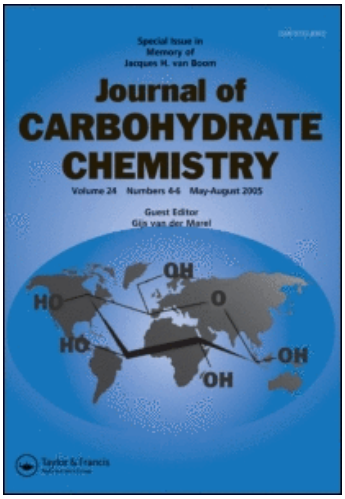

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CATALYTIC HYDROGENATION OF PHOSPHATE ENOL ESTERS PRESENT IN BRANCHED CHAIN DIENEPYRANOSIDES IN A ROUTE TO THROMBOXANE ANALOGS FROM D-GALACTOSE.

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ABSTRACT

Branched-chain conjugated dienepyranosides including vinyl phosphate esters were subjected to catalytic hydrogenation under different conditions. Heterogeneous catalysts led to isomerization products that were resistant to further hydrogenation. On the other hand, under homogeneous conditions, complete stereoselective hydrogenation was achieved. Methyl 2,4-dideoxy-3-*O*-diethoxyphosphoryl-4-*C*-[(methoxycarbonyl)methyl]-α-D-*ribo*-hexopyranoside (**6b**), a potential precursor of thromboxane analogs, was obtained.

INTRODUCTION

The thromboxane A_2 (TXA_2) is a central member of the arachidonic acid cascade and causes platelets to clump and aggregate.[1a,b] TXA_2 is transformed rather rapidly into

thromboxane B_2 (TXB_2),[2] which unlike its precursor, is biologically inert as a platelet aggregating agent; nevertheless, it is a valuable substrate for the study of a variety of biochemical processes.[3a,b] Whereas TXA_2 has been prepared by total synthesis only once,[4] several approaches to its stable metabolite TXB_2 have been reported.[5a-c] As a general strategy the tetrahydropyran part was adapted from various glucose derivatives and the two side chains were attached by Wittig-type olefinations.[5a]

In previous work, we have described the synthesis of key intermediates for the preparation of thromboxane analogs starting from D-galactose.[6] We have also reported the synthesis of methyl 2,4-dideoxy-4-*C*-[*E*(alkyloxycarbonyl)methylene]-3-*O*-dialkoxy-phosphoryl-α-D-*glycero*-hex-2-enopyranosides as a result of anomalous Horner-Wadsworth-Emmons reactions on pyranosic 3,4-enuloses.[7] The most remarkable features of this process were the phosphorylation of the enolic oxygen at C-3 and the uncommon stereospecificity observed. The unsaturated branched chain sugars obtained were useful for our synthetic purposes, since after catalytic hydrogenation these compounds would yield suitable synthetic precursors bearing the required stereochemistry in the mono and bicyclic ring systems of thromboxane B_2 and thromboxane A_2, respectively. Since no previous report on catalytic hydrogenation of these systems was found in the literature we studied this reaction on the conjugated dienic system of vinyl phosphates **1a-e** under different conditions. Using homogeneous catalysis we prepared methyl 2,4-dideoxy-3-*O*-diethoxyphosphoryl-4-*C*-[(methoxy-carbonyl)methyl]-α-D-*ribo*-hexopyranoside (**6b**) from methyl 6-*O*-benzoyl-2,4-dideoxy-4-*C*-[*E*(ethoxycarbonyl) methylene]-3-*O*-diethoxy-phosphoryl-α-D-*glycero*-hex-2-enopyranoside (**1e**) with a 58% overall yield.

Compound **6b** possesses the required stereochemistry and suitable functionality present in the tetrahydropyran moiety of precursors of thromboxane analogs.

RESULTS AND DISCUSSION

Heterogeneous catalytic hydrogenation of dienepyranosides **1a-e** with either 10% Pd/C; 20% $Pd(OH)_2$/C or W-7 Raney nickel under standard conditions, resulted, in nearly all cases, in the isolation of the dihydro derivatives **2a-e** as major products (Figure 1 and Table 1). ^1H and ^{13}C NMR data supported the structures assigned (Tables 2 and 3).

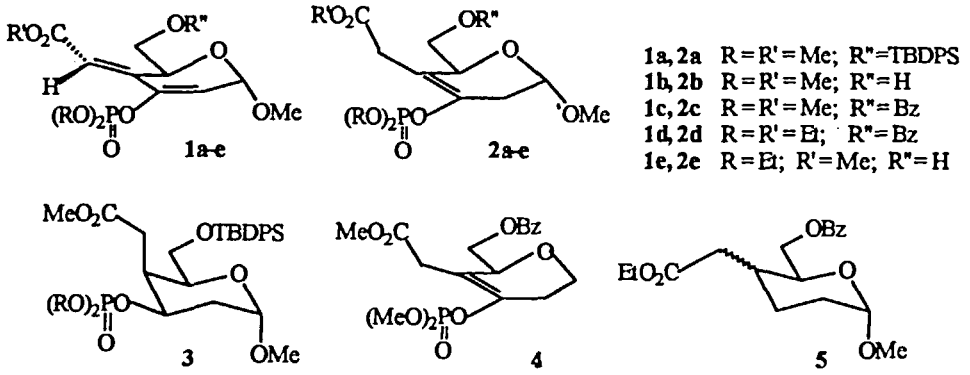


Figure 1

Table 1. Results of Heterogeneous Catalytic Hydrogenations of Compounds **1a-e.**

entry	Compd	HydrogenationConditions	Product	% Yield
1	**1a**	H_2 (350 kPa) / Pd 10 % (C); Raney nickel W-7 or $Pd(OH)_2$ 20 % (C) / EtOAc : MeOH 5 : 1	**2a**	77
2	**1a**	H_2 (333 kPa) / Raney nickel W-7 (excess) / MeOH	**2a**	44
			3	25
3	**1b**	H_2 (415 kPa) / Raney nickel W-7 / MeOH	**2b**	72
4	**1c**	H_2 (4275 kPa) / Pd 10 % (C); / EtOAc	**2c**	80
5	**1c**	H_2 (210 kPa) / $Pd(OH)_2$ 20 % (C); / HOAc	**4b**	71
6	**1d**	H_2 (188 kPa) / $Pd(OH)_2$ 20 % (C); / EtOAc	**2d**	68
7	**1d**	H_2 (362 kPa) / Raney nickel W-7 / EtOAc	**2d**	57
			5	35
8	**1e**	H_2 (224 kPa) / Pd 10 % (C); / EtOAc	**2e**	84

The ability of palladium to catalyze the migration of a double bond, especially when a tetrasubstituted olefin is formed, can explain the results obtained.[8, 9] Platinum, a more potent catalyst than palladium for reducing hindered double bonds, was considered, but the idea was dropped, since reductive cleavage of enol phosphate groups can take place with remarkable ease.[10]

Table 2 ^{1}H NMR Data for Compounds **2a-e**

Compd	H-1 ($^{3}J_{1,2}$)	H-2 ($^{2}J_{2,2'}$)	H-2' ($^{4}J_{P,2'}$)	H-5 ($^{3}J_{5,6}$)($^{3}J_{5,6'}$)	H-6,6'	H-7 ($^{2}J_{7,7'}$)	H-7'	OMe (C-1)
2a	5.08	2.31	2.42	4.19	3.71*	3.09	3.38	3.41
	(3.0)	(15.8)	(9.2)	(6.1) (8.9)		(16.2)		
2b	5.12	2.63	2.67	4.43*		3.12	3.40	3.44
	(0.3)	(16.8)	(10.2)			(16.3)		
2c	5.09	2.44	2.63	4.40*		3.09	3.38	3.41
	(1.3)	(16.4)	(9.7)			(14.8)		
2d	5.11	2.39	2.54	4.42*		3.08	3.38	3.41
	(2.1)	(16.5)	(9.5)			(15.8)		
2e	5.08	2.31	2.59	4.15	3.64; 3.76	3.05	3.39	3.41
	(1.8)	(17.8)	(10.6)	(6.0) (3.3)	$^{2}J_{6,6'}$ 11.8	(16.2)		

* Centre of multiplet of overlapping signals

Table 3 ^{13}C NMR Data for Compounds **2a,c-e**

Compd	C-1	C-2	C-3 ($^{2}J_{C,P}$)	C-4 ($^{3}J_{C,P}$)	C-5	C-6	C-7	C-8	OMe (C-1)
2a	98.0	31.3	145.5	114.9	68.0	66.0	30.0	170.7	55.5
			(6.6)	(11.2)					
2c	98.1	31.2	145.0	115.0	65.9	65.4	29.8	170.7	55.6
			(8.0)	(9.0)					
2d	98.0	31.4	144.9	114.7	65.3	60.7	29.7	170.2	55.6
			(7.6)	(8.3)					
2e	98.2	31.2	145.6	114.3	67.7	63.0	29.1	170.9	55.7
			(7.0)	(8.0)					

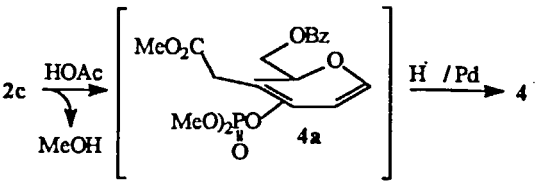
On the other hand, reduction of **1a** over large amounts of W-7 Raney nickel afforded, after HPLC chromatography, **2a** in 44% yield, together with the tetrahydro derivative, methyl 6-*O*-(*tert*-butyldiphenyl)silyl-2,4-dideoxy-4-*C*-[(methoxycarbonyl)-methyl]-3-*O*-(dimethoxyphosphoryl)-α-D-*lyxo*-hexopyranoside (**3**) in 25 % yield (entry 2). The ^{13}C NMR spectrum for the last compound did not show signals for olefinic carbons.

Qualitative analysis of its NOESY spectrum showed the existence of NOE between H-2 and H-7 and between H-3 and H-5, in agreement with the proposed structure, and *syn* addition of hydrogen from the more hindered side bearing an axial methoxy group at C-1. Loss of stereoselectivity of the reaction has been reported when an excess of catalyst is used.[11] The exocyclic double bond is the first site of hydrogen addition, and the axial orientation of the resulting chain at C-4 would induce the hydrogenation of the endocyclic double bond to give the tetrahydro derivative **3** with the *lyxo* configuration.

Even when the protecting group at OH-6 in compound **1a** was removed in an attempt to improve the adsorption of the substrate to the catalyst surface, only the dihydroderivative **2b** was obtained.

It has been reported that the use of relatively high hydrogen pressures and relatively small quantities of catalyst favour *cis* addition of hydrogen from the less hindered side of a double bond without isomerization.[12] However, hydrogenation of **1c** with 10% palladium-on-charcoal under high pressure gave only partially reduced **2c** (entry 4). Similar results were obtained for the hydrogenation of the dienic system in **1c** with a freshly reduced palladium-on-charcoal catalyst in glacial acetic acid[13] under 210 kPa, but, in this case, hydrogenolysis of the glycosidic linkage also occurred, and dihydropyran **4** was the only product isolated from the reaction mixture (Scheme 1 and entry 5). Compound **4** might be obtained through the glycal **4a**, formed *via* elimination of methyl alcohol from **2c** in acetic acid; in fact, glycal **4a** was detected by NMR after treatment of **2c** with glacial acetic acid at room temperature. Even when direct hydrogenolysis of allylic oxygenated substituents has been reported before, it was not taken into account because no hydrogenolysis was observed in any of the cases under study.

Similar results were obtained when catalytic hydrogenation using palladium catalysts was performed on the analogous ethyl enol phosphates **1d** and **1e** affording partially hydrogenated products **2d** and **2e** (entries 6-8), but in this case, reduction of **1d** on Raney nickel W-7 under normal conditions yielded also, as a minor component, the 1:1 mixture of diastereomeric hydrogenolysis products **5** (entry 7). Whereas the diethyl vinyl phosphate group in **1d** was removed to give the mixture **5**, dimethyl vinyl phosphate groups were resistant under all the conditions examined (entries 1-5). The effect of changing the nature of alkyl substituents in the phosphate group is unclear, but they may



Scheme 1

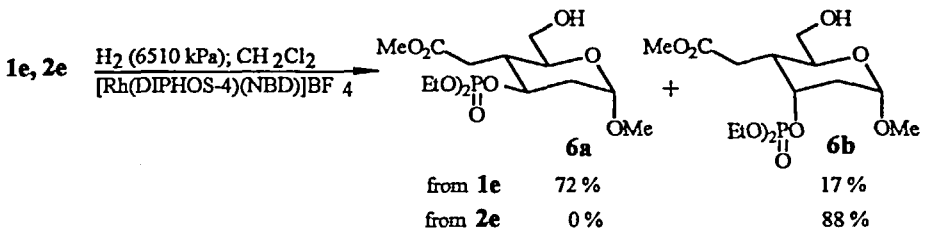
alter the steric requirements or influence the preferred mode of adsorption through anchor effects.

In view of these results, it was evident that isomerization was faster than hydrogenation for compounds **1a-e** when heterogeneous catalysts like palladium or nickel were used under all the conditions tested.

It has been reported that the rhodium hydride complex derived from [Rh(DIPHOS-4)(NBD)]BF_4 (Brown's catalyst)[14] is quite effective for hydroxy-directed hydrogenation of hydroxy olefins and some rather sterically hindered dienes.[15a-c] With this catalyst, homogeneous hydrogenation of chiral allylic and homoallylic olefins can be accomplished with a high degree of diastereoselectivity at high pressures, since at atmospheric pressure the rates of hydrogenation and olefin isomerization are similar.[15a] When this catalyst was employed for the hydrogenation of compound **1e** (6510 kPa, 6h), analysis by HPLC showed the formation, in 89% overall yield, of a 72:17 mixture of diastereomers characterised as methyl 2,4-dideoxy-3-*O*-(diethoxyphosphoryl)-4-*C*-[(methoxycarbonyl) methyl]-α-D-*arabino*-hexopyranoside (**6a**) and methyl 2,4-dideoxy-3-*O*-(diethoxy-phosphoryl)-4-*C*-[(methoxycarbonyl)methyl]-α-D-*ribo*-hexopyranoside (**6b**), respectively (Scheme 2).

No olefinic signals were observed in the ^{13}C NMR spectra of products **6a** and **6b**, indicating complete reduction, but the desired product **6b**, which has the required stereochemistry and suitable functionality present in the tetrahydropyran moiety of thromboxanes, was the one in minor proportion.

The stereochemistry of the products was determined on the basis of their ^1H NMR spectra (Table 4). For **6a**, a *trans* axial-axial three bonds coupling constant of 11.8 Hz



Scheme 2

Table 4. ^{1}H NMR Data for Compounds **6a** and **6b**

Compd	H-1	H-2	H-2'	H-3	H-4	H-5	H-6,6'	H-7	H-7'
	($^3J_{1,2}$)	($^3J_{2,3}$)	($^3J_{2',3}$)	($^3J_{3,4}$)	($^3J_{4,5}$)($^3J_{4,7}$)	($^3J_{5,6}$)		($^2J_{7,7'}$)	
		($^2J_{2,2'}$)		($^3J_{3,P}$)	($^3J_{4,7'}$)	($^3J_{5,6'}$)			
6a	4.81	1.62	2.17	4.42	2.11	3.78	3.46*	2.39	2.65
	(2.9)	(11.3)	(6.6)	(11.3)	(11.8)(9.6)	(2.8)		(16.4)	
		(12.5)		(4.7)	(4.0)	(5.7)			
6b	4.67	1.66	2.27	4.89	2.22	3.79	3.58*	2.67	2.44
		(4.7)	(2.0)	(0.0)	(11.0)(1.8)	(5.7)		(16.2)	
		(10.5)		(11.7)	(4.1)	(2.8)			

* Centre of multiplet of overlapped signals

between H-5 and H-4 was observed, indicating an equatorial orientation of the acetic acid chain at C-4 in a $^4C_1$ conformation; moreover, a significant NOE between H-5 and H-3 was also observed, suggesting the 1,3-diaxial orientation of these protons and, hence, equatorial orientation of the diethoxyphosphoryloxy group at C-3. In the same way, ^{1}H NMR spectra for compound **6b** showed a ^3J 11.0 Hz between H-5 and H-4, but in this case, no coupling between H-4 and H-3 was observed, indicating that H-3 is equatorially oriented and that the diethoxyphosphoryloxy group is axial. Additional proofs were obtained by the signals in the ^{13}C NMR spectra of **6b** (table 5), in which pyranose ring carbon atoms appear at higher field than the corresponding carbons of **6a**, in accord with its axially oriented diethoxyphosphoryloxy group.[16a, b]

Table 5. ^{13}C NMR Data for Compounds **6a** and **6b**

Compd	C-1	C-2	C-3 ($^2J_{C,P}$)	C-4 ($^3J_{C,P}$)	C-5	C-6	C-7	C-8	OMe (C-1)
6a	100.1	34.5	74.3 (5.5)	43.0 (7.5)	69.2	65.3	32.0	172.8	55.1
6b	98.4	33.1	71.8 (5.1)	40.1 (6.3)	67.9	66.0	30.1	173.0	55.8

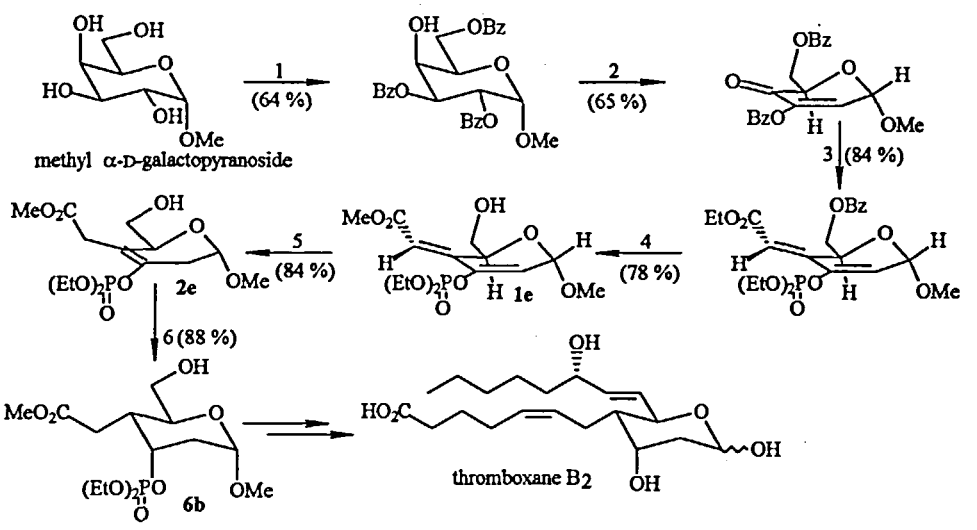
Hydroxyl-directed hydrogenation of the exocyclic double bond of **1e** proceeded with a high level of 1,3-asymmetric induction to give the *R*-configuration at C-4 of the pyranose ring in both products **6a** and **6b**. This result led us to consider the hydrogenation of the dihydroderivative **2e** to obtain the desired product **6b**, because in this compound both directing groups are in homoallylic position with respect to the endocyclic double bond. Hydrogenation of substrate **2e** (7240 kPa) gave a complete reversal of selectivity, and the fully functionalized tetrahydropyran **6b** was obtained in excellent yield (88%) after flash chromatography.

The synthesis of the tetrahydropyranoside **6b** in good overall yield from methyl α-D-galactopyranoside, (20%, scheme 3) is possible due to the stereoselectivity obtained by hydrogenation of compound **2e**. Compound **6b** may be a potentially suitable synthetic precursor of thromboxane analogs since it bears the stereochemistry and functionality of some key intermediates used in the synthesis of thromboxane B_2.[15a]

The chemistry of the construction of the chain appendixes in these structures is well known.[5]

EXPERIMENTAL

General methods. Column chromatography was performed on Silica Gel 60. TLC was carried out on precoated aluminum plates (0.1 mm) of Silica Gel 60 F-254; detection was effected by exposure to UV light and by spraying the plates with 5% (v/v) H_2SO_4 in



Scheme 3

ethanol, followed by heating. ^{1}H NMR spectra were recorded at 200.13 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 50.1 MHz in $CDCl_3$. Chemical shifts are given in ppm downfield from TMS. ^{31}P NMR spectra were recorded at 121.5 MHz in $CDCl_3$. Chemical shift are given in ppm from 85% H_3PO_4. IR spectra were recorded with an FT-spectrometer. FABMS (positive-ion mode from glycerol) spectra were obtained employing a ZAB-VSEQ hybrid mass spectrometer.

General procedure for heterogeneous catalytic hydrogenations. All reactions were performed using a standard Parr apparatus, at room temperature, with shaking. The initial pressure is detailed in each case. Palladium catalysts were purchased from Aldrich Chemical Co. and were prehydrogenated before use. Ethyl acetate was distilled over W-7 Raney nickel and methyl alcohol was dried by refluxing over magnesium metal prior to use. The reactions were monitored by TLC. After reaction, the catalyst was filtered off, and the solution was concentrated to a syrup, which was purified by column chromatography.

Methyl 6-*O*-(*tert*-Butyldiphenyl)silyl-2,4-dideoxy-4-*C*-[(methoxycarbonyl)-methyl]-3-*O*-(dimethoxyphosphoryl)-α-D-*glycero*-hex-3-enopyranoside (2a). A solution of **1a** (581 mg; 1.01 mmol) in 75 mL EtOAc:MeOH = 5:2 was treated with 0.43 g of 10% Pd/C under 350 kPa of H_2 for 3 h. After chromatographic purification, 0.45 g (0.77 mmol; 77%) of **2a** were obtained. $[\alpha]_D$ + 5.5° (*c* 1.35, $CHCl_3$). IR.: ν_{max} (cm^{-1}): 1738 (C=O, methoxycarbonyl); 1265 (P=O, phosphoryl). For ^1H and ^{13}C NMR data, see Tables 2 and 3.

Anal. Calcd for $C_{28}H_{39}O_9PSi$: C, 58.12; H, 6.79; Found: C, 58.56 H, 7.15.

Methyl 6-*O*-(*tert*-Butyldiphenyl)silyl-2,4-dideoxy-4-*C*-[(methoxycarbonyl)-methyl]-3-*O*-(dimethoxy phosphoryl)-α-D-*lyxo*-hexopyranoside (3). A mixture of 366 mg (0.63 mmol) of **1a** in 56 mL of MeOH and W-7 Raney nickel (5.86 g) was hydrogenated under 333 kPa of H_2 for 8 h. After HPLC purification (Nucleosil NH_2, (5 μm, 200 x 16 mm); hexane:EtOAc=1:1); two compounds were isolated and characterized as olefin **2a**.160 mg (44%) and tetrahydro derivative **3** (91 mg; 25%) as a minor component: $[\alpha]_D$ + 67.4° (*c* 0.89; $CHCl_3$). IR.: ν_{max} (cm^{-1}): 1742 (C=O, methoxycarbonyl); 1280 (P=O, phosphoryl). ^1H NMR δ 7.28-7.67 (m, 10 H, H_{aryl}), 4.85 (s, 1H, H-1), 4.62 (dt, 1H, $J_{3,4}$ =$J_{2',3}$ = 2.2 Hz, $J_{P,H}$ = 4.2 Hz, H-3), 3.74 - 3.85 (m, 3H, H-5,6,6'), 3.72 (s, 3H, O$C\underline{H}_3$ methoxycarbonyl), 3.67 (d, 3H, $J_{P,H}$ = 3.1 Hz, O $C\underline{H}_3$, methoxyphosphoryl), 3.65 (d, 3H, $J_{P,H}$ = 3.1 Hz, O$C\underline{H}_3$, methoxyphosphoryl), 3.50 (s, 3H, anomeric O$C\underline{H}_3$), 3.14 (m, 1H; H-4), 2.90 (dd, 1H; $J_{4,7'}$ = 3.1 Hz, $J_{7,7'}$ = 16.9 Hz; H-7'), 2.64 (dd, 1H, $J_{4,7}$ = 10.7 Hz; H-7'), 1.77 (dd, 1H, $J_{2',3}$ = 2.2 Hz, $J_{2,2'}$ = 10.1 Hz, H-2' (α)), 1.27 (d, 1H, H-2 (β)), 1.05 (s, 9H, (($C\underline{H}_3$)$_3$C); ^{13}C NMR; δ 172.03 ($\underline{C}$=O, C-8); 127.52 - 136.12 (C_{aryl}); 100.09 (C-1); 69.32 (C-3); 65.91 (C-5); 63.38 (C-6); 55.79 (anomeric O$C\underline{H}_3$); 54.95 and 55.06 (O$C\underline{H}_3$, methoxyphosphoryl), 51.81 (O$C\underline{H}_3$, methoxycarbonyl), 40.27 (C-4), 34.70 (C-2), 29.67 (C-7), 26.65 (($\underline{C}H_3$)$_3$C), 19.16 ((CH$_3$)$_3\underline{C}$).

Anal. Calcd for $C_{28}H_{41}O_9PSi$: C, 57.92; H, 7.12; Found: C, 58.06; H, 7.22.

Methyl 2,4-Dideoxy-4-*C*-[(methoxycarbonyl)methyl]-3-*O*-(dimethoxyphosphoryl)-α-D-*glycero*-hex-3-enopyranoside (2b).

a) Cleavage of (*tert*-butyldiphenyl)silyl group in 1a with fluoride; synthesis of 1b. A solution of **1a** (367 mg, 0.635 mmol) in $MeNO_2$ (1.7 mL) was treated with 2.0 mL of solution 0.38 M in 2,6-lutidinium fluoride and 0.57 M in tetrabutylammonium fluoride

in $MeNO_2$. After 3 h, the reaction mixture was diluted with dichloromethane (50 mL) and successively washed with 10% $KHSO_4$ w/v and 10% NaCl w/v. The organic layer was dried (Na_2SO_4), and filtered, and the filtrate was conentrated to dryness. After column chromatography (EtOAc:hexane = 3:1), the major product obtained was **1b** (0.82 g; 0.24 mmol; 38 %). $[\alpha]_D$ + 51.7° (*c* 1.42, $CHCl_3$); IR: ν_{max} (cm^{-1}): 3250 - 3620 (HO); 1730 (C=O, methoxycarbonyl); 1295 (P=O, phosphoryl). ^1H NMR δ 6.27* (s, 1H, H-1), 6.26* (s, 1H, H-7), 6.11 (s, 1H, H-2), 4.56 (m, 1H, H-5), 3.85 (s, 3H, $OC\underline{H}_3$ methoxycarbonyl), 3.59-3.81 (m, 2H, H-6,6'), 3.78 (s, 3H, $OC\underline{H}_3$ methoxyphosphoryl), 3.75 (s, 3H $OC\underline{H}_3$, methoxyphosphoryl), 3.53 (s, 3H, anomeric $OC\underline{H}_3$), 1.65 (HO). ^{13}C NMR δ 166.13 ($\underline{C}$=O, C-8); 141.83* (C-4); 141.25* (C-3); 117.98 (C-2); 113.49 (C-7); 95.24 (C-1); 68.34 (C-5); 64.58 (C-6); 56.14 (anomeric $O\underline{C}H_3$); 54.24 and 54.22 ($O\underline{C}H_3$, methoxyphosphoryl); 52.68 ($O\underline{C}H_3$, methoxycarbonyl). *The signals may be interchanged.

b) Catalytic hydrogenation of 1b with W-7 Raney nickel. Synthesis of 2b. A mixture of **1b** (593 mg; 1.75 mmol) in 60 mL of MeOH and Raney nickel W-7 (1.61 g) was shaken under 415 kPa. After 6 h the reaction mixture was processed in the usual way, and gave, after purification 426 mg (1.25 mmol; 72 %) of **2b**. $[\alpha]_D$ + 2.9° (*c* 1.20; $CHCl_3$). For ^1H NMR data see Table 2.

Anal. Calcd for $C_{12}H_{21}O_9P$: C, 42.36; H, 6.22; Found: C, 42.09; H, 6.03.

Methyl 6-*O*-Benzoyl-2,4-dideoxy-4-*C*-[(methoxycarbonyl)methyl]-3-*O*-(dimethoxyphosphoryl)-α-D-*glycero*-hex-3-enopyranoside (2c). A solution of **1c** (355 mg; 0.80 mmol) in EtOAc (60 mL) was hydrogenated under 4275 kPa in presence of 10% Pd/C (780 mg). After 4 h and using the procedure already described for workup, compound **2c** was obtained (0.28 g, 0.64 mmol; 80 %) as a syrup; $[\alpha]_D$ + 5.1° (*c* 1.31, $CHCl_3$). IR.: ν_{max} (cm^{-1}): 1727 (C=O, methoxycarbonyl); 1737 (C=O, benzoate); 1302 (P=O, phosphoryl). For ^1H and ^{13}C NMR data see Tables 2 and 3.

Anal. Calcd for $C_{19}H_{25}O_{10}P$: C, 51.36; H, 5.67; Found: C, 51.71; H, 5.58.

2-(*S*)-Benzoyloxymethyl-2,5-dihydro-3-methoxycarbonylmethyl-4-dimethoxyphosphoryloxy-2-H-pyran (4b). 361 mg of 20 % $Pd(OH)_2/C$ suspended in 45 mL of glacial HOAc were hydrogenated under 210 kPa during 30 min; then a solution of **1c** (294 mg; 0.66 mmol) in 22 mL of glacial HOAc was added. This mixture was hydrogenated under 280 kPa during 90 min and then poured into a mixture of dichloromethane (150

mL) and saturated solution of $NaHCO_3$ (200 mL). After using the same procedure reported previously, compound **4 b** was obtained (0.20 mg; 0.47 mmol; 71%). $[\alpha]_D$ - 29.9° (*c* 2.18, $CHCl_3$). HRMS, Mol. mass calcd for $C_{18}H_{24}O_9P$ (M + H) 415.3604, found 415.3603. ^1H NMR δ 7.34 - 8.05 (m, 5H, H_{aryl}), 4.40 (d, 2H, $J_{2,7} = J_{2,7'} = 5.3$ Hz, H-7, 7'), 4.27 (s, 2H, H-2, H-6'(α)), 4.05 (dt, 1H, $J_{5',6} = 4.6$ Hz, $J_{5,6} = 9.8$ Hz, $J_{6,6'} = 9.8$ Hz, H-6 (β)), 3.85 (d, 3H, $J_{P,H} = 0.6$ Hz, $OC\underline{H}_3$, methoxyphosphoryloxy), 3.79 (d, 3H, $J_{P,H} = 0.6$ Hz, $OC\underline{H}_3$, methoxyphosphoryloxy), 3.68 (s, 3H, $OC\underline{H}_3$ methoxycarbonyl), 3.20 (d, 1H, $J_{8,8'} = 21$ Hz, H-8'), 3.12 (d, 1H, H-8), 3.12 (m, 1H, $J_{5,5'} = 16.2$ Hz, H-5' (α)), 2.44 (dd, 1H, H-5 (β)). ^{13}C NMR δ 170.37 (<u>C</u>=O, C-9); 166.31 (<u>C</u>=O; benzoate); 140.39 (d; $J_{C,P}$ = 7,7 Hz; C-4); 128.32 - 133.05 (C_{aryl}); 114.92 (d; $J_{C,P} = 8.1$ Hz; C-3); 72.43 (C-2); 67.13 (C-6); 66.15 (C-7); 54.84 and 54.72 ($O\underline{C}H_3$, methoxyphosphoryloxy); 51.86 ($O\underline{C}H_3$, methoxycarbonyl); 31.66 (C-5); 29.95 (C-8).

Methyl 6-*O*-Benzoyl-2,4-dideoxy-4-*C*-[(ethoxycarbonyl)methyl]-3-*O*-(diethoxy phosphoryl)-α-D-*glycero*-hex-3-enopyranoside (2d). Compound **1d** (496 mg; 1.02 mmol) dissolved in 100 mL of EtOAc was treated with 356 mg of 20 % $Pd(OH)_2/C$ under 188 kPa during 5 h. After workup and chromatographic purification, compound **2d** (340 mg; 0.70 mmol; 68%) was obtained. $[\alpha]_D$ + 8.9° (*c* 3.53, $CHCl_3$). found: C, 54.65; H, 6.60. IR.: ν_{max} (cm^{-1}): 1730 (C=O, ethoxycarbonyl); 1720 (C=O, benzoate); 1280 (P=O, phosphoryl). ^{31}P NMR δ -6.16 (s; phosphoryl). For ^1H and ^{13}C NMR data see Tables 2 and 3.

Anal. Calcd for $C_{22}H_{31}O_{10}P$: C, 54.32; H, 6.42. Found: C, 54.65; H, 6.60.

Mixture of methyl 6-*O*-benzoyl-2,3,4-trideoxy-4-*C*-[(ethoxycarbonyl)methyl]-α-D-*erythro*-hexopyranoside and methyl 6-*O*-benzoyl-2,3,4-trideoxy-4-*C*-[(ethoxy carbonyl)methyl]-α-D-*threo*-hexopyranoside (5). Treatment of a solution of **1d** (625 mg; 1.29 mmol) in EtOAc (95 mL) with H_2 (362 kPa) in presence of W-7 Raney nickel during 8 h yielded, after the usual procedure, a mixture of diastereomeric products **5** (147 mg; 0.45 mmol; 35%). HPLC by Nucleosil-100, (5 μm; 250 x 8 mm) column; hexane: EtOAc = 4:1 (flow = 1.00 mL/min) as solvent and UV (260 nm) detection, showed a double signal with retention times of 3.02 min and 3.61 min. IR.: ν_{max} (cm^{-1}): 1737 (C=O, ethoxycarbonyl); 1716 (C=O, benzoate). ^1H NMR δ 7.35 - 8.10 (m, 5H, H_{aryl}), 4.67 and

4.54 (1H, H-1), 4.01-4.32 (m, 5H, H-5,6,6', $C\underline{H}_2O$ ethoxyl); 3.38 and 3.35 (s, 3H, $OC\underline{H}_3$, ratio 1.7:1), 1.47-2.66 (m, 7H, H-2,2', H-3,3', H-4,4', H-7,7'), 1.25 (t, 3H, $C\underline{H}_3$ ethoxyl). ^{13}C NMR δ 172.44 ($\underline{C}$=O, C-8), 166.40 ($\underline{C}$=O; benzoate), 128.35-133.78 (C_{aryl}), 101.00 and 99.86 (C-1), 67.31 and 66.62 (C-5); 66.36 ($\underline{C}H_2O$ ethoxycarbonyl); 60.42 and 60.27 (C-6); 54.75 and 54.66 ($O\underline{C}H_3$); 36.17; 35.29; 33.28; 27.21; 23.95; 22.11; 21.97 (C-2; C-3; C-4 and C-7); 14.20 ($\underline{C}H_3$, ethoxycarbonyl).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19; Found: C, 64.04; H, 6.98.

Methyl 2,4-Dideoxy-3-*O*-(diethoxyphosphoryl)-4-*C*-[*E*-(methoxycarbonyl) methylene]-α-D-*glycero*-hex-2-enopyranoside (1e). A solution of **1d** (1.7063 g; 3.52 mmol) in 85 mL of dried MeOH was treated with 454 mg (3.29 mmol) of dry K_2CO_3 during 20 h at room temperature and stirred in the dark under nitrogen. After neutralization (Amberlite IR-120), the resin was filtered and the filtrate was concentrated to dryness. After flash chromatography, 1.05 g (2.76 mmol; 78%) of **1e** were obtained. $[\alpha]_D$ + 46.9° (*c* 1.08, $CHCl_3$). IR.: ν_{max} (cm^{-1}): 3200 - 3650 (HO); 1720 (C=O); 1260 (P=O, phosphoryl). ^1H NMR δ 6.80 (d, 1H, $J_{1,2}$= 6.9 Hz, H-1), 6.57 (s, 1H, H-7), 6.47 (d, 1H, H-2), 4.59 (m, 1H, H-5), 3.88-4.06 (m, 4H, $C\underline{H}_2O$ diethoxyphosphoryl), 3.72 (d, 2H, $J_{5,6}$= $J_{5,6'}$= 5.0 Hz, H-6, 6'), 3.52 (s, 3H, $OC\underline{H}_3$ methoxycarbonyl), 3.35 (s, 3H, anomeric $OC\underline{H}_3$), 2.83 (s, 1H, HO), 1.01-1.08 (m, 6H, $C\underline{H}_3$ diethoxyphosphoryl). ^{13}C NMR δ 165.69 ($\underline{C}$=O, C-8), 141.61* (d, $J_{C,P}$ = 6.0 Hz, C-3), 140.98* (d, $J_{C,P}$= 5.0 Hz, C-4), 117.86 (d, $J_{C,P}$= 4.0 Hz, C-7), 113.48 (C-2), 95.35 (C-1), 68.49 (C-5), 64.95 and 64.92 ($\underline{C}H_2O$ ethoxyphosphoryl), 64.66 (C-6); 55.16 (anomeric $O\underline{C}H_3$), 51.69 ($O\underline{C}H_3$ methoxycarbonyl); 16.18 and 16.04 ($\underline{C}H_3$, ethoxyphosphoryl). *The signals may be interchanged.

Methyl 2,4-Dideoxy-3-*O*-(diethoxyphosphoryl)-4-*C*-[(methoxycarbonyl) methyl] -α-D-*glycero*-hex-3-enopyranoside (2e). A solution of **1e** (671 mg; 1.83 mmol) in 140 mL of EtOAc was treated with 10 % Pd/C (822 mg) under 224 kPa for 6 h. After workup and chromatographic purification, compound **2e** (0.57 g; 1.54 mmol; 84%) was obtained. $[\alpha]_D$ + 3.9° (*c* 0.78, $CHCl_3$). IR.: ν_{max} (cm^{-1}): 3450 (HO); 1740 (C=O, methoxycarbonyl); 1270 (P=O, phosphoryl). For ^1H and ^{13}C NMR data see tables 2 and 3.

Methyl 2,4-Dideoxy-3-*O*-(diethoxyphosphoryl)-4-*C*-[(methoxycarbonyl) Methyl]-α-D-*arabino*-hexopyranoside (6a) and its epimeric Methyl 2,4-Dideoxy-3-*O*-

(diethoxyphosphoryl)-4-*C*-[(methoxycarbonyl)methyl]-α-D-*ribo*-hexopyranoside (6b). To a dry glass 22 mL bomb were added 44.3 mg (58 μmol) of [Rh(DIPHOS-4)(NBD)]BF_4 and 261 mg (0.71 mmol) of **1e** in 20 mL of anhydrous dichloromethane (distilled from CaH_2), and the bomb was flushed with nitrogen. After several flushes with hydrogen (1500 kPa), the bomb was pressurized to 6514 kPa and stirred at room temperature for 6 h. The reaction solution was filtered through a silica gel plug, washing with ethyl acetate. After evaporation a chromatographic homogeneous syrup was obtained. Analytic HPLC (Nucleosil NH_2 (5μm of 200 x 16 mm) column; EtOAc), showed two products with retention times of 47.15 and 51.42 min and relatives areas of 72.10 and 16.77 %; which were characterized as **6a** and **6b**, respectively.

Compound **6b** was obtained in 88% yield from compound **2e** using the same procedure, under an initial pressure of H_2 of 7237 kPa, after HPLC purification by flash chromatography.

For **6a** :$[\alpha]_D$ + 103.5° (*c* 0.49, $CHCl_3$); IR.: ν_{max} (cm^{-1}): 3425 (HO); 1730 (C=O, methoxycarbonyl); 1280 (P=O, phosphoryl).

Anal. Calcd for $C_{14}H_{27}O_9P$: C, 45.41; H, 7.35; Found: C, 45.69; H, 7.51.

For **6b** : $[\alpha]_D$ + 143.7° (*c* 1.62, $CHCl_3$); IR.: ν_{max} (cm^{-1}): 3475 (HO); 1733 (C=O, methoxycarbonyl); 1290 (P=O, phosphoryl).

Anal. Calcd for $C_{14}H_{27}O_9P$: C, 45.41; H, 7.35; Found: C, 45.87; H, 7.70.

^1H and ^{13}C NMR data for **6a** and **6b**, see Tables 4 and 5.

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