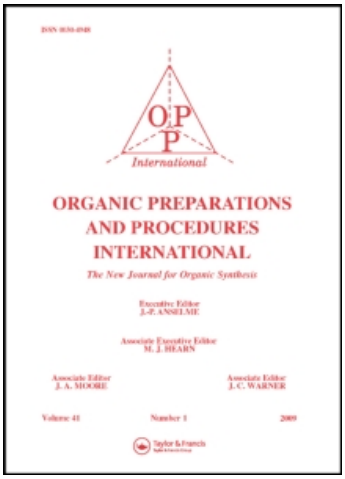

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SYNTHESES OF l-IDURONYL SYNTHONS. A REVIEW

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SYNTHESES OF L-IDURONYL SYNTHONS. A REVIEW

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INTRODUCTION

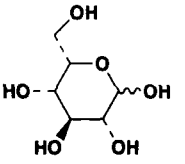
L-Iduronic acid is a typical component of several mammalian glycosaminoglycans, *i.e.* heparin, heparan sulfate and dermatan sulfate, where it plays an important role in various biological processes.[1] Heparin has attracted considerable attention because of its anticoagulant properties, which are at the origin of its clinical use in preventing venous thrombosis. The structure of heparin consists of a carbohydrate backbone made up of alternating 1,4-linked uronic acid (D-glucuronic or L-iduronic) and glucosamine residues. Understanding the action of heparin prompted the development of low-molecular-weight heparins with improved antithrombotic activity.[2] To study the stucture-activity relationship of such polymers, there is a need for chemically pure oligosaccharide sequences which can be only prepared by chemical syntheses.[2b]

The preparation of L-iduronic acid derivatives is much more complicated than that of glucuronic acid derivatives since neither L-iduronic acid nor L-idose are available as starting materials. The preparation of L-ido synthons is a key point in glycoaminoglycan oligosaccharide synthesis and there is a constant need for their efficient preparation. Several routes for the preparation of L-idose from D-glucose have been proposed involving epimerization at C-5 of glucose derivatives. This can be achieved through displacement of a leaving group by a nucleophile or through acid hydrolysis of 5,6-anhydro intermediates formed by intramolecular displacement of a leaving group at C-5. Several other methods for the preparation of L-idose such as hydroboration of a 5,6-enoside or radical reaction generally lead to a mixture of epimers that must be separated afterwards. The reaction of organometallics with pentodialdoses offers, at times, total L-ido selectivities. Other original approachs to L-idose derivatives such as the intramolecular Tishchenko reaction or Bayer-Villiger oxidation are also worth mentioning.

I. DIRECT EPIMERIZATION

L-Idose is a rare sugar which only differs from D-glucose by configuration at C-5. A

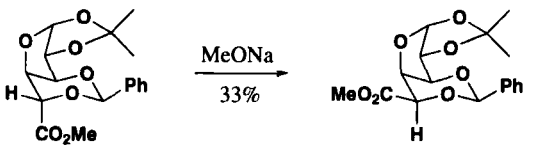
synthetic route based on isomerization at C-5 of D-glucuronic acid to give L-iduronic acid is attractive, because of the availability of the former. An early claim[3] of readily achieved direct epimerization of D-glucopyranosyluronic acid derivative into corresponding L-ido derivative in aqueous alkali was later shown to be incorrect by two groups.[4]



(1)

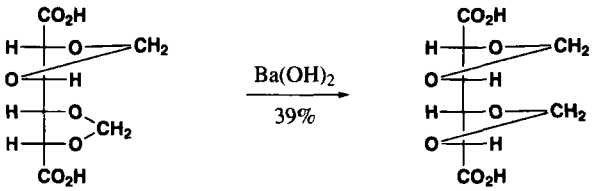
L-idose

The epimerization of 2-*O*-(4-*O*-methyl-α-D-glucopyranosyluronic acid)-D-xylitol promoted by aqueous sodium hydroxide gave the corresponding L-iduronic acid derivative in low yield, the major product arising by β-elimination.[5] More recently, Baggett and Smithson prepared, in low yields, derivatives of L-iduronic acid by epimerization of D-glucuronic acid derivatives that were constrained to adopt a conformation having C-6 in an axial disposition, so that the L-iduronic acid derivatives would be thermodynamically more stable.[6] Thus, methyl 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone, was epimerized to the L-ido analogue in 33% yield (*Eq. 2*).



(2)

The presence of a functional group such as an amide or a nitrile instead of an ester at position C-5 did not allow a better yield for the epimerization, since extensive decomposition was observed. In another example, a D-glucuronic acid derivative was isomerized to a mixture containing the corresponding L-iduronic acid derivative, but the components were not separated.[7] In contrast, di-*O*-methylene derivatives of D-glucaric and D-mannaric acids are readily converted into the corresponding L-idaric acid derivatives (*Eq. 3*).[8]

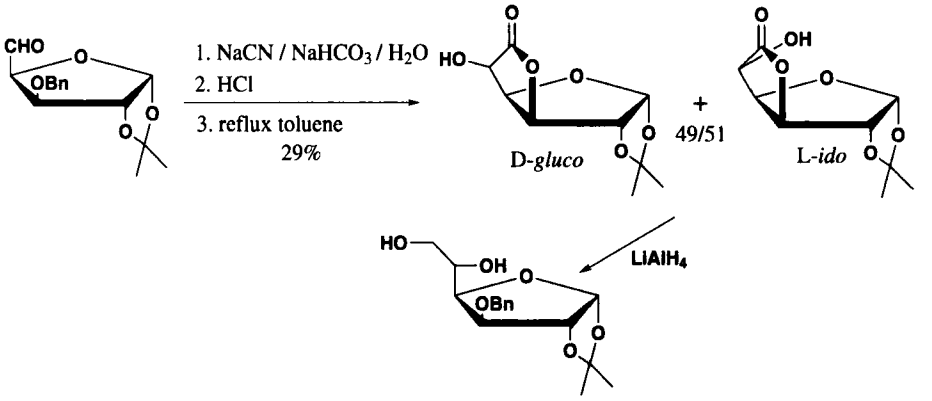


(3)

It has been suggested that this facile isomerization is due to the presence of axial carboxyl groups in the D-glucaric and D-mannaric acid derivatives, which results in conversion into the more stable L-idaric acid derivatives having equatorial carboxyl groups. It thus appears that the essential features in any derivative of D-glucuronic acid to be used for efficient isomerization to L-iduronic acid are that the aldehyde group should be masked and that the carboxyl group should be constrained to an axial position.[9]

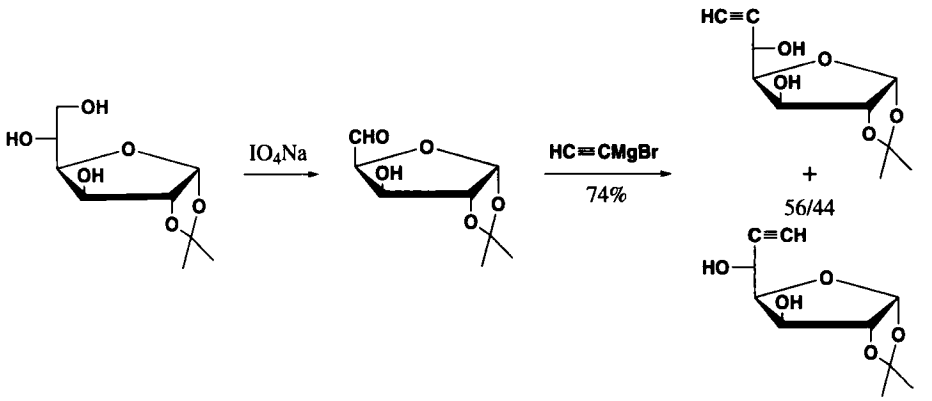
II. CONDENSATION OF NUCLEOPHILES ON PENTODIALDOSES

In 1955, Wolfrom and co-workers reported the condensation of sodium cyanide onto 1,2-*O*-isopropylidene-D-xylo-dialdopentofuranose.[10] The mixture of the epimeric cyanohydrins was converted to the corresponding lactones. After separation, expected 1,2-*O*-isopropylidene-L-idofuranurono-γ-lactone was reduced by lithium aluminium hydride into 1,2-*O*-isopropylidene-L-idofuranose (*Eq. 4*). It was shown that the proportion of the two epimeric products depended in part on the conditions under which the cyanohydrin synthesis took place.



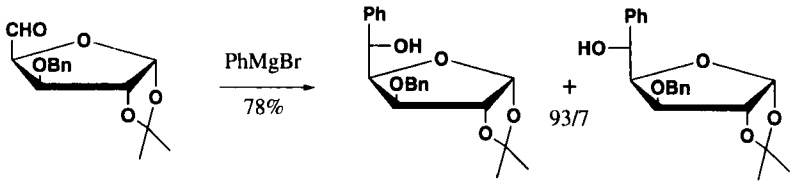
(4)

Until 1986, α-D-xylo-dialdose derivatives were not considered as precursors to L-ido-compounds, since the addition of Grignard reagents onto dialdose derivatives was generally reported to exhibit low diastereofacial selectivity. For instance, Horton and co-workers described the ethynylation of periodate-oxidized 1,2-*O*-isopropylidene-α-D-glucofuranose by ethynylmagnesiumbromide. This reaction led to a mixture of C-5 epimeric products in a 56/44 ratio (*Eq. 5*).[11,7]



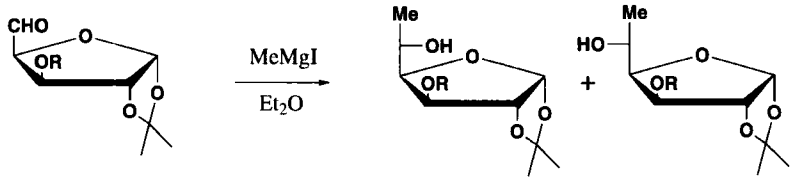
(5)

In contrast, 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-phenyl-α-L-idopentofuranose was successfully obtained by stereoselective addition of ethereal phenylmagnesiumbromide to 3-*O*-benzyl aldehyde[12] (prepared in four steps from D-glucose, 53% overall yield.) (*Eq. 6*).[13] This reaction has been used in 1992 and 1993 as key step in two syntheses of goniofufurone, an anti-tumor compound.[14]



(6)

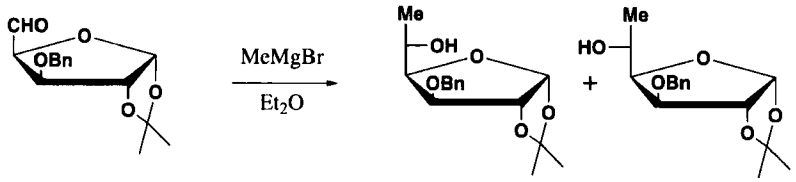
In 1986 and 1991, the addition of methylmagnesiumiodide to pentodialdoses was investigated,[15] and the results of those studies revealed interesting L-ido/D-gluco ratios in the product composition (*Eq. 7*). The stereoselectivity of the reaction was reversed in the presence of crown ethers.



(7)

R = Me : 70/30
R = Bn : 93/7 75% (with $TiCl_4$)

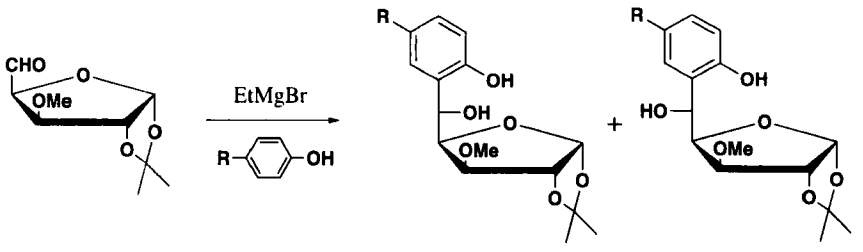
Similar L-ido stereoselectivities were observed with methylmagnesium bromide.[15b] The L-ido stereoselectivity could be improved with addition of Lewis acid such as titanium tetrachloride or zinc chloride (*Eq. 8*).



(8)

Et_2O : 63/37 68%
$ZnCl_2$: 77/23 75%
$TiCl_4$: 82/18 68%

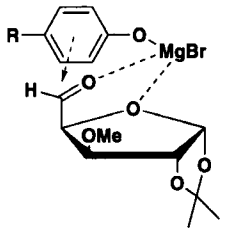
In 1989, highly stereoselective arylations of dialdoses using metal phenolates were reported (*Eq. 9*).[16] The direction of this arylation was very dependent on the nature of the metal species involved, since the use of triisopropoxytitanium salts of phenols led to the reversal of the stereochemistry.



(9)

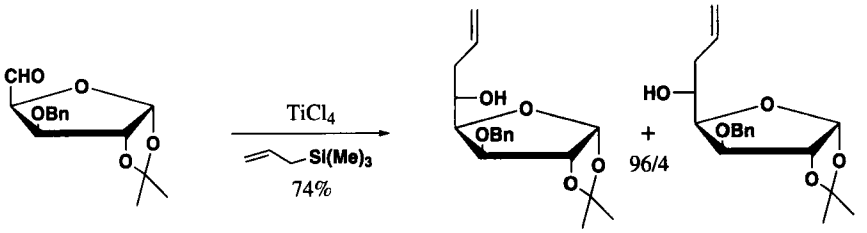
R = H: 97/3 65%
R = *t*Bu: 97/3 78%

Thus, the use of a highly oxyphilic metal promoter (MgBr) which would be chelated between the aldehyde function and the pyran oxygen would favor a *syn* conformer with the consequence that the aromatic ring attacks from the less hindered *si*-face of prochiral C-5 (*Eq. 10*).



(10)

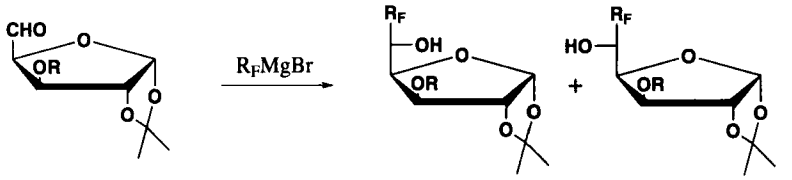
On the other hand, silyl reagents also gave a high L-ido selectivity only with added oxyphilic chelating Lewis acids (*Eq. 11*).[17] A similar result was obtained in 1995 by Loh and his group who involved ytterbium trifluoromethanesulfonate [$Yb(OTf)_3$] in aqueous media. Thus, the L-ido isomer



(11)

was obtained in a 88% yield and a 94/6 ratio.[18] The choice of the Lewis acid plays an important role in the diastereofacial selectivity of the reaction. Thus, the same reaction carried out in presence of $BF_3.Et_2O$ or $SnCl_4$ led to reversed selectivity.

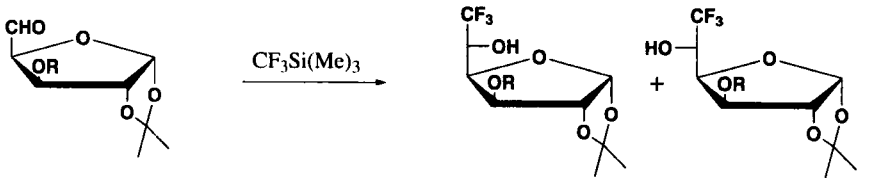
Fluorinated derivatives of carbohydrates have attracted the attention of organic and bioorganic chemists, due to the properties induced by fluorine. Weakly fluorinated sugars, containing one or two fluorine atoms, have been widely studied as part of bioactive molecules.[19] In order to prepare new fluorinated carbohydrates derivatives, Portella *et al.* have studied the stereoselectivity of the nucleophilic F-alkylation of carbonylated carbohydrates by trimethylsilyl or bromomagnesium reagents (*Eq. 12*).[20]



(12)

R = Bn $R_F = C_4F_9$: 64% >95/5
R = Bn $R_F = C_6F_{13}$: 57% >95/5
R = allyl $R_F = C_4F_9$: 68% >95/5
R = allyl $R_F = C_6F_{13}$: 60% >95/5

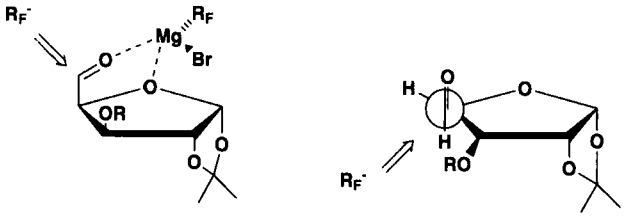
Better yields but lower selectivities were observed with trifluoromethyltrimethylsilane (*Eq. 13*).



(13)

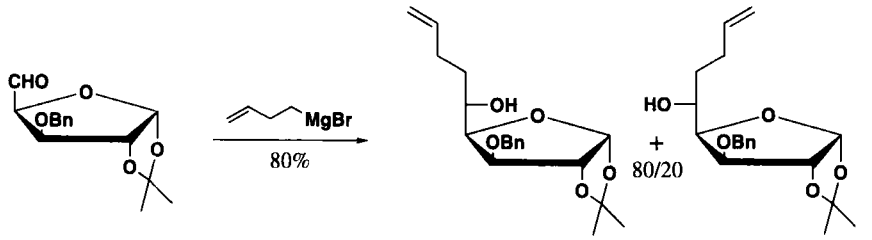
R = Bn : 95% 80/20
R = allyl : 98% 88/12

Comparison with literature data reveals the enhanced stereoselectivity exhibited by perfluoroorganometallic reagents; it is noteworthy that the stereoselectivity with fluorinated reagents is higher than with non-fluorinated ones for both magnesium and silicon reagents. These results could be explained in terms of chelated (with F-alkylmagnesium bromide) or non-chelated (with F-alkyl TMS) transition states (*Eq. 14*).



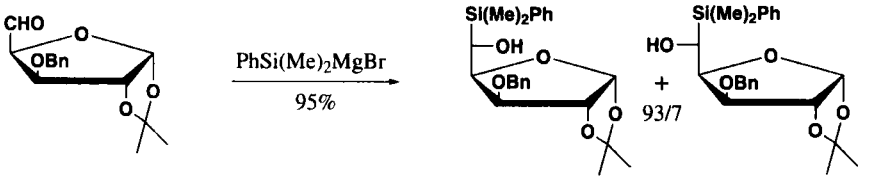
(14)

In order to prepare *bis*-tetrahydrofurans from carbohydrates, the Grignard reagent of 3-bromobut-1-ene has been recently condensed on 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylo-dialdose in a 80:20 ratio in THF (*Eq. 15*).[21]



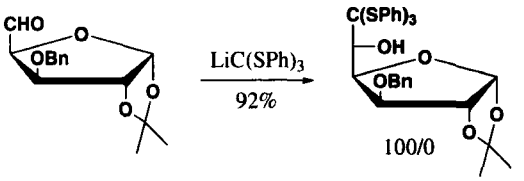
(15)

In 1999, Zamojski *et al.* examined the chain elongation of derivatives of pentoses using several unusual Grignard reagents.[22] The reaction between dimethylphenylsilyl Grignard reagent and 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose afforded L-ido product in a 93:7 ratio and a 95% yield (*Eq. 16*). An opposite stereoselectivity was generally observed in the case of alkoxy-methyl Grignards.



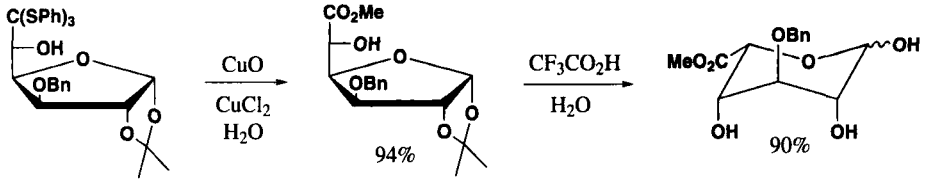
(16)

Very recently, a total L-ido selectivity has been obtained by Bonnafé and his group who added *tris*-(phenylthio)methyllithium to the usual aldehyde (*Eq. 17*).[23] This reaction constitutes one of



(17)

the most attractive routes to various useful L-iduronyl synthons such as methyl(3-*O*-benzyl-L-idopyranosid)uronate (*Eq. 18*).



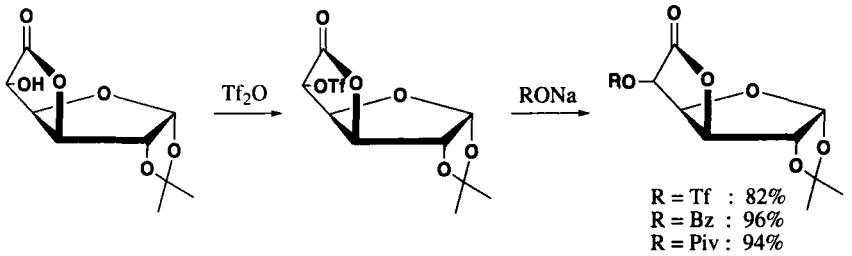
(18)

III. DISPLACEMENT OF A LEAVING GROUP BY A NUCLEOPHILE AT C-5 OF A GLUCOFURANOSE DERIVATIVE

The inversion of configuration at C-5 of glucose derivatives can be achieved through displacement of a leaving group by a nucleophile. This reaction has been performed either on 1,2-*O*-isopropylidene-α-D-glucofuranose derivative or on 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone, both substituted at C-5 by a leaving group.

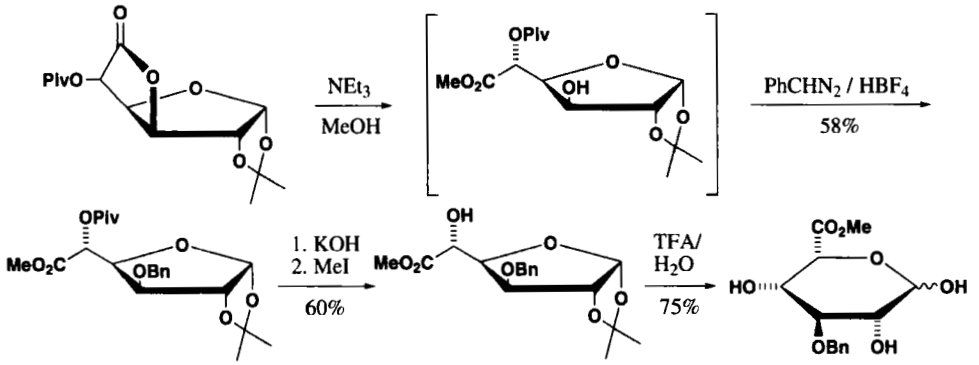
a. Reaction of 1,2-O-Isopropylidene-α-D-glucofuranurono-6,3-lactone

A simple, high yield and three-step synthesis of 1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone has been reported by Weidmann. Inexpensive and commercially available D-glucuronolactone was easily transformed into the corresponding isopropylidene derivative.[24] Indeed, it was demonstrated that the triflyl group introduced at C-5 by esterification with triflic anhydride, exhibited excellent leaving properties when subjected to various oxygen nucleophiles such as sodium benzoate or sodium triflate. Thus, the L-ido derivative was obtained in high yields very smoothly and without by-product formation. More recently, Lassaletta applied the same methodology using sodium pivaloate as the nucleophile (*Eq. 19*).[25]



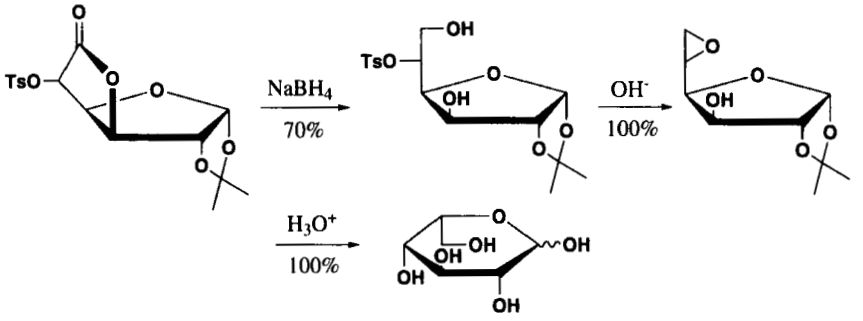
(19)

After selective opening of the lactone ring, the hydrolysis of the isopropylidene acetal performed in aqueous trifluoroacetic acid afforded the L-iduronic acid derivative according to Sinaÿ and co-workers (*Eq. 20*).[26]



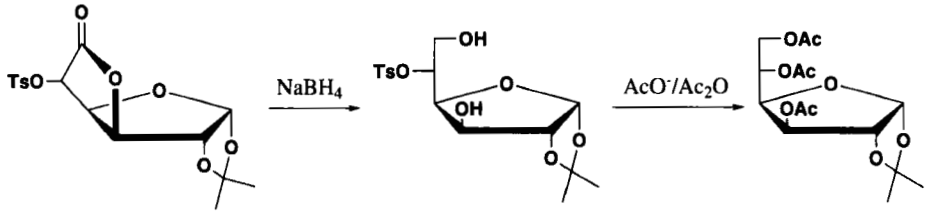
(20)

On the other hand, Defaye *et al.* proposed a simple synthesis of L-idose based on the conversion of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranurono-6,3-lactone into the corresponding 5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose derivative by buffered borohydride reduction. L-Idose was then obtained quantitatively by acid hydrolysis of the 5,6-epoxide resulting from alkaline treatment of the tosylate (*Eq. 21*).[27]



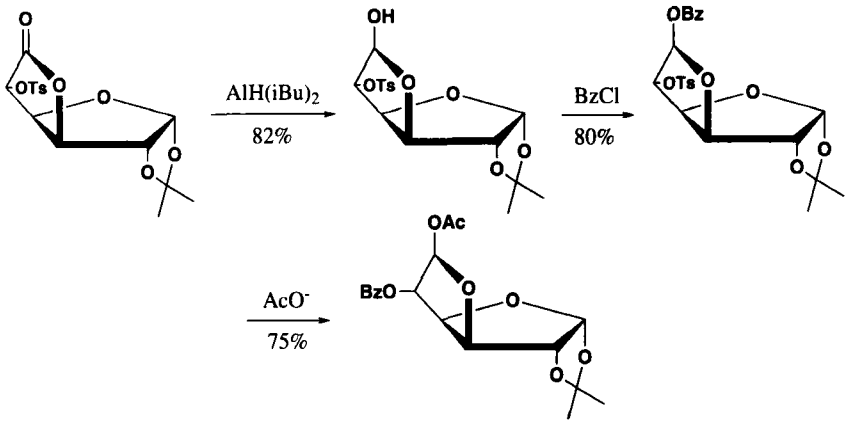
(21)

In 1983, Baggett *et al.* using the tosylate of the same starting glucofuranose shown in *Eq. 20*, carried out an inversion reaction into the corresponding acetate, by conducting the reaction in the presence of an anion-exchange resin in acetic anhydride (*Eq. 22*).[28] A 27% overall yield was obtained from the starting lactone.



(22)

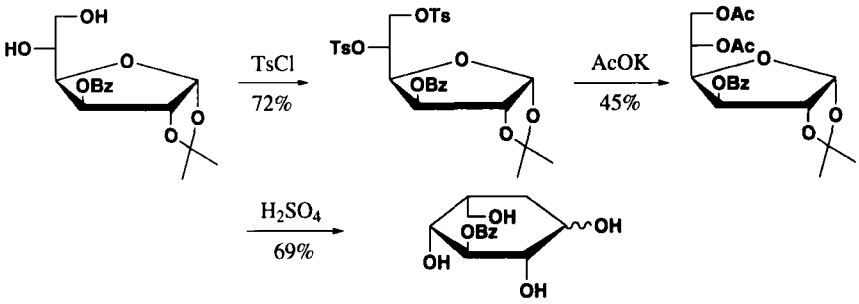
A similar approach involving lactone reduction, appropriate protection of the resulting lactol and inversion of configuration at C-5 by a neighbouring group reaction has been reported by Weidmann (*Eq. 23*).[29]



(23)

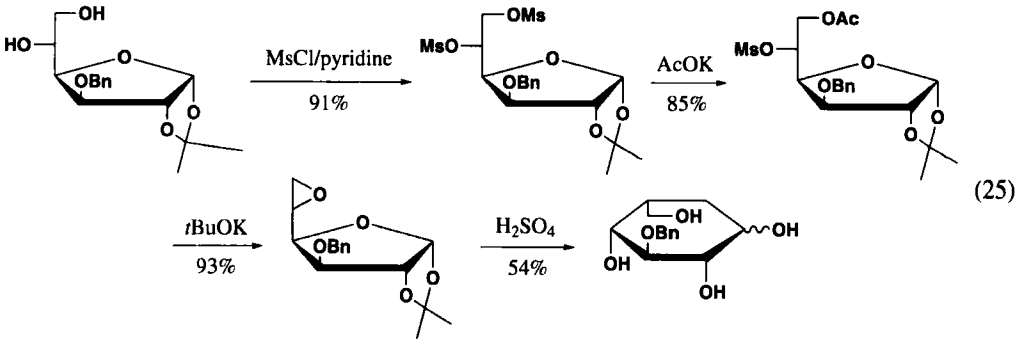
b. Reaction of 1,2-O-Isopropylidene-α-D-glucofuranose

In 1976, Kiss and Wyss reported the inversion of configuration at C-5 of a D-glucofuranose bearing two *p*-toluenesulfonate groups.[30] Thus, 5,6-di-*O*-*p*-toluenesulfonate α-D-glucofuranose was treated with potassium acetate in acetic anhydride leading to 3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose. The latter afforded 3-*O*-benzyl-L-idose by hydrolysis with dilute sulfuric acid (*Eq. 24*).



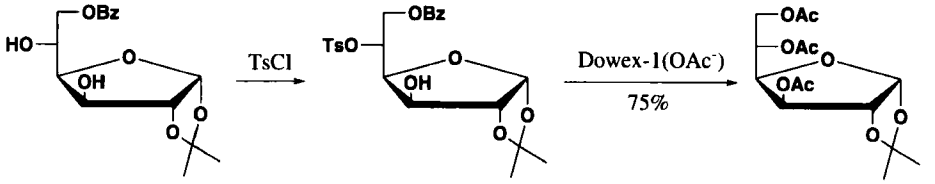
(24)

Another route involving one more step and a better overall yield was devised by van Boeckel and co-workers in 1985.[31] Thus, 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose was first mesylated, and the primary mesylate group was selectively substituted using potassium acetate. Afterwards, treatment with potassium *t*-butoxide, followed by acid hydrolysis afforded the expected β-L-idofuranose derivative (*Eq. 25*).



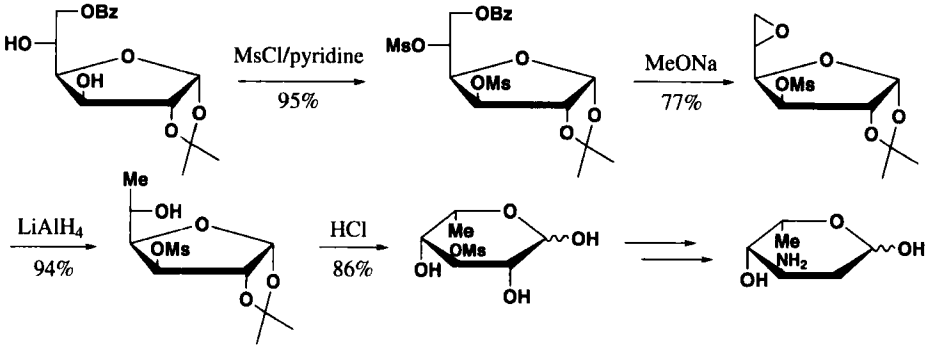
(25)

In 1967, Perchemlides reported a route starting from 6-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose.[32] The replacement of the tosylate group was achieved in the presence of a suspension of dry Dowex-1(OAc$^-$) in acetic anhydride (*Eq. 26*).



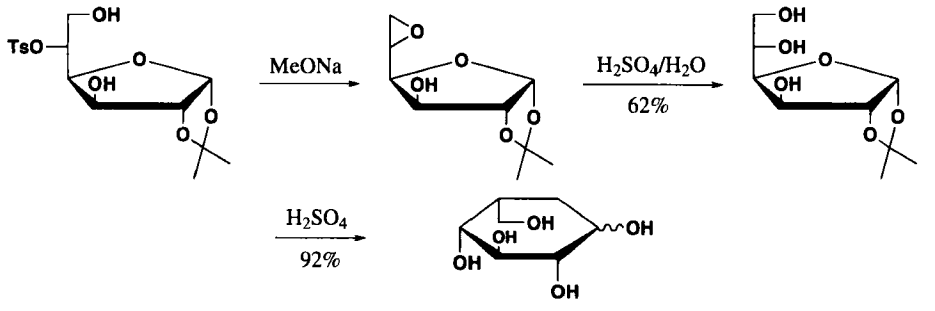
(26)

A similar methodology was applied in 1981 to the synthesis of the antibiotic daunosamine (*Eq. 27*).[33] The acid hydrolysis of the intermediate 5,6-anhydro-1,2-*O*-isopropylidene-β-L-idofuranose



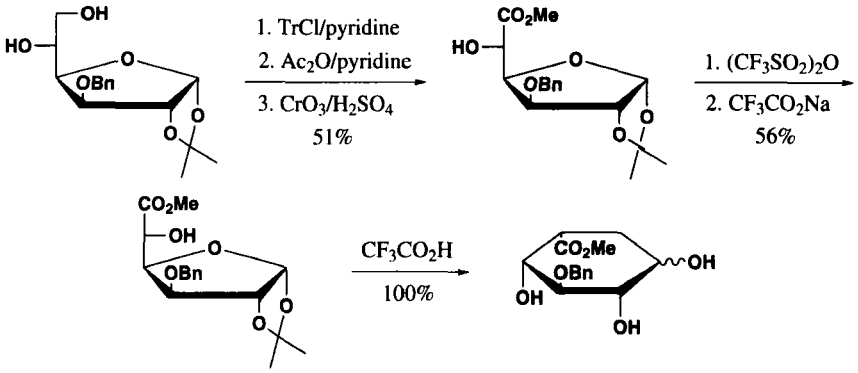
(27)

was examined by Baggett and his group in 1984 (*Eq. 28*).[34]



(28)

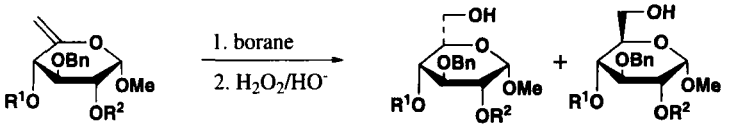
Around the same time, Sinaÿ et al. reported a very attractive preparation of 3-*O*-benzyl-L-ido-pyranuronic acid derivatives involving treatment of a triflate with sodium trifluoroacetate (*Eq. 29*).[35] This strategy has been recently used by Suda in order to prepare various model disaccharides which bind to platelets.[36]



(29)

IV. HYDROBORATION OF 5,6-ENOSIDES

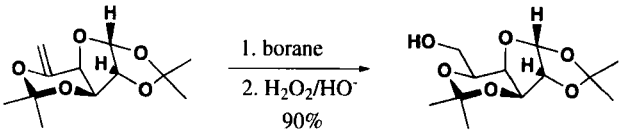
Hydroboration of exo-glucal derivatives may be particularly useful as a route to idose and iduronic acid analogues since conformational preferences may favor the production of the ido epimer. This reaction has been reported both for monosaccharide and disaccharide structures. After preliminary results reported by Lehmann[37] in 1966, Sinaÿ and his group have examined the diastereoselectivity of the hydroboration of variously substituted exo-glucal derivatives.[38] Previous studies showed that the formation of L-ido products is favored when the substituent at C-1 was located on the opposite side of attack by the electrophile at C-5.[39] Variously protected methyl α-D-xylo-hex-5-enopyranosides were subjected to hydroboration, and to a 90/10 ratio could be observed; thus this reaction constitutes an efficient and well-suited route to L-iduronic acid derivatives (*Eq. 30*).



(30)

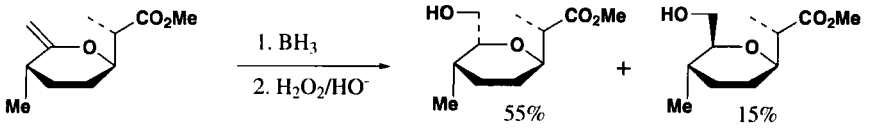
R^1	R^2	borane	Yield (%)	Ido/Gluco	Ref.
Ac	Bn	BH_3	----	60/40	39a
H	Bn	BH_3	91%	77/23	39a
TBDMS	Bz	9BBN	60%	90/10	39b
H	Bz	BH_3	74%	80/20	39b
H	H	$BH_3.S(Me)_2$	80%	80/20	39b
Bn	Bn	BH_3	84%	83/17	40

More recently, Hung *et al.*[41] observed total stereoselectivity during the course of the hydroboration of diacetone α-D-glucose. Indeed, 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranoside was obtained in 90% yield as a single adduct (*Eq. 31*).



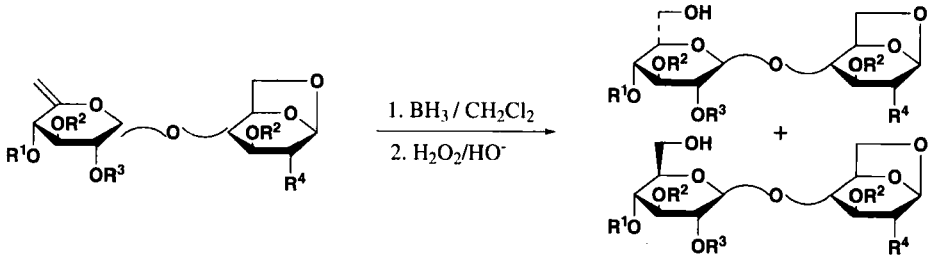
(31)

The hydroboration has been applied to the synthesis of antibiotics such as neomycin B in 1998[40] and antibiotic X-14547A (*Eq. 32*). [42]



(32)

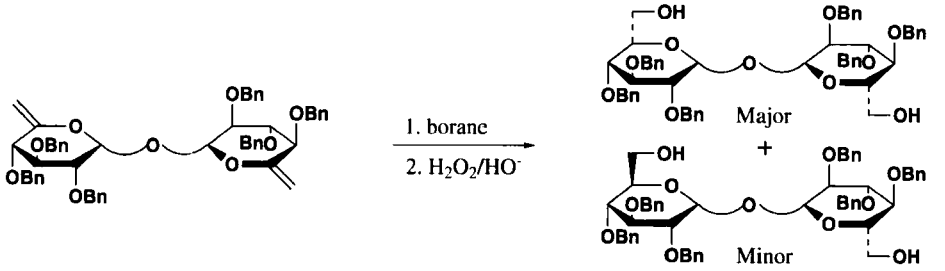
Disaccharides including an L-ido-pyranosyluronic acid moiety constitute building blocks for the synthesis of a partial structure of heparin. Kuzuhara *et al.* have used readily available disaccharides such as cellobiose and reported for the first time, the hydroboration of unsaturated disaccharides in 1983.[43] Unfortunately, only low diastereoselectivities were observed (*Eq. 33*).



(33)

R^1	R^2	R^3	R^4	Yield (%)	Ido/Gluco
Bn	Bn	Bn	Bn	90%	33/67
H	Bn	Bz	N_3	57%	33/67

Recently, the same group converted inexpensive trehalose into a novel disaccharide, β-L-idopyranosyl β-L-idopyranoside, through a double diastereoselective hydroboration of the 5,5'-di-eno intermediate (*Eq. 34*).[44] Subsequently, the major compound bearing the double ido-configuration was

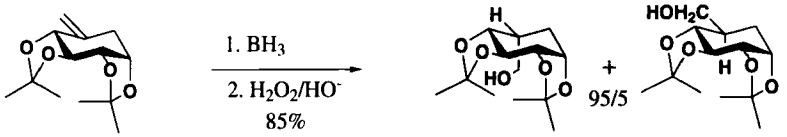


(34)

transformed through a four step-sequence into L-iduronic acid.

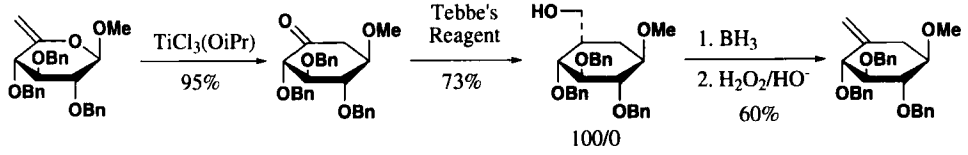
borane	Yield (%)	Maj/Min
9BBN	93%	90/10
BH_3•$S(Me)_2$	82%	78/22

Carba-sugars also called pseudo-sugars, are carbocyclic sugar mimetics in which the endocyclic oxygen atom of the sugar is replaced by a methylene group. As a consequence of this substitution, carba-sugars are hydrolytically stable analogues of their parent sugars and are of interest as tools for the elucidation of the role of sugar hydroxyl groups in biological systems. Moreover, by virtue of their structure, many of these substances are endowed with an interesting range of biological activity in the areas of antibiotics,[45] antiviral and anticancer therapy,[46] sweeteners,[47] enzyme inhibitors,[48] *etc.* Perhaps, the most elegant syntheses of carba-β-L-idopyranose were provided by Ferrier[49] and Barton,[50]who involved a highly stereoselective hydroboration (*Eq. 35*).



(35)

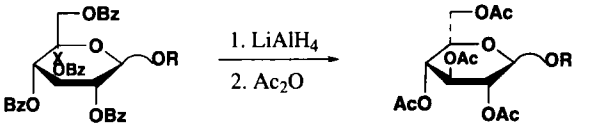
More recently, this reaction has been used by Sinaÿ and co-workers in the course of their synthesis of carbocycles by titanium (IV)-promoted conversion of carbohydrates (*Eq. 36*).[51]



(36)

V. REDUCTION OF 5-BROMO-D-GLUCOPYRANOSES

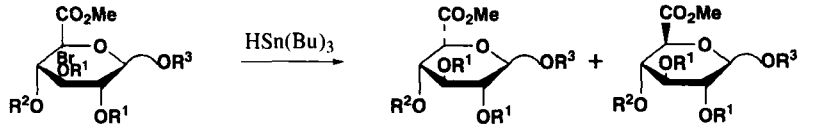
The Ferrier's photobromination of D-glucopyranoses provided 5-bromo-derivatives in good yields.[52] Reduction of these products offered a simple route to α-L-idopyranosides. Initially, Ferrier studied the reduction of halogenated compounds in presence of lithium aluminium hydride and isolated the sole α-L-ido derivative (*Eq. 37*).[53]



(37)

X = Br, R = Ph : 26%
X = Cl, R = Me : 39%
X = Cl, R = Et : 46%

In 1986, Chiba and Sinaÿ carried out the reduction of various 5-bromo-β-D-glucopyranuronates with tributyltin hydride which provided the expected L-idopyranuronates together with the D-gluco derivatives (*Eq. 38*).[54] The stereoselectivity of this reaction has been explained by postulating

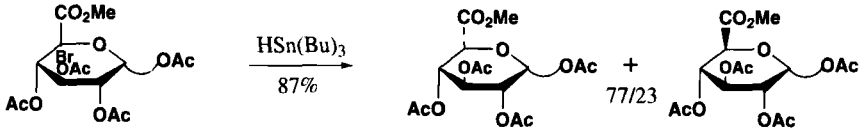


(38)

the formation of an intermediate, bent σ -radical. Thus, this radical reaction allowed the epimerization of a D-gluco pyranosyluronic acid derivative into its L-ido analogue without extensive concomitant β-elimination.

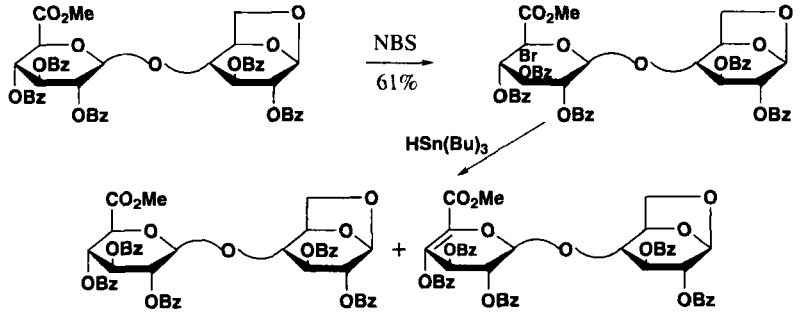
R^1	R^2	R^3	Yield (%)	Ido/Gluco
Ac	Ac	Me	82%	46/54
Me	Me	Me	77%	45/55
Me	Ac	Me	81%	46/54
Ac	Ac	Ac	90%	30/70

In 1994, Medakovic reported the reduction of the α-anomer of methyl tetra-*O*-acetyl-D-glucopyranuronate.[55] The reaction was carried out at lower temperature than previously reported, which resulted in a higher yield of the desired compound. Also, the choice of starting compound was the key in determining the higher yield of L-ido product (*Eq. 39*). Thus, this methodology constituted an efficient isomerization of α-D-gluco pyranuronates to β-L-ido analogues.



(39)

In the course of a program based on the partial synthesis of heparin, Kuzuhara and his group examined the configurational inversion at C-5 in the D-glucosyl group of cellobiose.[43a] Unfortunately, all attempts at the reductive replacement of the bromo substituent in the desired stereochemical fashion failed; the sole reduction product obtained along with corresponding 4'-alkenic derivative had the undesired stereochemistry (*Eq. 40*). The use of triphenyltin hydride or sodium cyanoborohydride was also unsuccessful.

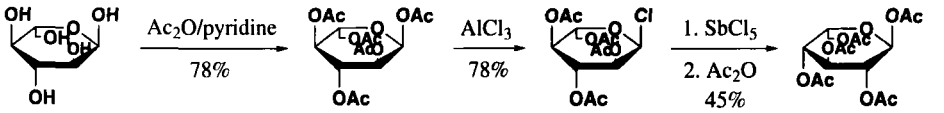


(40)

VI. SYNTHESIS OF L-IDO DERIVATIVES STARTING FROM SUGARS OTHER THAN D-GLUCOSE

a. From L-Glucose

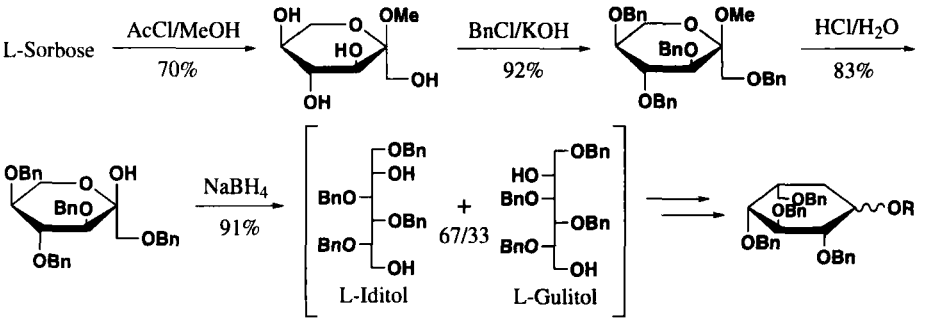
In 1978, Weissmann and co-workers reported the preparation of α-L-idose pentaacetate from the commercially available L-glucose by using Paulsen's methodology involving an elegant acetoxonium ion rearrangement of the intermediate glycosyl chloride (*Eq. 41*).



(41)

b. From L-Sorbose

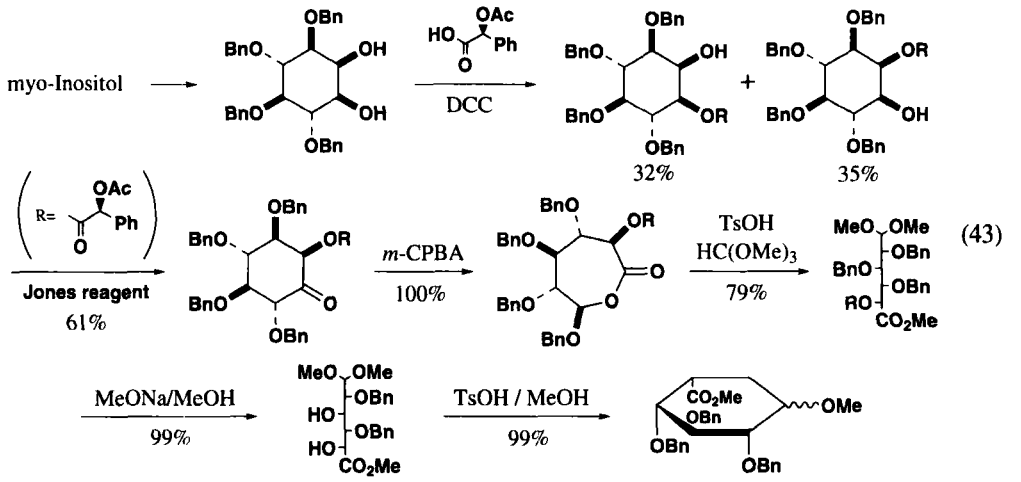
An original route to L-idopyranose derivatives has been described by Rao and his group who involved L-sorbose as starting material.[58] The latter was transformed successively into methyl α-L-sorbopyranoside, methyl 1,3,4,5-tetra-*O*-benzyl-α-L-sorbopyranoside, and 1,3,4,5-tetra-α-benzyl-L-sorbopyranose. Reduction of the latter compound with sodium borohydride in methanol gave, a 2:1 mixture of 1,3,4,5-tetra-*O*-benzyl-L-iditol and -L-gulitol was obtained. After chromatography, the L-ido epimer was oxidized by treatment with aqueous acetic acid to corresponding L-idopyranose derivative (*Eq. 42*).



(42)

c. From Myo-inositol

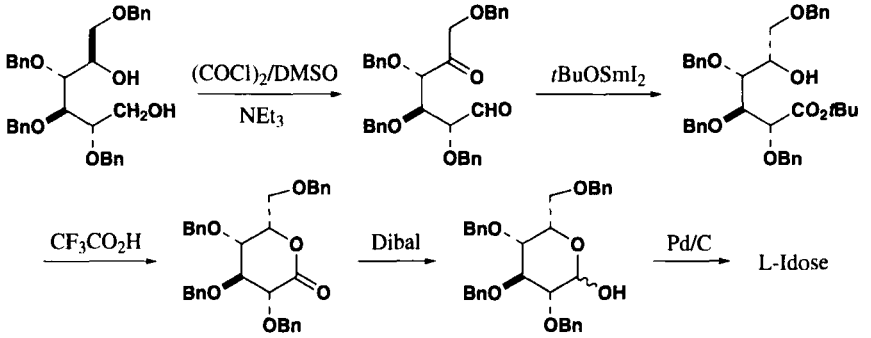
In 1988, Ogawa and co-workers reported an original approach to L-idopyranosiduronic acid derivatives starting from myo-inositol and involving a regioselective Bayer-Villiger oxidation (*Eq. 43*).[59]



(43)

d. From D*-Glucitol*

Recently, Iadonisi and his group have showed that an intramolecular Tishchenko reaction could potentially be exploited as the key-step for a straightforward synthesis of rare L-sugars such as L-idose.[60] Aldulose was first generated from 2,3,4,6-tetra-*O*-benzyl-D-glucitol through a double Swern oxidation and then treated with tBuOSmI$_2$. The t-butyl ester thus formed was then submitted to lactonization, reduction and debenzylation to give L-idose with an overall 65% yield from 2,3,4,6-tetra-*O*-benzyl-D-glucitol (*Eq. 44*). Thus, the highly stereoselective Tishchenko reaction constitutes the key-step of an original and convenient synthesis of L-idose.

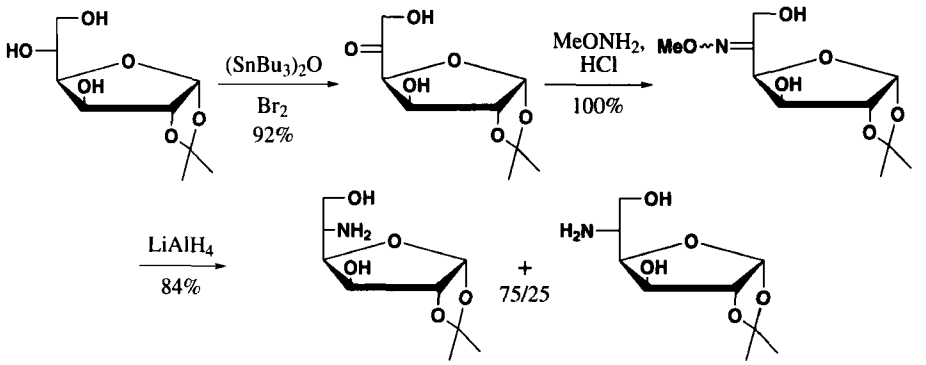


(44)

VII. OTHER REACTIONS

a. Reduction of Oximes

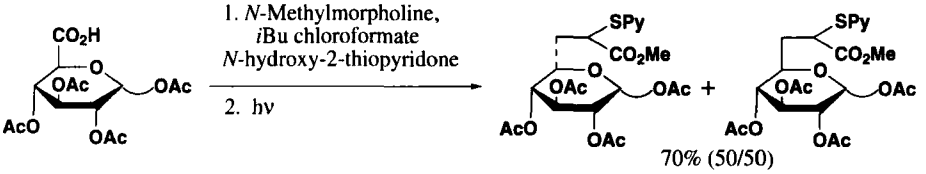
In 1988, Tsuda *et al.* reported a practical synthesis of nojirimycin, a glucosidase inhibitor.[61] Commercially available 1,2-isopropylidene-D-glucofuranose was first regioselectively oxidized at the C5-hydroxyl group and the resulting ketone was converted to the corresponding oxime. According to the nature of the reducing agent, the stereoselectivity of the reduction of the oxime was very different. For instance, when lithium aluminium hydride was utilized, the ido-isomer was obtained in three-fold excess over the gluco-isomer (*Eq. 45*).



(45)

b. Radical Decarboxylation via Thiohydroxamic Esters

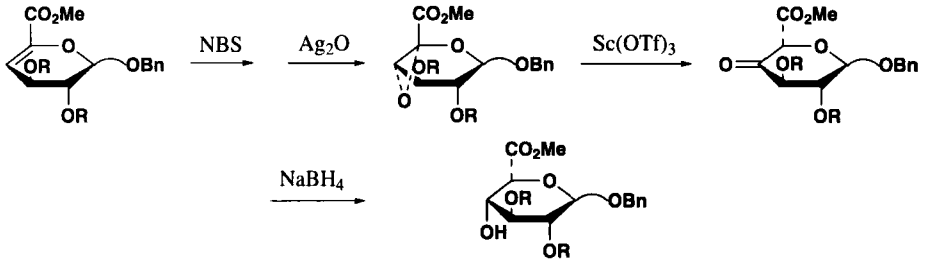
In 1994, Barton and his group reported the radical decarboxylation of 1,2:3,4-di-*O*-isopropylidene-D-galacturonic acid.[62] The corresponding thiohydroxamic ester of the latter, when photolyzed in the presence of methyl acrylate, led to a mixture of two isomers in 70% yield with inversion of configuration at carbon 5 in a 1/1 ratio (*Eq. 46*). In spite of a low stereoselectivity, this radical reaction constitutes an original route to various L-ido derivatives. For instance, an oxidation-elimination of the thiopyridyl group can yield the corresponding unsaturated esters.



(46)

c. Lewis Acid-Catalyzed Rearrangement of Epoxides

In 1997, Linhardt and co-workers reported a regio- and stereoselective synthesis of α-L-idopyranosiduronic acids from Δ4-uronates, based on a Lewis acid-catalyzed rearrangement of epoxides followed by an hydride reduction.[63] The Δ4-uronate was first converted to corresponding bromohydrin which was then transformed into the epoxide in good yields. Treatment of the epoxide with scandium (III) triflate led to the C-4 keto derivative of which reduction by sodium borohydride afforded the α-L-idopyranosiduronic acid as the major compound (*Eq. 47*).

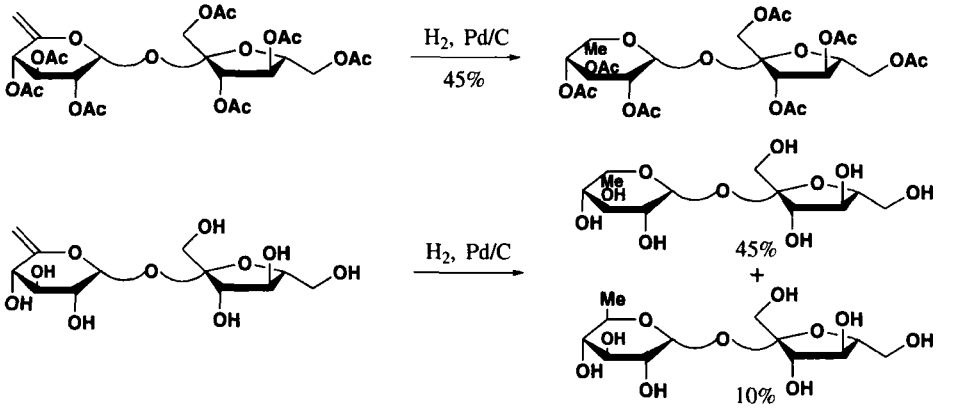


(47)

R = Piv : 63% (from epoxide)
R = TIPS : 53% (from epoxide)

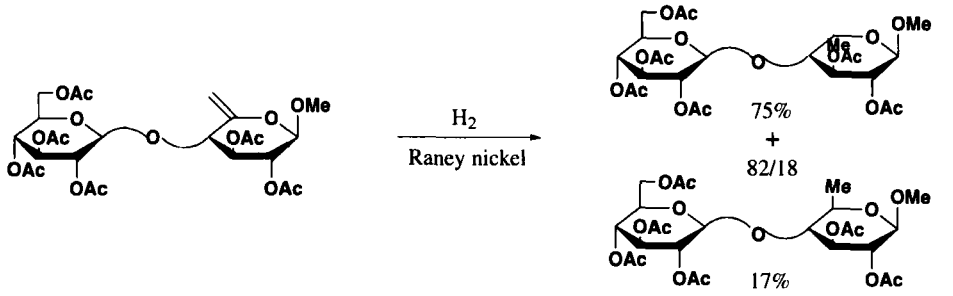
d. Hydrogenation of 5- and 5'-Ene Saccharides

β-D-Fructofuranosyl 6-deoxy-β-L-idopyranoside heptaacetate has been obtained as the sole product in 45% yield by hydrogenation over Pd/C of its corresponding 5-ene derivative.[64] On the other hand, the hydrogenation of the non-esterified derivative under the same conditions provided a mixture of the L-ido and D-gluco isomers in yields of 45% and 10%, respectively (*Eq. 48*). In the same



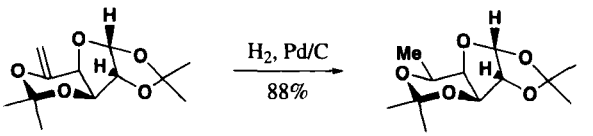
(48)

way, Takeo observed a similar stereoselectivity from the hydrogenation of a 5-enopyranoside arising from cellobiose over Raney nickel (*Eq. 49*).[65] However, hydrogenation over Pd/C gave an inversed stereoselectivity since the D-gluco isomer was obtained in 88% yield along with minor L-ido isomer (6% yield).



(49)

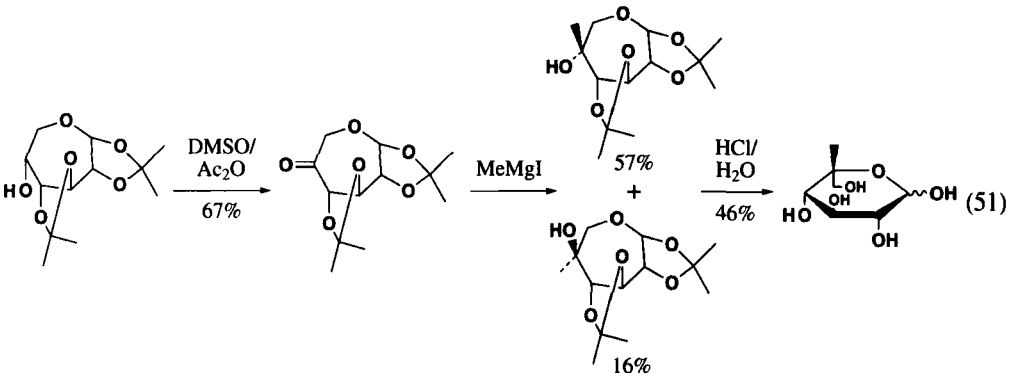
More recently, Hung *et al.* reported the hydrogenation of diacetone α-D-glucose in the presence of Pd/C leading to 6-deoxy-1,2:3,5-di-O-isopropylidene-b-L-idofuranoside as a single diastereoisomer (*Eq. 50*).[41]



(50)

e. Oxidation-Reduction of 1,2:3,4-Di-O-Isopropylidene-α-D-Glucoseptanose

1,2:3,4-Di-*O*-isopropylidene-α-D-glucoseptanose has been isolated from the products of the reaction of D-glucose with acetone in the presence of sulfuric acid.[66] In 1990, Stevens and his group reported an original preparation of L-idose derivatives starting from this D-glucose derivative.[67] The latter was oxidized to the corresponding ketone and then methylmagnesium iodide was added to yield the two 5-C-methyl compounds. After chromatographic separation, 1,2:3,4-di-5-C-methyl-L-idoseptanose was submitted to hydrolysis to give 5-C-methyl-L-idose (*Eq. 51*).



(51)

VIII. CONCLUSION

The great need for L-iduronic acid in bioorganic studies has prompted its chemical syntheses and of its precursor, L-idose, which is not readily accessible in nature. Most of those synthetic methods involved a selective inversion of the configuration at C-5 of D-gluco derivatives in various ways. Nearly 70 years after the discovery of heparin, the synthesis of L-iduronic acid derivatives continues to be a challenge. Indeed, a survey of the literature reveals that most of the reports on the synthesis of iduronates residues often describe long, tedious routes to afford the final products in moderate overall yields.

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