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D-GLUCOFURANURONO-6,3--LACTONES. STRUCTURE, REACTIVITY AND SYNTHETIC POTENTIAL.

Structures and nomenclature of D-glucurono-6,3-lactones are presented. Reactions in the tetrahydrofuran ring, in the lactone ring and involving both rings are discussed, demonstrating the high synthetic potential of these lactones. In the first case syntheses of O-glucuronides, biological important N-glucuronides and glucofuranosyluronolactone halides are described. Also esterification and etherification reactions of the hydroxyl group, as well as the regiospecific protection of the OH-1 and OH-2, by formation of 1,2-O-alkylidene derivatives are reported. Reduction and oxidation reactions allow L-gulono-1,4-lactones, D-mannurono-6,3-lactones and D-glucaro-1,4;6,3-lactones to be obtained. Elimination reactions, oxidation and reduction reactions involving the lactone ring are discussed, as well as nucleophilic reactions and inversion of configuration, which allow L-idurono-6,3-lactones to be attained. Syntheses of 5-deoxy sugars, amino sugars and 5-deoxy-5-C-methylenic sugars are described. L-Gulofuranurono-6,3-lactone is obtained after consecutive oxidation and reduction reactions involving both rings.

I. INTRODUCTION

D-Glucofuranurono-6,3-lactone [1] (**1**) is the cyclic form of D-glucofuranuronic acid (**4**), one of the three constitutional isomers (**2**), (**3**), and (**4**) of D-Glucuronic acid (Fig. 1), which could be expected to exist among others referred later on. This substance is biologically very important as a constituent of polisaccharides such as heparin, hyaluronic acid and hemicellulose. In animal organisms D-glucuronic acid acts a antipoisoning agent [2].

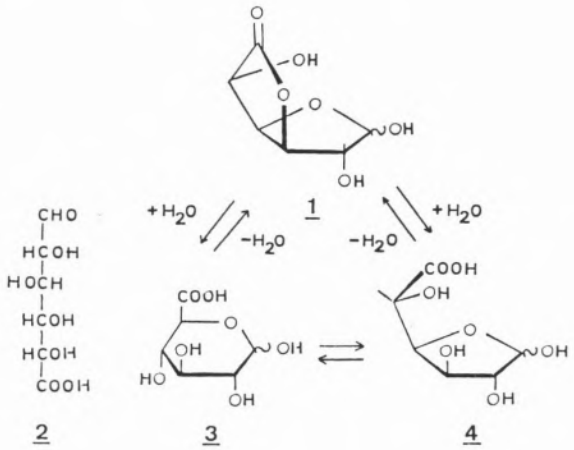


Fig.1

Synthetic methods to obtain D-glucuronic acid by oxidation of D-glucose derivatives were compiled by March [3]. Recently a new oxidation method was developed by Isbell [4]. In aqueous solution D-glucuronic acid exists in the six membered ring form (pyranosidic form) **3**. A second ring like the lactone ring in **1** makes the five ring form (furanosidic form) thermodynamically more stable.

D-Glucuronic acid is isolated only in the form of D-glucofuranurono-6,3-lactone (**1**) in the crystalline state.

Owen, Peat and Jones [5a] synthesized the first derivatives of **1**. After reaction with acidic methanol, they obtained methyl-α-D- and methyl-β-D-glucofuran(osid)urono-6,3-lactones (**5**) and (**6**) respectively [5b] (Fig. 2).

These compounds as well as the 1,2-O-isopropylidenic derivatives [6] like 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) [7] should be stable in alkaline conditions. Nevertheless they reduce the alkaline Fehling- and Benedict solutions as well as Tollens reagent. The non-stoichiometric consumption of the alkaline solutions, also observed by Osman [6] and his coworkers, was not understood during 35 years. The treatment of the derivatives **5**, **6** and **7** with bases,

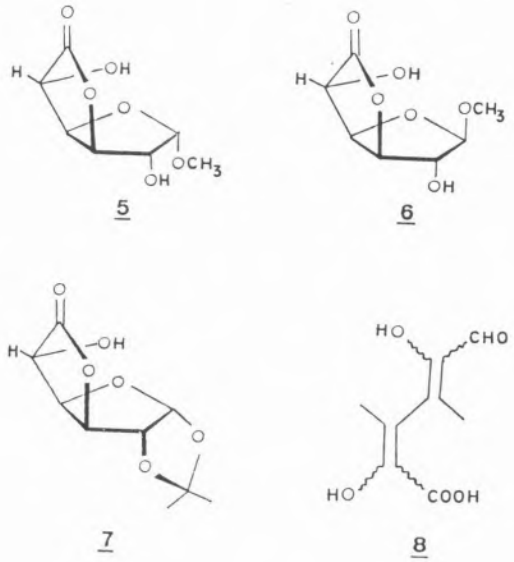


Fig. 2

for example 1,5-diazabicyclo[5,4,0]undec-5-en (DBU) [8] made the isolation of reducing products such as the 2,5-dihydroxy-6-oxo-2,4-hexadienic acids **8** possible. The formation of these substances also explains the reducing behaviour of the derivatives **5**, **6** and **7** in alkaline solutions, which could never be understood when taking their structure into account, because they do not contain any reducing functional group.

The chemistry of D-glucofuranurono-6,3-lactone (**1**) and derivatives have kept organic chemists very busy demonstrating the high synthetic potential of these products for the last forty years [9].

II. STRUCTURE

D-Glucofuranurono-6,3-lactone (**1**) has the structure of a 2,6-dioxabicyclo [3, 3, 0] octane system (**9**). This projection formula for bicyclic systems is similar to the Haworth projection formula for monocycles. It shows more clearly than Fischer projections **10** bonding between atoms and proportions of the molecule (Fig. 3). The numeration of carbon atoms is made according to Fischer. The nomenclature D, L to describe the stereochemistry of the molecules is normally used, although in some special cases [10] the R, S designation of Cahn, Ingold and Prelog nomenclature will be applied to define configuration of chiral centers present in the molecule.

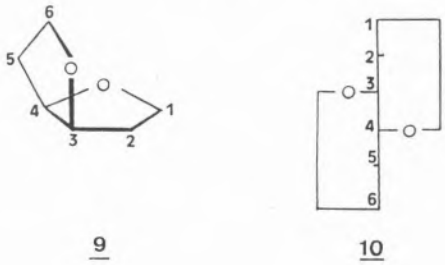


Fig. 3

16 diastereomers are possible in monosaccharides with six carbon atoms. Nevertheless only four of them have the D-*threo* configuration in the carbon atoms C-3 and C-4, which is necessary for the cyclisation 1-4 and 6-3. These four isomers have configurations D-*gluco*, D-*manno*, L-*ido* and L-*gulo*. Depending on the nature of the functional groups present in C-1 and C-6 (methylene-, carbonyl- or hydroxymethylene groups) different derivatives can be obtained with the structure of 2,6-dioxabicyclic[3,3,0]octane system, namely 1, 4; 3,6-dianhydrohexites **11**, 3,6-anhydrohexofuranoses **12**, 3,6-anhydrohexonolactones **13**, hexodialdo-1,4; 6,3-difuranoses **14** and hexaro-1,4; 6,3-dilactones **15** (Fig. 4).

The structure of the D-glucofuranurono-6,3-lactone (**1**) shows a lactone ring L fused with a tetrahydrofuran ring T in positions C-3 and

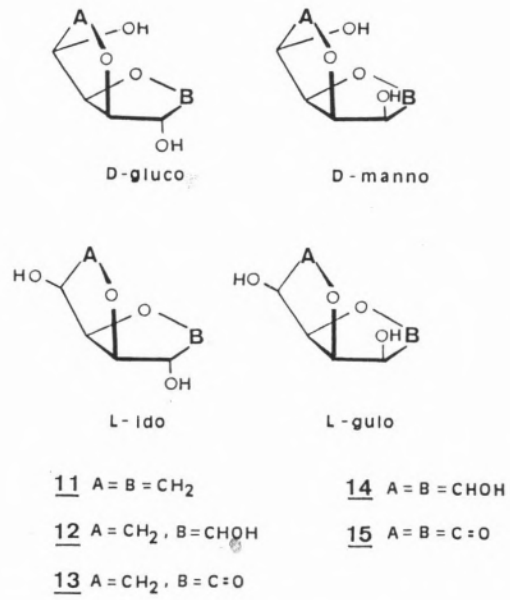


Fig. 4

C-4 (Fig. 5). The lactol group at C-1 is a hemiacetal with two possible configurations at C-1, corresponding to two diastereomers, the α- and β-anomers (α-D- and β-D-glucofuranurono-6,3-lactones). In solution an open chain form **16** (revealed by its reducing properties) and the anomers α and β are in equilibrium giving rise to mutarotation, because of the rapid opening and closing of the tetrahydrofuran ring T.

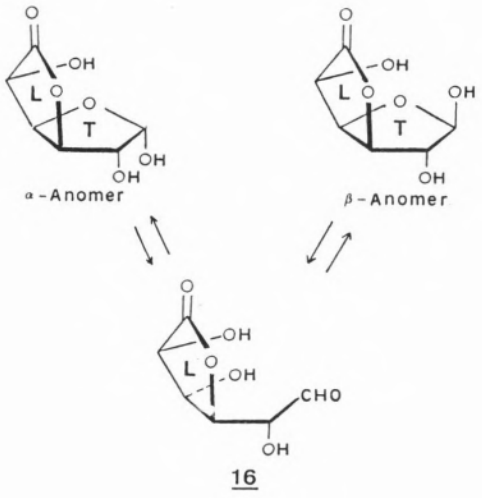


Fig. 5

III. REACTIVITY AND SYNTHETIC POTENTIAL

The reactivity of D-glucofuranurono-6,3-lactones depends on their structure and is described in the three following paragraphs, according to:

1. Reactions in the tetrahydrofuran ring
2. Reactions in the lactone ring
3. Reactions that involve both rings

1. Reactions in the Tetrahydrofuran Ring

Hydroxyl groups in this ring are bonded to the carbon atoms C-1 and C-2 and have a different nature. OH-1 (bonded to C-1) belongs to a lactol group, a hemiacetal that can be selectively protected through the formation of glucuronosides **17** by reaction with alcohols R-OH in acid conditions [5] (Fig. 6), leaving OH-2, a secondary alcohol, free for other reac-

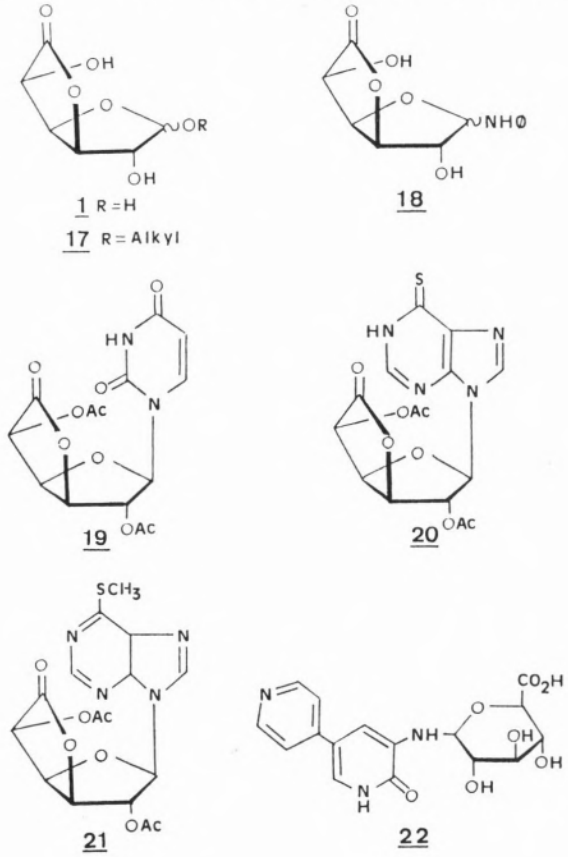


Fig. 6

tions as for example esterifications [9], etherifications [9] and oxidations [11].

The condensation of **1** with aromatic primary amines like aniline yields (D-glucofuranosylamine)urono-6,3-lactones **18** [12], which are easily transformed into the corresponding uronic acids. These are biologically interesting substances because of their similarity to some naturally occuring antibiotics containing hexuronic acid moieties like blasticidin S.

N-Glucofuranuronosides such as the uracil- **19** [13], mercaptopurinyl- **20** [14] and methylmercaptopurinyl- **21** [14] derivatives, these last two showing antitumor activity, result from reaction of the β-anomer of per-O-acylated D-glucuronolactone with silylated uracil and purines (Fig. 6).

Cardiotonic agents such as the N-glucuronide **22** and salts, were easily obtained from **1** in a sodium hydroxide/water solution by reaction with amrinone in water/acetic acid at 70-80°C during one hour [15].

D-Glucofuranosylurono-6,3-lactone halides like the bromo- [16], chloro- [17] and fluoro- [18] derivatives, respectively **23**, **24** and **25** are obtained handling per-O-acylated D-glucofuranurono-6,3-lactones with hydrogen halides or halides of aluminum or titanium (Fig. 7).

A regiospecific protection of hydroxyls OH-1 and OH-2 simultaneously can be reached by reaction with carbonyl compounds in acid conditions, obtaining 1,2-O-alkylidenes. The most 1,2-O-alkylidenes used in carbohydrate chemistry are the isopropylidene- **7** [6, 7, 19, 20], cyclohexylidene- **26** [21], cyclopentylidene- **27** [22] and benzylidene- **28** [23] derivatives.

They are particularly interesting when reacting only with the hydroxyl group OH-5, a secondary alcohol like OH-2. Smooth acid hydrolysis easily regenerates the free hydroxyl groups at C-1 and C-2, after the appropriate modifications at C-5 had been made.

Acylation of uracils is easily accomplished by acyloxonium salts like **30**. This is the intermediate product formed after treatment of 1,2-O-benzylidene-5-O-tosyl-α-D-glucofuranurono-6,3-lactone (**29**) with tetrafluoroborotriphenylmethane $(C_6H_5)_3CBF_4$ in acetonitrile, followed by addition of 2,4-bis-O-(trimethylsilyl)uracil that permits obtaining N-benzoyl uracil **31** from uracil [24] (Fig. 7). Selective reduction of the lactol group from D-glucuronolactone **1** by

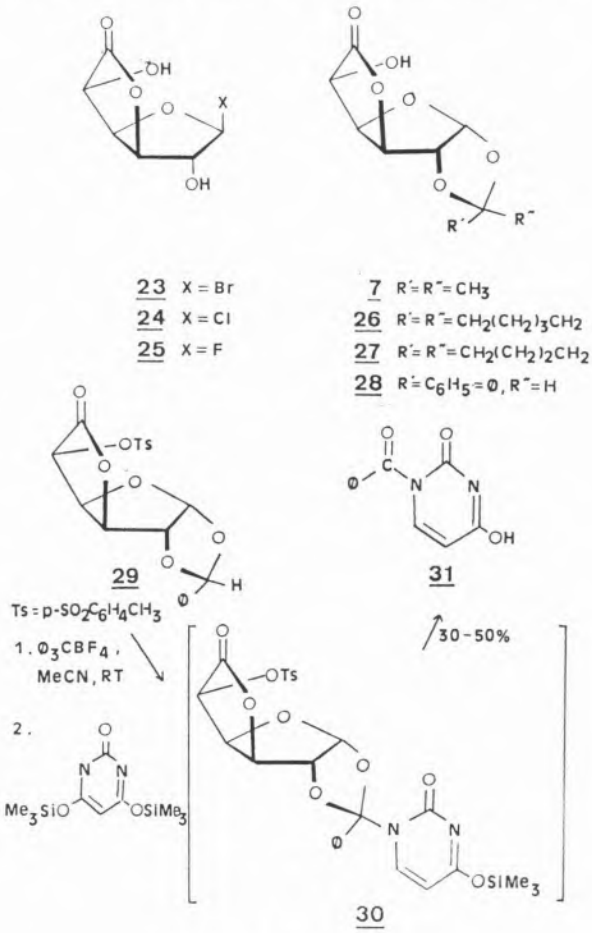


Fig. 7

ruthenium catalysed hydrogenation affords the synthesis of L-gulono-1,4-lactone **32** [25] (Fig. 8). The oxidation of lactol- to lactone function, after protection of the free hydroxyl groups OH-2 and OH-5 is easily accomplished with dimethylsulfoxide-acetic anhydride, resulting in the formation of D-glucaro-1,4;6,3-dilactones like **33** [26]. The oxidation of the hydroxyl function OH-2 with dimethylsulfoxide-phosphorous pentaoxide, after protection of OH-1 and OH-5, followed by stereospecific reduction of the 2-ulose **34** with sodium

borohydride/zinc chloride at room temperature, allows the synthesis of D-mannurono-6,3-lactone **35** [11]

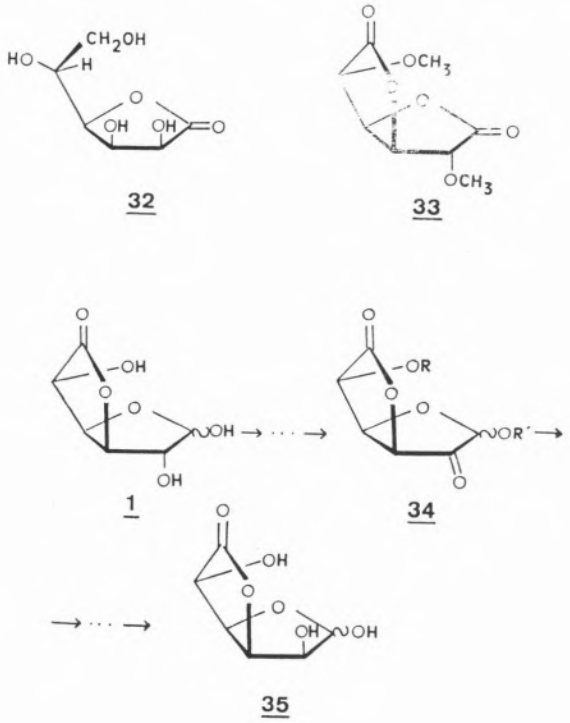


Fig. 8

2. Reactions in the Lactone Ring

2.1 ELIMINATION

D-Glucofuranurono-6,3-lactones have an acidic proton in the α-position to the carbonyl group of the lactone ring and a β-substituted hydroxyl function. This is a structure of an aldol system, that has a tendency to elimination reactions in basic conditions. 2,5-Dihydroxy-6-oxo-2,4-hexadienic acids like **8** (Fig. 9) were isolated from **7** by treatment with DBU [8]. This base abstracts the H-5 proton with the formation of the intermediary product **36**, which cannot be isolated because it also contains an acidic proton H-2 in the α-position to the aldehyde group. The double elimination leads to the formation of **8**. Using a basic reducing agent like sodium borohydride in aprotic solvents, which reduces the aldehyde group of **36**, the isolation of **37** [27] is possible. In Purdie methylations, moist silver oxide functioning as a base originates the elimination and also oxidizes the intermediary product **36** to the carboxylic acid, which is methylated to **38** [5, 28] (Fig. 9).

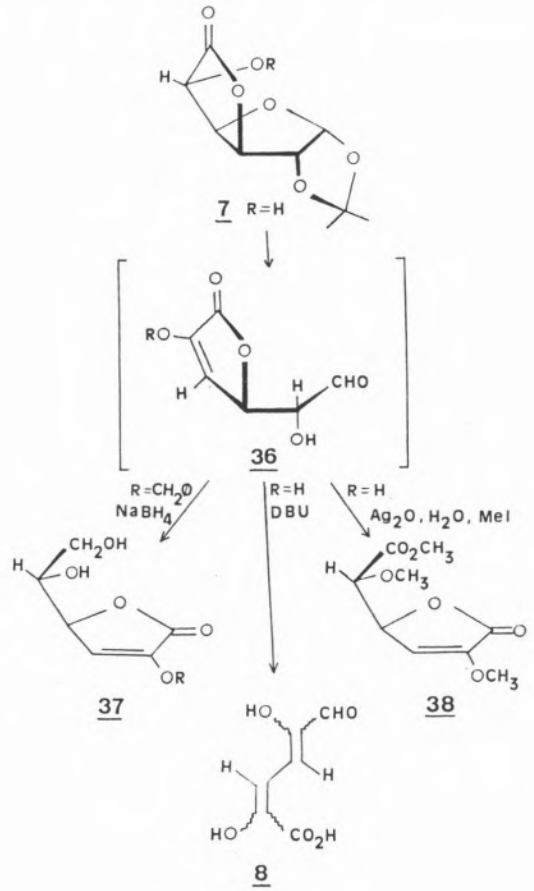
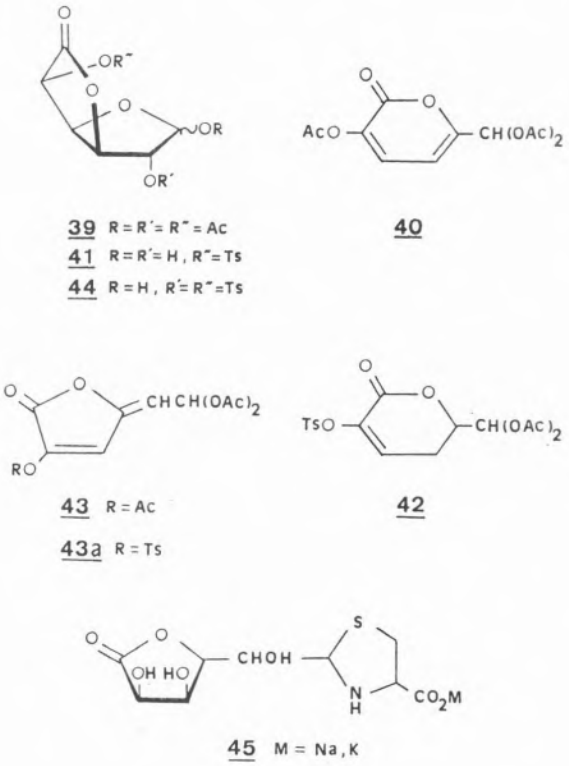


Fig. 9

More recently other products were isolated from elimination reactions of acetylated-, tosylated D-glucuronolactones and D-Glucuronolactone thioacetal [29]. 3-Acetoxy-6-diacetoxymethylpyran-2-one (**40**) was isolated from D-glucuronolactone triacetate (**39**) by treatment with potassium acetate in acetic anhydride containing 18-crown-6 ether at 60°C in 60% yield [30] (Fig. 10). A mixture of **42** in 34% yield and the furane derivative **43** in 30% yield was obtained from 5-O-tosylglucuronolactone **41** under similar reaction conditions at 50°C. The derivative **43a** was isolated from 2,5-di-O-tosylated product

44 only in 15% yield. Treatment of **41** with acetic anhydride and triethylamine leads to the formation of **42**, **43** and γ-pyrone-2-carboxylic acid [31].

Cysteine-glucuronosalts like **45** were prepared treating L-cysteine with **1** at room temperature in the presence of sodium hydrogen carbonate or potassium carbonate [32] (Fig. 10).



39 R = R' = R'' = Ac
41 R = R' = H, R'' = Ts
44 R = H, R' = R'' = Ts

40

43 R = Ac
43a R = Ts

42

45 M = Na, K

Fig. 10

2.2 NUCLEOPHILIC ATTACK. REACTIONS WITH INVERSION OF CONFIGURATION

Nucleophilic substitution reactions in carbon C-5 are quite limited due to structural reasons. On the one hand, depending on the basicity of the nucleophiles, elimination reactions can compete with substitution. On the other hand the nucleophilic attack to the carbonyl group of the lactone ring can occur, leading to a selective opening of this ring. A subsequent reduction allows the synthesis of D-glucofuranose derivatives [27, 33] and 1,5-disaccharides like **46** in 72% yield, by using the reagents sodium borohydride in methanol and acetanhydride in pyridine [34] (Fig. 11).

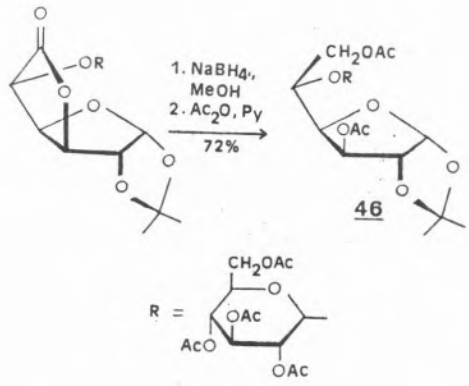


Fig. 11

Nucleophilic substitution reactions at C-5 are only possible when the nucleophile is weakly basic like chloride for example, or when there is a very easily leaving group at C-5 like chlorosulfate. In the first case nucleophilic reactions promoted by the reagent phosgenimmonium chloride are included, which transforms 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) into 5-chloro-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone (**47**) [35] (Fig. 12). This nucleophilic reaction occurs with the inversion of configuration in C-5, allowing an L-*ido* derivative to be obtained from a D-*gluco* configurated substance in 92% yield [35].

Parolis [36, 37] used the reagent sulfuryl chloride in pyridine by -14°C to synthesize the chlorosulfate derivative **48**, which could not be isolated [37], leading to the formation of **47** under inversion of configuration in 80% yield.

1,2-O-Isopropylidene-β-L-idofuranurono-6,3-lactone (**50**) was easily obtained from the 5-O-trifluoromethanesulfonate **49** after treatment with trifluoroacetate and hydrolysis in 82% yield [38], or with nitrite ion in 73% overall yield from **7** [39].

Attempts to oxidize hydroxyl group OH-5 to ulose and reduce it to get the L-*ido* derivative (the method that allowed to obtain D-mannurono-6,3-lactone (**35**) from D-glucuronolac-

tones (Fig. 8) failed, leading to the epimeric mixture L-*ido*/D-*gluco*, in which the D-*gluco* derivative is the main constituent [40]. Nuclear magnetic resonance ^{13}C signals of both epimers were unambiguously assigned by means of 2D-^{1}H-^{13}C correlated NMR experiments [41].

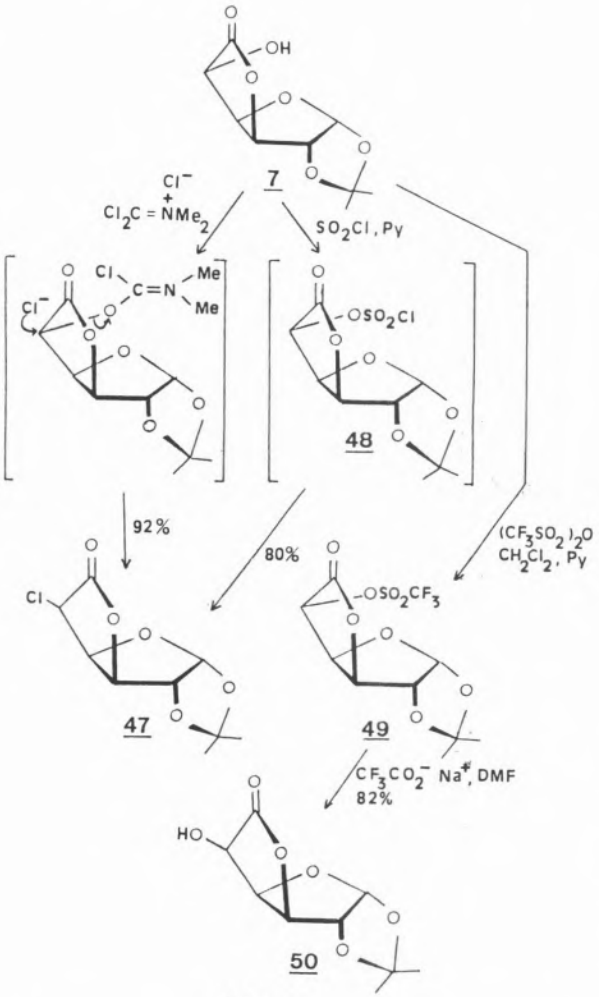


Fig. 12

Mixtures of the diastereomers with the configurations D-*gluco*/L-*ido* were also obtained after treatment of 1,2-O-isopropylidene-5-O-tosyl-α-D-glucofuranurono-6,3-lactone (**51**) with lithium bromide in dimethylformamide [42]. A new method using dibromotriphenylphosphorane allows the stereospecific synthesis of 5-bromo-5-deoxy-1,2-O-isopropylidene-β-L-idofuranurono-6,3-lactone (**52**) from **7** in 75% yield [43]. Reaction of **7** with diethyl azodicarboxylate/triphenylphosphane/nitric acid [44] leads to formation of the epimeric mixture of the 5-azide derivatives **54** and **55**. Diethyl azodicarboxylate/triphenylphosphane/trifluoroacetic acid was used to obtain 1,2-O-isopropylidene-β-L-iduronolactone **50** from the α-D-glucuronolactone derivative **7** in 50% yield [45] (Fig. 13). More recently β-L-ido-

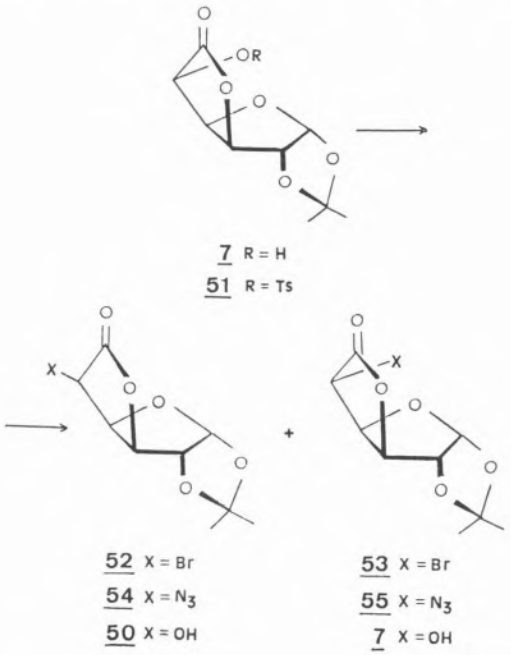


Fig. 13

furanuronates like **57** were obtained by epimerization of the corresponding α-D-*gluco* derivative **56** by treatment with dry methanol containing sodium methoxide at 0° C, but only in 33% yield, being the starting material recovered also in 33% yield. The isolation of the lactone **50** was possible after catalytic hydrogenolysis of **57** with palladium on charcoal in acidic methanol [46] (Fig. 14). The global yield of **50** from **7** is 5%. Baggett [47] used 5-O-tosyl-glucuronolactone (**51**) as a substrate to synthesize 4-methylcoumarin-7-yl-α-L-idopyranosiduronic acid **60**, a fluorogenic substrate for α-L-iduronidase. The inversion of configuration was achieved from **58**, the acetylated reduction product of **51**, with an anion-exchange (AcO^-) resin in acetic anhydride in 67% yield (Fig. 14).

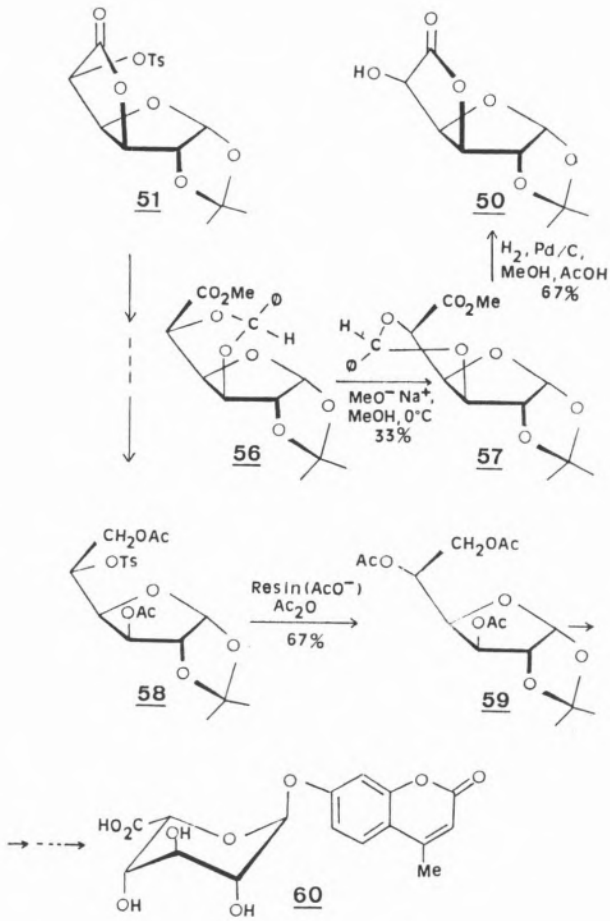


Fig. 14

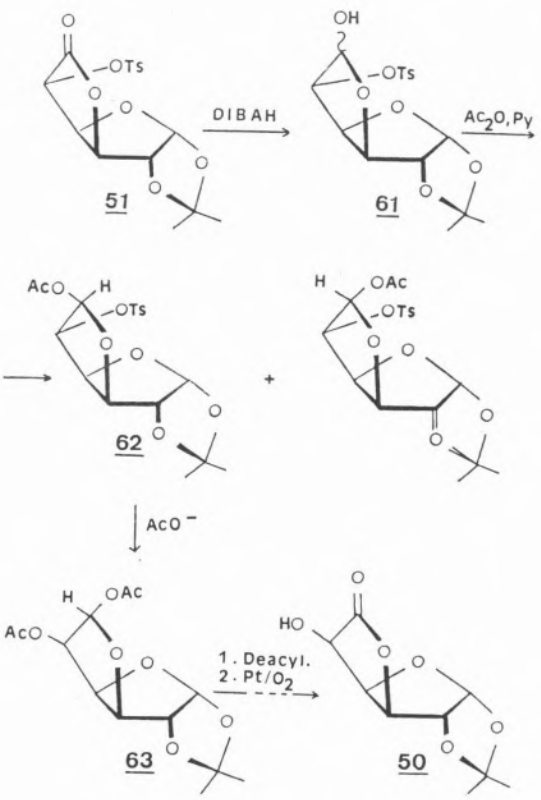


Fig. 15

β-L-Iduronolactone derivatives can also be synthesized from α-D-glucuronolactones without epimerization on C-5. This method involves partial reduction of the lactone- to the lactol group with diisobutylaluminum hydride (DIBAH), obtaining the dialdodifuranose **61**. After acylation, neighbouring group effect of the 6-acetyl (or benzoyl) group of the 6-*exo*-anomer **62** in the presence of acetate ions in a S_Ni reaction, allows the L-idodialdodifuranose derivative **63** to be formed. With the 6-*endo* anomer no reaction occurs, because the mentioned effect is not possible. L-Iduronolactone **50** is obtained after cleavage of protecting groups and oxidation on C-6 with Pt/O_2 at room temperature (Fig. 15) [48].

2.3 OXIDATION REACTIONS

A large variety of reagents has been used to oxidize the hydroxyl group OH-5. Synthesis of 1,2-O-isopropylidene-α-D-*xylo*-5-hexulofuranurono-6,3-lactone (**65**) could be accomplished by oxidation of **7** with chromium trioxide in glacial acetic acid [49], activated manganese dioxide [50, 51] oxygen in the presence of platinum [52], dimethylsulfoxide-phosphorous pentaoxide [53], ruthenium tetraoxide [54], dimethylsulfide-N-chlorosuccinimide [55]. Another method in which very pure 5-uloses like **65** in very good yields are obtained consists of a two step reaction (Fig. 16). **7** is first transformed into the 5-nitrate derivative **64** with acetic anhydride/nitric acid at -20°C. The ulose **65** is isolated after treatment of **64** with piperidine in diethyl ether [54]. The high yields observed in this elimination confirm that the 5-hydroxyl function of **7** has a pro-

nounced reactivity due to the neighbourhood of the carbonyl group.

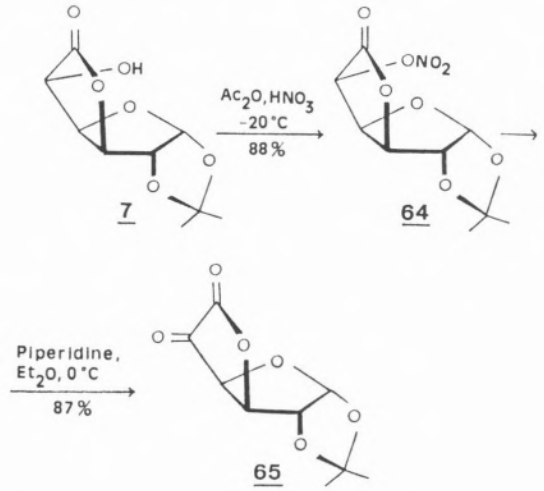


Fig. 16

2.4. REDUCTION REACTIONS

The lactone function can be partially reduced to the lactol group by using DIBAH and subsequent formation of dialdodifuranoses such as **66** [48]. Full reduction to the primary alcohol with lithium aluminum hydride or sodium borohydride results in the formation of D-glucofuranoses such as **67** [11, 27, 33] (Fig. 17).

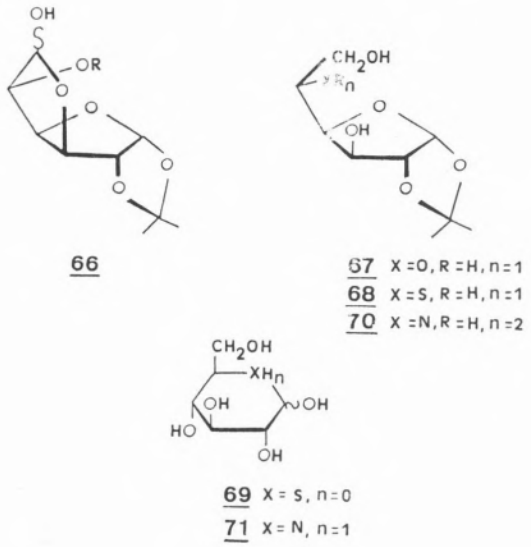


Fig. 17

Using D-glucuronolactone **1** as starting material, substances like 5-thio-D-glucose **69** [56] as well as the antibiotic nojirimycin **71** [57] were obtained in several steps via the reduction products **68** and **70** respectively.

2.5. SYNTHESIS OF AMINO SUGARS

D-Glucurono-6,3-lactones are also appropriate substrates for the introduction of terminal amino groups. After ammonolysis [58, 59] of lactones like **72** to the amide **73**, protection of the hydroxyl group OH-3 and dehydration to the nitrile **74**, a final hydrogenation makes the formation of 6-amino-6-deoxy-D-glucofuranoses like **75** in good yields possible [60, 61] (Fig. 18).

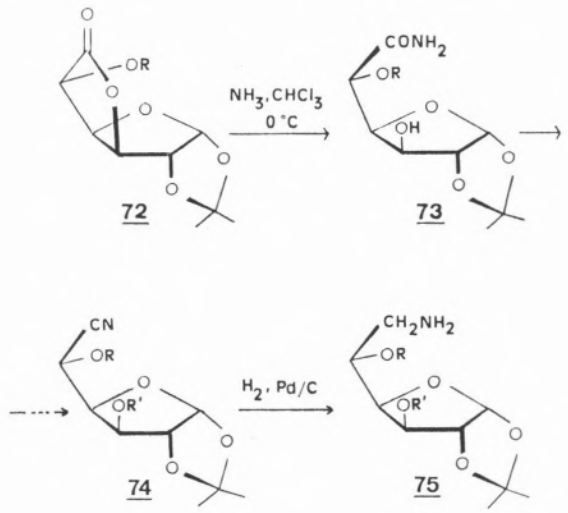
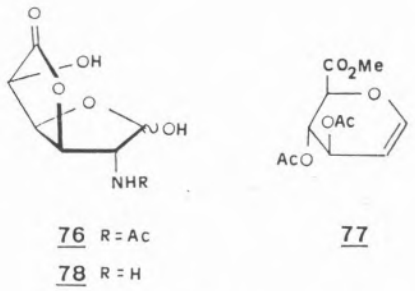


Fig. 18

The synthesis of 2-acetamido-2-deoxy-D-glucofuranurono-6,3-lactone (**76**) was recently developed using the glycal ester **77** as starting material [62]. 1,5-Dideoxy-1,5-imino-L-gulitol is formed on borohydride reduction of 2-amino-2-deoxy-D-glucofuranurono-6,3-lactone (**78**) [63] (Fig. 19).

2.6 FORMATION OF 5-DEOXY COMPOUNDS

Deoxy compounds are quite common in nature and some of them have important antimicrobial activity, among others. Paulsen and Stoye [21] obtained 5-deoxyhexuronolactones after a fragmentation reaction [64] of α-mesyloxyhydrazides. Treatment of 1,2-O-cyclohexylidene-5-O-mesyl-α-D-glucofuranurono-6,3-lactone (**79**) with dry hydrazine results in obtaining 5-O-mesylhydrazide **80**, which is fragmented



76 R = Ac
78 R = H

77

Fig. 19

in the presence of alkali to the ketene **81** (Fig. 20). After intramolecular ring closure the 5-deoxylactone **82** is formed in 30% yield. With hydrazine in excess the 5-deoxyhydrazide **83** will be isolated. Hydrogenation in the presence of Raney Nickel to form the amide **84** and acid hydrolysis transforms it into the 5-deoxy-α-D-*xylo*-hexofuranurono-6,3-lactone (**85**).

The modification of this method using hydrazine hydrate (much easier to handle than dry hydrazine) and N-bromosuccinimide to oxidize 5-deoxyhydrazide **83** directly to 5-deoxylactone **82** succeeded in overall yield of 50% [43]. This method simplified the synthesis of 5-deoxyhexurono-6,3-lactones and enhanced considerably the yields compared to those of the Paulsen method. Nevertheless the reagents dibromotriphenylphosphorane and

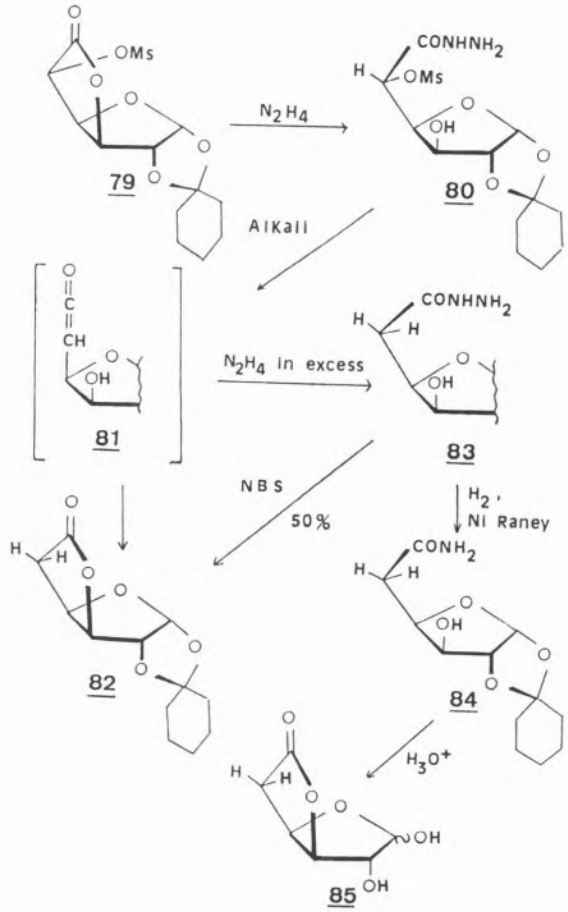


Fig. 20

triphenylphosphane were shown to be the best method to obtain the 5-deoxyhexuronolactones [43]. In the first step of this synthesis 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**7**) is transformed into the 5-bromo-5-deoxy derivative **52** after treatment with dibromotriphenylphosphorane — Horner reaction [65]. This 5-bromolactone is the intermediate product to obtain 5-deoxylactones and for that purpose does not need to be isolated. It reacts with the hydrobromic acid formed in the first step, and triphenylphosphane to give 5-deoxyhexuronolactones like **86**, which was isolated directly from **7** in 50% yield (Fig. 21). The use of pyridinium chlorochromate (PCC), which is known to oxidize enol ethers to esters and lactones [66], made the synthesis of **86** from **87** possible, but only in 30% yield [43].

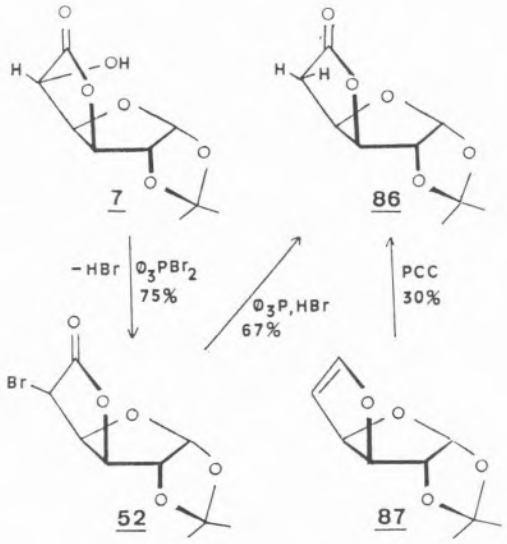


Fig.21

2.7 METHYLENATION ON C-5

The synthesis of 5-deoxy-5-C-methylenic-hexuronolactones was accomplished in good yields via Wittig reactions of 5-hexulolactone **65** using resonance stabilized phosphoranes (Fig. 22). The hemiacetal **88**, which is in solution in equilibrium with the 5-ulose **65**, was used as a substrate to obtain (E)- and (Z)-5-deoxy-5-C-(ethoxycarbonyl)methylene-1,2-O-isopropylidene- α -D-*xylo*-hexofuranurono-6,3-lactones (**89**) and (**90**) respectively in 51% and 27% yields after reaction at room temperature in chloroform [67] with ethoxycarbonylmethylenetriphenylphosphorane [68] (Fig. 22). Treatment of **88** with carbamoylmethylenetriphenylphosphorane [69] under the same reaction conditions only leads to the formation of the **E** isomer **91** in 70% yield [67].

Of great biological importance is the synthesis of 5-deoxy-5-C-methylene-hexuronolactones, which contain the α-methylene- γ -lactone unit responsible for cytostatic, insecticidal, antifeedant and plant growth regulating activities [70, 71]. The mechanism of its action consists of an irreversible inhibition of sulfhydryl enzymes by a Michael type reaction, in which the electrophilic methylene group is

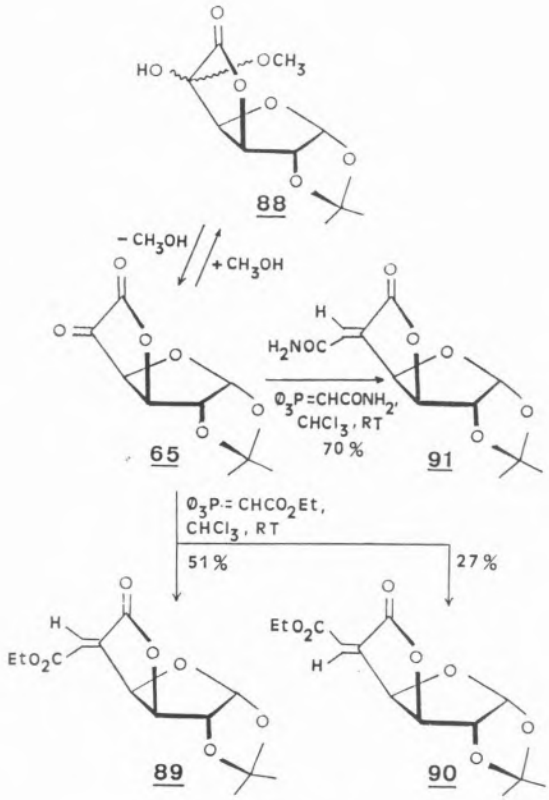


Fig.22

added to the sulfhydryl group of the enzyme. Sugar derivatives containing this unit are already known [72, 73, 74, 75]. The synthesis of 5-deoxy-1,2-O-isopropylidene-5-C-methylene-α-D-*xylo*-hexurono-6,3-lactone (**92**) has also been successfully performed [67]. Due to the tendency of D-glucuronolactones to elimination reactions, most of the known methods to transform α-deoxylactones into α-methylene-lactones [76, 77] that involve basic conditions, cannot be used in these substrates. Wittig reactions with methylenetriphenylphosphorane and 5-hexulolactones like **65** to produce **92** did not succeed [78], also because of the extremely basic conditions of the reagent (Fig. 23). The synthesis of the sugar phosphorane **93**, to react with paraformaldehyde as the carbonyl partner [79] could not be performed. Treating 5-bromo-5-deoxy-1,2-O-isopropylidene-β-L-ido- and/or α-D-glucofuranurono-6,3-lactones (**52**) and/or (**53**) respectively, with triphenylphosphane, an instable phosphonium salt **94** and 5-deoxy-α-D-*xylo*-hexuronolactone **86** were obtained. The elimi-

nation of HBr to get the sugar phosphorane **93** did not succeed using several basic reagents such as sodium carbonate in water/ /methanol solution [80], and also using epoxides, known to produce dehydrohalogenation [81] such as ethylene oxide, propylene oxide and epichlorohydrine. The only product isolated was **86** [78] (Fig. 23). The presence of triphenylphosphane and HBr, spontaneously obtained as a result of the acidity of proton H-5 from the phosphonium salt, which is abstracted from its own anion bromide, generates the necessary conditions to synthesize **86** from **52** and **53**.

Other mild reagents known to transform α-deoxy- γ -butyrolactones into α-methylene-γ-butyrolactones like methylmethoxymagnesium carbonate (H_3C-O-CO_2-Mg-O-CH_3) with subsequent Mannich reaction [82] and also the reagents trioxymethylene and methylanilinium trifluoroacetate [83] ($CF_3CO_2^-$ $H_2N^+(CH_3)C_6H_5$), used to synthesize

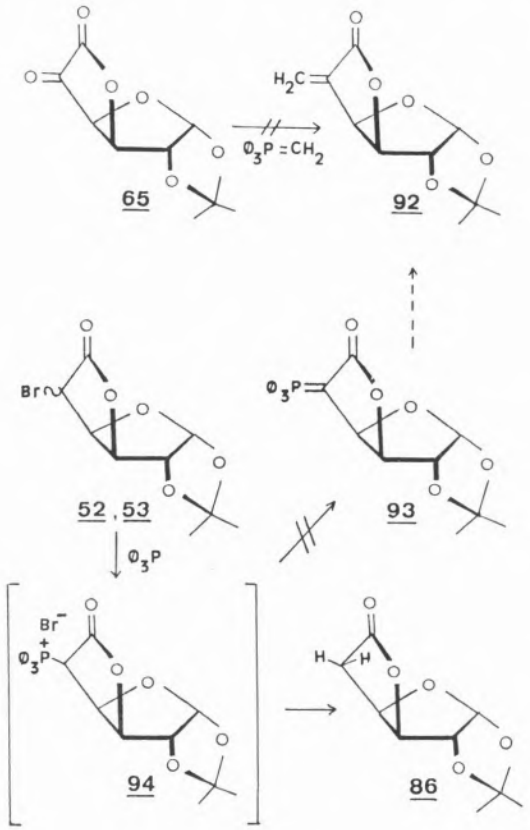


Fig. 23

α-methylene-γ-ketones, could not transform **86** into **92** successfully [78]. Vinyl carbamates are known to be easily transformed into α-methylenelactones by treatment with DIBAH and then with ammonium chloride solution in good yields [84]. The synthesis of the vinyl carbamate **95** from **86** with Bredereck reagent (formaminal methyl ester — $HC(N(CH_3)_2)_2(OCH_3)$) is only possible in very low yield (3%) (Fig. 24). The main product isolated was **96** [78], similar to other products known in the literature, which result from amidation produced by Bredereck reagents [85].

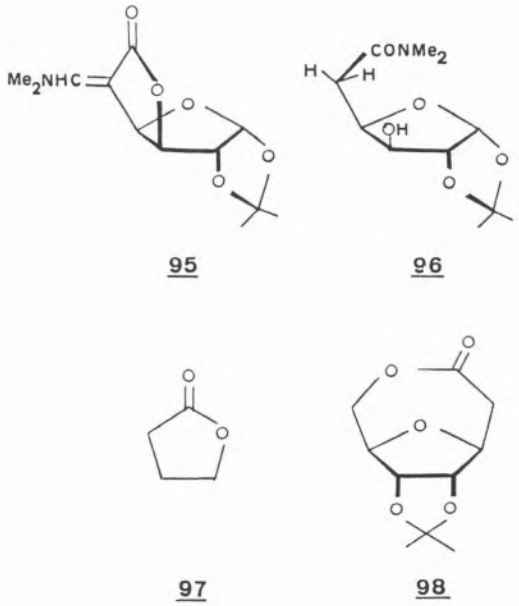


Fig. 24

These experiments show clearly that these bicyclic lactones have a reactivity quite different from that of γ-butyrolactones like **97**, and also lactones of other bicyclic systems like **98**, where a seven ring fused lactone is present [87]. These compounds are easily transformed with Bredereck reagents into vinyl carbamates and then into α-methylenelactones in good yields.

Due to all the structural limitations of D-*gluco*-, L-*ido* and D-*xylo*-hexurono-6,3-lactones, the synthesis of **92** was only possible when developing a strategic concept using 3,6-anhydro-1,2-O-isopropylidene-α-D-*xylo*-5-

hexulofuranose (**99**) as the substrate [67] (Fig. 25), where instead of the carbonyl-, a methylene group -CH_2 in carbon C-6 is present. A Wittig reaction with methylenetriphenylphosphorane in tetrahydrofuran at 0°C succeeded in obtaining **100** in 68% yield, an allyl ether which is easily oxidized with selenium dioxide/acetic acid in dioxane by 65°C to the 5-deoxy-5-C-methylene-hexodialdofuranose (1,4) (**101**) in 65% yield. Final oxidation with silver carbonate/celite by 80°C in toluene made the synthesis of **92** possible [67] (Fig. 25).

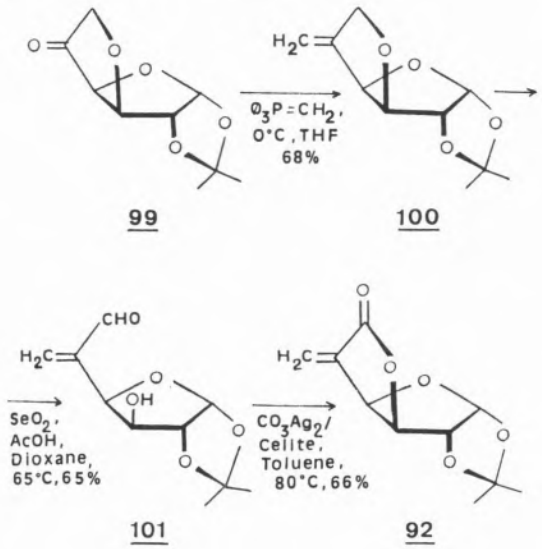


Fig. 25

Introduction of fluorine atoms into the methylenic carbon from α-methylene-γ-lactones produces substances which are also reactive against nucleophiles [88]. Synthesis of 5-deoxy-5-C-difluoromethylene-1,2-O-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone (**102**) was possible from **65** with dibromodifluoromethane-triphenylphosphane-zinc [89] in acetonitrile [78] (Fig. 26).

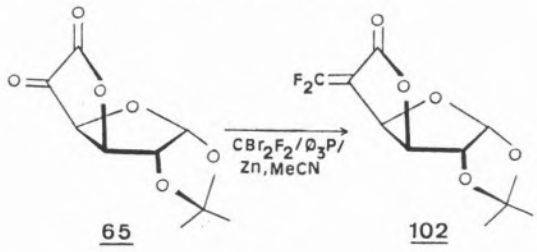


Fig. 26

3. Reactions on both Tetrahydrofuran- and Lactone Rings

The hydroxyl function OH-5 can be selectively protected in transesterifications [90] and etherifications [50, 91] in the presence of OH-2 because of its pronounced reactivity due to the neighbourhood of the carbonyl group. Nevertheless the tosylation of D-glucuronolactone **1** with p-toluenesulfonyl chloride in pyridine yields directly 5-O-tosyl-D-glucuronolactone and 2,5-di-O-tosyl-D-glucuronolactone [92].

Oxidation of OH-5 can be made in the presence of free OH-2 by catalytic dehydrogenation [93] because hydroxyl functions of bicyclic systems in positions *exo* do not react in such conditions [94].

Consecutive reduction and oxidation reactions on the positions C-1 and/or C-6 are also possible and enhance the already too large synthetic importance of D-glucurono-6,3-lactones. By a similar strategy L-gulofuranurono-6,3-lactone (**103**) can be synthesized from D-glucuronolactone **1** (Fig. 27). After reduction of the lactone group on C-6 from **1** to lactol and oxidation of the lactol group on C-1 from **1** to lactone, using the necessary intermediary steps for protection of hydroxyl functions and

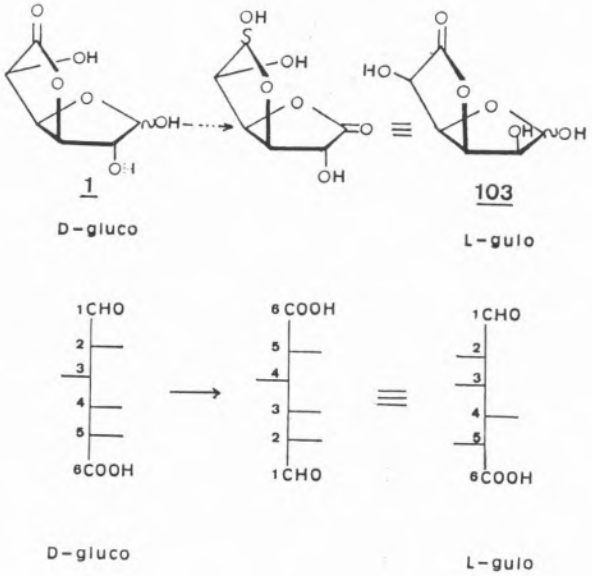


Fig. 27

cleavage of protecting groups, L-*gulo*- is obtained from the D-*gluco* configurated compound [95]. This is called pseudo-inversion. The exchange between the positions of the lactone- and of the lactol functions does not modify the configuration of the chiral carbon atoms. Obtaining L-gulo- from D-glucofuranurono-6,3-lactone (**1**) by this method is the consequence of the convention used to enumerate the carbon atoms of the main chain. The new numeration begins on the carbon atom with the lower oxidation number, which implies the inversion of configuration on C-2 and C-5 (Fig. 27).

IV CONCLUSION

The reactivity of D-glucurono-6,3-lactones makes them very valuable in organic synthesis. They are excellent substrates to the synthesis of the epimers in C-2 and/or C-5, with the formation of products with D-*manno*-, L-*ido*- and L-*gulo* configurations.

Nuleophilic substitution reactions at C-5 originate inversion of configuration or epimeric mixtures of D-*gluco*- and L-*ido* compounds, depending on the reagents used. The occurence of these epimeric mixtures is due to the structure of these bicyclic systems having C-5 on the position α to the lactone group. Nucleophilic reactions on C-5 of dialdodifuranoses or furanoses, partially and fully reduced products, where the lactone group is not present anymore, do not originate epimeric mixtures.

Another very important structural characteristic of these substances is their high tendency to elimination reactions. Responsible for it is the presence of the acidic proton H-5 in α-position to the lactone group and the β-substituted hydroxyl function. The discovery of the elimination products alllowed the understanding of the reducing behaviour of apparently non-reducing sugars.

The high synthetic potential of D-glucurono-6,3-lactones has been demonstrated. They are used to obtain deoxy sugars, amino sugars and other substances of great biological importance such as antibiotics, fluorogenic substrates for α-L-iduronidase, α-methylenated-γ-lactones, cardiotonic agents and antitumor glucofuranuronosides. D-Glucofuranurono-6,3-lactone (**1**) is also one of the substrates transformed into vitamine C by enzymic synthesis in the liver of the rat [96].

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RESUMO

**D-glucofuranurono-6,3-lactonas.
Sua estrutura, reactividade
e potencial sintético**

Após a apresentação da estrutura e da nomenclatura das D-glucurono-6,3-lactonas, é ilustrada a sua elevada reactividade através de reacções que envolvem o anel tetra-hidrofurano, o anel lactona ou ambos os anéis. As sínteses de O-glucurónidos, de N-glucurónidos biologicamente activos e de halogenetos de glucofurano-siluronolactonas são exemplos de reacções no anel tetra-hidrofurano. São também mencionadas reacções de esterificação e de eterificação do grupo hidroxilo bem como a protecção regioespecífica de OH_1 e de OH-2 através da formação de grupos 1,2-O-alquilideno. É apresentada a preparação de L-gulono-1,4-lactonas, de D-glucaro-1,4;6,3-lactonas e de D-manurono-6,3-lactonas, por meio de reacções de redução e/ou de oxidação do grupo lactol ou de OH-2, conforme o caso.

Em relação às reacções que envolvem o anel lactona são discutidas a eliminação, a oxidação, a redução e a substituição nucleófila e inversão de configuração, que permite a obtenção de L-idurono-6,3-lactonas. É também ilustrada a síntese de aminoaçúcares, de 5-desoxi- e de 5-desoxi-5-C-metilenoaçúcares.

A preparação da L-gulofuranurono-6,3-lactona é realizada por reacções consecutivas de oxidação e de redução nos anéis tetra-hidrofurano e lactona.