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Samarium(II) Iodide Mediated Intramolecular Homolytic Substitution at Selenium: Preparation of 5-Seleno-D-pentopyranose Sugars From Common Pentose Starting Materials

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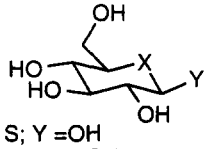
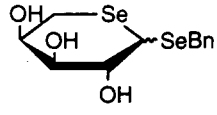
Abstract: Treatment of 2,3,4-tri-O-benzyl-5-benzylseleno-5-deoxyribose (**9**) with samarium(II) iodide in THF affords 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-ribopyranose (**10**) in 50% isolated yield in a process most likely involving intramolecular homolytic substitution at the selenium atom. In a similar fashion, 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-xylopyranose (**16**) and 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-arabanopyranose (**17**) were prepared from analogous precursors in 21 and 12% yields respectively.

It is well accepted that carbohydrates play an important role in a vast array of biological processes. Modified carbohydrates such as nitrogen, phosphorus and sulfur containing monosaccharides are of interest due to their wide variety of pharmacological activity and physiochemical properties. 5-Deoxy-5-thio-D-glucose (**1a**) has been shown to to be a potent inhibitor of cellular D-glucose transport and also selectively toxic to hypoxic tumor cells.[1] Other examples include, *nojirimycin* (**1b**), *deoxynojirimycin* (**1c**) and the butylated analogue (**1d**). These compounds are well known to show antibacterial activity and have been proposed as chemotherapeutic agents to treat HIV infection since the discovery that these compounds alter the carbohydrate structure of the HIV glycoprotein, *gp120*, resulting in the blocking of the HIV-T cell interaction.[2] Selenium analogues of these important compounds (eg. **1e**) may also be expected to show interesting properties.



1a: X = S; Y =OH
b: X = NH; Y =OH
c: X = NH; Y =H
d: X = NBu; Y =H
e: X = Se



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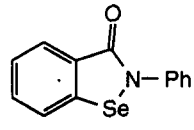

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There are very few reports of carbohydrates containing selenium in the ring position.[3] Those that have been reported (eg. **2**) were prepared in very poor yield.[3] Selenium-containing compounds are finding important roles as new generation pharmaceuticals. For example, *Ebselen* (**3**) was recently featured in *Drugs of the Future* as an antioxidant, antiinflammatory agent and hepatoprotectant and is currently undergoing phase III clinical trials in Japan.[4] In addition, *selenazofurin*, a selenium-containing glycoside, has been shown to exhibit both antiviral and antitumor properties,[5] while several other simple selenides have been shown to

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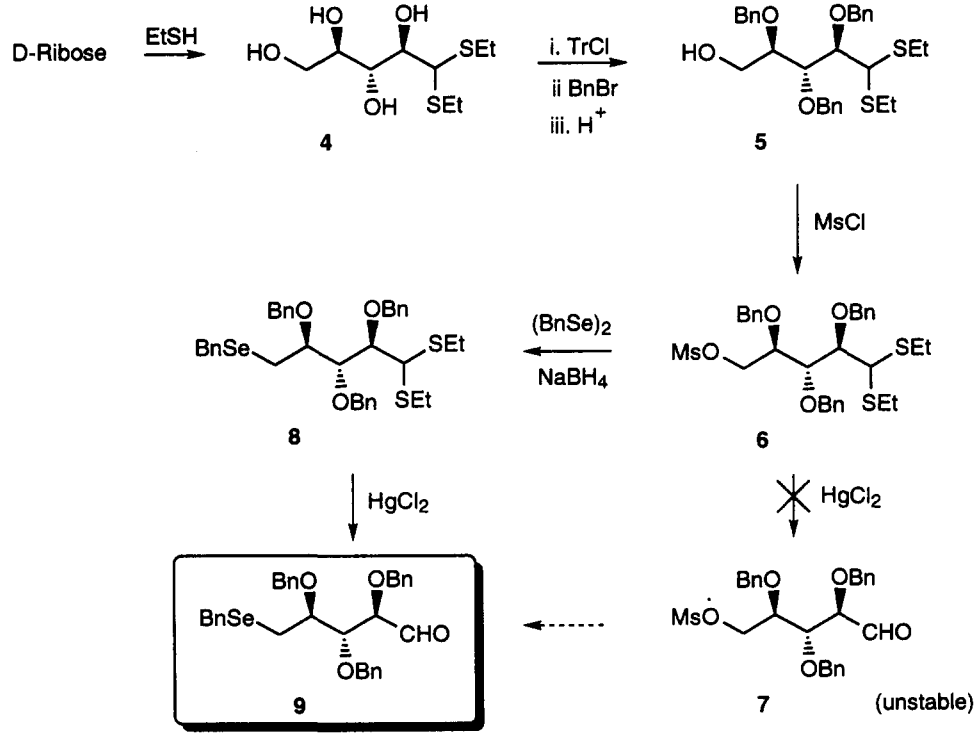
provide effective treatments for several diseases including Kwashiokor[6] (a protein malnutrition disorder) and Keshan Disease[7] (a form of cardiomyopathy). Given that scarcity of (ring) selenium-modified carbohydrates, it is clear that a synthetically useful method for the preparation of selenium-containing carbohydrates is required.

As part of ongoing investigations, we were interested in the preparation of novel selenium-containing carbohydrates related to **1e**. Given our recent successes in the preparation of selenium-containing higher heterocycles through the use of intramolecular free-radical homolytic substitution chemistry,[8] we began to explore the possibility of constructing the carbohydrates of interest through the use of analogous free-radical chemistry. We now report that 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-ribopyranose (**10**), 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-xylopyranose (**16**), and 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-arabanopyranose (**17**), can be prepared in acceptable yields by treatment of suitable precursor aldehydes with samarium(II) iodide in THF / HMPA.

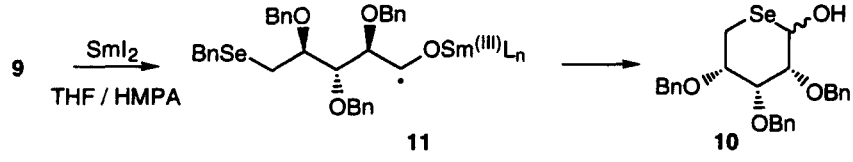
Scheme 1



Our first target precursor was 2,3,4-tri-O-benzyl-5-benzylseleno-5-deoxyribose (**9**) which was prepared according to the sequence shown in Scheme 1. Accordingly, D-ribose was transformed into 2,3,4-tri-O-benzyl-D-ribose diethyl thioacetal (**5**) following the procedure of Tadano and coworkers.[9] Further treatment with methanesulfonyl chloride afforded the mesylate (**6**) in 88% yield. Deprotection of the aldehyde with mercuric chloride gave **7** as an unstable oil. As the sensitivity of aldehyde (**7**) precluded further synthetic manipulation, we chose instead to treat **6** with sodium benzylselenoate, generated by the reduction of dibenzyl diselenide with sodium borohydride in ethanol which provided benzylselenide (**8**) in 39% yield; further deprotection with $HgCl_2$ afforded the required precursor (**9**) in 71% yield.

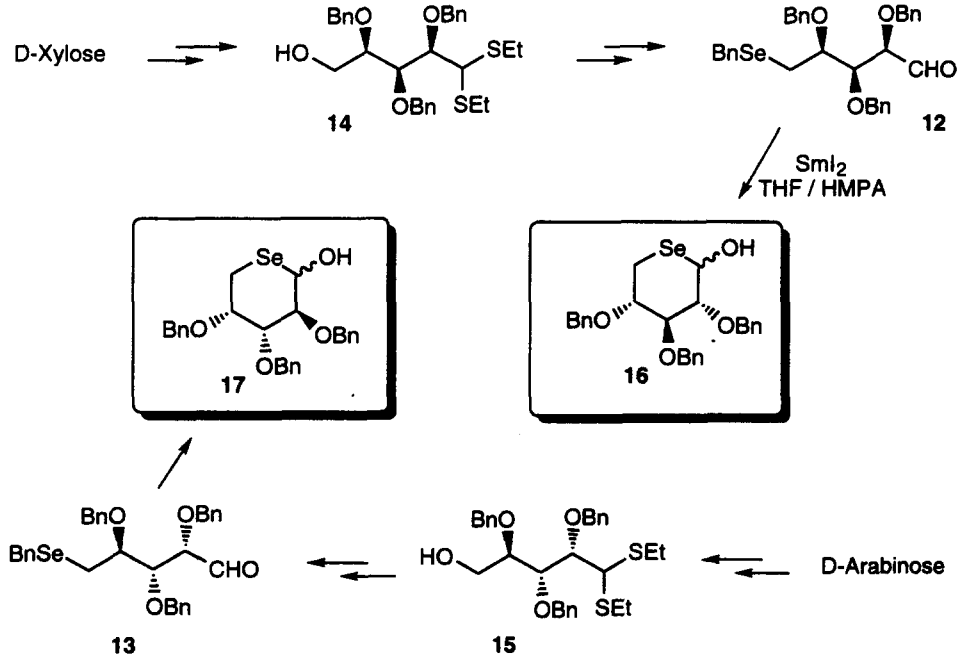
When **9** was treated with 2.5 equivalents of samarium(II) iodide in THF / HMPA, TLC analysis revealed the absence of starting material (**9**) after 20 minutes. To our delight, separation of the crude reaction mixture by flash chromatography afforded 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-ribopyranose[10] (**10**) in 50% yield. Presumably, **10** is formed by intramolecular homolytic substitution of the radical centre in **11**, generated by the reaction of the aldehyde moiety in **9** with SmI_2, at the selenium atom with expulsion of the benzyl group (Scheme 2).

Scheme 2



In order to explore the versatility of the samarium(II) iodide mediated procedure described above, D-xylose and D-arabinose were converted into the radical precursors, 2,3,4-tri-O-benzyl-5-benzylseleno-5-deoxyxylose (**12**) and 2,3,4-tri-O-benzyl-5-benzylseleno-5-deoxyarabinose (**13**) respectively (via the known thioacetals[9] (**14**, **15**)) (Scheme 3). Once again, treatment of **12** or **13** with samarium(II) iodide in THF / HMPA afforded 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-xylopyranose[10] (**16**) or 2,3,4-tri-O-benzyl-5-deoxy-5-seleno-D-arabinopyranose[10] (**17**) in 21 and 12% yield, respectively.

Scheme 3



It should be noted that selenosugars (**10**, **16**, **17**) were isolated as a pair of anomers in each case, as evidenced by ^1H NMR spectroscopy. We are unable to determine configuration of the dominant diastereoisomer at this time.

In summary, we have demonstrated that 5-selenopentopyranose sugars are accessible through samarium(II) iodide mediate intramolecular homolytic substitution at the selenium atom in suitably constructed precursors. These transformations represent the first examples of SmI_2 mediated homolytic substitution chemistry and provide further examples of rare 5-selenopentopyranose carbohydrates.

Acknowledgments

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10. Typical procedure: **2,3,4-Tri-O-benzyl-5-deoxy-5-seleno-D-ribopyranose (10)**. Dry HMPA (0.4 mL) was added to a stirred solution of SmI_2 in THF (5 mL, 0.1M) and the solution flushed with nitrogen. 2,3,4-Tri-O-benzyl-5-benzylseleno-5-deoxyribose (**9**) (100 mg, 0.17 mmol) in THF (3 mL) was added via syringe and the resultant solution stirred for 4 h. A further aliquot of SmI_2 (5 mL) was added and the solution stirred overnight at which time TLC analysis indicated the absence of **9**. Satd. $NaHCO_3$ (20 mL) was added, the mixture extracted with ether, the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was separated by flash chromatography (10% ethyl acetate in petrol) to afford **10** as a mixture of anomers (40 mg, 50%). ^1H NMR δ 2.4 – 2.9 (2H, m), 3.1 – 4.3 (4H, m), 4.5 – 4.9 (6H, m), 5.38 (0.5H, m, anomer A), 5.42 (0.5H, m, anomer B), 7.18-7.40 (15H, m). $[\alpha]_D^{25}$ ($CHCl_3$) = +11.4°. HRMS $[M+Na]^+$: calcd for $C_{26}H_{28}O_4{}^{80}SeNa$ 507.1046, found 507.1051.