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Review Paper

Progress in O- Glycosylation of Pregnanes

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Abstract: Pregnane glycosides have been isolated from both plants and animals. In view of the diverse biological activity exhibited by this naturally occurring class of compound, its synthesis has long been pursued by researchers from different parts of the world. The present review includes methods adopted for the synthesis of different glycosyl donors by following appropriate protection-deprotection strategies and consequently glycosidically linking them with the pregnanes. Biological activity of these synthetic derivatives has also been summarised.

1. Introduction

A number of reviews have been written about Pregnanes and Pregnane glycosides but to the author's best knowledge there is no review in literature that accounts exclusively for the synthesis or glycosidation of pregnanes. Although a review regarding glycosylation of steroids was reported in literature in 2004[1] but it did not take into account all categories of pregnanes. Thus the present review concentrates on all the O-glycosidation methods that have been applied for the synthesis of pregnane glycosides till Dec 2011.

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Pregnane O-glycosides are compounds in which there is a semiacetal linkage between the reducing group of the sugar and an alcoholic hydroxyl group of the pregnanes. During the last three decades, a lot of work has been done on the isolation of pregnane glycosides from plants. This important class of compound has been reported to possess diverse pharmacological activity [2-7]. These biologically potent compounds, which were isolated from natural sources in meagre quantities, hence not much structure activity relationship could be carried out. But they have provided interesting 'lead' for the development of new drugs. A number of pregnane derivatives are drugs, but they are poorly absorbed through the intestines. Conjugating these pregnanes with appropriate carbohydrate moiety not only increases their hydrophilic character, but it

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also increases its efficacy and reduces toxicity relative to the parent compound [8, 9]. **A** remarkable progress has been made during the last several years in glycoside synthesis. The process involves generation of a glycosidic bond between the hydroxyl group of the pregnane moiety called the acceptor and the anomeric carbon of the sugarmoiety-the donor, which bears the leaving group (Figure 1).

There are several glycosidation methods, based mostly on the reactivity of the glycosyl donors that have been adopted for pregnane glycoside synthesis. From the survey of the literature, methods adopting different types of glycosyl donors for the synthesis of pregnane glycosides have been classified into five main groups:
(i)Glycosyl halides (ii) Trichloroacetimidate. (iii) 1-O acyl sugars. (iv) Thioglycosides. (v) Other Chemical methods.

(i) Glycosyl halides

Methods described for glycosidation of pregnanes, using glycosyl halides as donors are mostly based on the classical Koenigs-Knorr method of synthesis [10]. Though this method of glycosidation has been critically reviewed [11-13] but it still represents the most versatile and generally accepted method of glycosidation. This glycosylation process chiefly uses glycosyl bromides and chlorides as glycosyl donors and their subsequent reaction with pregnane- acceptor, in the presence of silver salt, chiefly silver carbonate (Ag_2CO_3). A number of variants for this procedures have subsequently been developed and each adopting different type of silver catalyst like silver triflate, silver oxide, Fetizon's reagent (silver carbonate deposited on celite) etc. One of the important variant of Koenigs-Knorr procedure is the Helferich procedure in which the reaction of glycosyl halide with an alcoholic component is catalyzed by mercury salt (chiefly mercury II-cyanide) [14-15] Solvents commonly used during the glycosidation process are ether, benzene, toluene, acetonitrile and dichloromethane. Molecular sieves, Drierite are added to the reaction to ensure removal of water, produced during the course of reaction.

Classical methods using metal salts of silver or mercury however have some severe, partly inherent, disadvantages such as low thermal stability and sensitivity of hydrolysis of many glycosyl halides and the need for stoichiometric quantities of metal salts which are either expensive or hazardous in nature. Moreover the use of mercury salts have also been reported to give products contaminated with organomercury complexes. As a result methods were suggestive involving use of other catalyst like cobalt carbonate, zinc oxide and zinc fluoride.

Acetylated 3β-O-β-glycosyl pregnane derivatives were synthesized by reaction of a new polyhydroxypregnane with peracetylated 1-bromoderivative of D-glucose and D-galactose by classical Koenigs-Knorr procedures, using silver carbonate/diatomite as catalyst [16]. The results are summarized in Table 1 and Figure 2.

A rapid and efficient procedure for glycosylation of pregnanes was established by adopting modified Koenigs-Knorr procedure and using Silver maleinate as catalyst [17]. Peracetylated β-pregnane glycosides were synthesized by reaction of various pregnanes at room temperature with peracetylated 1-bromo derivative of D-fucose. Silver maleinate as catalyst showed a superior purity profile for newly formed pregnane glycosides than silver perchlorate, silver salicylate, Fetizon's reagent or

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mercury cyanide. Silver maleinate forced the sugar moiety into the desired β-configuration (Figure 3).

Synthesis of 5α-pregnane-3β, 14β, 20β-triol 3-α-L-rhamnopyranoside and its 20-silyl derivative was achieved by first converting uzarigenin acetate to 20-silyl pregnane derivative. Treatment of this silyl derivative with 2, 3, 4-tri-O-acetylrhamnopyranose and Fetizon's reagent, followed by hydrolysis with KOH/EtOH gave the 20 silyl glycoside. Removal of the silyl protecting group with tetra-n-butyl ammonium fluoride gave the pregnane glycoside [18] (Figure 4).

In an alternative route uzarigenin was converted to 20-keto methyl pregnane derivative, which on reaction with 2, 3, 4-tri-O-acetylrhamnopyranosyl bromide and Fetizon's reagent gave the triacetate glycoside which on workup led to dehydrated product, mild hydrolysis of this product with Et3N/MeOH/H2O gave the unsaturated glycoside (Figure 5).

As part of the structure –activity investigation for the synthesis of pregnane derivatives and its glycosides that bind to the cardiac glycoside recognition site on Na^+,K^+-ATPase and inhibit the enzyme (the sodium pump) in membranes, cells and tissues, glycosidation of 20-acetamido isomers with acetobromorhamnose as glycosyl donor was carried out in presence of mercuric cyanide as catalyst. Amongst them 20β- acetamideo-3β-(α-L-rhamnopyranosyloxy)-5β-pregnan-14-ol binds more strongly to the cardiac glycoside recognition site of the heart muscle in comparison to its 20α-isomer[19] (Figure 6). The receptor binding affinity of the 5β and 5α pregnane glycosides was also ascertained. The 5β glycoside showed greater binding affinity than the 5α glycosides.

Glycosidation of 20α-silyl ether was also carried out with acetobromorhamnose in presence of Fetizon's reagent, followed by hydrolysis gave a mixture of glycosides. The glycoside with 20-hydroxyl group, binds less strongly to the cardiac glycoside recognition site of heart muscle [19] (Figure 7).

Synthesis of 14β, 20β-dihydroxy-3β (β-D-glucopyranosyloxy) was achieved by treatment of 20-β protected pregnane derivative with tetraacetylbromoglucose in the presence of silver carbonate/celite and mercury cyanide and mercury bromide [20] (Figure 8). The glycoside was found to have enhanced ability to inhibit the sodium pump in the red blood cells.

Synthesis of glucoside 3β-[(β-D-glucopyranosyl)]-14-hydroxy-14β-pregn-4-en-20-one was also reported. This glycoside which enhanced the contractibility of isolated cardiac muscle was found to be ten times more potent than the aglycone [21].

Four possible monoglucosides of pregn-5-ene-3β-20R-diol were synthesized along with a mixture of four possible 3, 20-diglucosides using 1-bromo-2, 3, 4, 6-tetra-O-acetyl-β-D-glucopyranose or 1-fluoro-2, 3, 4, 6-tetra-O-benzyl-β-D-glucopyranose as glycosyl donors. The reaction was carried out using silver oxide/tetramethylurea and silver trifluoromethanesulfonate (silver triflate) or trimethylsilyl trifluoromethanesulfonate as catalyst. Besides this a number of α-glucosides of pregn-5-ene-3β-20R-diol were also obtained using 1-fluoro-2, 3, 4, 6-tetra-O-benzyl-1-deoxyglucose as glycosyl donor [22] (Figure 9).

Pregnane glycosides and the unique glycosidase activity of the colon specific

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microflora, forms the basis of a new colon specific drug-delivery system. Drug glycosides are hydrophilic and thus poorly absorbed from the small intestines. Once this pregnane glycoside reaches the colon it is cleaved by the bacterial glycosidase releasing the free pregnane drug to be absorbed by the colonic mucosa. This concept has well been illustrated by the synthesis of a number of pregnane glycosides by modified Koenigs- Knorr methods in which the bromo sugars (glucose and galactose) were coupled with appropriate pregnane drugs like dexamethasone, Prednisolone, Hydrocortisone, Fludrocortisone etc in presence of silver carbonate[8,9] (Table 2,3 and Figure 10a, 10b).

Besides cardioactive steroids, two pregnane genins with different β-side group at C-17 were converted to their corresponding β-D-glucosides and β-D-galactosides [23] (Figure 11), by adopting modified Koenigs-Knorr procedure in which silver salicylate in place of silver carbonate was used as catalyst. This procedure was simple and fast.

Cortisol metabolism in humans involves various transformations. Most of the metabolites of cortisol such as tetrahydrocortisol, tetrahydrocortisone, 20α-cortol, 20α –cortolone, allotetrahydrocortisol, cortolic acid and their epimers are secreted in the urine mainly as conjugates with glucuronic acid. The level of urinary 17-hydroxy corticosteroids has long been used as an index of adrenocorticoid activity. For use in metabolic studies and immunoassays the synthesis of 3- and 21-monoglucuronides of a number of cortisol derivatives was carried out. The introduction of glucuronyl residue methyl 2,3,4-tri-O-acetyl-1-deoxy –α-D-glucuronate into C-3 and C-21 position of substituted corticosteroid derivatives was achieved by adopting Koenigs- Knorr procedures in the presence of silver carbonate as catalyst[24-30] (Table 4,Figure 12).

Synthesis of glucuronides of a number of pregnane drugs like Budesonide and Dexamethasone have also been reported [31-32]. Both the glycosides, which were found to be potentially useful for the treatment of colonic inflammatory bowel diseases, were synthesized by modified Koenigs- Knorr in the presence of silver carbonate as catalyst.

The synthesis of methyl 3α-yl 2, 3, 4-tri-O-acetyl-β-D glucopyranosiduronates of 5β-pregnane -3α, 17,20α-triol and its 6-ene-triol derivative has been reported by using improved Koenigs- Knorr methods using silver oxide as a catalyst. These glucuronides were then treated with carrier free tritium to obtain both the hapten and radioligand, essential for the establishment of radioimmunoassay for urinary pregnanetriol-3α-glucuronide [33] (Figure 13).

Increased secretion of 5β-pregnane 3α, 20α-diol during luteal phase of the ovarian cycle is the accepted evidence for the formation of a functioning corpus luteum and likewise the progressive rise in the excretion of this compound during pregnancy is associated with the normal development of the placenta. This pregnane derivative is excreted in the form of its 3α-glucuronide derivative. In order to monitor the progress of difficult pregnancy, synthesis of 5β-pregnane 20α-ol-3α-yl-glucuronides of 20-hydroxy pregnane derivatives were carried out by adopting improved Koenigs- Knorr methods using cadium carbonate as a new and effective catalyst. Radioimmunoassay of the said compounds was then carried out [34] (Figure 14, Table 5).

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Synthesis of 3-glucosiduronate, 21-glucosiduronate and 3, 21-diglucosiduronates of 3α, 21-dihydroxy-5β-11, 20-dione have also been reported. The process involved reaction of the pregnane genin with methyl acetobromoglucuronate in the presence of silver carbonate[35].

Steroidal 17-hydroxy 21-oic acids collectively called cortoic acids constitute 5-25% of urinary metabolites of cortisol in humans. For the purpose of developing methods for the analysis of urinary pregnanes, synthesis of 3-glucuronides of cortoic acid derivatives was also carried out [28, 36] (Figure 15, Table 6).

(ii) Trichloroacetimidate method

Trichloroacetimidate mediated method of glycosidation reported by Schmidt et al[37] as an alternative to Koenigs-Knorr procedure appears to be one of the most ideal glycosidation protocols. The glycosyl donor O-glycosyl trichloroacetimidate is prepared by reacting the hemiacetal sugar with trichloroacetonitrile in the presence of bases such as NaH, K_2CO_3 or DBU resulting in a kinetic or thermodynamic product (α or β) depending upon the catalyst taken[38]. In this way the anomeric oxygen has been transformed into a good leaving group. The glycosylation step involves reaction between the acceptor and glycosyl donor under mild acid conditions. Acids such as $BF_3.ET_2O$ or TMSOTf are mostly used in catalytic amount [39]

A number of glycosides including the pregnane glycoside bearing the disaccharide of OSW-1(a natural saponin with potent antitumor activity) were synthesized by adopting the trichloroacetimidate procedures. These glycosides were then evaluated for their anti-tumor activity [40, 41] (Figure 16).

Synthesis of some novel C-16 substituted pregnane glycosides were also accomplished with imidate method using boron trifluroide as catalyst [42] (Figure 17).

Synthesis of two sulfated pregnane glycosides Forbeside E3 and E1 and a number of structurally related pregnane glycosides have been reported [43] (Figure 18, Table 7). The sulfated glycosides, Forbeside E3 and E1 were earlier isolated from star fish *Asterias forbesi*.

(iii) 1-O-Acyl Sugars

An advantage of using the 1-O-acylated sugars as glycosyl donors is their ease of preparation. The most common anomeric functional groups used is the acetyl group. But other acyl groups like benzoyl and p-nitrobenzoyl group have been used as they are good anomeric leaving group. The glycosidation of these glycosyl donors with acceptors is usually carried out in the presence of Lewis acid catalyst like $SnCl_4$, $FeCl_3$, $BF_3.Et_2O$, TMSOTf, $TrClO_4$ [44-45] .
Synthesis of the pregnane glycoside was also accomplished by treating 3β-hydroxy-pregn -5, 16-diene-20-one with glucose penta acetate in the presence of stannic chloride [46] (Figure 19)

(iv) Thioglycosides

There are methods in which the anomeric carbon is activated by placing sulphur in place of exocyclic hemiacetal oxygen. This thioglycosidation procedure was first reported by Ferrier [47]. Glycosidation procedures using thioglycosides as glycosyl donors have attracted attention because of their stability, accessibility and compatibility [48]. Since then a number of variations have been reported [49-50].

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An electrochemical O-glycosylation of pregnane using thioglycosides as glycosyl donors in the presence of catalytic amount of trifluoromethanesulfonate as supporting electrolyte has been reported. The pregnane glycoside was obtained in good yield and high electro-efficiency [51] (Figure 20).

Thioglycosides on reaction with benzenesulphenyl triflate (TfOSPh) led to the formation of glycosyl triflate in the presence of 2, 6-di-tert-butyl-4-methylpyridine (DTBMP). This highly reactive glycosyl donor then reacted in an S_N2 type reaction with C-20 hydroxy pregnane to give the corresponding pregnane glycoside in high yield and selectivity [52-53] (Figure 21).

(v) Other Chemical Methods

2, 3-Unsaturated-O-glycosides have been reported to play an important role in the synthesis of number of antibiotics [54], oligosaccharides [55], complex carbohydrates [56] and a number of natural products [57]. Besides they are also important building blocks in a number of bioactive molecules [58]. 2,3-Unsaturated-O-glycosides of pregnenolone, an important pregnane that acts as a powerful neurosteroid in the brain, coordinating the transmission of messages from neuron to neuron, has been synthesized in high α-selectivity by the well known Ferrier rearrangement[59]. The process involves reaction of pregnenolone with 3, 4, 6-tri-O-acetyl glucal in the presence of (S)-camphorsulphonic acid [60] and $ZnCl_2/Al_2O_3$ [61] respectively as catalyst (Figure 22).

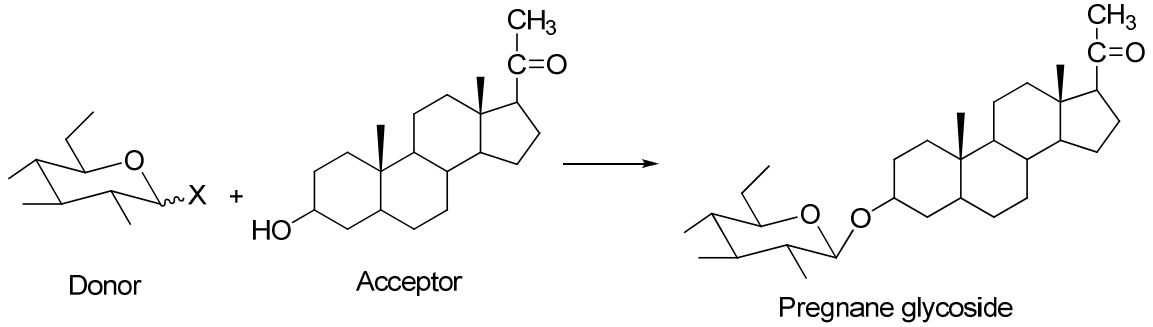

Figure 1: Glycosylation of Pregnanes

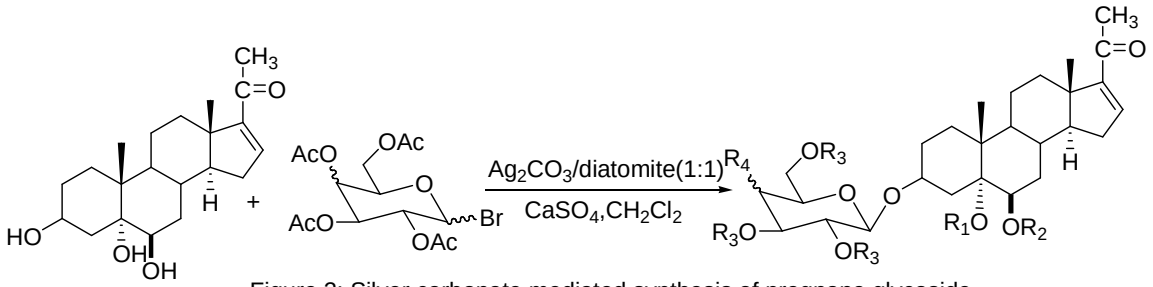

Figure 2: Silver carbonate mediated synthesis of pregnane glycoside, using peracetylated 1-bromo derivative of D-glucose and D-galactose

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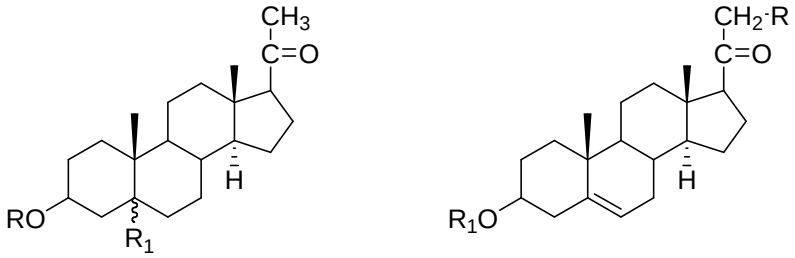
Table 1: Glycosidation of polyhydroxy pregnane

R_1	R_2	R_3	R_4
H	H	OAc	Eq OAc
H	OAc	OAc	Eq OAc
H	OAc	H	Eq OH
H	H	OAc	Axial OAc
H	OAc	OAc	Axial OAc
H	OAc	H	Axial OH



R_1= αH, R = fucose

R_1= βH, R = fucose

R= H, R_1 = fucose

R= OH, R_1 = fucose

Fig 3: Silver maleinate mediated synthesis of pregnane glycoside

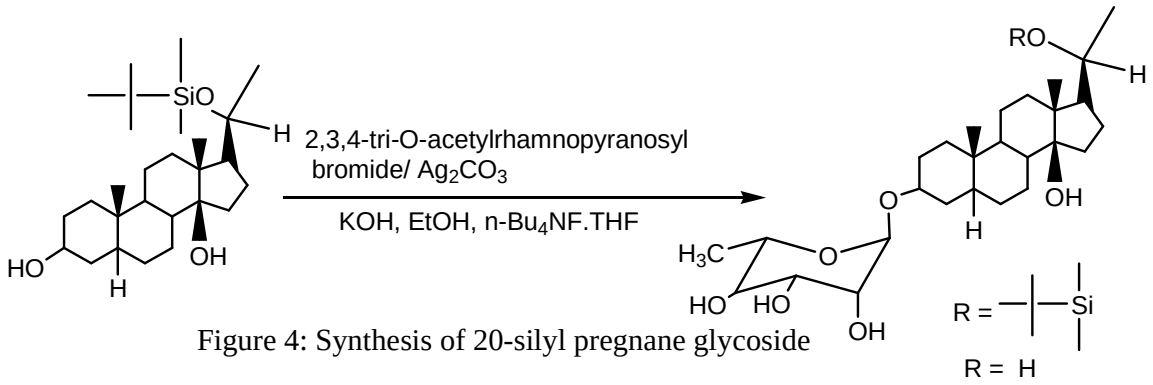


Figure 4: Synthesis of 20-silyl pregnane glycoside

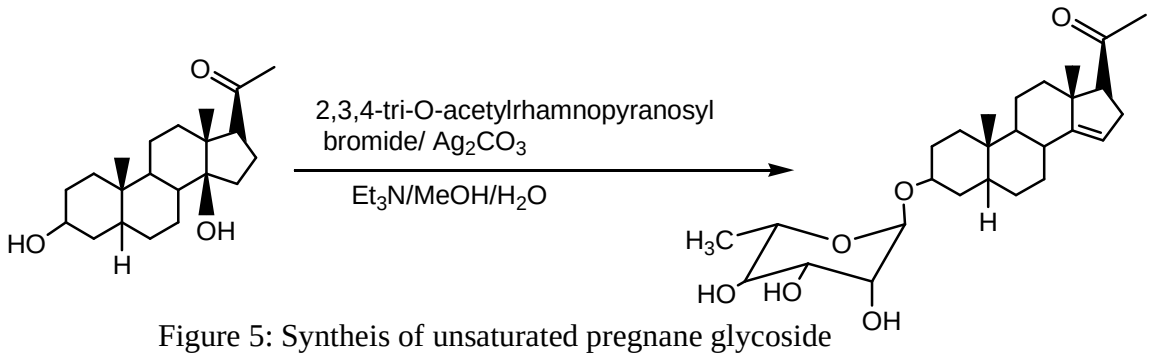


Figure 5: Syntheis of unsaturated pregnane glycoside

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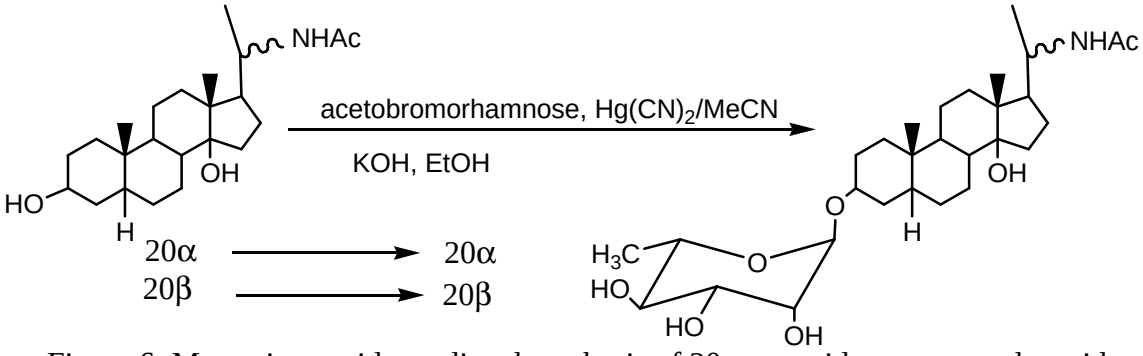

Figure 6: Mercuric cyanide mediated synthesis of 20-acetomido pregnane glycoside

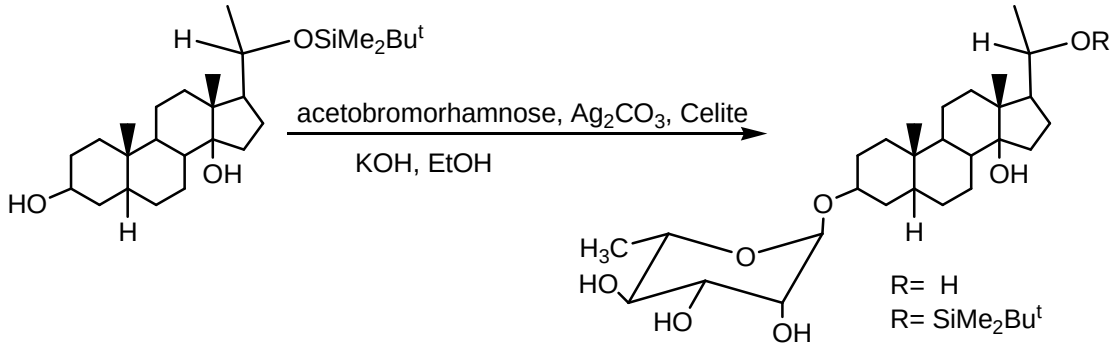

Figure 7: Synthesis of 20-hydroxyl pregnane glycoside

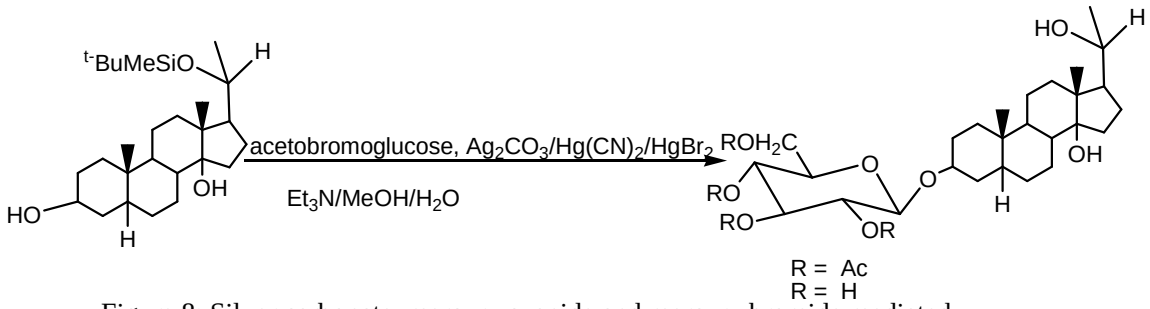

Figure 8: Silver carbonate, mercury cyanide and mercury bromide mediated synthesis of pregnane glycoside.

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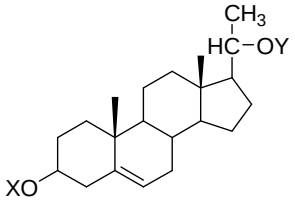

X = tetra-O-acetyl-β-D-glucopyranoside, Y =H
X=β-D-glucopyranoside, Y=H
X= C_6H_5CO, Y= tetra-O-acetyl-β-D-glucopyranoside
X= CH_3CO, Y= tetra-O-acetyl-β-D-glucopyranoside
X=α-D-glucopyranoside, Y=H
X=tetra-O-benzyl-α-D-glucopyranoside, Y= C_6H_5CO
X= tetra-O-benzyl-β-D-glucopyranoside, Y= C_6H_5CO
X= tetra-O-benzyl-α-D-glucopyranoside, Y= H
X= tetra-O-benzyl-β-D-glucopyranoside, Y= H
X=C_6H_5CO, Y= tetra-O-benzyl-α-D-glucopyranoside
X=C_6H_5CO, Y= tetra-O-benzyl-β-D-glucopyranoside
X=Y=β-D-glucopyranoside
X=β-D-glucopyranoside, Y=α-D-glucopyranoside
X=α-D-glucopyranoside, Y=β-D-glucopyranoside
X=Y=α-D-glucopyranoside
X=Y=tetra-O-benzyl-β-D-glucopyranoside
X=tetra-O-benzyl-β-D-glucopyranoside, Y=tetra-O-benzyl-α-D-glucopyranoside
X=tetra-O-benzyl-α-D-glucopyranoside, Y=tetra-O-benzyl-β-D-glucopyranoside
X=Y= tetra-O-benzyl-α-D-glucopyranoside
X= Y= tetra-O-benzyl-β-D-glucopyranoside

Fig 9: Synthesis of mono and diglucosides of pregn-5-ene-3β-20R-diol

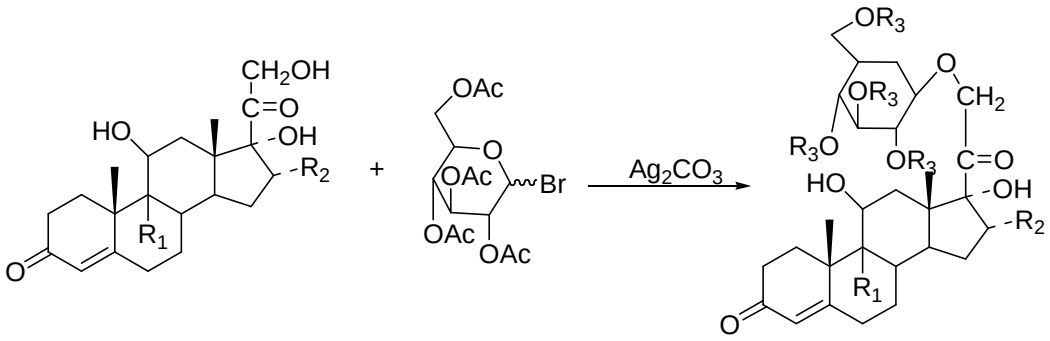

Figure 10a: Synthesis of C-21 glucosides of pregnane drugs

Table 2: Synthesis of glucosides of pregnane drugs

Double Bond	R_1	R_2	R_3	Drug
$\Delta^{1,2}$	F	CH_3	Ac	Dexamethasone
$\Delta^{1,2}$	H	H	Ac	Prednisolone
$\Delta^{1,2}$	F	CH_3	H	Dexamethasone
$\Delta^{1,2}$	H	H	H	Prednisolone
	F	H	Ac	Fludrocortisone
	H	H	Ac	Hydrocortisone
	F	H	H	Fludrocortisone
	H	H	H	Hydrocortisone

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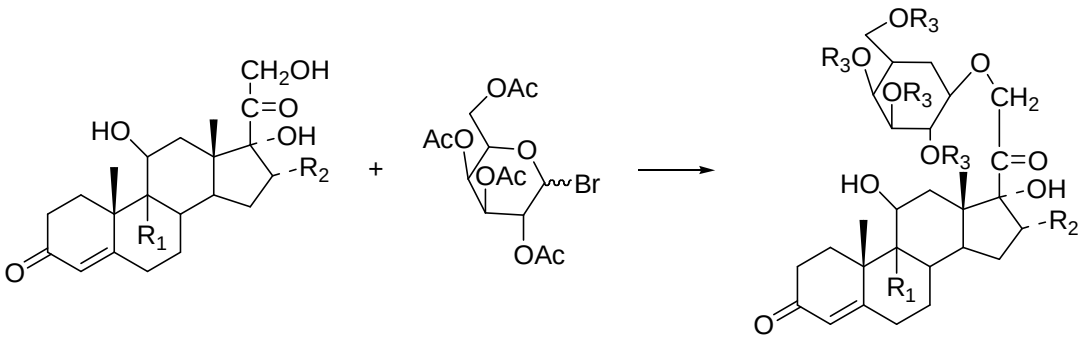
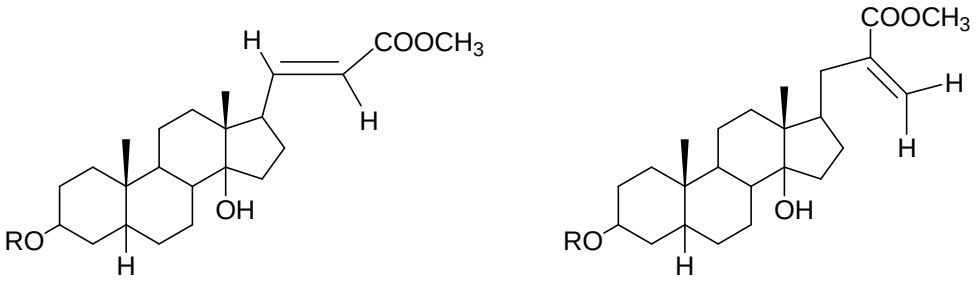


Figure 10b: Synthesis of C-21 galactosides of pregnane drugs

Table 3: Synthesis of galactosides of pregnane drugs

Double Bond	R_1	R_2	R_3	Drug
$\Delta^{1,2}$	F	CH_3	Ac	Dexamethasone
$\Delta^{1,2}$	H	H	Ac	Prednisolone
$\Delta^{1,2}$	F	CH_3	H	Dexamethasone
$\Delta^{1,2}$	H	H	H	Prednisolone
	F	H	Ac	Fludrocortisone
	H	H	Ac	Hydrocortisone
	F	H	H	Fludrocortisone
	H	H	H	Hydrocortisone



R = β-D-tetra-O-acetylglucose
R = β-D-glucose
R = β-D-tetra-O-acetylgalactose
R = β-D-galactose

Figure 11: Synthesis of some novel pregnane glycosides

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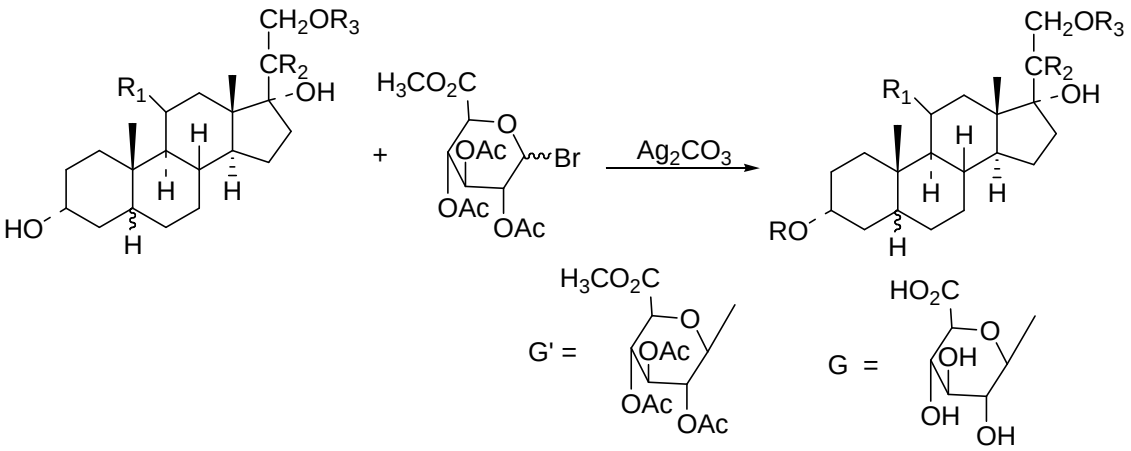

Figure 12: Synthesis of C-3 and C-21 glucosiduronates of cortisol derivatives

Table 4: Synthesis of C-3 and C-21glucosiduronates of cortisol derivatives

H-5	R	R_1	R_2	R_3
β	G′	OH	=O	Ac
β	G′	H_2	=O	Ac
β	G′	=O	=O	Ac
β	G′	=O	=O	H
β	G	=O	=O	H
β	G	H_2	=O	H
β	G′	H_2	=O	H
β	G′	OH	=O	H
β	G′	OH	=O	H
β	G′	OH	=O	Ac
β	Ac	OH	=O	G′
β	G	OH	=O	H
β	H	OH	=O	G
β	G′	OH	=O	Ac
β	Ac	OH	=O	G′
β	G	OH	=O	H
β	H	OH	=O	G
β	G′	OH	β, HOAc	Ac
β	G′	=O	β, HOAc	Ac
β	G′	OH	α, HOAc	Ac
β	G′	=O	α, HOAc	Ac
β	G	OH	β, HOH	H
β	G	=O	β, HOH	H
β	G	OH	α, HOH	H
β	G	=O	α, HOH	H
α	G′	H_2	=O	Ac
α	G	H_2	=O	H
α	Ac	H_2	=O	G′

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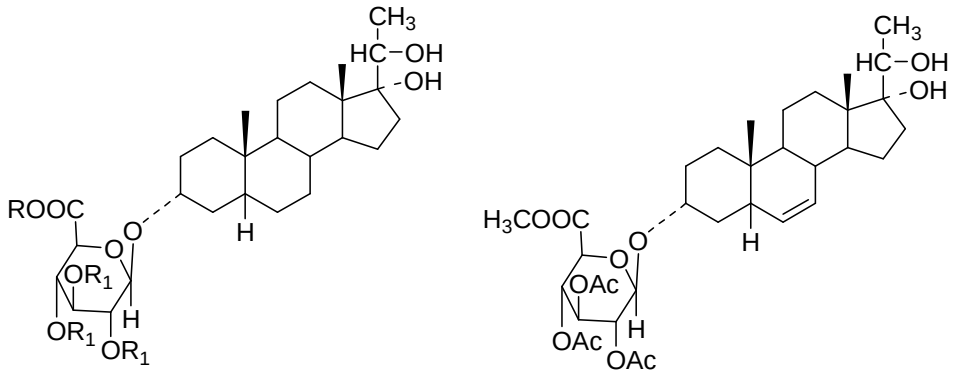
α	H	H_2	=O	G
β	G′	H_2	α, HOAc	Ac
β	G′	H_2	β, HOAc	Ac
β	G	H_2	α, HOH	H
β	G	H	β, HOH	H
α	G′	OH	=O	Ac
α	G	OH	=O	H
α	Ac	OH	=O	G′
α	H	OH	=O	G
α	G′	=O	=O	Ac
α	G	=O	=O	H
α	Ac	=O	=O	G′
α	H	=O	=O	G
α	G′	OH	α, HOAc	Ac
α	G′	=O	α, HOAc	Ac
α	G′	OH	β, HOAc	Ac
α	G′	=O	β, HOAc	Ac
α	G	OH	α, HOH	H
α	G	=O	α, HOH	H
α	G	OH	β, HOH	H
α	G	=O	β, HOH	H



R = CH_3, R_1 = Ac
R = H , R_1 = H

Figure 13: Silver oxide mediated synthesis of C-3 glucosiduronates of 5β- pregnane - 3α,17,20α-triol and its 6-ene-triol derivative

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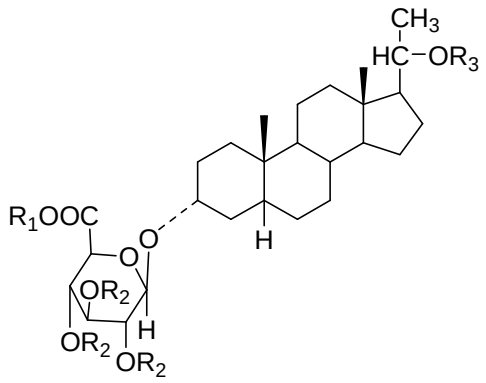

Figure 14: Synthesis of 3α-glucuronides of pregnanediols

Table 5: Synthesis of glucuronides of pregnanediols

Double Bond	R_1	R_2	R_3
	Me	Ac	Ac
	Na	H	H
	H	H	H
$\Delta^{6,7}$	Me	Ac	Ac
$\Delta^{6,7}$	Na	H	H
$\Delta^{6,7}$	H	H	H

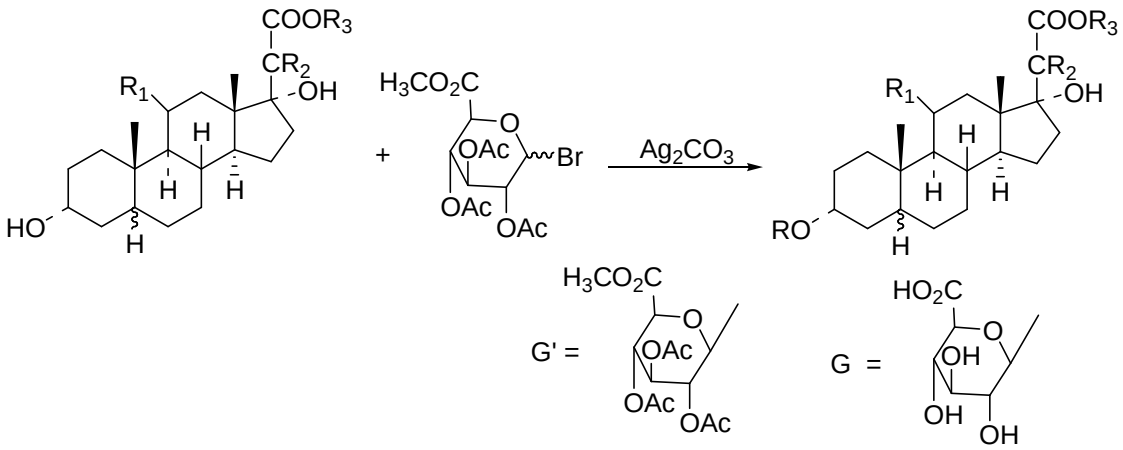

Figure 15: Synthesis of C-3 glucuronides of cortoic acid derivatives

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Table 6: Synthesis of glucuronides of cortoic acid derivatives

H-5	R	R_1	R_2	R_3
β	G′	=O	α,HOAc	Me
β	G′	=O	β,HOAc	Me
β	G	=O	α,HOH	H
β	G	=O	β,HOH	H
β	G′	H	α,HOAc	Me
β	G′	H	β,HOAc	Me
β	G	H	α,HOH	H
β	G	H	β,HOH	H

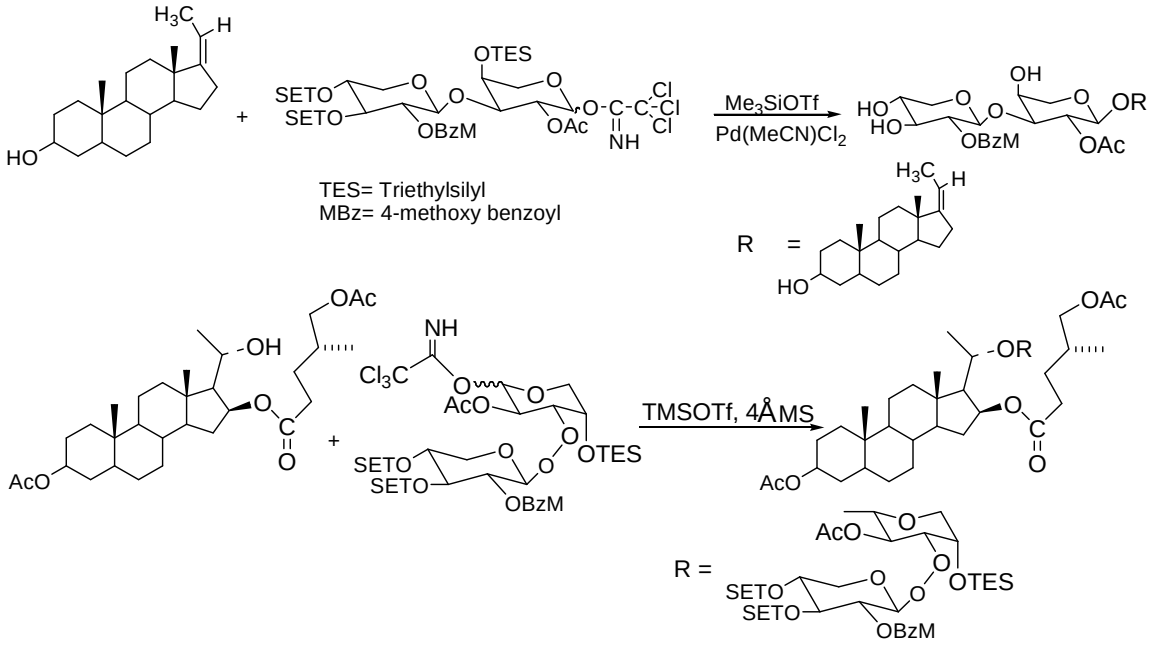

Figure 16: Synthesis of pregnane glycosides bearing the disaccharide moiety of OSW-1

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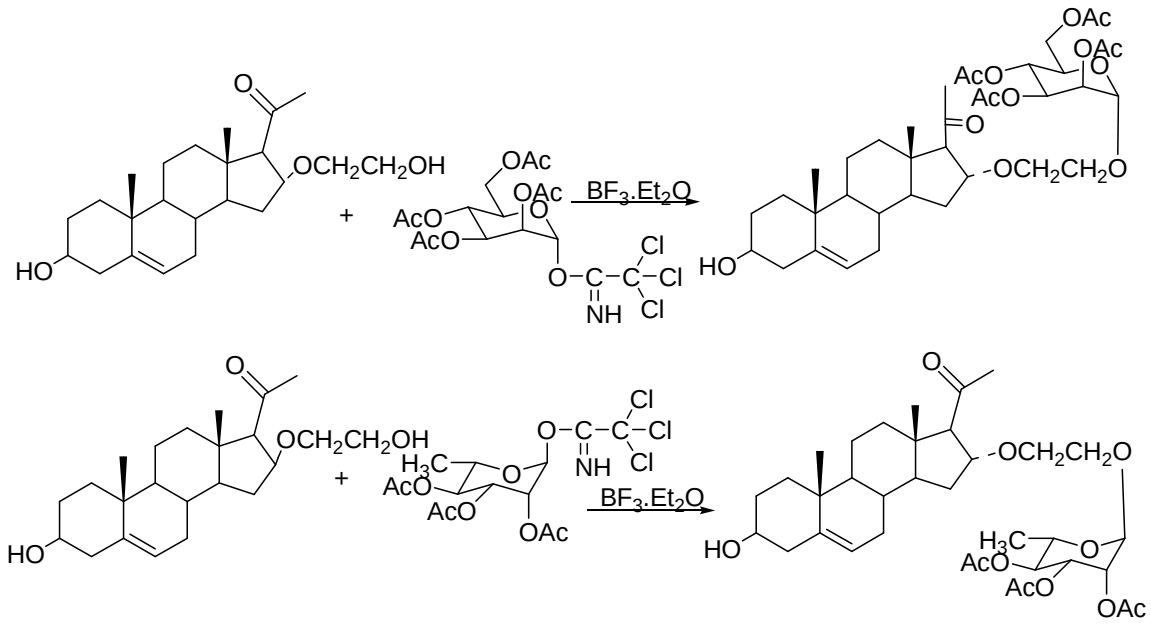

Figure 17: First reported synthesis of glycosidation in the pregnane side chain

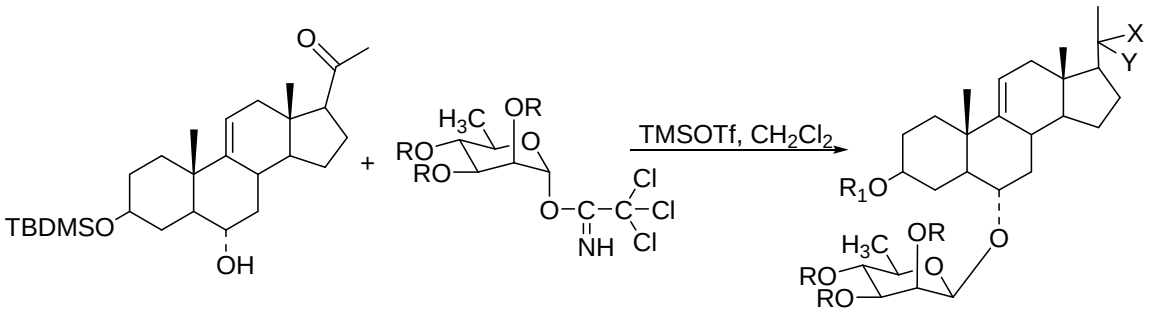

Figure 18: First reported synthesis of Forbeside E3 and E1

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Table 7: Synthesis of Forbeside 3 and Forbeside 1

R	R_1	X, Y
OAc	TBDMS	=O
OAc	H	=O
OAc	SO_3.PyH	=O
OH	NaO_3S	=O (Forbeside 3)
OH	NaO_3S	X=H, Y=OH (Forbeside 1)

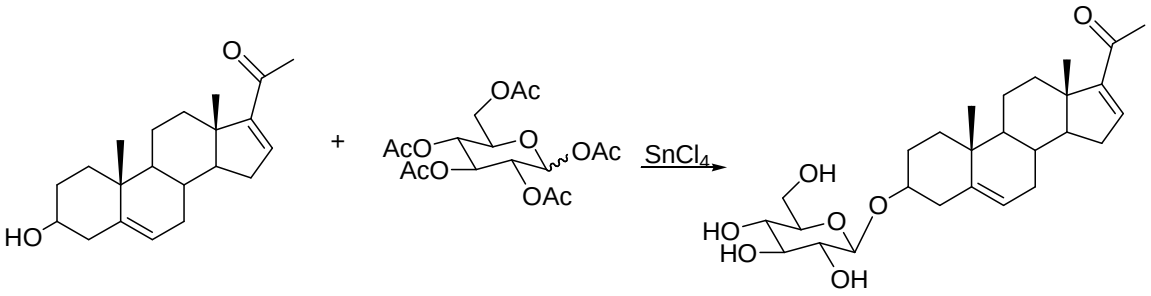

Figure 19: Synthesis of pregnane glycoside by 1-O-acyl method

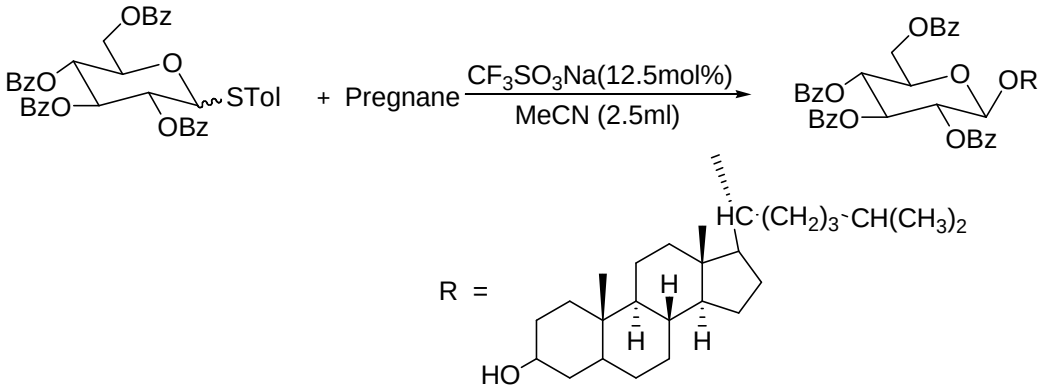

Figure 20: Synthesis of pregnane glycoside from thioglycoside

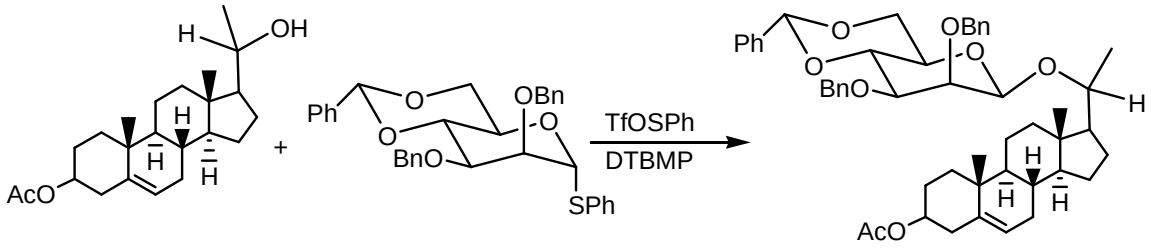

Figure 21: Synthesis of pregnane glycoside via glycosyl triflate

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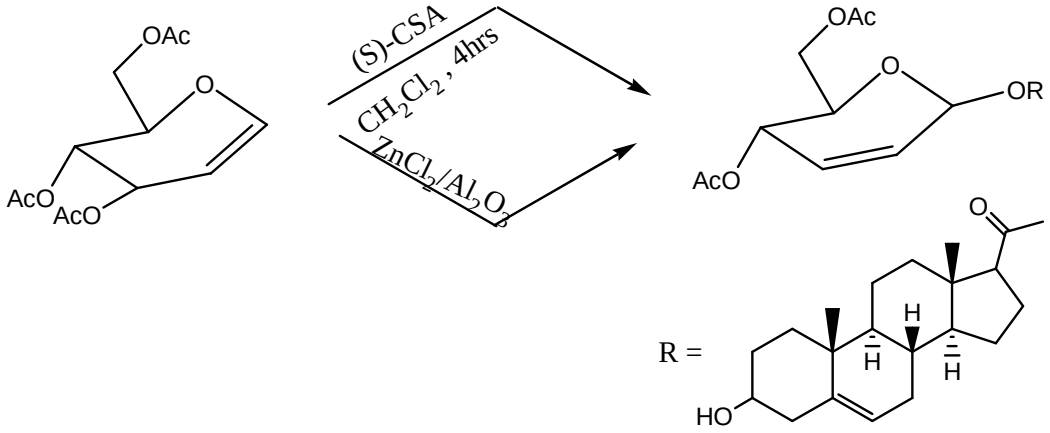

Figure 22: Synthesis of 2,3-unsaturated-O-glycoside of pregnenolone by Ferrier rearrangement

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