, 5*R*, 6*R*, 7*R*,)-7-Hydroxy-6-benzyloxy-5-benzyloxymethyl-4-benzyloxy-3-hydroxymethyl-2,8-dioxabicyclo-[3.2.1]octane (13). A solution of isomer **8c** (40 mg, 0.065 mmol), treated as described above, led to **13** (19 mg, 58%) as colorless crystals, m. p. 99°C. $[\alpha]_D$ = -12° (c 0.42, $CHCl_3$). IR ν_{max} 3558, 3550, 3531 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38-7.21 (15 H, m, H-arom), 5.25 (1 H, s, H-1), 4.70 (1 H, d, J = 11.9, H-a CH_2 Bn), 4.58 (1 H, d, J = 5.4, H-a CH_2 Bn), 4.55 (1 H, d, J = 5.4, H-b CH_2 Bn), 4.49 (1 H, d, J = 14.5, H-a CH_2 Bn), 4.46 (1 H, d, J = 14.5, H-b CH_2 Bn), 4.43 (1 H, d, J = 11.9, H-b CH_2 Bn), 4.26 (1 H, d, J = 8.0, H-4), 4.12 (1 H, s, H-6), 3.99 (1 H, d, J = 4.6, H-7), 3.86 (1 H, d, J = 10.8, H-10a), 3.79 (1 H, ddd, J = 8.0, 4.1, 2.5, H-3), 3.75 (1 H, dd, J = 12.3, 2.5, H-9a), 3.44 (2 H, m, H-10b and H-9b), 2.53 (1 H, d, J = 4.6, OH-7) ppm. ^{13}C NMR ($CDCl_3$) δ 137.7 (C), 137.6 (C), 137.5 (C), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.8 (CH) , 102.7 (CH, C-1), 86.6 (C, C-5), 86.0 (CH), 80.6 (CH), 74.7 (CH), 74.7, 73.8 (CH_2), 73.0 (CH_2), 72.4 (CH), 68.1 (CH_2), 62.2 (CH_2) ppm.

(6*R*)-Methyl-2-*O*-methoxymethyl-3-*O*-benzyl-4-*C*-(hydroxy-(2,2-dimethyl[1,3]-dioxolan-4-yl)-methyl)-5-*O*-benzyl-α-D-xylo/β-L-arabino-furanoside (14). A mixture of diols **8** (405 mg. 0.95 mmol) and dibulyltin oxide (260 mg, 1.05 mmol, 1.1 equiv) in toluene (20 mL) was refluxed for 17 h with continuous removal of water, then concentrated to 5 ml. After cooling to rt, tetrabutylammonium iodide (385 mg, 1.05 mmol, 1.1 equiv.) and benzyl bromide (230 μL, 1.9 mmol, 2 equiv) were added and the mixture heated under reflux for 2 h. The toluene was evaporated under reduced pressure, and the residue purified by chromatography on silica gel (gradient elution, 1:6 to 1:2 EtOAc/PE) to afford **12** (445 mg, 91%) as a mixture of three isomers. Physical data of one of these isomers isolated in pure form: Colorless oil: $[\alpha]_D$ = +38.5° (c 1.60, $CHCl_3$). IR ν_{max} cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37-7.25 (10 H, m, H-arom), 4.86 (1 H, d, J = 4.4, H-1), 4.77-4.63 (4 H, m, CH_2 MOM and Bn), 4.56 (1 H, d, J = 9.7), 4.47 (1 H, d, J = 9.7), 4.30 (2 H, m, H-2 and H-6), 4.20 (1 H, d, J = 8.5, H-3), 3.99 (2 H, m, H-5 and H-7a), 3.86 (1 H, dd, J = 8.2, 7.9, H-7b), 3.54 (2 H, s, H-4'), 3.39 (6 H, s, OMe), 3.05 (1 H, d, J = 8.4, OH), 1.41 (3 H, s, CH_3 acetonide), 1.35 (3 H, s, CH_3 acetonide) ppm. ^{13}C ($CDCl_3$) δ 138.0 (C), 137.5 (C), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 108.9 (C, acetonide), 100.7 (CH, C-1), 96.9 (CH_2 MOM), 86.4 (CH), 82.3 (CH), 78.6 (C, C-4), 74.5 (CH), 74.4 (CH_2), 73.7 (CH_2), 73.5 (CH_2), 69.5 (CH), 67.1 (CH_2 Bn), 55.5 (CH_3), 54.9 (CH_3), 26.3, 25.6 (CH_3) ppm. $C_{23}H_{38}O_9$ (518.60): calcd. C 64.85, H 7.39; found C 64.63, H 7.11.

(1*S*,2*R*,3*R*,4*S*,5*S*,6*R*)-6-Hydroxymethyl-4-hydroxy-benzyloxymethyl-3-benzyloxy-2-hydroxy-7,8-dioxabicyclo[3.2.1]octane (15).). To a solution of one of the above isomers **14** (50 mg, 0.09 mmol) in methanol (1 mL), was added aqueous 0.5N HCl (1 mL), and the mixture heated under reflux for 72 h. Dichloromethane (4 mL) and aqueous saturated $NaHCO_3$ (4 mL) were added and the product extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by chromatography on silica gel (gradient elution, 1:2 to 2:1 EtOAc/PE) afforded **15** (13 mg) as a colorless solid, m. p. 129-130°C (petroleum ether-ethyl acetate). $[\alpha]_D$ = +62° (c 1.10, $CHCl_3$). IR ν_{max} 3554 cm^{-1}. MS (CI, NH_3) m/z 420 ($MH^+ + NH_3$), 403 (MH^+), 311 (M – Bn). ^1H NMR ($CDCl_3$) δ 7.39-7.27 (10 H, m), 5.36 (1 H, d, J = 2.0, H-1), 4.91 (1 H, d, J = 11.5, H-a CH_2 Bn), 4.71 (1 H, d, J = 11.5, H-b CH_2 Bn), 4.62 (2 H, s, CH_2 Bn), 4.39 (1 H, dd, J = 5.7, 5.6, H-6), 4.26 (1 H, s, H-5), 3.80 (1 H, d, J = 9.6, H-9a), 3.77 (1 H, d, J = 9.6, H-9b), 3.59 (3 H, m, H-10, H-3), 3.47 (1 H, ddd, J = 8.3, 6.0, 2.0, H-2), 3.01 (1 H, s, OH-4), 2.24 (1 H, d, J = 6.0, OH-2), 2.11 (1 H, dd, J = 5.3, 5.1, OH-10) ppm. ^{13}C NMR ($CDCl_3$) δ 138.6, 137.6 (C, Bn), 128.6 (CH), 128.5 (CH), 127.9 (CH), 101.9 (CH, C-1), 82.9 (C), 79.8 (C, C-4), 77.1 (CH), 76.2 (CH), 75.2(CH_2),, 73.9 (CH_2), 73.9 (CH), 69.3 (CH_2), 64.6 (CH_2) ppm.

Aknowledgement: We thank Hoechst Marion Roussel and the CNRS for a grant (BDI to P. F.).

References

1. For a review of the chemistry and biology of the zaragozic acids (squalestatins) see: Nadin, A.; Nicolaou, K. C. *Angew. chem. Int. Ed. Engl.* **1996**, *35*, 1622-1656. For more recent approaches see: Hegde, S. G.; Myles, D. C. *Tetrahedron Lett.* **1997**, *38*, 4329-4332. Xu, Y.; Johnson, C. R. *Tetrahedron Lett.* **1997**, *38*, 1117-1120. Paterson, I.; Feßner, K.; Finaly, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1997**, *38*, 4301-4304. Ito, H.; Matsumoto, M.; Yoshizawa, T.; Takao, K.; Kobayashi, S. *Tetrahedron Lett.* **1997**, *38*, 9009-9012. Brogan, J. B.; Zercher, C. K. *Tetrahedron Lett.* **1998**, *39*, 1691-1694. Kataoka, O.; Kitagaki, S.; Watanabe, N.; Kobayashi, J.; Nakamura, S.; Shiro, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 2371-2374. Martin, S.; Naito, S. *J. Org. Chem.* **1998**, *63*, 7592-7593. Tsubuki, M.; Okita, H.; Honda, T. *Synlett*, **1998**, 1417-1419. Koshimizu, H.; Baba, T.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **1999**, *40*, 2777-22780. Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Synlett*, **1999**, 697-700.

2. Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S. *Angew. chem. Int. Ed. Engl.* **1994**, *33*, 2190-2191. Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115-9125. Caron, S.; Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126-9134.

3. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825-10826. Ibid, *J. Am. Chem. Soc.* **1995**, *117*, 8106-8125. Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111-12112 Sato, H.; Nakamura, S.; Watanabe, N.; Hashimoto, S. *Synlett*, **1997**, 451-454. Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337-3340.

4. Handa, S.; Tsang, R.; McPhail, A. T.; Fraser-Reid, B. *J. Org. Chem.* **1987**, *52*, 3489-3491 and references cited therein. See also: Mazeas, D.; Skysdrup, T.; Beau, J-M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 909-912 and references cited therein.

5. Jones, G. H.; Taniguchi, M.; Tegg, D.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 931-936.

6. Gurjar, M. K.; Das, S. K.; Sadalapure, K. S. *Tetrahedron Lett.* **1995**, *36*, 1933-1936. Gurjar, M. K.; Das, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **1995**, *36*, 1937-1940.

7. Ireland, R. E. ; Norbeck, C. K. *J. Am. Chem. Soc.* **1985**, *107*, 3279-3285

8. McVinish, L. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 923-926. Mann, R. K.; Parson, J. G.; Rizzacasa, M. A. *J. Chem. Soc., Perkin Trans. 1*, **1998**,1283-1293.

9. Werschkun, B.; Thiem, J. *Synthesis*, **1999**,121-137.

10. Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317-3318. Tomooka, K.; Kikuchi, M.; Igawa, K.; Keong, P.-H.; Nakai, T. *Tetrahedron Lett.* **1999**, *40*, 1917-1920.

11. Portions of this work have been reported in preliminary form: Fraisse, P.; Hanna, I.; Lallemand, J. Y. *Tetrahedron Lett.* **1998**, *39*, 7853-7856.

12. Dhavale, D. D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 4100-4105. Boyer, F. D.; Pancrazi, A.; Lallemand, J. Y. *Synth. Commun.* **1995**, *25*, 1099-1108.

13. Prepared from D-mannitol according to the literature procedure: Schmid, C.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6-13.

14. For the effect of zinc enolate see for examples: House, H. O.; Crumrine, S. D.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.*, **1973**, *95*, 3310-3324. See also the first reference of note 4.

15. For of the use of $CeCl_3$ see: Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.*, **1984**, *25*, 4233-4236. Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.*, **1983**, *24*, 5233-5236. Nagasawa, K.; Kanbara, H.; Matsushita, K.; Ito, K. *Tetrahedron Lett.*, **1985**, *26*, 6477-6480. Al-Said, N. H.; Liu, H.-J. *Tetrahedron Lett.*, **1991**, *32*, 5473. Shang, X.; Liu, H.-J. *Synth. Commun.*, **1995**, *25*, 2155-2159. Bartoli, G.; Bosco, M.;Van Beek, J.; Sambri, L.; Marcantoni, E.*Tetrahedron Lett.*, **1996**, *37*, 2293-2296.

16. A small amount of THF must be added in order to prevent solidification of the reaction mixture at –100•C. Nevertheless, performing the reaction in a non-coordinating solvent such as toluene was found to greatly improve both the yield and the reproducibility. For a similar observation, see: D. Alker, D. Neville Jones, G. M. Taylor, W. W. Wood, *Tetrahedron Lett.* **1991**, *32*, 1667-1670.

17. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

18. The selectivity observed during the aldol reaction appeared to be highly dependent on the metal enolate; the use of $ZnCl_2$ led to a 95:5 mixture of ketoesters **6** albeit in a lower yield and with poor reproducibility.

19. X-ray crystal data for **12**: Crystals of **12**, $C_{29}H_{32}O_7$ were grown from a petroleum ether-ethyl acetate solution of the compound. Data were collected at 150± 0.1K on af Nonius KappaCCD diffractometer using Mo Kα (λ = 0.71073Å) radiation and a graphite monochromator. The crystal structure was solved and refined using the maXus package and final refinement was conducted using Shelxl97. The compound crystallises in space group $P2_1$, a = 12.5380(5)Å, b = 8.1940(4)Å, c = 13.3580(7)Å, β = 116.663(3)°; V = 1226.42(10)Å^3 ; Z = 2 ; dcalc = 1.334g/cm^3 ; μ = 0.095cm^{-1} ; F(000) = 524. A total of 4429 unique reflexions were recorded in the range 2•• θ • 26.7• of which 547 were considered as unobserved ($F^2 < 2\sigma(F^2)$), leaving 3882 for solution and refinement. The hydrogen atoms were included as riding contributions in the final stages of least-squares refinement while using anisotropic temperature factors for all other atoms. The final agreement factors were $wR_2 = 0.1216$, $R_1 = 0.0408$, G.O.F. = 1.077.

20. X-ray crystal data for **13:** Crystals of **13**, $C_{29}H_{32}O_7$ were grown from a petroleum ether-ethyl acetate solution of the compound. Data were collected at room temperature on af Nonius CAD4 diffractometer using Cu Kα (λ = 1.54180) radiation and a graphite monochromator. The compound crystallises in space group $P2_12_12_1$, a = 21.863(8)Å, b = 11.457(2) Å, c = 10.638(2) Å ; V = 2664.7(19)Å^3 ; Z = 4 ; dcalc = 1.228g/cm^3 ; μ = 0.714 cm^{-1} ; F(000) = 1048. A total of 2187 unique reflexions were recorded in the range 4•• θ •60• of which 186 were considered as unobserved ($F^2 < 2.0\sigma(F^2)$), leaving 2001 for solution and refinement. . The structure was refined as above to yeld final agreement factors $wR_2 = 0.0925$, $R_1 = 0.0845$, G.O.F. = 1.07.

21. For a review see: David, S.; Hanessian, S. *Tetrahedron*, **1985**, *41*, 643-663.

22. See for examples: Caron, S.; McDonald, A. I.; Heathcock, C. H. *J. Org. Chem.*, **1995**, *60*, 2780-2785. Paterson, I.; Feßner, K.; Finaly, M. R. V.; Jacobs, M. F. *Tetrahedron Lett.* **1996**, *37*, 8803-8806. Xu, Y.; Johnson, C. R. *Tetrahedron Lett.* **1997**, *38*, 1117-1120. Hegde, S. G.; Myles, D. C. *Tetrahedron* **1997**, *53*, 11179-11190. Armstrong, A.; Jones, L. H.; Barsanti, P. A. *Tetrahedron Lett.* **1998**, *39*, 3337-3340.