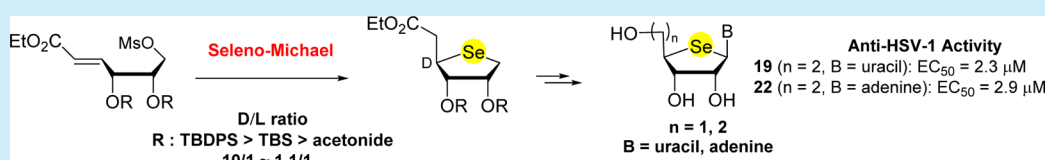


Stereoselective Synthesis of 4'-Selenonucleosides via Seleno-Michael Reaction as Potent Antiviral Agents

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S Supporting Information



ABSTRACT: Based on the hypothesis that the bulky selenium atom, with 4p orbitals, can sterically hinder the approach of a cellular kinase to 5'-OH for phosphorylation, 4'-selenonucleosides with one-carbon homologation were designed and synthesized via a novel seleno-Michael reaction, with the stereoselectivity controlled by steric effects. 5'-Homo-4'-selenonucleosides ($n = 2$) demonstrated potent antiherpes simplex virus (HSV-1) activity, indicating that the bulky selenium atom might play a key role in preventing phosphorylation by cellular kinases, resulting in no antiviral activity.

Natural DNA and RNA building blocks have served as valuable resources for the development of new therapeutic agents, such as antiviral and anticancer agents.¹ Modifications of the furanose ring at the 2'- and/or 3'-position have resulted in many clinically useful drugs, such as AraC, AZT, and gemcitabine.^{1,2} However, these 4'-oxo-nucleosides, referred to as first-generation nucleosides, suffer from many drawbacks, such as drug resistance, bone marrow and mitochondrial toxicity, and chemical instability.¹ To overcome these side effects, 4'-thio-³ and 4'-carbonucleosides,⁴ which are bioisosterically related to 4'-oxonucleosides, were developed as second-generation nucleosides. Currently, only abacavir is used clinically as an anti-AIDS agent, although several second-generation nucleosides are in clinical trials. The lack of efficacy among second-generation nucleosides prompted the design of a new template for nucleoside drug development.

Recently, we⁵ and another group⁶ reported 4'-selenonucleosides as the next generation of nucleosides. However, most of the synthesized 4'-selenonucleosides showed no significant antiviral or anticancer activity, most likely due to the absence of phosphorylation by cellular kinases. Among these, 2'-F-4'-Se-AraC showed potent anticancer activity;^{5d} however, it was not phosphorylated in the cell, indicating that it is not a cellular DNA/RNA polymerase inhibitor, unlike AraC.⁷

The inability of cellular kinases to phosphorylate 4'-selenonucleosides may be attributed to a conformation different from those of 4'-oxo- or 4'-thionucleosides, which was demonstrated by their X-ray crystal structures.⁵ We also hypothesized that the approach of the cellular kinase to the 5'-hydroxyl group for cellular phosphorylation is hindered by the bulky selenium atom, which possesses 4p orbitals.

As illustrated in Figure 1, it was hypothesized that the absence of cellular phosphorylation could be due to the presence of the bulky selenium in 4'-selenonucleosides; it was felt that this might

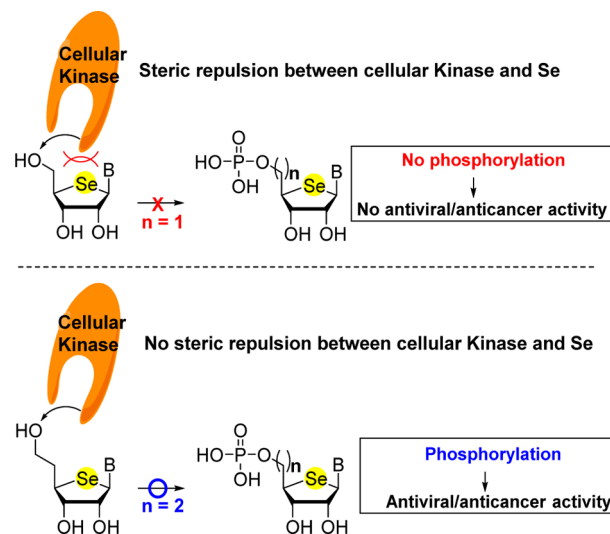


Figure 1. Rationale for the design of 5'-homo-4'-selenonucleosides.

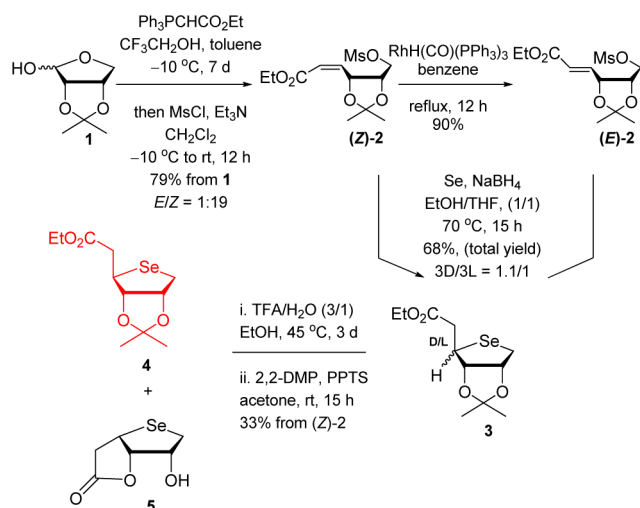
be relieved by one-carbon homologation. Thus, we designed and synthesized 5'-homo-4'-selenonucleosides ($n = 2$) using a novel seleno-Michael reaction as a key step, along with the synthesis of normal 4'-selenonucleosides ($n = 1$), and we evaluated them for antiviral activity (Figure 1). Herein, we now report on these efforts.

To synthesize the key homoseleno sugar **4**, a novel seleno-Michael reaction was employed as the key step, as shown in Scheme 1.

2,3-O-Isopropylidene-L-erythrofuranose (**1**)⁸ was treated with $\text{Ph}_3\text{PCHCO}_2\text{Et}$ at -10°C in the presence of trifluoroethanol⁹ to

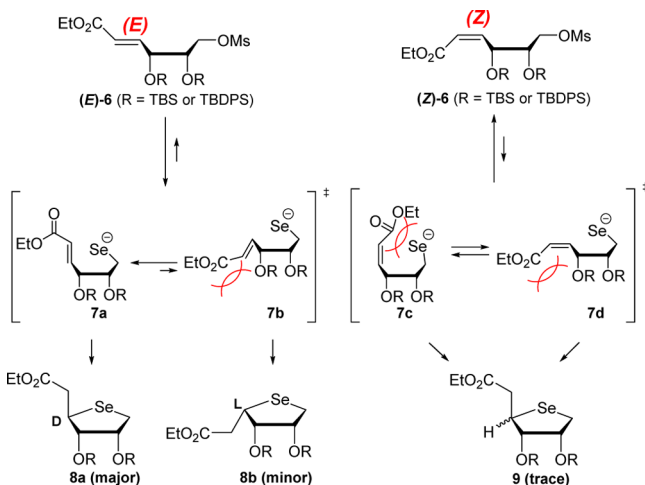
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Scheme 1. Synthesis of Key Selenosugar 3 Using a Seleno-Michael Reaction with *E*- and *Z*-Alkenes

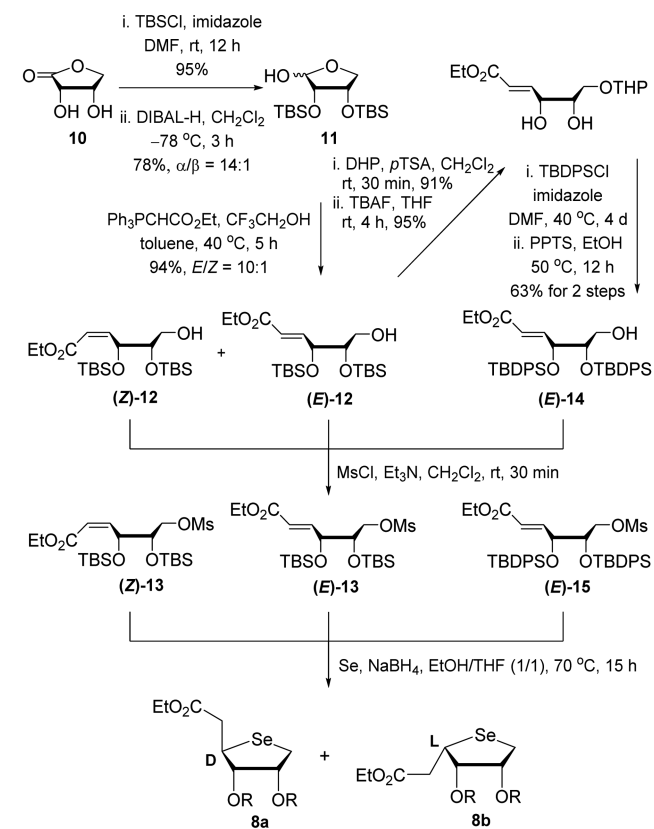
avoid an oxa-Michael reaction. This step was followed by mesylation to afford (*Z*)-2 as the major isomer in an $E/Z = 1/19$ ratio. The seleno-Michael reaction of (*Z*)-2 proceeded smoothly upon treatment with selenium powder and NaBH_4 in EtOH to afford the seleno-Michael adduct 3 as a separable $D/L = 1.1:1$ diastereomeric mixture. To examine the difference in reactivity between the *E*- and *Z*-isomers in the seleno-Michael reaction, the (*Z*)-isomer 2 was isomerized to the (*E*)-isomer 2 in the presence of a Rh catalyst.¹⁰ Under the same conditions, the seleno-Michael reaction of (*E*)-2 yielded adduct 3 as a separable $D/L = 1.1:1$ diastereomeric mixture, indicating that the 2,3-acetonide did not induce facial selectivity in the seleno-Michael reaction. To readily isolate the target compound from the mixture, 3 was hydrolyzed with aqueous TFA and then treated with 2,2-dimethoxypropane in the presence of *p*-TsOH to yield the desired *D*-isomer 4 and the undesired lactone 5, which formed from the *L*-isomer.

To increase the ratio of the desired *D*-isomer, we studied the steric effects in the seleno-Michael reaction. Models indicated that the transition state of the seleno-Michael reaction might be shifted to favor the desired *D*-isomer 8a if a bulky protecting group such as TBS or TBDPS was introduced, as depicted in Scheme 2. The seleno-Michael reaction of the *E*-isomer, (*E*)-6,

Scheme 2. Change in the Transition State in the Seleno-Michael Reaction To Favor the *D*-Isomer Based on Steric Effects

was expected to proceed via 7a over 7b because of the steric effects of the bulky protecting group, thus affording 8a and 8b as the major and minor products, respectively. The seleno-Michael reaction of the *Z*-isomer, (*Z*)-6, was not expected to proceed, since it would have to pass through the unfavored transition states 7c and 7d. Thus, only trace amounts of 9 were expected to be produced.

Accordingly, we synthesized substrates for the seleno-Michael reaction with TBS or TBDPS as bulky protecting groups, as illustrated in Scheme 3. Treatment of *L*-erythrono- γ -lactone (10)

Scheme 3. Facial Selectivity in the Seleno-Michael Reaction of *E*- and *Z*-Alkenes with Bulky Protecting Groups

entry	substrate	protecting group (R)	ratio 8a:8b	yield* (%)
1	(<i>Z</i>)-2	acetonide	1.1:1	68%
2	(<i>E</i>)-2	acetonide	1.1:1	68%
3	(<i>Z</i>)-13	TBS	trace	trace
4	(<i>E</i>)-13	TBS	4:1	70%
5	(<i>E</i>)-15	TBDPS	10:1	15%

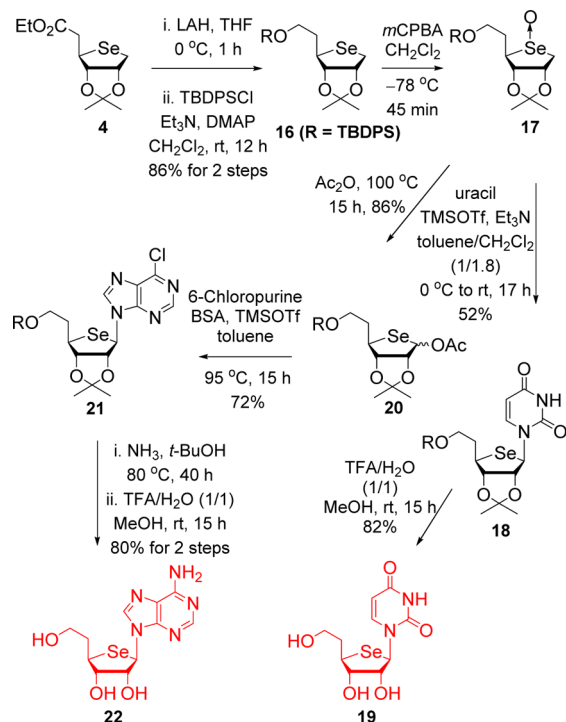
*Total yield (8a + 8b)

with TBSCl followed by reduction with DIBAL-H yielded lactol 11, which exists in its cyclic hemiacetal form ($\alpha/\beta = 14:1$). Wittig reaction of 11 with $\text{Ph}_3\text{PCHCO}_2\text{Et}$ at 40°C produced a 1:10 mixture of (*Z*)-12 and (*E*)-12 in 94% total yield. Mesylation of (*Z*)-12 and (*E*)-12 yielded the substrates (*Z*)-13 and (*E*)-13, respectively, for use in the seleno-Michael reaction. The seleno-Michael reaction of (*E*)-13 under the same conditions as those in Scheme 2 afforded the desired *D*-isomer 8a and the undesired

α -isomer **8b** in a 4:1 ratio, whereas the same reaction with (*Z*)-**13** failed to give the corresponding adducts. To further study the steric effects in the seleno-Michael reaction, the TBS groups of (*E*)-**13** were replaced with bulkier TBDPS groups in (*E*)-**15**. As expected, the ratio of **8a** and **8b** was greatly increased to 10:1, but resulted in a low yield because of the remaining starting material (62%). These results demonstrated that the steric effects shown in Scheme 2 played a major role in controlling the transition states and favored the formation of **8a**.

To synthesize the 5'-homo-4'-selenonucleosides, the seleno-sugar **4** was reduced with LAH and further protected with TBDPS to give **16** (Scheme 4). Oxidation of **16** with *m*CPBA

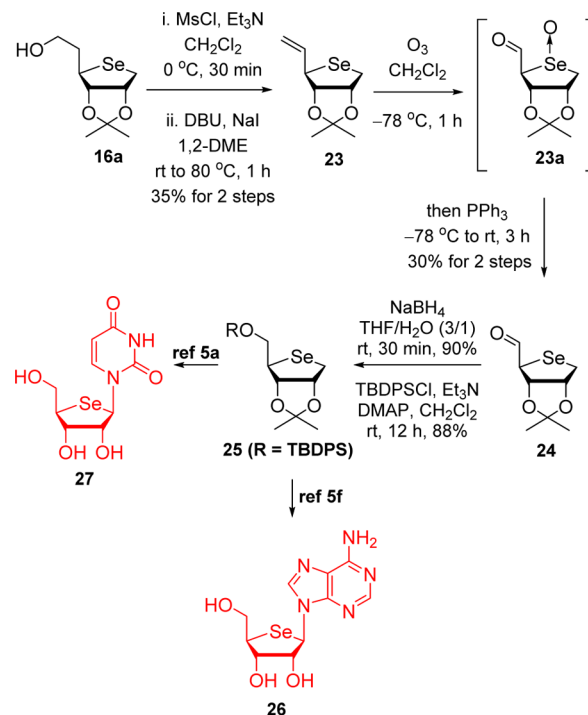
Scheme 4. Synthesis of 5'-Homo-4'-selenonucleosides



yielded the glycosyl donor **17**, which was condensed with uracil under Pummerer-type conditions^{5a} to afford the protected nucleoside **18**. Removal of the protecting group from **18** yielded the final 5'-homo-4'-selenouridine **19**. To synthesize 5'-homo-4'-selenoadenosine **22**, the glycosyl donor **17** was converted to the glycosyl donor **20** by heating with acetic anhydride at 100 °C. Condensation of **20** with silylated 6-chloropurine in the presence of TMSOTf as a Lewis acid yielded the protected 6-chloropurine derivative **21**. Treatment of **21** with *tert*-butanol ammonia followed by acidic hydrolysis yielded the final 5'-homo-4'-selenoadenosine **22**.

In addition to 5'-homo-4'-selenonucleosides, 4'-selenonucleosides **26** and **27** were synthesized from the same intermediate, **16a** (R = H), as shown in Scheme 5. Compound **16a** was converted to alkene **23** by mesylation followed by an elimination reaction. Ozonolysis of **23** produced aldehyde **23a**; however, the selenium was also oxidized. Thus, **23a** was further treated with triphenylphosphine to afford the desired aldehyde **24**.¹¹ Reduction of **24** followed by protection of the resulting alcohol with TBDPS afforded the known intermediate **25**.^{5a} Intermediate **25** was converted to the desired 4'-selenonucleosides **26** and **27** according to our previously published procedures.^{5a,f}

Scheme 5. Synthesis of 4'-Selenonucleosides



The synthesized final nucleosides **19**, **22**, **26**, and **27** were assayed for antiviral activity. As expected, 5'-homo-4'-selenonucleosides **19** and **22** exhibited antiherspes simplex virus (HSV-1) activity (EC_{50} = 2.3 and 2.9 μ M, respectively), but the corresponding 4'-selenonucleosides **27** and **26** exhibited no antiviral activity up to 100 μ M probably because cellular phosphorylation did not occur.

In conclusion, we have designed and synthesized 5'-homo-4'-selenonucleosides via a novel seleno-Michael reaction to study the steric effects of the bulky selenium atom on phosphorylation by cellular kinases. The facial selectivity of the seleno-Michael reaction was controlled by steric effects. To our best knowledge, this seleno-Michael reaction is the first example to be utilized for the synthesis of carbohydrates. One-carbon homologation resulted in potent antiviral activity being observed, by allowing the 5'-homo-4'-selenonucleosides to be phosphorylated by cellular kinases. These findings indicate that the bulky selenium played an important role in preventing phosphorylation by cellular kinases. It is expected that this study can be extended to other inactive 2'- and/or 3'-modified-4'-selenonucleosides and greatly contribute to the discovery of new biologically active nucleosides. The cellular phosphorylation study of 4'-selenonucleosides (n = 1, 2) will be reported elsewhere.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and copies of ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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