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Chemistry of tetrathiomolybdate and tetraselenotungstate: Applications in carbohydrate chemistry*

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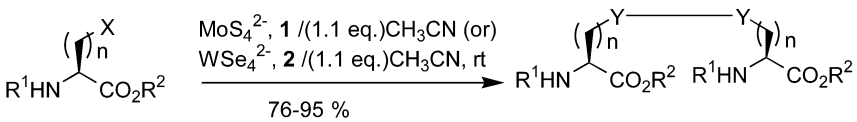
Abstract: An efficient one pot synthesis of thio and selenolevoglucosans from 1,6-diactivated carbohydrate derivatives has been achieved using benzyltriethylammonium tetrathiomolybdate, $[BnNEt_3]_2MoS_4$, as a sulfur transfer reagent and tetraethylammonium tetraselenotungstate, $[Et_4N]_2WSe_4$, as a selenium transfer reagent, respectively. The methodology has also been extended to the synthesis of 1,5-epithio and 1,5-episeleno pentoses.

INTRODUCTION

The reagents, benzyltriethylammonium tetrathiomolybdate, $[BnNEt_3]_2MoS_4$ **1** [1], and tetraethylammonium tetraselenotungstate, $[Et_4N]_2WSe_4$ **2** [2], have been shown to be useful for sulfur and selenium transfer reactions, respectively, in organic synthesis. Synthesis of disulfides from alkyl halides [3], ring opening of epoxides [4], tandem sulfur transfer/reduction/Michael addition [5] in one pot, and reduction of aryl azides to amines [6] and alkyl azides to imines [6] have been reported from our laboratory using the reagent tetrathiomolybdate **1**. It has also been used for the selective deprotection of propargyloxycarbonyl (**Poc**) protective group for amines [7] in peptides and for alcohols [8] in carbohydrate chemistry. Recently, a regioselective reduction of anomeric azides [9] to amines using the reagent **1** has been reported. Reagent **1** has also been used, as a sulfur transfer reagent, for the synthesis of phosphorothioate oligonucleotides [10]. On the other hand, tetraselenotungstate **2** has been used for the formation of diselenides [2b] from alkyl halides and in the synthesis of selenium analogs of several amino acid derivatives [11] (Scheme 1).



Scheme 1

In this article, we report on the utility of reagents **1** and **2** toward an efficient synthesis of thio and selenolevoglucosans, which are excellent synthons for the synthesis of deoxy sugar derivatives, involving a one pot sulfur/selenium transfer/reduction thiation/selenation reactions.

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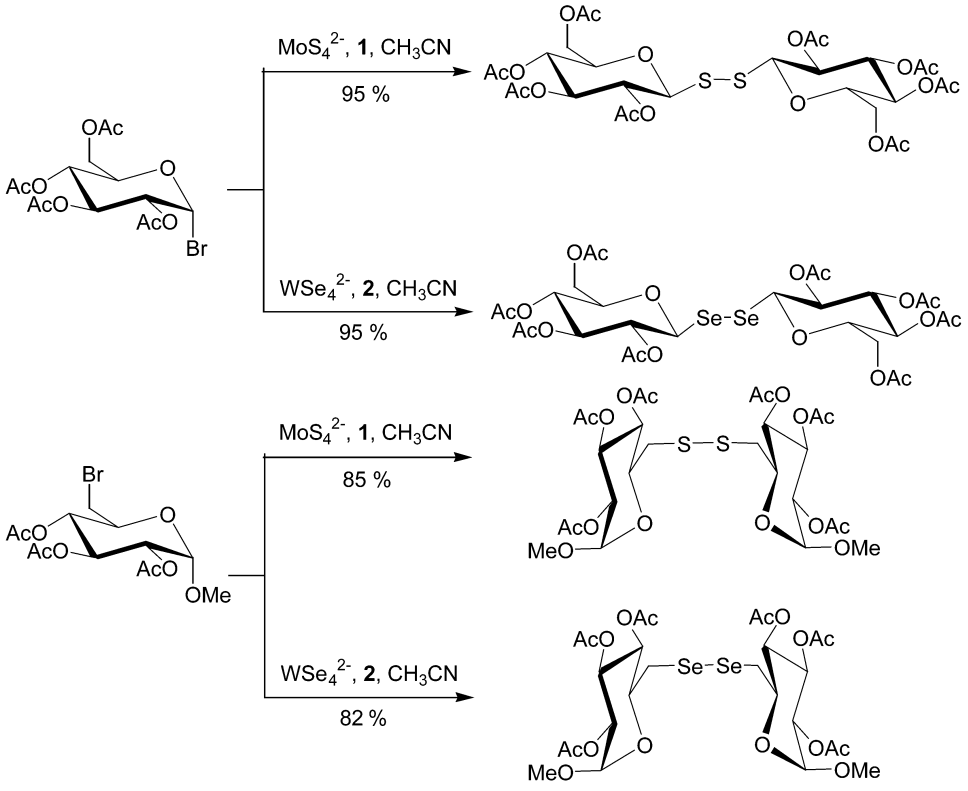
SYNTHESIS OF SUGAR DISULFIDES AND SUGAR DISELENIDES

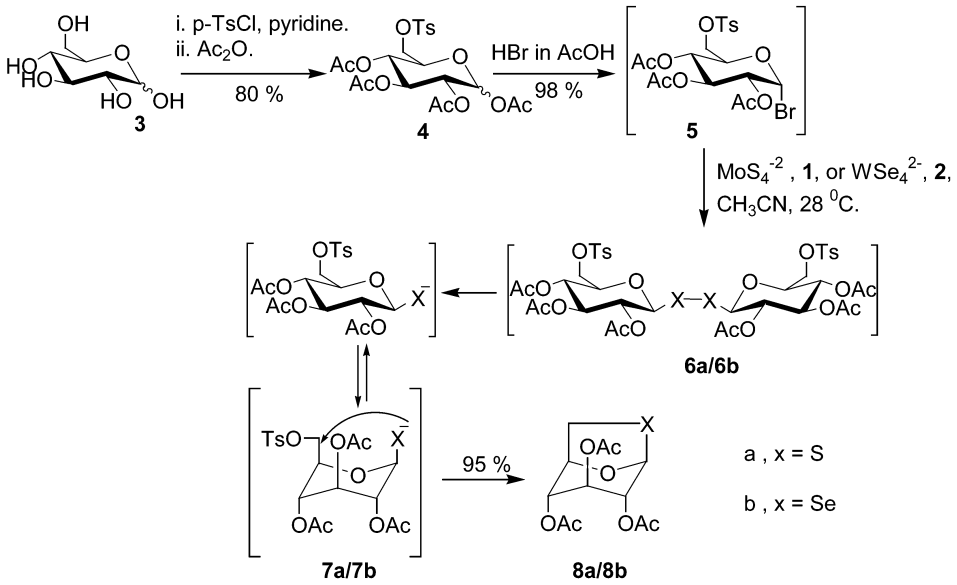
Using the reagents **1** or **2** (1.1 equiv) we previously reported the synthesis of sugar disulfides [3c] and sugar diselenides, respectively [2b] (Scheme 2).



Scheme 2

1,6-EPITHIO AND 1,6-EPISELENO-β-D-GLUCOPYRANOSES

Thioglycosides have become increasingly important as glycosyl donors in the synthesis of oligosaccharides [12]. In particular, the 1,6-epithio derivative **8a** and 1,6-episeleno-β-D-glucopyranose **8b** are important building blocks in the synthesis of a variety of deoxy sugars since the two most reactive centers at C-1 and C-6 are bridged and provide an opportunity for further synthetic manipulation. Akagi reported the first synthesis of thiolevoglucosan **8a** in moderate yields [13], and subsequently similar approaches to **8a** have been published [14]. More recently, a series of papers has been published on the efficient synthesis and use of 1,6-dideoxy-1,6-epithio and 1,6-dideoxy-1,6-episeleno sugars as glycosyl donors for the preparation of 6-deoxy sugars [15]. Our reagent tetrathiomolybdate **1** was used successfully for the first time by Stick for the synthesis of thiolevoglucosan **8a** [15a], and we decided to expand and explore the versatility of reagent **1** in the synthesis of a variety of levoglucosan derivatives (Scheme 3). It was also of interest to study the use of tetraselenotungstate **2** for the synthesis of selenolevoglucosan derivatives (Fig. 1).



Scheme 3

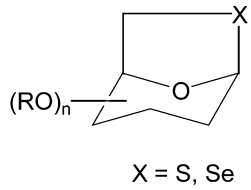


Fig. 1

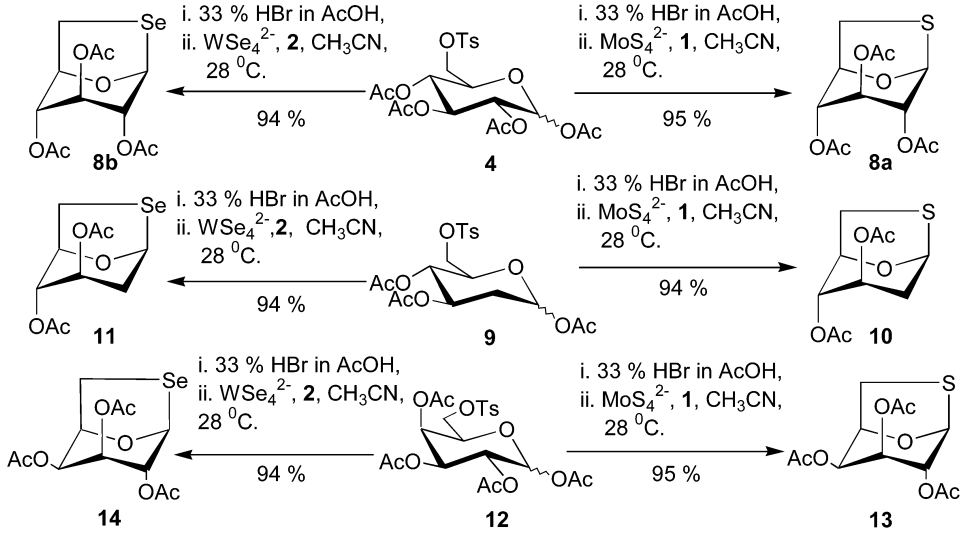
Synthesis of 1,6-epithio and 1,6-episeleno sugar deravatives

Treatment of 6-*O*-tosyl-1,2,3,4-tetra-*O*-acetyl-α-D-glucopyranoside **4** with HBr in acetic acid gave the corresponding glycosyl bromide **5**. The glycosyl bromide **5** was directly treated with tetrathiomolybdate **1** (1.2 equiv, CH_3CN, 28 °C, 0.5 h) to afford 2,3,4-tri-*O*-acetylthiolevoglucosan **8a** in 95 % yield. Similarly, the reaction of **5** with tetraselenotungstate **2** (1.2 equiv, CH_3CN, 28 °C, 0.5 h) led to the formation of 2,3,4-tri-*O*-acetylselenolevoglucosan **8b** in 94 % yield. The facile formation of 1,6-anhydrosugars **8a** and **8b** from **5** can be visualized to take place via sulfur transfer or selenium transfer at the anomeric carbon to form intermediate disulfide/diselenide **6a/6b**. The formation of sugar disulfide/diselenide from pyranosyl bromides with **1** or **2** has already been demonstrated in our laboratory [2b,3c]. The intermediate **6** possibly undergoes reductive cleavage to give the corresponding thiolate **7a** or selenoate **7b** involving an induced redox process [5] followed by displacement of the tosylate (Scheme 3).

Encouraged by these results, we applied this methodology to different carbohydrate derivatives. Treatment of 2-deoxy-1,3,4-tri-*O*-acetyl-6-*O*-tosyl-α-D-glucopyranoside **9** [16] with HBr/acetic acid followed by the reaction with **1** gave 2-deoxy-3,4-di-*O*-acetythiolevoglucosan **10** [17] and on reaction with **2** afforded 2-deoxy-3,4-di-*O*-acetyselenolevoglucosan **11** in excellent yields. Compounds **10** and **11** can serve as excellent precursors toward the synthesis of natural products containing 2,6-dideoxy carbohydrate moieties. These can also be directly used as glycosyl donors as the anomeric position has been activated with sulfur/selenium.

The methodology was also extended to a galactose derivative. Treatment of 6-*O*-tosyl-1,2,3,4-tetra-*O*-acetylgalactose **12** [15a] with HBr/acetic acid gave the corresponding galactose bromide, which

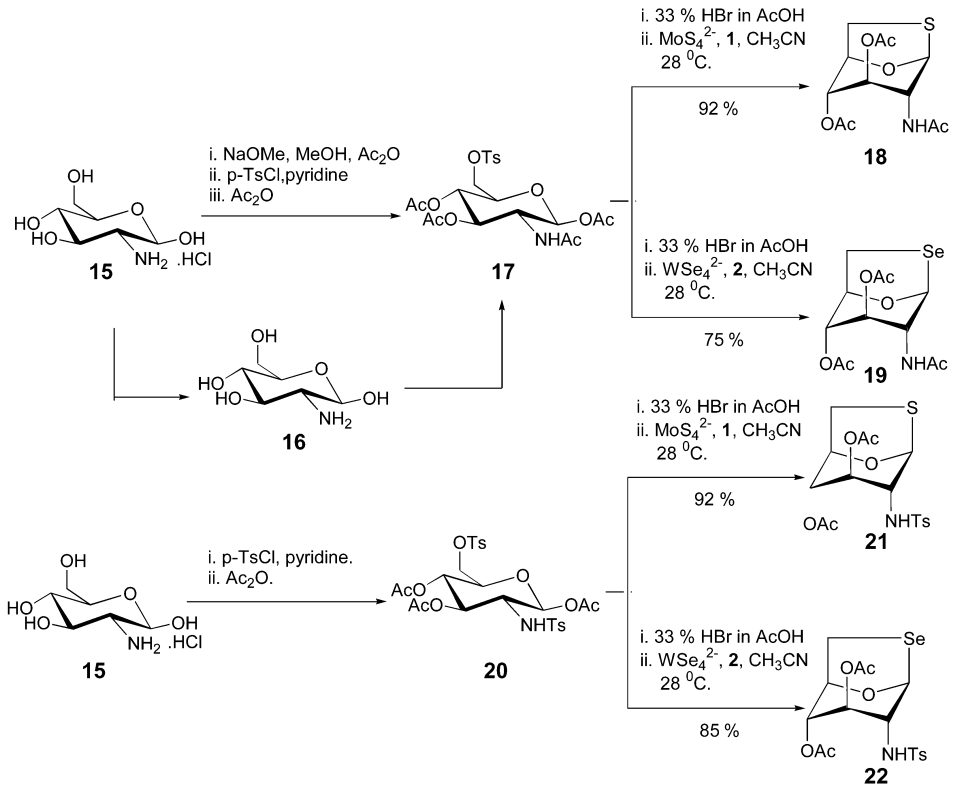
upon treatment with **1** gave the corresponding 1,6-epithio derivative **13** [15a] (95 %) and on treatment with **2** yielded 1,6-episeleno-β-D-galactopyranose **14** (94 %) (Scheme 4).



Scheme 4

Synthesis of 2-deoxy-2-amino-1,6-epithio and 1,6-episeleno sugar derivatives

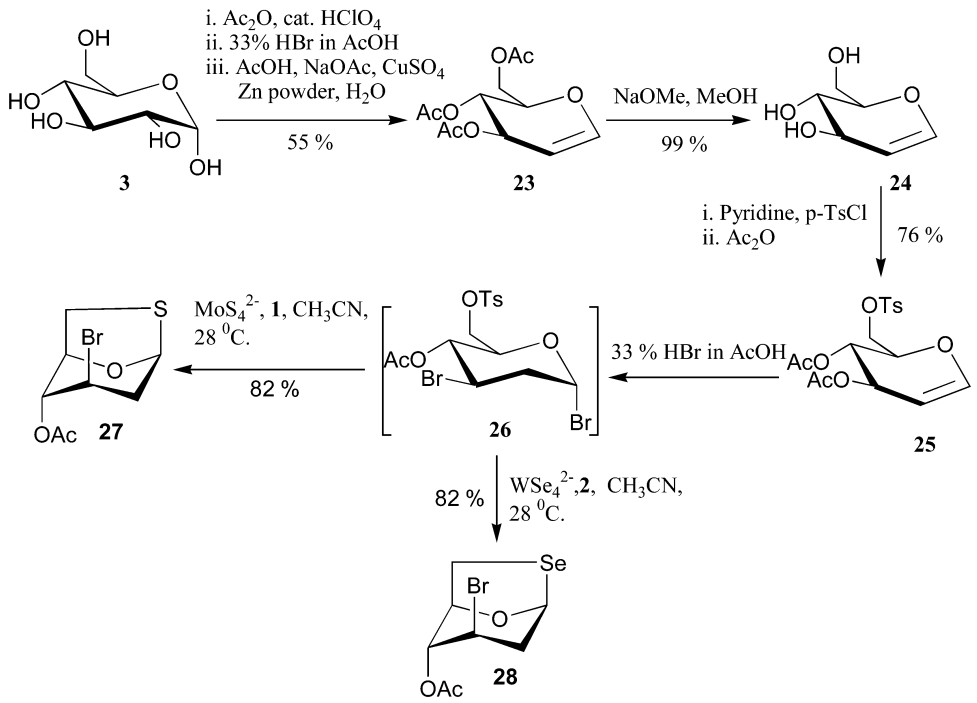
Deoxy amino sugars are also of synthetic interest because of their increased therapeutic capabilities. In 1975, Yamamoto et al. [18] reported the synthesis of 2-acetamido-3,4-di-*O*-aetyl-2-deoxy-thiolevoglucosan **18** starting from 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranosyl ethylxanthate. After this report, no other synthetic procedures were published for the synthesis of amino-thiolevoglucosans. Our attempt toward the synthesis of 2-acetamido-3,4-di-*O*-aetyl-2-deoxy-thiolevoglucosan **18** started from the glucosamine hydrochloride **15**. Neutralization of glucosamine hydrochloride **15** with NaOMe/MeOH followed by treatment with Ac_2O gave the corresponding *N*-acetylglucosamine **16** [19] in 90 % yield. Tosylation of **16** followed by acetylation furnished 2-acetamido-1,3,4-tri-*O*-acetyl-2-deoxy-6-*O*-*p*-toluenesulfonyl-β-D-glucopyranose **17** [20] in moderate yield (50 %). Treatment of **17** with HBr/AcOH followed by treatment with MoS_4^{2-} (**1**) or WSe_4^{2-} (**2**) furnished 2-acetamido-3,4-di-*O*-aetyl-2-deoxy-thiolevoglucosan **18** or 2-acetamido-3,4-di-*O*-aetyl-2-deoxy-selenolevoglucosan **19**, respectively, in excellent yield (95 and 75 %) (Scheme 5). On the other hand, treatment of glucosamine hydrochloride **15** with *p*-toluene sulfonylchloride in pyridine followed by acetylation gave the corresponding di-tosyl glucosamine derivative **20** in good yield (60 %). Compound **20** upon treatment with HBr in acetic acid followed by reaction with **1** afforded 2-deoxy-2-tosylamino-3,4-di-*O*-acetyl-1,6-epithioglucose **21** (87 %) and on treatment with **2** gave 2-deoxy-2-tosylamino-3,4-di-*O*-acetyl-1,6-episelenoglucose **22** (85 %) (Scheme 5).



Scheme 5

Synthesis of 2-deoxy-3-halo-1,6-epithio and 1,6-episeleno sugar derivatives

2,3,6-Trideoxy systems are present as terminal sugars in natural products like aclacinomycin and act as intermediates in the synthesis of antibiotic amicetin [21]. In order to achieve the synthetic precursor for this class of molecules, we have chosen 3,4,6-tri-*O*-acetyl-D-glucal **23** [22] as a starting material. Deprotection of the acetates from **23** using NaOMe/MeOH gave glucal **24** in 99 % yield, which was selectively tosylated at C-6 hydroxyl and then acetylated the C-3 and C-4 hydroxyls using pyridine and acetic anhydride to furnish 6-*O*-tosyl-3,4-di-*O*-acetyl-D-glucal **25** [23] in 76 % yield. Compound **25** was treated with HBr/acetic acid to get the dibromide **26** [16], which on treatment with tetrathiomolybdate **1** gave 2,3-dideoxy-3-bromo-4-*O*-acetyl-1,6-epithioglucopyranose **27** and on reaction with tetraselenotungstate **2** afforded 2,3-dideoxy-3-bromo-4-*O*-acetyl-1,6-episelenoglucopyranose **28**, respectively, in very good yields (82 %) (Scheme 6).



Scheme 6

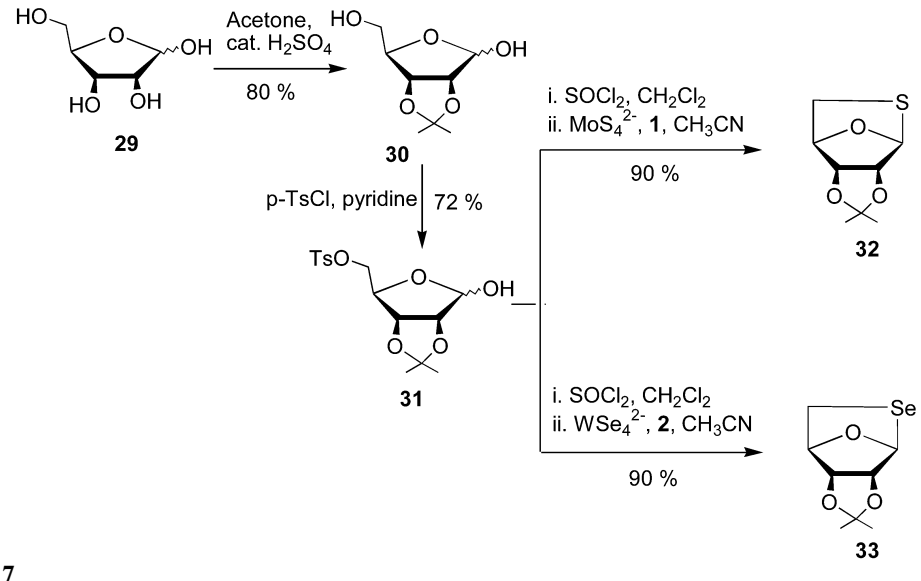
Synthesis of 1,5-epithio and 1,5-episleno-D-ribose derivatives

It was of interest to extend the scope of this reaction to the synthesis of 1,5-epithio/episeleno pentose derivatives. Accordingly, treatment of D-ribose **29** in acetone with cat. H_2SO_4 gave the selectively protected 2,3-isopropylidine-D-ribose **30** [24] in 85 % yield.

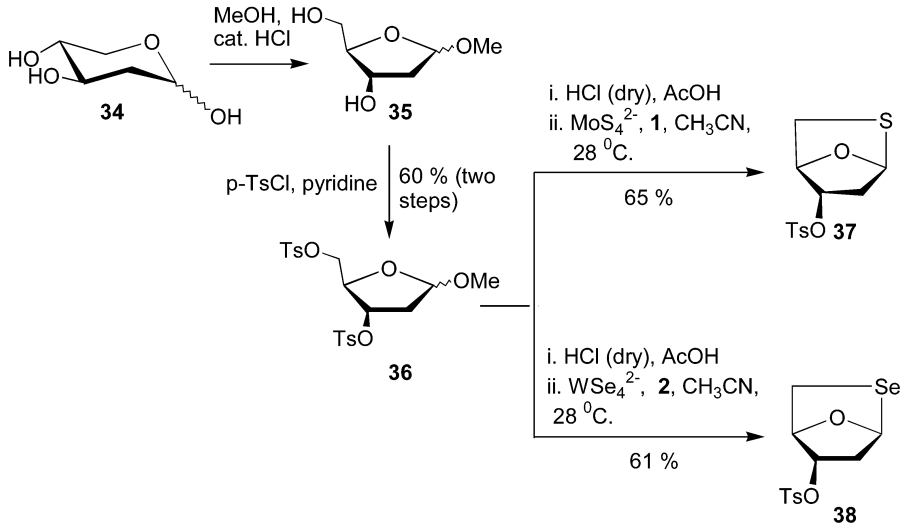
Reaction of **30** with *p*-TsCl/pyridine furnished 5-*O*-tosyl-2,3-isopropylidine-D-ribose **31** [25] in 80 % yield. Treatment of 5-*O*-tosyl-2,3-isopropylidine-D-ribose **31** with $SOCl_2$ in dichloromethane gave the corresponding ribosyl chloride which was immediately treated with **1** to give the corresponding 1,5-epithio-2,3-isopropylidine-D-ribose **32** [26], and treatment of **31** with **2** afforded 1,5-episeleno-2,3-isopropylidine-D-ribose **33** in very good yields (Scheme 7).

In studies directed toward the synthesis of 2,5-dideoxy ribose derivatives, 2-deoxyribose **34** was treated with cat. HCl in methanol to get the methyl-2-deoxy-ribofuranoside **35** [27] in 90 % yield. Compound **35** was treated with *p*-TsCl in pyridine to furnish methyl 2-deoxy-3,5-di-*O*-tosyl-D-*erythro*-pentoside **36** [28]. Treatment of **36** with dry HCl in glacial acetic acid gave the corresponding 2-deoxy-3,5-di-*O*-tosyl-D-*erythro*-pentosyl chloride derivative, which upon treatment with **1** gave 2-deoxy-1,5-epithio-3-*O*-tosyl-ribose **37** (65 %) and on reaction with **2** afforded 2-deoxy-1,5-episeleno-3-*O*-tosyl-ribose **38** (61 %) (Scheme 8).

It is important to mention that these 1,5-epithio or 1,5-episelenopentoses (**32**, **33**, **37**, and **38**) are excellent precursors for the synthesis of deoxynucleotides as well as for the synthesis of 2,3-dideoxy-3-thiocytidine (3TC), [(+)-(2*S*,5*R*)-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine] (+)-BCH-189 which are potent anti-human immunodeficiency virus (HIV) active [29] and anti-human hepatitis B virus active [30].



Scheme 7



Scheme 8

CONCLUSION

In conclusion, we have developed an efficient methodology for the synthesis of epithio and episeleno hexoses and pentoses in good to excellent yields utilizing tetrathiomolybdate **1** and tetraselenotungstate **2** as key reagents for effecting the desired transformation. These derivatives are excellent precursors for the preparation of 6-deoxy, 1,6-dideoxy, 2,6-dideoxy, and 2,3,6-trideoxy hexoses as well as for 5-deoxy and 2,5-dideoxy pentose derivatives.

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