Tetrahedron Vol. 45, No. 1, pp. 269 to 276, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
© 1989 Pergamon Press plc

STEREOSELECTIVITY IN THE FORMATION OF UNSATURATED WITTIG PRODUCTS AND STEREOSPECIFICITY IN THEIR ELECTROPHILE INDUCED CYCLIZATION TO C-GLYCOSIDES.

F. J. LOPEZ HERRERA*, M. S. PINO GONZALEZ, M. NIETO SAMPEDRO and R. M. DOMINGUEZ ACIEGO

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

(*Received in UK* 8 *June* 1988)

Abstract.- The stereoselective synthesis of E and Z unsaturated Wittig products derivated from 2,3-O-isopropylidene-5--O-trityl-D-ribofuranose (3) and 2,3:5,6-di-O-isopropylidene--D-mannofuranose (4) was described, as well as their stereospecific cyclization induced by iodine, to C-glycosides. The absolute configurations at the anomeric center and at the C-α of the aglycone rest, were established by chemical and spectroscopic methods.

INTRODUCTION

The synthesis of highly functionalized C-glycosides is of great interest in a) the synthesis of naturally occurring C-nucleosides and their analogues; and b) as chiral templates[1]. We are interested in determining and controlling the stereochemistry of the two new quiral carbons of the C-C bond, created at the anomeric center, in the synthesis of C-glycosides.

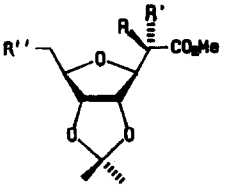
This was partially the subject of a previous paper[2], in which we described the synthesis of R and S epimers of 1 by the Wittig reaction of methoxycarbonylbromomethylenetriphenylphosphorane (2a) and 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (3), and determined the configuration at the C-α of the aglycone. Similar products have been prepared by electrophilic induced cyclization[3] of the E or Z α,β-unsaturated products, obtained by Wittig reaction from the non-halogenated ylide 2b and similar ribose derivatives.

Any of the previous papers had not established definitely the configuration at the C-α of the aglycone in the resulting cyclic products. Consequently, we decided to determine this configuration in similar products by chemical methods and by spectroscopic correlation of these products with the previously reported analogous[2].

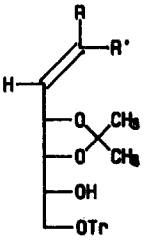
Results and Discussion

First, we studied the effect of the solvent and the temperature on the stereochemistry of the unsaturated Wittig product resulting from the reaction of ylide methoxycarbonylmethylenetriphenylphosphorane (2b) with 3 or with the 2,3:5,6-di-O-isopropylidene-D- mannofuranose (4). The major effect was caused by the solvent and then by the temperature. Thus, in the reaction

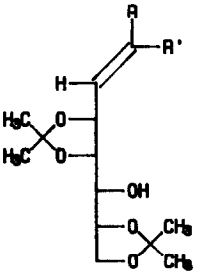
of **2b** with **3** in methylene chloride at reflux, we obtained 71.5% of isomer **5-Z**, 28.5% of **5-E** and only traces of cyclic isomers **6**. The same solvent, but at room temperature led to a higher stereoselectivity, yielding 90.0% of **5-Z**, 10.0% of **5-E** and traces of **6**. Finally, using n-hexane at reflux, we obtained only 28.5% of **5-Z** and 71.5% of **5-E**, besides traces of **6**. Unfortunately, we cannot obtain similar results from the reaction of **2b** with **4**, a reaction which only yielded the isomer **7-E**, using benzene or the more polar methylene chloride. Only traces of **7-Z** were obtained in methylene chloride, always with cyclic product **8**. All isomers were purified by chromatography.



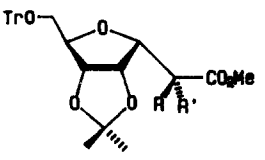
	R	R'	R''
1 (R)β	Br	H	OTr
1 (S)β	H	Br	OTr
6β	H	H	OTr
9β	H	I	OTr
12β	H	I	OH
14β	H, OAc		OTr



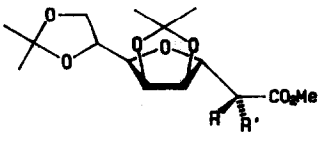
	R	R'
5E	CO_2Me	H
5Z	H	CO_2Me



	R	R'
7E	CO_2Me	H
7Z	H	CO_2Me

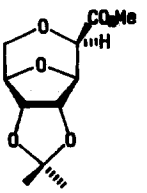


	R	R'
6α	H	H
10α	I	H

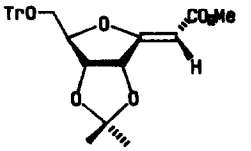


	R	R'
8α	H	H

	R	R'
8β	H	H
11β	I	H



13



15

Although the values of $^3J_{2,3}$ for **5-Z** and **5-E** are not very differents, the chemical shifts of H-4 are. This is due to the anisotropic effect of the carbonyl group of the Z isomer; the H-4 is deshielded in the Z isomers, which produces a higher value for the chemical shift. This result is in agreement with similar E/Z assignments[3a,4,11].

These results permit us to establish the relation between the polarity of the solvent and the formation of the Z and E isomers: lower polarity increase the E configuration. To our knowledge, this fact had not been verified by testing for unsaturated sugar derivatives obtained from the Wittig reaction. Sometimes, the acyclic products were cyclized without knowing the correct assignation of their configuration[5].

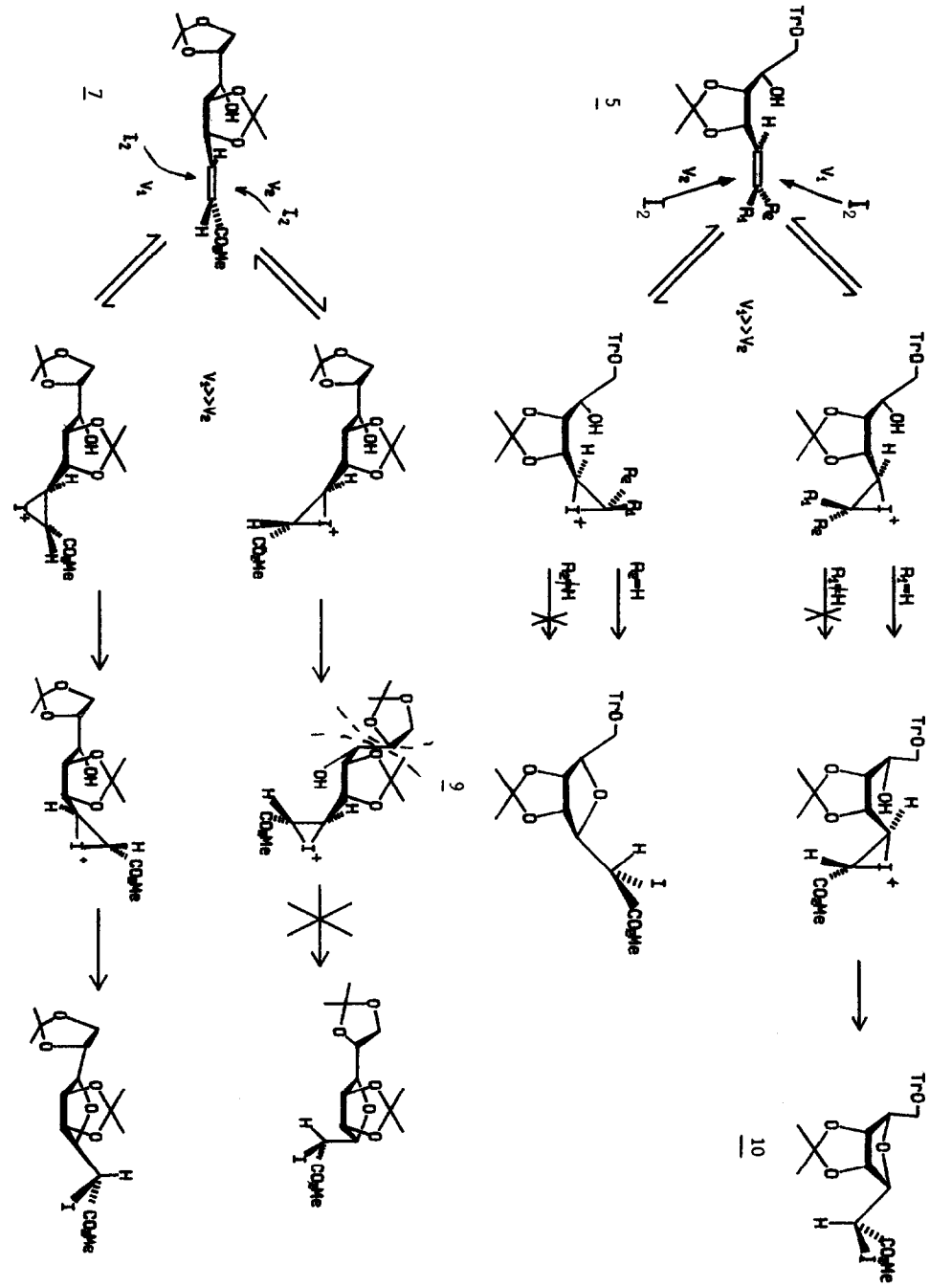
In this way, it was possible to avoid the use of the tedious process of isomerization[5,3a] from **5-Z** to **5-E**. Moreover, the lack of formation of **7-Z** has little synthetic relevance as we show later. In this context, we are in a position to study the electrophilic cyclization process for these unsaturated products. Thus, we treated each of them separately with iodine in ether, shaking them with an aqueous solution of sodium bicarbonate at low temperature and for several hours. In all cases, a sole and different product was isolated, **9** from **5-Z**, **10** from **5-E** and **11** from **7-E**, showing an apparently complete stereoselectivity as has been reported in similar cases[3a]. This can be attributed to several causes: the selectivity in the iodine approach, the reversibility of the iodonium formation, the regio and stereospecificity of the internal iodonium displacement and the steric interactions of the methoxycarbonyl group, as we show in the Scheme I. It would seem that the trapping by the internal nucleophile is synchronous with the formation of iodonium ion, in this kinetically controlled process; but this step by step scheme helps to explain the experimental results.

The anomeric configuration of all of them, was assigned by well established spectroscopic methods[5a,1d,7]. The C-2 configuration of **9** was finally assigned by previous transformation in the dianhydro derivative **13** via **12**. The SN_2 intramolecular substitution process inverts the configuration at C-2, leading an unique product **13**. (This cyclization was induced by silver trifluoroacetate in DMSO). The complete configuration assignment of **13** was accomplished by 2D-homonuclear dipolar correlation (NOESY). Moreover, NMR spectra of **9** was practically the same as the bromine analog **1**, and that of **13** the same as the resulting product of a similar reaction from **1**, previously reported[2].

These results are in agreement with the previous tentative assignments for similar cyclic reaction products. Thus, **11** must be the proposed structure and in accordance with this, the hypothetical compound **7-Z** would produce a C-2(R),α- derivative, which can be obtained in another way as previously reported[2,8].

Finally, we have studied the substitution at C-2 of **9** and **10**. We used potassium acetate in DMSO and in the presence of 18-crown-6 ether. The isomer "exo" **9** yielded a mixture of the two C-2, ß-epimers **14** (5:3, R/S by ^1H NMR spectroscopy) as well as the elimination product **15** in a (3:1 for **14/15**) proportion. Conversely, **10** only yielded the unsaturated product **15**, which can be interpretated as the result of a great steric hinderance to the approximation of the nucleophile. This fact, as well as the previously reported exclusive formation of "exo" anomers, in the Wittig reaction of **(2)** and **(3)**[2] or **(4)**[8] in thermodynamic conditions, leads us to conclude that in these α-substituted C-glycosides, the "exo" anomers are thermodynamically the more stable ones.

SCHEME I



T A B L E I

^{1}H-NMR chemical shifts (200 MHz, in $CDCl_3$, δ ppm)

Product	H-2	H-3	H-4	H-5	H-6	H-7a	H-7b	CMe2		MeO	Trityl	Others
5Z	5.92 dd	6.18 dd	5.69 ddd	4.37 dd	3.75 m		3.28 m	1.35	1.34	3.72	7.2-7.5	
5E	6.09 dd	7.08 dd	4.81 ddd	4.18 dd	3.68 m		3.32 m	1.4	1.3	3.72	7.2-7.5	
9	4.63 dd	4.30 dd	4.97 dd	4.72 dd	4.18 ddd	3.25 dd	3.14dd	1.52	1.34	3.62	7.2-7.5	
10	4.45 d	4.90 dd	4.95 dd	4.67 dd	4.24 m	3.30 dd	3.00dd	1.57	1.48	3.80	7.2-7.5	
11	4.38 d	4.04 dd	4.83 dd	4.72 dd	3.55 dd	4.31 ddd	---	1.45	1.35	3.72	---	3.95 dd(8a,8b) 1.34(CMe2)
12	4.61 d	4.07 dd	4.75 dd	4.83 dd	4.1[illegible]	3.83 dd	3.63 dd	1.5	1.35	3.75	---	

T A B L E I I

Coupling Constants (Hz)

Product	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7a}$	$J_{6,7b}$	$J_{7a,7b}$	Others
5Z	11.6	1.2	8.0	6.4	7.6				
5E	15.6	1.7	4.8	5.6	9.2				
9	5.1	-	4.0	6.7	4.0	2.9	4.0	12.1	
10	10.0	-	3.9	6.0	1.0	3.6	3.9	10.1	
11	10.5	-	3.4	6.0	3.5	7.9			5.7 ($J_{7,8a}$), 4.7($J_{7,8b}$)
12	5.1	-	4.0	6.7	4.0	2.9	4.0	12.1	9.0 ($J_{8a,8b}$)

T A B L E I I I

^{13}C-NMR chemical shifts of the products 5E, 9 and 10 (in $CDCl_3$, δ ppm)

Product	C-1	C-2	C-3	C-4	C-5	C-6	C-7	CMe2	CMe2	MeO	Others
5E	166.5	121.8	143.7	- 78.0,	76.8 ,	69.2 -	65.1	109.4	27.5 25.3	51.5	87.0(CTr), 143.9, 128.6, 127.9, 127.0 (Tr)
9	170.0	19.8	85.4	83.1	81.3	85.0	64.0	114.0	26.0 28.0	52.5	86.5(CTr), 143.5, 128.6, 127.9, 127.0 (Tr)
10	170.5	15.7	-- 85.4,	84.6,	83.0,	82.0 ---	64.9	112.6	26.4 25.1	52.9	87.4(CTr), 143.5, 129.0, 128.0, 127.0 (Tr)

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded with a Beckman Aculab IV spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker WP 200 SY spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Mass spectra were obtained with a Hewlett Packard 5988A. Elemental analyses were carried out in the Microanalysis Service of the University of Málaga, in a Perkin-Elmer 240. Preparative thick layer chromatography was performed with silicagel 60 PF_{254} (Merck 7747), thin layer chromatography with silicagel 60 F_{254} (Merck 5719), column chromatography, with silicagel 60 of 0.063-0.200 mm (Merck 7734), and flash column chromatography with silicagel 60 of 0.040-0.063 mm (Merck 9385).

Methyl Z-2,3-dideoxy-4,5-O-isopropylidene-7-O-trityl-D-ribo-2-heptenonate (5-Z) and methyl E-2,3-dideoxy-4,5-O-isopropylidene-7-O-trityl-D--ribo-2-heptenonate (5-E). Three experiments were carried out with 2 g (4.63 mmol) of 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose **(3)**, and 2.32 g (6.94 mmol) of methoxycarbonylmethylenetriphenylphosphorane **(2b)**: (a) were refluxed for 24 h in 50 mL of methylene chloride, (b) refluxed for 22 h in 100 mL of hexane, and (c) dissolved at room temperature in 100 mL of methylene chloride for 48 h; with mechanical stirring in all cases. The reaction was monitorized by tlc (2:1 hexane/ethyl acetate). Solvents were removed under vacuo and the resultant syrup purified by column chromatography (first with hexane alone and later with a small proportion of ethyl acetate added) to yield a mixture of esters **5-Z** and **5-E** which were then separated by thick layer chromatography (5:2:1 hexane/methylene chloride/ether), to give:

(a) 5:2 **5-Z/5-E**, total yield: 83%.
(b) 2:5 **5-Z/5-E**, total yield: 86%.
(c) 7:1 **5-Z/5-E**, total yield: 90%.

5-Z: Rf 0.73 (2:1:0.5 hexane/methylene chloride/ethyl ether); UV λmax 220 nm (ε 11275, MeOH); $(\alpha)_{20}^{D}$ +53.3°(c 0.5, MeOH); MS m/e 488 (M^+), 473 (M^+-Me), 411 (M^+-Ph), 245 (M^+-Tr), 243 (Tr^+).

Anal. Calc. for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 74.12; H, 6.65.

5-E: Rf 0.68 (2:1:0.5 hexane/methylene chloride/ethyl ether); UV λmax 230 nm (ε 7568, MeOH); $(\alpha)_{20}^{D}$ +10.8°(c 0.83, MeOH); MS m/e 488 (M^+), 473 (M^+-Me), 429 (M^+-CO_2Me), 411 (M^+-Ph), 245 (M^+-Tr), 243 (Tr^+).

Anal. Calc. for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.71.

Methyl E-2,3-dideoxy-4,5:7,8-di-O-isopropylidene-D-manno-2-octenonate(7-E)[8]. A solution of 2 g (7.7 mmol) of 2,3:5,6-di-O-isopropylidene-D--mannofuranose **(4)** and 3.7 g (11 mmol) of methoxycarbonylmethylenetriphenylphosphorane **(2b)**, in 25 mL of dry benzene, were refluxed for 6 h. The reaction was monitorized by tlc or ^1H NMR. Solvent was removed and the residue was dissolved first in 20 mL of dry ethyl ether and after in 10:2 ethyl ether/petroleum ether to separate Ph_3PO and ylide rest. The filtrate was concentrated (1.7 g) and purified by flash column chromatography (4:1 hexane/ethyl acetate) to give a mixture of 8α and 8β5a (0. 24 g, 12%) and pure **7-E**[9] (1.2 g, 60%).

7-E : Rf 0.67 (chloroform); IR νmax (film): 1723, 1666 cm^{-1}; $(\alpha)_{20}^{D}$ +15.8°(c 0.4, $CHCl_3$).

Anal. Calc. for $C_{15}H_{24}O_7$: C, 56.66; H, 7.84. Found: C, 56.96; H, 7.59.

Methyl 3,6-anhydro-2-deoxy-2-iodo-4,5-O-isopropylidene-7-O-trityl-D--glycero-D-altro-heptonate (9) and methyl 3,6-anhydro-2-deoxy-2-iodo-4,5--O-isopropylidene-7-O-trityl-D-glycero-D-manno-heptonate (10)[10]. 145 mg (0.3 mmol) of one of the isomers **5-Z** or **5-E** were treated with 381 mg (1.5 mmol) of iodine in ethyl ether (2.5%), and shaken with an aqueous saturated solution of 183 mg of $NaCO_3H$, at 0°C. The reaction was monitorized by tlc (3:1 hexane/ethyl acetate) and after 24 h or 36 h respectively, a solution of sodium thiosulfate was added to decolorate the ether layer. The aqueous solution was washed several times with ethyl ether, and the ether solutions joined and concentrated to yield a syrup which was purified by thick layer chromatography (4:1 hexane/ethyl ether), to give the corresponding cyclic iodoacetate.

9.- Yield : 70%; Rf 0.67 (2:1 hexane/ethyl acetate) and 0.52 (3:3:1 hexane/chloroform/ethyl ether); UV λmax 213 (ε 13000, MeOH); IR νmax (KBr): 1730, 1380, 1080 cm^{-1}; $(\alpha)_{20}^{D}$ -11.1° (c 0.5, MeOH); EM m/e 599 (M^+-Me), 537 (M^+-Ph), 487 (M^+-I), 243 (Tr^+).

Anal. Calc. for $C_{30}H_{31}O_6I$: C, 58.64; H, 5.08. Found: C, 58.5; H, 5.13.

10.- Yield : 70%; Rf 0.67 (2:1 hexane/ethyl acetate) and 0.59 (3:3:1 hexane/chloroform/ethyl ether); UV λmax 218 (ε 14900, MeOH); IR νmax (KBr): 1730, 1380, 1030 cm^{-1}; $(\alpha)_{20}^{D}$ -25.7° (c 0.5, MeOH); EM m/e 599 (M^+-Me), 537 (M^+-Ph), 487 (M^+-I), 243 (Tr^+).

Anal. Calc. for $C_{30}H_{31}O_6I$: C, 58.64; H, 5.08. Found: C, 58.63; H, 5.00.

Methyl 3,6-anhydro-2-deoxy-2-iodo-4,5:7,8-di-O-isopropylidene-D-erithro-L-manno-octanonate (11). To a solution of 785 mg (3 mmol) of iodine (2.5%) in ethyl ether, were added 100 mg (0.316 mmol) of **7-E**, and shaken with an aqueous saturated solution of $NaHCO_3$ (518 mg, 6.17 mmol) at 0ºC. The reaction was monitorized by tlc (4:1 hexane/ethyl acetate) and after 24 h was treated with a solution of sodium thiosulfate to decolorate the ether layer. Working up as above for **9** and **10**, a mixture of **11** besides the secondary products **8α** and **8β** in a 17:2:3 proportion (^1H NMR) was produced. **11** was purified by thick layer chromatography (yield 55%).

11 : Rf 0.37 (4:1 hexane/ethyl acetate); UV λmax 206 nm (ε 3040, MeOH); $(\alpha)_{20}^{D}$ +29.10°(c 0.27, $CHCl_3$); EM m/e 427 (M^+-Me), 315 (M^+-I) and 199 (M^+-Tr).

Methyl 3,6-anhydro-2-deoxy-2-iodo-4,5-O-isopropylidene-D-glycero-D-altro-heptonate (12). 25.6 mg (0.042 mmol) of **9** were dissolved in 2 mL of $CDCl_3$ and treated with 4 drops of TFA and 1 drop of D_2O. The reaction was monitorized by ^1H NMR and after 3 h, the solution was neutralized with $NaHCO_3$ and then purified by thick layer chromatography (3:1 hexane/ethyl acetate) to yield 10.5 mg (68%) of **12**.

12 : Rf 0.24 (2:1 hexane/ethyl acetate); $(\alpha)_{20}^{D}$ +13.8°(c 0.5, MeOH); EM m/e 357 (M^+-Me), 229 (M^+-Me-I-1).

Methyl 2,7:3,6-dianhydro-4,5-O-isopropylidene-D-glycero-D-allo-heptonate (13). To a solution of 25 mg (0.067 mmol) of **12** in D_6-DMSO, was added a small amount of silver trifluoroacetate. After one hour, heating at 80ºC and monitorizing the transformations by ^1H NMR, the solution was purified by thick layer chromatography (7:2 hexane/ethyl acetate) to yield 11 mg of **13** (66%). Spectral data are identical to those described previously[2].

Methyl 3,6-anhydro-2-acetyl-4,5-O-isopropylidene-7-O-trityl-D-glycero-D-allo- and D-glycero-D-altro- heptonates (14). 32.7 mg (0.053 mmol) of **9** were treated with 18 mg (0.10 mmol) of potassium acetate and a catalytic amount of 18-crown-6 ether in DMSO to dissolution. It was heated at 60ºC for 4 h, monitorizing by ^1H NMR, showing the formation of a mixture of the two C-2 epimers of **14** and the unsaturated product **15** in a 3:1 proportion. It was purified by thick layer chromatography (15:1 hexane/ethyl acetate), giving 15 mg of the mixture of **14** (52% of both isomers) and 7.5 mg of **15** (29%). The products obtained showed the same spectra as the previously reported compounds[2].

Methyl Z-3,6-anhydro-2-deoxy-4,5-O-isopropylidene-7-O-trityl-D-ribo-2-hept-enonate (15). 30 mg (0.048 mmol) of **10** were treated with potassium acetate for 12 h, working up as above, to give 16 mg of the same unsaturated product **15** (68.5%), after purification.

Acknowledgment. We thank the Comisión Asesora de Investigación Científica y Técnica for finantial support (ref. PB85-471).

REFERENCES

1.- a) Suhadolnik, R. J. "Nucleoside Antibiotics" Wiley Interscience, New York, 1970. b) Hanessian, S.; Pernet, A. G., Adv. Carbohydr. Chem. Biochem., **13**, 303 (1976). c) López Herrera, F. J.; Uraga Baelo, C., Carbohydr. Res., **139**, 95 (1984). d) Ibid., Carbohydr. Res., **143**, 161 (1985). e) Masamune, S.; Mc Carthy, "Macrolides", Ed. S. Omura, Cap. 4, Academic Press, New York, 1984.

2.- Pino González, M. S.; Domínguez Aciego, R. M.; López Herrera, F. J., Tetrahedron, **44**, 3715 (1988).

3.- a) Freeman, F.; Robarge, K. D., Tetrahedron Lett., **26**, 1943 (1985). b) Ibid., Carbohydr. Res., **137**, 89 (1985). c) Akrem, A. A.; Kvasyuk, E. I., Mikhailopulo, I. A.; Prikota, T. I., Zh. Obsh. Khim., (Engl. Transl.), 1111 (1977).

4.- a) López Herrera, F. J.; Pino González, M. S., Carbohydr. Res., **152**, 283 (1986); b) Valpuesta Fernández, M; López Herrera, F. J.; Lupión Cobos, T.; Planas Escribano, G, Carbohydr. Res., **118**, 286 (1983).

5.- a) Ohrui, H.; Gordon II, J.; Moffatt, J. G.; Maddox, M. I.; Christensen, A. T.; Byram, S. K., J. Am. Chem. Soc., **97**, 4602 (1975). b) Kane, P. D.; Mann, J., J. Chem. Soc., Chem. Commun., 224 (1983).

6.- Gais, H. J., Angew. Chem. Int. Ed. Engl., **23**, 143 (1984).

7.- As Freeman et als. had reported[3a] for the D-ribose derivatives, the α-anomeric configuration for the ethyl ester of the D-mannose derivative **11** (Akrem et als.3d), only supported by the coupling constants $J_{2,3}$ and $J_{3,4}$, appears to be wrong.

8.- Unpublished results for the manno-analogues.

9.- Zhdanov, Yu. A.; Uzlova, L. A., J. Gen. Chem., (Engl. Trans.), **41**, 1401, (1971).

10.- Compounds **9**, **10** and **11** could be named as: methyl 2(S)-iodo-2-(5-O-trityl-2,3-O-isopropylidene-ß-D-ribofuranosyl)acetate (**9**); methyl 2(S)-iodo-2-(5-O-trityl-2,3-O-isopropylidene-α-D-ribofuranosyl)acetate (**10**); methyl 2(R)-iodo-2-(2,3:5,6-di-O-isopropylidene-ß-D-mannofuranosyl)acetate (**11**).

11.- Drew, M. G. B., Kane, P. D., Mann, J. and Naili, M., J. Chem. Soc. Perkin Trans. I, 433 (1988).