Products from Furans. VII [1]. A General Route for the Synthesis of α-(1,2-*cis*) and β-(1,2-*trans*) Glycoconjugates *via* 1-*O*-Acyl and 1-*O*-Ethoxycarbonyl-2-azido-2,3-dideoxyglycopyranosides

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A methodology for the synthesis of 2,3,6-trideoxy- and 2,3-dideoxy-2-aminoglycosides is presented. 2,3-Dideoxyhex-2-enopyranos-4-uloses (named also as 2*H*-pyran-3(6*H*)-ones) were used for the synthesis of 1-*O*-acetyl, 1-*O*-ethyloxycarbonyl and 1-*S*-phenyl-2,3,6-trideoxy-(or 2,3-dideoxy)-2-azidoglycopyranosyl donors. Glycosidation of the above thio-ethers with a variety of alcohols in the presence of *N*-bromosuccinimide as activator yielded predominantly α-glycosides, while acetates afforded β-glycosides when TMSOTf was used as a promoter. The coupling of carbonates using tin tetrachloride or TMSOTf proved to be the most successful procedure, yielding the β-glycoside as the predominant product. Thus, glycoconjugates of aminosugars, steroids and aminoacids have been synthesized.

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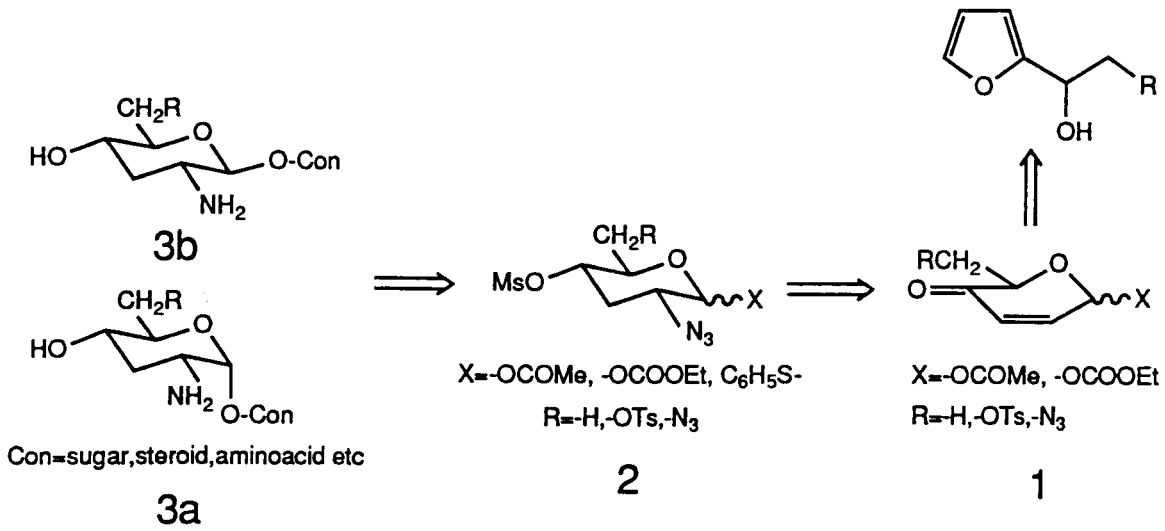
Introduction.

Glycoconjugates of deoxyaminosugars play an important role in the chemistry of life [2]. Glycoproteins [3], glycolipids [4] and aminosaccharides are responsible for the construction and properties of the cell membranes [5], while aminocyclitol antibiotics [6] and cardiac glycosides [7] are examples indicating the pharmacological significance of deoxyaminoglycosides. The orientation of the glycosidic bond (α or β) is crucial for the biological properties or the therapeutical value of the glycoconjugate. Since no universal method for glycosidation has been found, the availability of glycosyl donors is of great importance due to the central role of such reactions in organic synthesis, in assembling complex frameworks containing sugar or deoxyaminosugar moieties linked by α or β glycosidic bonds. It is also important to have various polydeoxy aminosugars available as starting materials for the synthesis of certain polydeoxy aminocyclitol antibiotics, since it is known [6] that they exhibit stronger activity against resistant bacteria than the oxygenated analogs. The preparation, however, of trideoxy or dideoxy aminosugars is generally a difficult synthetic task and several steps are usually required. On the other hand, glycosidation of aminosugars is a tedious procedure, since direct synthesis is not possible and blocking and deblocking of elaborate derivatives is necessary.

We present here a general route for the synthesis of 2-amino-2,3,6-trideoxy - (or 2,3-dideoxy) - glycopyranosyl conjugates with sugars, steroids or aminoacids. Our methodology is as follow (Scheme 1): A selected 6-acyloxy- or 6-ethoxycarbonyloxy-protected enone **1**, is first transformed to the desired azido-deoxy derivative **2**, which is subsequently coupled by a stereoselective glycosidation procedure to the target α or β glycoconjugate **3a** or **3b**. 2,3-Di-

Scheme 1



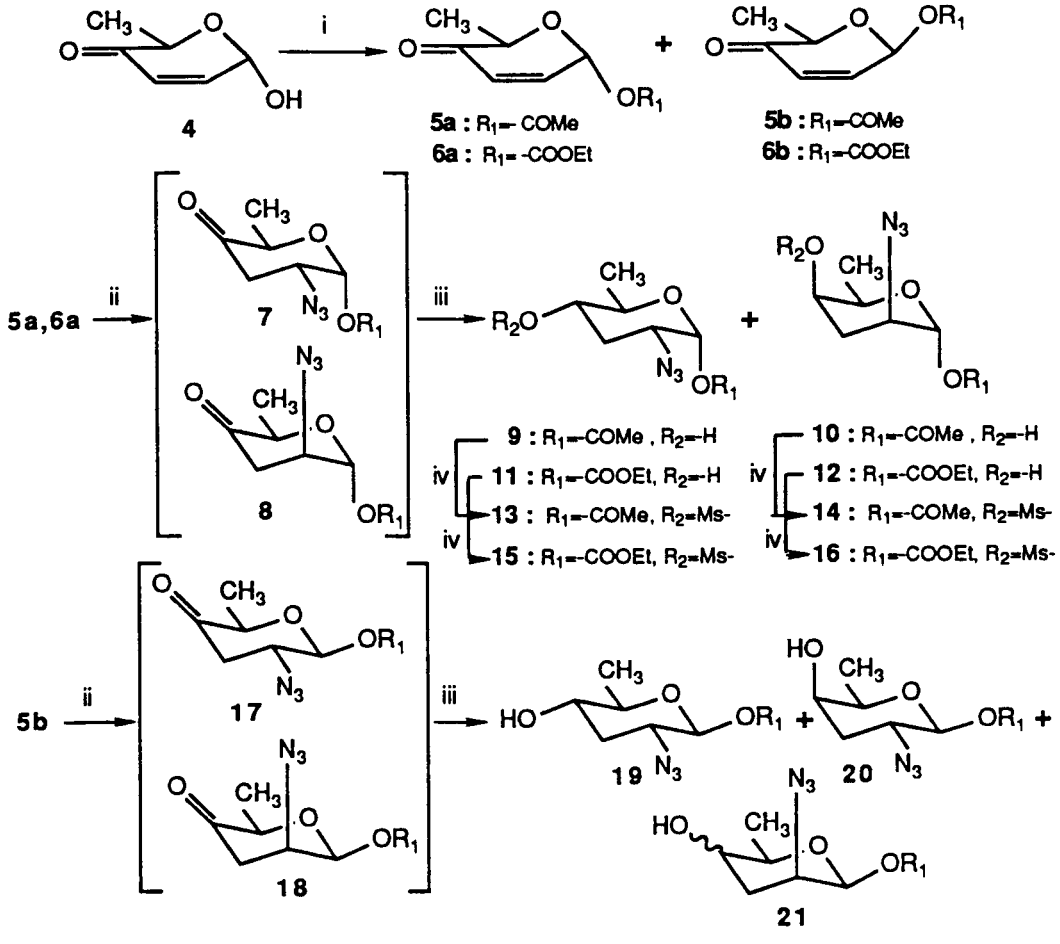
deoxyhex-2-enopyranos-4-uloses (named also as 2*H*-pyran-3(6*H*)-ones **1**, were selected as starting materials, since they are easily prepared from furfuryl alcohols and they give access to a variety of "deformed sugars" [1b-d,-8,9]. Some years ago we had proposed the use of **1** as promising substrates for selective glycosidations [10]. Since then, several methods have been developed for coupling 1-*O*-acyl-sugars [11] or their thio-aryl [12] and halo-derivatives [13] with alcohols. 1-*O*-Acyl-sugars, may also serve as substrates for the synthesis of *C*-glycosides [14]. The above methods have been successfully applied in our process. Furthermore, we have found that the 1-*O*-ethyl-oxycarbonyl group, which has been rarely used for glycosidations [15], can be easily coupled with an alcohol in the presence of a Lewis acid or TMSOTf as a promoter. Thus, the α-anomer of **2** (X = OCOOEt) stereoselectively furnished, β-glycosides with several glycosyl acceptors in high yield.

Results and Discussion.

Synthesis of Glycopyranosyl Donors.

Derivatives of the general formula **1** may be prepared either from carbohydrate precursors or by oxidative rearrangement of furyl carbinols [16]. The second route which is more versatile regarding the substitution at C-2, is usually used for the synthesis of series of analogs of biologically active compounds. It has to be noted that the biological screening of this type of compounds has been carried out on racemates. Thus, 2,3,6-trideoxy-DL-hex-2-enopyranos-4-ulose (2-methyl-2*H*-pyran-3(6*H*)-one), **4** (Scheme 2) was used as a model molecule for demonstrating our process. Acetylation of pure α-anomer of **4** yielded stereospecifically the α-anomer **5a**, (pyridine-acetic anhydride). The β-anomer **5b** was synthesized only as a mixture with **5a** (ratio 5:4), by the acetic anhydride/sodium acetate procedure. By increasing the temperature and the reaction

Scheme 2



Reagents : i) Ac_2O, AcONa, benzene or ClCOOEt, Et_3N, CH_2Cl_2 ; ii) NaN_3, AcOH, THF, H_2O ; iii) $NaBH_4$; iv) MsCl, Et_3N, CH_2Cl_2.

time, the formation of the β-anomer was favored but the total yield was lowered. The optimum conditions were found to be 1 hour at 60°. On the other hand, a mixture of carbonate anomers was prepared by treatment of **4** with ethyl chloroformate and triethylamine, yielding **6a** and **6b** in a ratio 3:1.

The stereochemical outcome of the attack of the azide anion on the enones **5a** and **6a** was the same as for the previously reported methyl hex-2-enopyranos-4-ulosides [17]. Treatment of **5a** with sodium azide in aqueous acetic acid, yielded in 5 minutes the kinetically favored product **8** which after several days at 0° was epimerized to the thermodynamicly favored product **7** (Figure 1). The ratio was stabilized after 6 days at 0° with no detectable by-products. Carrying out the reaction under conditions of kinetic control [17a] (in 1.7 *M* solution of hydrazoic acid in chloroform), isomer **8** was the sole isomer formed (Figure 2). However, under the above conditions, a number of by-products was also formed.

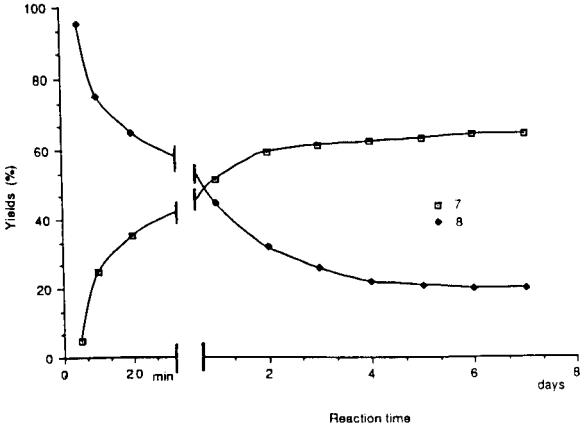


Figure 1: Relationship between yields of 7 and 8 and reaction time. The reaction of **5a**(100mg) with NaN_3 (110mg) in 1ml H_2O:AcOH (1:2) was performed in an NMR tube at room temperature for 1day and at 0°C for 6 more days beeing monitored by NMR spectroscopy. Calculations were based on the intergration of the angular Me.

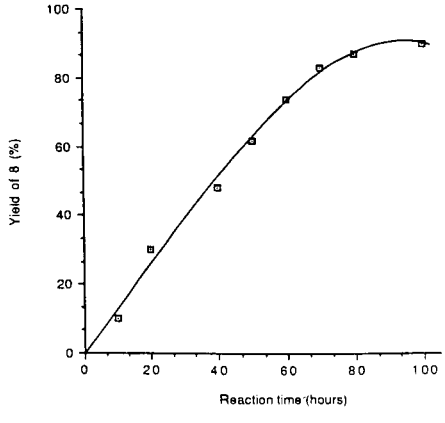


Figure 2 : Relationship between yield of 8 and reaction time. The reaction of **5a** (100mg) with 2ml of a $CDCl_3$ solution (~1.7M in NaN_3), was performed in an NMR tube at room temperature and was monitored as in Figure 1.

All the azide adducts were unstable, giving a retro-Michael reaction during work up. In order to avoid this transformation (retro-Michael), the carbonyl group was reduced *in situ* by sodium borohydride/methanol in the presence of acetic as a buffering agent.

The above reduction of **7** and **8** was found to be stereospecific in both cases (acetate and carbonate), yielding the arabino (**9**, **11**) and the lyxo (**10**, **12**) isomers. A more convenient solvent for the above azide addition and *in situ* reduction was found to be tetrahydrofuran/water, which results in the formation of both **9** and **10** (or **11** and **12**) in high yield (ratio 3:1).

The addition of the azide anion on the β-anomer **5b** was more stereoselective, furnishing in high yield the thermodynamically favored adduct **17** in tetrahydrofuran/water media (**17**:**18**, 9:1). However, the *in situ* reduction of **17** was not as stereoselective as for the α-anomer and a mixture of all possible stereoisomers was formed. The *arabino* product **19** was again the predominant one (**19**:**20**:**21**; 10:4:1. The two epimers of **21** were not separated).

Finally, mesylation of these deoxysugars afforded in high yield the target glycosyl donors **13** and **15**. It was found that the separation of the stereoisomers was more effective after the mesylation step. Thus, **13** was synthesized in 65% total yield from **4**, utilizing only one chromatographic purification and **15** in 52% total yield from **6a**. The yield of the latter compound, was lower because solvolysis of the carbonate was taking place to some extent during the reaction sequence.

The versatility of 1-*O*-acyl protected sugars is shown in Scheme 3. Solvolysis of the acetate **13** or the carbonate **15**, furnished almost quantitatively the anomeric mixture of hexopyranoses **22** and **23**. The latter pair of anomers may be considered as protected 2-amino-2,3,6-trideoxy-glycopyranosyl acceptors. The acyl derivatives can be also effectively transformed into thio-glycosides using thiophenol and tin tetrachloride as the catalyst. Thus, **24**, **26** and **27** were prepared from **13** in high yield (Scheme 3). In the case of **13** the reaction proceeded almost stereospecifically, yielding **24** in 92% yield and anomer **25** in only 3% yield. On the contrary, the *lyxo* analog **14** afforded both anomers **26** and **27** in a 1:1 ratio. The nmr chemical shifts and coupling constants of the *arabino* and *lyxo* compounds presented in this paper are tabulated in Tables II and III.

Glycosidation Procedures.

The above prepared glycosyl donors can be useful precursors for the synthesis of deoxyaminosugar conjugates, steroidal glycoconjugates, as well as glycoproteins. In order to demonstrate this we used the following glycosyl acceptors: methanol, *N*-carbobenzoxyserine methyl ester and methyl 2,3,4-tri-*O*-acetyl-α-D-glycoside as primary alcohols and androsterone (axial -OH) and *epi*-androsterone

Scheme 3

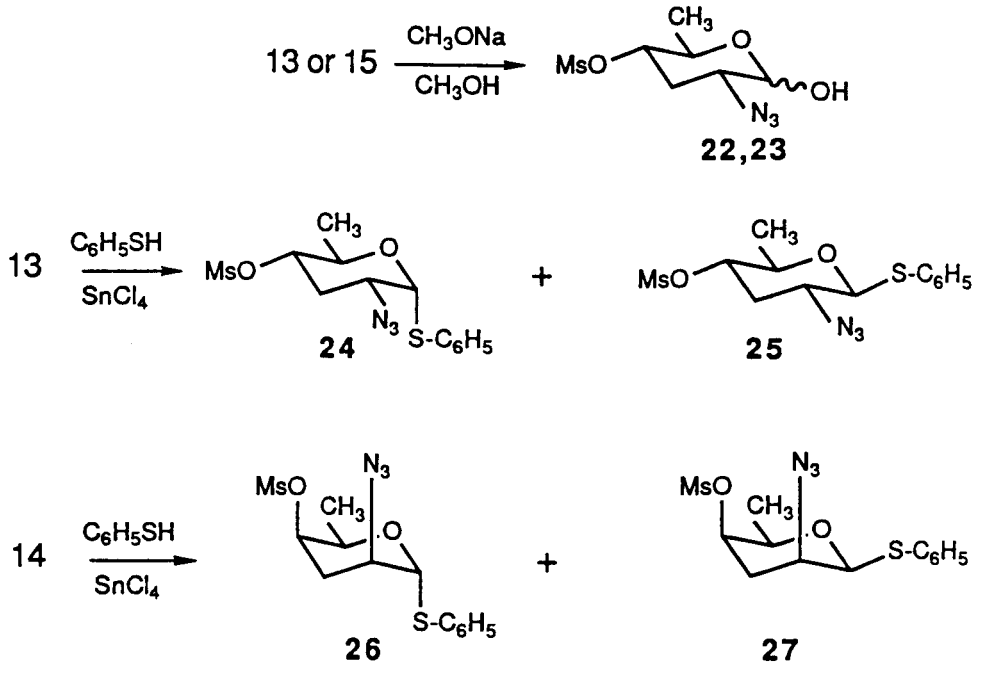
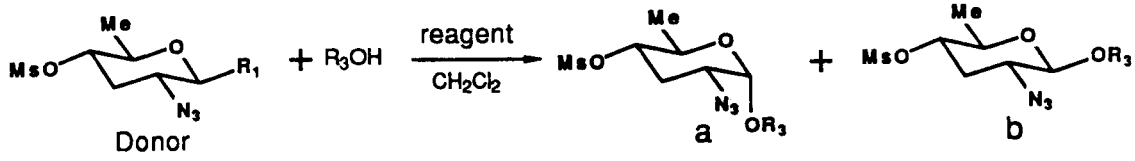
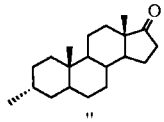
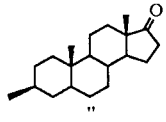
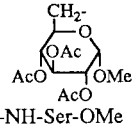


Table I

Glycosidations of **13**, **15** and **24** with Several Alcohols and Reagents

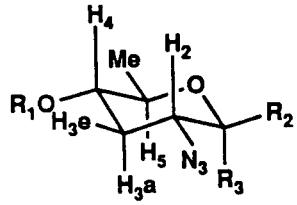


Entry	Donor	Alcohol R3	(eq)	Reagent	(eq)	Time in h	Yield %	Products [b]	(a:b)
1	**15**: R_1 = -OCOOEt		(2.5)	$SnCl_4$	(1.2)	4	86	**29a:29b**	(2:8)
2	"	"	(1.6)	"	(1.3)	4	75 [a]	"	
3	"	"	(0.8)	"	(0.8)	24	53 [a]	"	
4	"		(1.4)	TMSOTf	(1.4)	6	82	**29b**	
5	**13**: R_1 = -OAc	"	(1.4)	"	(1.2)	3	68	"	
6	**24**: R_1 = C_6H_5S-	"	(2.2)	NBS	(1.9)	0.3	81	**29a:29b**	(8:2)
7	**15**: R_1 = -OCOOEt		(1.5)	$SnCl_4$	(1.3)	3	74	**30a:30b**	(3:7)
8	**24**: R_1 = C_6H_5S-	"	(2.4)	NBS	(1.9)	0.3	85	**30a:30b**	(9.5:0.5)
9	**15**: R_1 = -OCOOEt	CH_3	(4.8)	$SnCl_4$	(1.7)	3	89	**31a:31b**	(4:6)
10	**24**: R_1 = C_6H_5S-	"	(6.5)	NBS	(1.2)	0.3	92	**31a:31b**	(6:4)
11	**15**: R_1 = -OCOOEt		(1.3)	$SnCl_4$	(1.3)	24	42 [a]	**32a:32b**	(3:7)
12	"	Z-NH-Ser-OMe	(1.4)	TMSOTf	(1.4)	6	76	**33a:33b**	(1:9)
13	**24**: R_1 = C_6H_5S-	"	(1.3)	NBS	(1.3)	0.3	62	**33a:33b**	(9:1)
14	**13**: R_1 = -OAc	"	(1.2)	TMSOTf	(1.4)	3	71	**33b**	

[a] Starting materials were detected on tlc. [b] The ratio is refered to the diastereomeric pair of anomers.

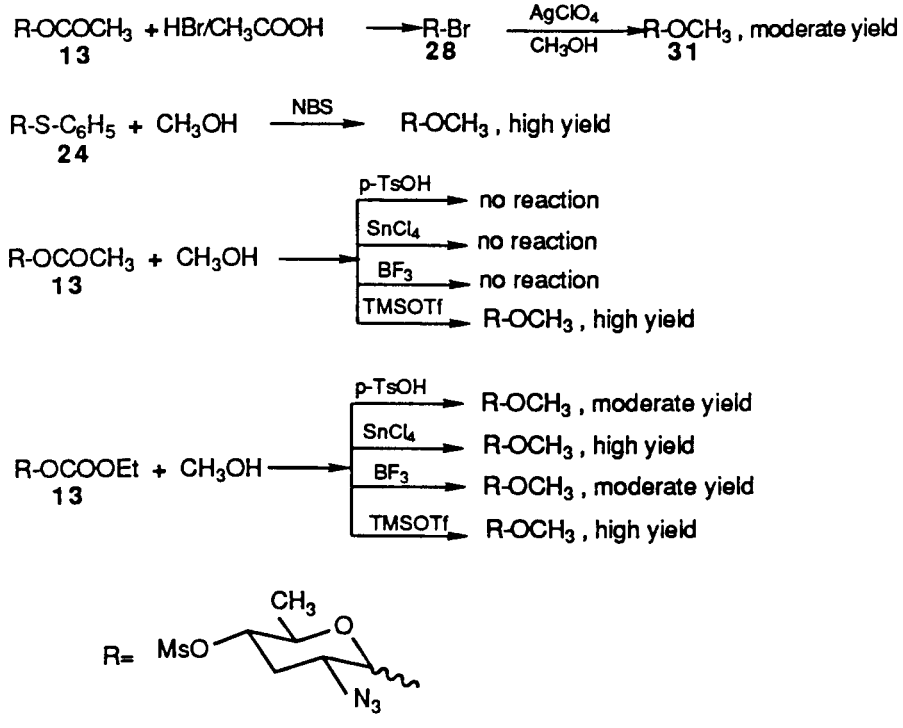
Table II

^{1}H NMR 400 MHz Chemical Shifts (ppm) and Coupling Constants (Hz) of *Ribo*-derivatives

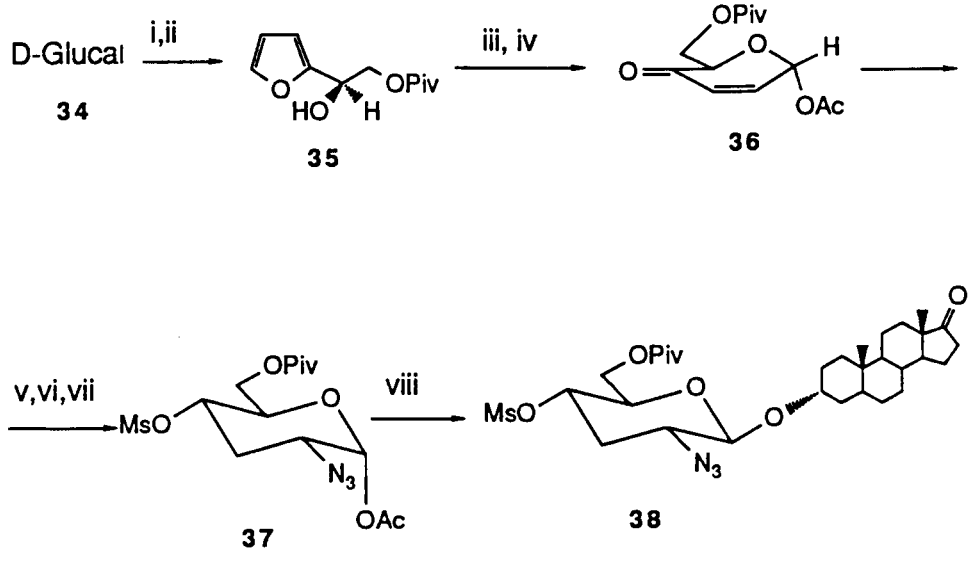


	R_2 = -H	H_2	H_{3e}	H_{3a}	H_4	H_5	Me	R_1	R_3
13	6.11 d $J_{1,2}$ = 3.6	3.48 d $J_{2,3e}$ = 4.1 $J_{2,3a}$ = 12.4	2.59 dt $J_{3e,3a}$ = 11.7 $J_{3e,4}$ = 4.5	2.24 q $J_{3a,4}$ = 11.2	4.38 dq $J_{4,5}$ = 9.8	3.86 dq $J_{5,Me}$ = 6.2	1.30 d	3.09 s R_1 = $MeSO_2$-	2.20 s R_3 = -OCOMe
15	5.96 d $J_{1,2}$ = 3.8	3.55 dt $J_{2,3e}$ = 4.5 $J_{2,3a}$ = 12.8	2.58 dt $J_{3e,3a}$ = 11.7 $J_{3e,4}$ = 4.7	2.25 q $J_{3a,4}$ = 11.2	4.38 dq $J_{4,5}$ = 9.8	3.93 dq $J_{5,Me}$ = 6.2	1.29 d	3.03 s R_1 = $MeSO_2$-	1.37t/4.28 q J = 7.2 R_3 = -OCOOEt
22	5.21 d $J_{1,2}$ = 3.5	3.31 dt $J_{2,3e}$ = 3.8 $J_{2,3a}$ = 12.5	2.47 dt $J_{3e,3a}$ = 12.0 $J_{3e,4}$ = 4.6	2.30 q $J_{3a,4}$ = 12.0	4.32 dq $J_{4,5}$ = 9.8	4.08 dq $J_{5,Me}$ = 6.2	1.28 d	3.08 s R_1 = $MeSO_2$-	1.7 bd R_3 = -OH
24	5.46 d $J_{1,2}$ = 4.8	3.94 dt $J_{2,3e}$ = 4.5 $J_{2,3a}$ = 12.5	2.54 dt $J_{3e,3a}$ = 12.1 $J_{3e,4}$ = 4.2	2.08 q $J_{3a,4}$ = 10.6	4.36 m $J_{4,5}$ = 9.0	4.36 m $J_{5,Me}$ = 5.8	1.31 d	3.08 s R_1 = $MeSO_2$-	7.20 m R_3 = C_6H_5S-
29a	4.85 d $J_{1,2}$ = 3.2	3.10 m	2.43 m	2.25 m	4.3 m	3.08 m $J_{5,Me}$ = 6.2	1.26 d	3.07 s R_1 = $MeSO_2$-	H3'/16': 3.9 m/2.4 q Me: 1.56 s/0.86 d R_3 = androsterone
30a	4.92 d $J_{1,2}$ = 3.4	3.11 m $J_{2,3a}$ = 11.5	2.43 m $J_{3e,3a}$ = 12.0 $J_{3e,4}$ = 4.5	2.89 q $J_{3a,4}$ = 11.2	4.31 dt $J_{4,5}$ = 10	4.08 dq $J_{5,Me}$ = 6.4	1.26 d	3.06 s R_1 = $MeSO_2$-	H3'/16': 3.9 m/2.4 q R_3 = epi-androsterone
31a	4.66 d $J_{1,2}$ = 3.2	3.4 m $J_{2,3e}$ = 4.8 $J_{2,3a}$ = 11.5	2.45 dt $J_{3e,3a}$ = 11.5 $J_{3e,4}$ = 4.8	2.26 q $J_{3a,4}$ = 11.2	4.3 m $J_{4,5}$ = 10	3.81 dq $J_{5,Me}$ = 6.4	1.29 d	3.06 s R_1 = $MeSO_2$-	3.47 s R_3 = -OMe
33a	4.74 d $J_{1,2}$ = 3.2	3.15 m	2.43 m	2.18 q $J_{3e,3a}$ = 11.5	4.3 m	3.75 m $J_{5,Me}$ = 6.2	1.23 d	3.04 s R_1 = $MeSO_2$-	Z-: 7.35 m, 5.14/OMe: 3.8 s NH-: 5.72, J = 7.5 4.58 m 1H, 4.05 m, 2H R_3 = *N*-Z-Ser-OMe
37	6.15 d $J_{1,2}$ = 3.2	3.5 m	2.7 dt $J_{3e,3a}$ = 11.5 $J_{3e,4}$ = 4.5	2.3 m	4.74 dq $J_{4,5}$ = 9.5	3.95 dt J_{5,CH_2} = 3.4	-CH_2- 4.3 m	3.09 s R_1 = $MeSO_2$-	2.15 s, R_3 = -OCOMe Piv = 1.25 s
19	5.47 d $J_{1,2}$ = 8.3	3.45 m $J_{2,3e}$ = 4.6 $J_{2,3a}$ = 10.8	2.36 dt $J_{3e,3a}$ = 12.6 $J_{3e,4}$ = 4.8	1.47 dt $J_{3a,4}$ = 12.4	3.45 m	3.45 m $J_{5,Me}$ = 5.8	1.29 d	2.1 bd R_1 = -H	2.15 s R_2 = -OCOMe
23	4.54 d $J_{1,2}$ = 8.1	3.34 dt $J_{2,3e}$ = 4.8 $J_{2,3a}$ = 11.3	2.65 dt $J_{3e,3a}$ = 12.4 $J_{3e,4}$ = 4.8	1.72 q $J_{3a,4}$ = 11.2	4.31 dq $J_{4,5}$ = 9.4	3.59 dq $J_{5,Me}$ = 6.2	1.38 d	3.09 s R_1 = $MeSO_2$-	1.58 bd R_2 = -OH
29b	4.35 d $J_{1,2}$ = 7.7	3.36 m $J_{2,3e}$ = 5.0	2.54 dt $J_{3e,3a}$ = 12.5 $J_{3e,4}$ = 5	1.61 overlapped	4.3 m	3.46 dm $J_{5,Me}$ = 6.4	1.32 d	3.03 s R_1 = $MeSO_2$-	H3'/16': 4.0 m/2.4 q Me: 1.56 s/0.83 d R_2 = androsterone
31b	4.21 d $J_{1,2}$ = 7.8	3.52 m $J_{2,3e}$ = 5.0 $J_{2,3a}$ = 12.5	2.55 dt $J_{3e,3a}$ = 12.5 $J_{3e,4}$ = 5.0	1.65 q $J_{3a,4}$ = 12.5	4.3 m $J_{4,5}$ = 9.5	3.51 dq $J_{5,Me}$ = 6.4	1.35 d	3.03 s R_1 = $MeSO_2$-	3.57 s R_2 = -OMe
33b	4.3 d $J_{1,2}$ = 7.5	3.35 m	2.55 m	1.95 q $J_{3e,3a}$ = 11.5	4.2 m	3.9 m $J_{5,Me}$ = 6.2	1.23 d	3.01 s R_1 = $MeSO_2$-	Z-: 7.35 m, 5.14/OMe: 3.8 s NH-: 5.72, J = 7.5 4.58 m 1H, 4.05 m, 2H R_3 = *N*-Z-Ser-OMe
38	4.35 d $J_{1,2}$ = 7.4	3.38 m	2.6 dt $J_{3e,3a}$ = 11.8 $J_{3e,4}$ = 4.8	1.65 overlapped	4.3 m	3.87 dt J_{5,CH_2} = 3.2	-CH_2- 4.3 m	3.09 s R_1 = $MeSO_2$-	H3'/16': 3.9 m/2.5 q Me: 1.55 s/0.82 d Piv = 1.25 s

Scheme 4



Scheme 5



Reagents : i) $HgSO_4$, 0.002M H_2SO_4 ; ii) PivCl, Et_3N, CH_2Cl_2; iii) NBS, THF/water 4/1, 0°, 10 min; iv) pyridine/ Ac_2O, 5°, overnight; v) NaN_3, water, THF, AcOH, overnight; vi) $NaBH_4$, MeOH 0° ; vii) MsCl, Et_3N, CH_2Cl_2, 5°, 1hour; viii) androsterone, CH_2Cl_2, TMSOTf, 0°–RT, 6hours.

(equatorial -OH) as secondary alcohols (Table I). In all the following glycosidation examples the glycosides which are prepared from the racemic mixtures **13**, **14** and **15** yield pairs of diastereoisomers. The evaluation of the reactivity of the above glycosyl donors and the yields of the synthesized α and β anomers is based on calculations on diastereomeric pairs. At the end of the paper (Scheme 5) there is an example applied on an optically pure donor.

The reactivity of the glycosyl donors prepared so far is depicted in Scheme 4. We were able to apply the classic Koenigs-Knorr reaction procedure in the case of **13** at controlled conditions, since the presence of the mesyl group makes the halogenation step difficult. Thus, bromination of **13** was performed with acetic acid/hydrobromic acid in low temperature without stirring. The resulting bromide was subsequently coupled with methanol in methylene chloride using silver carbonate as the catalyst, affording the methyl glycoside **29** in moderate yield (Scheme 4). Paulsen *et al* [13a], have reported a great number of applications concerning the glycosidation of 1-*O*-acetyl-2-azido-hexopyranoses *via* the bromide or the chloride intermediates.

Better results were obtained in the coupling of the thioether derivatives of the acetates. Thus, **24** gave predominantly the α-anomer of several conjugates, using *N*-bromosuccinimide as the activator [12a] (Table 1, entries 6, 8, 10 and 13).

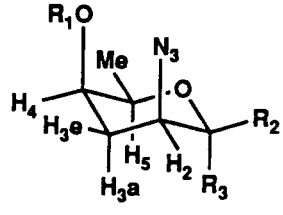
Conjugation of Acetates and Carbonates.

Though *p*-toluenesulfonic acid has been effectively used as catalyst for the glycosidation of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzylglucose with several donors [11b], it gave no reaction when applied to **13** (Scheme 4). Acetate **13** proved also inactive in the presence of Lewis acids, as has already been observed by other researchers in similar cases [18]. However, **13** proved to be a suitable glycosyl donor at the presence of TMSOTf as a promoter [11c], yielding selectively the β-glycoside (Table 1, entries 5, 14).

On the contrary, carbonates reacted easily either with *p*-toluenesulfonic acid or Lewis acids, as well as with TMSOTf (Scheme 4), yielding selectively the less thermodynamically favored β-anomer (Table 1). The best results were achieved with tin tetrachloride and TMSOTf. The reaction with tin tetrachloride was completed within 3 to 4 hours, when a 2.5-fold excess of the acceptor was used (Table 1, entry 1). When equimolecular amounts of both the donor and the acceptor or a slight excess of the acceptor was used, the starting material remained in the reaction mixture even though longer reaction times were utilized (Table I, entries 2, 7 and 11). On the contrary, when an excess of the donor was used, there was no complete

Table III

^{1}H NMR 400 MHz Chemical Shifts(ppm) and Coupling Constants (Hz) of *Lyxo*-derivatives



	R_2 = -H	H_2	H_{3e}	H_{3a}	H_4	H_5	Me	R_1	R_3
10	6.06 s $J_{1,2}$ = 0	3.58 bd	2.16 q $J_{3e,4}$ = 4.0	2.16 q $J_{3a,4}$ = 3.0	3.71 q $J_{4,5}$ = 1.4	4.02 dq $J_{5,Me}$ = 6.6	1.26 d	2.73 bd R_1 = H-	2.13 s R_3 = -OCOMe
14	6.08 s $J_{1,2}$ = 0	3.60 m $J_{2,3e}$ = 2.6 $J_{2,3a}$ = 4.2	2.47 m $J_{3e,3a}$ = 15.6 $J_{3e,4}$ = 2.9	2.32 dt $J_{3a,4}$ = 3.5	4.75 q $J_{4,5}$ = 1.9	4.18 dq $J_{5,Me}$ = 6.4	1.39 d	3.16 s R_1 = $MeSO_2$-	2.13 s R_3 = -OCOMe
16	5.91 s $J_{1,2}$ = 0	3.69 m $J_{2,3e}$ = 1.4 $J_{2,3a}$ = 4.0	2.48 m $J_{3e,3a}$ = 15.8 $J_{3e,4}$ = 1.5	2.37 dt $J_{3a,4}$ = 4	4.74 q $J_{4,5}$ = 1.7	4.22 dq $J_{5,Me}$ = 6.4	1.32 d	3.16 s R_1 = $MeSO_2$-	1.34 t/4.16 q J = 7.2 R_3 = -OCOOCH$_2$CH$_3$
26	5.48 s $J_{1,2}$ = 0	3.82 m $J_{2,3e}$ = 2.0 $J_{2,3a}$ = 3.8	2.47 dq $J_{3e,3a}$ = 15.8 $J_{3e,4}$ = 2.9	2.29 dt $J_{3a,4}$ = 4.1	4.76 q $J_{4,5}$ = 1.9	4.58 dq $J_{5,Me}$ = 6.4	1.31 d	3.15 s R_1 = $MeSO_2$-	7.4 m R_3 = C_6H_5S-
	R_3 = -H								R_2
27	4.85 d $J_{1,2}$ = 1.8	3.93 q $J_{2,3e}$ = 2.1 $J_{2,3a}$ = 4.2	2.75 dt $J_{3e,3a}$ = 16.0 $J_{3e,4}$ = 2.5	2.17 dt $J_{3a,4}$ = 4	4.72 m $J_{4,5}$ = 1.5	3.77 dq $J_{5,Me}$ = 6.4	1.39 d	3.18 s R_1 = $MeSO_2$-	7.4 m R_3 = C_6H_5S-

consumption of the acceptor (Table I, entry 3). The amount of the catalyst also plays an important role in the rate of the reaction and a slight excess (about 1.2 equivalents) was needed for higher yields. An excess of the acceptor and the catalyst was also found to be important in the case of TMSOTf for better results (Table I, entries 4 and 12).

Thus α-glycosides were prepared from thiophenyl donors and β-glycosides from acyl donors. The stereoselectivity was very good to excellent in both cases with the exception of methanol (see Table I).

Finally, the above methodology was applied to an optically active substrate (Scheme 5). D-Glucal was converted to 2-hydroxy-2-furylethanol employing the conditions described by Gonzalez *et al* [19]. Selective protection of the primary hydroxyl group with pivaloyl chloride gave compound **35**. Oxidation of **35** with *N*-bromosuccinimide [1d], and subsequent acetylation of the alcohol formed, yielded optically active 1-*O*-acetyl-6-*O*-pivaloyl-2,3-dideoxy-α-D-hex-2-enopyranos-4-ulose **36**. Treatment of **36** with sodium azide in tetrahydrofuran/water in the presence of acetic acid and *in situ* reduction with sodium borohydride as before, gave a mixture of epimers which was mesylated and the epimers were separated by column chromatography affording optically active **37** as the main product (overall yield from **35** 46%). Glycosidation of **37** with androsterone using TMSOTf as a promoter, afforded β-glycoside **38** in 73% yield.

We are now investigating all the reaction parameters in order to achieve better stereoselectivity in an effort to apply this methodology using other glycosyl donors.

Conclusion.

1-*O*-Acetyl, 1-*O*-ethyloxycarbonyl and 1-*S*-aryl-2-azido-glycopyranosyl donors have been stereoselectively synthesized in high yields. Glycosidation of steroid, sugar and aminoacid glycosyl acceptors afforded stereoselectively the α- or β-anomers. Carbonates gave very satisfactory results. Thus, 1-*O*-Ethyloxycarbonyl may be proved to be a suitable protective group for a glycosyl donor in selective glycosidations.

EXPERIMENTAL

General Methods.

All melting points are in degrees centigrade and were determined in open capillary tubes with a Buchi melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian 60 MHz spectrometer (Model 360 EM) or on a Bruker instrument (400 MHz), in deuteriochloroform. Chemical shifts are reported in parts per million from tetramethylsilane as an internal reference (δ 0.00). The coupling constants are given in Hertz. Infrared (ir) spectra were obtained on a Perkin-Elmer Model 283B infrared spectrophotometer. Mass spectra and elemental analysis were performed at the University of Thessaloniki, Greece.

Commercial sodium borohydride 98% (Merck), androsterone, epi-androsterone (Aldrich), TMSOTf (Sigma) and tin tetrachloride (Merck) were used without further purification. Tetrahydrofuran, pyridine, acetic anhydride, thiophenol, mesyl chloride, triethylamine and ethyl chloroformate were distilled before use. Methylene chloride was distilled from calsium hydride and kept over 4 Å molecular sieves. *N*-Bromosuccinimide used for glycosidations was recrystallized from benzene. Methyl 3,4,5-tri-*O*-acetyl-6-*O*-trityl-α-D-glycopyranoside was detritylated in formic acid:ethyl ether 1:1, at room temperature for 1 hour.

All reactions were monitored by thin layer chromatography (tlc), carried out on silica precoated plates with fluorescent indicator UV_{254} (Merck). Chromatographic separations were performed on columns packed with silica (Merck). Yields refer to chromatographically and spectroscopically (^{1}H nmr) homogeneous materials, unless otherwise stated.

6-Hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one **4**.

2-Acetylfuran (30 g) was reduced with lithium aluminum hydride in tetrahydrofuran-ether. The crude 2-furfuryl alcohol was treated with *N*-bromosuccinimide according to the literature [1d] to yield a yellow oil, which was chromatographed with ether-hexane 1:1 as the eluant.

Pure α-anomer **4** (18 g, yield 52% based on acetylfuran) was obtained after evaporation of the solvents containing the faster moving spot (Rf = 0.26), as a pale yellow oil, which afforded large white needles from ether-hexane, after standing for several days at −5°, mp 62-63° (lit 62-65°); ir (potassium bromide): ν max (cm^{-1}) 3390 bd [-OH], 1700 [conj ketone], 1090, 1000 [COC], 2990, 2930; ^{1}H nmr: (400 MHz) δ 6.90 (dd, 1H, H-5, $J_{5,6}$ = 3.4, $J_{4,5}$ = 10.2], 6.11 [d, 1H, H-4, $J_{4,6}$ = 0], 5.64 [d, 1H, H-6], 4.72 [q, 1H, H-2, J = 6.8], 3.35 [bd, 1H, -OH], 1.4 [d, 3H, Me].

The slower moving spot (Rf = 0.20) was the β-anomer of **4** which was contaminated with the α-anomer and could not be crystallized, yield 15% (based on acetylfuran); ir (neat): ν max (cm^{-1}) 3385 bd [-OH], 1700 [conj ketone], 1090, 1010 [COC], 2990, 2935; ^{1}H nmr: (400 MHz) δ 6.95 [dd, 1H, H-5, $J_{5,6}$ = 1.4, $J_{4,5}$ = 10.0], 6.16 [dd, 1H, H-4, $J_{4,6}$ = 1.6], 5.68 [m, 1H, H-6], 4.24 [dq, 1H, H-2], J = 6.7, $J_{2,6}$ = 1.2], 3.63 [bd, 1H, -OH], 1.46 [d, 3H, Me].

6-Acetyloxy-2-methyl-2*H*-pyran-3(6*H*)-one **5a** and **5b**.

In 200 ml of benzene was added **4** (10 g, 0.078 mole), powdered sodium acetate (7 g, 0.084 mole) and acetic anhydride (50 ml). The mixture was heated at 60° for 1 hour. Then it was allowed to cool down and poured into an ice-water-sodium carbonate solution and extracted with ether. The organic layer was washed with saturated ammonium chloride, brine, dried and evaporated to yield an oil. Column chromatography with ether:hexane 3:7 as the eluant, gave two compounds:

The faster moving compound (Rf = 0.25) was the α-anomer **5a**. White crystals of **5a** (6 g, yield 45%) were obtained from ether-hexane, mp 36-37°; ir (potassium bromide): ν max (cm^{-1}) 1755, 1220, 1170 [acetate], 1700, 1590 [conj ketone], 2880, 2995, 2945; ^{1}H nmr: (400 MHz) δ 6.89 [dd, 1H, H-5, $J_{5,6}$ = 3.2, $J_{4,5}$ = 10.2], 6.49 [d, 1H, H-6, $J_{4,6}$ = 0], 6.23 [d, 1H, H-4], 4.61 [q, 1H, H-2, J = 6.7], 2.11 [s, 3H, -COMe], 1.42 [d, 3H, Me]; ms: m/e (relative intensity), 170 (1), 111 (20), 126 (50), 43 (51), 84 (100).

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.78; H, 6.10.

The lower moving compound (Rf = 0.23) was the β-anomer **5b**. White crystals of **5b** (5 g yield 38%) were obtained from ether-hexane, mp 26-28°; ir (potassium bromide): ν max (cm^{-1}) 1755, 1220, 1120 [acetate], 1700 [conj ketone], 2880, 2995, 2945; ^1H nmr: (400 MHz) δ 6.89 [dd, 1H, H-5, $J_{5,6}$ = 2.4, $J_{4,5}$ = 10.2], 6.56 [m, 1H, H-6], 6.24 [dd, 1H, H-4, $J_{4,6}$ = 0.9], 4.39 (q, 1H, H-2, J = 7.0], 2.16 [s, 3H, -COMe], 1.50 [d, 3H, Me]; ms: m/e (relative intensity), 170 (1), 111 (93), 126 (29), 43 (100), 84 (100), 29 (44).

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.60; H, 6.17.

Preparation of **5a**.

Compound **4** (4 g, 0.031 mole) was added in a solution of 20 ml of acetic anhydride and 24 ml of pyridine. The mixture was allowed to stand for 24 hours at 7°. The redish reaction mixture was poured into 300 ml of ice-water and extracted with ether (3 x 100 ml). After successive washings of the combined organic layers with 0.5*N* hydrochloric acid, water, saturated sodium bicarbonate, saturated ammonium chloride and brine, decoloration with Norite and evaporation of the solvents, 4.6 g of a colorless oil was collected. This oil, was crystallized as before yielding 4.4 g of white crystals of analytically pure **5a** (yield 83%).

6-[[(Ethyloxy)carbonyl]oxy]-2-methyl-2*H*-pyran-3(6*H*)-one **6a** and **6b**.

Compound **4** (15 g, 0.117 mole) was dissolved in 300 ml of methylene chloride. Triethylamine (22 ml, 0.218 mole) and ethyl chloroformate (15 ml, 0.139 mole) were added portionwise at 0-5°. After half an hour the mixture was successively washed with water, saturated sodium bicarbonate, saturated ammonium chloride and brine and the oil residue was chromatographed with ethyl acetate:hexane 2:8.

The fractions with the faster moving spot (Rf = 0.5, ether:hexane 1:1) gave after evaporation of the solvent 15 g (yield 64%) of compound **6a** as a colorless oil; ir (neat): ν max (cm^{-1}) 1750, 1250 [OCOO], 1700, [conj ketone], 2980, 2940; ^1H nmr: (60 MHz) δ 6.8 [dd, 1H, H-5, $J_{5,6}$ = 3.2, $J_{4,5}$ = 10.2], 6.15 [d, 1H, H-6], 6.0 [d, 1H, H-4, $J_{4,6}$ = 0], 4.5 [q, 1H, H-2, J = 6.5], 4.15 [q, 2H, $-CH_2-$, J = 6.8], 1.45 [d, 3H, Me], 1.3 [t, 3H, Me(Et)].

Anal. Calcd. for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 54.22; H, 5.93.

Fractions with the slower moving spot (Rf = 0.3) gave 1.5 g (yield 6.4%) of compound **6b** as pale yellow oil; ir (neat): ν max (cm^{-1}) 1750, 1250 [OCOO], 1700, [conj ketone], 2950, 2940; ^1H nmr: (60 MHz) δ 6.8 [dd, 1H, H-5, $J_{5,6}$ = 2.4, $J_{4,5}$ = 10.2], 6.2 [dd, 1H, H-6, $J_{4,6}$ = 1.2], 6.05 [dd, 1H, H-4], 4.3 [m, 1H, H-2], 4.1 [q, 2H, $-CH_2-$, J = 6.8], 1.45 [d, 3H, Me], 1.3 [t, 3H, Me(Et)].

1-*O*-Acetyl-2-azido-2,3,6-trideoxy-α-DL-*ribo*-hexopyranose **9** and 1-*O*-Acetyl-2-azido-2,3,6-trideoxy-α-DL-*lyxo*-hexopyranose **10**.

Compound **5a** (5.5 g, 0.032 mole) was dissolved in 250 ml of tetrahydrofuran at 5° followed by addition of 30 ml of glacial acetic acid. Twenty-five ml of aqueous sodium azide solution (6 g, 0.086 mole) was added dropwise to the reaction mixture. After stirring for 24 hours at room temperature the mixture was cooled to 0° and sodium borohydride (about 3 g) was added portionwise with vigorous stirring. The reaction was monitored on tlc. When the spot of the previous product (Rf = 0.7) had disappeared, the mixture was extracted with ether, the organic layer was washed with water, saturated sodium bicarbonate, saturated ammonium chloride and brine and the oily residue was chromatographed with ether-hexane (3:7) as the eluant. Two products were separated:

Compound **9** was obtained as a colorless oil (3.05 g, yield 44%), Rf = 0.5 in ether:hexane 1:1, two passes; ir (neat): ν max (cm^{-1}) 3450 bd [-OH], 2103 [$-N_3$], 1750 [acetate], 2980, 2910; ^1H nmr: (60 MHz) δ 5.6 [d, 1H, H-1, $J_{1,2}$ = 3.2], 3.6 [bd, 1H, -OH], 2.0 [s, 3H, COMe], 1.2 [d, 3H, Me, J = 5.9]; ms: m/e (relative intensity), 144 (1), 127 (1), 43 (100) 57 (100), 81 (13).

Compound **10** was obtained as white crystals from ether:hexane (2.45 g, yield 35%), Rf = 0.46, mp 52-54°; ir (potassium bromide): ν max (cm^{-1}) 3500 bd [-OH], 2100 [$-N_3$], 1740 [acetate], 2980, 2930; ^1H nmr: see Table III; ms: m/e (relative intensity), 144 (2), 127 (7), 43 (100), 57 (80), 81 (40), 72 (52).

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.40; H, 6.22; N, 19.47.

1-*O*-Acetyl-2-azido-2,3,6-trideoxy-β-DL-*ribo*-hexopyranose **19** and 1-*O*-Acetyl-2-azido-2,3,6-trideoxy-β-DL-*xylo*-hexopyranose **20**.

Compound **5b** (2.25 g, 0.013 mole) was treated as before. Column chromatography (ether:hexane 1:1) gave three compounds:

Compound **19** (1.5 g, yield 53%) was obtained as white crystals from ether:hexane, mp 68-69°; ir (potassium bromide): ν max (cm^{-1}) 3450 bd [-OH], 2104 [$-N_3$], 1760 [acetate], 2990, 2940; ^1H nmr: see Table II; ms: m/e (relative intensity), 144 (3), 127 (5), 43 (100), 57 (80), 81 (30).

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.55; H, 6.16; N, 19.26.

Compound **20** (0.57 g, yield 20%) was obtained as white crystals from ether:hexane, mp 15-17°; ir (neat): ν max (cm^{-1}) 3550 bd [-OH], 2110 [$-N_3$], 1760 [acetate], 2990, 2940; ^1H nmr: (60 MHz) δ 5.6 [d, 1H, H-1], $J_{1,2}$ = 8.6], 3.5 [m, 2H, H-2, H-4], 3.8 [q, 1H, H-5, $J_{5,Me}$ = 6.2], 2.7 [bd, 2H, H-3e, -OH], 1.9 [s, 3H, COMe], 1.2 [d, 3H, Me]; ms: m/e (relative intensity), 144 (1), 127 (5), 43 (100), 57 (40), 81 (50), 72 (60).

Compound **21** (0.06 g, yield 2.5%) was obtained as colorless oil and was a mixture of two isomers; ir (neat): ν max (cm^{-1}) 3500 bd [-OH], 2100 [$-N_3$], 1750 [acetate], 2990, 2930; ^1H nmr: (60 MHz) δ 5.6 [d, 1H, H-1, $J_{1,2}$ = 3.2], 1.9 [s, 3H, COMe], 1.2 [two d, 3H, Me, J = 6.2]; the other peaks were unresolved. From the coupling constant of H-1 and the multiplicity of the angular methyl peek at 1.2 ppm, it was assumed that **21** was a mixture of epimers at C-4.

1-*O*-Acetyl-2-azido-4-*O*-mesyl-2,3,6-trideoxy-α-DL-*ribo*-hexopyranose, **13**.

Compound **9** (0.65 g) was dissolved in 35 ml of methylene chloride at 0°. Triethylamine (2 ml) and mesyl chloride (1 ml) were added. The reaction was stirred for 1 hour at 5°. The mixture was diluted with ether. The organic layer was washed to neutrality and after evaporation of the solvents, a yellow oil was obtained, which afforded 0.72 g of white crystals from ethyl acetate-ether-hexane, yield 81%, mp 129-130° dec at 124°; ir (potassium bromide): ν max (cm^{-1}) 1756, 1220 [acetate], 2107 [$-N_3$], 1325, 1172, 940 [Ms], 2990, 2940, 2910; ^1H nmr: see Table II.

Anal. Calcd. for $C_9H_{15}N_3O_6S$: C, 36.86; H, 5.15; N, 14.33. Found: C, 37.03; H, 5.05; N, 14.30.

Preparation of **13** from **5a**.

Compound **5a** (2.3 g, 0.0135 mole) was dissolved in 17 ml of glacial acetic acid at 5°. Ten ml of aqueous sodium azide (3 g, 0.043 mole) was added dropwise to the mixture. The reaction was left seven days at 7°. The mixture was diluted with ethanol (10 ml). Sodium borohydride (about 1.5 g) was added in portions with

vigorous stirring while the temperature was kept below 5°. After the end of the reaction was confirmed (tlc), the mixture was treated in the conventional manner and the oil residue obtained was dissolved in 70 ml of methylene chloride at 0°. Triethylamine (4 ml) and mesyl chloride (2 ml) were added and the reaction was treated as before. Column chromatographic separation (ethyl acetate:hexane 1:1) of the oily residue gave two compounds:

White crystals (2.65 g, total yield from **5a** 58%) of **13** were obtained as before.

White crystals of **14** (0.55 g, yield 12%) were obtained from ethyl acetate:hexane, mp 117-118°; ir (potassium bromide): ν max (cm^{-1}) 1750 (acetate), 2097 [$-N_3$], 1335, 1170 [Ms], 2990, 2940; ^1H nmr: see Table III.

Anal. Calcd. for $C_9H_{15}N_3O_6S$: C, 36.86; H, 5.15; N, 14.33. Found; C, 37.03; H, 5.05; N, 14.30.

Preparation of **15** from **6a**.

Compound **6a** (15 g, 0.075 mole) was dissolved in 300 ml of tetrahydrofuran and 60 ml of acetic acid. Thirty ml of an aqueous solution of sodium azide (20 g, 0.29 mole) was added portionwise at 0°. The reaction was stirred for 8 hours at room temperature and treated as before, yielding after column chromatographic separation with hexane:ether 6:4, three products in order of elution:

2-Azido-4-*O*-mesyl-2,3,6-trideoxy-β-DL-*ribo*-hexopyranose **(23)** (2.5 g, yield 13%) was obtained as a colorless oil; see next preparation for characterization of **23**.

1-*O*-Carbamoyl-2-azido-4-*O*-mesyl-2,3,6-trideoxy-α-DL-*ribo*-hexopyranose **(15)** (13.5 g, yield 56%) was obtained as a colorless oil which solidified upon freezing, mp 25-30°; ir (neat): ν max (cm^{-1}) 1755, 1255 [OCOO], 2100 [$-N_3$], 1340, 1172 [Ms], 2985, 2940, 855; ^1H nmr: see Table II.

Anal. Calcd. for $C_{10}H_{17}N_3O_7S$: C, 37.15; H, 5.30; N, 13.00. Found: C, 37.36; H, 5.13; N, 13.12.

1-*O*-Carbamoyl-2-azido-4-*O*-mesyl-2,3,6-trideoxy-α-DL-*lyxo*-hexopyranose **(16)** (0.39 g, yield 1.6%) was obtained as a colorless oil; ir (neat): ν max (cm^{-1}) 1752 [OCOO], 2103 [$-N_3$], 1340, 1170 [Ms], 2990, 2930, 855; ^1H nmr: see Table III.

Solvolysis of **13** and **15**.

Compound **13** (100 mg) was suspended in 20 ml of methanol. Sodium methoxide (1/20 equivalent was added and the mixture was stirred at room temperature for 3 hours. The reaction was neutralized with carbon dioxide and concentrated. Ether was added and the mixture was filtered and concentrated to yield 80 mg (yield 93%) of a colorless oil, homogeneous on tlc (Rf = 0.4, ether:hexane 4:6), which on ^1H nmr proved to be a mixture of α-**22** and β-**23** anomers (ratio between **22** and **23**, 3:1); ir (neat): ν max (cm^{-1}) 3320 bd [-OH], 2103 [$-N_3$], 1350, 1172, 940 [Ms], 1100, 1130 [COC], 2990, 2925, 825; ^1H nmr: see Table II (assignment was made on the ^1H nmr from the mixture).

The same process was followed for **15**, which afforded mixture of anomers **22** and **23** in 93% yield.

Phenyl 2-Amino-4-*O*-mesyl-2,3,6-trideoxy-1-thio-α-DL-*ribo*-hexopyranoside **24**.

Compound **13** (1.3 g) was dissolved in 30 ml of methylene chloride at 0°. Thiophenol (1.2 ml) and boron trifluoride etherate (0.6 ml) were added. After 1 hour of stirring at room temperature saturated sodium bicarbonate was added and the mixture was extracted with methylene chloride. The organic layer was washed to neutrality, dried, evaporated and chromatographed with ethyl acetate:hexane 6:4, yielding two compounds:

Compound **24** (1.35 g, yield 89%) was obtained as white fluffy crystals from ether:hexane, mp 70-71°; Rf = 0.6; ir (potassium bromide): ν max (cm^{-1}) 2100 [N_3], 1335, 1170 [Ms], 730 [C-S]; ^1H nmr: see Table II.

Anal. Calcd. for $C_{13}H_{17}N_3O_4S_2$: C, 45.47; H, 4.99; N, 12.24. Found: C, 45.40; H, 4.80; N, 12.07.

Compound **25** (100 mg, yield 6%) was obtained as a yellow oil, Rf = 0.2; ir (neat): ν max (cm^{-1}) 2100 [N_3], 1335, 1170 [Ms], 740 [C-S]; ^1H nmr: (60 MHz) δ 7.0 [m, 5H, aromatic], 4.5 [d, 1H, H-1, $J_{1,2}$ = 6.8], 3.8 [m, 2H, H-2, H-4], 2.9 [s, 3H, Ms], 2.2 [m, 2H, H-3, H-3'], 1.2 [d, 3H, Me].

Anal. Calcd. for $C_{13}H_{17}N_3O_4S_2$: C, 45.47; H, 4.99; N, 12.24. Found; C, 45.50; H, 4.84; N, 12.01.

Phenyl 2-Azido-4-*O*-mesyl-2,3,6-trideoxy-1-thio-α-DL-*lyxo*-hexopyranoside **26**.

Compound **14** (0.1 g) was dissolved in 5 ml of methylene chloride at 0°. Thiophenol (0.1 ml) and boron trifluoride etherate (0.05 ml) were added and the reaction was stirred for 0.5 hour. Treatment of the mixture as before and chromatographic separation afforded two compounds:

Compound **26** (45 mg, yield 38%) was obtained as white crystals from ether:hexane, mp 74-75°; Rf = 0.6; ir (potassium bromide): ν max (cm^{-1}) 2100 [N_3], 1350, 1175 [Ms], 740 [C-S]; ^1H nmr: see Table III.

Anal. Calcd. for $C_{13}H_{17}N_3O_4S_2$: C, 45.47; H, 4.99; N, 12.24. Found: C, 45.55; H, 5.18; N, 12.11.

Compound **27** (45 mg, yield 38%) was obtained as white crystals from ether:hexane, mp 78-79°; Rf = 0.4; ir (potassium bromide): ν max (cm^{-1}) 2103 [N_3], 1330, 1178 [Ms], 745 [C-S]; ^1H nmr: see Table III.

General Procedure for Glycosidation of Thioether **24** with *N*-Bromosuccinimide.

The reported procedure [12a] was followed exactly with the exception of the use of 1.5-1.9 fold excess of *N*-bromosuccinimide. The elution solvent for the steroid analogs was toluene:ethyl acetate 9:1 and the Rf values are given for this solvent for two passes.

In the following examples, a pair of diastereomeric anomers should be formed. In no case were these isomers separated on tlc or confirmed by ^1H nmr. Thus, the data given below are refered to as a diastereomeric mixture of anomers.

Methyl 2-Azido-4-*O*-mesyl-2,3,6-trideoxy-DL-*ribo*-hexopyranosides **31a** and **31b**.

Compound **24** (80 mg, 0.23 mmole) was dissolved in 7 ml of methylene chloride and stirred for 30 minutes with 4 Å molecular sieves. Methanol (0.5 ml, 15 mmoles) and *N*-bromosuccinimide (70 mg, 0.48 mmole) were added and after 30 minutes the reaction was over (tlc ether:hexane 4:6). After the usual work up and chromatographic separation, 57 mg (92% yield) of a colorless oil was obtained. This product though homogeneous on tlc (Rf = 0.55) was mixture of both anomers, see Table I, entry 10; ir (neat): ν max (cm^{-1}) 2101 [N_3], 1360, 1175 [Ms], 2990, 2940; ^1H nmr: see Table II (assignment was made on the ^1H nmr from the mixture).

5α-Androstan-3α-(2'-azido-4'-*O*-mesyl-2',3',6'-trideoxy-α-DL-*ribo*-hexopyranosyl)-17-one **29a**.

Compound **24** (80 mg, 0.23 mmole), androsterone (150 mg, 0.5 mmole) and *N*-bromosuccinimide (70 mg, 0.4 mmole) in 5 ml of methylene chloride were treated as before. Column chromatographic separation gave 98 mg (81% yield) of an oil, a mixture of both anomers (Table I, entry 6). Crystallization from ethyl acetate:hexane gave the pure α-anomer **29a** as a white solid, mp 125-127°; Rf = 0.4; ir (potassium bromide): ν max (cm^{-1}) 2102 [N_3], 1740 [C=O], 1365, 1180 [Ms], 2940, 2860; ^1H nmr: see Table II.

Anal. Calcd. for $C_{26}H_{41}N_3O_6S$: C, 59.63; H, 7.89; N, 8.02. Found: C, 59.35; H, 7.85; N, 7.90.

5α-Androstan-3β-(2'-azido-4'-*O*-mesyl-2',3',6'-trideoxy-α-DL-*ribo*-hexopyranosyl)-17-one **30a**.

Compound **24** (100 mg, 0.29 mmole), *epi*-androsterone (200 mg, 0.69 mmole) and *N*-bromosuccinimide (100 mg, 0.56 mmole) in 5 ml of methylene chloride were treated as before. Column chromatographic separation gave 130 mg (85% yield) of an oil, a mixture of both anomers (Table I, entry 8). Crystallization from ethanol gave the pure α-anomer **30a** as a white solid (dec at 122-124°); Rf = 0.36; ir (potassium bromide): ν max (cm^{-1}) 2103 [N_3], 1735 [C=O], 1355, 1180 [Ms], 2940, 2860; ^1H nmr: see Table II.

Anal. Calcd. for $C_{26}H_{41}N_3O_6S$: C, 59.63; H, 7.89; N, 8.02. Found: C, 59.57; H, 7.72; N, 8.15.

N-Benzyl(carbonyloxy)-*O*-(2-azido-4-*O*-mesyl-2,3,6-trideoxy-α-DL-*ribo*-hexopyranosyl)serine Methyl Ester, **33a**.

Z-Serine methyl ester (95 mg, 0.4 mmole) was treated as before with **24** (100 mg, 0.29 mmole) and *N*-bromosuccinimide (70 mg, 0.39 mmole) in 5 ml of methylene chloride (Table I, entry 13). Column chromatography separation gave compound **33a** as a white solid (113 mg, 60% yield), mp 104-107°; ir (potassium bromide): ν max (cm^{-1}) 2105 [N_3], 1750, 1515 [NHCO], 1735 [-COO-], 1350, 1180 [Ms], 2990; ^1H nmr: see Table II.

Anal. Calcd. for $C_{19}H_{26}N_4O_8S$: C, 48.51; H, 5.53; N, 11.98. Found: C, 48.75; H, 5.21; N, 12.02.

General Procedure for Glycosidation of Carbonate **15** with Tin Tetrachloride.

The carbonate and the related alcohol were dissolved in freshly dried methylene chloride at 0° under nitrogen. Into the reaction mixture was added tin tetrachloride dropwise, the cooling bath was removed after a while and the reaction was stirred for 3 to 6 hours. For less than a 1 g scale the reaction was neutralized with triethylamine, reduced *in vacuo* to a small volume and chromatographed. For a larger scale, extraction was performed with methylene chloride, washings of the organic layers with 5% hydrochloric acid, neutralization with sodium bicarbonate and subsequent column chromatographic separation.

Methyl 2-Azido-4-*O*-mesyl-2,3,6-trideoxy-DL-hexopyranosides, **31a** and **31b**.

Compound **15** (100 mg, 0.3 mmole), methanol (0.5 ml, 15 mmoles) and tin tetrachloride (0.53 mmole) were treated in 5 ml of methylene chloride according to the general procedure, yielding 74 mg (89%) of a colorless oil, mixture of both anomers (see Table I, entry 8), identical upon ir and tlc with that obtained from **24** with the *N*-bromosuccinimide procedure.

5α-Androstan-3α-(2'-azido-4'-*O*-mesyl-2',3',6'-trideoxy-β-DL-*ribo*-hexopyranosyl)-17-one, **29b**.

Compound **15** (130 mg, 0.4 mmole), androsterone (190 mg, 0.65 mmole) and tin tetrachloride (0.53 mmole) were treated in 5 ml of methylene chloride as before, affording after column chromatographic separation, an oil (170 mg, 81%), a mixture of both anomers (see Table I, entry 2). Crystallization from ethyl acetate/hexane gave pure **29b** as a white solid, mp 130-131°; Rf = 0.34; ir (potassium bromide): ν max (cm^{-1}) 2100 [N_3], 1742 [C=O], 1365 d, 1180 d, 960 [Ms], 1080, 1040, 1020 [COC], 2940, 2860, 865; ^1H nmr: see Table II.

Anal. Calcd. for $C_{26}H_{41}N_3O_6S$: C, 59.63; H, 7.89; N, 8.02. Found: C, 59.45; H, 7.63; N, 7.86.

5α-Androstan-3β-(2'-azido-4'-*O*-mesyl-2',3',6'-trideoxy-β-DL-*ribo*-hexopyranosyl)-17-one, **30b**.

Compound **15** (200 mg, 0.62 mmole), *epi*-androsterone (260 mg, 0.90 mmole) and tin tetrachloride (0.8 mmole) were treated in 5 ml of methylene chloride as before, affording after column chromatographic separation, an oil (240 mg, 74%), a mixture of both anomers (see Table I, entry 7). Crystallization from methanol gave pure **30b** as a white solid, 135-137° dec, Rf = 0.3; ir [potassium bromide]: ν max (cm^{-1}) 2100 [N_3], 1736 [C=O], 1350, 1175, 935 [Ms], 1090, 1050, 1030, 955 [COC], 2940, 2860, 850, 525; ^1H nmr: see Table II.

Anal. Calcd. for $C_{26}H_{41}N_3O_6S$: C, 59.63; H, 7.89; N, 8.02. Found: C, 59.65; H, 7.70; N, 8.18.

Methyl 2,3,4-Triacetyl-(2'-azido-4'-*O*-mesyl-2',3',6'-trideoxy-β-DL-*ribo*-hexopyranosyl)-α-D-glucoside **32b**.

Compound **15** (0.62 mmole), methyl-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (0.8 mmole) and tin tetrachloride (0.8 mmole) were treated in 5 ml of methylene chloride as before, affording after column separation (ethyl acetate/hexane 4:6), an oil (yield 42%), mixture of both anomers (see Table I, entry 11), Rf = 0.6; ir (potassium bromide): ν max (cm^{-1}) 2105 [N_3], 1755 [C=O], 1365, 1175 [Ms], 2940; ^1H nmr δ [4.62 d, J = 4.2 and 4.11 d, J = 7.8, 1H, anomeric of ribo-sugar], [1.28 d and 1.34 d, J = 5.8, 3H, Me], [3.07 s and 3.05 s, 3H, Ms], 2.08-2.01 [6 singlets, OAc], 3.42 s and 3.44 s, 3H, OMe], 5.4 [2 doublets, J = 5, 1H, anomeric of glucoside].

General Procedure for Glycosidation of Carbonate **15** with TMSOTf.

Compound **15** (100 mg) and 1.4 equivalents of androsterone or *Z*-NH-Ser-OMe, were stirreed for 6 hours with TMSOTf (1.4 equivalents) in 5 ml of dry methylene chloride at room temperature under nitrogen. The reaction was quenched with triethylamine. Column chromatography purification afforded in both cases the β-anomer (**29b** and **33b** respectively, Table I, entries 4 and 12).

N-Benzyloxycarbonyl-*O*-(2-azido-4-*O*-mesyl-2,3,6-trideoxy-β-DL-*ribo*-hexopyranosyl)serine methyl ester **33b** was obtained as a colorless oil; ir (methylene chloride): ν max (cm^{-1}) 2100 [N_3], 1755, 1520 [NHCO], 1735 [-COO-], 1310, 1160 [Ms], 2990; ^1H nmr: see Table II.

General Procedure for Glycosidation of Acetate **13** with TMSOTf.

Compound **13** (100 mg) and 1.2 equivalents of androsterone or *Z*-NH-Ser-OMe were stirred for 5 hours with trimethylsilyl trifluoromethanesulfonate (1.3 molar excess) in 5 ml dry of methylene chloride at room temperature for 5 hours under nitrogen. Work up in the usual way, gave in both cases the β-anomer (**29b**

and **33b** respectively, see Table I, entries 5 and 14).

Glycosidation of Acetate **13** with Methanol *via* the Bromide **28**.

Compound **13** (250 mg) was dissolved in 2 ml of methylene chloride at −15°. Hydrobromic acid 30% (1.2 ml) in acetic acid was added without stirring. The reaction was allowed to stand for 2.5 hours under nitrogen and warm up to −5°. Then, it was diluted with 20 ml dry toluene and concentrated *in vacuo*. The same process was repeated once more, the product was extracted with methylene chloride from a solid by-product and crystallized from toluene:hexane affording compound **28** (200 mg, yield 67%) as a slight brown solid, Rf = 0.3 in ether:hexane 1:1; ir (potassium bromide): ν max (cm^{-1}) 2100 [N_3], 1340, 1170, 940 [Ms], 1100, 990 [COC], 520 d [C-Br], 2990, 2940; ^1H nmr (60 MHz) δ 6.25 [d, 1H, H-1, $J_{1,2}$ = 3], 4.2 [m, 2H, H-5, H-4], 3.6 [m, 1H, H-2], 3.1 [s, 3H, Ms], 2.4 [m, 2H, H-3, H-3'], 1.3 [d, 3H, Me, $J_{5,Me}$ = 6].

In 5 ml of methylene chloride were added, freshly prepared silver carbonate (150 mg), dry calcium sulfate (250 mg) and 100 mg of methanol. The mixture was stirred for 1 hour. One hundred mg of **28** was added and the reaction was stirred overnight at room temperature under nitrogen. The mixture was filtrated from Celite, concentrated and chromatographed yielding 50 mg (52%) of an oil, a mixture of anomers of **31a** and **31b**.

2-Hydroxy-2-furylethyl Pivaloate **35**.

Pivaloyl chloride (13.2 g, 0.11 mole) was added dropwise to a solution of triethylamine (12 g, 0.12 mole), dimethylaminopyridine (2.1 g, 0.02 mole) and 12.8 g (0.1 mole) of furan glucol (prepared according to the literature [19] from D-glucal) in 80 ml of methylene chloride at 0°. The ice-bath was removed and the reaction mixture was stirred for 5 hours more before quenching with a saturated solution of ammonium chloride and extraction with ether. Column chromatographic separation (ether:hexane 1:1) gave 16.5 g (yield 78%) of **35** as a colorless oil; ir (neat): ν max (cm^{-1}) 3450 [OH], 1750 [OCO] 885, 740 [furan]; ^1H nmr: (60 MHz) δ 6.9 [d, 1H, J = 1.5, furan], 5.8 [m, 2H, furan], 4.8 [dt, 1H, J_{CH-CH_2-} = 5.1 Hz, $J_{H,OH}$ = 4.8], 3.1 [m, 2H, $-CH_2-$], 2.75 [d, 1H, OH].

1-*O*-Acetyl 6-*O*-Pivaloyl-2,3-dideoxy-α-D-hex-2-enopyranos-4-ulose **36**.

N-Bromosuccinimide (7 g, 0.055 mole) was added portionwise to a solution of **35** (10.6 g, 0.05 mole) in tetrahydrofuran:water (4:1) at 0°. Five minutes after the addition of *N*-bromosuccinimide was over, the mixture was worked up with saturated solutions of potassium iodide and sodium thiosulfate and extracted with ether. The organic layer was washed with water to neutrality, dried (magnesium sulfate) and concentrated to afford 11 g of the related pyranone as a yellow oil (one spot on tlc). This crude alcohol was diluted in a mixture of acetic anhydride and pyridine and allowed to stand overnight at 7°. After the conventional work up and column chromatographic separation (ether:hexane 3:7) a colorless oil was obtained which after crystallization from ether afforded 10 g (yield 74% for two steps) of **36** as white crystals, mp 92-93°; $[\alpha]_D^{15}$ = +107.4° (c = 1, chloroform); ir (potassium bromide): ν max (cm^{-1}) 1755 [broad], 1680 [allylic carbonyl]; ^1H nmr (60 MHz) δ 6.6 [dd, 1H, H_5, $J_{4,5}$ = 10.2, $J_{5,6}$ = 3.4], 6.2 [d, 1H, H_6, $J_{4,6}$ = 0.0], 5.7 [d, 1H, H_4], 3.5 [m, 2H, $-CH_2-$], 2.2 [s, 3H, OAc], 1.25 [s, 9H, pivaloyl].

Anal. Calcd. for $C_{13}H_{18}O_6$: C, 57.78; H, 6.67. Found: C, 57.89; H, 6.51.

1-*O*-Acetyl-2-azido-4-*O*-mesyl-6-*O*-pivaloyl-2,3-dideoxy-α-D-*ribo*-hexopyranose **37**.

Compound **36** (2.7 g, 0.01 mole) was subsequently treated with sodium azide and sodium borohydride as before yielding a mixture of epimers which was mesylated as before, yielding after column chromatographic separation (benzene:ethyl acetate, 8:2, Rf = 0.4) and crystallization from ethyl acetate/hexane 2.4 g, (yield 62% for three steps) of **37** as white crystals, mp 121-122°; $[\alpha]_D^{15}$ = +119.5° (c = 1, chloroform); ir (potassium bromide): ν max (cm^{-1}) 2100 [N_3], 1760, 1750 [esters], 1370, 1170 [$-SO_2-$]; ^1H nmr: see Table II.

Anal. Calcd. for $C_{14}H_{23}N_3O_8S$: C, 42.86; H, 5.87; N, 10.71. Found: C, 42.64; H, 5.75; N, 10.54.

The *lyxo* isomer of **37** (Rf = 0.3) was also isolated (0.6 g, 16% yield).

5α-Androstan-3α-(2'-azido-4'-*O*-mesyl-6'-pivaloyl-2,3-dideoxy-β-D-*ribo*-hexopyranosyl)-17-one **38**.

Compound **37** (100 mg, 0.25 mmole), androsterone (150 mg, 0.5 mmole) and TMSOTf (0.35 mmole) were treated in 5 ml of methylene chloride as before, affording after column chromatographic separation (benzene:ethyl acetate 9:1), **38** (117 mg, yield 73%) as a colorless oil; $[\alpha]_D^{15}$ = +95.2° (c = 0.5, chloroform); ir (neat): ν max (cm^{-1}) 2100 [N_3], 1750 [ester], 1735 [carbonyl], 1360, 1190 [$-SO_2-$]; ^1H nmr: see Table II.

Anal. Calcd. for $C_{31}H_{49}N_3O_8S$: C, 59.71; H, 7.86; N, 6.74. Found: C, 59.64; H, 7.58; N, 6.61.

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