# CARBOHYDRATES CONTAINING SELENIUM

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Abstract - This review describes all the synthetically important methods which have been developed for the preparation of seleno-sugars.

Contents

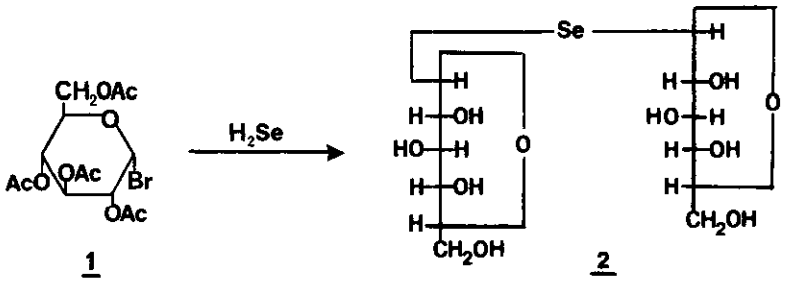


## 1. INTRODUCTION

Organoselenium compounds constitute a significant class of heteroorganic compounds because of their role in synthetic and bioorganic chemistry.[1] While the importance of sulfur in biomolecules has long been known, the occurrence of selenium in naturally occurring seleno-sugars in Astragalus racemosus has just been demonstrated.[2] Selenium has also attracted much attention since the discovery of a Se-depending enzyme, gluthathione peroxidase.[3] Moreover, the chemotherapeutic activity of selenopurines and selenoquanosines is well known.[4] The fact that the chemistry of seleno-sugars is relatively little known in contrast to its potential importance as anti-tumor agents as was recently reported,[5] has encouraged us to collect the literature in this area.

## 2. METHODS OF SYNTHESIS OF SELENO-GLYCOSIDES

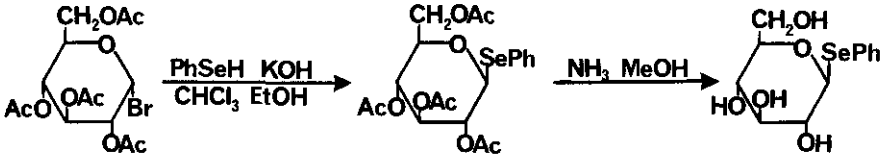
The first seleno-sugar, selenoisotrehalose, was prepared in 1917 by the action of hydrogen selenide on 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1).




1 2

The same literature also records several compounds related to β-D-glucopyranosyl selenide[6] and methyl 6-seleno-bis-(6-deoxy-β-D-glucopyranoside)[6a] which can be oxidized to the corresponding selenoxide.[6b]

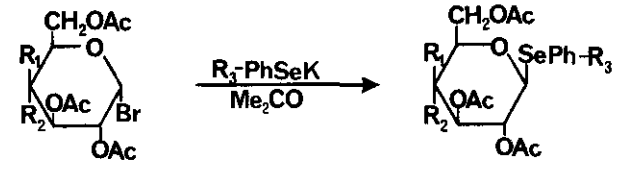
Bonner and Robinson[7] describe the preparation of phenyl β-D-selenoglycoside.




1 3 4

Attempts to oxidize the selenide linkage in compound (4) to the corresponding selenoxide with either hydrogen peroxide or potassium permanganate results in cleavage with the formation of diphenyl selenide and (after reacetylation) D-glucose pentaacetate.

Wagner and Lehmann[8] report the preparation of several phenolic β-D-selenoglycosides.

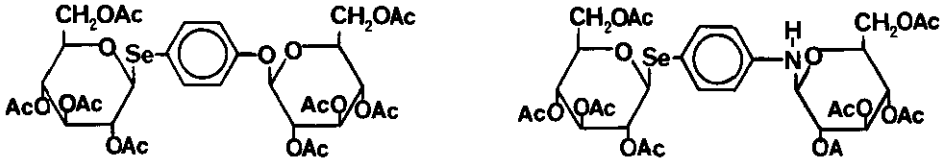



1 $R_1$=H, $R_2$=OAc

5 $R_1$=OAc, $R_2$=H

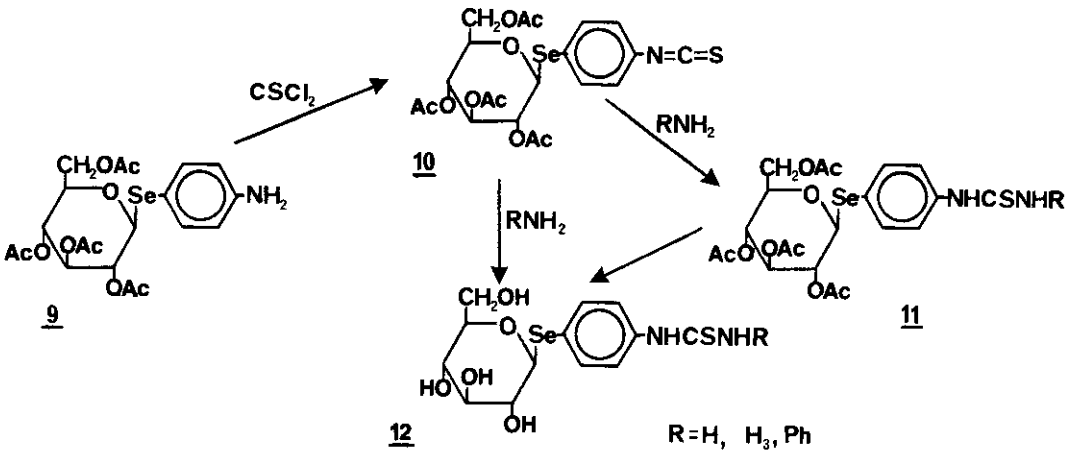
6 $R_3$=H, 4-$CH_3$, 4-Cl, 2-$CH_3$

Wagner's group reports the synthesis of O-Se- and N-Se-bisglycoside of 4-hydroxy- and 4-amino-selenophenol (7) and (8)[9] using the approach previously given.[8]

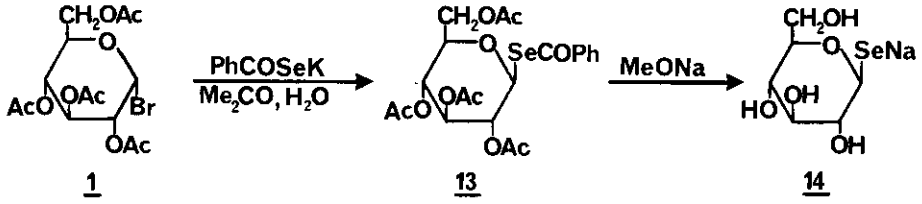



7 8

Wagner and Nuhn[10] have also prepared some hetero derivatives of 4-(O-tetraacetyl-β-D-glucopyranosylseleno)-aniline (9).

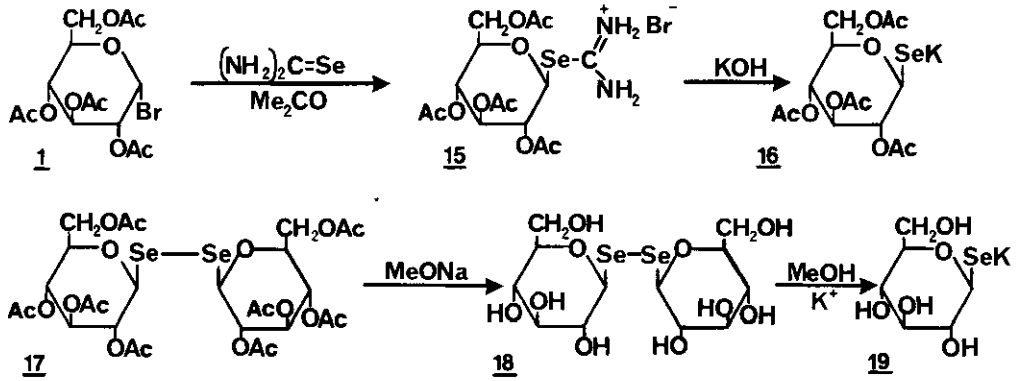



Kocourek and coworkers[11] synthesize the sodium salt of 1-selno-D-glucose as depicted in (14). This selenolate sugar may be used in the preparation of selenoglycosides and other derivatives.



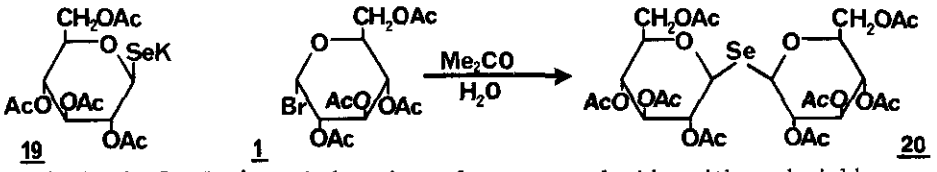

It is to be noted that selenium analogs are generally less chemically stable than their sulfur counterparts.

Another method of preparation of seleno-sugars via a selenopseudo-ureido derivatives is given by Wagner and Nuhn.[12] The reactions sequence starts with α-acetobromoglucose or α-acetobromo-xylose.



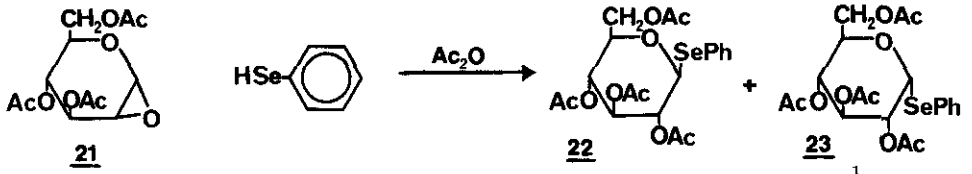

Symmetric and unsymmetric sugar-selenides are obtained in good yields by the condensation reaction of the potassium salt of 2,3,4,6-O-tetraacetyl-1-seleno-D-glucose with an α-acetobromosugars

such as that of D-glucose, D-galactose or D-xylose.



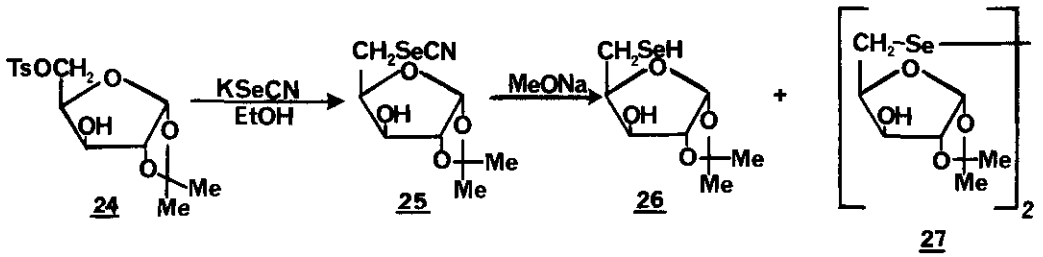
Deacetylation by Zemplen's method produces free sugar-selenides with good yields.

A mixture of α- and β-phenylselenoglycosides is formed by the epoxide ring opening of the Brigl's anhydride (21) by selenophenol.[13] The selenoglucopyranosides obtained can be separated by thin layer chromatography.

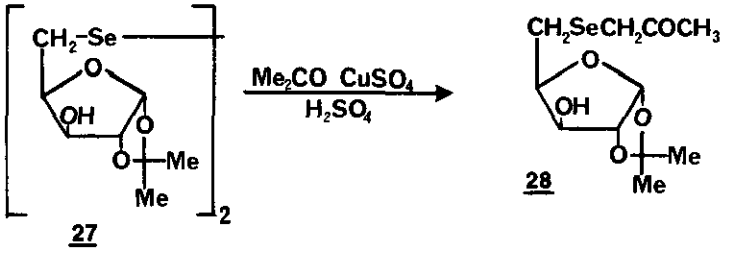


The purity, configuration and conformation of the glycosides are confirmed by $^{1}H$ NMR spectra. Interestingly, the protons cis to the aglycon are shifted to lower field, when compared with O- and -S series of glycosides.

Nucleophilic displacement of the p-tolylsulfonyl group in 1,2-O-isopropylidene-5-O-p-tolylsulfonyl-α-D-xylofuranose by potassium selenocyanate have been reported by Van Es and Whistler.[14] Treatment of 5-deoxy-5-selenocyanate (25) with methanolic sodium methoxide produces a mixture of 5-deoxy-5-selenoderivative (26) and the corresponding diselenide.

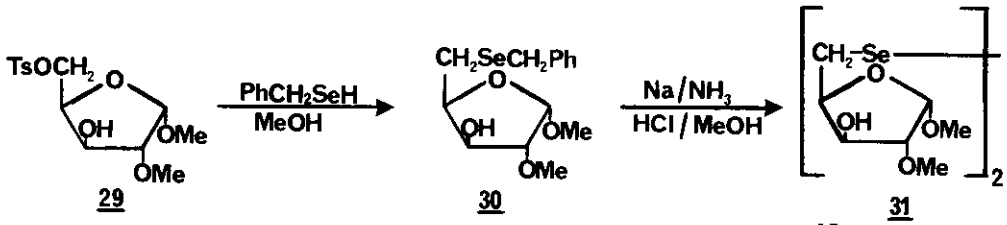


Rabelo and Van Es[15] provide the synthesis of the next derivatives of 5-seleno-D-xylofuranose. The diselenide (37) previously obtained[14] reacted with acetone in the presence of sulphuric acid and copper (II) sulphate to give the seleno-ether (28).



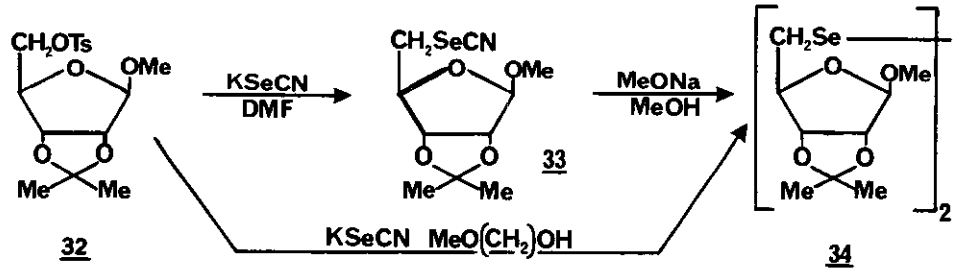
The same ether can be obtained indirectly by cleavage of the diselenide with bromine, followed by treatment of the resulting intermediate selenoyl bromide with acetone in the presence of potassium thiocyanate.

Treatment of α-D-anomer of methyl-2-O-methyl-5-O-p-tolylsulfonyl-α-D-xylofuranoside (29) with the benzyl selenolate ion to give the corresponding 5-selenobenzyl derivative (30). Reduction of this compound with sodium in ammonia, followed by treatment with methanolic hydrogen chloride produces the 5-5-diselenobis(methyl-2-O-methyl-D-xylofuranoside) (31). Attempts to prevent the oxidation to the diselenides by conducting the reaction in the presence of hypophosphorous acid have not been successful.



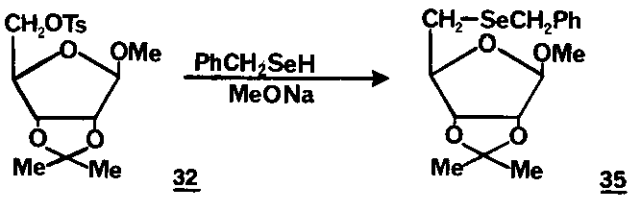

29 30 31

Van Es's group also report a synthesis of 5-seleno-D-ribose derivatives.[17] Displacement of tosyloxy group of (32) with potassium selenocyanate gave 5-selenocyanate derivative (33) which by treatment with sodium methoxide gave the diselenide, 5,5'-diselenebis(methyl-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside) (34). This diselenide (34) was also obtained from the tosyl derivative (32) by prolonged treatment with potassium selenocyanate in boiling methoxyethanol or by treatment with bis(methoxymagnesium) selenide, as illustrated.



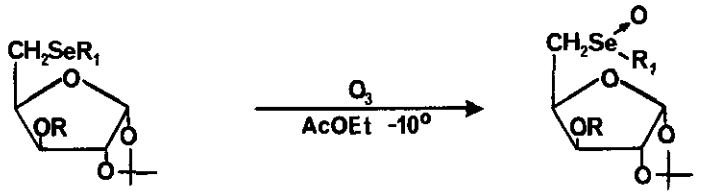

32 33 34

Displacement of tosyloxy group of (32) with the benzyl selenolate ion gives smoothly methyl-5-seleno-benzyl-2,3-O-isopropylidene-5-seleno-β-D-ribofuranoside (35).




32 35

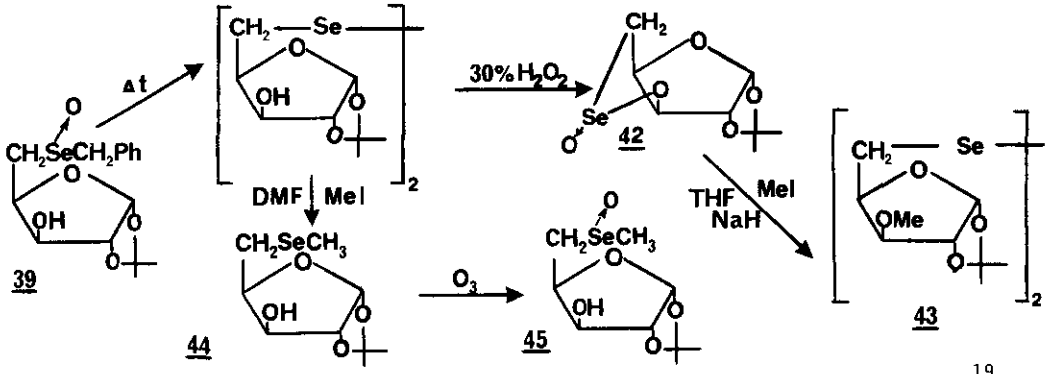
Oxidation of sugar selenides to appropriate selenoxides has been reported by Rabelo and Van Es.[18]



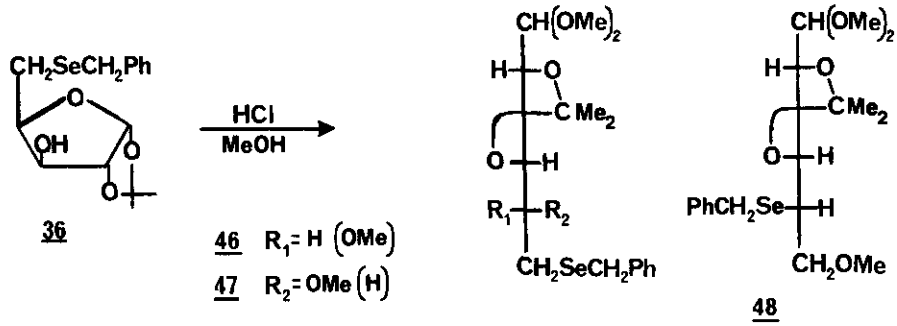

**36** R=H, $R_1$=$CH_2Ph$
**37** R=Me $R_1$=$CH_2Ph$
**38** R=$R_1$=Me

**39,40,41**

Selenooxides very easily decompose on warming, regenerating the parent selenide. Moreover, thermal degradation of benzyl selenoxide (39) gives diselenide (27) and benzaldehyde, oxidation of the diselenide affords a compound which is tentatively identified as the internal selenic ester (42) which on methylation yields a diselenide (43). Methylation of diselenide (27) gave selenide (44), which on oxidation gave a mixture of oxides, that exist in two isomeric forms, as shown by $^1$H-nmr. This is a second example of preparation of oxides of seleno-sugars.




Methanolysis of the 5-seleno-benzylderivative (36) gives the acyclic acetals (46) and (47).[19]

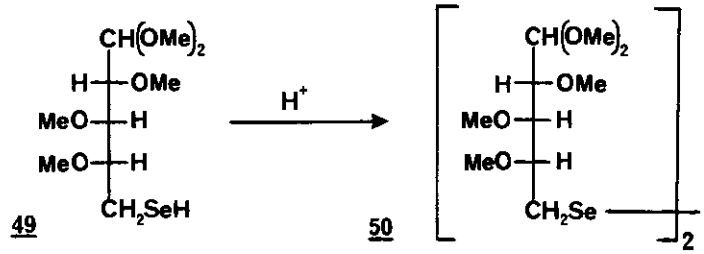



**46** $R_1$= H (OMe)
**47** $R_2$= OMe (H)

Formation of the isomers (46) and (47) may be explained from the production of the dimethylacetal of 2,3-isopropylidene derivatives of (36) and the participation and migration of a methoxyl

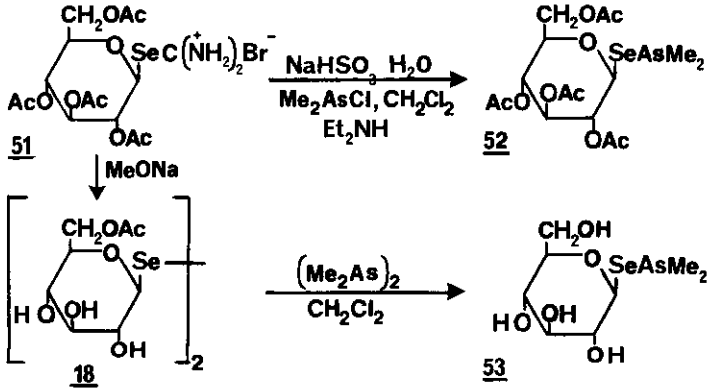
group from C-1 to C-4 to give (47) and by participation of the Se-benzyl group to give the 4,5-episelenonium intermediate which is opened by a methoxyl group from C-1 to give (46). The episelenonium intermediate can also be opened by methanol to give (48).

Attempted cyclization of 2,3,4-tri-O-methyl-5-seleno-L-arabinose dimethylacetal (49) in acidic solution gave the diselenide (50).[20]



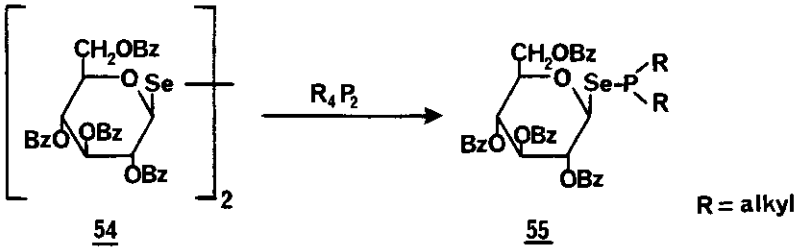

49 50

Zingaro's group reports the synthesis of selenoglucose esters of the diorganyl group including those containing phosphorus, arsenic and antimony.[5] 1-Seleno-dimethylarsino-1-seleno-β-D-glucopyranose has been synthesized.[21]




51 52 18 53

Dialkylphosphinous esters of β-seleno-D-glucose are prepared via the reaction of symmetrical tetraalkyldiphosphines with bis-(2,3,4,6-tetra-O-benzoyl)-β-D-glucopyranosyl)-diselenide (54).[22]

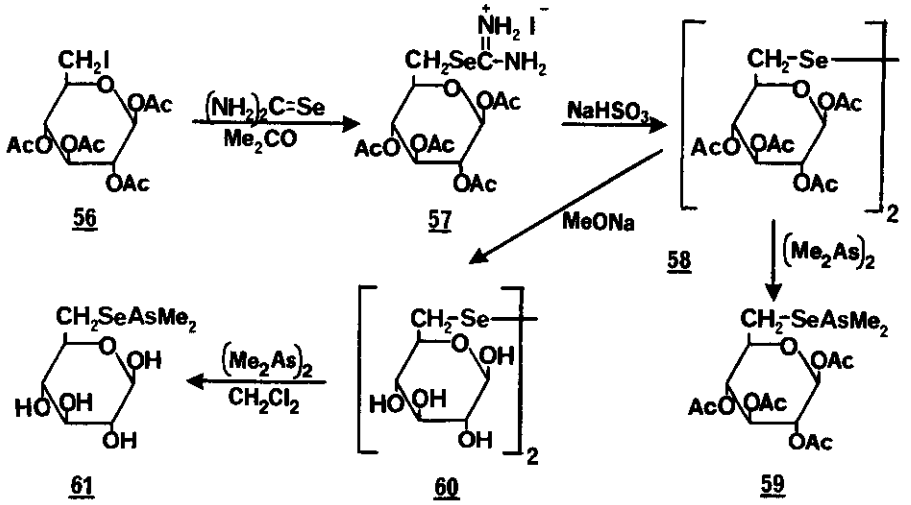



54 55

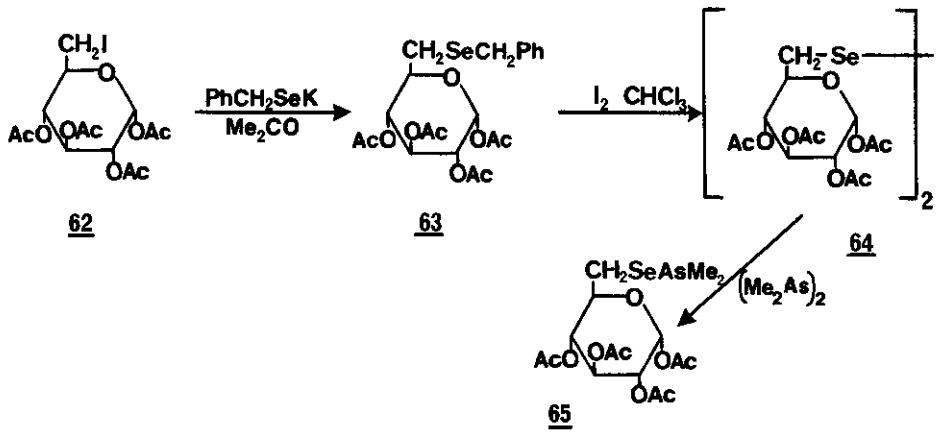
The antimony analogues are prepared by the use of an analogous series of reactions. However, the use of dimethylstibine halides in the two phase water-dichloromethane reaction is obviated by the extreme hydrolytic instability of the antimony halogen bond. Therefore, these derivatives were prepared exclusively by the addition of tetramethyldistibine to the diselenide as

has been reported.[23]

6-Se-dimethylarsino-6-seleno-β-D-glucopyranose is synthesized by methods similar to those used to prepare the related 1-substituted derivatives.[24]



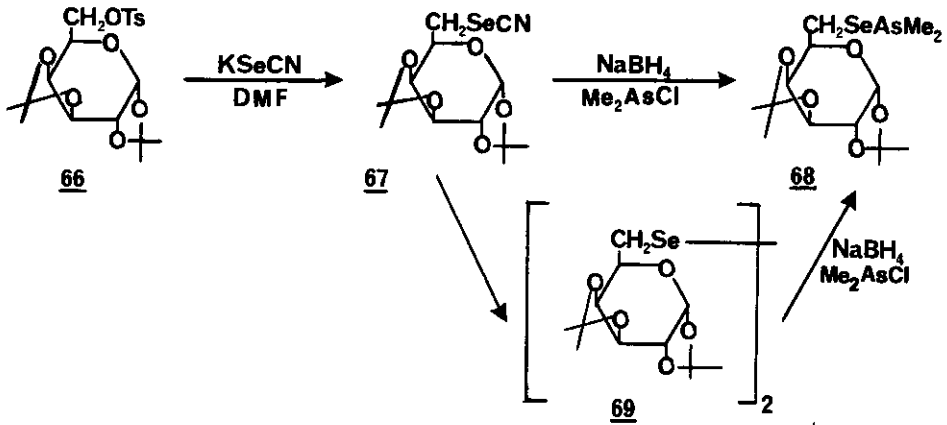

Synthesis of 1,2,3,4-tetra-O-acetyl-6-Se-benzoyl-6-seleno-α-D-glucopyranose, (63) 6,6'-diseleno-bis-1,2,3,4-tetra-O-acetyl-α-D-glucopyranose, (64) as well as 1,2,3,4-tetra-O-acetyl-6-Se-dimethylarsino-6-seleno-α-D-glucopyranose (65) is reported by Zingaro's group.[25]



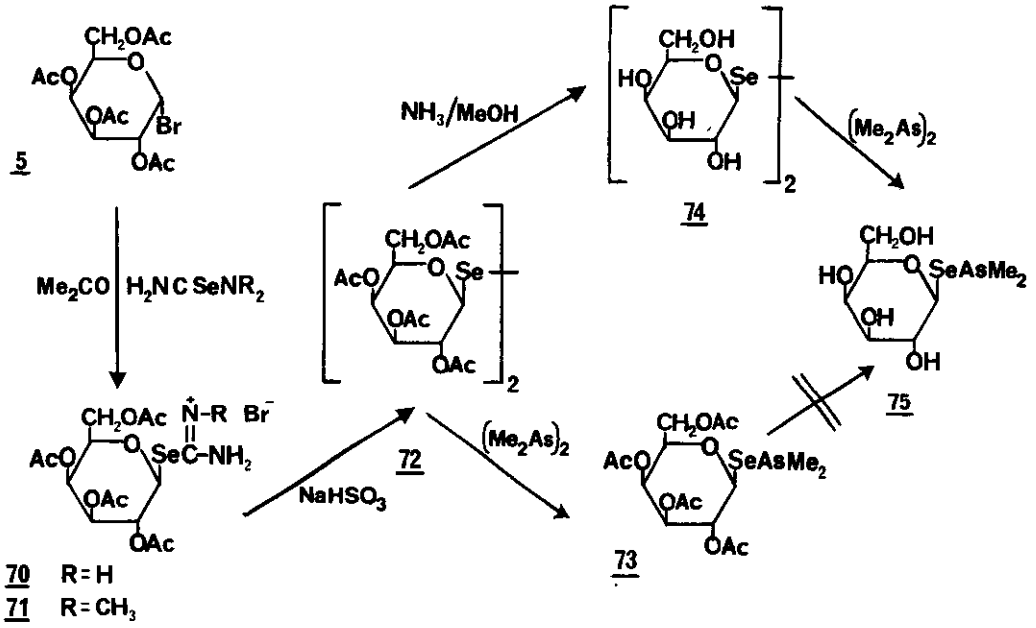

Attempts to prepare N,N-dimethylseleno-pseudoureido derivatives by the reaction of 1,2,3,4-tetra-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranose (62) with N,N-dimethylselenourea were unsuccessful.

It is interesting that the diselenides can be used as alkylating reagents for seleno and thio-substituted nucleosides and related compounds.[27]

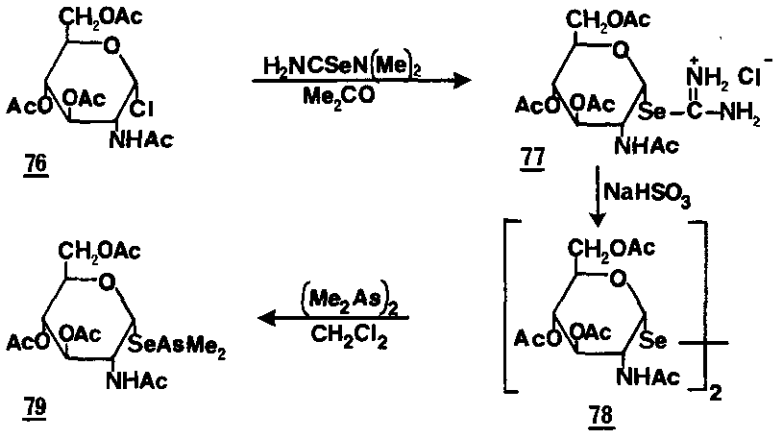
6-Seleno-D-galactose esters of dimethylarsinous acid have been synthesized by the reaction of appropriate 6-selenol with dimethylarsinous chloride.[26]




Hydrolysis of isopropylidene groups in the ester (69) by means of Dowex-1 ($H^+$) in aqueous methanol also removes the dimethylarsenyl group and the parent D-galactose ester is not produced.[26] Daniel and Zingaro[5a] report the synthesis of dimethylarsinous acid esters of 1-seleno-D-galactose.

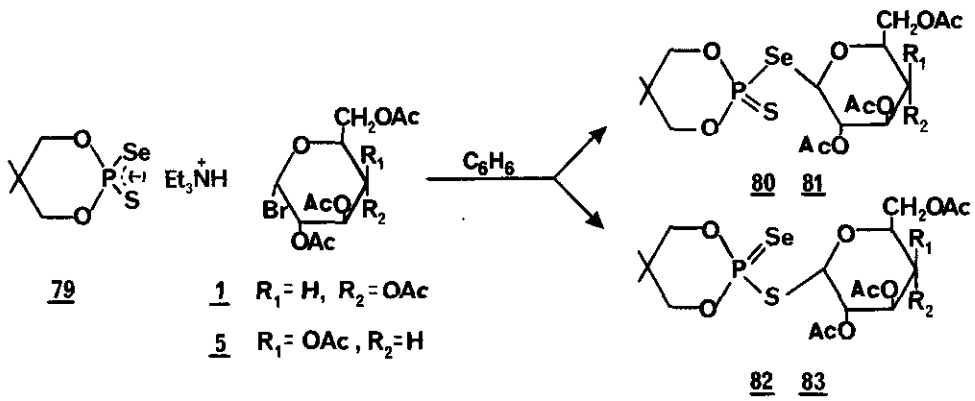



They report another example of this class of compounds by the method previously employed in the synthesis of the 1-seleno-D-galactose. The synthesis of 1- and 6-selenodimethylarsin-2-acetamido-2-deoxy-α-D-glucopyranose [28] is illustrated.



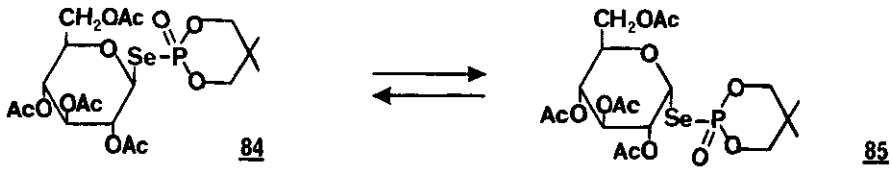

The coupling constant and chemical shift of the anomeric proton ($J_{1,2}$ = 4Hz δ = 5.38 ppm) of diselenide (78) is indicative of α-D-anomeric configuration in contrast with the previous report on the similar reaction of 1-halogenosugars with selenourea[11] as well as with selenophenolate ion.[12] 2-Acetamido-1,3,4-tri-O-acetyl-2-deoxy-6-Se-dimethylarsino-6-seleno-α-D-glucopyranose is prepared in the same manner as using 2-acetamido-1,3,4-tri-O-acetyl-3-deoxy-6-iodo-α-D-glucopyranose as starting product.

Michalska's group, working on seleno-sugars in connection with organophosphorus chemistry, report an interesting result on the reaction of glycosylation of organic phosphorus thio- and seleno acids.[29-31] The reaction of triethylammonium salt of 2-thio-2-seleno-5,5-dimethyl-1,3,2-dioxyphosphorinane with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1) and 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (5) gave two types of products (80-81) and (82-83).[29]

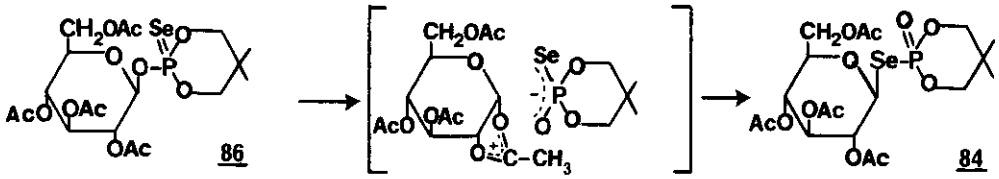



Analogous reaction of α-D-glycosyl bromides with triethylammonium salts of seleno acids of phosphorus is reported. Interesting transformations of derivatives obtained has also been reported.[30]

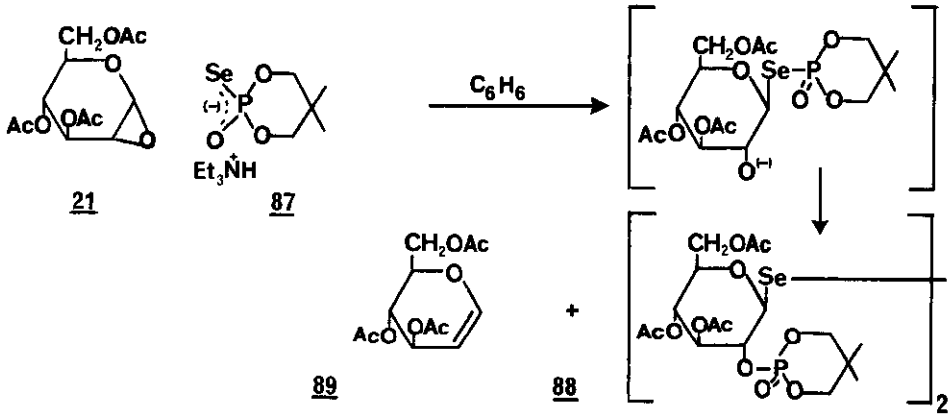
The first is anomerization of the selenoate (84) under heating in boiling xylene.



The second is a selenono-selenolo rearrangement of a selenono ester (86), to the selenoate (84).



Reaction of 3,4,6-tri-O-acetyl-1,2-anhydro-α-D-glucopyranose (Brigl's anhydride) (21) with triethylammonium salt of 2-oxo-2-seleno-5,5-dimethyl-1,3,2-dioxaphosphorinane gives diselenide (88) and a 1,2-unsaturated sugar (89), 3,4,6-tri-O-acetyl-D-glucal in quantitative yield.

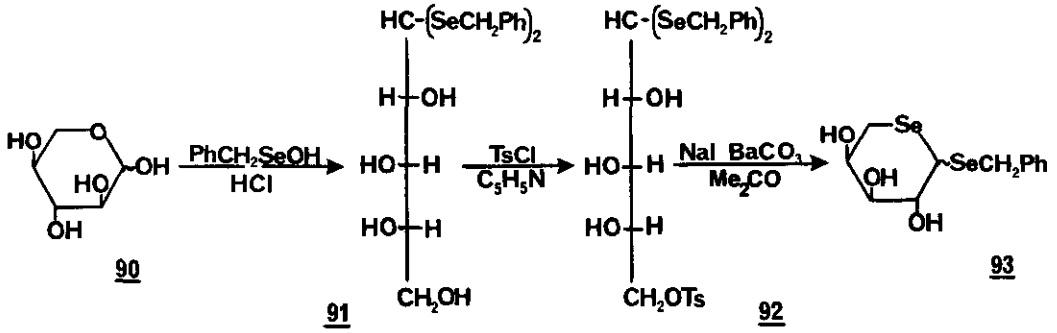


This reaction is generallized for other models of anhydrosugars and is a new method for the preparation of unsaturated sugars.[31]

3. METHODS OF SYNTHESIS OF SELENO SUGARS WITH SELENIUM IN THE SUGAR RING

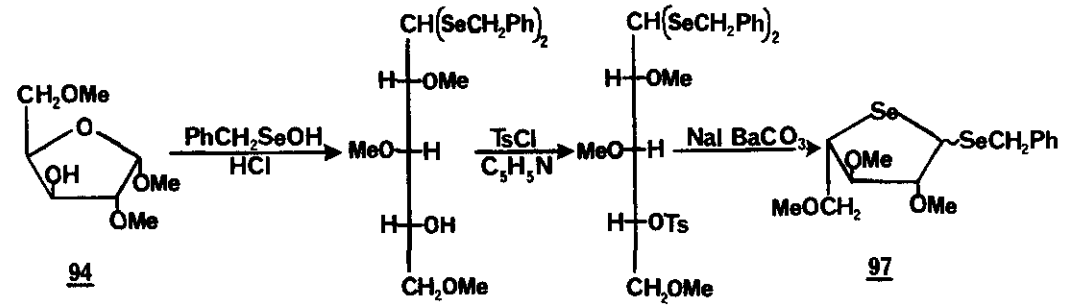
Whereas, the introduction of sulfur, nitrogen atoms as the atom in furanose and pyranose rings of monosaccharides has been successful, the introduction of selenium has usually failed. For example, reaction of 1,2-O-isopropylidene-5-seleno-D-xylofuranose[14] with methanolic hydrogen chloride does not give the required methyl-5-seleno-D-xylopyranose, but instead produces dehydration between C-2 and C-5 resulting in the formation of D-threo-2,3,4,5-tetrahydro-3,4-dihydroxy-

2-seleno phene-2-carbaldehyde dimethylacetal.[14] Moreover, treatment of various O-methylpentose derivatives with methanolic hydrogen chloride also does not give required derivatives with selenium as the hetero-atom in the sugar ring but leads to the formation of the corresponding diselenides.[15,17] The corresponding diselenide is also obtained by cyclization of 2,3,4-tri-O-methyl-5-seleno-L-arabinose dimethylacetal in acidic solution.[20] Van Es's group reported the first successive introduction of a selenium atom as the sugar ring hetero-atom, in L-arabinose, D-ribose and in D-xylose.[20] *Treatment of L-arabinose dibenzyl diselenoacetal* (91). On mono-p-toluenesulfonylation of the acetal (91) the 5-O-tosyl derivative (92) is produced which on treatment with iodide ions gives benzyl 1,5-diseleno-L-arabinopyranoside (93).



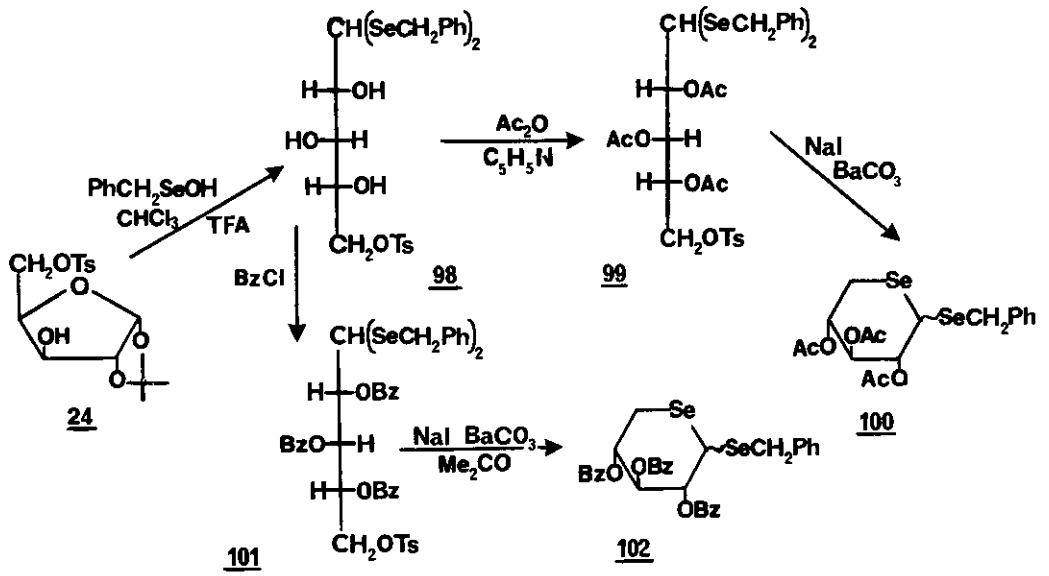

90 91 92 93

The introduction of a selenium atom into the furanose ring has been accomplished by the p-toluenesulfonylation of 2,3,5-tri-O-methyl-D-xylose dibenzyl diselenoacetal (95) [obtained from 2,3,5-tri-O-methyl-D-xylofuranoside (94)] and treatment of the 6-O-tosyl derivative with iodide ions to give benzyl 2,3,5-tri-O-methyl-1,4-diseleno-L-arabinofuranoside (97).



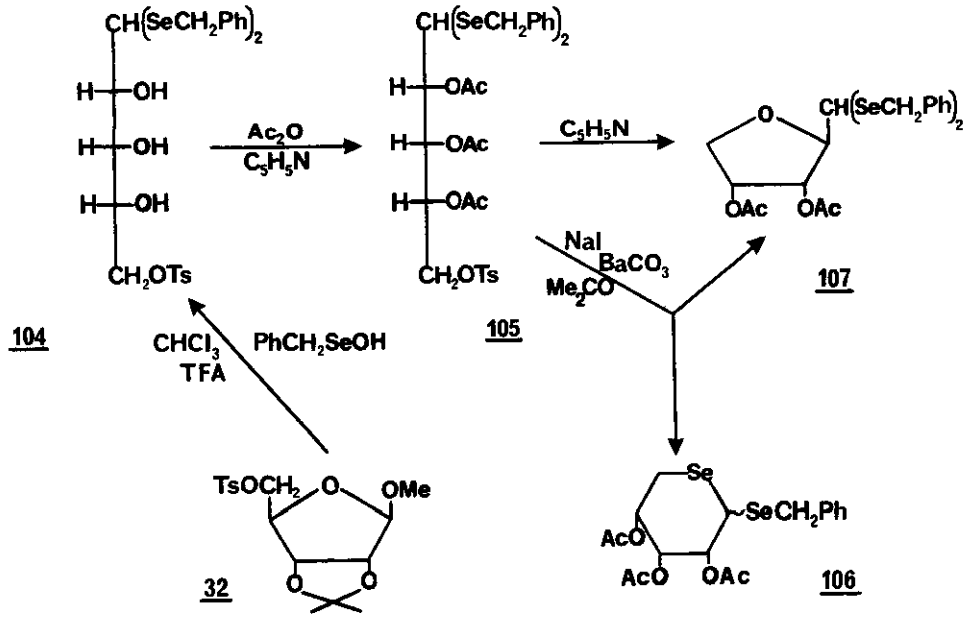

94 95 96 97

Cyclization of 2,3,4-tri-O-acetyl-5-O-p-tolylsulfonyl-D-xylose dibenzyl diselenoacetal (99) gives benzyl 2,3,4-tri-O-acetyl-1,5-diseleno-α-D-xylopyranoside (101).



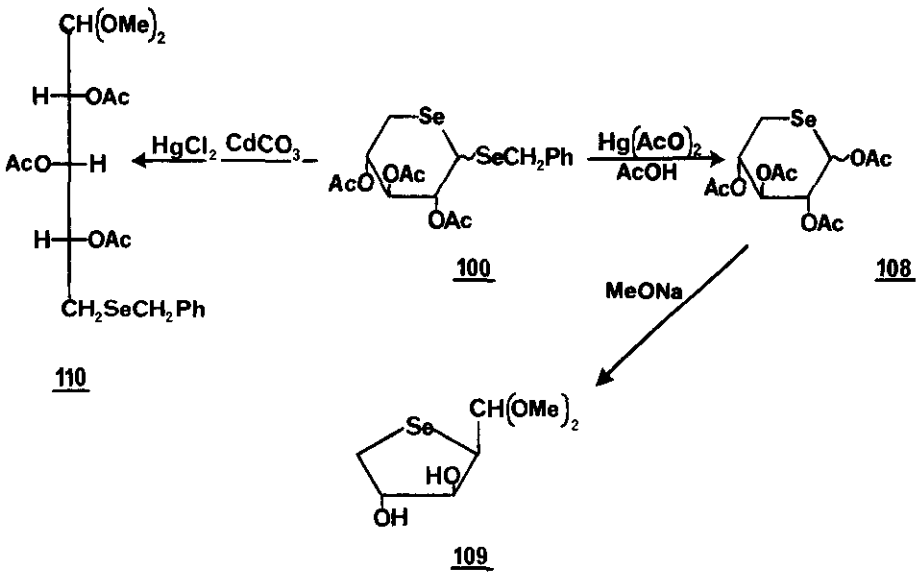

Similarly, benzyl derivative (101) gives benzyl 2,3,4-tri-O-benzyl-1,5-diseleno-α-D-xylopyranoside (102).

Benzyl 2,3,4-tri-O-acetyl-1,5-diseleno-D-ribopyranoside (106) can be synthesized in the same manner as (97) and (100) from the 2,3,4-tri-O-acetyl-5-O-p-tolylsulfonyl-D-ribose dibenzyl diselenoacetal (105) which was prepared from methyl-2,3-O-isopropylidene-5-O-tolylsulfonyl-β-D-ribofuranoside (32).



Coproduct (107) in the cyclization reaction was independently prepared from acetal (105) by treatment with pyridine.

The glycosidic benzylseleno group is smoothly removed from (100) with mixture of mercuric acetate and acetic acid, whereas, deacetylation of resulted derivative (108) by methanolysis gives the D-threo-2,3,4,5-tetrahydro-3,4-dihydroxy-2-selenophene-2-carbaldehyde dimethyl acetal (109).




110 100 108 109

Treatment of selenobenzyl glycoside (100) with mercuric chloride and cadmium carbonate in methanol yields 2,3,4-tri-O-acetyl-5-selenobenzyl-5-seleno-D-xylose dimethyl acetal (110) instead of expected appropriate methyl glycoside.

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