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CHEMISTRY OF THIO- AND SELENOLEVOGLUCOSANS

R RAMESH, P RAMU SRIDHAR AND S CHANDRASEKARAN[†*]

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012 (India)
[†]Jawaharlal Nehru Center for Advanced Scientific Research, Jakkur, Bangalore (India)

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Thio- and selenolevoglucosans are very useful precursors for the synthesis of deoxy glucopyranosides, which are important structural elements in many naturally occurring glycoconjugates. While this review focuses mainly on the chemistry of thio- and selenolevoglucosans application of a general methodology to the synthesis of the corresponding pentose derivatives is briefly outlined.

Key Words: Thiolevoglucosans; Selenolevoglucosans; Deoxy sugars; Tetrathiomolybdate; Tetraselenotungstate

Introduction

Deoxy sugars are found in biological systems either as single structural elements or more frequently as part of oligosaccharide moieties in glycoconjugates.[1] In many biologically important molecules, deoxy sugars are critical substructures required for carbohydrate-protein recognition processes.[2] They often play an important role in the mechanism of action of many drugs, in particular for the DNA interaction of anti cancer drugs as well as in their binding to RNA.[3] For instance, the cytostatic activity of the different landomycins, anti-tumor compounds of the angucycline group,[4] directly depends on the length of the phenol-glycosidically linked deoxy oligosaccharide chains (Fig. 1).

6-Deoxy sugars are among the most important of the deoxy sugars. For example, the cell surface carbohydrates of various bacteria have antigenic determinants possessing a 3,6-dideoxy sugar such as abequose (3,6-dideoxy-D-*xylo* hexose) or paratose (3,6-dideoxy-D-*ribo* hexose).[5]

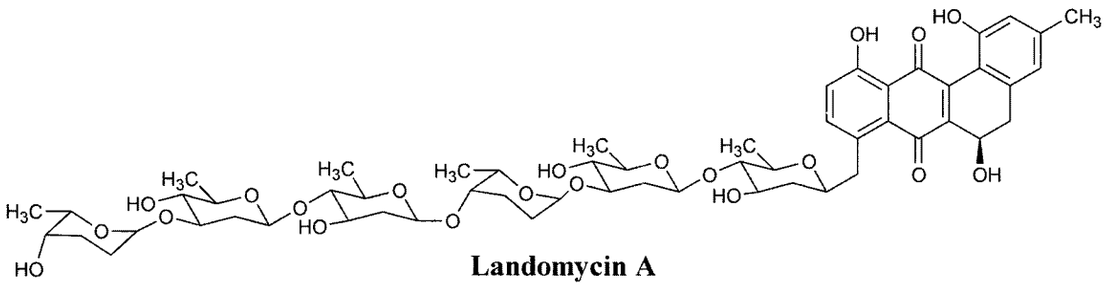
The synthesis of deoxy sugars can easily be achieved through the corresponding epithio or episeleno sugars.[6,7] 1,6-epithio/episelenohexoses (Fig. 2) are the most useful molecules in this regard, which have a conformational constraint enforced on them by the 1,6-thio/seleno bridge together with the protection of two of the most reactive hydroxyls at C1 and C6, providing a good deal of synthetic potential. 1,6-Dideoxy-1,6-epithio-β-D-glucopyranose and its episeleno counterpart, commonly known as thio- and selenolevoglucosans,[8] **1** (Fig. 2) respectively, are the most studied species of this kind. They are surrogates for 6-deoxy-β-D-glucopyranosides and are excellent model systems for studies of these epithio and episeleno derivatives.

*Author for correspondence *Tel:* +91-80-2293 2404;
Fax: +91-80-2360 2423; *E-mail:* scn@orgchem.iisc.ernet.in

Thio- and Selenolevoglucosans: Surrogates for 6-Deoxy-β-D-Glucopyranosides

Thioglycosides[9] and selenoglycosides[10] have been shown to be excellent glycosyl donors. The inherent stability of these compounds towards a variety of reagents has made them starting points for the synthesis of a number of complex carbohydrate derivatives. Thio- and selenolevoglucosans match thio and selenoglycosides as glycosyl donors. Stick *et al* have developed a relative reactivity scale for these species towards various glycosyl acceptors.[11] Based on their observations Stick *et al.* have published a general approach towards the synthesis of 6-deoxy sugars starting from thio- or selenolevoglucosans (Scheme 1).[6,7]

The required activation and glycosylation of the triacyl derivative **2** has been achieved with *N*-iodosuccinimide / trifluoromethanesulfonic acid to yield the disulfide or diselenide, **3**. A rationale for the formation of **3** is presented in Scheme 2.
The possible involvement of a sulfonium ion **5** is speculated based on the report of Lundt and Skelbæk-Pederson who synthesized the crystalline sulfonium salt **6** (Figure 3) and demonstrated its utility as a glycosyl donor.[12] They have treated **6** with a number of nucleophiles and have isolated and characterized disulfides analogous to **3**.



Landomycin A

Fig. 1

1,6-epithio/episeleno hexose Thio/selenolevoglucosan, **1**

Fig.2

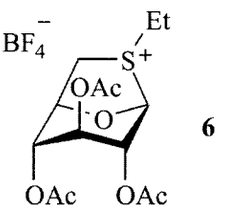


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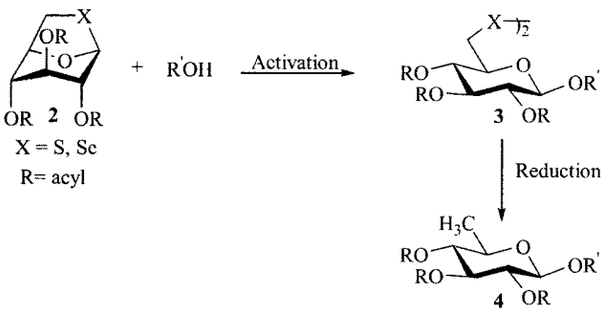
Fig. 3



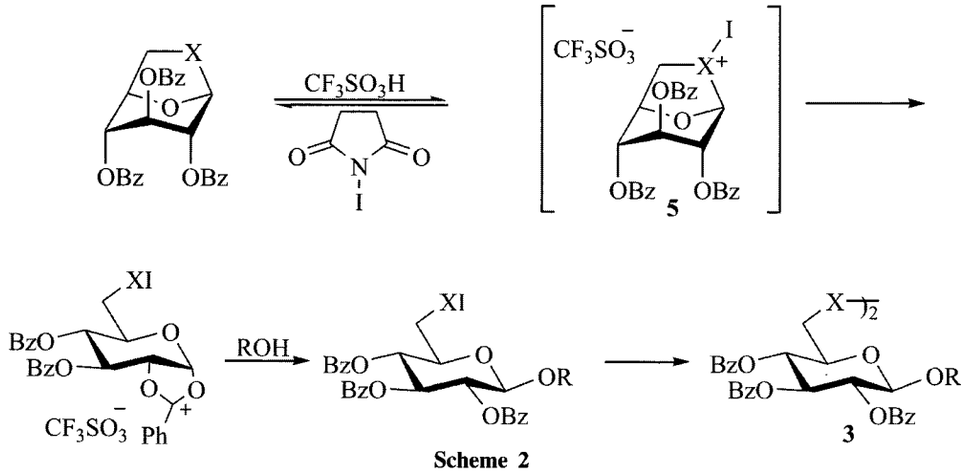
Scheme 1

The desulfurization or deselenization of **3** can be achieved with Raney Nickel in ethanol or with tributylstannane and α,α′-azobisisobutyronitrile respectively. Stick *et al.* have reported the synthesis of a number of 6-deoxy-β-D-glucosides based on the method described above, starting from **2**.[7] The synthesis of the deoxy disaccharide **7** from the tribenzoylated selenolevoglucosan **8** and benzyl 2,3,6-tri-O-benzyl-β-D-glucopyranoside, **9** is shown in Scheme 3.

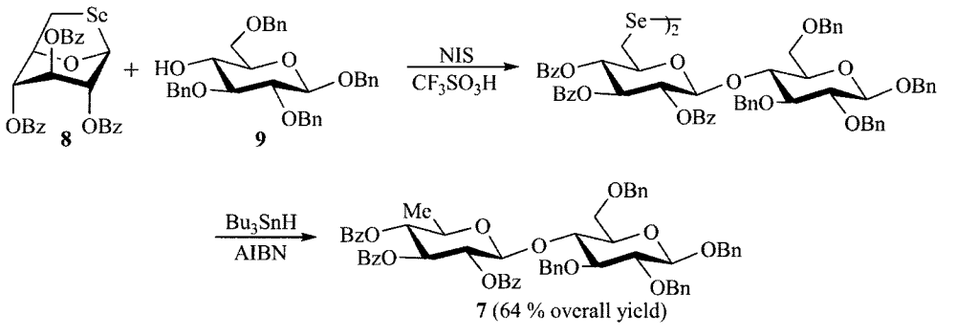
Stick and coworkers have further explored the chemistry of thiolevoglucosans by oxidizing them to the corresponding sulfoxides and sulfones .[13]

Synthesis of Thio- and Selenolevoglucosans

Molecules analogous to thio- and selenolevoglucosans have been known for sometime. Though there were isolated reports dealing with their synthesis, there has not been much exploration into their chemistry partly due to the difficulty in their synthesis. However, earlier reports from Stick and coworkers[14] and recent reports from our own laboratory[15] have opened up easier and efficient methods for the synthesis of these molecules. The earlier reports on the synthesis of



Scheme 2



Scheme 3

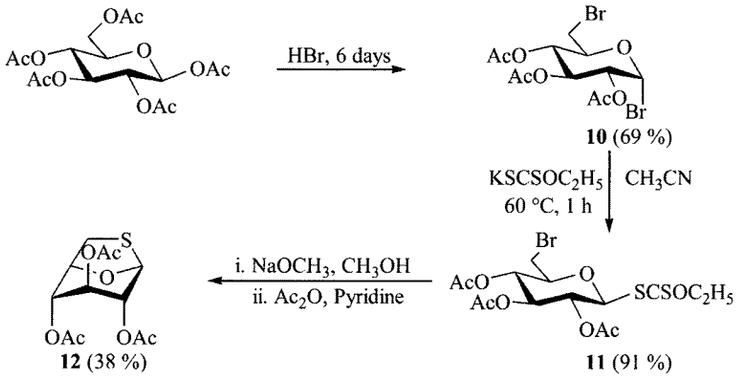
thiolevoglucosan have relied on the base treatment of molecules having a thioester at C1 or C6 and a good leaving group at C6 or C1 respectively. The first synthesis of thiolevoglucosan was achieved by Akagi *et al* in 1963.[8] The method included an early introduction of sulfur as an anomeric ethylxanthate to a hexopyranose, **10** to get **11**, and then exposure of the thiolate ion, derived using sodium methoxide, to a leaving group conveniently located at C6, installing the 1,6-epithio bridge (Scheme 4).

In 1967, Tejima *et al.* reported the synthesis of 2-deoxy thiolevoglucosan **14**, using a related strategy, starting from triacetyl-D-glucal **13** (Scheme 5).[16]

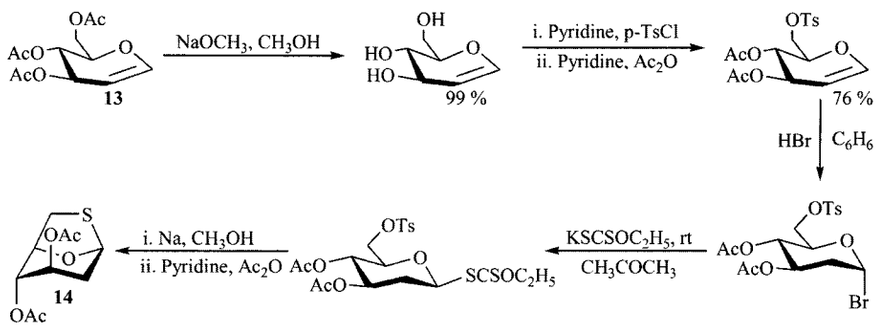
Another strategy involves the treatment of a thioacetate moiety at C6 with cysteamine (2-aminoethane thiol) and 1,4-dithioerythritol in HMPA, to expose a thiolate ion that would then attack a leaving group at C1 forming the epithio bridge (Scheme 6).[17]

The treatment of doubly activated hexopyranose **15**, having leaving groups at both C1 and C6, with sulfide ion (generated *in situ* from hydrogen sulfide and triethylamine) also afforded thiolevoglucosan **12** in 74 % yield (Scheme 7).[14]

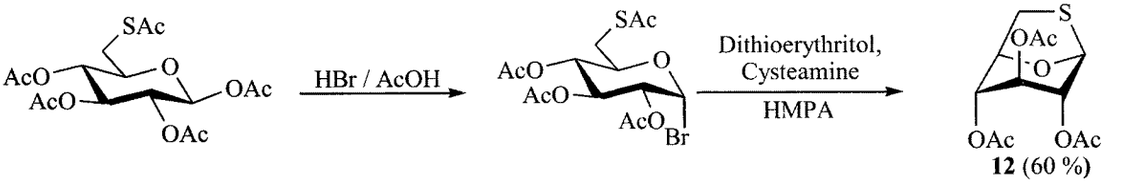
Driguez *et al.* have published the most reliable and simplest of the available methods for the preparation of thiolevoglucosans involving the



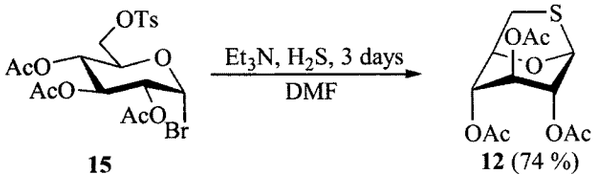
Scheme 4



Scheme 5

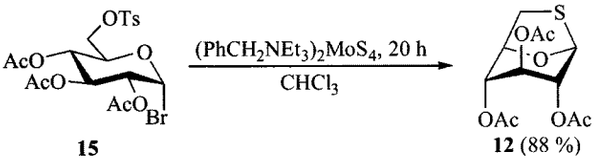


Scheme 6



Scheme 7

treatment of the bromide **15**, with benzyltriethylammonium tetrathiomolybdate to get **12** in 88 % yield (Scheme 8).[14]



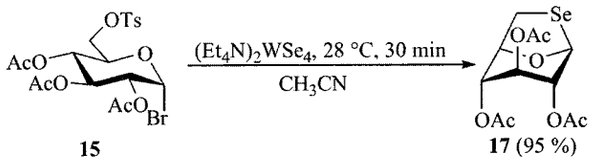
Scheme 8

Driguez *et al.* have also published the first synthesis of tri-*O*-acetyl selenolevoglucosan **16** in good yield, by treating the bromo tosylate **15** with sodium hydrogen selenide in dimethyl formamide (Scheme 9).[14]

Subsequent deacetylation of **16** with sodium methoxide in methanol yielded the selenolevoglucosan **17** in very good yield.

Use of Benzyltriethylammonium Tetrathiomolybdate, 18 and Tetraethylammonium Tetraselenotungstate, 19 in the Facile Synthesis of Thio- and Selenolevoglucosans

The chemistry of tetrathiomolybdate **18** and tetraselenotungstate **19** has been studied extensively in our laboratory. Tetrathiomolybdate as its benzyltriethylammonium salt **18**[18] and tetraselenotungstate as the tetraethylammonium salt **19**[19] have been used as sulfur and selenium transfer reagents, respectively. Though Stick and coworkers have used tetrathiomolybdate **18**, for the preparation of thiolevoglucosans,[14] an extensive study of this easy and high yielding route for the synthesis of various thiolevoglucosan derivatives was not taken up. From our experiences with the chemistry of tetraselenotungstate **19**[19] it seemed reasonable that it could probably be used for the synthesis of selenolevoglucosans. Accordingly, treatment of the bromo tosylate **15** with tetraselenotungstate **19** yielded the 1,6-episeleno derivative, **17** in 95 % yield (Scheme 10), and this methodology is superior to the method previously reported.[15]

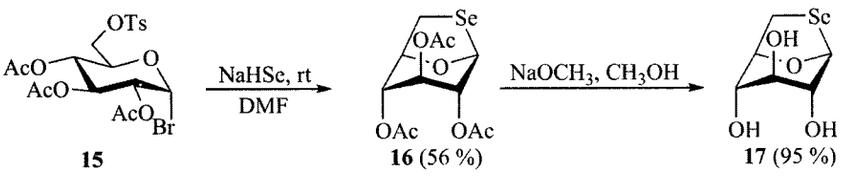


Scheme 10

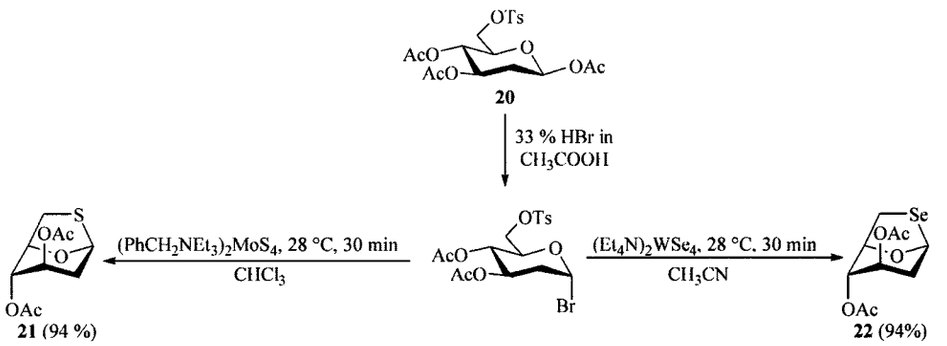
The use of reagents **18** and **19** for the synthesis of a number of thio- and selenolevoglucosan derivatives has recently been reported from our laboratory.[15]

Synthesis of 2-deoxy-3,4-di-*O*-acetyl thio- and Selenolevoglucosans

Treatment of 2-deoxy-1,3,4-tri-*O*-acetyl-6-*O*-tosyl-*á*-D-glucopyranoside **20** with HBr in acetic acid followed by the reaction with **18** afforded 2-deoxy-3,4-di-*O*-acetylthiolevoglucosan **21** and on treatment with **19** afforded 2-deoxy-3,4-di-O-



Scheme 9



Scheme 11

acetylselenolevoglucosan **22** in excellent yields (Scheme 11).[15]

Compounds **21** and **22** are potential precursors for the synthesis of a variety of natural products containing 2,6-dideoxy carbohydrate moieties, like the landomycins.[4]

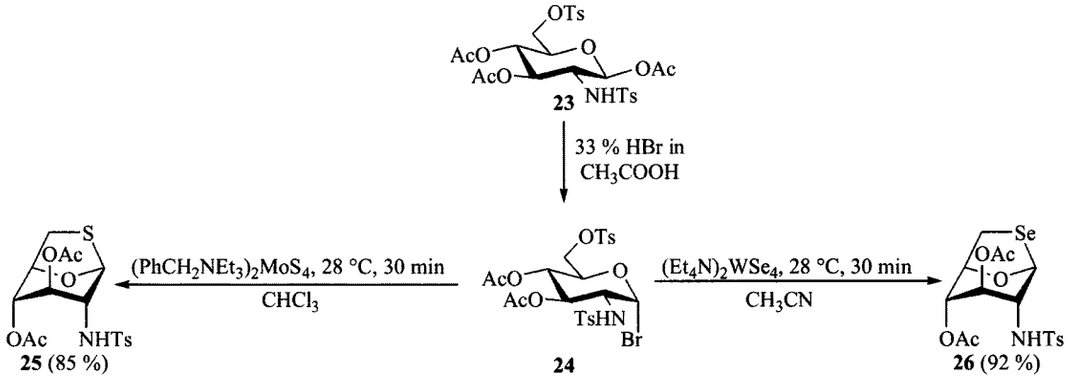
Synthesis of 2-deoxy-2-amino thio- and Selenolevoglucosans

Deoxy amino sugars are of synthetic interest because of their increased therapeutic potential. In 1975, Tejima *et al.* reported the synthesis of 2-acetamido-2-deoxy thiolevoglucosan starting from activated β-D-glucopyranosyl ethylxanthate.[20] There were no other synthetic procedures available for the synthesis of 2-amino derivatives of epithio or episeleno sugars until our recent report.[15] A simple strategy involves the conversion of the ditosyl glucosamine derivative **23** to the bromide **24** which on treatment with tetrathiomolybdate **18** gave 2-deoxy-2-tosylamino-3,4-di-*O*-acetyl-1,6-epithioglucose **25** and **24** on treatment with tetraselenotungstate **19** resulted in the formation of 2-deoxy-2-tosylamino-3,4-di-*O*-acetyl-1,6-episelenoglucose **26** in excellent yields (Scheme 12).

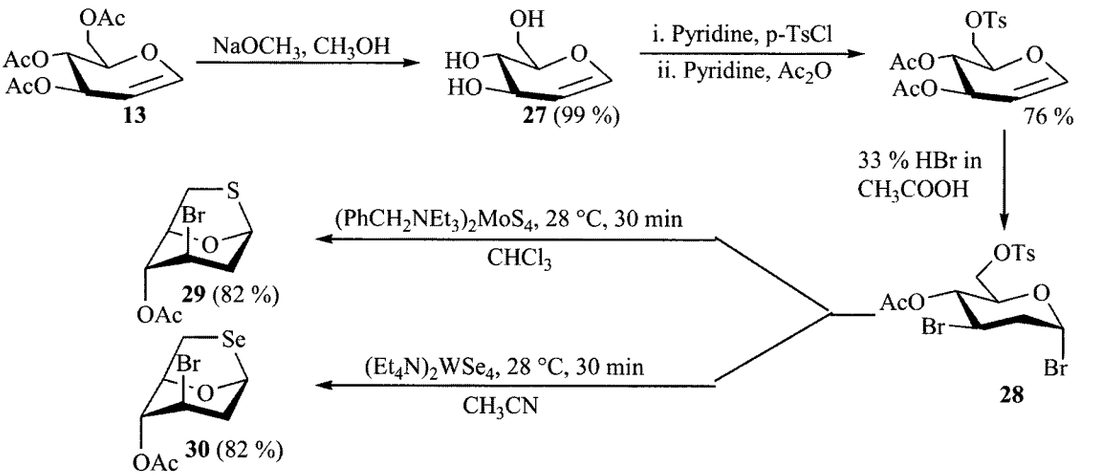
Synthesis of 2-deoxy-3-halo-1,6-epithio and Episeleno Sugars

2,3,6-Trideoxy sugars are present as terminal sugars in natural products like aclacinomycin and act as intermediates in the synthesis of antibiotic amicetin.[21] 2-Deoxy-3-halo-1,6-epithio or episeleno sugars can be interesting precursors for these trideoxy systems. An easy approach towards the synthesis of such systems starting from 3,4,6-triacetyl glucal **13** has been reported.[15] Triacetyl glucal **13** on deprotection with sodium methoxide in methanol yielded glucal **27**, which was selectively tosylated at C6 hydroxyl and then was subjected to acetylation followed by bromination to furnish the dibromide **28**. Compound **28** on treatment with **18** gave 2,3-dideoxy-3-bromo-4-*O*-acetyl-1,6-epithioglucopyranose **29** and on reaction with **19** afforded 2,3-dideoxy-3-bromo-4-*O*-acetyl-1,6-episelenoglucopyranose **30** respectively, in very good yields (Scheme 13).

Compounds **29** and **30** can easily be glycosylated, desulfurized or deselinized and then debrominated to get 2,3,6-trideoxy sugar derivatives. It is also important to note that **29** and **30** are very useful synthons for the synthesis of 3-amino-2,3,6-



Scheme 12



Scheme 13

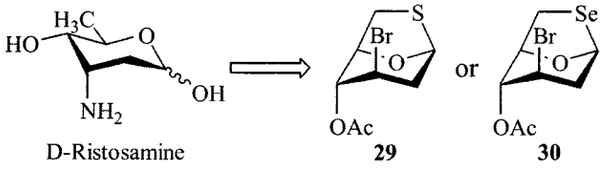


Fig. 4

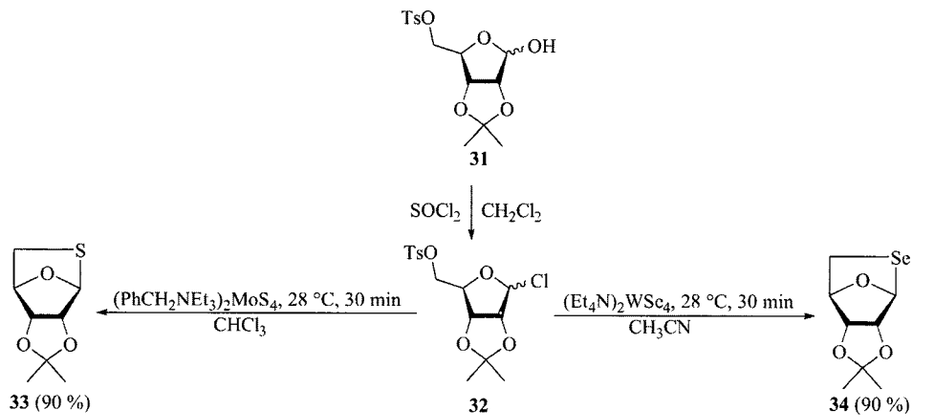
trideoxy sugar derivatives like D-ristosamine (Fig. 4).[22]

Synthesis of 1,5-epithio and 1,5-episeleno Pentose Derivatives

The methodology based on **18** and **19** for the synthesis of 1,6-epithio and 1,6-episeleno hexoses works equally well for the synthesis of 1,5-epithio and 1,5-episeleno pentoses.[15] For example, the reaction of the ribosyl chloride derivative **32**, derived from 5-*O*-tosyl-2,3-isopropylidine-D-ribose **31**, on reaction with tetrathiomolybdate **18** afforded 1,5-epithio-2,3-isopropylidine-D-ribose **33**[23] and on treatment with tetraselenotungstate **19** gave 1,5-episeleno-2,3-isopropylidine-D-ribose **34** in very good yields (Scheme 14). Though compound **33** has been synthesized previously (55%) from the anomeric thioacetate derivative of D-ribose, the present method using tetrathiomolybdate **1** is more efficient in terms of overall yield and the number of steps involved.[23]

Conclusion

Though epithio and episeleno sugar derivatives have long been known, investigations in to the reactions and properties of these molecules have been limited, owing in part to the difficulty in preparing these compounds. The use of benzyltriethylammonium tetrathiomolybdate, **18**



Scheme 14

and tetraethylammonium tetraselenotungstate, **19** with suitably activated sugar derivatives have made the synthesis of diversely functionalized epithio and episeleno derivatives an easy task. It is believed that the recent reports towards the synthesis of these molecules, especially with **18** or **19** would trigger further work towards the synthesis of many interesting thio- and seleno- sugar derivatives.

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