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Condensation of D-Mannosaldehyde Derivatives with Ethyl Diazoacetate. An Easy and Stereoselective Chain Elongation Methodology for Carbohydrates: Application to New Syntheses for KDO and 2-Deoxy-β-KDO.

Fidel J. López-Herrera* and Francisco Sarabia-García

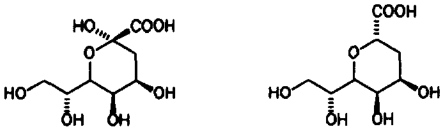
Departamento de Bioquímica, Biología Molecular y Química Orgánica. Facultad de Ciencias
Universidad de Málaga. 29071 Málaga. Spain.

Abstract: (3R and 3S) β-Hydroxy-α-diazocarbonyl compounds **4** (100%, 3:2), **9** (35%, 100:0), **14** (74%, 7:2) and **18** (100%, 100:0), prepared from 2,3,4,5,6-penta-O-acetyl- (**3**), penta-O-benzyl- (**8**), 2,3:5,6-di-O-isopropylidene-4-O-(tert-butyldimethylsilyl)- (**13**), and 2,3:5,6-di-O-isopropylidene-4-O-acetyl-D-mannosaldehyde (**17**), respectively, were acetylated, and the resulting β-acetoxy-α-diazocarbonyl compounds treated with rhodium diacetate to give the corresponding α-enol esters, **6** (100%), **11** (35%), **16** (100%) and **20** (100%), which are potentially α-keto esters. Molecular mechanics calculations were used in order to justify the stereoselectivity observed in the initial addition process. The problematic removal of the protecting groups from the α-enol esters is disccussed. Finally, hydrazinolysis of the α-enol acetates (to quench the labile resulting α-keto ester as the corresponding and less reactive hydrazines), mild oxidation to the corresponding α-diazoesters, deprotection, and final oxidation of the diazo group with m-chloroperbenzoic acid, gave KDO in good yield. Intermediate products were used in the completely stereoselective synthesis of 2-deoxy-β-KDO, a potent inhibitor for CMP-KDO synthetase. © 1997 Published by Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The aldol-type condensation of an aldehyde or ketone with a diazo compound is well-known and has proven to be an efficient method of chain elongation.[1] When the diazo compound is stabilized (e.g. an α-diazo carbonyl), the main condensation product under basic conditions is a β-hydroxy-α- diazo carbonyl compound.[2] A few years ago, our group undertook the study of this type of reaction of carbohydrates and their synthetic potential.[3] We found that highly reactive aldehydo-sugars underwent condensation in the absence of a catalyst to yield β-hydroxy-α-diazo carbonyl compounds in a high yield and with high stereoselectivity, simply by mixing the reactants. These preliminary results prompted us to study the reaction of ethyl diazoacetate with higher monosaccharide derivatives and to investigate other chemical transformations of the resultant highly functionalized products.[4] Thus, we reported the completely stereoselective photochemical[5] or rhodium mediated[6] Wolff rearrangements and the fully stereoselective alkylation of different oxy-diazo carbonyl compounds with trialkylboranes.[7] This paper, reports on synthesis of the major natural aldonic acid 3-deoxy-D-manno-2-octulosonic acid **1** (KDO) and its 2-deoxy-analogue **2**, using the rhodium mediated rearrangement of β-acetoxy-α-diazo ester derivatives.

KDO is an essential component of the cell wall lipopolysaccharide of Gram-negative bacteria and exopolysaccharides.[8] 2-Deoxy-β-KDO is the most potent inhibitor of CMP-KDO synthetase, an enzyme involved in the biosynthetic pathway of lipopolysaccharides in Gram-negative bacteria.[9] The synthesis of these products[10,11] has received much attention on account of their potential use in the development of a new class of antibiotics .



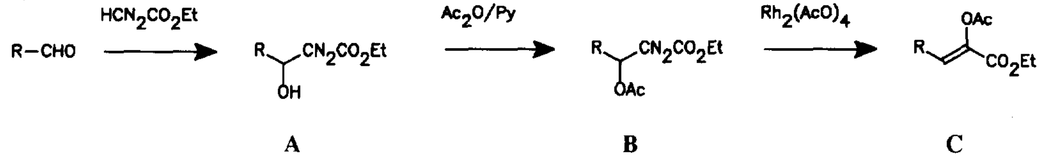
1 KDO 2 2-Deoxy-b-KDO

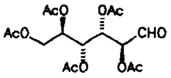
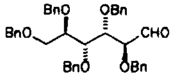
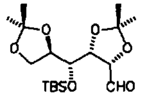
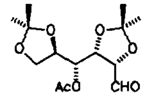
Figure 1

RESULTS AND DISCUSSION

Synthesis of KDO, 1. The key step of our synthetic approach to KDO **1** is based on the well-known rearrangement of β-acetoxy-α-diazo esters (B) to the corresponding α-acetoxy-α,β-unsaturatedcarboxylates (C), mediated by rhodium diacetate[12] (Scheme 1). This last product is in fact the acetate of the enol form of an α-keto ester, the functionality found in KDO. Thus, a β-oxy-α-diazo ester had to be prepared from a D-mannose derivative, namely the readily available 2,3,4,5,6-penta-O-acetyl-D-mannosaldehyde **3**.[13] The reaction of **3** with ethyl diazoacetate in the absence of solvent and a catalyst, gave quantitatively the condensation products **4a**:**4b** in a 3:2 ratio, albeit after a lengthy reaction time (7 days). We used molecular mechanics calculations (MM2, Osawa's modification[14]), in order to account for the low stereoselectivity observed in this reaction. We found 115 relative minimun energies corresponding to different conformers obtained by rotation of the C1-C2, C2-C3, C3-C4, C4-C5 and C5-C6 bonds, of which those with the less hindered *re* carbonyl face exhibited the larger populations. These results account for the low reaction diastereoselectivity and allowed us to establish the absolute configuration of C-3 in each isomer (e.g. 3-R for the major isomer). The conformer with the minimun energy (population 9.121%) is depicted in figure 2; its *re*-face is the most favourable for the attack. Resolution of the two C-3 epimers was impossible, so the mixture was acetylated and treated with a catalytic amount of rhodium diacetate to give a mixture of *Z*:*E* enol acetates **6a**:**6b**[15] in a 3:2 ratio and in almost quantitative yield . Acid hydrolysis of **6a**:**6b** with TFA did not lead to the desired α-keto ester derivative. Rather, it gave the elimination product **7** (Scheme 1), a previously reported product and a key intermediate in the synthesis of the 4-deoxy analogue of KDO.[13] On the other hand, taking in acount the low yield reported for the basic hydrolysis (Zemplen conditions) of the methyl ester analogue of **6** to give a lactone derivative of KDO,[16] we attempted the use of ammonia solution. Unfortunately, the result was a complex mixture, containing no KDO. These results revealed the need to use protecting groups that could be removed under more neutral conditions.

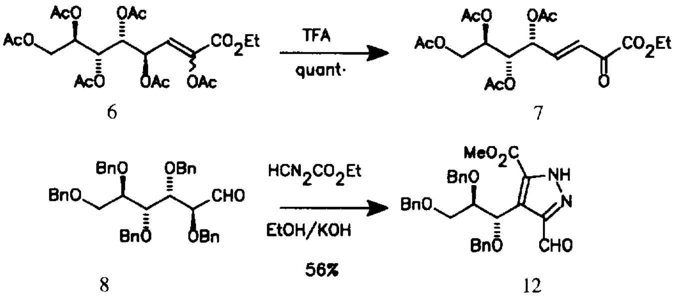
Table 1. Yield and stereoselectivity in the synthesis of β-oxy-αdiazo esters and α-enol esters



R-CH=O	Compound type A Yield (3R:3S)	Compound type B Yield	Compound type C Yield (Z:E)
 (3)	**4a:4b** 100% (3:2)	**5a:5b** 98% (3:2)	**6a:6b** 100% (3:2)
 (8)	**9** 35% (100:0)	**10** 95% (100:0)	**11** 35% (100:0)
 (13)	**14a:14b** 74% (7:2)	**15a:15b** 100%(7:2)	**16a:16b** 100% (7:2)
 (17)	**18** 100% (100:0)	**19** 100% (100:0)	**20a:20b** 100% (1:1)

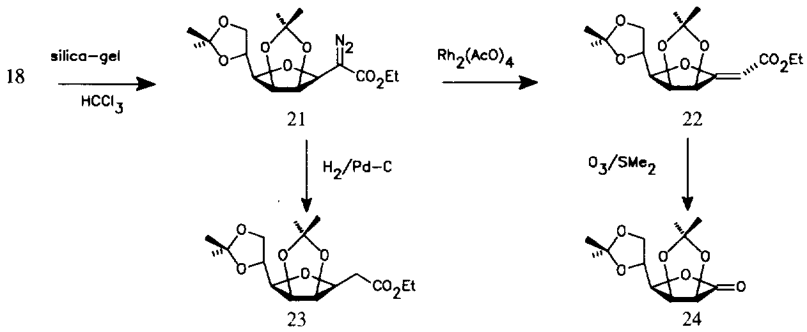
Thus, we chose penta-O-benzyl-D-mannosaldehyde **8**.[17] Condensation of **8** with ethyl diazoacetate gave **9** as single diastereoisomer, but in low yield (35% after purification). The complete stereoselectivity observed was consistent with an MM2 conformational analysis of **8**. The lowest-energy conformer (figure 3) and four others, which combined accounted for about 90% of the population, had the *re* face of the carbonyl group as the less hindered for addition. Consequently, the main stereoisomer formed may have been 3-R. The low yield of the condensation may be attributable to the severe steric hindrance of the benzyl groups adjacent to the aldehyde. Attempts to increase the reaction yield by employing basic conditions (10% MeOH-KOH) led to rather a different result: the pyrazoline derivative **12** in a 56% yield. In fact, this product, which resulted from benzyloxy elimination and cycloaddition of diazoacetate to the resulting alkene, was to be expected as it had previously been reported to occur in reactions with unstabilized, strongly alkaline sulphur ylides.[18] Therefore, we decided to continue our synthetic approach to KDO from **9**, which was acetylated and decomposed by rhodium acetate to alkene **11**, but again in a disappoint yield (35%).

At this point, we decided to examine the condensation reaction with di-O-isopropylidene derivatives in order to avoid elimination side reactions. Thus, 2,3:5,6-di-O-isopropylidene-4-O-tert-butyldimethylsilyl-D-mannose **13**[19] and the 4-O-acetyl analogue **17**[20] were prepared from 2,3:5,6-di-O-isopropylidene mannofuranose in six and three steps, respectively.



Scheme 1

The results of the condensation of both aldehydes was different as regards to the chemical and stereoselectivity yields. From **13**, a 7:2 mixture of **14a**:**14b** was obtained in a 74% yield after 7 days. Conformational analysis by MM2 showed the *re* face of the minimum energy conformer (population 75%) to be less hindered with regard to reagent approach, whereas the *si* face was found to be hindered by the TBS group. However, other low energy conformers had a more accessible *si* face. This theoretical study may account for the stereoselectivity observed and for the 3-R configuration of the major isomer. Conversely, condensation of **17** furnished only one diastereoisomer **18** in almost quantitative yield after a shorter reaction time (8 hours). The lowest-energy conformer (figure 5) and others with major population contributions (92% of the overall population) clearly exhibited their *re* face as the more favoured for the attack by the reagent, whereas their *si* face was fully hindered by the acetoxy group at C-4. When **18** was further purified by chromatography on silica gel, partial conversion to the furanoside derivative **21** was observed. In fact, exposure of **18** to silica gel led to complete transformation to **21** after several days in chloroform. The structure of **21** was stablished via decomposition to the Z olefin **22**[21], mediated by rhodium diacetate, and subsequent ozonolysis to the well-known D-mannonic γ-lactone **24**.[22]



Scheme 2

On the other hand, hydrogenolysis of **21** gave the previously reported **23**,[23] in quantitative yield. The transformation of **18** into **21** occurred with acetyl migration from the hydroxyl group at C-6 to the free one at C-3, and subsequent nucleophilic displacement of the acetate by the free hydroxyl group at C-6. This intramolecular reaction only is possible if the absolute configuration at C-3 is 3-R (the one we assigned it on the basis of the theoretical results obtained in the conformational study of the aldehyde **17**).

In order to prevent cyclization of **18** to **21**, the crude product was acetylated to give **19** (93% yield from **17**). Similarly, the mixture **14a**:**14b** was acetylated to **15a**:**15b** in a 98% yield, and each diastereoisomer was separated by flash chromatography on silica gel. The reaction of these acetylated products (**15a**:**15b** and **19**) with rhodium diacetate in chloroform gave quantitatively the olefins **16a**:**16b** and **20a**:**20b**. Interestingly, **19** led to a 1:1 mixture of *Z*:*E* olefins while each diastereoisomer of **15** led to a single olefin (Z or E). Conversion of the enol acetates **16** and **20** to their ketone derivatives was attempted using both MeOH/MeONa and TFA hydrolysis. However, complex mixtures were obtained in both cases, and neither where no di-O-isopropylidene KDO derivative was detected in the former case or free KDO in the later. The lack of success was ascribed to the well-known instability of KDO in acid media[24] and the ketone under basic conditions.

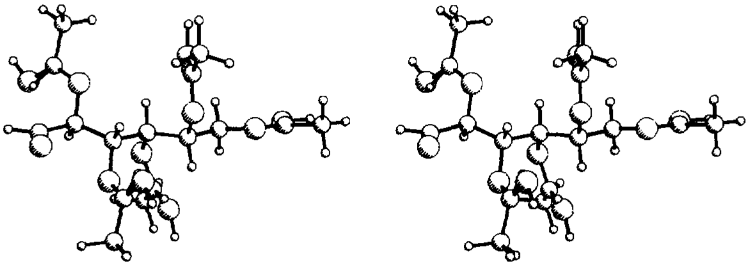


Figure 2

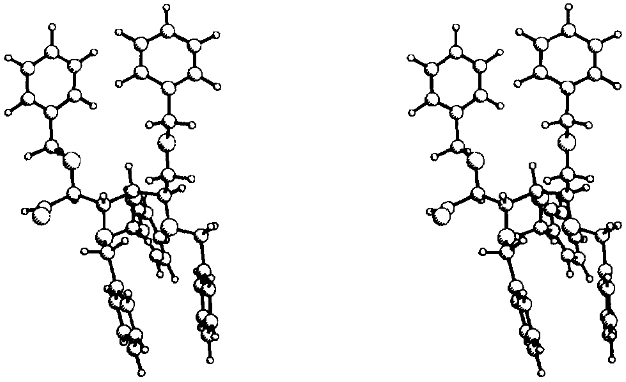


Figure 3

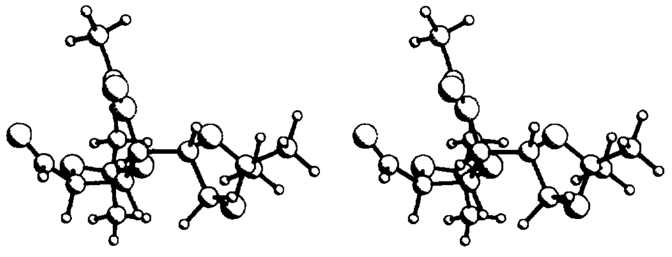


Figure 4

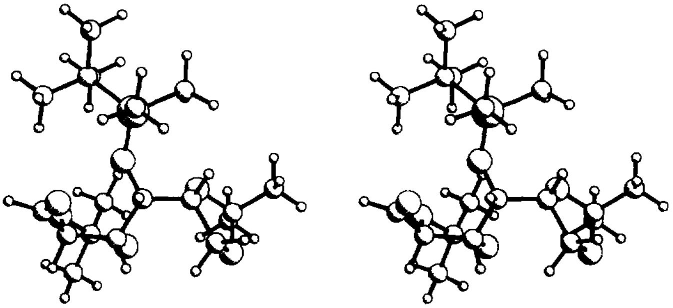
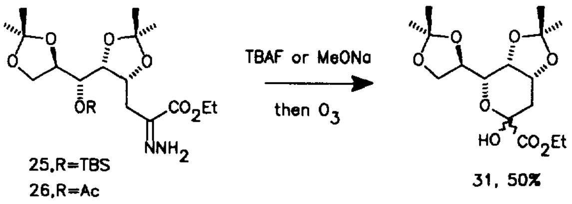
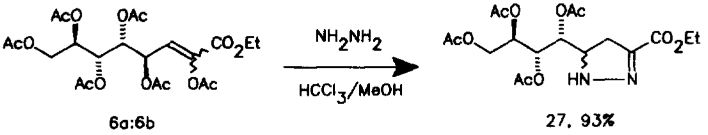


Figure 5

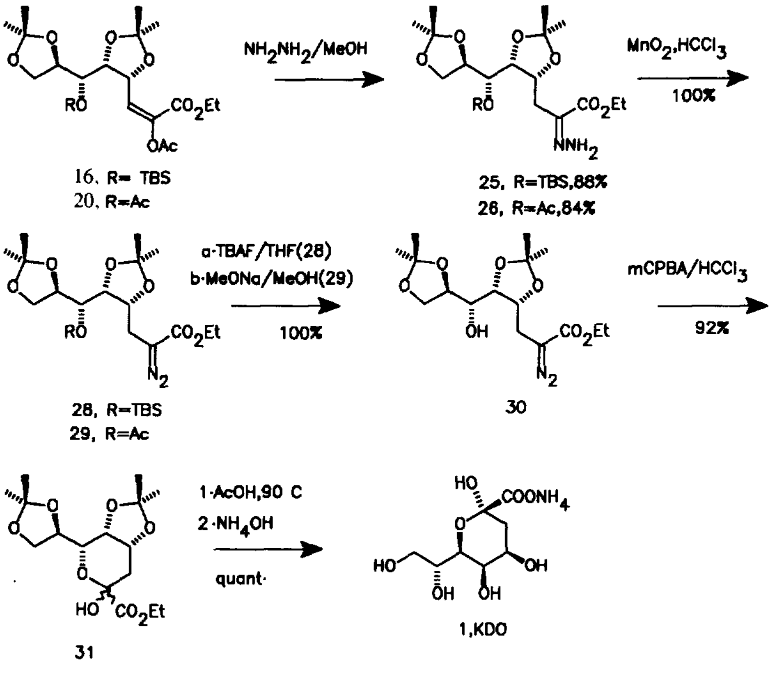
Thus, it was necesary to modify our KDO approach by including an additional step, namely the quenching of the α-keto esters resulting from hydrazinolysis (1M hydrazine solution in methanol) of the starting enol acetates. In fact, we reasoned that the resulting hydrazones should be more stable than the corresponding α-keto esters under basic conditions. Thus, hydrazones **25** and **26** were obtained in 88 and 84% yield, respectively, after purification (Scheme 3). The simple synthesis of **6**, prompted us to react it with hydrazine, but again acetoxy elimination occurred and product **27** was obtained. The conversion of these stable hydrazones to the corresponding ketones was initially attempted by ozonolysis, but the yield was too low (a mixture of several products was obtained).





Scheme 3

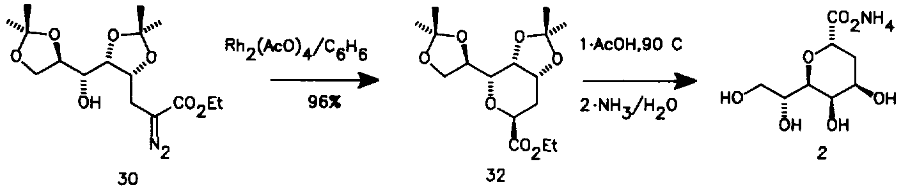
Thus, due to the mild reaction conditions, oxidation of the hydrazone group to the diazo species by manganese dioxide was attempted (Scheme 4). The diazo compounds **28** and **29**, obtained in quantitative yield, were treated with tetrabutylammonium fluoride and MeONa, respectively, to yield the hydroxy diazo derivative **30** in almost quantitative yield in both cases. Finally, oxidation with m-CPBA in chloroform gave the KDO derivative **31** in good yield (92%).KDO ammonium salt was prepared by reaction of **31** with 90% AcOH and subsequent treatment with ammonia. Recrystallization from water:acetone afforded pure, crystalline KDO which was identical with an authentic sample purchased from SIGMA.[25]



Scheme 4

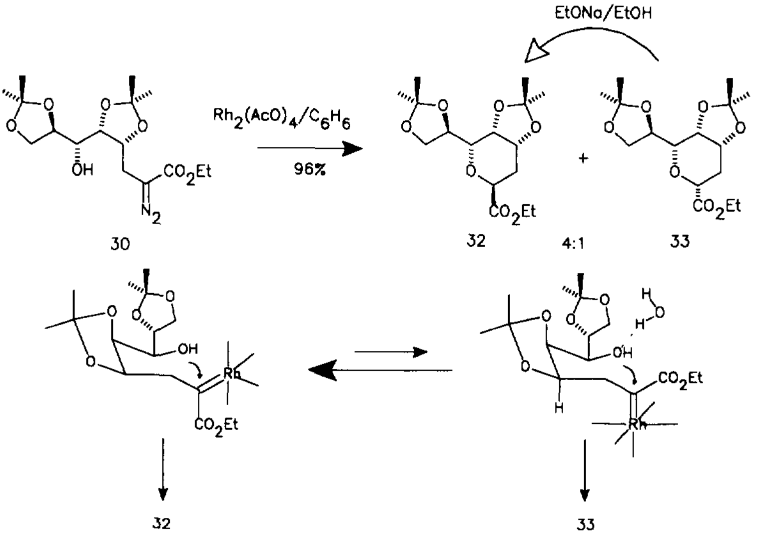
Synthesis of 2-deoxy-β-KDO, 2. Product **30** was of a particular interest not only for the preparation of KDO as described above, but also to synthesize the 2-deoxy analogue, the most potent inhibitor for the CMP-KDO synthetase.[7] This analogue should be formed by intramolecular insertion of the carbene species into the OH group.

Rhodium diacetate seems to be the catalyst of choice for this reaction.[26] Thus, **30** was reacted with a catalytic amount of rhodium diacetate in anhydrous benzene under nitrogen atmosphere, with immediate nitrogen release. Within a few minutes, **30** was transformed into the expected product **32** (96% after purification). This was the only product detected; its alpha configuration was demonstrated by comparisson with reported data.[11] Interestingly, decomposition of diazo compound **30**, mediated either by silver oxide or by UV light, always led to complex mixtures, where alkene resulting from the 1,2-hydrogen shift could be identified as the main product.



Scheme 5

When this reaction was carried out in chloroform or wet benzene, a 4:1 mixture of α:β anomers **32** and **33** was obtained. In order to justify this stereochemical result, we postulated a potential conformational equilibrium involving the rhodium carbenoid intermediate.



Scheme 6

Kinetic control would lead to the α- anomer, as observed under anhydrous conditions. When the solvent was not anhydrous, solvatation of the free hydroxyl group of **30** should favour the conformational equilibrium (thermodynamic control) so, the stereoisomers mixture should be obtained as was indeed the case. However, basic treatment of **33** with sodium ethylate in ethanol produced epimerization to give a 4:1 mixture of **32**:**33**. Finally, the ammonium salt of 2-deoxy-β-KDO **2** was prepared under the same conditions used in KDO synthesis and unequivocally identified by comparison with reported data.[9]

EXPERIMENTAL

Melting points are given uncorrected. IR spectra were recorded on a Beckman Aculab IV spectrophotometer, wavenumbers are expressed in cm^{-1}. ^1H-NMR spectra were obtained at 200 MHz on a Bruker WP 200SY and at 500 MHz on a Bruker AMX using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm (relative to the signal for $CHCl_3$ as internal reference), notations indicate the signal multiplicity (s, singlet, d doublet, t triplet, q quadruplet, m, multiplet). Coupling constants are expressed as J values in Hertz units. Mass spectra were recorded on a Hewlett-Packard 5988A instrument. Microanalyses were performed by the "Servicio de Microanálisis de la Universidad de Málaga". Exact masses were recorded on a Kratos MS 80 RFA instrument of the University at Seville. Specific rotations were measured with a Perkin-Elmer 241 polarimeter. The silica gel for column chromatography was Merck silica-gel 60 No. 7736. Analytical thin layer chromatography was performed on Merck silica gel 60 No. 7747.

4-O-(tert-Butyldimethylsilyl)-2,3:5,6-di-O-isopropylidene-*aldehydo*-D-mannose 13.- This aldehyde was prepared by modification of the Setoi[19] method in the silylation step: To a solution containing 1 g of 1-benzoyl-2,3:5,6-di-O-isopropylidene-D-mannitol in 20 mL of anhydrous tert-butylmethyl ether was added 0.7 g of N,N-diisopropyl-N-ethylamine (DIPEA). The solution was cooled at 0°C, and a solution of 0.8 g of tert-butyldimethylsilane trifluormethanosulfonate (Tf-TBS) dissolved in 4 mL of tert-butyldimethyl ether was added dropwise. After 5 h with stirring, the resulting suspension was filtered and the filtrate concentrated in vacuo to obtain 1.6 g of 1-benzoyl-4-O-(tert-butyldimethylsilyl)-2,3:5,6-di-O-isopropylidene-D-mannitol, virtually pure. Oxidation to the aldehyde **13** was performed according to McLeod et al[10g], after removal of the benzoyl group. ^1H-NMR. ($CDCl_3$) δ ppm : 9.74 (d, 1H, $J_{1,2}$= 2.1 Hz, H-1), 4.49 (dd, 1H, $J_{2,3}$ = 6.0 Hz, H-2), 4.19 (dd, 1H, $J_{5,6}$= 6.0 Hz, $J_{6,6'}$= 8.5 Hz, H-6), 4.12 (ddd, 1H, $J_{5,4}$= 8.4 Hz, $J_{5,6'}$= 7.3 Hz, H-5), 4.01 (dd, 1H, $J_{3,4}$= 7.0 Hz, H-3), 3.89 (dd, 1H, H-4), 3.78 (dd, 1H, H-6'), 1.54, 1.37, 1.36 and 1.32 (4s, 12H, 2 $C\underline{Me}_2$), 0.85 (s, 9H, $OSiC\underline{Me}_3$), 0.07 and 0.06 (2s, 6H, $-OSi(\underline{Me})_2$).

4-O-Acetyl-2,3:5,6-di-O-isopropylidene-*aldehydo*-D-mannose 17.- A solution containing 3 g of the alkene 5-O-acetyl-1,2-dideoxy-3,4:6,7-di-O-isopropylidene-D-manno-1-heptenitol[20] in 50 mL of chloroform was bulbed with ozone (1.1 mL O_3/s) at 0°C. After 150 min., the reaction is complete and 12 mL of SMe_2 is added. The solution was kept at 0°C for 12 h and the solvent removed in vacuo. An amount of 3 g of aldehyde **17**, virtually pure (100%) was obtained. ^1H-N.M.R. ($CDCl_3$) δ ppm : 9.51 (d, 1H, $J_{1,2}$= 1.78 Hz, H-1), 5.02 (dd, 1H, $J_{3,4}$= 2.1 Hz, $J_{4,5}$= 6.6 Hz, H-4), 4.62 (dd, 1H, $J_{2,3}$= 7.8 Hz, H-3), 4.39 (dd, 1H, H-2), 4.14 (q, 1H, J= 6.3 Hz, H-5), 3.90 (dd, 1H, $J_{5,6}$= 5.9 Hz, $J_{6,6'}$= 8.7 Hz, H-6), 3.79 (dd, 1H, $J_{5,6'}$= 6.3 Hz, H-6'), 1.96 (s, 3H, $OCO\underline{Me}$), 1.52, 1.33, 1.29 and 1.26 (4s, 12H, 2 $C\underline{Me}_2$).

β-Hydroxy-α-diazo esters from *aldehydo*-D-mannose derivatives. General Procedure. The *aldehydo*-mannose was mixed homogeneusly with 1.2 eq of ethyl diazoacetate in the absence of solvent, at r.t. in the dark. The reaction time required for completion of the reaction was from 8 h to one week. The crude mixture was finally purified by chromatography on silica gel.

Ethyl 4,5,6,7,8-penta-O-acetyl-2-deoxy-2-diazo-D-*glycero*-D-*manno* and D-*gluco*-octanoate 4a:4b. Amounts of 5.2 g of **3** and 2 g of ethyl diazoacetate were reacted. After one week, the entitled product was obtained in virtually quantitative yield. Further purification by chromatography on silica gel (hexane:AcOEt 1:1) provided 5.4 g of **4a:4b** as a viscous yellow liquid (82%). I.R. ν_{max} (cm^{-1}) : 3478 (-OH), 2991, 2111 ($C=N_2$), 1753, 1692 (C=O), 1430. U.V. λ_{max}($CHCl_3$): 256 nm. ^1H-NMR ($CDCl_3$) δ ppm : 5.50-5.19 (m, 3H, major isomer, 3H, minor isomer, H-5, 6, 7), 5.16-4.87 (m, 1H, major isomer, 1H, minor isomer, H-4), 4.75 (t, 1H, $J_{3,4}$= $J_{3,OH}$= 5.3 Hz, H-3, major isomer), 4.25-4.15 (m, 2H, both isomer, H-8, H-8'), 4.05 (c, 2H, J =7.2 Hz, $-CO_2\underline{CH}_2CH_3$), 2.18-2.02 (10s, 30H, 10 -$OCO\underline{Me}$), 1.20 (2t, 6H, J = 7.2 Hz, 2 $-CO_2CH_2\underline{CH}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 172.02, 170.49, 170.44, 169.88, 169.85, 169.79, 169.72, 169.69, 169.58, 169.54 (10 -$O\underline{C}OMe$, both isomer), 165.69 (C-1), 71.52 (C-4, major isomer), 71.13 (C-4, minor isomer), 68.44, 68.11, 67.72 (C-5, C-6, C-7, major isomer), 70.33, 68.73, 68.27 (C-5, C-6, C-7, minor isomer), 67.64 (C-3, major isomer), 67.19 (C-3, minor isomer), 66.62 (C-8, major isomer), 65.83 (C-8, minor isomer), 61.66 and 61.46 (2 $-CO_2\underline{C}H_2CH_3$), 20.88, 20.73, 20.69, 20.62, 20.53, 20.49, 20.36, 20.24 (-$OCO\underline{Me}$), 14.28 and 14.05 (2 $-CO_2CH_2\underline{C}H_3$). Elemental analysis: Calcd. for $C_{20}H_{28}O_{13}N_2$ C, 47.62 %; H, 5.59 %; N, 5.55 %. Found: C, 47.52 %; H, 5.50 %; N, 5.21%.

Ethyl 4,5,6,7,8-penta-O-benzyl-2-deoxy-2-diazo-D-*glycero*-D-*manno*-octulosonate 9. An amount of 3 g of the aldehyde **8** was reacted with 0.8 g of ethyl diazoacetate for 7 days. Chromatography on silica gel (hexane:AcOEt 6:1) provided 1.2 g of the entitiled product **9**, as a yellow liquid. (35%). I.R. ν_{max} (cm^{-1}) : 3455 (-OH), 2931, 2107 ($C=N_2$), 1685 (C=O), 1453. U.V. λ_{max}($CHCl_3$): 250 nm. ^1H-NMR ($CDCl_3$) δ ppm : 7.33-7.12 (m, 25H, Ph), 4.88 (dd,1H, $J_{3,OH}$=5.1Hz, $J_{3,4}$ =6.0 Hz, H-3), 4.66-4.61 and 4.49-4.43 (m, 10 H, 5 $\underline{CH}_2Ph$), 4.14 (c, 2H, J =7.0 Hz), 4.01-3.87 (m, 2H, H-5, H-6), 3.84-3.69 (m, 3H, H-4, H-7 y H-8), 3.67 (m, H-8'), 3.15 (d, $J_{3,OH}$ = 5.1 Hz, -OH), 1.16 (t, 3H, J = 7.0 Hz, $-CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 167.3 (C-1), 138.9, 138.7, 138.5, 138.2, 137.9 (-Ph), 129.5-127 (-Ph), 81.5 (C-4), 80.1, 79.4 and 78.8 (C-5, C-6 and C-7), 74.8, 74.2, 73.7, 73.2 and 72.1 ($-CH_2Ph$), 69.8 (C-8), 67.9 (C-3), 61.4 ($-CO_2\underline{C}H_2CH_3$), 14.5 ($-CO_2CH_2\underline{C}H_3$). Elemental analysis: Calcd. for $C_{45}H_{48}O_8N_2$ C, 72.56 %; H, 6.50 %; N, 3.76 %. Found: C, 72.89 %; H, 6.40 %; N, 3.42 %.

Ethyl 2-deoxy-2-diazo-4,5:7,8-di-O-isopropylidene-6-(tert-butyldimethylsilyl)-D-*glycero*-D-*manno* and D-*gluco*-octulosonate 14a:14b. Reaction time, 7 days. Purification by chromatography on silica gel (hexane:ethyl acetate 5:1) provided a 3.5:1 mixture of **14a:14b** in a 74% yield. I.R. ν_{max} (cm^{-1}) : 3462 (-OH), 2991-2864, 2109 ($C{=}N_2$), 1691 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.94 (dd, 1H, $J_{3,OH}$ = 5.3 Hz, $J_{3,4}$ = 2.0 Hz, H-3, major isomer), 4.61 (dd, 1H, $J_{3,OH}$ = 4.8 Hz, $J_{3,4}$=8.7 Hz, H-3, minor isomer), 4.28 (dd, 1H, $J_{3,4}$ = 2.0 Hz, $J_{4,5}$=5.3 Hz, H-4, major isomer), 4.18 and 4.17 (2q, 4H, J=7.1Hz, $-CO_2C\underline{H}_2CH_3$, both isomers), 4.15-4.05 (m, H-7, H-8, major isomer, and H-5, H-6,H-7, H-8, minor isomer), 4.00 (dd, $J_{8,8'}$=8.7Hz, $J_{7,8'}$=4.7Hz, H-8', minor isomer), 3.97 (dd, 1H, $J_{5,6}$=7.1 Hz, $J_{4,5}$=5.3 Hz, H-5, major isomer), 3.89 (dd, 1H, $J_{5,6}$=7.1 Hz, $J_{6,7}$=5.5 Hz, H-6, major isomer), 3.79 (t, 1H, $J_{7,8'}$=$J_{8,8'}$=7.4 Hz, H-8', major isomer), 3.92 (1H, $J_{3,OH}$=4.8 Hz, OH, minor isomer), 2.61 (d, 1H, $J_{3,OH}$=5.6 Hz, OH), 1.57, 1.49, 1.43, 1.35 (CMe_2, major isomer), 1.38, 1.34, 1.30, 1.29 (CMe_2, minor isomer), 1.23 (t, $CO_2CH_2C\underline{H}_3$, major isomer), 1.22 (t, $CO_2CH_2C\underline{H}_3$, minor isomer), 0.84 and 0.83 (2s, -Si-tBu, both isomers), 0.078 (1s, 6H, $-SiMe_2$, major isomer), 0.071 and 0.065 (2s, 6H, $SiMe_2$, minor isomer). ^{13}C-NMR (major isomer) ($CDCl_3$) δ ppm : 166.25 (C-1), 109.71 and 107.81 (2 $\underline{C}Me_2$), 79.82 (C-4), 77.45 (C-6), 76.91 and 70.37 (C-5 and C-7), 67.51 (C-3), 66.95 (C-8), 60.71 ($CO_2\underline{C}H_2CH_3$), 27.45, 25.95, 25.26 and 25.23 (2 $C\underline{Me}_2$), 25.82 ($SiC\underline{Me}_3$), 18.35 ($Si\underline{C}Me_3$), 14.36 ($CO_2CH_2\underline{C}H_3$), 1.74 and 1.33 ($Si\underline{Me}_2$). MS: minor isomer: 399 (M$^+$-15 (Me)-28(N_2)-46), 357, 300, 241, 101,73 (b. p); major isomer:399 (M$^+$-15-28-46), 299, 241, 101, 73 (b. p.). Elemental analysis: Calcd. for $C_{22}H_{40}O_8N_2Si$: C, 54.09 %; H, 8.19 %; N, 5.73 %. Found: C, 54.44 %; H, 8.08 %; N, 5.19 %.

Ethyl 6-O-acetyl-2-deoxy-2-diazo-4,5:7,8-di-O-isopropylidene-D-*glycero*-D-*manno*-octulosonate 18. An amount of 3 g of **17** was reacted with 1.5 g of ethyl diazoacetate. After 8 h, the reaction was complete, with vitually quantitative formation of **18**. Decomposition on silica gel hindered further purification. $[\alpha]_D^{20}$ - 5.0º (c 3.4, $CHCl_3$). I.R. ν_{max} (cm^{-1}) : 3452 (-OH), 2109 ($C{=}N_2$), 1746, 1686 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.43 (dd, 1H, $J_{6,7}$ = 5.6 Hz, $J_{5,6}$ = 1.9 Hz, H-6), 4.57 (d, 1H, $J_{3,4}$ = 10 Hz, H-3), 4.43 (dd, 1H, $J_{5,6}$ = 1.9 Hz, $J_{4,5}$=6.1 Hz, H-5), 4.25 (ddd, 1H, $J_{7,8}$=6.2 Hz, $J_{7,8'}$=6.7 Hz, $J_{6,7}$=5.6 Hz, H-7), 4.21 (q, 2H, J=7.1Hz, $-CO_2C\underline{H}_2CH_3$), 3.99 (dd, 1H, $J_{8,8'}$=8.6 Hz, $J_{7,8}$=6.2 Hz, H-8), 3.95 (dd, 1H, $J_{3,4}$=10 Hz, $J_{4,5}$=6.1Hz, H-4), 3.90 (dd, 1H, $J_{7,8'}$=6.7 Hz, $J_{8,8'}$=8.6 Hz, H-8'), 2.10 ($COC\underline{H}_3$), 1.45, 1.36 (2s, $C\underline{Me}_2$), 1.33 (1s, 6H, $C\underline{Me}_2$), 1.26 (t, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$).^{13}C-NMR ($CDCl_3$) δ ppm: 170.29 ($\underline{C}OCH_3$), 170.05 (C-1), 109.13 and 109.02 (2 $\underline{C}Me_2$), 75.90 (C-4), 75.08 (C-6), 73.87 (C-5), 70.07 (C-7), 69.29 (C-3), 65.95 (C-8), 60.88 ($CO_2\underline{C}H_2CH_3$), 26.77, 26.39, 25.35 and 25.20 (2 $C\underline{Me}_2$), 21.03 ($CO\underline{C}H_3$), 14.29 ($CO_2CH_2\underline{C}H_3$). MS: 313 (M$^+$-28 (N_2)-15(Me)-60(AcOH)), 283, 255, 213 (b. p.), 167, 101.

β-Acetoxy-α-diazo esters from *aldehydo*-D-mannose derivatives. General procedure. To a solution of 1 mmol of β-hydroxy-α-diazo ester in 5 mL of pyridine, 1 mL of acetic anhydride was added. After 8 h, the crude mixture was poured into water-ice, and extracted with chloroform (3 x 1). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo. Excess pyridine was removed under high vacuum and the entitled products were obtained nearly pure in 98-100% yields.

Ethyl 3,4,5,6,7,8-hexa-O-acetyl-2-deoxy-2-diazo-D-*glycero*-D-*manno* and D-*gluco*-octulosonate 5a:5b. 98%. as a yellow syrup. UV= 256 nm. I.R. ν_{max} (cm^{-1}) : 2108 ($C{=}N_2$), 1758 and 1701 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.71 (d, 1H, $J_{3,4}$ = 0.8 Hz, H-3, major isomer), 5.70 (d, 1H, $J_{3,4}$ = 0.75 Hz, H-3, minor isomer), 5.55 (dd, 1H,

$J_{3,4}$= 0.8 Hz, $J_{4,5}$=2.8 Hz, H-4, major isomer), 5.47-5.25 (m, H-5 and H-6, major isomer and H-4, H-5 and H-6, minor isomer), 4.97-4.89 (m, H-7, both isomers), 4.14 (2q, 4H, J=7.1Hz, both isomers, $-CO_2C\underline{H}_2CH_3$), 4.09-3.89 (m, H-8, H-8' both isomers), 2.04, 2.03, 2.01, 2.00, 1.99, 1.98, 1.97, 1.96, 1.94 (9s, $COC\underline{H}_3$, both isomers), 1.19 (t, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.35, 169.81, 169.76, 169.68, 169.65, 169.62, 169.45, 169.24, 169.07 ($\underline{C}OCH_3$), 164.45, 163.90 ($\underline{C}O_2Et$), 69.75 (C-4, major isomer), 69.36 (C-4, minor isomer), 67.99, 67.84, 67.48 (C-5, C-6, C-7), 67.87, 67.08, 66.99 (C-5, C-6, C-7, minor isomer), 67.27 (C-3, major isomer), 64.51 (C-3, minor isomer), 61.68 (C-8, minor isomer), 61.53 (C-8, major isomer), 61.39 ($CO_2\underline{C}H_2CH_3$, major isomer), 61.30 ($CO_2\underline{C}H_2CH_3$, minor isomer), 20.77, 20.70, 20.51, 20.44, 20.37, 20.18 ($CO\underline{C}H_3$), 14.24 and 14.19 ($CO_2CH_2\underline{C}H_3$). Elemental analysis: Calcd. for $C_{22}H_{30}O_{14}N_2$: C, 48.35 %; H, 5.49 %; N, 5.13 %. Found: C, 47.87 %; H, 5.39 %; N, 5.43 %.

Ethyl 3-O-acetyl-4,5,6,7,8-penta-O-benzyl-2-deoxy-2-diazo-D-*glycero*-D-*manno* octulosonate 10. 95% as a yellow syrup. $[\alpha]_D^{20}$ -14.8 º (c 0.99, Cl_3CH). I.R. ν_{max} (cm^{-1}) : 2114 ($C{=}N_2$), 1735 and 1691 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 7.40-7.0 (m, 25 H, $CH_2\underline{Ph}$), 6.1 (d, 1H, $J_{3,4}$=1.8 Hz, H-3), 4.8-4.4 (m, 10H, $\underline{C}H_2Ph$), 4.2 (q, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.3-4.15 (m, 2H, H-4, H-5), 4.05-3.90 (m, 3H, H-6, H-7, H-8), 3.72 (dd, $J_{7,8'}$=3.2 Hz, $J_{8,8'}$=7.8 Hz, H-8'), 2.0 ($COC\underline{H}_3$), 1.27 (t, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.9 ($\underline{C}OCH_3$), 164.7 (C-1), 142.5, 139.5, 139.4, 139.2, 139.0 (quaternary Ph), 129-127 ($\underline{C}H$ aromatics), 81.5 (C-4), 79.7, 79.5, 78.9 (C-5, C-6, C-7), 75.0, 73.9, 73.5, 72.1 and 70.5 ($\underline{C}H_2Ph$), 73.6 (C-3), 69.6 (C-8), 61.4 ($CO_2\underline{C}H_2CH_3$), 21.3 ($CO\underline{C}H_3$), 14.7 ($CO_2CH_2\underline{C}H_3$). Elemental analysis:Calcd. for $C_{47}H_{50}O_9N_2$: C, 71.74 %; H, 6.40 %; N, 3.56 %. Found: C, 72.04 %; H, 6.28 %; N, 3.32 %.

Ethyl 3-O-acetyl-2-deoxy-2-diazo-4,5:7,8-di-O-isopropylidene-6-(tert-butyldimethylsilyl)-D-*glycero*-D-*manno* and D-*gluco*-octulosonate 15a:15b. 100% as a yellow syrup. Separation of both diastereoisomers was perfomed by chromatography on silica gel (hexane:ethyl acetate 10:1).

Major isomer **15a**: I.R. ν_{max} (cm^{-1}) : 2112 ($C{=}N_2$), 1753 and 1702 (C=O). $[\alpha]_D^{20}$ 95.15 º (c 2.3, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 6.10 (d, 1H, $J_{3,4}$=2 Hz, H-3), 4.37 (dd, 1H, $J_{3,4}$=2 Hz, $J_{4,5}$=5.0 Hz, H-4), 4.3-4.1 (m, 3H, H-7, $CO_2CH_2CH_3$), 4.05 (dd, 1H, $J_{7,8}$=5.0 Hz, $J_{8,8'}$=8.3 Hz, H-8), 3.83 (dd, 1H, $J_{4,5}$=5.0 Hz, $J_{5,6}$=7.1 Hz, H-5), 3.73 (dd, 1H, $J_{5,6}$=7.1, $J_{6,7}$=3.5 Hz , H-6), 3.68 (dd, 1H, $J_{7,8'}$=4.7 Hz, $J_{8,8'}$= 8.3 Hz, H-8'), 2.10 (s, 3H, COMe), 1.53, 1.49, 1.37 and 1.32 (4s, 12H, $2CMe_2$), 1.22 (t, 3H, CO_2Et), 0.05 and 0.03 (2s, 6H, $SiMe_2$). ^{13}C-NMR ($CDCl_3$) δ ppm : 168.9 ($\underline{C}OCH_3$), 164.7 (C-1), 110.62 and 108.26 ($2\,\underline{C}Me_2$), 80.54 (C-4), 79.12 and 77.46 (C-5 and C-6), 69.11 (C-3), 72.09 (C-7), 67.66 (C-8), 60.73 ($CO_2\underline{C}H_2CH_3$), 25.97 and 25.42 ($C\underline{Me}_2$), 25.85 (Si-tBu), 21.24 ($CO\underline{C}H_3$), 18.34 ($C\underline{Me}_3$), 14.47 ($CO_2CH_2\underline{C}H_3$), 1.96 and 1.03 ($Si\underline{Me}_2$). MS: 487 (M^+-28-15), 215, 199, 101, 43 (b.p.). Elemental analysis: Calcd. for $C_{24}H_{42}O_9N_2Si$: C, 54.33 %; H, 7.92 %; N, 5.28 %. Found: C, 53.98 %; H, 7.67 %; N, 4.91 %.

Minor isomer **15b**: $[\alpha]_D^{20}$ -110.9 º (c 1.74, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.66 (d, 1H, $J_{3,4}$=5.8 Hz, H-3), 4.47 (m, 1H), 4.20 (q, 2H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.18-3.85 (m, 5H), 2.07 (s, 3H, COMe), 1.43, 1.38, 1.30 and 1.28 (4s, 12H, $2\,C\underline{Me}_2$), 1.23 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 0.83 (s, 9H, t-Bu), 0.02 and 0.00 (2s, 6H, $SiMe_2$). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.0 ($\underline{C}OCH_3$), 165.1 (C-1), 109.82 and 108.2 ($2\,\underline{C}Me_2$), 79.8 (C-4), 77.1 and 76.5 (C-5 and C-

6), 69.9 and 69.7 (C-3 and C-7), 65.1 (C-8), 61.2 ($CO_2\underline{C}H_2CH_3$), 26.5, 26.3, 25.8 and 25.1 (2 $C\underline{Me}_2$), 26.1 (Si-tBu), 21.1 ($CO\underline{C}H_3$), 18.5 ($C\underline{Me}_3$), 14.4 ($CO_2CH_2\underline{C}H_3$), 1.8 and 1.2 ($Si\underline{Me}_2$). Exact mass: Calcd. for $C_{24}H_{42}O_9N_2Si$: (-N_2-Me)= 487.2111. Found : 487.2139.

Ethyl 3,6-di-O-acetyl-2-deoxy-2-diazo-4,5:7,8-di-O-isopropylidene-D-*glycero*-D-*manno*-octulosonate 19. 100% as a yellow syrup. $[\alpha]_D^{20}$ 2.8 ° (c 0.54, Cl_3CH). UV: 254 nm. I.R. ν_{max} (cm^{-1}) : 2113 (C=N_2), 1753 and 1701 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.43 (dd, 1H, $J_{5,6}$=1.9 Hz, $J_{6,7}$=5.9 Hz, H-6), 4.57 (d, 1H, $J_{3,4}$=10.0 Hz, H-3), 4.43 (dd, 1H, $J_{5,6}$=1.9 Hz, $J_{4,5}$=6.1 Hz, H-5), 4.27-4.14 (m, 4H, H-6, H-4, $CO_2\underline{CH}_2CH_3$), 3.99 (dd, 1H, $J_{7,8}$=6.2 Hz, $J_{8,8'}$=8.7 Hz, H-8), 3.90 (dd, 1H, $J_{7,8'}$=6.7 Hz, $J_{8,8'}$=8.7 Hz, H-8'), 2.10 and 2.05 (2s, 6H, 2 OCO$\underline{Me}$), 1.45 and 1.36 (2s, 6H, $C\underline{Me}_2$), 1.33 (s, 6H, $C\underline{Me}_2$), 1.25 (t, J=7.1 Hz, $CO_2CH_2\underline{CH}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.29 and 170.05 ($O\underline{C}OCH_3$), 164.7 (C-1), 109.13 and 109.02 (2 $\underline{C}Me_2$), 75.90 (C-4), 75.08 (C-6), 73.87 (C-5), 70.07 (C-3), 69.29 (C-7), 65.95 (C-8), 60.88 ($CO_2\underline{C}H_2CH_3$), 26.77, 26.40, 25.35, 25.20 (2 $C\underline{Me}_2$), 21.03 and 20.98 ($CO\underline{C}H_3$), 14.29 ($CO_2CH_2\underline{C}H_3$). MS: 415 (M$^+$-28-15), 357, 315, 269, 140, 101, 43 (b.p.). Elemental analysis: Calcd. for $C_{20}H_{30}O_{10}N_2$: C, 52.40 %; H, 6.55 %; N, 6.11 %. Found: C, 52.11 %; H, 6.54 %; N, 6.10 %.

Reactions of β-acetoxy-α-diazo esters with dirhodium tetraacetate. General procedure. A solution of β-acetoxy-α-diazo ester in chloroform was treated with a catalytic amount of rhodium diacetate (1%) under a nitrogen atmosphere. After 30 min of nitrogen release, the solution was filtered and the solvent removed to obtain the olefin in quantitative yield.

Z,E **Ethyl 4,5,6,7,8-penta-O-acetyl-2-acetoxy-2,3-dideoxy-D-*manno*-2-octenoate 6a:6b.** I.R. ν_{max}(cm^{-1}): 2993, 1753, 1686 and 1218. ^{1}H-NMR ($CDCl_3$) δ ppm : 6.31 (d, 1H, $J_{3,4}$=9.1 Hz, H-3), 6.25 (dd, 1H, $J_{3,4}$=9.7 Hz, $J_{4,5}$=8.5 Hz, H-4, minor isomer), 5.64 (dd, $J_{3,4}$=9.1 Hz, $J_{4,5}$=7.0 Hz, H-4, major isomer), 5.65 (d, $J_{3,4}$=9.7 Hz, H-3, minor isomer), 5.54 (t, J=8.9 Hz), 5.42 (dd, 1H, J=2.2 Hz, J=9.1 Hz, major isomer), 5.31 (dd, 1H, J=2.2 Hz, J=6.2 Hz, major isomer), 5.26 (dd, 1H, J=2.2 Hz, J=4.7 Hz, minor isomer), 5.14-5.02 (m, H-7, both isomers), 4.30-4.01 (m, $CO_2\underline{CH}_2CH_3$, H-8, H-8', both isomers), 2.21-2.00 (12s, COMe, both isomers), 1.28 and 1.27 (2t, 6H, $CO_2CH_2\underline{CH}_3$, both isomers). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.38, 170.23, 169.90, 169.81, 169.63, 169.37, 169.21, 169.12, 168.79, 168.35 ($\underline{C}OCH_3$), 160.73 and 160.45 (C-1), 141.97 (C-2, major isomer), 141.70 (C-2, minor isomer), 124.85 (C-3, minor isomer), 122.71 (C-3, major isomer), 69.06 (C-4, major isomer), 68.98 (C-4, minor isomer), 67.69, 67.66, 67.17 (C-5, C-6, C-7, major isomer), 67.89, 67.49, 67.07 (C-5, C-6, C-7, minor isomer), 65.68 (C-8, minor isomer), 65.17 (C-8, major isomer), 61.78 and 61.76 ($CO_2\underline{C}H_2CH_3$), 21.61, 20.83, 20.56, 20.48, 20.40, 20.04 and 19.99 ($OCO\underline{C}H_3$), 14.03 and 13.94 ($CO_2CH_2\underline{C}H_3$). Elemental analysis: Calcd. for $C_{22}H_{30}O_{14}$: C, 50.97 %; H, 5.83 %. Found: C, 51.06 %; H, 6.08 %.

E **Ethyl 4,5,6,7,8-penta-O-benzyl-2-acetoxy-2,3-dideoxy-D-*manno*-2-octenoate 11.** A complex mixture was obtained and **11** was isolated by chromatography on silica gel (hexane:ethyl acetate 6:1) in a 35% yield. $[\alpha]_D^{20}$ -2.52 ° (c 0.63, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 7.4-7.1 (m, 25 H, $CH_2\underline{Ph}$), 6.6 (d, 1H, $J_{3,4}$=9.1 Hz, H-3), 4.8-4.5

(m, 10H, $C\underline{H}_2Ph$), 4.3-4.1 (m, H-4, H-5, $CO_2C\underline{H}_2CH_3$), 4.05-3.6 (m, 4H, H-6, H-7, H-8 and H-8'), 2.10 (s, 3H, OCOMe), 1.41 (t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$).

***Z,E* Ethyl 2-O-acetyl-2,3-dideoxy-4,5:7,8-di-O-isopropylidene-6-(tert-butyldimethylsilyl)-D-*manno*-octuloso-2-enoate 16a:16b.** Each diastereoisomer **15a:15b** provided a single stereoisomer **16a:16b** respectively. Major isomer **16a**: $[\alpha]_D^{20}$ = 9.4 º (c 0.64, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.77 (d, 1H, $J_{3,4}$=10.1 Hz, H-3), 5.38 (dd, 1H, $J_{3,4}$=10.1 Hz, J=5.3 Hz, H-4), 4.22 (c, 2H, J=7.1 Hz, CO_2Et), 4.00 (ddd, 1H, H-7), 3.89 (dd, 1H, J=5.3 Hz, J=8.4 Hz, H-8), 3.85-3.72 (m, 3H), 2.07 (s, 3H, COMe), 1.36, 1.24, 1.22 and 1.16 (4s, 12H, $2CMe_2$), 1.20 (t, 3H, CO_2Et), 0.77 (s, 9H, Si*t*Bu), 0.0 (s, 6H, $SiMe_2$). ^{13}C-NMR ($CDCl_3$) δ ppm : 169.02 (COMe), 161.36 (CO_2Et), 139.67 (C-2), 127.22 (C-3), 108.75 and 108.57 (CMe_2), 80.32 (C-4), 75.83 (C-6), 71.53 (C-5), 70.89 (C-7), 65.14 (C-8), 61.65 (CO_2Et), 28.29, 26.12, 25.48 and 25.09 ($2CMe_2$), 25.90 (SitBu), 20.32 (OCOMe), 18.42 ($SiCMe_3$), 13.95 (CO_2Et), 1.6 and 1.4 (2s, 6H, $SiMe_2$). MS: 487 (M^+-15), 387, 329, 269, 187, 101, 43 (b. p.).
Minor isomer **16b**: $[\alpha]_D^{20}$ = 25 º (c 1.08, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 6.46 (d, 1H, $J_{3,4}$=9.5 Hz, H-3), 4.76 (dd, 1H, $J_{4,5}$=5.2 Hz, $J_{3,4}$= 9.5 Hz, H-4), 4.19 (c, 2H, CO_2Et), 3.98-3.74 (m, 5H), 2.18 (s, 3H, OCOMe), 1.43, 1.29, 1.26 and 1.24 (4s, 12H, $2CMe_2$), 1.24 (t, 3H, CO_2Et), 0.84 (s, 9H, SitBu), 0.08 and 0.07 (2s, 6H, $SiMe_2$). ^{13}C-NMR ($CDCl_3$) δ ppm : 168.20 (OCOMe), 161.41 (C-1), 140.10 (C-2), 125.09 (C-3), 109.38 and 108.55 (CMe_2), 80.27 (C-4), 77.20 (C-6), 71.69 (C-5), 71.03 (C-7), 66.55 (C-8), 61.66 (CO_2Et), 28.24, 25.93, 25.54 and 25.21 ($2CMe_2$), 25.87 (SitBu), 20.23 (OCOMe), 18.37 ($SiCMe_3$), 13.98 (CO_2Et), 1.5 and 1.3 (2s, 6H, $SiMe_2$). MS: 487 (M^+-15), 387, 329, 269, 215, 186, 101, 43 (b. p.). Exact mass of **16a:16b**: Calcd. for $C_{24}H_{42}O_9Si$(-15)= 487.2363. Found: 487.2363.

***Z,E* Ethyl 2,6-di-O-acetyl-4,5:7,8-di-O-isopropylidene-2,3-dideoxy-D-*manno*-octuloso-2-enoate 20a:20b.** A 1:1 mixture of **20a:20b** was obtained. **Z-20a**: ^{1}H-NMR ($CDCl_3$) δ ppm : 5.81 (d, 1H, $J_{3,4}$=7.1 Hz, H-3), 5.47 (t, 1H, $J_{3,4}$= $J_{4,5}$=7.1 Hz, H-4), 4.98 (dd, 1H, $J_{6,7}$=5.7 Hz, $J_{6,5}$=2.1 Hz, H-6), 4.65 (dd, 1H, $J_{5,4}$=7.1 Hz, $J_{5,6}$=2.1 Hz, H-5), 4.18 (q, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.19 (q, 1H, H-7), 3.94 (dd, 1H, $J_{8,8'}$=8.6 Hz, $J_{7,8}$=6.0 Hz, H-8), 3.86 (dd, 1H, $J_{8,8'}$=8.6 Hz, $J_{7,8'}$=6.4 Hz, H-8'), 2.15 (s, 3H, OCOMe, en C-2), 2.04 (s, 3H, OCOMe), 1.48, 1.34, 1.30, 1.29 (4s, 2 CMe_2), 1.25 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). **E-20b**: ^{1}H-NMR ($CDCl_3$) δ ppm : 6.40 (d, 1H, J3,4=7.2 Hz, H-3), 4.98 (dd, 1H, $J_{6,5}$=2.0 Hz, $J_{6,7}$=6.6 Hz, H-6), 4.91 (t, 1H, $J_{4,3}$=$J_{4,5}$=7.2 Hz, H-4), 4.47 (dd, 1H, $J_{5,6}$=2.0 Hz, $J_{4,5}$=7.2 Hz, H-5), 4.32-4.12 (m, 3H, H-7, $CO_2C\underline{H}_2CH_3$), 3.97 (dd, 1H, $J_{8,8'}$=8.6 Hz, $J_{7,8}$=6.0 Hz, H-8), 3.85 (dd, 1H, $J_{8,8'}$=8.6 Hz, $J_{7,8'}$=6.3 Hz, H-8'), 2.21 (s, 3H, OCOMe, at C-2), 2.06 (s, 3H, OCOMe), 1.51, 1.35 and 1.32 (3s, 12H, 2 CMe_2), 1.27 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). **20a:20b**: ^{13}C-NMR ($CDCl_3$) δ ppm : 169.42, 169.39, 168.87 and 168.03 (Ac), 161.34 and 160.66 (C-1), 139.67 and 138.94 (C-2), 129.87 and 126.01 (C-3), 109.76, 109.51, 109.17, 108.92 ($\underline{C}Me_2$), 77.19 and 75.33 (C-4), 75.05, 74.94, 73.13, 72.08, 70.47 and 70.25 (C-5, C-6 and C-7), 66.01 and 65.68 (C-8), 61.81, 61.72 ($CO_2\underline{C}H_2CH_3$), 26.51, 26.49, 26.40, 26.36, 25.37 and 25.22 ($C\underline{Me}_2$), 21.20 and 21.12 (Ac at C-2), 20.28, 20.26 (Ac), 13.95 and 13.91 ($CO_2CH_2\underline{C}H_3$). FAB: 453 (M^+ +Na), 415, 387, 373, 315, 287, 213, 195 (b.p.), 167, 143. MS: 415 (M^+-15), 357, 315, 255, 186 (b. p.), 140, 101. Exact mass: Calcd. for $C_{20}H_{30}O_{10}$(-15)= 415.1604. Found: 415.1606.

5-Formyl-3-methoxycarbonyl-4-(1,2,3-tri-O-benzyl-D-*erithro*-propyl)-pyrazol 12. To a solution of the aldehyde **8** (1 g, 1.58 mmoles) in 5 mL of methanol, 0.2 g of ethyl diazoacetate (10% excess), and 0.5 ml of a 10% solution of KOH in methanol were added. After 2 h, the reaction was complete and the crude mixture was diluted with 10 mL of water and extracted with chloroform (3 x 5mL). Purification by chromatography on silica gel (hexane:ethyl acetate 6:1) provided 0.457 g of the entitled product **12** as a yellow liquid (56%).$[\alpha]_D^{20}$ = +22.8 º (c 1.9, Cl_3CH). U.V.: 246 nm. I.R.: 3178 (NH), 1720 (HC=O), 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 10.47 (s, 1H, CH=O), 7.28-7.12 (m, 15H, $OCH_2\underline{Ph}$), 5.53 (d, 1H, $J_{4,5}$=2.6 Hz, H-4), 4.77 (s, 2H, $OC\underline{H}_2Ph$), 4.56 (d, 1H, J=11.6 Hz, $OC\underline{H}_2Ph$), 4.48 (d, 1H, J=11.6 Hz, $OC\underline{H}_2Ph$), 4.33 (s, 2H, $OC\underline{H}_2Ph$), 4.12 (dt, 1H, $J_{5,4}$=2.6 Hz, $J_{5,6}$=$J_{5,6'}$=5.6 Hz, H-5), 3.97 (s, 3H, CO_2Me), 3.53 (dd, 1H, $J_{5,6}$=5.6 Hz, $J_{6,6'}$=10.3 Hz, H- 6), 3.47 (dd, 1H, $J_{5,6'}$=5.6 Hz, $J_{6',6}$=10.3 Hz, H-6'). ^{13}C-NMR ($CDCl_3$) δ ppm : 187 (C-1), 162 (CO_2Me), 146, 143, 121 (C=C), 138, 137 and 136.5 (aromatic quaternary carbons), 128-126 (aromatic CH), 79.8 (C-4), 73.1, 72.9 and 71.8 (OCH_2Ph), 72.4 (C-5), 69.2 (C-6) and 52.4 (CO_2Me). Elemental analysis: Calcd. for $C_{30}H_{30}O_6N_2$: C, 70.02 %; H, 5.88 %; N, 5.44 %. Found: C, 70.05 %; H, 5.79 %; N, 5.80 %.

Ethyl 5,6,7,8-tetra-O-acetyl-2,3,4-trideoxy-2-keto-D-*arabino*-octuloso-3-enoate 7. To a solution of the mixture **6a:6b** in chroroform, a few drops of trifluoracetic acid were added. The crude mixture was stirred overnight at room temperature. The unsaturated ketone **7** was formed quantitatively and its NMR spectroscopic features were consistent with reported data[16]. ^{1}H-NMR ($CDCl_3$) δ ppm : 6.91 (dd, 1H, $J_{4,5}$=3.8 Hz,$J_{4,3}$=16.0 Hz, H-4), 6.61 (dd, 1H, $J_{3,4}$=16.0 Hz, $J_{3,5}$=1.0 Hz, H-3), 5.72 (ddd, 1H, $J_{4,5}$=3.8 Hz, $J_{5,6}$=2.5 Hz, $J_{3,5}$=1.0 Hz, H-5), 5.38 (dd, 1H, $J_{5,6}$=2.5 Hz, $J_{6,7}$=9.0 Hz, H-6), 5.14 (ddd, 1H, $J_{6,7}$=9.0 Hz, $J_{7,8'}$=4.0 Hz, $J_{7,8}$=3.0 z, H-7), 4.26 (c 2H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.19 (dd, 1H, J8,8'=12.5 Hz, $J_{7,8}$=3.0 Hz, H-8), 4.05 (dd, 1H, H-8'), 2.01, 2.14 (2s, 12H, OCOMe), 1.36 (t, 3H, $CO_2CH_2CH_3$).

Ethyl 3,6-anhydro-4,5:7,8-di-O-isopropylidene-2-deoxy-2-diazo-D-*glycero*-D-*talo*-octanoate 21. To a solution of 0.57 g of **18** in 10 mL of chloroform,silica gel was added untill a gel was formed. The suspension was kept with stirring at room temperature for 3-4 days. Them, TLC analysis revealed depletion of the starting material. Purification by chromatography on silica gel (hexane:ethyl acetate 4:1), provided 0.36 g of **21** as a yellow liquid (74%). $[\alpha]_D^{20}$ = +32.5 º (c 0.89, Cl_3CH). I.R.: 2105 ($C=N_2$), 1680 (C=O).^{1}H-NMR ($CDCl_3$) δ ppm : 4.72 (m, 2H, H-4, H-5), 4.39 (d, 1H, $J_{3,4}$=2.4 Hz, H-3), 4.33 (ddd, 1H, $J_{7,8'}$=5.1 Hz, $J_{7,8}$=5.5 Hz, $J_{6,7}$=7.5 Hz, H-7), 4.16 (q, 2H, J=7.2 Hz, $-CO_2C\underline{H}_2CH_3$), 4.03 (dd, 1H, J7,8=5.5 Hz, $J_{8,8'}$=8.7 Hz, H-8), 3.97 (dd, 1H, $J_{7,8'}$=5.1 Hz, $J_{8,8'}$=8.7 Hz, H-8'), 3.47 (dd, 1H, $J_{5,6}$=2.4 z, $J_{6,7}$=7.5 Hz, H-6), 1.38 (s, 6H, CMe_2), 1.31 and 1.27 (2s, 6H, CMe_2), 1.20 (t, 3H, J=7.2 Hz, $-CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 161.7 (C-1), 112.6, 109.1 (2 CMe_2), 81.84 (C-3), 80.45 and 80.18 (C-4, C-5), 74.71 (C-7), 72.90 (C-6), 66.87 (C-8), 60.92 ($CO_2\underline{C}H_2CH_3$), 26.88, 25.18, 24.94 and 24.15 (2 CMe_2), 14.45 ($-CO_2CH_2\underline{C}H_3$). Elemental analysis: Calcd. for $C_{16}H_{24}O_7N_2$: C, 53.93 %; H, 6.79 %; N, 7.86 %. Found: C, 53.58 %; H, 6.96 %; N, 8.09 %.

Ethyl Z-3,6-anhydro-4,5:7,8-di-O-isopropylidene-2-deoxy-D-*manno*-2-octenoate 22. The diazo compound **21** was decomposed, mediated by rhodium diacetate, under similar conditions as described before, to obtain **22** quantitatively. $[\alpha]_D^{20}$ = +158.2 º (c 0.29, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 5.10 (dd, 1H, J4,5=5.4 Hz, $J_{2,4}$=0.9 Hz, H-4), 5.07 (d, $J_{2,4}$=0.9 Hz, H-2), 4.74 (dd, 1H, $J_{4,5}$=5.4 Hz, $J_{5,6}$=3.5 Hz, H-5), 4.47 (ddd, 1H, $J_{6,7}$=7.9 Hz, $J_{7,8}$=5.0 Hz, $J_{7,8'}$=4.7 Hz, H-7), 4.34 (dd, 1H, $J_{6,7}$=7.9 Hz, $J_{5,6}$=3.5 Hz, H-6), 4.16 (dd, 1H, $J_{8,8'}$=9.0 Hz, $J_{7,8}$=5.0 Hz, H-8), 4.10 (q, 2H, $CO_2C\underline{H}_2CH_3$), 4.07 (dd, 1H, $J_{7,8'}$=4.7 Hz, $J_{8,8'}$=9.0 Hz, H-8'), 1.45 and 1.43 (2s, CMe_2), 1.37 (s, 6H, CMe_2), 1.23 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 168.79 (C-1), 165.35 (C-2), 114.34 and 109.73 (2 CMe_2), 92.67 (C-3), 84.65 (C-4), 81.63 (C-5), 76.79 (C-7), 72.81 (C-6), 66.52 (C-8), 59.62 ($CO_2\underline{C}H_2CH_3$), 27.16, 26.95, 26.12 and 25.28 (2 CMe_2), 14.29 (-$CO_2CH_2\underline{C}H_3$). MS: 313 (M^+-15), 283, 255, 213 (b. p.), 167, 125 and 101. Exact mass: Calcd. for $C_{16}H_{24}O_7$: 328.1522. Found: 328.1501

2,3:5,6-di-O-isopropylidene-D-mannonolactone 24. A solution containing 0.2 g of the alkene **22** in 5 ml of anhydrous chloroform was treated with ozone at 0ºC. After 30 min, TLC analysis revealed the completion of the reaction.Then, 1 mL of SMe_2 was added and the resulting solution was kept at 0ºC during 3 h. Finally, the solvent was removed in vacuo to obtain lactone **24** quantitatively as a colourless solid. NMR spectroscopic data were consistent with the reported values[22].

Ethyl 3,6-anhydro-4,5:7,8-di-O-isopropylidene-2-deoxy-D-*glycero*-D-*galacto*-octanoate 23. A suspension containing 40 mg of **21**, in 25 mL of ethyl acetate and Pd/C as catalyst was hydrogenated at a pressure of 50 lb/in^2 at room temperature. After 12 h, the suspension was filtered and the filtrate cocentrated in vacuo to a colourless syrup.The product, **20**, was previously described in the bibliography[23].

Treatments of α-enolacetates with hydrazine. General procedure. To a solution containing 1 mmol of the enol acetate in 10 mL of chloroform, 2 mL of 1M solution of hydrazine in methanol was added. After 10 min under vigorous stirring at room temperature, the reaction was complete. The resulting solution was diluted with 20 mL of water, the organic layer was collected and the aquose phase was extracted with chloroform (2 x 10 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated to obtain a crude mixture consisting almost exclusively of the corresponding hydrazone. Further purification by chromatography on silica gel provided the pure hydrazone.

3-Ethoxycarbonyl-5-(1,2,3,4-tetra-O-acetyl-D-*arabino*-butyl)-2-pyrazoline 27. Purification by chromatography on silica gel (hexane:ethyl acetate 4:1), 93%. $[\alpha]_D^{20}$ = -36.9 º (c 2.60, Cl_3CH). I.R.: 3373 (NH), 1745 (C=O), 1429.^{1}H-NMR ($CDCl_3$) δ ppm : 6.57 (d, 1H, $J_{4,NH}$=2.8 Hz, NH), 5.31 (dd, 1H, $J_{6,7}$=9.4 Hz, $J_{5,6}$=1.7 Hz, H-6), 5.24 (dd, 1H, $J_{4,5}$=8.4 Hz, $J_{5,6}$=1.7 Hz, H-5), 4.99 (dt, 1H, $J_{6,7}$=9.4 Hz, $J_{7,8}$=$J_{7,8'}$=3.0 Hz, H-7), 4.22 (q, 2H, $CO_2C\underline{H}_2CH_3$), 4.15 (d, 2H, $J_{7,8'}$=$J_{7,8}$=3.0 Hz, H-8, H-8'), 3.84 (dddd, $J_{3,4}$=11.3 Hz, $J_{3',4}$=11.1 Hz, $J_{4,5}$=8.4 Hz, $J_{4,NH}$=2.8 Hz, H-4), 2.90 (dd, 1H, $J_{3,3'}$=17.2 Hz, $J_{3,4}$=11.3 Hz, H-3), 2.72 (dd, 1H, $J_{3,3'}$=17.2 Hz, $J_{3',4}$=11.1 Hz, H-3'), 2.11, 2.03, 2.02 and 2.00 (4s, 12H, COMe), 1.28 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$).^{13}C-NMR ($CDCl_3$) δ ppm : 170.69, 170.37, 169.92 and 169.72 (4 OCOMe), 162.09 (CO_2Et), 143.06 (C-2), 70.69 (C-6), 68.54, 67.46 (C-5, C-7), 61.34(C-8)

61.15 (C-4), 61.01 (CO_2Et),33.82 (C-3),20.63,20.54 and 20.46 (OCOMe), 14.07 (CO_2Et). Elemental analysis: Calcd. for $C_{18}H_{26}O_{10}N_2$ C, 50.23 %; H, 6.04 %; N, 6.51%. Found: C, 50.47 %; H, 5.74 %; N, 6.32 %.

Ethyl 2,3-dideoxy-2-hydrazone-4,5:7,8-di-O-isopropylidene-6-(tert-butyldimethylsilyl)-D-*manno*-octulosonate 25. Purification by chromatography on silica gel (hexane:ethyl acetate 4:1), 88%. $[\alpha]_D^{20}$ = -35.71 ° (c 1.4, Cl_3CH). I.R.: 3418, 3333, 3253 (NH), 1707 (C=O), 1640 (C=N). ^{1}H-NMR ($CDCl_3$) δ ppm : 6.42 (wide s, 2H, $=NNH_2$), 4.40 (dd, 1H, $J_{3,4}$=1.6 Hz, $J_{3',4}$=11.0 Hz, $J_{4,5}$=4.9 Hz, H-4), 4.25 (q, 2H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.14 (dd, 1H, J7,8=6.1 Hz, $J_{8,8'}$=7.8 Hz, H-8), 4.08 (dt, 1H, $J_{6,7}$=6.1 Hz, $J_{7,8}$=6.1 Hz, $J_{7,8'}$=7.8 Hz, H-7), 3.97 (dd, 1H, $J_{4,5}$=4.9 Hz, $J_{5,6}$=8.9 Hz, H-5), 3.94 (dd, 1H, $J_{6,7}$=6.1 Hz, J_{56}=8.9 Hz, H-6), 3.87 (t, 1H, $J_{7,8'}$=$J_{8,8'}$=7.8 Hz, H-8'), 2.85 (dd, 1H, $J_{3,4}$=11.0 Hz, $J_{3,3'}$=14.0 Hz, H-3), 2.74 (dd, 1H, $J_{3',4}$=1.6 Hz, $J_{3,3'}$=14.0 Hz, H-3'), 1.56, 1.43, 1.37 and 1.29 (4s, 12H, CMe_2), 1.34 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 0.90 (s, 9H, OSi-tBu), 0.12 (s, 6H, $Si\underline{Me}_2$).^{13}C-NMR ($CDCl_3$) δ ppm : 165.10 (C-1), 137.59 (C-2), 109.89 and 108.38 ($\underline{C}Me_2$), 80.55 (C-6), 77.16 and 73.22 (C-5 and C-7), 72.09 (C-4), 67.89 (C-8), 61.20 ($CO_2\underline{C}H_2CH_3$), 27.80, 26.41, 25.72 and 25.57 (2 $C\underline{Me}_2$), 27.13 (C-3), 25.93 (OSi-t$\underline{Bu}$), 18.45 ($SiCMe_3$), 14.34 ($CO_2CH_2\underline{C}H_3$), 1.87 and 1.09 ($SiMe_2$). Exact mass: Calcd. for $C_{22}H_{42}O_7N_2Si$: 474.2771. Found: 474.2824.

Ethyl 6-O-acetyl-2,3-dideoxy-2-hydrazone-4,5:7,8-di-O-isopropylidene-D-*manno*-octulosonate 26. Purification by chromatography on silica gel (hexane:ethyl acetate 2:1), 85%. $[\alpha]_D^{20}$ = -82 ° (c 3.0, Cl_3CH). I.R.: 3418, 3333, 3253 (NH), 1715 (C=O), 1640 (C=N).^{1}H-NMR ($CDCl_3$) δ ppm : 6.58 (s, 2H, $=NNH_2$), 5.15 (dd, 1H, J=1.1 Hz, J=6.2 Hz, H-6), 4.39-4.33 (m, 2H, H-4, H-5), 4.28 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.21 (q, J=6.3 Hz, H-7), 4.00 (dd, 1H, $J_{7,8}$=6.3 Hz, $J_{8,8'}$=8.7 Hz, H-8), 3.91 (dd, 1H, $J_{7,8'}$=6.3 Hz, $J_{8,8'}$=7.8 Hz, H-8'), 2.93 (dd, 1H, $J_{3,4}$=2.0 Hz, $J_{3,3'}$=13.8 Hz, H-3), 2.43 (dd, 1H, $J_{3',4}$=10.1 Hz, $J_{3'3}$=13.8 Hz, H-3'), 2.13 (s, 3H, COMe), 1.51, 1.38, 1.35 and 1.30 (4s, 12H, 2 CMe_2), 1.34(t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 169.82 (OCOMe), 164.83 (C-1), 137.38 (C-2), 109.09 (CMe_2), 76.27 (C-5), 75.75 (C-4), 75.39 (C-7), 70.79 (C-6), 65.95 (C-8), 61.31 ($CO_2\underline{C}H_2CH_3$), 26.43, 26.32, 25.37 and 25.34 (2 CMe_2), 21.29 (OCO$\underline{Me}$), 14.25 ($CO_2CH_2\underline{C}H_3$). Exact mass: Calcd. for $C_{18}H_{30}O_8N_2$: 402.2002. Found: 402.2006.

Ethyl 2,3-dideoxy-2-diazo-4,5:7,8-di-O-isopropylidene-6-(tert-butyldimethylsilyl)-D-*manno*-octulosonate 28. To a solution of 0.24 g of **25** (0.5 mmol) in 5 mL of chloroform was added activated manganese dioxide in 10 fold excess. After 5 min. with vigorous stirring, the oxidation reaction was complete. The suspension was filtered through Celite and the filtrate concentrated under vacuum, to obtain 0.23 g of the diazo compound **28** (98%). This product did not require further purification. $[\alpha]_D^{20}$ = +9.1 ° (c 2.6 Cl_3CH). I.R.: 2110 ($C=N_2$), 1730, 1680 (C=O).^{1}H-NMR ($CDCl_3$) δ ppm : 4.25 (m, 1H, H-4), 4.22 (c, 2H, CO_2Et, J=7.1 Hz), 4.09 (dd, 1H, J=5.6 Hz, J=7.4 Hz, H-8), 3.90 (dd, 1H, J=5.3 Hz, J=6.1 Hz, H-5), 3.85-3.76 (m, 3H, H-6, H-7, H-8'), 2.66 (dd, 1H, J=2.6 Hz, J=14.5 Hz, H-3), 2.26 (dd, 1H, J= 11.1 Hz, J= 14.5 Hz, H-3'), 1.42, 1.40, 1.32 and 1.30 (4s, 12H, 2CMe_2), 1.23 (t, 3H, CO_2Et), 0.85 (s, 9H, SitBu), 0.09 and 0.08 (2s, 6H, $SiMe_2$).^{13}C-NMR ($CDCl_3$) δ ppm : 167.40 (C-1), 109.84 and 107.71 ($\underline{C}Me_2$), 80.16 (C-6), 77.05 and 76.24 (C-5 y C-7), 71.94 (C-4), 68.02 (C-8), 60.63 ($CO_2\underline{C}H_2CH_3$), 28.44

(C-3), 26.21, 25.87, 25.47 and 25.29 (2 $C\underline{Me}_2$), 25.92 (OSit$\underline{Bu}$), 18.43 (OSi$\underline{C}Me_3$), 14.54 ($CO_2CH_2\underline{C}H_3$), 1.15 and 1.08 ($SiMe_2$). MS: 429 (M^+-15-28), 387, 229, 199, 187, 171, 155, 129, 101, 73 (b. p.). Exact mass: Calcd. for $C_{22}H_{40}O_7N_2Si$ (-28-15): 429.2321. Found: 429.2308.

Ethyl 6-O-acetyl-2,3-dideoxy-2-diazo-4,5:7,8-di-O-isopropylidene-D-*manno*-octulosonate 29. The hydrazone **26** was treated with activated manganese dioxide under similar conditions that described before to obtain the diazo compound **29** in a 100% yield. This product did not require further purification. $[\alpha]_D^{20}$ = +49.0 º (c 5.2, Cl_3CH). I.R.: 2100 ($C{=}N_2$), 1745, 1690 (C=O), 1372. ^{1}H-NMR ($CDCl_3$) δ ppm : 5.16 (dd, J5,6=3.6 Hz, $J_{6,7}$=6.4 Hz, H-6), 4.36 (ddd, 1H, $J_{3',4}$=10.3 Hz, $J_{4,5}$=6.1 Hz, $J_{3,4}$=3.0 Hz, H-4), 4.29 (dd, 1H, $J_{5,6}$=3.6 Hz, $J_{4,5}$=6.1 Hz, H-5), 4.22 (q, 2H, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.18 (q, 1H, J=6.5 Hz, H-7), 4.03 (dd, 1H, $J_{7,8}$=6.5 Hz, $J_{8,8'}$=8.6 Hz, H-8), 3.88 (dd, 1H, $J_{7,8'}$=6.5 Hz, $J_{8,8'}$=8.6 Hz, H-8'), 2.58 (dd, 1H, $J_{3,4}$=3.0 Hz, $J_{3,3'}$=14.9 Hz, H-3), 2.37 (dd, 1H, $J_{3',4}$=10.3 Hz, $J_{3',3}$=14.9 Hz, H-3'), 2.12 (s, 3H, COMe), 1.47, 1.41, 1.36 and 1.35 (4s, 12H, 2 CMe_2), 1.28 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 169.92 (Ac), 167.08 (C-1), 109.43 and 108.85 ($\underline{C}Me_2$), 76.11 (C-5), 75.94 (C-4), 75.32 (C-7), 70.28 (C-6), 66.17 (C-8), 60.76 ($CO_2\underline{C}H_2CH_3$), 26.99, 26.30, 25.63 and 25.31 (CMe_2), 24.53 (C-3), 21.11 (OCO$\underline{Me}$), 14.43 ($CO_2CH_2\underline{C}H_3$). MS: 357 (M^+-15-28), 299, 197, 151, 101, 43 (b. p.). Exact mass: Calcd. for $C_{18}H_{28}O_8N_2$(-28-15): 357.1549. Found: 357.1564.

Ethyl 2,3-dideoxy-2-diazo-4,5:7,8-di-O-isopropylidene-D-*manno*-octulosonate 30. Procedure A: To a solution containing 0.6 g of **29** in 5 mL of methanol, 1.5 mL of a 0.1N solution of KOH in methanol was added. After 30 min, hydrolysis of the acetate was complete, and the crude mixture was diluted with chloroform (20 mL) and washed with water twice (2 x 20 mL). The organic phase was dried over anhydrous sodium sulphate and filtered, and the filtrate was concentrated in vacuo to a yellow liquid which corresponded to the pure entitled product (0.53 g, 100%). **Procedure B:** To a solution containing 0.2 g of the diazo compound **28** in 2 mL of anhydrous THF, 0.5 mL of a 1M solution of tetrabutylammoniun fluoride in THF was added dropwise and at 0ºC. After 30 min. the crude mixture was diluted with 5 mL of water and the organic layer was collected, dried over anhydrous sodium sulphate and, the solvent removed to obtain 0.15 g of **30** (98%). $[\alpha]_D^{20}$ = +30.5 º (c 0.54, Cl_3CH). U.V.: 218, 269 nm. I.R.: 3300 (OH), 2105 ($C{=}N_2$), 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.42 (ddd, 1H, $J_{3,4}$=9.2 Hz, $J_{4,5}$=6.9 Hz, $J_{3',4}$=3.3 Hz, H-4), 4.33 (dd, 1H, $J_{5,6}$=1.9 Hz, $J_{4,5}$=6.9 Hz, H-5), 4.23 (q, 2H, J=7.2 Hz, $CO_2C\underline{H}_2CH_3$), 4.15-3.98 (m, 3H, H-7, H-8, H-8'), 3.54 (dd, J6,7=$J_{6,OH}$=8.6 Hz, $J_{5,6}$=1.9 Hz, H-6), 2.74 (dd, $J_{3,3'}$=14.9 Hz, $J_{3,4}$=9.2 Hz, H-3), 2.64 (dd, 1H, $J_{3,3'}$=14.9 Hz, $J_{3',4}$=3.3 Hz, H-3'), 2.27 (d, 1H, J=8.6 Hz, OH), 1.47, 1.42, 1.38 and 1.36 (4s, 12H, 2 $C\underline{Me}_2$), 1.27 (t, 3H, J=7.2 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 167.36 (C-1), 109.49 and 108.23 ($\underline{C}Me_2$), 76.26 and 76.10 (C-5 and C-7), 75.68 (C-4), 70.38 (C-6), 67.20 (C-8), 60.67 ($CO_2\underline{C}H_2CH_3$), 27.02, 26.90, 26.68 and 25.16 (2 $C\underline{Me}_2$), 25.59 (C-3), 14.45 ($CO_2CH_2\underline{C}H_3$). Exact mass: Calcd. for $C_{16}H_{26}O_7N_2$(-15): 343.1505. Found: 343.1526. Calcd. for $C_{16}H_{26}O_7N_2$(-15-28): 315.1443. Found: 315.1439.

Ethyl 4,5:7,8-di-O-isopropylidene-3-deoxy-α,β-D-*manno*-2-octulopyranosonate 31. An amount of 0.25 g of m-chloroperbenzoic acid (MCPBA) was added to a cold solution of 0.53 g of the diazo compound **30** in 5 ml of chloroform in small portions during 15 min. The solution was stirred at 0°C for 30 min, during which nitrogen release was observed. After that time, TLC analysis revealed completion of the reaction. Then, the solution was washed with 10 mL of a 10% solution of sodium carbonate in water, and the organic layer was separated and dried over anhydrous sodium sulphate, filtered and concentrated. The crude obtained was the entitled product **31** as a 2:1 α:β anomeric mixture, practically pure as a colourless syrup (0.47 g, 92%). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.71 (dt, $J_{4,3a}$=2.5 Hz, $J_{4,3e}$=2.5 Hz, $J_{4,5}$=6.8 Hz, H-4, β anomer), 4.51 (ddd, 1H, $J_{3a,4}$=4.9 Hz, $J_{3e,4}$=6.7 Hz, $J_{4,5}$=6.4 Hz, H-4, α anomer), 4.48-4.3 (m, H-7 both anom.), 4.25-4.2 (m, $CO_2C\underline{H}_2CH_3$, H-5 both anom.), 4.15-4.10 (m, H-8 α anom., H8, H8', β anom.), 3.98 (dd, 1H, $J_{8,8'}$=8.5 Hz, $J_{7,8'}$=6.5 Hz, H-8', α anom.), 3.89 (dd, $J_{5,6}$=2.1 Hz, $J_{6,7}$=8.2 Hz, H-6 α anom.), 3.43 (dd, $J_{5,6}$=1.8 Hz, $J_{6,7}$=8.0 Hz, H-6, β anom.), 2.50 (dd, 1H, $J_{3a,3e}$=14.3 Hz, $J_{3e,4}$=6.7 Hz, H-3e, α anom.), 2.42 (d, 2H, $J_{3a3e,4}$=2.5 Hz, H-3a,3e, β anom.), 1.90 (dd, 1H, $J_{3a,3e}$=14.3 Hz, $J_{3a,4}$=4.9 Hz, H-3a, α anom.), 1.52, 1.49, 1.45, 1.37, 1.35 and 1.33 (CMe_2), 1.32 and 1.27 (2t, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm: 169.66 and 169.84 (C-1), 109.55, 109.34 and 109.18 ($\underline{C}Me_2$), 95.52 (C-2 α), 94.36 (C-2 β), 73.91, 73.86, 73.30, 72.34, 71.29, 70.66, 70.61 and 69.87 (C-4, C-5, C-6, C-7 both anom.), 67.13 (C-8 α), 68.85 (C-8 β), 62.39 (CO_2Et β), 61.97 (CO_2Et α), 32.23 (C-3 β), 30.91 (C-3 α), 27.39, 27.05, 26.91, 26.03, 25.70, 25.37, 25.06 and 24.23 (2 $C\underline{Me}_2$, both anom.), 14.11 and 13.99 (CO_2Et both anom.). MS: 331 (M^+-15, 26.4), 273 (17), 215 (7), 157 (14.5), 115 (44), 101 (60), 43 (100).

Ethyl 2,6-anhydro-3-deoxy-4,5:7,8-di-O-isopropylidene-D-*glycero*-D-*talo* and D-*glycero*-D-*galacto* octanoates 32 and 33: A solution containing 0.2 g of **30** in 5 mL of anhydrous benzene was treated with a catalytic amount of rhodium diacetate under a nitrogen atmosphere. Vigorous release of nitrogen was produced, TLC showed the reaction to be complete after 15 min. The suspension was filtered and the filtrate concentrated in vacuo to obtain a colourless syrup (0.19g) which was essentially product **32** (96%). When the insertion reaction was developed in wet benzene or chloroform, a 4:1 mixture of the products **32:33** was obtained in quantitative yield. Purification of the diastereoisomer mixture was accomplished by flash chromatography on silica gel (hexane: ethyl acetate 6:1). Product **32**: ^{1}H-NMR ($CDCl_3$) δ ppm : 4.60 (dt, $J_{3,4}$=$J_{3',4}$=2.9 Hz, $J_{4,5}$=8.0 Hz, H-4), 4.54 (dd, 1H, $J_{2,3}$=5.9 Hz, $J_{2,3'}$=11.4 Hz, H-2), 4.35 (dd, 1H, $J_{5,6}$=1.6 Hz, $J_{4,5}$=8.0 Hz, H-5), 4.24-4.10 (m, 5H, H-7, H-8, H-8', $CO_2C\underline{H}_2CH_3$), 3.51 (dd, 1H, $J_{5,6}$=1.6 Hz, $J_{6,7}$=8.4 Hz, H-6), 2.31 (ddd, 1H, $J_{3,3'}$=15.0 Hz, $J_{2,3}$=5.9 Hz, $J_{3,4}$=2.9 Hz, H-3), 1.86 (ddd, 1H, $J_{3,3'}$=15.0 Hz, $J_{2,3'}$=11.4 Hz, $J_{3',4}$=2.9 Hz, H-3'), 1.50, 1.43, 1.39 and 1.37 (4s, 2 $C\underline{Me}_2$), 1.30 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 172.94 (C-1), 109.39 and 109.29 ($\underline{C}Me_2$), 73.70 (C-7), 72.79 (C-6), 72.22 (C-5), 69.77 (C-2), 68.41 (C-4), 67.18 (C-8), 60.99 ($CO_2\underline{C}H_2CH_3$), 27.05, 26.67, 25.09 and 24.94 (2 $C\underline{Me}_2$), 26.18 (C-3), 14.20 ($CO_2CH_2\underline{C}H_3$). MS: 315 (M^+-15, 32), 257 (8.5), 187 (28), 169 (8), 123 (22.5), 101 (60), 43 (100). Elemental analysis: Calcd. for $C_{16}H_{26}O_7$: 58.17 %C, 7.93 %H. Found: 58.07 %C, 7.72 %H. Product **33**: $[\alpha]_D^{20}$ = +41.1 ° (c 0.18, Cl_3CH). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.5-4.3 (m, 2H, H-4, H-7), 4.21 (c, 2H, J= 7.1 Hz, $CO_2C\underline{H}_2CH_3$), 4.18 (dd, 1H, H-5), 4.08 (d, 2H, H-8, H-8'), 4.00 (dd, 1H, J= 6.0 Hz, J= 11.5 Hz, H-2), 3.51 (dd, 1H, $J_{6,7}$= 8.0Hz, $J_{5,6}$= 2.0Hz, H-6), 2.15 (ddd, 1H, $J_{3,3'}$=15.0 Hz, $J_{2,3}$=6.0 Hz, $J_{3,4}$=5.5 Hz, H-3), 1.93 (ddd, 1H, $J_{3,3'}$=15.0 Hz, $J_{2,3'}$=11.5 Hz, $J_{3',4}$=9.0 Hz, H-3'), 1.47, 1.39, 1.35 and 1.33 (4s, 2 $C\underline{Me}_2$), 1.26 (t, 3H, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$). ^{13}C-NMR ($CDCl_3$) δ ppm : 170.56 (C-1), 109.55 and 109.22 ($\underline{C}Me_2$), 75.81 (C-7), 74.28 (C-6), 72.47 (C-5), 71.31 (C-2), 71.22 (C-4), 66.88 (C-8), 61.11

($CO_2CH_2CH_3$), 30.61 (C-3), 27.42, 26.96, 25.98 and 25.38 (2 CMe_2), 14.09 ($CO_2CH_2CH_3$). MS: 315 (M^+-15, 32), 257 (8.5), 187 (28), 169 (8), 123 (22.5), 101 (60), 43 (100). Exact mass: Calcd. for $C_{16}H_{26}O_7$: 330.1678. Found: 330.1688.

Ammonium 2,3-dideoxy-2-keto-D-*manno*-2-octulosonate 1. A solution containing 0.2 g of **31** in 5 mL of 90% acetic acid was heated at 90ºC during 15 min. The crude solution was them cooled at room temperature and concentrated to dryness in vacuo. The syrup obtained was dissolved in 2 mL of ethanol and 2 mL of 30% ammonia solution was added. The resulting mixture was allowed to stand at 4ºC overnight. Then, the solvent was removed under high vacuum and the crude was redissolved in 2 mL of water and was liophilized. The resulting solid (0.14 g, 95%) exhibited identical NMR spectra and analytical features as an authentic sample of KDO ammonium salt purchased from SIGMA. Further purification was carried out by recrystallization in 85:15 acetone:water, to obtain 0.12 g of totally pure **2** as a white solid (81%). m.p. 121ºC. $[\alpha]_D^{20}$ = +40.3 º (c 0.57, H_2O). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.58-4.43 (m), 4.23-4.11 (m), 3.97-3.80 (m), 3.69-3.60 (m), 2.61 (dd, J=14.2 Hz, J=6.7 Hz), 2.39 (dd,1H, J=14.2 Hz, J=5.5 Hz), 2.19-1.87 (m).^{13}C-NMR ($CDCl_3$) δ ppm : 176.8 (C-1), 96.3 (C-2), 76.2, 69.3 66.7, 66.3 (C-4, C-5, C-6, C-7), 63.1 (C-8) and 33.7 (C-3).

Ammonium 2,3-dideoxy-α-D-*manno*-2-octulosonate 2. The preparation of **2** was accomplished using the same procedure described for **1**, from **32**, in a quantitative yield. Recrystallization was made in 85:15 acetone:water. m.p. 179ºC. $[\alpha]_D^{20}$ = +68.6 º (c 1.02, H_2O). ^{1}H-NMR ($CDCl_3$) δ ppm : 4.46 (dd, 1H, $J_{2,3}$= 1.1 Hz, $J_{2,3'}$= 6.5 Hz, H-2), 4.05 (d, 1H, $J_{4,5}$= 2.8 Hz, H-5), 3.94-3.84 (m, 3H, H-7, H-8, H-8'), 3.78 (ddd, 1H, $J_{4,5}$= 2.9 Hz, $J_{3,4}$= 5.2 Hz, $J_{4,3'}$= 12.3 Hz, H-4), 3.61 (d, 1H, $J_{6,7}$= 8.3 Hz, H-6), 2.27 (ddd, 1H, $J_{2,3}$= 1.1 Hz, $J_{3,4}$= 5.2 Hz, $J_{3,3'}$= 12.3 Hz, H-3), 2.10 (ddd, 1H, $J_{2,3'}$= 6.5 Hz, $J_{3,3'}$= $J_{3,4}$= 12.3 Hz, H-3').^{13}C-NMR ($CDCl_3$) δ ppm : 179.5 (C-1), 75.91, 75.65, 70.88, 68.44, 68.06 and 65.59 (C-4, C-5, C-6, C-7 and C-8) and 30.0 (C-3).

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17. The synthesis of the mannose aldehyde **8** was performed according to the following procedure: To a solution of 12 mL of benzyl bromide in 172 mL of anhydrous DMF was added in one portion 3.22 g of 80% sodium hydride. The suspension was cooled at 0ºC and 4.3 g of D-mannose Diethyl dithioacetal was slowly added to the stirred mixture. The resulting suspension was vigorously stirred for 2h 30 min. and after this time, methanol

was added dropwise to destroy the excess of sodium hydride. Finally, the solution was diluted with 500 mL of water and extracted with ter-butyldimethyl ether (3x1). The combined organic layers were washed with water, dried with anhydrous sodium sulphate, filtered and concentrated. The crude obtained (12g) was dissolved in 75 mL of acetone and 18 mL of water. This solution was treated with 13 g of cadmiun carbonate and a solution of 13 g of mercury chloride in 15 mL of acetone. After 2 h, the reaction was complete, then the suspension was filtered and the filtrate was concentrated and extracted with chloroform (4x1). The organic solution was washed with water, dried and concentrated to obtain 6.7 g of the pure aldehyde **8** (76%).

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