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Unstabilized Diazo Derivatives from Carbohydrates. Application to the Synthesis of 2-Deamino-tunicamine and Products Related to C-Disaccharides.

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Abstract: We applied a new synthetic method to C-disaccharides to obtain 2-deamino-tunicamine, the 2-hydroxy analogue of tunicamine, which is the main nucleus of tunicamycin antibiotics. 6-Deoxy-6-diazo-1:2,3:4-di-O-isopropylidene-D-galactopyranose was synthesized and reacted with methyl 2,3-O-isopropylidene-β-D-ribopentonodialdo-1,4-furanoside, to obtain a mixture of ketone and an epoxide with C-disaccharide structures. The epoxide was obtained in a reasonably good yield and full stereoselectivity, and was reduced to protected 2-deamino -tunicamine. Reduction of the ketone isomer, yielded the 7-epimer of 2-deamino-tunicamine. This is the first reported instance of an epoxy-C-disaccharide, the primary interest of which lies in its potential inhibition of glycosidase enzymes.

INTRODUCTION

The great interest aroused in the last few years by the synthesis of C-disaccharides, non-natural products in which the O-glycosidic bond is replaced by a methylene group, is justified by their properties as glycosidase inhibitors[1]. Since the first synthesis for this type of product reported by Sinaÿ[2], a number of methods for their syntheses using various C-C bond synthetic methodologies have been reported[3]. In this work we have developed the first synthesis for a C-disaccharide involving the well-known condensation reaction between a diazo compound and an aldehyde, which, to our knowledge, has never previously been used to prepare these products. Diazo derivatives from carbohydrates have indeed been used in the synthesis of C-nucleosides[4].

The reaction between a diazo-sugar and an aldehydic monosaccharide yields a ketone and an epoxide in mixture. Both products are very interesting. The ketone derivative can be transformed into a C-disaccharide by Wolff-Kishner reduction of its corresponding hydrazone. On the other hand, reduction of epoxide to an alkene and subsequent hydrogenation also generates the C-disaccharide. Epoxides are also of a high interest on account of their potentially acting as irreversible inhibitors for glycosidases, as demonstrated for an exocyclic epoxide of glucopyranose[5] and epoxide derivatives of cyclitols[6]. Moreover, reduction of the ketone function should give the corresponding C-disaccharide with hydroxyl group on the C-bridge, which is of a similar biological interest[7] (Scheme 1). In fact, in conection with this last type of products, numerous antibiotics belonging to the tunicamycin[8], streptovirudin[9] and corynetoxin[10] families include structurally the eleven-carbon atom amino-sugar Tunicamine **1** as the main component (Figure 1).

Several syntheses for **1** use the classical Henry's and Horner-type condensations[11], or hetero-Diels-Alder cycloaddition to build the pyranose ring[12]. The total synthesis of Tunicamycin has been similarly achieved[13]. In order to devise a synthetic strategy for building the undecose derivative **1**, some authors have synthesized 2-deamino-tunicamine **2** first. Thus, Secrist III et al.[14] approached **2** from an unstabilized phosphorane. More

recently, the total synthesis of **2** was accomplished by Wittig condensation between the two corresponding monosaccharides and subsequent stereoselective hydroboration[15]. This paper reports the synthesis of **2** and related products by aldol-like diazo condensation.

Scheme 1

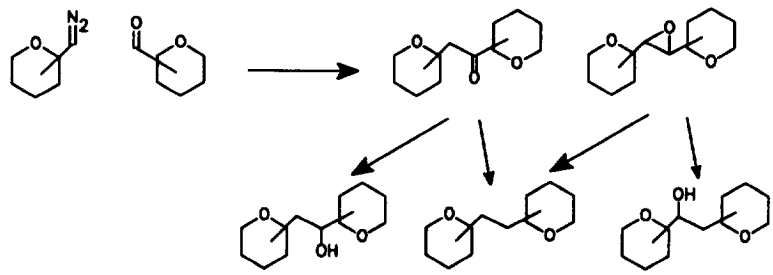
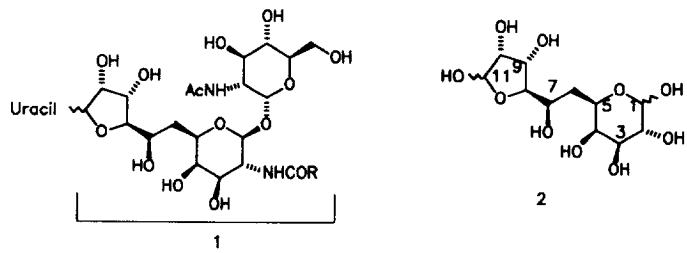


Figure 1



Tunicamycins

R=CH=CH(CH$_2$)nCH(CH$_3$)$_2$ n=7–11

R=CH=CH(CH$_2$)nCH$_3$ n=10–13

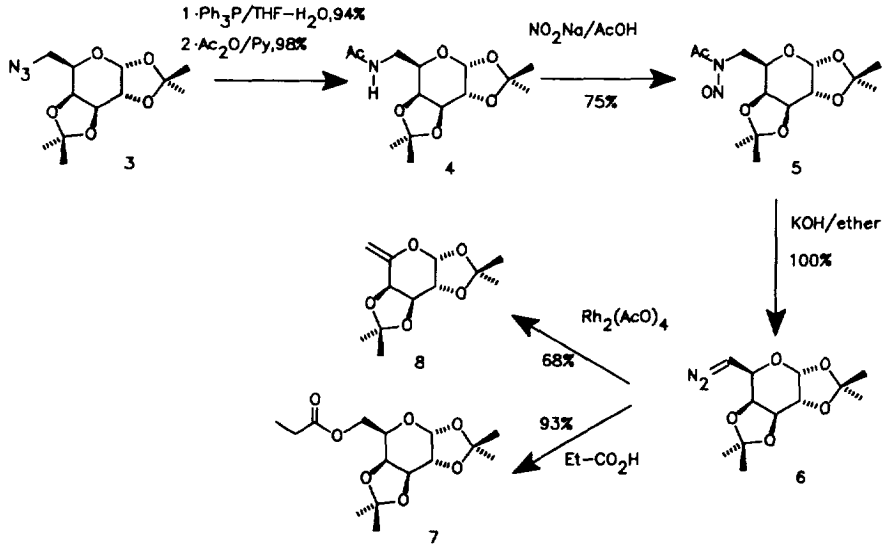
RESULTS AND DISCUSSION

The preparation of the undecose **2** by this new synthetic methodology requires that the diazo group be present in the galactose residue. Its synthesis was sucessfully carried out from the 6-azido-6-deoxy-1,2:3,4-di-O-isopropylidene-D-galactopyranose **3**[16] according to the scheme 2. The structure of the 6-deoxy-6-diazo derivative **6** was quite clear from its IR spectrum which exhibited a strong absortion band at 2081 cm^{-1}. In addition, decomposition with propionic acid and dirhodium (II) tetraacetate furnished the corresponding galactopyranosyl propionate **7** and the alkene **8** in a 93% and 68% yield respectively.

Condensation of the diazo compound **6** with the aldehyde **9**, synthesized from methyl 2,3-O-isopropylidene-β-D-ribofuranoside by Swern oxidation[17], was initially carried out in diethyl ether, at r.t. using no catalyst. The reaction was complete after 6 hours, and a 1:1 mixture of the ketone **10** and the epoxide **11** was obtained in a 82% yield after purification by column chromatography on silica-gel. The ketone was separated from the epoxide by crystallization in hexane:ethyl acetate. The 1:1 ketone:epoxide ratio obtained can be ascribed to the high reactivity of the aldehydic compound, which should give rise to the epoxide; however the high molecular volume of the starting diazo compound favors the ketone formation, as found for other diazo compounds[18]. In order to study the influence of the solvent polarity on the product ratio, the condensation was performed in various solvents. The results, summarized in table I show that increasing the polarity of the solvent

(e. g. using methanol or DMF) increased the proportion of ketone **10** up to a ratio of 5:1 when methanol was used. In non-polar solvents, the ratio was 1:1 (diethyl ether) or slightly higher in favor to the epoxide **11** (3:2) (n-hexane). An identical influence of the solvent on the reaction products was previously observed in the reaction of 2,3-O-isopropylidene-D-glyceraldehyde with diazomethane[19].

Scheme 2



Scheme 3

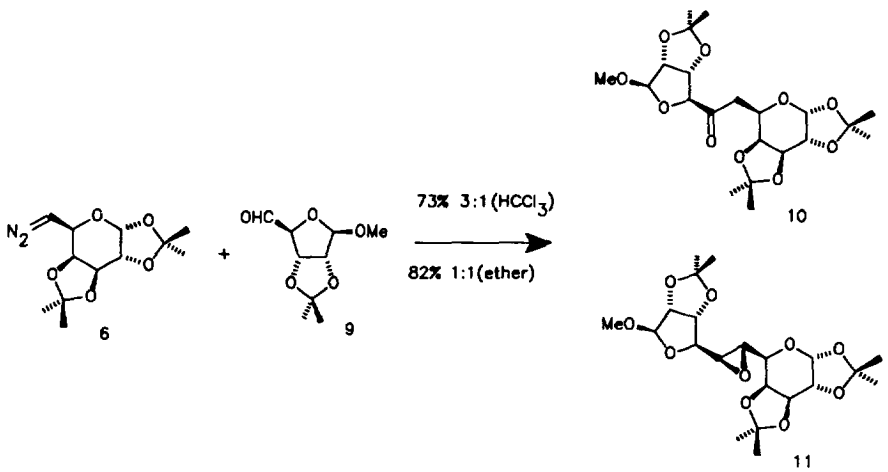


Table 1

Solvent	MeOH	DMF	Chloroform	Diethyl ether	n-hexane
Ratio 10/11	5:1	2:1	3:1	1:1	2:3

On the other hand, only one of the four possible epoxides was obtained. Such a high stereoselectivity can be ascribed to the double diastereoselectivity of the condensation since both reactants are chiral. The absolute configurations of the chiral sites of the epoxide **11** were determined by NMR analysis, chemical transformations and theoretical calculations. Firstly, the relative configuration was established from the H6,H7 coupling constant of this epoxide which was 2.0 Hz, the typical value for *trans* epoxides. In order to establish its absolute configuration, the epoxide was treated with Super-hydride, obtaining a 83% yield after purification of the alcohol **12**,[20] which was assigned the 2-deamino tunicamine configuration by comparison with the reported data[21]. Theoretical calculations of the starting aldehyde were also made in order to determine the preferred conformation of **9**. The more stable conformer (figure 2) clearly showed its *re* face as the most sterically favoured, which is consistent with the results.

Scheme 4

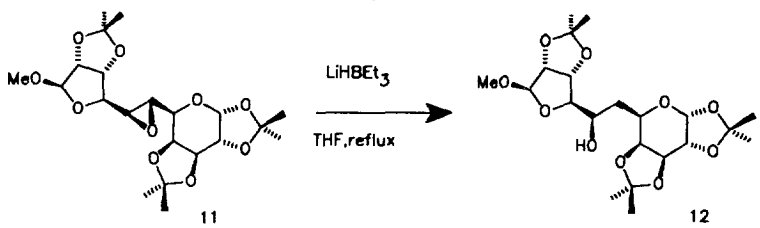
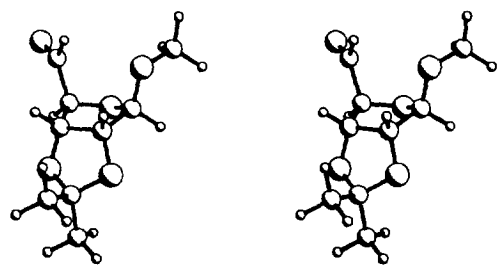


Figure 2



Finally, reduction of the ketone **10** should give the corresponding hydroxyl derivative, the tri-O-isopropylidene derivative of 2-deamino-tunicamine. The reduction was initially carried out with sodium borohydride at 25°C. The result was a mixture of the alcohols **12**:**13**, which was obtained quantitatively and in a 1:2 ratio. An identical stereochemical result was reported by Suami et al[11a] in the ketone reduction of a tunicamine derivative. In order to boost the stereoselectivity of the reduction, we used various bulky borohydrides and low temperatures. Alcohol **13** was obtained in completely stereoselectivity when Super-hydride or K-Selectride were used at -78°C and 25°C, respectively (table 2). The conformational analysis of the ketone **10** was consistent with the formation of the diastereoisomer **13**, the 7-epimer of 2-deamino tunicamine. The conformer with minimum energy (figure 3) showed that one of the two faces of the ketone was clearly favoured to be attacked by the nucleophilic reagent, whereas the other was hindered by the galactopyranose ring. The acetyl derivative of **13** was prepared to confirm the absolute configuration at C-7.

Scheme 5

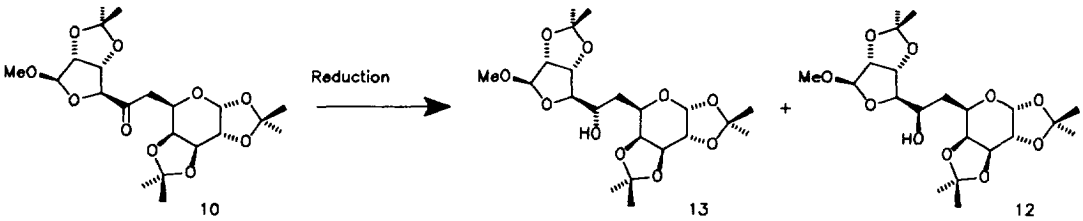
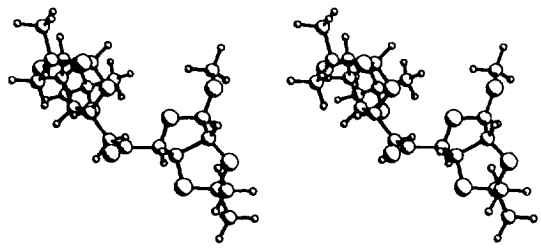


Table 2

Reagent	Temperature (°C)	Reaction time (min)	Ratio 13/12
BH4Na	25	5	2:1
BH4Na	-78	5	3:1
Super-hydride	25	5	76:24
Super-hydride	-78	5	100:0
K-selectride	25	5	100:0
K-selectride	-78	5	100:0

Figure 3



EXPERIMENTAL PART

Melting points are given uncorrected. IR spectra were recorded on a Beckman Aculab IV spectrophotometer; wavenumbers are expressed in cm^{-1}. ^1H-NMR spectra at 200 MHz were obtained on a Bruker WP 200SY using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm taking the signal of $CHCl_3$ as internal reference with notations indicating 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". Specific rotations were measured with a Perkin-Elmer 241 polarimeter. Silica gel for column chromatography was Merck silica-gel 60 No. 7736. Analytical thin-layer chromatography was perfomed on Merck silica-gel 60 No.7747.

6-Acetamido-6-deoxy-1,2:3,4-di-O-isopropylidene-D-galactopyranose (4): To a solution containing 15 g (52.6 mmol) of the 6-deoxy-6-azido derivative **3** in 100 mL of THF was added, in small portions, 15 g of triphenyl phosphine. After 3h, 50 mL of water was added and the solution stirred vigorously overnight. The organic phase was separated, dried over anhydrous magnesium sulphate and concentrated. The crude was dissolved in 45 mL of pyridine and treated with 17 mL of acetic anhydride. After 12 h, the crude mixture was poured over ice-water (400 mL) and then extracted with chloroform (4x1). The combined organic phase was dried over magnesium sulphate, filtered and concentrated. Column chromatography on silica gel (4:1 hexane:EtOAc) provided 15 g (95 %) of the product **4** as a colourless syrup[22].

6-(N-nitroso)-acetamido-6-deoxy-1,2:3,4-di-O-isopropylidene-D-galactopyranose (5): A solution containing 3.6 g (11.9 mmol) of **4** in 12 mL of glacial acetic acid and 60 mL of acetic anhydride was cooled at -10ºC. Under vigorous stirring, 18 g of sodium nitrite was slowly added over 1h. Then, the reaction medium was stirred for 8 h. The crude mixture obtained was poured over ice-water and extracted with diethyl ether (100 mL, 4x1). The organic phase was washed with 5% sodium hydrogen carbonate several times until all acetic acid was removed. Finally, washing with water, drying over sodium sulphate, filtering and concentration provided 2.9 g of the product **5** (75%) as a yellow solid. IR: 2944, 1735, 1521, 1383, 1072 cm^{-1}. ^{1}H-NMR (δ): 5.34 (d, $J_{1,2}$=4.9 Hz, H-1); 4.55 (dd, $J_{3,4}$= 7.8 Hz, $J_{3,2}$= 2.6 Hz, H-3); 4.47 (dd, $J_{6,6'}$= 13.7 Hz, $J_{6,5}$= 9.9 Hz, H-6); 4.22 (dd, $J_{2,1}$=4.9 Hz, $J_{2,3}$= 2.6 Hz, H-2); 4.13 (dd, $J_{4,3}$=7.8 Hz, $J_{4,5}$= 2.7 Hz, H-4); 3.84 (dt, $J_{5,6}$= 9.9 Hz, $J_{5,6'}$= $J_{5,4}$= 2.7 Hz, H-5); 3.51 (dd, $J_{6,6'}$= 13.7 Hz, $J_{6',5}$= 2.7 Hz, H-6'); 2.75 (s, 3H, -N(NO)COMe); 1.47, 1.38, 1.31and 1.24 (4s, 12H, C<u>Me</u>$_2$).

6-diazo-6-deoxy-1,2:3,4-di-O-isopropylidene-D-galactopyranose (6): A solution containing 2.4 g (7.2 mmol) of **5** in 40 mL of diethyl ether and 5 mL of methanol was treated with 10 mL of 40% KOH at 0ºC, under a nitrogen atmosphere in the dark, with stirring. After 5 min., the crude mixture was diluted with water, the organic layer separated and the aq. layer extracted with ether twice. The combined organic layers were dried over anhydrous sodium sulphate, filtered and concentrated in vacuo at 25 ºC to obtain 2.1 g of the pure product **6** as a yellow syrup (100%). (CAUTION: Unstabilized diazo compounds are potentially explosive. They are normaly used in solution. We observed no decomposition however during the manipulation of this compound or its isolation by solvent removal). IR: 2988, 2081, 1437, 1384 cm^{-1}. ^{1}H-NMR (δ): 5.55 (d, $J_{1,2}$=5.1 Hz, H-1); 4.60 (dd, $J_{3,4}$= 7.7 Hz, $J_{3,2}$= 2.6 Hz, H-3); 4.47 (dd, $J_{3,4}$= 7.7 Hz, $J_{4,5}$= 2.0 Hz, H-4); 4.30 (dd, $J_{2,1}$=5.1 Hz, $J_{2,3}$= 2.6 Hz, H-2); 4.25 (dd, $J_{5,6}$=7.6 Hz, $J_{4,5}$= 2.0 Hz, H-5); 3.99 (d, $J_{5,6}$= 7.6 Hz, H-6); 1.51 and 1.44 (2s, 6H, CMe_2), 1.33 (1s, 6H, C<u>Me</u>$_2$).

Methyl 2,3-O-isopropylidene-β-D-ribo-pentonodialdo-1,4-furanoside (9): To a solution of 1 mL of oxalyl chloride in 25 mL of anhydrous dichloromethane was added 1.7 mL of DMSO in 5 mL of CH_2Cl_2 at -60 ºC under nitrogen atmosphere. After 2 min, a solution containing 2 g of methyl 2,3-O-isopropylidene-β-D-ribofuranoside[23] in 10 mL of dichloromethane was added dropwise at -60º C. After 20 min, 7 mL of triethyl amine was added with stirring; once the crude mixture reached room temperature, some water was added. The organic layer was separated and the aq. phase extracted with CH_2Cl_2 (20 mL) twice. The combined organic layers were washed with 5%ClH, saturated sodium hydrogen carbonate and water, and dried over sodium sulphate. Finally, the solution was filtered, and concentrated in vacuo. The crude was 1.7 g of the pure aldehyde **9**. ^{1}H-NMR (δ): 9.53 (s, 1H, H-5); 5.03 (s, 1H, H-1); 4.99 (d, 1H, $J_{2,3}$=5.8 Hz, H-3); 4.44 (d, 1H, H-2); 4.41 (s, 1H, H-4); 3.40 (s, 3H, -OMe); 1.44 and 1.28 (2s, 6 H, C<u>Me</u>$_2$).

(1,2:3,4-di-O-isopropylidene-D-galactopyranos-6-yl)-propionate (7): A solution containing 0.1 g of **6** in 2 mL of diethyl ether was treated with 0.03 g of propionic acid. After 10 min of strong nitrogen release, the reaction was finished. The crude was purified by column chromatography on silica gel (3:1 hexane:EtOAc) to obtain 0.109 g of the ester **7** (93%). ^{1}H-NMR (δ): 5.51 (d, J=5.1, H-1); 4.6 (dd, H-3), 4.45-4.10 (m, H-2, H-4, H-6, H-6'); 4.0 (ddd, H-5), 2.35 (q, J=7.1, -CO_2CH_2); 1.49, 1.43, 1.31, 1.30 (4s, 12H, 2 CMe_2), 1.12 (t, 3H, -$CO_2CH_2CH_3$). MS (m/z): 301 (M^+-15, 65); 243 (14.5); 227 (10), 184 (20), 169 (30), 113 (39), 100 (58), 81 (100), 57 (83), 43 (67).

6-deoxy-1,2:3,4-di-O-isopropylidene-D-galacto-5-hexenoaldo-1,5-pyranose (8): A solution containing 0.1 g of **6** in 2 mL of chloroform was treated with dirhodium tetraacetate. As in the previous reaction, strong nitrogen release was observed. After 5 min, the reaction was complete. The crude mixture was purified by column chromatography on silica gel (5:1 hexane:EtOAc) to obtain 0.061 g of the alkene **8** (68%). ^{1}H-NMR (δ): 5.54 (d, $J_{1,2}$=5.1, H-1); 4.75, 4.57 (2s, H-3, H-4); 4.53 (H-6, H-6'); 4.23 (d, H-2); 1.47, 1,45, 1.37 and 1.34 (4s, 12H, CMe_2). ^{13}C-NMR (δ): 152.1 (C-5), 110.5 and 109.6 (2 $\underline{C}Me_2$); 100.5 (C-6); 97.1 (C-1); 73.1 (C-4); 72.5 (C-3); 71.0 (C-2); 26.9, 26.5, 26.0 and 24.8 (2 CMe_2). MS (m/z): 227 (M^+-15, 31.4); 184 (29), 169 (100), 155 (5), 127 (24), 97 (35), 69 (20), 43 (65).

Condensation of (6) with (9): To a solution consisting of 1 g of **9** in 10 mL of diethyl ether was added a solution containing 1.7 g of **6** in 10 mL of ether dropwise at 0 C. After 6 h under stirring, the reaction was complete. Column chromatography on silica gel (10:1 hexane:EtOAc) of the crude mixture provided 1.8 g of an unresolvable 1:1of the ketone **10** and the epoxide **11** (82%). The two were resolved by crystallization of the ketone **10** as a white solid in hexane:EtOAc. The same reaction in chloroform provided a 3:1 mixture of **10:11**, but in a 73% yield after purification.

Methyl 5-C-(6-deoxy-1,2:3,4-di-O-isopropylidene-D-galactopyranos-6-yl)-5-keto-2,3-O-isopropylidene-β-D-ribofuranoside (10): m.p. 124°C. $[\alpha]_D^{20}$ = -108.2° (c 3.31, $CHCl_3$). IR: 2992, 1718, 1384 cm^{-1}. ^{1}H-NMR (δ): 5.34 (d, 1H, $J_{1,2}$=5.1 Hz, H-1); 5.12 (dd, 1H, $J_{8,9}$= 0.8 Hz, $J_{9,10}$= 6.0 Hz, H-9); 4.87 (d, 1H, $J_{10,11}$= 1.3 Hz, H-11); 4.49 (dd, 1H, $J_{3,4}$= 7.8 Hz, $J_{3,2}$= 2.5 Hz, H-3); 4.45 (d, 1H, $J_{8,9}$= 0.8 Hz, H-8); 4.37 (dd, 1H, $J_{10,11}$= 1.3 Hz, $J_{9,10}$= 6.0 Hz, H-10); 4.25 (ddd, 1H, $J_{5,6}$= 7.0 Hz, $J_{5,4}$= 2.0 Hz, $J_{5,6'}$= 1.6 Hz, H-5); 4.18 (dd, 1H, $J_{2,1}$=5.1 Hz, $J_{2,3}$= 2.5 Hz, H-2); 4.09 (dd, 1H, $J_{4,3}$=7.8 Hz, $J_{4,5}$= 2.0 Hz, H-4); 3.29 (s, 3H, -OMe); 2.78 (dd, 2H, $J_{6,5}$= 7.0 Hz, $J_{6',5}$= 1.6 Hz, H-6, H-6'); 1.46, 1.34, 1.32 and 1.20 (4s, 12H, 2 $C\underline{Me}_2$); 1.21 (s, 6H, CMe_2). ^{13}C-NMR (δ): 196.70 (C-7); 112.21, 109.13 and 108.55 (3 $\underline{C}Me_2$); 109.93 (C-11); 96.28 (C-1); 89.42 (C-8); 84.33 (C-10); 80.12 (C-9); 72.04 (C-4), 70.74 (C-3); 70.20 (C-2); 63.68 (C-5); 56.13 (OMe); 39.68 (C-6); 26.30, 25.88, 25.67, 24.90, 24.84 and 24.45 (3 $C\underline{Me}_2$). MS (m/z): 429 (M^+-15); 344; 297; 271 (b. p.); 213; 155; 112: 43. Elemental analysis: Calcd for $C_{21}H_{32}O_{10}$ 56.75% C; 7.21% H. Found 56.91% C; 7.11% H.

Methyl (1,2:3,4:9,10-tri-O-isopropylidene-6,7-anhydro-L-*glycero*-L-*allo*-D-*galacto*-undecodialdo-1,5-pyranoside)-11,8-β-furanoside (11): Colourless liquid. $[\alpha]_D^{20}$ = -66.0° (c 0.5, $CHCl_3$). IR: 2990, 1384 cm^{-1}. ^{1}H-NMR (δ): 5.47 (d, 1H, $J_{1,2}$=4.9 Hz, H-1); 4.97 (s, 1H, H-11); 4.71 (d, 1H, $J_{9,10}$= 6.0 Hz, H-9); 4.58 (d, 1H, $J_{10,9}$= 6.0 Hz, H-10); 4.56 (dd, 1H, $J_{3,4}$= 7.6 Hz, $J_{3,2}$= 2.4 Hz, H-3); 4.29 (dd, 1H, $J_{4,3}$=7.6 Hz, $J_{4,5}$= 1.9 Hz, H-4); 4.27 (dd, 1H, $J_{2,1}$=4.9 Hz, $J_{2,3}$= 2.4 Hz, H-2); 3.99 (d, 1H, $J_{8,7}$= 6.3 Hz, H-8); 3.41 (dd, 1H, $J_{5,6}$= 6.6 Hz, $J_{5,4}$= 1.9 Hz, H-5); 3.36 (s, 3H, -OMe); 3.15 (dd, 1H, $J_{6,5}$= 6.6 Hz, $J_{6,7}$= 2.0 Hz, H-6); 3.00 (dd, 1H, $J_{7,8}$=6.3 Hz, $J_{7,6}$= 2.0 Hz, H-7); 1.53, 1.46, 1.44, 1.34, 1.29 and 1.23 (6s, 18H, 3 $C\underline{Me}_2$). ^{13}C-NMR (δ): 112.37, 109.53, 108.59 (3 $\underline{C}Me_2$); 108.93 (C-11); 96.04 (C-1), 86.30 (C-8); 85.25 (C-10); 81.44 (C-9); 71.10 (C-4); 70.61 (C-3); 70.40 (C-2); 68.41 (C-5); 57.80 (C-6); 54.87 (C-7); 54.81 (OMe); 26.33, 26.11, 25.94, 24.89, 24.25 (3 $C\underline{Me}_2$). MS (m/z): 429 (M^+-15); 371; 311; 243; 199; 141; 100; 43 (b. p.). Elemental analysis: Calcd for $C_{21}H_{32}O_{10}$ 56.75% C; 7.21% H. Found 56.54% C; 7.54 % H.

Methyl (1,2:3,4:9,10-tri-O-isopropylidene-6-deoxy-L-*allo*-α-D-*galacto*-undecodialdo-1,5-pyranoside)-11,8-β-furanoside (12): A volume of 1 mL of 1M Super-hydride in THF was added under a nitrogen atmosphere to a solution containing 0.1 of the epoxide **11** in 5 mL of anhydrous THF. The reaction mixture was then refluxed for 5 h. After which, the crude mixture was concentrated and purified by column chromatography on silica-gel (5:1 hexane:EtOAc) to obtain 83 mg of the product **12** (83%). Colourless liquid. $[\alpha]_D^{20}$ = -11.2° (c 2.24, $CHCl_3$). IR: 3467, 2992, 1384, 1070 cm^{-1}. ^{1}H-NMR (δ): 5.52 (d, 1H, $J_{1,2}$=5.0 Hz, H-1); 4.95 (s, 1H, H-11); 4.83 (d, 1H, $J_{9,10}$= 5.9 Hz, H-9); 4.61 (dd, 1H, $J_{3,4}$= 7.8 Hz, $J_{3,2}$= 2.4 Hz, H-3); 4.55 (d, 1H, $J_{10,9}$= 5.9 Hz, H-10); 4.30 (dd, 1H, $J_{2,1}$=5.0 Hz, $J_{2,3}$= 2.4 Hz, H-2); 4.23 (d, 1H, $J_{8,7}$= 3.4 Hz, H-8); 4.15-4.12 (m, 2H, H-4, H-5); 3.90 (dc, 1H, $J_{6,7}$= $J_{6',7}$= $J_{7,OH}$= 2.4 Hz, $J_{7,8}$= 3.4 Hz, H-7); 3.49 (w s, 1H, OH); 3.42 (s, 3H, -OMe); 1.95 (ddd,

1H, $J_{6,6'}$= 14.5 Hz, $J_{5,6}$= 10.5 Hz, $J_{6,7}$= 2.4 Hz, H-6); 1.59 (ddd, 1H, $J_{6,6'}$= 14.5 Hz, $J_{5,6'}$= 4.3 Hz, $J_{6',7}$= 2.4 Hz. H-6'); 1.55, 1.46, 1.45, 1.34, 1.33 and 1.30 (6s, 18H, 3 C<u>Me</u>$_2$). ^{13}C-NMR (δ): 112.01, 109.16, 108.74 (3 <u>C</u>Me$_2$); 110.26 (C-11); 96.46 (C-1), 91.36 (C-8); 85.87 (C-10); 80.44 (C-9); 73.60 (C-4); 70.99 (C-3); 70.59 (C-2); 68.55 (C-7); 64.28 (C-5); 55.85 (OMe); 33.52 (C-6); 26.39, 26.02, 25.97, 25.11, 24.70 and 24.41 (3 C<u>Me</u>$_2$). MS (FAB) (m/z): 447 (M^+); 431 (43.8); 415 (81); 339 (25); 356 (10); 223 (19); 157 (23.7); 139 (24); 129 (35.6); 115 (35.6); 113 (49.4); 111 (32.8); 101 (26); 100 (37); 85 (72); 59 (100). Exact mass calcd for $C_{21}H_{34}O_{10}$ - 15: 431.1917; found: 431.1918.

Methyl (1,2:3,4:9,10-tri-O-isopropylidene-6-deoxy-D-*tallo*-α-D-*galacto*-undecodialdo-1,5-pyranoside)-11,8-β-furanoside (13): A volume of 3 mL of 1M Super-hydride in THF was added under a nitrogen atmosphere at -78°C to a solution containing 1 g of the ketone **10** in 10 mL of THF. After 5 min, the reduction was complete. The crude mixture was then cooled at r.t. and 10 mL of water was added. The organic layer was separated and the aq. layer extracted with THF (3x1). The combined organic layers were dried over sodium sulphate, filtered and concentrated in vacuo. The crude obtained, 1 g, was the pure alcohol **13** (100%). Sodium borohydride at r.t or -78°C produced the mixture of hydroxyl derivatives **12:13** (see table 2). The major alcohol (**13**) was isolated by crystallyzation in hexane:EtOAc. The resulting mixture of alcohols, enriched with **12** was separated by HPLC (4:1 hexane:EtOAc, preparative scale). White solid. m. p. 148°C. $[\alpha]_D^{20}$= -52.2° (c 2.26, $CHCl_3$). IR: 3436, 2993, 1384, 1070 cm^{-1}. ^{1}H-NMR (δ): 5.48 (d, 1H, $J_{1,2}$=5.1 Hz, H-1); 4.93 (s, 1H, H-11); 4.82 (d, 1H, $J_{9,10}$= 5.9 Hz, H-9); 4.57 (dd, 1H, $J_{3,4}$= 7.8 Hz, $J_{3,2}$= 2.4 Hz, H-3); 4.54 (d, 1H, $J_{10,9}$= 5.9 Hz, H-10); 4.47 (d, 1H, $J_{8,7}$= 2.8 Hz, H-8); 4.27 (dd, 1H, $J_{2,1}$=5.1 Hz, $J_{2,3}$= 2.4 Hz, H-2); 4.15 (dd, 1H, $J_{4,5}$=1.9 Hz, $J_{4,3}$= 7.8 Hz, H-4); 3.92 (ddd, 1H, $J_{5,4}$= 1.9 Hz, $J_{5,6'}$= 5.6 Hz, $J_{5,6}$= 8.9 Hz, H-5); 3.77 (dddd, 1H, $J_{7,8}$=2.8 Hz, $J_{7,6'}$= 7.0 Hz, $J_{7,6}$=7.5 Hz, $J_{7,OH}$= 11.2 Hz, H-7); 3.42 (s, 3H, -OMe); 3.27 (d, 1H, $J_{7,OH}$= 11.2 Hz, -OH); 2.01 (ddd, 1H, $J_{6,6'}$= 13.8 Hz, $J_{5,6}$= 8.9 Hz, $J_{6,7}$= 7.5 Hz, H-6); 1.65 (ddd, 1H, $J_{6,6'}$= 13.8 Hz, $J_{5,6'}$= 5.6 Hz, $J_{6',7}$= 7.0 Hz, H-6'); 1.50, 1.43, 1.32, 1.30, and 1.29 (5s, 18H, 3 C<u>Me</u>$_2$). ^{13}C-NMR (δ): 111.97, 109.17, 108.44 (3 <u>C</u>Me$_2$); 110.48 (C-11); 96.57 (C-1), 89.43 (C-8); 85.61 (C-10); 82.45 (C-9); 72.39 (C-4); 70.95 (C-3); 70.46 (C-2); 68.61 (C-7); 64.66 (C-5); 55.84 (OMe); 34.11 (C-6); 26.45, 26.01, 25.79, 24.94, 24.84 and 24.51 (3 C<u>Me</u>$_2$). Elemental analysis: Calcd for $C_{21}H_{34}O_{10}$ 56.50% C; 7.62% H. Found 56.57% C; 7.56 % H.

Methyl (1,2:3,4:9,10-tri-O-isopropylidene-7-O-acetyl-6-deoxy-D-*tallo*-α-D-*galacto*-undecodialdo-1,5-pyranoside)-11,8-β-furanoside (14): A solution containing 1 g of **13** in 5 mL of pyridine was treated with 2 mL of acetic anhydride. After 4 h, the crude mixture was diluted with chloroform (20 mL) and poured over ice-water. The organic phase was separated and the aq. layer extracted with more chloroform (10 mL, 2x1). The combined organic layers were washed with 1M ClH, saturated sodium hydrogen carbonate, and brine. Finally, the solution was dried over anhydrous magnesium sulphate, filtered and concentrated. The crude obtained (1.1 g) was the pure O-acetyl derivative **14** as a colourless liquid (100%). $[\alpha]_D^{20}$= -69.6° (c 3.24, $CHCl_3$). IR: 2992, 2936, 1734, 1383 cm^{-1}. ^{1}H-NMR (δ): 5.44 (d, 1H, $J_{1,2}$=5.1 Hz, H-1); 5.02 (dt, 1H, $J_{6,7}$= $J_{6',7}$= 5.2 Hz, $J_{7,8}$= 7.1 Hz, H-7); 4.91 (s, 1H, H-11); 4.61 (dd, 1H, $J_{9,10}$= 5.9 Hz, $J_{9,8}$= 1.6 Hz, H-9); 4.53 (dd, 1H, $J_{3,4}$= 7.8 Hz, $J_{3,2}$= 2.4 Hz, H-3); 4.46 (d, 1H, $J_{10,9}$= 5.9 Hz, H-10); 4.26 (dd, 1H, $J_{2,1}$=5.1 Hz, $J_{2,3}$= 2.4 Hz, H-2); 4.26 (dd, 1H, $J_{8,7}$= 7.1 Hz, $J_{8,9}$= 1.6 Hz, H-8); 4.15 (dd, 1H, $J_{4,5}$=1.8 Hz, $J_{4,3}$= 7.8 Hz, H-4); 3.80 (dt, 1H, $J_{5,4}$= 1.8 Hz, $J_{5,6'}$= $J_{5,6}$= 7.0 Hz, H-5); 3.24 (s, 3H, -OMe); 2.00 (s, 3H, -OCOMe); 1.99-1.83 (m, 2H, H-6, H-6'); 1.44, 1.42, 1.39, 1.28, and 1.25 (6s, 18H, 3 C<u>Me</u>$_2$). ^{13}C-NMR (δ) : 170.42 (OCOMe); 112.47, 109.13, 108.36 (<u>C</u>Me$_2$); 109.48 (C-11); 96.43 (C-1); 87.43 (C-8); 85.35 (C-10); 81.26 (C-9); 72.10 (C-4); 71.25 (C-3); 70.77 (C-2); 70.21 (C-7); 64.29 (C-5); 55.09 (OMe); 31.54 (C-6); 26.61, 25.95, 25.65, 25.10, 24.85, 24.53 (C<u>Me</u>$_2$); 20.97 (OCOMe). MS (FAB) (m/z): 489 (M^+ +1, 5.3); 487 (12.8); 473 (64); 457 (100); 399 (20); 239 (18); 139 (23); 129 (59.9); 123 (21.7); 115 (53.4); 113 (58.6); 101 (24.8); 100 (46.5); 85 (71); 81 (57); 71 (53); 59 (75); 55 (67). Exact mass calcd for $C_{23}H_{35}O_{11}$ - 15: 473.2023; found: 473.2005.

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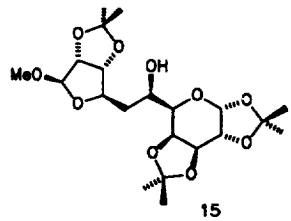
REFERENCES

1. [a] Sinnot, M. L. *Enzyme Mechanisms*, The Royal Soc. of Chem., London, **1987** p 259. [b] Elbein, A. D. *Comprehensive Medicinal Chemistry*; Vol. 2, Chapter 8, p. 365; Pergamon Press, **1990.** [c] Tvaroska, I. and Bleha, T. *Adv. Carbohydr. Chem. Biochem.*; **1989**, *47*, 45
2. Rouzaud, D. and Sinaÿ, P. *J. Chem. Soc. Chem. Commun.*, **1983**, 1353.
3. [a] Babirad, S. A.; Wang, Y. and Kishi, Y. *J. Org. Chem.*, **1987**, *52*, 1372. [b] Haneda, T.; Goekjian, P. G.; Kim, S. H. and Kishi, Y. *J. Org. Chem.*, **1992**, *57*, 490. [c] Martin, O. R. and Lai, W. *J. Org.Chem.*, **1993**, *58*, 176. [d] Giese, B. and Witzel, T. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 450. [e] Giese, B.; Hoch, M.; Lamberth, C. and Schmidt, R. R. *Tetrahedron Lett.*, **1988**, *29*, 1375. [f] Babirad, S. A.; Wang, Y. and Kishi, Y. *J. Org. Chem.*, **1987**, *52*, 1370. [g] Preuss, R. and Schmidt, R. R. *J. Carbohydr. Chem.*, **1991**, *10*, 887. [h] Bimwala, R. M. and Vogel, P. *Tetrahedron Lett.*, **1991**, *32*, 1429. [i] Wang, Y.; Babirad, S. A. and Kishi, Y. *J. Org. Chem.*, **1992**, *57*, 468. [j] Bimwala, R. M. and Vogel, P. *J. Org. Chem.*, **1992**, *57*, 2076. [k] Dyer, V. C. and Kishi, Y. *J. Org. Chem.*, **1988**, *53*, 3384. [l] Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. and Zucchelli, L. *J. Chem. Soc. Chem. Commun.*; **1989**, 1085.
4. Acton, E. M.; Ryan, K. J. and Goodman, L. *J. Chem. Soc., Chem. Commun.*, **1970**, 313.
5. Shulman, M. L.; Shiyan, S. D. and Khorlin, A. Y. *Carbohydr. Res.*, **1974**, *33*, 229.
6. [a] Atsumi, S.; Umezawa, K.; Jinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y. and Takeuchi, T. *J. Antibiotics*, **1990**, 99. [b] Legler, G. *Methods Enzymol.*, **1977**, *46*, 368.
7. [a] Schmidt, R. R. and Beyerbach, A. *Liebigs Ann. Chem.*, **1992**, 983. [b] Paton, R. M. and Penman, K. J. *Tetrahedron Lett.*, **1994**, *35*, 3163.
8. [a] Ito, T.; Kodama, Y.; Kawamura, K.; Suzuki, K.; Takatsuki, A. and Tamura, G. *Agric. Biol. Chem.*, **1977**, *41*, 2303; [b] Ito, T.; Takatsuki, A.; Kawamura, K.; Saito, K. and Tamura, G. *Agric. Biol. Chem.*, **1980**, *44*, 695; [c] Takatsuka, A.; Arima, K. and Tamura, G. *J. Antibiot.*, **1971**, *24*, 215.
9. Eckhardt, K.; Ihn, W.; Tresselt, D. and Krebs, D. *J. Antibiot.*, **1981**, *34*, 1631.
10. Edgar, J. A.; Frahn, J. L.; Cockrum, P. A.; Anderton, N.; Jago, M. V.; Culvenor, C. C. J.; Jones, A. J.; Murray, K. and Shaw, K. J. *J. Chem. Soc. Chem. Commun.*; **1982**, 222.
11. [a] Sasai, H.; Matsuno, K. and Suami, T. *J. Carbohydr. Chem.*, **1985**, *4*,215; [b] Ramza, J. and Zamojski, A. *Tetrahedron*, **1992**, *48*, 6123.
12. [a] Danishefsky, S. J. and Barbachyn, M. *J. Am. Chem. Soc.*, **1985**, *107*, 7761. [b] Danishefsky, S. J.; DeNino, S. L.; Chen, S.; Boisvert, L. and Barbachyn, M. *J. Am. Chem. Soc.*, **1989**, *111*, 5810.
13. [a] Suami, T.; Sasai, H.; Matsuno, K.; Suzuki, N.; Fukuda, Y. and Sakanaka, O. *Tetrahedron Lett.*; **1984**, *25*, 4533. [b] Kominato, K.; Ogawa, S. and Suami, T. *Carbohydr. Res.*; **1988**, *174*, 360. [c] Karpiesiuk, W. and Banaszek, A. *Carbohydr. Res.*; **1994**, *261*, 243.
14. Secrist III, J. A. and Wu, S. R. *J. Org. Chem.*, **1979**, *44*, 1434.
15. Karpiesiuk, W. and Banaszek, A. *VII European Symposium on Carbohydrates*,, A-096, Cracow, (Poland, 1993).
16. Corey, E. J.; Samuelsson, B. and Luzzio, F. A. *J. Am. Chem. Soc.*; **1984**, *106*, 3682.
17. Mancuso, A. J.; Huang, S-L and Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480.
18. Gutshe, D. *Org. Reactions*, N.Y., Vol. 8, **1954**, 364.
19. Hagen, S.; Anthonsen, T. and Kilaas, L. *Tetrahedron*, **1979**, *25*, 2583.
20. The alcohol by opening at C-7 of the epoxide **11** with Super-hydride was also obtained. However, its

isolation by column chromatography was not possible due to the decomposition on silica-gel. From the H-NMR spectra of the crude mixture of the opening reaction, it was possible to determine the ratio of the two alcohols which was 5:1 (**12:15**) and the spectroscopic data of **15**.



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^{1}H-NMR (δ): 5.52 (d, 1H, $J_{1,2}$=5.0 Hz, H-1); 4.95 (s, 1H, H-11); 4.61-4.51 (m, 3H, H-9, H-10, H-3); 4.42 (dd, 1H, $J_{2,3}$= 2.6 Hz, H-2); 4.30 (dd, 1H, $J_{5,4}$=1.9 Hz, $J_{5,6}$= 5.1 Hz, H-5); 4.15 (dd, 1H, $J_{4,3}$= 7.8 Hz, H-4); 4.03 (dq, 1H, J = 5.1 Hz, H-6); 3.51 (dd, 1H, J = 5.5 Hz, J = 2.0 Hz, H-8); 3.29 (s, 3H, -OMe); 2.65 (d, 1H, $J_{6,OH}$= 5.1 Hz, -OH); 2.1 (ddd, 1H, H-7); 1.6 (ddd, 1H, H-7'); 1.49, 1.42, 1.32, 1.30, and 1.29 (5s, 18H, 3 $C\underline{Me}_2$).
^{13}C-NMR (δ): 112.1, 109.2, 108.6 (3 $\underline{C}Me_2$); 109.9 (C-11); 85.60 (C-1); 84.1 (C-10); 83.4 (C-9); 70.8, 70.4, 69.9 (C-4, C-3, C-2); 68.1 (C-6); 67.5 (C-8); 55.6 (OMe); 38.5 (C-7); 26.5, 26.1, 25.8, 24.9, 24.8 and 24.5 (3 $C\underline{Me}_2$).

21. Ramza, J. and Zamojski, A. *Carbohydr. Res.*, **1992**, *228*, 205.
22. Szarek, W. A. and Jones, J. K. N. *Can. J. Chem.*,**1965**, *43*, 2345.
23. Leonard, N. J. and Carraway, K. L. *J. Heterocyclic Chem.*; **1966**, *3*, 485.

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