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The Synthesis of Octosyl Nucleosides Based on Intramolecular Oxyselenation of a Conjugated Diene

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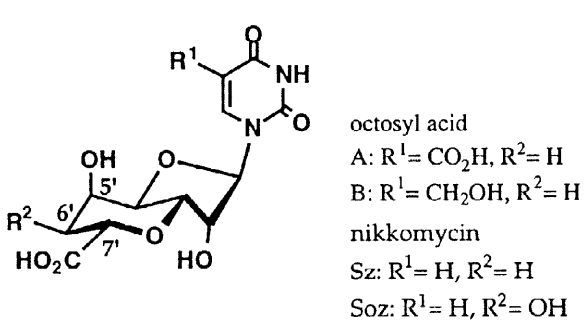
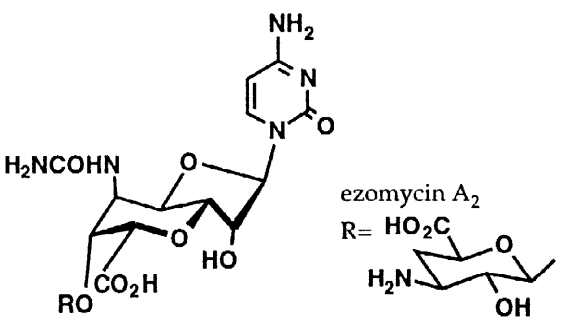
Abstract: A new stereoselective ring construction for 3,7-anhydrooctofuranosyl nucleoside, which is based on a 6-*endo-trig* oxyselenation of a conjugate diene, (5'*S*)-*C*-(4-phenyl-1,3-butadienyl)uridine, was developed. Because of the appropriate array of functionalities at the 5', 6', and 7'-positions, the cyclization product **14** can be considered to be a versatile synthon for the synthesis of a series of octosyl nucleoside antibiotics. Factors governing the efficiency of this cyclization are also discussed.

Keywords: Nucleosides; Radicals and radical reaction; Dienes; Selenonium ions

Among sugar-modified nucleoside antibiotics, there have been known a series of octosyl nucleosides as shown in Fig. 1.[1] Octosyl nucleosides not only exhibit a variety of biological activities but also have a characteristic chemical structure in the sugar portion: a rigid bicyclic skeleton called 3,7-anhydrooctofuranosyluronic acid, in which a furanoid ring is *trans*-fused to a pyranoid ring. One synthetic strategy for constructing the bicyclic system is based on six-membered ring closure of pentofuranose derivatives.[2),3)] Construction of the six-membered cyclic ether has been achieved by the following reactions: 1) *SN*2 reaction (intramolecular Williamson reaction),[2a), 2b),2d)] 2) 6-*exo-trig* oxymercuration,[2c)] and 3) 6-*exo-trig* radical cyclization.[2c)] Although these methods proceeded in highly stereoselective manner, they are applicable only to the target molecule. In this communication, we wish to present a new 6-*endo-trig* methodology, based on intramolecular oxyselenation of conjugated diene, (5'*S*)-*C*-(4-phenyl-1,3-butadienyl)uridine, where the resulting cyclization product has high potential for the synthesis of a series of octosyl nucleosides.



octosyl acid
A: $R^1 = CO_2H$, $R^2 = H$
B: $R^1 = CH_2OH$, $R^2 = H$
nikkomycin
Sz: $R^1 = H$, $R^2 = H$
Soz: $R^1 = H$, $R^2 = OH$



ezomycin A_2
R= HO_2C

Fig. 1

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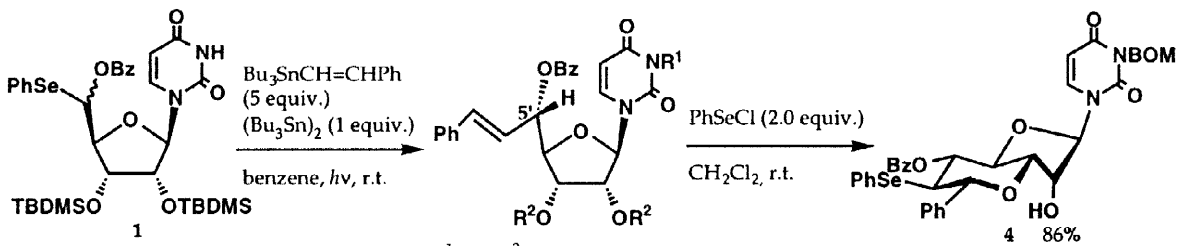
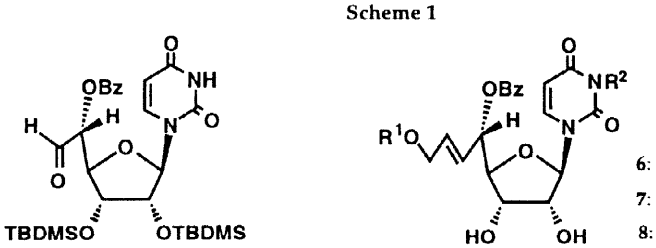
As we have already reported, the uridine 5'-monoselenoacetal **1** reacts with various types of radical acceptors to provide a stereoselective C-C bond formation at the 5'-position.[4] When styryltributylstannane was used as the radical acceptor, the (5'*S*)-*C*-styryl derivative **2** was obtained in a highly diastereoselective manner (>95% d.e., based on ^{1}H NMR analysis) (Scheme 1). In order to determine the configuration at the 5'-position, intramolecular oxyselenation of free nucleoside **3** was conducted by reaction with PhSeCl at room temperature. The cyclization reaction was found to proceed smoothly to afford the 3,7-anhydrooctofuranosyl nucleoside **4** in 86% yield. In spite of the ready access to **4**, the difficulty anticipated in transforming the 7'-phenyl group in **4** to a carboxylic group led us to investigate the preparation and the cyclization of other substrates.[5]

As the first substrate for cyclization, we selected the allyl alcohols **7** and **8**. Compounds **7** and **8** were prepared as follows: oxidative cleavage of the styryl moiety of **2** with $NaIO_4$-OsO_4 to give the aldehyde **5** (quant.); the Wittig reaction of **5** with Ph_3P=CHCHO followed by hydride reduction to afford allyl alcohol **6** (50%); protection of the allyl alcohol moiety. In the case of **7**, a N^3-benzyloxymethyl (BOM) group was introduced to give enough solubility to the substrate (Scheme 2). In contrast to the result of the reaction of **3**, the main pathway of the reaction between **7** and PhSeCl appeared to be a simple intermolecular electrophilic addition (chloro-selenation) to give **9** (6%) and **10** (13%) along with unidentified products. Only a trace amount of the desired cyclized product **11** (11%, isolated as its 2'-*O*-acetate) was detected in the case of **8**. The difference in the efficiency for intramolecular oxyselenation between the 5'-*C*-styryl derivative **3** and

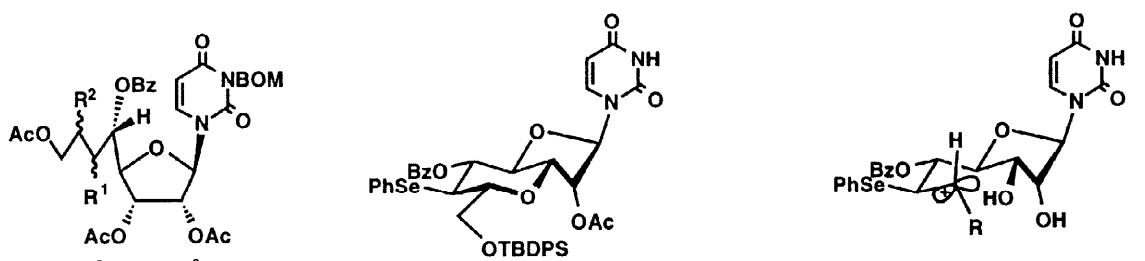


2: R^1= H, R^2= TBDMS
quant., >95% d.e.
3: R^1= CH_2OCH_2Ph (BOM), R^2= H

Scheme 1



6: R^1= R^2= H
7: R^1= Ac, R^2= BOM
8: R^1= TBDPS, R^2= H

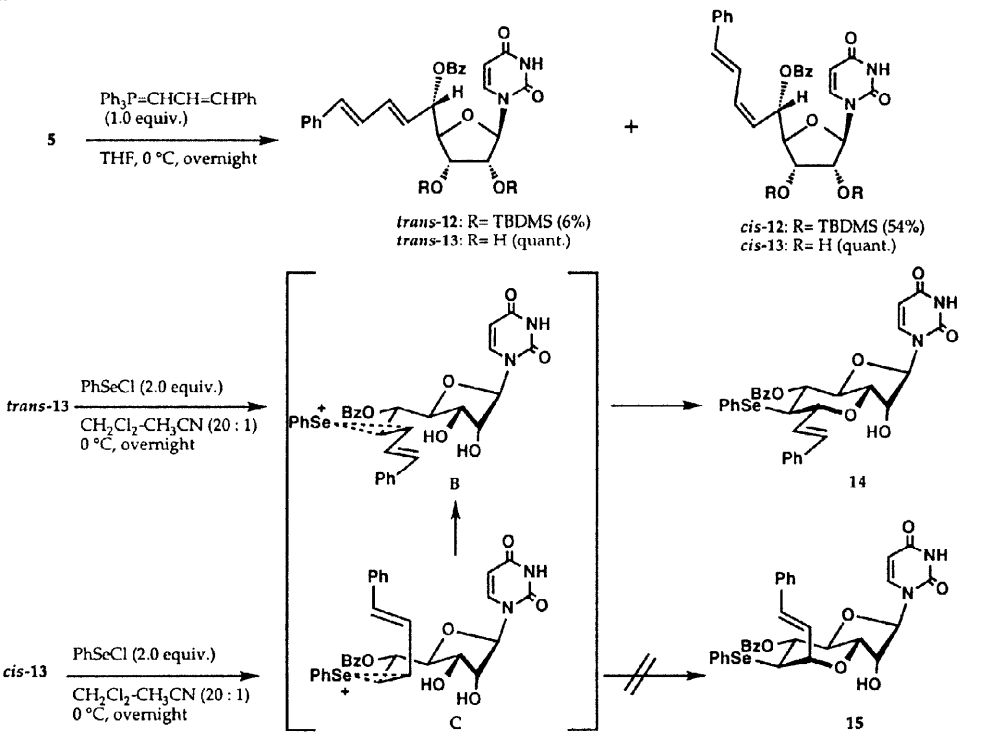


9: R^1= SePh, R^2= Cl
10: R^1= Cl, R^2= SePh

Scheme 2

the allyl alcohols **7** or **8** might be accounted for by the stability of the intermediate carbenium ion **A**. We considered that introduction of a (5'*S*)-*C*-(4-phenyl-1,3-butadienyl) group would encourage the cyclization pathway through its resonance effect.

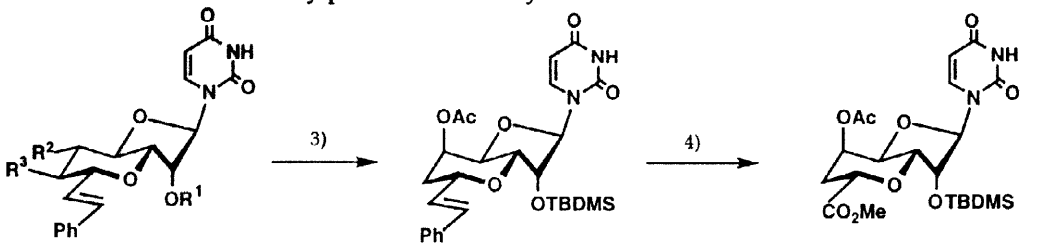
The conjugate diene **13** was prepared as shown in Scheme 3. Thus, Wittig reaction of the aldehyde **5** with Ph_3P=CHCH=CHPh in THF at 0 ℃ gave a mixture of *trans*-**12** (6%) and *cis*-**12** (54%), each of which was isolated by HPLC. Desilylation of **12** led to the precursor *trans*-**13** and *cis*-**13** quantitatively. Next, intramolecular oxyselenation was examined. Because of the low solubility of **13** to CH_2Cl_2, CH_3CN was used as a co-solvent. After optimizing the ratio of the two solvents to the oxyselenation, a mixture of CH_2Cl_2/CH_3CN in a ratio of 20/1 appeared to be a suitable solvent system. Thus, when *trans*-**13** was treated with PhSeCl (2 equiv.) in the mixed solvent at 0 ℃, the intramolecular oxyselenation was found to proceed efficiently in a 6-*endo*-*trig* manner and the desired cyclized product **14** was precipitated in the reaction medium (Scheme 3). After collection of the precipitate and chromatographic purification of the filtrate, **14** was obtained in 74% yield, without other stereoisomers. Under the identical conditions, *cis*-**13** also afforded **14** in 73% yield, instead of **15**. These results show that an incipient seleniranium ion **C** derived from *cis*-**13**, which has an unfavarable 1,3-steric repulsion of the styryl group, had been transformed into more stable intermediate **B** *via* an allylic carbenium ion. This finding enabled us to use a mixture of *trans*- **13** and *cis*-**13** to the oxyselenation; the desired **14** was precipitated from the reaction medium, and isolated in 75% yield simply by filtration.



Scheme 3

With the key intermediate **14** available in good yields we turned our attention to the transformation of **14** into octosylnucleoside antibiotics, which is demonstrated by an achievement of the synthesis of protected nikkomycin Sz **20** as shown in Scheme 4. Thus, silylation of **14** gave **16** in 79% yield. Removal of the 6'-phenylseleno group was carried out by treatment of **16** with Bu_3SnH and Et_3B in $PhCH_3$ at −78 ℃ under dry O_2. The inversion of the configuration at the 5'-position of **17** was accomplished by the following series of

reactions: debenzoylation (NaOMe), introduction of a chloromesyl group, and nucleophilic substitution with CsOAc in the presence of 18-crown-6 in benzene.[6] Compound **19** thus obtained was subjected to oxidative cleavage of the 7'-styryl group. Treatment of the resulting aldehyde with pyridinium dichromate (PDC) in the presence of MeOH furnished the fully protected nikkomycin Sz **20**.



16: R^1= $SiEt_3$, R^2= OBz, R^3= SePh
17: R^1= $SiEt_3$, R^2= OBz, R^3= H
18: R^1= TBDMS, R^2= OH, R^3= H

19 **20**

Conditions;
1) Bu_3SnH, Et_3B, O_2/PhMe, –78 °C (90%)
2) (a) Bu_4NF/THF, r.t. (quant.), (b) TBDMSCl, imidazole/DMF, 60 °C (quant.), (c) NaOMe/MeOH, r.t. (quant.)
3) (a) $ClCH_2SO_2Cl$/py, r.t. (quant.), (b) CsOAc, 18-crown-6/benzene, reflux (76%)
4) (a) OsO_4, $NaIO_4$/aq-dioxane, r.t. (76%), (b) PDC, MeOH/DMF, r.t. (42%)

Scheme 4

In conclusion, we have developed a new method for synthesizing 3,7-anhydrooctofuranosyl nucleoside based on highly stereoselective *6-endo-trig* oxyselenation of the conjugate diene, (5'*S*)-*C*-(4-phenyl-1,3-butadienyl)uridine. Beause the resulting cyclized product **14** has appropriate substituents at the 5'-, 6'-, and 7'-postions, we believe that **14** serves as a common intermediate for the synthesis of various types of octosyl nucleosides.

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